Effective Health Care Program

Comparative Effectiveness Review
Number 51

Dietary Supplements in Adults Taking Cardiovascular Drugs

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Dietary Supplements in Adults Taking Cardiovascular Drugs

Structured Abstract

Background. A substantial proportion of patients with cardiovascular diseases use dietary supplements in anticipation of benefit. This also poses risks of adverse events from supplement-drug interactions and nonadherence associated with polypharmacy.

Objectives. For supplements commonly used by patients with cardiovascular disease, we examined benefits, harms, and effects on cardiovascular drug pharmacokinetics of coadministration of dietary supplements with cardiovascular drugs. We also sought evidence regarding variability among subgroups, and of statistical interactions between supplements and drugs.

Data Sources. We searched MEDLINE®, Embase, the Cochrane Library, International Bibliographic Information on Dietary Supplements (IBIDS), and Allied and Complementary Medicine Database (AMED), as well as gray literature, from inception to September 2011.

Study Selection. Following a predefined protocol, two reviewers included experimental and observational studies comparing a supplement plus cardiovascular drug versus drug alone published in English or German; other languages were excluded due to concerns with study quality and applicability.

Data Extraction. One reviewer extracted data into a standardized electronic form, assessed study risk of bias, graded the strength of the body of evidence, and reported its applicability. Study risk of bias and strength of evidence regarding gradable outcomes were independently verified, as was a random 10 percent subset of all data.

Data Synthesis. Sixty-seven randomized controlled trials, two controlled clinical trials, and one observational study contributed evidence of limited validity in highly selected populations. Evidence was insufficient for all gradable clinical efficacy and harms outcomes (e.g., mortality, thrombotic events, serious adverse events) because there were few, small studies per supplement. One pragmatic trial in women showed no benefit from coadministering vitamin E with aspirin on a composite cardiovascular outcome. Evidence for most intermediate outcomes of efficacy was insufficient or of low strength and suggested no effect. Notable findings were incremental improvement of triglyceridemia with omega-3 fatty acid supplementation, stabilization of international normalized ratio with vitamin K added to warfarin therapy, and improved high-density lipoprotein cholesterol (HDL-C) with added garlic. Clinically nonsignificant or otherwise inconclusive changes were noted for pharmacokinetic outcomes.

Limitations. The evidence base principally consisted of underpowered short-term studies in selected populations, generally with moderate risk of bias.

Conclusions. Limitations of the evidence base precluded meaningful conclusions across most supplement-drug combinations. Low-strength evidence indicates benefits of omega-3 fatty acids, vitamin K, and garlic coadministration on specific intermediate outcomes. Evidence regarding harms was inconclusive. Care providers and researchers should query supplement use to improve care and to facilitate research regarding drug-supplement interactions.

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Executive Summary

Background

The American Heart Association estimates that more than 81 million American adults (one-third of all adults) have at least one form of cardiovascular disease (CVD).[1] CVD is broadly defined to include all the disorders of the arterial system, including the heart and coronary arteries, the arterial supply to the brain, and the peripheral arterial system. CVD manifests typically as hypertension, angina, myocardial infarction (MI), heart failure, stroke and transient ischemic attacks (TIAs), and intermittent claudication or blockage. While there has been progress in the control of CVD, it demands huge investments from the health care system, and represents great burdens and lost opportunities for individuals, families, and society overall.

In addition to lifestyle and dietary recommendations, frontline treatment for prevention and treatment of CVD is primarily pharmaceutical, with patients requiring, on average, 6.3 concomitant prescription drugs from, on average, 5.9 different drug classes for primary and secondary prophylaxis of the disease itself and management of associated comorbidities.[2-4]

Complementary and alternative medicine (CAM) refers to preventive and therapeutic modalities not generally considered to be part of conventional medicine,[5] including dietary supplements. CAM utilization has increased dramatically in North America over the past decades in both the general and CVD populations.[6,7]

The National Health Interview Survey indicated that Americans spent a total of $34 billion out of pocket on CAM in 2007.[8] Estimates suggest that approximately one-third to two-thirds of people suffering from heart failure or other cardiovascular disease use dietary supplementation and are thus placed at risk for potential adverse events from interactions with other pharmacologically active agents and nonadherence associated with polypharmacy.[7,9-13] With compromised physiology due to aging, the elderly are most vulnerable to the adverse events of any drug interaction. On the other hand, addition of a dietary supplement to conventional cardiovascular drugs may confer benefit. Evidence of both benefits and harms of adding a supplement to cardiovascular drugs has been reported.[6,14]

Incorporation in clinical practice of knowledge regarding the impact of concomitant use of cardiovascular medications and dietary supplements requires access to reliable drug-supplement information, as well as physicians' commitment to documenting patients' supplement use.[15,16] While a substantial amount of research and data is available describing drug–drug interactions in various populations, the evidence for drug-supplement interactions or simply add-on supplement effect is unclear, especially in the CVD populations.

Objectives

The objective of this Comparative Effectiveness Review was to systematically synthesize and grade the strength of evidence of benefits and harms of adding a dietary supplement to cardiovascular drugs routinely prescribed in outpatient settings. A related objective included assessment of whether the altered outcomes of efficacy and/or effectiveness and harms are a result of a simple add-on effect of a dietary supplement or more complex interactions with the cardiovascular drug. Supplement–drug interactions were examined by investigating evidence of statistical and pharmacokinetic interactions.

These objectives were framed in the following Key Questions.

In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared with cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement[s]) on:

Key Question 1. Clinical cardiovascular effectiveness/efficacy outcomes (e.g., mortality and specific cardiovascular or cerebrovascular conditions such as myocardial infarction and stroke)?

(a) Do the effect estimates of clinical cardiovascular outcomes vary by age, ethnicity, gender, or health status?
(b) Is there a measurable interaction between cardiovascular drugs and dietary supplements for clinical cardiovascular outcomes?

Key Question 2. Intermediate cardiovascular efficacy outcomes (e.g., lipids, blood pressure, electrocardiographic measurements, serum markers, bleeding, and coagulation times)?

(a) Do the effect estimates of intermediate cardiovascular outcomes vary by age, ethnicity, gender, or health status?
(b) Is there a measurable interaction between cardiovascular drugs and dietary supplements for intermediate cardiovascular outcomes?

Key Question 3. Clinical or intermediate harms outcomes (e.g., organ toxicity, serious adverse events, withdrawal due to adverse events)?

(a) Do the effect estimates of harms outcomes vary by age, ethnicity, gender, or health status?
(b) Is there a measurable interaction between cardiovascular drugs and dietary supplements for harms outcomes?

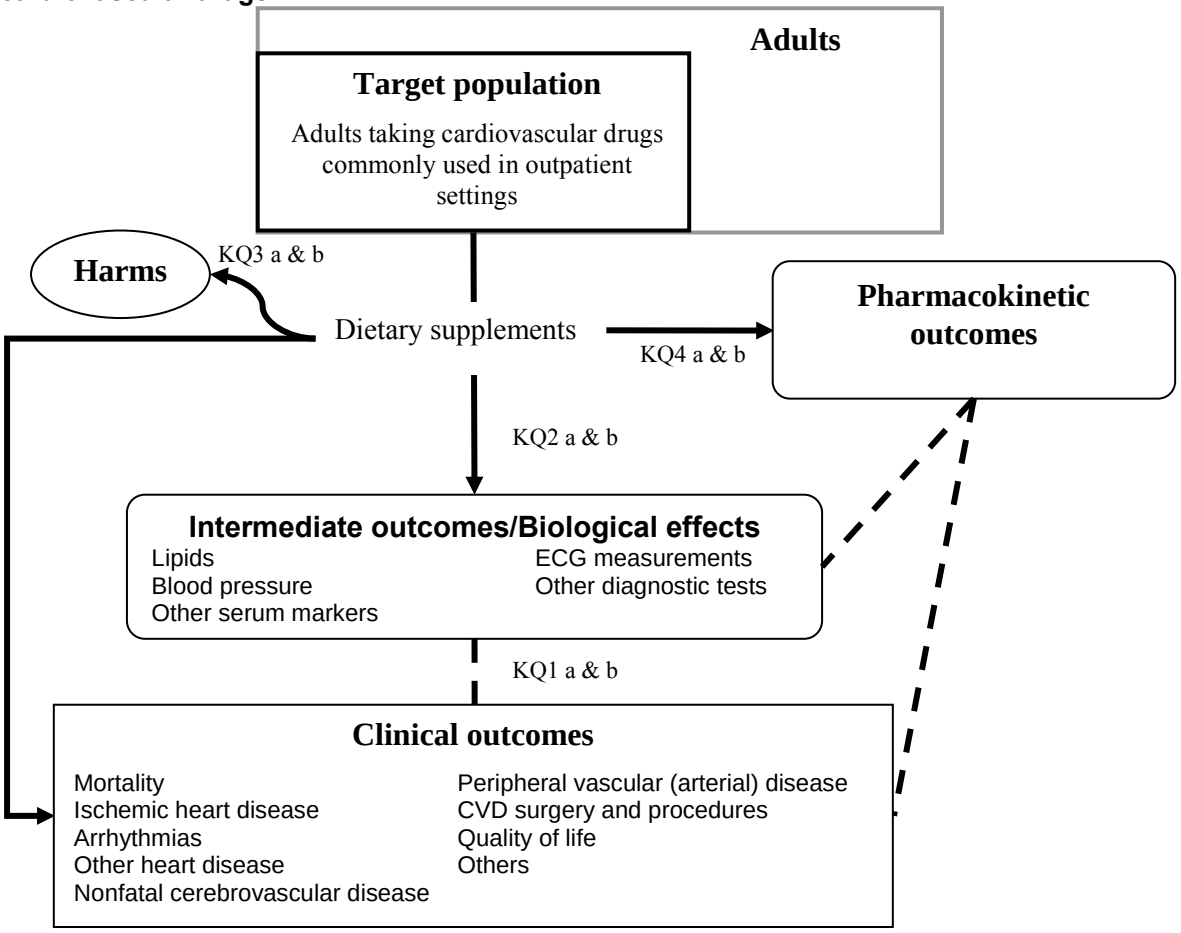
Key Question 4. Pharmacokinetic outcomes (e.g., half life [$t_{1/2}$], area under the concentration curve [AUC]) of cardiovascular drugs of interest?

(a) Do the effect estimates of pharmacokinetic outcomes vary by age, ethnicity, gender, or health status?
(b) Is there a measurable interaction between cardiovascular drugs and dietary supplements for pharmacokinetic outcomes?

Analytic Framework

The expectations behind using a dietary supplement with prescription cardiovascular drugs are improvement in the disease process (or its prevention) and reduction in harms related to cardiovascular drugs. These effects might come about through either an add-on effect of a supplement or its biological interaction with a cardiovascular drug. Benefits and harms are measured as outcomes that may be clinical outcomes, their proxy surrogates, or pharmacokinetic parameters. The analytic framework in Figure A depicts the causal pathways forming the basis of the Key Questions.

Figure A. Analytic framework of dietary supplement coadministration with routinely prescribed cardiovascular drugs



Note: CVD = cardiovascular disease; ECG = electrocardiography; KQ = Key Question.

Methods

Input From Stakeholders

Preliminary broad searches identified the necessity to focus this review, so we formulated the population, intervention, comparator, and outcome (PICO) analytic framework and Key Questions in consultation with the Key Informants during a topic refinement stage. The range of dietary supplements was narrowed to include only those most commonly taken along with cardiovascular drugs and for which there was no recent review. A fifth Key Question, regarding P450 isozyme activity and cellular drug transport mechanisms, was dropped. The Key Informants included clinicians (cardiologists, naturopathic doctors, clinical pharmacology specialist, and nutritionist), a patient/consumer advocate, and systematic review research methodologists. The public were invited to provide comments on the Key Questions. During the review process, we followed an a priori research protocol developed with the clinical and methodological input of a Technical Expert Panel (TEP) of specialist clinicians and methodologists. The protocol followed the Effective Health Care Program's Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[17]

Data Sources and Searches

We searched the following electronic databases from inception to September 1, 2011: MEDLINE®, Embase, the Cochrane Library (CENTRAL, CDSR, DARE, and HTA), International Bibliographic Information on Dietary Supplements (IBIDS), and Allied and Complementary Medicine Database (AMED). We developed peer-reviewed search strategies (shown in Appendix A of the full report) using a broad range of controlled vocabulary to address the various synonyms associated with this topic, as well as to cover any evolutionary gaps associated with the introduction of certain vocabulary terms. We also searched trial registries (e.g., ClinicalTrials.gov, Current Controlled Trials, Clinical Study Results, World Health Organization Clinical Trials), the Cambridge Scientific Abstracts Conference Papers Index, and Scopus.

Results were refined using filters for systematic reviews, randomized controlled trials (RCTs), non-RCTs and observational studies, and safety. A more specific strategy related solely to herb-drug interactions was run in the same databases using only a systematic review filter.

We also contacted TEP members and the Scientific Resource Center at the Agency for Healthcare Research and Quality.

Study Selection

Two reviewers screened titles, abstracts, and full-text reports, with conflicts resolved by consensus or third-party adjudication. A primary study was eligible if it:

- Was published in English or German.
- Examined a dietary supplement. A dietary supplement was defined as a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance, or a concentrate metabolite, constituent, or extract intended to increase the total dietary intake made for ingestion in pill, capsule, tablet, powder, or liquid form not represented for use as conventional food or as the sole item of a meal or diet).
- Compared the effect of adding a dietary supplement to cardiovascular medication(s) to the same cardiovascular medication(s) or to another dietary supplement (from the list above) added to the same cardiovascular medication(s).
- Evaluated use of a dietary supplement intended for ingestion as pill, capsule, tablet, powder, or liquid. The dietary supplements considered were coenzyme Q10, *Echinacea*, garlic, ginger, *Ginkgo biloba*, *Panax ginseng*, American ginseng, hawthorn, oral magnesium, niacin (no more than 250 mg/day), omega-3 fatty acids/fish oils, red yeast rice extract, resveratrol, vitamin A, vitamin D with or without calcium, vitamin E, and vitamin K. This list was selected after extensive discussions with the TEP and reference to surveys of the general and cardiovascular populations in the Unites States.[7,18-23]
- Included cardiovascular drugs that were commonly used in outpatient settings (Table 1 of full report).
- Reported clinical or surrogate cardiovascular efficacy or harms, or pharmacokinetic outcomes, in any adult population.
- Was a randomized controlled trial, nonrandomized trial, or observational study with an independent concurrent or historical control group including at least five participants. For Key Question 4, studies employing participants as their own controls were also eligible. (This was a post hoc decision in light of the relevance of this design for study of pharmacokinetic interactions.)

Good-quality English language systematic reviews on the topic were also eligible. However, a systematic review could replace de novo synthesis of evidence only when the review was deemed to be current, obviating the need to update it.

Studies included after full-text screening were removed from data synthesis because of one or more of the following reasons:

- Cardiovascular drug(s) were not taken by at least 80 percent of participants in RCTs. Including such studies would have severely limited the applicability of evidence.
- The study reported effect estimates that did not reflect a comparison of supplement plus drug(s) versus drug(s) alone (or plus another supplement).
- No relevant outcome was reported in the study or the outcome data were not received from the authors of the studies. (Authors were contacted for data clarification and additional outcome data when data were recognized to have been recorded but not reported in the published study—for example, outcome data without a measure of dispersion.)
- The design of the study was lower in the hierarchy of evidence (i.e., nonrandomized experimental or observational study in the presence of higher quality RCT evidence) and did not meaningfully add to the evidence already included by being a longer term or pragmatic study reporting conclusive results.
- Studies included cardiovascular drugs not marketed in the United States.
- Administration dose and/or frequency of the dietary supplement was not quantified.

Data Extraction and Risk-of-Bias Assessment

One reviewer extracted relevant data from each study and a second reviewer independently verified data for a 10 percent random sample of studies. Extraction items included general study characteristics (e.g., year of publication, study design); population characteristics (e.g., inclusion/exclusion criteria, age, race, level of activity, condition); intervention characteristics (e.g., dose, duration, details about comparators, level of care); and outcomes (i.e., clinical and surrogate outcomes of efficacy and harms, and pharmacokinetic outcomes) with their estimates. During the data extraction process, one reviewer with a clinical background rated study populations' 10-year coronary heart disease (CHD) risk according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines.[24]

We assessed study risk of bias according to outcome, using generic items for confounding and various types of bias (e.g., selection, performance, detection, and attrition bias) separately for each study design. Selected items from the McMaster Quality Assessment Scale of Harms were also incorporated into the risk-of-bias assessment for harm-related outcomes. Certain criteria were specific to particular study designs; for example, allocation generation and concealment applied only to RCTs.[25] For gradable outcomes, one reviewer rated the overall risk of bias for the study as low, moderate, or high risk, and a second reviewer independently verified the assessment. Outcomes were rated as high risk of bias if there was an apparent and major flaw in the study that would invalidate results. Appendix C in the full report provides the detailed individual study data and risk-of-bias ratings.

Grading the Strength of the Body of Evidence and Applicability

In principle, a body of evidence originating in randomized trials starts with a presumed high strength of evidence and is downgraded across the domains when there is important overall risk of bias for contributing studies, inconsistency in the direction of the intervention effect, indirectness of the outcome of interest (e.g., a surrogate outcome rather than a clinical health outcome), or imprecision in effect estimates of an extent that neither important benefit nor harm can be ruled out. For nonrandomized studies, the body of evidence starts with a presumed low strength of evidence but may be upgraded across certain domains. The strength of a body of evidence was graded based on the following four domains, per published guidance: overall risk of bias by outcome, consistency, directness, and precision.[26]

Gradable important outcomes for this review were identified a priori in consultation with the TEP (Table A). This was done because customarily only a subset of important outcomes that are more meaningful for decisionmaking concerning each specific Key Question are chosen.[26]

A methodologist and a content expert graded the strength of the body of evidence as "high," "moderate," "low," or "insufficient." From a larger list of outcomes of interest for each Key Question (see the Methods section of the full report).[26,27]

Table A. A priori outcomes for grading the strength of evidence

Key Question	Outcomes
1	Mortality (all-cause and vascular death); myocardial ischemic events (fatal myocardial infarction, nonfatal myocardial infarction, unspecified myocardial infarction, and acute coronary syndromes); cerebrovascular events (hemorrhagic/ischemic/unspecified stroke); quality of life; hospitalization; arrhythmia; and clinical outcomes of peripheral arterial disease
2	Blood pressure (systolic and diastolic); lipid profile (low-density lipoprotein, high-density lipoprotein, and non-high-density lipoprotein cholesterol and triglycerides); international normalized ratio for coumarin derivatives; incidence of metabolic syndrome; and change in 10-year Framingham risk profile
3	Serious adverse events (composite outcome according to the Food and Drug Administration definition of serious adverse events);[27] withdrawal due to adverse events; clinical bleeding (intracranial, gastrointestinal, genitourinary, subretinal, etc.); renal dysfunction (e.g., proteinuria, elevated creatinine, need for transplant, glomerular filtration rate); hepatotoxicity (elevated enzymes or fulminant failure); and QT prolongation
4	Area under the plasma cardiovascular drug concentration-time curve (AUC), maximum drug concentration (C_{max}), drug half-life ($t_{1/2}$), and oral clearance

The strength of evidence was graded insufficient when there was no evidence for an outcome, when the direction of the estimates was inconsistent between studies without an identifiable cause, or when the body of evidence from the contributing study/studies was underpowered for the outcome of interest (imprecise estimate). When an effect estimate was associated with a confidence interval (CI) that was not only nonsignificant, but wide enough that the clinical action would differ if the upper versus the lower boundary of the CI represented the truth, we rated the effect as imprecise. This reflected our uncertainty regarding clinically important benefit or harm, or a clinically unimportant difference in effect estimates between the contrasting interventions.

Following published guidance, we summarized the determinants of applicability of the body of evidence for outcomes with conclusive results.[28] Studies that evaluated representative patient populations in usual or routine care conditions and lasting long enough to meaningfully measure health outcomes of both benefits and harms were considered pragmatic or effectiveness studies. In contrast, studies examining intermediate efficacy outcomes in highly selected patients were considered efficacy studies.[29]

Data Synthesis and Analysis

All analyses compared the combination of dietary supplement plus cardiovascular drug with cardiovascular drug alone or plus placebo or plus another dietary supplement. Meta-analyses were carried out when there was clinical and methodological homogeneity. For pharmacokinetic outcomes, we followed the U.S. Food and Drug Administration (FDA) guidance for analysis and interpretation of drug interaction studies—that is, the zone of bioequivalence is recommended to be between the lower and upper bound of the 90 percent geometric mean ratio (GMR), with a CI between 0.8 and 1.25.[30]

We did not pool experimental and observational studies, but did pool parallel studies with valid crossover randomized trials. We did not consider precrossover data for synthesis except when it was judged that the treatment given to participants in a given crossover trial was not appropriate for the condition under consideration.[31,32] Similarly, we did not pool crossover trials that had not employed a sufficient washout period between the two treatment periods because of bias arising from carryover treatment effects. We did not meta-analyze observational studies because of the differences in adjustment for confounders and residual confounding.

Meta-analysis was considered when studies were randomized trials that included similar populations, compared the same type of dietary supplement versus comparator treatment, and reported the same outcome measures in the same statistical format (e.g., mean difference or GMR). Relative risk (RR) and post-treatment mean differences (MDs) were meta-analyzed using the DerSimonian and Laird random-effects model,[33] and Peto odds ratios were calculated when event rates were less than1 percent.[32]

For studies with zero events in some arms or sparse data overall, we pooled using the fixed-effects Mantel-Haenszel method without continuity correction.[34] Studies with zero events in both arms were excluded from meta-analysis.[32] Where applicable, we examined statistical heterogeneity by calculating the synergy index (detailed in the Methods section of the full report).[35] The synergy index estimates the supplement-drug statistical interaction when the effect observed with the combination is of a magnitude that is greater than or less than would be anticipated in an additive model, knowing the independent effects of the supplement and drug. An S-index (ratio of effects measured to additive calculation) greater than 1 describes a positive interaction (synergism), and an S-index less than 1 indicates a negative interaction (antagonism). Statistical heterogeneity was assessed using Cochran's Q ($\alpha = 0.10$) and the I^2 statistic.

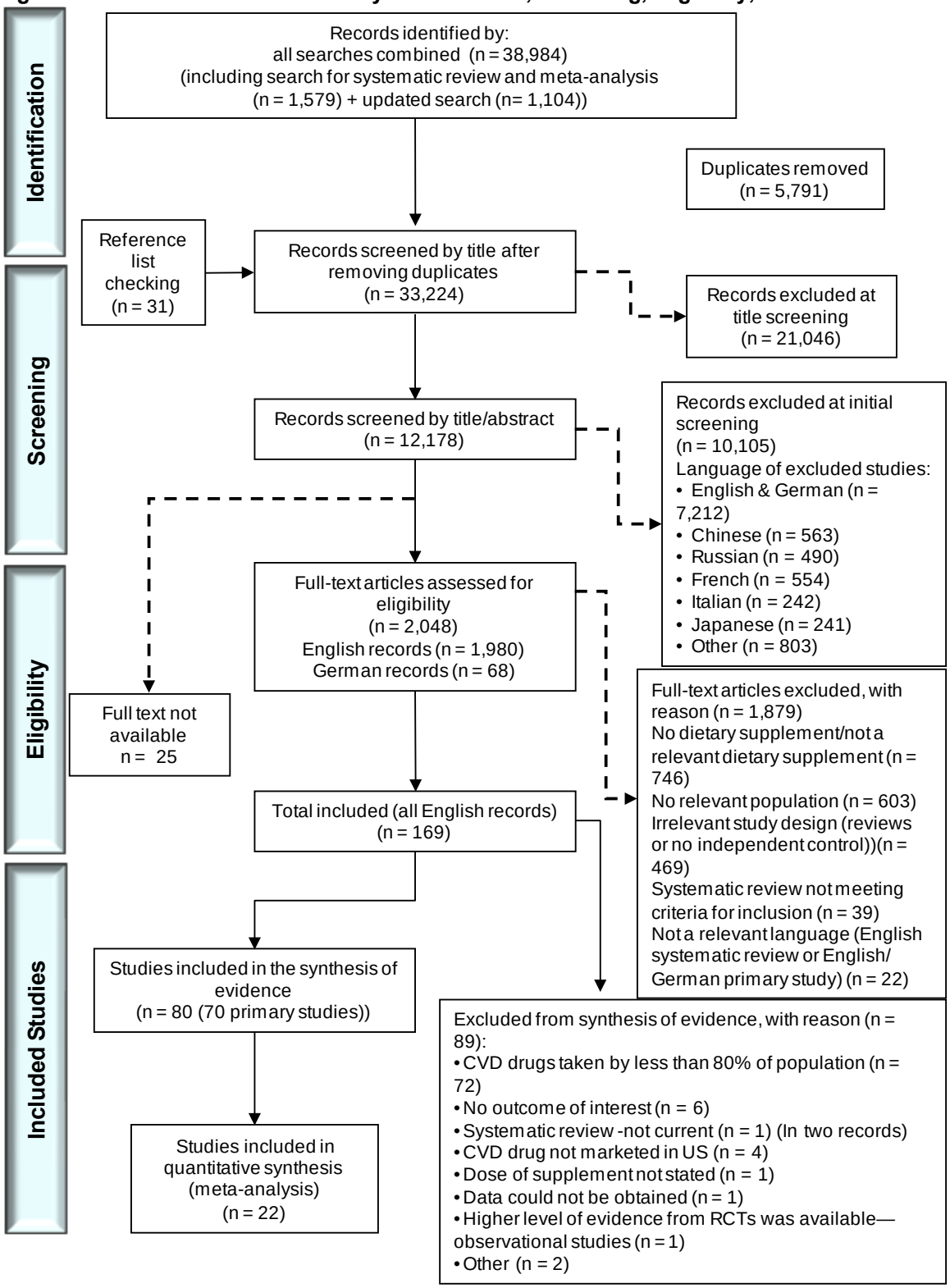
Outcome results were considered to be inconclusive when the pooled estimate or the single contributing study estimate had confidence intervals wide enough to incorporate both clinically important benefit and harm (i.e., type II error suggesting underpowered studies unable to precisely conclude benefit, harm, or no difference between treatments). Results were also considered to be inconclusive when studies could not be pooled—for example, when similar outcomes were reported in different statistical formats in studies or study results pointed in opposite directions. When inconclusive results were associated with a gradable outcome, strength of evidence was deemed insufficient.

Results

Overview

The PRISMA flow diagram summarizes the number of records screened and included (Figure B).

Figure B. PRISMA flow chart of study identification, screening, eligibility, and inclusion



Note: CVD = cardiovascular disease; RCT = randomized controlled trial.

In total, 38,984 records were identified by searches of databases (including gray literature, reference list checking, and search for systematic reviews and meta-analyses) and screened for eligibility. Seventy unique English-language studies (in 80 published articles), including one of observational design, contributed evidence. No systematic reviews were found to be eligible for evidence synthesis. Additionally, we found no relevant unique German publications. Twenty-two studies contributed to meta-analyses in this review.

Table B shows the most relevant risk-of-bias criteria for the randomized and controlled clinical trials included (n = 69).

Table B. Risk-of-bias criteria and conflict of interest for all RCTs and CCTs

Item	Percent of Total Studies (n = 69)		
	Yes	No	Unclear
Adequate generation of allocation sequence	25	3	72
Allocation concealment	9	0	92
Comparability of groups	25	9	67
Blinding of allocated intervention	22	27	52
Freedom from potential for conflict of interest	29	28	43

Note: Percents may not add to 100 due to rounding.
Abbreviations: CCT = controlled clinical trial; RCT = randomized controlled trial.

Key Question 1. Clinical cardiovascular effectiveness/efficacy of cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement

Evidence for Key Question 1 is shown in Table C.

Table C. Evidence for the clinical outcomes—Key Question 1

Outcome	Supplement + Cardiovascular Drug(s)
Insufficient strength of evidence **Conclusion: Inconclusive** **Single underpowered studies for each combination precluded meaningful conclusions**	
All-cause mortality	Coenzyme Q10 (33 mg TID) + ACE inhibitors *Ginkgo biloba* (40 mg QID) + Antiplatelet agents Omega-3 fatty acids (4 g/day + Statins or aspirin or warfarin or fenofibrate Vitamin K (150 μg/day) + Coumarin derivative[a]
Quality of life	Coenzyme Q10 (100 mg/day) + ACE inhibitors
Myocardial infarction	Oral magnesium (365 mg/day) + Beta-blockers Omega-3 fatty acids (1.8 g eicosapentaenoic acid +1.2 g docosahexaenoic acid) + Aspirin + Calcium channel antagonists Vitamin K (100-150 μg/day) + Coumarin
Arrhythmia	Omega-3 fatty acids (4 g/day) + Statins
Stroke	Vitamin E (0.4 g/day) + Aspirin Vitamin K (150 μg/day) + Coumarin[b]
Ischemic stroke, hemorrhagic stroke, and TIA	Vitamin E (600 IU/day) + ASA (aspirin)

[a]Small trial reported 1 death.
[b]Underpowered trial contributed evidence.
Note: Evidence was "insufficient" for all outcomes, so applicability is not presented.
Abbreviations: ACE = angiotensin-converting enzyme; QID = 4 times daily (every 6 hours); TIA = transient ischemic attack; TID = 3 times daily.

Twenty-one randomized controlled trials contributed evidence for Key Question 1.[36-56] No data were available from observational studies. Generally, across all combinations of dietary supplements and cardiovascular drugs, the strength of evidence of the gradable outcomes of comparative efficacy or effectiveness was graded insufficient. Type II error could not be excluded due to the low statistical power of mostly short-term efficacy trials. In addition, strict inclusion criteria excluded patients with uncontrolled comorbidities and acute ischemic events.

Coenzyme Q10. Insufficient evidence was found for the effect of coenzyme Q10 coadministered with angiotensin-converting enzyme (ACE) inhibitors on all-cause mortality and quality of life in 30 mostly male patients with left ventricular dysfunction over a 3-month period.[54] Adherence to simvastatin with or without supplement coadministration was 98 percent during a 12-week pilot study in 22 patients with previous statin-related myalgia.[38]

Ginkgo biloba. With no deaths observed, insufficient evidence for mortality was found for *G. biloba* coadministered with aspirin and/or pentoxyphilline during a 4-week underpowered study in 33 South Asians with previous ischemic stroke.[48]

Magnesium. In a crossover trial of oral magnesium aspartate or placebo administered daily for 8 weeks to a selected group of 40 hypertensive patients with no comorbidities on therapeutic doses of beta-blockers, a single event of myocardial infarction was noted.[42]

Omega-3 fatty acids. Insufficient evidence from underpowered efficacy studies addressed the outcomes of mortality (in 50 healthy men)[36] and arrhythmia (in 122 highly selected dyslipidemic patients)[40] when omega-3 fatty acids were coadministered with statins. In three short-term efficacy trials of omega-3 fatty acid and statin coadministration, statin adherence as judged by pill count was found to be greater than 95 percent in both treatment groups.[37,44,53]

Insufficient evidence from single efficacy trials did not demonstrate a difference in the outcome of all-cause mortality when study cardiovascular drugs were aspirin (291 high-risk patients followed for 1 year with 9 deaths), warfarin (319 high-risk patients followed for 1 year with 5 deaths), and fenofibrate (unclear 10-year CHD risk in 167 participants with hypertriglyceridemia followed for 8 weeks with no deaths).[47,56]

Insufficient evidence addressed the outcome of acute myocardial infarction in a 6-month efficacy study of omega-3 fatty acids in addition to therapeutic doses of aspirin plus calcium channel antagonist following successful coronary angioplasty in 58 participants.[51]

Vitamin E. Insufficient evidence with sparse events of stroke and transient ischemic attack was provided by an efficacy trial of vitamin E plus aspirin versus aspirin alone in 100 highly selected patients with previous neurologic deficit.[49]

Vitamin K. Insufficient evidence was found for mortality and stroke. In one 6-month efficacy trial in 70 selected groups of patients with unstable international normalized ratios (INRs) anticoagulated with warfarin with coadministered vitamin K, no stroke and 1 death were observed.[41]

Other supplement-cardiovascular drug combinations and outcomes. Three notable trials reported outcomes that were not a priori gradable outcomes.

One pragmatic trial in 19,934 women randomized to vitamin E plus aspirin versus aspirin alone for 10 years noted no significant differences for the composite outcome of nonfatal myocardial infarction, nonfatal stroke, and vascular death (RR, 0.95; 95 percent CI, 0.79 to 1.13).[39] Although components of the composite outcome were gradable, it was not possible to discern if shifts in the incidence of stroke and heart attack might have been obscured in this composite outcome.

Inconsistent evidence on rates of restenosis following successful coronary angioplasty, best explained by differences in study population, design, and treatment, was found with omega-3 fatty acids added to conventional antiplatelet therapy and calcium channel antagonists.[51,52] When 82 highly selected male patients took omega-3 fatty acids daily along with therapeutic doses of aspirin, dipyridamole, and calcium channel antagonists, significantly lower rates of restenosis (at least 50 percent reduction in diameter) were observed compared with the cardiovascular drugs alone (RR, 0.40; 95 percent CI, 0.20 to 0.82); however, the mean percentage reduction in luminal diameter was not significantly different between the two groups.[52] No differences were noted in rates of restenosis when a similar but lower quality trial was conducted in 107 South Asians in India who were not taking dipyridamole.[51]

Underpowered studies addressed other outcomes that were not graded per the a priori protocol. These included exacerbation of congestive heart failure, number of patients undergoing cardiac procedures, graft occlusion, neurologic recovery score, coronary vasospasm, and number of angina attacks for various dietary supplement and cardiovascular drug combinations. Most studies were short-term efficacy trials.

No data were identified for hospitalization or peripheral arterial disease for any supplement-cardiovascular drug(s) combination.

No evidence on outcomes of clinical efficacy/effectiveness was found for *Echinacea*, garlic, ginger, ginseng, hawthorn, supplemental doses of niacin (not more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, or vitamin D (with or without calcium) supplementation coadministered with a cardiovascular drug.

Key Question 1a. Do the effect estimates of clinical cardiovascular outcomes vary by age, ethnicity, gender, or health status?

A paucity of studies of supplement-drug combinations for which data were available precluded exploration of heterogeneity in terms of preidentified subgroups or documentation of any dose-response effect.

Key Question 1b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for clinical cardiovascular outcomes?

No study analyzed statistical interactions between a supplement and a cardiovascular drug in terms of clinical outcomes.

Key Question 2. Intermediate cardiovascular efficacy outcomes of cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement

Evidence for Key Question 2 is shown in Table D.

Table D. Evidence for the gradable intermediate efficacy outcomes—Key Question 2

Outcome Measure	Dietary Supplement + CV Drug (s)	Conclusion, Effect Estimate	Applicability
Low strength of evidence			
Lipid profile	Co-Q10 (200 mg/day) + Fenofibrates	No difference for HDL-C (1 study) MD,1.55 mg/dL (95% CI, -6.78 to 3.68)	Mean age: 53 years Mixed gender High CHD risk 12 weeks treatment
Lipid profile	Garlic (4 g/day) + Nitrates	In favor of combination for HDL-C (1 study) MD, 8.40 mg/dL (95% CI, 1.91 to 14.89)	Unknown age, gender High CHD risk 12 weeks treatment
Lipid profile	Garlic (4 g/day) + Warfarin	In favor of combination for HDL-C (1 study) MD, 4.50 mg/dL (95% CI, 0.19 to 8.81)	Mean age: 56 years Mixed gender High CHD risk 12 weeks treatment
Lipid profile	Omega-3 fatty acids (3.6 g/day omega-3 to 9.2 g/day fish oil) + Statins	In favor of combination: TG (2 studies pooled) MD, -74.95 mg/dL (95% CI, -95.80 to -54.10) No difference for: HDL-C (7 studies pooled) MD, 1.70 mg/dL (95% CI, -1.52 to 4.92) LDL-C (6 studies pooled) MD, -1.06 mg/dL (95% CI, -5.28 to 3.16) Achieving LDL-C and HDL-C targets (1 study) RR, 0.93 (95% CI, 0.84 to 1.03) and 1.00 (95% CI, 0.90 to 1.10), respectively	Mean age: 45-63 years Mixed or unclear CHD risk Mixed gender Up to 25 weeks treatment
Lipid profile	Omega-3 fatty acids (1.8 g/day) + Calcium channel blockers + Aspirin	In favor of combination for TG (2 studies not pooled) -81.00 mg/dL (95% CI, -125.30 to -36.70) and -54.00 mg/dL (95% CI, -94.1 to -13.90)	Mean age: 57 years 85% males High CHD risk 4-6 weeks treatment
Lipid profile	Omega-3 fatty acids (3.2 g/day) + Calcium channel blockers + Aspirin + Dipyridamole	In favor of CV drug alone for LDL-C (1 study) 21.00 mg/dL (95% CI, 3.30 to 38.70) In favor of combination for TG (1 study) -81.0 mg/dL (95% CI, -125.30 to -36.70)	Mean age: 56 years 100% males High CHD risk Up to 12 weeks treatment

Table D. Evidence for the gradable intermediate efficacy outcomes—Key Question 2 (continued)

Outcome Measure	Dietary Supplement + CV Drug (s)	Conclusion, Effect Estimate	Applicability
Low strength of evidence (continued)			
Lipid profile	Vitamin E (900 mg/day) + Nifedipine	In favor of combination for LDL-C (1 study) MD, -39.83 mg/dL (95% CI, -71.29 to -8.37) In favor of combination for TG (1 study) MD, -23.91 mg/dL (95% CI, -35.89 to -11.93)	Elderly Mixed gender High CHD risk 12 weeks treatment
Blood pressure	Omega-3 fatty acids (2 g/day) + Statins	In favor of combination for SBP (1 study) MD, -8.50 mmHg (95% CI, -16.33 to -0.66) No difference for DBP (1 study) MD, 0.20 mmHg (95% CI, -4.76 to 5.16)	Mean age among groups: 44-53 years Mixed gender Mixed CHD risk 5 weeks treatment
Blood pressure	Omega-3 fatty acids (4 g/day fish oil) + Statins	Median reductions from baseline in SBP (1 study) (-5.00 vs. 0.30 mmHg, p = 0.008) and DBP (-3.30 vs. -1.80 mmHg, p = 0.045)	Mean age: 58 years Mixed gender Unclear CHD risk 6 weeks treatment
Blood pressure	Omega-3 fatty acids (3-5 g/day) + ACE inhibitors	No difference between groups for SBP (2 studies pooled): MD, -0.51 mm/Hg (95% CI, -10.59 to 9.57) or for DBP: MD, -1.75 mm/Hg (95% CI, -5.98 to 2.48)	Mean age: 40-55 years Mixed gender Unclear CHD risk 6-25 weeks treatment
INR	Vitamin K (150 µg /day) + Anticoagulants	In favor of combination (1 study) RR for % of time in therapeutic range, 9.0% (95% CI, 1.42 to 16.57) RR for n achieving stable INR, 2.56 (95% CI, 1.24 to 5.28)	Elderly (age range 58-85 years) Mixed gender Unclear CHD risk 25 weeks treatment

Table D. Evidence for the gradable intermediate efficacy outcomes—Key Question 2 (continued)

Outcome	Dietary supplement + CV Drug (s)
Insufficient strength of evidence **Conclusion: Inconclusive (type II error or inconsistent direction of estimates)**	
Lipid profile	***All lipid(s):*** Coenzyme Q10 (100 mg/day) + Statins; Coenzyme Q10 (200 mg/day) + Fenofibrate; Garlic (4 g/day) + Warfarin; Garlic (4 mL/day) + Statins/Aspirin *Gingko biloba* (120 mg/day) + Antiplatelets Magnesium (365 mg/day) + Hydrochlorothiazide Omega-3 fatty acids (4 g/day) + Fenofibrate; Omega-3 fatty acids (3 g/day) + Calcium channel blockers; Omega-3 fatty acids (4 g/day) + Niacin/Aspirin; Omega-3 fatty acids (10 g/day) + Aspirin; Omega-3 fatty acids + Statins Vitamin E (0.6g/day) + Gemfibrozil; Vitamin E (100 mg/day, 100 IU/day) + Statins ***Only specific lipid(s):*** **TG:** Niacin (250 mg/day) + Propranolol Garlic (4 g/day) + Nitrates Omega-3 fatty acids + ACE inhibitors Magnesium (4.5 g/day) + Hydrochlorothiazide Vitamin E (900 mg/day) + Antiplatelet agents **LDL-C:** Omega-3 fatty acids (1.8 g/day) + Calcium channel blockers + Aspirin **HDL-C:** Vitamin E (900 mg/day) + Nifedipine Omega-3 fatty acids (1.8 g/day) + Calcium channel blockers + Aspirin; Omega-3 fatty acids (3.2 g/day) + Calcium channel blockers + Aspirin + Dipyridamole
Blood pressure	Coenzyme Q10 (200 mg/day) + Fenofibrates (systolic blood pressure) *Echinacea* (5 g/day) + Warfarin Garlic (4 g/day) + Warfarin *Gingko biloba* (120 mg/day) + Aspirin; *G. biloba* (300 mg/day) + Antiplatelet thienopyridines; *G. biloba* (120 mg/day) + Cilostazol Magnesium (4.5 g/day) + Hydrochlorothiazide; Magnesium (3.65 g/day) + Beta-adrenergic antagonists Omega-3 fatty acids (10 g/day) + Aspirin; Omega-3 fatty acids (4 g/day) + Beta-blockers Vitamin E (600 mg/day) + Furosemide; Vitamin E (900 mg/day) + Nifedipine; Vitamin E (600 mg/d) + Gemfibrozil
INR	*Echinacea* (5 g/day) + Warfarin Garlic (4 g/day) + Warfarin Ginger (3.6 g/day) + Warfarin *Gingko biloba* (2 g/day) + Warfarin Ginseng (1.5-2 g/day) + Warfarin Omega-3 fatty acids (4 g/day) + Warfarin
QT prolongation	Vitamin E (400 IU/day) + Statins

Note: CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; DBP = diastolic blood pressure; HDL–C = high-density lipoprotein-cholesterol; INR = international normalized ratio; LDL-C = low-density lipoprotein-cholesterol; MD = mean difference; RR = relative risk; SBP = systolic blood pressure; TG = triglycerides.

Fifty-seven RCTs and two non-RCTs were included for this Key Question. No relevant observational study was identified. Study participants in most studies had mixed (low and/or moderate) or unclear CHD risk (27.1 percent and 37.3 percent, respectively).Study quality was variable. In the majority of RCTs, the generation of allocation sequence (78 percent) and allocation concealment (93 percent) were unclear. In about 20 percent of studies, participants, health care providers, or outcome assessors were blinded to treatment allocation. This information was not clear for 56 percent of the studies.

The majority of evidence on intermediate outcomes was contributed by small underpowered RCTs whose statistically nonsignificant results with wide confidence intervals could rule out neither important benefits nor harms. Due to this imprecision, the strength of evidence for several gradable outcomes was rated insufficient (inconclusive results). When a significant effect was observed, we graded the strength of evidence to be low because of limitations in the internal validity of studies, surrogacy of outcomes, and generally poor to absent reproducibility among

studies in the direction of effect estimates (Table D). None of the studies reported outcomes evaluating incidence of metabolic syndrome, incidence of hypotension, carotid-intima media thickness, or change in 10-year Framingham risk profile.

Coenzyme Q10. Evidence was available from four RCTs with unclear CHD risk (49 Asians ith hypercholesterolemia[57]), mixed CHD risk (44 participants with statin-induced myalgia[38]), and high CHD risk (40 participants with diabetes and dyslipidemia[58] and 30 participants with ischemic or idiopathic dilated cardiomyopathy[54]). Overall, no significant differences (grade: insufficient; results inconclusive) were seen between the combination of coenzyme Q10 plus a cardiovascular drug versus drug alone in post-treatment levels of:

- C-reactive protein (statins).
- High-density lipoprotein-cholesterol (HDL-C) (statins or fenofibrate).
- Non-HDL-C (fenofibrate).
- Total cholesterol (statins or fenofibrate).
- Triglycerides (statins or fenofibrate).
- Ejection fraction (ACE inhibitors).
- Systolic blood pressure (SBP) (fenofibrates).

Lowgrade evidence was avaiable from one trial indicating no significant difference in high density lipoprotein-cholesterol (HDL-C) for the combination of coenzyme Q10 plus fenofibrate versus fenofibrates alone.

Echinacea. In one small study in 12 healthy male participants (low CHD risk),[59] post-treatment levels of INR and platelet aggregation were not significantly different in the combination of Echinacea plus warfarin than with warfarin alone. The results were inconclusive.

Garlic. Four studies examined the effects of garlic in combination with warfarin (48 participants with unclear CHD risk[60] and 16 males with low CHD risk[61]), nitrates (60 participants with high CHD risk[62]), and statins plus aspirin (19 participants with high CHD risk[63]).

The effect of garlic plus warfarin versus warfarin alone on post-treatment lipid profile, blood pressure, INR, platelet aggregability, and platelet count was not significant (inconclusive; grade: insufficient)[60,61] except for significant improvement of HDL-C levels for garlic plus warfarin versus warfarin alone (grade: low).[60]

In participants with coronary artery disease (high CHD risk), the combination of garlic plus nitrates[62] significantly improved total cholesterol (MD, −28.20 mg/dL [95 percent CI, −48.30 to −8.10]) and HDL-C levels, but not triglyceride levels (MD, −10.30 mg/dL [95 percent CI, −27.60 to 7.00]).

The effects of garlic combined with statins plus aspirin[63] on lipid profile, C-reactive protein, platelet count, and Agaston calcium score were not significantly different from those of statins plus aspirin in participants with coronary artery disease (Framingham risk >20 percent).

Ginger. In one trial of 12 healthy male participants there was no significant difference in post-treatment INR (inconclusive; grade: insufficient) or platelet aggregability between participants taking the combination of ginger plus warfarin versus warfarin alone.[64]

Ginkgo biloba. Five RCTs investigated this supplement in combination with antiplatelet agents (acetylsalicylic acid,[65,66] clopidogrel,[67] or ticlopidine[68]), an anticoagulant (warfarin[64]), or a

vasodilator (cilostazol[67]). For *G. biloba* plus antiplatelet agents (104 participants in total, mixed CHD risk),[65,66] the differences in clotting time, partial thromboplastin time, platelet count, lipid parameters, and blood pressure were not significant (results for lipids and blood pressure inconclusive; grade: insufficient).

The pooled results of two trials (24 participants with mixed CHD risk,[68] 10 participants with low CHD risk[67]) indicated no significant differences in platelet aggregation and bleeding time between the *G.biloba* plus antiplatelet combination versus antiplatelet-only groups. Similarly, *G. biloba* (200 mg of *G. biloba* leaf, 9.6 mg of ginkgo flavonglycosides, 2.4 mg of ginkgolides and bilobalide three times/day) plus warfarin did not result in significantly different post-treatment levels of platelet aggregability or INR (result for INR inconclusive; grade: insufficient) in 12 healthy males.[64] In one trial, however,[67] platelet aggregability (MD, 18.00 percent [95 percent CI, 1.92 to 34.08]) and bleeding time (MD, 1.02 minutes [95 percent CI, 0.10 to 1.94]) were significantly better in the *G. biloba* plus cilostazol combination group than the cilostazol-only group.

Ginseng. Three RCTs investigated various ginseng products in combination with warfarin.[69-71] The results from these studies for INR were conflicting (inconclusive; grade: insufficient). Two trials showed no significant difference (25 participants with high CHD risk,[69] 12 males with low CHD risk[71]). One trial (20 participants with low CHD risk[70]) showed a significant difference, with lower peak INR and AUC of INR in the combination versus control group (MD, -0.19 [95 percent CI, -0.36 to -0.07] for peak INR and -0.43 [95 percent CI -1.00 to -0.09] for AUC of INR). The differences in prothrombin time,[69] platelet count,[69] or platelet aggregability[71] between the ginseng-warfarin combination and warfarin-only groups were not significant (results were inconclusive).

Hawthorn. One small trial[72] found no significant difference in an ECG measure (PR interval, which is measured from the beginning of the P wave to the beginning of the QRS complex) between participants receiving hawthorn plus digoxin and those receiving digoxin alone (results inconclusive) in 11 adults at low risk for CHD.

Magnesium. Three RCTs investigated oral magnesium in combination with hydrochlorothiazide[73,74] or beta-adrenergic antagonists[42] in participants with hypertension. In two trials, SBP and DBP (diastolic blood pressure) did not differ significantly between the magnesium hydrochlorothiazide combination versus hydrochlorothiazide-alone groups in the study with 18 participants with unclear CHD risk[73] or the study with 21 participants with low/moderate CHD risk[74] (inconclusive; grade: insufficient). Similarly, in another study,[42] neither SBP nor DBP was significantly different in 39 participants receiving the combination of magnesium plus beta-adrenergic antagonists versus those receiving beta-adrenergic antagonists alone. In one trial,[73] post-treatment total cholesterol and triglyceride levels were not significantly different between the magnesium-hydrochlorothiazide combination versus hydrochlorothiazide-alone groups (inconclusive; grade: insufficient).

Niacin (no more than 250 mg/day). One RCT in 28 participants with hyperlipoproteinemia (unclear CHD risk)[75] investigated niacin in combination with propranolol. Post-treatment levels of triglycerides and total cholesterol were not significantly different between the group receiving niacin plus propranolol and the groups receiving propranolol alone (inconclusive; grade:

insufficient). This study was judged to be at high risk of bias because groups were administered different dosages of propranolol (20 mg and 60 mg).

Omega-3 fatty acids. Twenty-four RCTs investigated the use of omega-3 fatty acids plus cardiovascular drugs (statins, ACE inhibitors, calcium channel blockers alone or with other cardiovascular drugs, fenofibrates, niacin plus aspirin, aspirin, beta-blockers, or an anticoagulation agent) versus cardiovascular drugs alone.

The effect on post-treatment triglyceride (TG) levels of adding the supplement to statins was modified according to baseline levels of triglycerides. Specifically, in participants with higher mean baseline levels of TG (greater than 200 mg/dL) there was a statistically significant pooled mean reduction in post-treatment TG levels in the combination arm (two trials, grade: low).[40,76] In contrast, the meta-analysis of four studies with participants with lower levels of TG at baseline (under 200 mg/dL) showed no significant difference between the groups (grade: insufficient). Pooled analyses for levels of HDL-C (seven trials), LDL-C (six trials), and total cholesterol (six trials) showed no significant differences (grade: low) in participants with mixed or unclear CHD risk. The mean SBP was significantly lowered in the supplement-statin combination group (grade: low) in 22 participants with hyperlipemia. Evidence was inconclusive for the outcomes of total cholesterol/HDL-C ratio, non-HDL-C, lipoprotein A, diastolic blood pressure, and bleeding time. Additionally, for nongradable outcomes such as C-reactive protein and blood coagulation parameters (prothrombin time (PT), activated partial thromboplastin time [aPTT], platelet aggregation), there were no significant differences between combination and control groups.

Trials of 43 elderly males undergoing angioplasty using omega-3 fatty acids-statins combinations reported post-treatment levels of non-HDL-C, total cholesterol/HDL-C ratio, and platelet count that were conflicting (opposite direction of effect estimates) and thus inconclusive (grade: insufficient).

In trials using omega-3 fatty acids-ACE inhibitors combination treatment, there were no changes in blood pressure (no difference; grade: low), but significantly more participants experienced at least 50 percent reduction in proteinuria in favor of the combination treatment (RR, 4.00 [95 percent CI, 1.40 to 11.30]).[77]

In one trial using omega-3 fatty acids-fenofibrate combination treatment in participants with high triglyceride levels,[56] the incidence of hypertension was not significantly different in the combination versus control group (RR, 0.98 [95 percent CI, 0.14 to 6.85]).

In one trial[50] using omega-3 fatty acids-calcium channel blockers combinations, there was no significant difference between the combination and control groups in post-treatment lipid profile (inconclusive; grade: insufficient). Two other trials using aspirin in addition to calcium channel blockers found significant differences in triglycerides (grade: low) in favor of the combination treatment.[51,52] These trials were not pooled because dipyridamole was an additional drug in one trial and not in another.

In one underpowered trial (14 participants with atherogenic dyslipidemia, unclear CHD risk[78]), post-treatment lipid profile did not differ significantly between the combination of omega-3 fatty acids plus niacin and aspirin versus niacin and aspirin (inconclusive; grade: insufficient). In one trial (11 participants with unclear CHD risk), treatment with 3 or 6 g/day omega-3 fatty acids plus warfarin versus warfarin resulted in no significant difference in post-treatment INR values between groups (no numeric data provided).

Vitamin E. Ten RCTs and one controlled clinical trial[79] examined the use of vitamin E with antiplatelet agents (aspirin or ticlopidine),[80] aspirin,[49] furosemide,[81] gemfibrozil,[79] nifedipine,[82] or statins.[46,83-87]

In one trial,[80] post-treatment total cholesterol and triglyceride levels were not significantly different between the groups receiving vitamin E-antiplatelet agent (aspirin or ticlopidine) combination versus aspirin or ticlopidine alone in 16 participants with carotid atherosclerosis (inconclusive; grade: insufficient). Platelet aggregation was significantly decreased with vitamin E supplementation plus aspirin compared with aspirin alone (MD, -1.70 per cm^2 [95 percent CI, -2.06 to -1.34]).[49]

The effect of vitamin E-furosemide combination on blood pressure was not significantly different from that of furosemide alone in 24 participants with essential hypertension (inconclusive; grade: insufficient).[81] The vitamin E-nifedipine combination significantly lowered total cholesterol (MD, -35.96 mg/dL [95 percent CI, -46.96 to -24.96]), LDL-C (grade: low), and triglycerides (grade: low), but not HDL-C (inconclusive, grade: insufficient) or SBP (inconclusive, grade: insufficient) in 30 elderly subjects at high risk of CHD.[82]

There was no significant difference in lipid profile across trials using vitamin E-gemfibrozil or vitamin E-statins combinations when compared with the cardiovascular drug alone (inconclusive; grade: insufficient). (See pooled analyses for HDL-C, LDL-C, total cholesterol, and triglycerides.) Likewise, there was no significant difference in blood pressure (inconclusive; grade: insufficient) for vitamin E-gemfibrozil combination, and no significant difference in C-reactive protein, prothrombin time, and platelet count for vitamin E-statins combinations compared with cardiovascular drug(s) alone.

Vitamin K. In one trial,[41] percentage of time INR was in therapeutic range was improved in the group receiving vitamin K-coumarin derivative (warfarin) combination compared with warfarin alone. In addition, number of participants achieving stable INR was higher in combination than with warfarin alone.

Overall evidence indicates that supplementation with vitamin K may improve the stability of anticoagulant therapy (grade: low).

Other supplements. No evidence was identified for effects of red yeast rice extract, resveratrol, vitamin A, or vitamin D in combination with cardiovascular drugs on intermediate outcomes.

Key Question 2a. Do the effect estimates of intermediate cardiovascular outcomes vary by age, ethnicity, gender, or health status?

Sparse evidence precluded exploration of heterogeneity in the effect estimates for harms across preidentified subgroups.

Key Question 2b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for intermediate cardiovascular efficacy outcomes?

Two studies contributed to the evidence regarding statistical interaction between cardiovascular drugs and dietary supplements for this section.[44,78] One study assessed statistical interaction using general linear modeling.[44] No significant interactions were observed between the combination of omega-3 fatty acids and statins with regard to changes in lipid profile (HDL-

C, LDL-C, total cholesterol, triglycerides, non-HDL-C) in 52 obese men with dyslipidemia and insulin resistance (moderate/moderately high risk for CHD).[44] Authors of another trial[78] conducted a formal assessment of statistical interaction using ANOVA (analysis of variance) and found that the decrease in triglyceride levels resulting from the combination of omega-3 fatty acids plus niacin was more than twice the additive effect of either therapy alone in 29 participants with atherogenic dyslipidemia (unclear CHD risk).

Key Question 3. Clinical or intermediate harms with cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement

Evidence for Key Question 3 is shown in Table E.

Table E. Evidence for the gradable harms outcomes—Key Question 3

Outcome Measure	Dietary Supplement + CV Drug(s)
Insufficient strength of evidence Conclusion: Inconclusive (type II error or inconsistent direction of estimates)	
Serious adverse events	Coenzyme Q10 (100-200 mg/day) + Statins *Ginkgo biloba* (300 mg/day) + ASA; *G. biloba* + Warfarin Magnesium (365 mg/day) + Beta-adrenergic antagonists Omega-3 fatty acids (3-4 g/day) + Statins or fenofibrate
Withdrawal due to adverse events	Coenzyme Q10 (3-4 g/day) + Statins or fenofibrate *Echinacea* (5 g/day) + Warfarin *Ginkgo biloba* (40 mg/day) + ASA and/or pentoxiphylline; *G. biloba* (2 g/day) + Warfarin; *G. biloba* (240 mg/day) + Digoxin Ginseng (3 g/day) + Warfarin Magnesium (365 mg/day) + Hydrochlorothiazide; Magnesium (365 mg/day) + Beta-adrenergic antagonists Niacin (250 mg/day) + Beta-adrenergic antagonists Omega-3 fatty acids (4 g/day) + ASA; Omega-3 fatty acids (4-9 g/day) + Statins; Omega-3 fatty acids (3 g/day) + Ramipril and/or irbesartan; Omega-3 fatty acids (4 g/day) + ASA + Dipyridamole + Calcium channel blockers; Omega-3 fatty acids (4 g/day) + Fenofibrate; Omega-3 fatty acids (3 or 6 g/day) + Warfarin Vitamin E (400 IU/day) + ASA; Vitamin E (1350 IU/day) + Nifedipine
Bleeding (major, minor, and undefined)	Garlic (10 mL/day) + Warfarin *Ginkgo biloba* (300 mg/day) + ASA Ginseng (3 g/day) + Warfarin Omega-3 fatty acids (4 g/day) + ASA; Omega-3 fatty acids (4-9 g/day) + Statins; Omega-3 fatty acids (3 g/day) + Ramipril and/or irbesartan; Omega-3 fatty acids (4 g/day) + ASA + Dipyridamole + Calcium channel blockers; Omega-3 fatty acids (mean 3 g/day) + ASA + Clopidogrel; Omega-3 fatty acids (3 or 6 g/day) + Warfarin Vitamin E (400 IU/day) + ASA Vitamin K (5 mg/day) + Warfarin
Renal dysfunction (abnormal glomerular filtration rate, creatinine, blood urea nitrogen, serum potassium)	Coenzyme Q10 (100-200 mg/day) + ACE inhibitors; Coenzyme Q10 (100-200 mg/day) + Statins; Coenzyme Q10 (200 mg/day) + Fenofibrate *Ginkgo biloba* (300 mg/day) + ASA; *G. biloba* (80 mg/day)+ Ticlopidine Magnesium (365 mg/day) + Hydrochlorothiazide Omega-3 fatty acids (4-9 g/day) + Statins; Omega-3 fatty acids (4 g/day) + Fenofibrate Vitamin E (400 IU/day) + Statins; Vitamin E (1350 IU/day) + Nifedipine
Hepatotoxicity (abnormal liver enzymes)	Coenzyme Q10 (100-200 mg/day) + Statins; Coenzyme Q10 (100-200 mg/day) + ACE inhibitors Omega-3 fatty acids (4-9 g/day) + Statins Vitamin E (400 IU/day) + Statins
Corrected QT interval	Vitamin E (400 IU/day) + Statins

Note: ACE = angiotensin-converting enzyme; ASA = acetylsalicylic acid (aspirin); CV = cardiovascular.

A total of 58 studies contributed evidence for Key Question 3. One included study was a retrospective cohort study examining omega-3 fatty acids and antiplatelet agents; it had important limitations in design and reporting, as it was unclear regarding participant selection, confounding, and blinding of outcome assessors.[88] The rest of the studies were RCTs, mostly of moderate risk of bias for the gradable outcomes of harms (serious adverse events, withdrawal due to adverse events, renal dysfunction, hepatotoxicity, QT interval, and bleeding). Most of these studies recruited a small number of participants and were underpowered for the outcomes of harm.

Meta-analyses were possible for some omega-3 fatty acids studies. Other evidence could not be pooled because either there was a single study per outcome or zero events in both treatment arms.

For all combinations of dietary supplement and cardiovascular drug, the strength of evidence for all gradable outcomes was insufficient due to inconsistent effect estimates across studies suggesting conflicting findings with no obvious explanation or statistically nonsignificant estimates with wide confidence intervals (Table E). Most crossover trials incorporated an adequate washout period, so carryover effect was not a major concern.

Coenzyme Q10. Five short-term (up to 12 weeks duration) small RCTs that included participants with mixed (moderate and high risk)/unclear[38,57,89] or high [54,58] CHD risk examined coenzyme Q10 plus statins, fenofibrate, ACE inhibitors, or, in one study, vitamin E added to statins. No statistically significant differences were observed for total adverse events,[54,57] abnormalities in fasting blood glucose,[57,58] myoglobin,[57] creatine phosphokinase (CPK),[57,58,89] electrocardiogram (ECG),[58] or retinopathy.[58] However, the studies were underpowered to detect differences in these harms.

One RCT of 32 participants with statin-induced myopathic symptoms[89] found a significantly greater number of subjects with reduced myopathic pain (RR, 4.18 [95 percent CI, 1.50 to 11.46]) and lower pain severity scores on the Brief Pain Inventory (MD, -1.76 [95 percent CI, -2.93 to -0.58]) and pain interference score (MD, -1.43 [95 percent CI, -2.76 to -0.10]) in the combination group (coenzyme Q10 100 mg/day plus statins) versus vitamin E (400 IU/day) plus statin group. A small pilot RCT of 44 participants with self-reported myalgia unable to take adequate doses of statins[38] did not find a significant difference in myalgia, using a visual analog scale, or in number of participants tolerating simvastatin (RR, 1.23 [95 percent CI, 0.80 to 1.90]) in participants taking coenzyme Q10 plus statins versus statin-alone groups.

Echinacea. One small RCT of 12 healthy volunteers examined Echinacea plus a single dose of warfarin versus warfarin alone. No withdrawals due to adverse events or other adverse events were observed.[59]

Garlic. Four small short-term RCTs examined garlic in combination with warfarin, nitrates, or statins plus aspirin in healthy males[61] or those with cardiovascular conditions.[60,62,63] No significant between-group differences were observed across gradable and nongradable outcomes such as fasting blood glucose,[60,62,63] anemia,[60] and leukopenia.[63] Wide confidence intervals for differences in bleeding and fasting blood glucose precluded drawing any meaningful conclusions.

Ginkgo biloba. Seven small RCTs examined G. biloba plus warfarin, digoxin, aspirin, aspirin and/or pentoxiphylline, nitrates, cilostazol or clopidogrel, or ticlopidine.[48,64-68,90] The subjects either were healthy volunteers,[64,65,67,68,90] had experienced acute ischemic stroke,[48] or had peripheral arterial disease.[66] Two of these studies included only a single dose of cilostazol/clopidogrel[67] or ticlopidine,[68] so their results should be interpreted with caution. Across all cardiovascular medications, nonsignificant results were observed for gradable outcomes (i.e., withdrawal due to adverse events, bleeding, renal dysfunction, hepatotoxicity, and serious adverse events). Nonsignificant results were also found for all other harms, such as total adverse events,[66,67,90] upset stomach,[66] anemia,[65,66] abnormal white blood cell count,[65] gastrointestinal events,[48,90] diarrhea,[64] constipation,[64] hypoglycemia,[66] hyperglycemia,[66] leukopenia,[66] thrombocytopenia,[66] and abnormal ECG.[66] These studies were underpowered to detect any differences in harms outcomes.

Ginseng. Three RCTs examined the effects of Panax ginseng,[69,71] American ginseng,[70] and Korean ginseng[71] plus warfarin versus warfarin alone. No statistically significant effects were observed in gradable outcomes (i.e., withdrawal due to adverse events, bleeding, renal dysfunction, and hepatotoxicity) or nongradable outcomes such as prothrombin time, total adverse events, headache, dizziness, indigestion, INR above 3.5, diarrhea, constipation, hematocrit, and anemia.[69] These trials were all small and underpowered.

Hawthorn. One RCT examined hawthorn plus digoxin versus digoxin alone in eight healthy volunteers.[72] No statistically significant differences were observed in incidence of flatulence, nausea, insomnia, headache, and dizziness.

Magnesium. Two small RCTs in hypertensive subjects examined the effects of magnesium plus hydrochlorothiazide or beta-adrenergic antagonists.[42,73] No statistically significant differences were observed for withdrawal due to adverse events,[42,73] renal dysfunction,[42,73] serious adverse events,[42] diarrhea,[73] vomiting,[73] nausea,[73] adverse events,[73] hypercalcemia,[73] abnormal fasting blood glucose,[73] or abnormal ECG.[73]

Niacin (not more than 250 mg/day). One RCT of 20 subjects with hyperlipoproteinemia investigated the effects of niacin plus propranolol versus propranolol alone.[75] No statistically significant differences were found in nausea and flushing or in hypotension. This study was at high risk of bias because groups received different dosages of propranolol (20 mg in combination group and 60 mg in monotherapy group).

Omega-3 fatty acids. Twenty-two studies (21 RCTs and 1 retrospective cohort study) examined omega-3 fatty acids plus statins,[36,37,40,53,91-97] aspirin,[47,52,78,98,99,99] aspirin and clopidogrel,[88] aspirin in combination with dipyridamole and calcium channel blockers,[52] warfarin,[47,55] ramipril and/or irbesartan,[77] or fenofibrate.[56] These studies were generally small and underpowered. They recruited healthy subjects, or subjects with CHD or risk factors for CHD.

For omega-3 fatty acids plus statins versus statins alone, meta-analyses yielded nonsignificant estimates for serious adverse events, withdrawal due to adverse events, elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT), total adverse events, dyspepsia, headache, constipation, upper respiratory infection, and elevated creatine kinase (CK)/creatine phosphokinase (CPK). However, a significantly elevated fasting blood glucose in

the omega-3 fatty acids plus statin group was observed in one RCT.[40] For omega-3 fatty acids in combination with other cardiovascular drugs, no significant differences were found in harms outcomes.

Vitamin E. Ten RCTs examined vitamin E plus aspirin,[39,49,100] nifedipine,[82] furosemide,[81] or statins.[46,83,84,86,87] No statistically significant differences were observed for total adverse events,[100] incidence of headache,[100] gastrointestinal discomfort,[100] incidence of cancer,[39] abnormalities in fasting blood glucose,[81,82] glycosylated hemoglobin,[87] leukopenia,[46] or anemia.[46] These studies recruited subjects who were healthy, or who had CHD or risk factors for CHD. Sample sizes were generally small, except for one study that recruited over 9,000 women.[39]

Vitamin K. One RCT of 6 months duration examined the effects of vitamin K plus warfarin versus warfarin alone.[41] No significant differences were found for bleeding[41] or withdrawal due to adverse events.[41] This study recruited 70 participants with indications for anticoagulant therapy.

Other supplements. No evidence on clinical harms was identified for the effects of ginger, red yeast rice extract, resveratrol, vitamin A, or vitamin D in combination with cardiovascular drugs.

Key Question 3a. Do the effect estimates of clinical or intermediate harms vary by age, ethnicity, gender, or health status?

Sparse evidence precluded exploration of heterogeneity in the effect estimates for harms across preidentified subgroups.

Key Question 3b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for harms outcomes?

One RCT presented data that would allow examination of the interaction between vitamin E supplements and the cardiovascular medication aspirin. This RCT found no significant difference in the rates of adverse events (headache, gastrointestinal discomfort, and withdrawal due to adverse events) among treatment regimes.[100]

Key Question 4. Pharmacokinetic outcomes with cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement

Evidence for Key Question 4 is shown in Table F.

Table F. Strength of evidence for the gradable pharmacokinetic outcomes—Key Question 4

Outcome Measure	Dietary Supplement + CV Drug(s)	Conclusion	Applicability of Evidence
Low strength of evidence			
AUC_{∞}, C_{max}, half-life, and clearance (S- and R-warfarin)	*Echinacea* (5 g/day) + Warfarin Ginger (3.6 g/day) + Warfarin *Ginkgo biloba* (25 mg single dose) + Warfarin	No clinically significant interactions	Healthy volunteer pharmacokinetic studies using single dose of 25 mg warfarin
AUC_{∞}, half-life, and clearance (S- and R-warfarin)	Garlic (4 g/day) + Warfarin	No clinically significant interactions	Healthy volunteer pharmacokinetic study using single dose of 25 mg warfarin
AUC_{∞}, half-life, and C_{max} (ticlopidine)	*Ginkgo biloba* (80-240 mg/day) + Ticlopidine	No clinically significant interactions	Healthy Korean males given single dose of 250 mg of ticlopidine
C_{max}, half-life, and clearance (S- and R-warfarin)	Ginseng (25 mg single dose) + Warfarin	No clinically significant interactions	Healthy volunteer pharmacokinetic study of American and Korean ginseng and either 3 doses of 5 mg warfarin over 3 days of week 1 and week 4 or a single dose of 25 mg warfarin
AUC_{ss}, C_{max} (statin)	Omega-3 fatty acids (4 g/day) + Rosuvastatin or atorvastatin	No clinically significant interactions	Healthy volunteer studies based on therapeutic doses of statins for 14 days

Outcome Measure	Dietary Supplement + CV Drug
Insufficient strength of evidence **Conclusion: Inconclusive (potential for type II error or inconsistent direction of estimates)**	
C_{max} (S- and R-warfarin)	Garlic (4 g/day) + Warfarin
AUC_{∞}, C_{max}, half-life, and clearance (digoxin)	*Ginkgo biloba* (80-240 mg/day) + Digoxin
AUC_{∞} (warfarin)	Ginseng (3 g/day) + Warfarin
Half-life and clearance (rosuvastatin and atorvastatin and/or metabolites)	Omega-3 fatty acids (4 g/day) + Rosuvastatin or atorvastatin
AUC_{ss}, C_{max}, half-life, and clearance (beta-hydroxysimvastatin)	Omega-3 fatty acids (4 g/day)/ + Simvastatin; Garlic (3600μg of allicin twice daily) + Statins
AUC_{∞}, C_{max}, half-life, and clearance (digoxin)	Hawthorn (900 mg/day) + Digoxin

Note: AUC_{∞} = area under the curve to infinity; AUC_{ss} = area under the curve at steady-state; C_{max} = maximum concentration; CV = cardiovascular.

Twelve randomized controlled trials contributed evidence on pharmacokinetic outcomes.[36,59,61,64,68,70-72,90,93,95,101] No data were available from observational studies. Generally, these studies were open-label crossover RCTs of moderate risk of bias for the gradable outcomes, including between 8 and 50 healthy volunteers. Six studies investigated cardiovascular drug kinetics following a single dose.[59,61,64,68,71,90] The clinical significance of the interaction was evaluated using the FDA guidance.[30] According to this guidance, the statistical significance of interactions alone cannot determine the clinical significance of interactions. Interactions are deemed significant when the 90 percent confidence intervals of the geometric mean ratio (GMR) fall clearly outside of the default no-effect range of 0.80 to 1.25.

It must be noted that the evidence of pharmacokinetic interactions may not translate into altered clinical effectiveness or harms. Also, evidence originating in healthy young adults may

not be applicable to older CVD patients taking cardiovascular drugs due to possible differences in abilities to absorb, metabolize, and excrete drugs.

Echinacea. Evidence of low strength demonstrated no clinically significant interactions between a mixture of 600 mg of *Echinacea angustifolia* root plus 675 mg of *E. purpurea* root given four times a day for a period of 2 weeks and a single dose of 25 mg warfarin. The 90 percent upper and lower bound of GMR for the individual warfarin pharmacokinetic parameters were within the 0.80 to 1.25 boundaries of bioequivalence (Table F).[59]

Garlic. Interactions of 7.4 mg/day of allicin pretreatment for 2 weeks with a single dose of 25 mg warfarin are unclear. Low-strength evidence suggested no clinically relevant interactions for some pharmacokinetic outcomes, while for other important outcomes the strength of evidence was graded as insufficient.[61] Evidence from one garlic-statin trial demonstrated insufficient evidence for pharmacokinetic interactions between the supplement (3600 μg of allicin twice daily) and 20 mg single doses of both simvastatin and pravastatin.[101] Interactions and bioequivalence could not be clearly established.

Ginger. Evidence of low strength demonstrated no clinically significant interactions between 7-day pretreatment with ginger and a single 25 mg dose of warfarin.[64]

Ginkgo biloba. Evidence of low strength demonstrated no clinically significant interactions between 7-day pretreatment with *G. biloba* and a single 25 mg dose of warfarin.[64] Low-strength evidence revealed no clinically significant interactions between single doses of *G. biloba* and ticlopidine.[68] Insufficient evidence addressed interactions between 7-day pretreatment with *G. biloba* and single doses of digoxin. While pharmacokinetic outcomes showed statistically nonsignificant changes, data were not reported as GMRs, so meaningful conclusions could not be drawn.[90]

Ginseng. *Panax ginseng* (Korean ginseng) coadministered with warfarin demonstrated no clinically significant interactions based on evidence of low strength.[71] In contrast, interactions of American ginseng (*P. quinquefolius* 2 g/day from weeks 2 to 4) with warfarin were unclear. Low-strength evidence suggested no clinically relevant interactions for some pharmacokinetic outcomes, while for other important outcomes the strength of evidence was graded as insufficient.[70]

Hawthorn. In a trial of hawthorne (84.3 mg/day of oligomeric procyanidines) added to digoxin for 21 days versus digoxin alone for 10 days, no significant differences in pharmacokinetic outcomes were observed between groups. As analyses evaluated mean differences instead of GMRs, we could not exclude type II error and graded the strength of evidence as insufficient for clinically significant interactions.[72]

Omega-3 fatty acids. Three open-label randomized crossover studies in 24 to 50 healthy adult volunteers investigated interactions between omega-3 fatty acids and various statins.[36,93,95] Each study compared a statin (rosuvastatin, atorvastatin, or simvastatin) coadministered with 4 g/day of omega-3 fatty acids versus statin alone over a 14-day period. Insufficient evidence for interactions with simvastatin precluded meaningful conclusions about interactions because

pharmacokinetic outcomes were analyzed as differences in arithmetic means, yielding nonsignificant results with potential for type II error.[95] Interactions with rosuvastatin or atorvastatin were unclear because for some of the pharmacokinetic outcomes there was low-strength evidence suggesting no clinically relevant interactions, while for other important pharmacokinetic outcomes the strength of evidence was graded as insufficient.[36,93]

Other supplements. No studies were found examining pharmacokinetic interactions between a cardiovascular drug and coenzyme Q10, magnesium, niacin (no more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, vitamin D with or without calcium supplementation, vitamin E, or vitamin K.

Key Question 4a. Do the effect estimates of pharmacokinetic outcomes vary by age, ethnicity, gender, or health status?

A paucity of evidence for supplement-drug combinations precluded exploration of heterogeneity in terms of preidentified subgroups such as age and gender.

Key Question 4b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for pharmacokinetic outcomes?

Statistical interaction data were not reported in any pharmacokinetic study.

Discussion

Patients with cardiovascular disease commonly take dietary supplements along with prescription drugs, but this review uncovered a paucity of high-quality research into benefits and interactions of drugs coadministered with some of the most common supplements. No trials were identified for most potential combinations, while those that were found were generally underpowered efficacy trials of short duration in highly selected populations.

Clinical outcomes were reported in a sparse collection of inconclusive trials; therefore, evidence on important gradable clinical outcomes was rated insufficient. Findings of note include inconsistent evidence of decrease in rates of coronary artery restenosis following successful angioplasty with coadministration of omega-3 fatty acids in two trials with aspirin and other cardiovascular drugs. Also, evidence from a well-powered pragmatic trial in women showed no benefit of adding vitamin E to daily aspirin on the composite outcome of nonfatal myocardial infarction, nonfatal stroke, and vascular death; evidence on individual vascular events was not available.

For most intermediate outcomes of efficacy, such as lipid profile, blood pressure, and INR, we found either insufficient evidence or evidence of low strength demonstrating no effect; however, evidence indicated that omega-3 fatty acids (2 to 4 g/day) likely do not interfere with the efficacy of statin therapy or calcium channel blockers in the presence of antiplatelet agents, but may provide independent benefit in resolving hypertriglyceridemia. There is evidence of low strength that supplemental vitamin K (0.1 to 0.15 mg/day) may help to stabilize INR when given with warfarin. Also, garlic (4 to 10 g/day) may not interact negatively with nitrates and warfarin, and may confer independent benefit in improving HDL-C and total cholesterol. However, our confidence in the validity and reproducibility of these benefits on intermediate outcomes is low.

Safety of intake of dietary supplements concomitant with prescription cardiovascular medications is largely unclear due to insufficient evidence. Evidence regarding benefit of

coenzyme Q10 in reducing myalgia in participants with statin-induced myopathic pain is based on two small RCTs and is inconclusive. One study found benefit of supplementation of coenzyme Q10 versus vitamin E added to statins, while another pilot study reported no significant differences between groups using simvastatin with or without coenzyme Q10 in myalgia and tolerance for statin therapy.

Evidence of low strength demonstrated no clinically significant pharmacokinetic interactions when *Echinacea*, ginger, or *Ginkgo biloba* were coadministered with warfarin or when *G. biloba* was coadministered with ticlopidine. Insufficient or conflicting evidence addressed most other supplement-drug pharmacokinetic interactions.

Without an adequate evidence base from the literature, variability in effects across clinically important subgroups (e.g., age, ethnicity, gender, and health status) could not be assessed.

Limitations of our systematic review process include our restriction of the number of dietary supplements of interest to 16 of the most commonly used; this was necessary given limitations of resources and review time. Up to 30 percent of included studies were assessed to have potential for financial conflict of interest, and approximately 45 percent did not report funding information. Given the uncertainties involved in interpreting asymmetry tests for publication bias in most reviews, especially in the presence of heterogeneity in effect estimates, we did not plan to investigate publication bias in this review.[102,103] In fact, a recent recommendation is that tests for funnel plot asymmetry should be used only in a minority of meta-analyses that include at least 10 studies of unequal sizes per analysis without substantial heterogeneity in their effect sizes.[104] We did not adopt other means of evaluating publication bias and selective outcome reporting, such as comparing publications with study protocol, because of time and resource limitations. Seemingly, another limitation could be the exclusion of indirect evidence of drug interactions derived from surrogate measures, such as alterations in probe drug metabolism, that highlight effects on enzymes involved in drug metabolism. As such evidence traditionally originates in healthy volunteers, the applicability of such evidence would have been as much of a concern as for the pharmacokinetic outcomes we examined, whose applicability was restricted to healthy volunteers with uncompromised drug metabolism. In order to make causal inferences possible for translation into practice, we also excluded combinations of multiple dietary supplements with cardiovascular drugs. For example, a given combination of multivitamins coadministered with a cardiovascular drug or drugs would be limited both in causal inference of supplement–drug(s) interactions and in applicability to the specific doses and combinations of vitamins employed as intervention in the study. Finally, we considered potential benefits, harm, or bioequivalence independently for pharmacokinetic outcomes, according to the FDA guidance.[30] In the absence of guidance regarding intermediate outcomes, we did not draw conclusions on the two sides of clinical decisionmaking, such as "unknown benefit but harm is unlikely" and "unknown harm but benefit is unlikely."

Available evidence poorly addresses the safety and effectiveness of coadministration of dietary supplements with cardiovascular drugs. Given the steady increase in the use of dietary supplements for self-care and the identified gaps in research, we make the following recommendations for future research.

1. First and foremost, future research with dietary supplements should involve substances for which the identity of the agents can be clearly ascertained and the chemical composition well characterized and, ideally, standardized. If the active ingredients or biologic activity of these substances is not known, then studies to characterize these variables, identify mechanisms of action, and describe safety should precede clinical

efficacy studies. According to the 2011-15 strategic plan of the National Center for Complementary and Alternative Medicine (NCCAM), clinical trials of dietary supplements will not be supported without documentation of biology and mechanism of action.[105]

2. As extant literature is largely based on few small-size efficacy studies of limited internal validity examining intermediate outcomes, future supplement-cardiovascular drug interaction trials should focus on meaningful clinical outcomes, be appropriately powered and rigorously conducted and reported, and provide precise measurements of both clinical effectiveness and harms outcomes.
3. Most studies were conducted in specialty settings, excluded patients with comorbidities or uncontrolled comorbidities, and did not include ethnic and racial minorities; prospective trials should be representative of the population taking cardiovascular drugs in terms of comorbidities, setting, and racial distribution. They should also collect data and undertake subgroup analysis for age, gender, race, comorbidities (e.g., liver or renal compromise), and genotypic polymorphisms of the cytochrome P450 enzyme.
4. A substantial number of pharmacokinetic interaction studies did not report and analyze pharmacokinetic outcomes according to FDA guidance for bioequivalence studies.[30] Future experiments of drug interactions must evaluate pharmacokinetic outcomes as geometric mean ratios with predefined margins of bioequivalence. Future studies of drug interactions must report pharmacokinetic outcomes as geometric mean ratios. This would allow statistically allow statistically significant as well as nonsignificant outcomes to be interpreted in terms of clinical significance, using predefined margins of bioequivalence.
5. Given the dearth of studies examining interactions between specific supplements and cardiovascular drugs, future clinical trials and observational studies that explore the effect of cardiovascular drugs should additionally assess the use of dietary supplements and include this in the reporting of results. One way to facilitate this would be to consider inclusion of inquiry about dietary supplement use and other CAM care in reporting guidelines such as CONSORT (CONsolidated Standards of Reporting Trials).
6. Phase I trials of cardiovascular drugs should include older populations and, if possible, a pharmacokinetic assessment that includes dietary supplement usage.
7. As subgroups were underrepresented in existing studies, future studies investigating supplement-drug interactions should examine vulnerable subgroups such as the elderly, those with compromised renal and liver functions, and patients with multiple comorbidities.
8. When possible, comparative effectiveness studies should include a statistical analysis for supplement–drug interactions, and the trials should be powered accordingly.
9. Until well-powered experimental studies are conducted to examine dietary supplement-drug coadministration, evidence from well-conducted prospective observational studies should be sought. Observational studies compliant with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines should be powered appropriately to address predefined endpoints of both efficacy and safety in a naturalistic setting, where the population sampled is reflective of the population for which these data would be meaningful.[106]
10. Given the difficulty and resource-intensive nature of clinical trials, other sources of data should be considered to derive information regarding drug-dietary supplement interactions. Possibilities include synthesis of reports of adverse events made to both

FDA and the Pharmacovigilance program at Health Canada. In addition, electronic health record linkages between databases of dietary supplement use and cardiovascular drug prescription may also add to the sparse evidence on supplement–cardiovascular drug interaction that currently exists.

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Introduction

Vascular disease is a preventable condition that is the leading contributor to mortality in the United States[107], and second place in Canada after cancer.[108] Vascular disease includes peripheral vascular disease evident in hypertension; cardiovascular disease such as angina pectoris, myocardial infarction and heart failure; and cerebrovascular disease such as transient ischemic attack (TIA) and stroke.

The American Heart Association estimates that more than 81 million American adults (one-third of all American adults) have at least one form of cardiovascular disease (CVD), broadly defined to include all vascular disease.[1] While there has been progress in the control of CVD, it demands huge investments from the health care system and represents great burdens and lost opportunities for individuals, families and society overall.

In addition to lifestyle and dietary recommendations, front line treatment for prevention and treatment of cardiovascular disease is primarily pharmaceutical, with patients requiring on average 6.3 concomitant prescription drugs, from on average 5.9 different drug classes, for primary and secondary prevention of the disease itself and management of associated comorbidities.[2-4] The prescription drugs considered in this review are summarized in Table 1.

Table 1. Cardiovascular drugs of interest

Cardiovascular Drug Category	Drug Class	Drugs of Interest	
Beta adrenergic antagonists		acebutalol betaxolol bisoprolol carvedilol labetalol metoprolol	nadolol nebivolol pindolol propranolol sotalol timolol
Calcium channel antagonists	Dihydropyridine	amlodipine felodipine isradipine nicardipine	nifedipine nimodipine nisoldipine
	Non-Dihydropyridine	diltiazem	verapamil
Renin-angiotensin-aldosterone system antagonists	Angiotensin-converting enzyme inhibitors (ACE inhibitors)	benazepril captopril enalapril fosinopril lisinopril	moexipril perindopril quinapril ramipril trandolapril
	Angiotensin II receptor blockers (ARBs)	candesartan eprosartan irbesartan losartan	olmesartan telmisartan valsartan
	Renin inhibitors	aliskiren	
	Aldosterone receptor antagonist	eplerenone spironolactone	

Table 1. Cardiovascular drugs of interest (continued)

Cardiovascular Drug Category	Drug Class	Drugs of Interest	
Vasodilators	Central vasodilators	clonidine guanabenz	guanfacine methyldopa
	Direct vasodilators	diazoxide hydralazine	minoxidil
	Nitrates	isosorbide dinitrate	
		nitroglycerin	
	Phosphodiesterase inhibitors	sildenafil tadalafil	vardenafil cilostazol
	Prostacycline	alprostadil epoprostenol	iloprost treprostinil
	Endothelin antagonist	bosentan	ambrisentan
	Miscellaneous vasodilators	papaverine isoxsuprine	rauwolfia alkaloids
Alpha adrenergic blockers		doxazosin prazosin	terazosin
Antiarrhythmic drugs	Class 1a	disopyramide procainamide	quinidine
	Class 1b	mexilitine	
	Class 1c	encainide flecainide	propafenone
	Class III	amiodarone dofetilide	dronedarone
Inotropic agents		digoxin	
Antilipemic agents	Bile acid sequestrants	colestipol colesevelam	cholestyramine resin
	Cholesterol absorption inhibitor	ezetimibe	
	Fibric acid Derivatives	fenofibrate	gemfibrozil
	HMG-CoA reductase Inhibitors	atorvastatin fluvastatin lovastatin	pravastatin rosuvastatin simvastatin
	Miscellaneous	niacin>250 mg/day*	
Anticoagulants	Coumarin derivatives	warfarin	
	Heparins	dalteparin enoxaparin	heparin tinzaparin
Antiplatelet agents		acetylsalicylic acid (ASA)	clopidogrel ticlopidine
Diuretics	Loop diuretics	bumetanide ethacrynic acid	furosemide torsemide
	potassium-sparing (K-sparing)	amilioride	triamterene
	Thiazide	chlorothiazide hydrochlorothiazide methyclothiazide	bendroflumethazide polythiazide
	Thiazide-like	chlorthalidone indapamide	metolazone

Note: * Niacin at not more than 250 mg/day doses was considered to be a dietary supplement.

Complementary and alternative medicine (CAM) refers to preventive and therapeutic modalities not generally considered to be part of conventional medicine,[5] including dietary supplements. CAM utilization has increased dramatically in North America over the past decades in both the general and cardiovascular disease populations.[6,7] The National Health

Interview Survey (NHIS) indicated that a total of $34 billion in annual out-of-pocket expenditures was spent on CAM in 2007.[8] Of this amount, 44 percent was spent on non-vitamin, non-mineral supplements.[8] Estimates suggest that approximately one-third to nearly two-thirds of people suffering from heart failure or other cardiovascular disease use some form of dietary supplements, and are thus placed at risk for potential adverse events from interactions among pharmacologically active agents.[7,9-11] To further complicate the issue, dietary supplements in the US are not regulated in the same manner as drugs. According to the Dietary Supplement Health and Education Act of 1994, manufacturers of supplements are not held to the same standards as manufacturers of prescription and over-the-counter drugs with respect to providing evidence of efficacy and safety prior to marketing.[109] Furthermore, dietary supplements are not required to obtain United States Food and Drug Administration (FDA) approval, nor are there any FDA regulations that require evidence of purity, quality or composition prior to marketing. These products are available in pharmacies, grocery stores, health food stores, and via the internet, and are often consumed by patients without the knowledge of their care providers under the mistaken impression that supplements are safe, or without adverse effects. The purported benefits of dietary supplements are widespread and largely unsubstantiated. Many supplements have been suggested to be beneficial in various forms of cardiovascular disease (i.e., coenzyme Q10, omega-3 fatty acids and vitamin E for cardioprotection, garlic for hypercholesterolemia, hawthorn for congestive heart failure) with varying levels of evidence supporting these claims.[110] The dietary supplements considered in this review, and the proposed mechanisms of action for selected supplements with purported cardiovascular benefits, are summarized in Table 2.

Table 2. Dietary supplements considered in this review

Supplement category	Supplement	Proposed Mechanism of Action	Purported Outcome Effect (*italics – evidence unclear*)
Vitamins and minerals	Niacin (≤ 250 mg/day)*	Vasodilator, antioxidant, increases degradation and reduces synthesis of cholesterol	At higher doses Lipid lowering Anti-atherogenic
	Vitamin A (beta carotene)†	Lipid soluble antioxidant	*Anti-atherogenic* *Cardioprotective*
	Vitamin D†	Blood mineral homeostasis	Replete levels provide anti-hypertension, cardioprotective effect
	Vitamin E	Lipid soluble antioxidant	*Anti-atherogenic* *Cardioprotective* *With high doses, bleeding risk*
	Vitamin K	Involved in the endogenous production of clotting factors	Reversal of warfarin associated bleeding Stabilize warfarin dosing/titration
	Magnesium	Essential cofactor in the Na-K-ATPase enzyme system, coronary vasodilator	Anti-arrhythmic Cardioprotective (thrombolytic) *Controls hypertension*

Table 2. Dietary supplements considered in this review (continued)

Supplement category	Supplement	Proposed Mechanism of Action	Purported Outcome Effect (*italics – evidence unclear*)
Herbs or other botanicals	Ginseng (American - *Panax quinquefolius;* Asian - *Panax ginseng)*	Largely unknown but proposed to have adaptogenic immunomodulatory and neuroprotective properties	"Tonic" improving exercise and mental capacity Anti-carcinogenic, stress reducing, and neuroprotective
	Echinacea (*E. purpurea, E. angustifolia*)	Immunostimulant	Symptom control for mild upper respiratory tract infections
	Garlic supplements (*Allium sativum*)	Inhibitor of HMG-CoA reductase, antioxidant, inhibitor of platelet aggregation	Lipid lowering Anti-atherogenic Antithrombotic Lowers blood pressure *Possible bleeding risk*
	Ginger supplements (*Zingiber officinale*)	Anti-inflammatory effect, inhibitor of platelet aggregation	Anti-emetic *Anti-atherogenic Cardioprotective Antithrombotic*
	Ginkgo (*Ginkgo biloba*)	Antioxidant Neuroprotectant Circulatory stimulant	Memory enhancement associated with dementia, Alzheimers *Possible bleeding risk*
	Omega-3 fatty acids	Anti-inflammatory Modulates VLDL and chylomycron metabolism	Lower triglycerides and CHD risk Anti-atherogenic High dose risks in CHD of bleeding, altered blood sugar, increased LDL-C, arrhythmia
Refined dietary substances, to increase the total dietary intake (e.g., enzymes or tissues from organs or glands)	Coenzyme Q10	Cofactor in oxidative respiration Fat soluble antioxidant (Endogenous production decreases with age)	Antiatherogenic Used in cardiovascular conditions for deficiency (natural or statin-induced)
	Red yeast rice extract	Inhibitor of HMG-CoA reductase	Lipid lowering
	Resveratrol	Antioxidant Anti-inflammatory	Anti-cancer Cardioprotective
	Hawthorn	Enhances intracellular calcium sensitivity in cardiomyocytes Increases degradation and reduces synthesis of cholesterol	Symptom control in CHF Lipid lowering Anti-atherogenic Ionotropic for arrhythmias

Notes: The primary source for this table is the Natural Standard database of Foods, Herbs and Supplements (http://naturalstandard.com/databases/herbssupplements/all/)

***** Niacin at higher doses was considered to be a cardiovascular drug.

† The following vitamin analog forms are considered pharmaceutical drugs and were therefore excluded:
Analogs of vitamin A [bexarotene, fenretinide; 13-cis-retinoic acid (isotretinoin, Accutane); 9 –cis retinoic acid (Alitretinoin); and all trans retinoic acid (ATRA) (tretinoin)]; and
Analogues of vitamin D [Calcitriol; dihydrotachysterol (DHT); alfacalcidiol (1α-(OH)D3); calcipotriol; tacalcitol; 19-nor-1,25(OH)2D2 (19-norD2), oxacalcitriol (OCT), 22-oxa-1,25(OH)2D3; paricalcitol; doxercalciferol; 1α-hydroxyvitamin D2 (1α-(OH)D2); falecalcitriol]

Abbreviations: CHD = coronary heart disease; CHF = congestive heart failure; HMG-CoA = 3-hydroxy-3-methyl-glutaryl coenzyme A; LDL-C = low density lipoprotein cholesterol.

People at risk of or suffering from cardiovascular disease often take dietary supplements alongside prescribed drugs. The use of supplements may complement standard care, or may have a detrimental effect on the pharmacodynamics or pharmacokinetics of standard care. Given the uncertainty, and potential for harm, we need to understand better the risks and benefits, or lack thereof, associated with concomitant usage.

An example whereby the addition of a dietary supplement may confer benefit would be combining coenzyme Q10 with statin therapy. Amongst other actions, coenzyme Q10 has been

shown to lower cholesterol, specifically low-density lipoprotein cholesterol,[6] and while not proven, it is plausible that coenzyme Q10 reduces myalgia associated with statin therapy.[111,112]

Alternatively, the concomitant use of dietary supplements and cardiovascular drugs may lead to detrimental outcomes directly (i.e., either clinical or surrogate outcomes) or indirectly. For example, key factors within coagulation pathways are directly affected by garlic, fish oil, fenugreek, saw palmetto, *Ginkgo biloba* and danshen, which all have been shown to inhibit blood coagulation.[10,113-115] However, increased bleeding is a serious potential risk when these dietary supplements are coupled with common anticoagulants like aspirin, warfarin, or ticlopidine. Conversely other supplements, even a seemingly innocuous one like green tea extract, that contains vitamin K, may counteract the anticoagulant effects of certain drugs and thus limit their effectiveness.[116] Similarly, drug-dietary supplement interactions can negatively impact surrogate outcomes, as illustrated by metabolic enzyme induction. St. John's wort for example, taken often for the treatment of depression, is a potent inducer of the CYP3A4 enzyme.[117] This enzyme is involved in the oxidative metabolism of many synthetic drugs,[114,115,118-121] including cardiac glycosides, beta-adrenergic blockers, calcium channel blockers, statins, angiotensin receptor antagonists, and anticoagulants.[10,114,116] Increasing the metabolism of any of these drugs with use of this popular herbal product could reduce their effectiveness and potentially result in serious clinical consequences. Conversely, if prescription medication dosage is adjusted in the context of regular ingestion of a CYP3A4 enzyme inhibitor, then supplement cessation may result in excessive drug levels with other serious clinical consequences.

Concomitant use of dietary supplements and cardiovascular drugs may also affect clinically relevant outcomes indirectly. Risks for both non-adherence and interactions inevitably increase with the number of medications and supplements taken, and this is of greatest concern in the elderly.[12,13] In addition to concerns of polypharmacy, the elderly also experience physiological changes that make them more susceptible to interactions, as a consequence of alterations in metabolism and excretion, affecting both pharmacodynamics and pharmacokinetics.[122,123] The increasing morbidity that occurs within older populations suffering from CVD, in conjunction with greater potential for drug interactions, makes this subgroup particularly important to explore.

Thus, understanding the potential for drug-supplement interactions and consequences of such interactions is essential for clinicians and patients when prescribing medications, or advising or deciding to add dietary supplements to current medication and supplement regimes.

Incorporation in clinical practice of knowledge regarding the impact of concomitant use of cardiovascular disease medications and dietary supplements requires access to reliable drug-supplement information, as well as a commitment to documentation by clinicians.[15,16]

As a consequence of U.S. drug regulatory policy, much more research and data are available describing drug-drug interactions than drug-supplement interactions. Comprehensive systematic review of interactions between dietary supplements and drugs specifically in patients taking prescription medications for cardiovascular disease is clearly needed. Recently published systematic reviews addressing aspects related to this topic are not comprehensive, or focus on different populations of interest.[115,119,121] This synthesis evaluates literature that addresses meaningful clinical outcomes, as well as important surrogate or intermediate outcomes, in the context of patients concurrently taking prescription drugs and dietary supplements for prevention and treatment of CVD.

The Key Questions examined in this review are as follows:

In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared to cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement[s]) on:

1. clinical cardiovascular effectiveness/efficacy outcomes (e.g., mortality and specific cardiovascular or cerebrovascular conditions such as myocardial infarction [MI] and stroke)?
   (a) Do the effect estimates of clinical cardiovascular outcomes vary by age, ethnicity, gender, or health status?
   (b) Is there a measurable interaction between cardiovascular drugs and dietary supplements for clinical cardiovascular outcomes?
2. intermediate cardiovascular efficacy outcomes (e.g., lipids, blood pressure, electrocardiographic measurements, serum markers, bleeding, and coagulation times)?
   (a) Do the effect estimates of intermediate cardiovascular outcomes vary by age, ethnicity, gender, or health status?
   (b) Is there a measurable interaction between cardiovascular drugs and dietary supplements for intermediate cardiovascular outcomes?
3. clinical or intermediate harms outcomes (e.g., organ toxicity, serious adverse events, withdrawal due to adverse events)?
   (a) Do the effect estimates of harms outcomes vary by age, ethnicity, gender, or health status?
   (b) Is there a measurable interaction between cardiovascular drugs and dietary supplements for harms outcomes?
4. pharmacokinetic outcomes (e.g., T1/2, area under the concentration curve [AUC]) of cardiovascular drugs of interest?
   (a) Do the effect estimates of pharmacokinetic outcomes vary by age, ethnicity, gender, or health status?
   (b) Is there a measurable interaction between cardiovascular drugs and dietary supplements for pharmacokinetic outcomes?

Methods

The methods for this Comparative Effectiveness Review follow the methods suggested in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews, Version 1.0 published by the Agency for Healthcare Research and Quality (AHRQ).[17] Unless stated otherwise, all methods and analyses were determined a priori and documented in a research protocol that was publicly posted by AHRQ for comments. Screening of literature and inclusion/exclusion of studies were tracked and presented according to the PRISMA methodology.[124]

Topic Development and Refinement

This evidence report addresses several Key Questions regarding the effects of concomitant use of specific dietary supplements and cardiovascular drugs compared with cardiovascular drugs alone or with different dietary supplements. The original topic nomination was for a comparative effectiveness review (CER) of the risks and benefits for elderly patients taking cardiovascular medication concomitantly with herbal supplements. Discussions were held with Key Informants representing the FDA, the National Center for Complementary and Alternative Medicine (NCCAM), and several other institutions on scope of the topic, research questions to be asked, and methodology of evidence synthesis to be adopted. The panel included clinicians (e.g., cardiologists, naturopathic doctors, a clinical pharmacology specialist, and a nutritionist), a patient (consumer), and systematic review research methodologists.

As preliminary searching indicated scarce data in the elderly subgroup, it was decided with the Key Informants to broaden the review topic to the benefits and risks of dietary supplement use in adults taking drugs for prevention and treatment of cardiovascular disease (CVD). Subgroups of interest were added to a preliminary list of demographic and clinical categories that included those with renal dysfunction and genetic polymorphisms in CYP2D6, 2C9, and 2C19. Drug-functional food and drug-conventional food interactions were considered but it was decided that should be evaluated as a separate research project due to the size of such an undertaking. Five research Key Questions were finalized in the topic refinement process regarding the comparative efficacy, effectiveness, harms and pharmacokinetics of a dietary supplement coadministered with a cardiovascular drug. Subquestions sought to investigate subgroup effects and evidence of specific drug-supplement statistical interaction. An indirect question enquired about evidence based on human studies that some of the most commonly used dietary supplements cause alterations in cytochrome P450 isozyme activity and in cellular drug transport mechanisms.

All dietary supplements, according to the Dietary Supplement Health and Education Act of 1994 (DSHEA) definition, were of investigational interest. The dietary supplement was defined as one of the following substances:

- a vitamin;
- a mineral;
- an herb or other botanical;
- an amino acid;
- a dietary substance for use by man to supplement the diet by increasing the total dietary intake (e.g., enzymes or tissues from organs or glands); or
- a concentrate, metabolite, constituent or extract.

Furthermore, it must also conform to the following criterion:

- intended for ingestion in pill, capsule, tablet, powder or liquid form not represented for use as a conventional food or as the sole item of a meal or diet.

AHRQ's Effective Health Care Program posted the proposed Key Questions for public comment on their Web site from August 16 through September 13, 2010. In response, the following five general comments were received: (1) the review scope should be restricted to the most common dietary supplements and cardiovascular drugs; (2) the review should focus on patient-oriented outcomes; (3) the review should examine issues related to quality, dose and purity of the dietary supplements of interest; (4) the review should distinguish between regular and occasional users of dietary supplements; (5) the review should distinguish between nutrient and non-nutrient supplements. The Evidence-based Practice Center (EPC), with input from Key Informants and the Technical Expert Panel (TEP), reviewed and refined the Key Questions to ensure that the questions were specific and explicit about what information was being reviewed.

Protocol and Project Scope Amendment

The review according to the approved topic refinement document was proven to require resources beyond those allocated to the EPC center. The search of included data bases yielded more than 32,000 records; beyond expectations founded on targeted search during topic refinement. A random 10 percent title, abstract and full text screening was conducted to estimate the final size of the review and the projected number of included studies was beyond review resources. Several telephone and e-mail discussions were held with the TEP members and the Task Order Officer. Finally, three modifications were made as an amendment to the original research protocol based on the topic refinement document:

- Restrict to dietary supplements commonly used in adults and elderly taking cardiovascular medication for which current evidence on possible drug-supplement interaction is lacking. With input from the TEP, and surveys of the general and cardiovascular populations in the Unites States reported in literature,[7,18-23] the revised list of dietary supplements was arrived at as follows:
  A. dietary supplements commonly perceived to provide cardiovascular benefit, with a high probability of being used simultaneously with cardiovascular drugs: coenzyme Q10; garlic; ginger; *Ginkgo biloba*; ginseng; multivitamins; vitamin A or beta carotene; vitamin D; vitamin E;omega-3 fatty acids or fish oils; niacin; and magnesium.
  B. other dietary supplements commonly used by the population using cardiovascular drugs, for which there is some reason to believe there may be an interaction with cardiovascular drugs: *Echinacea*; St. John's wort; red yeast rice; resveratrol; hawthorn; and vitamin K.
  C. supplements falling into categories A or B may be omitted from the list if there is already well understood interaction and a review would be redundant. On this basis, it was proposed that these be excluded: St. Johns wort; therapeutic doses of niacin (greater than 250 mg/day); and magnesium as infusion or injection.
- Eliminate the indirect question enquiring about alterations in cytochrome P450 isozyme activity and in cellular drug transport mechanisms.
- Restrict foreign-language report inclusion to German only.

Language restriction was based on the fact that during the screening of the 10 percent random sample of a total of 32, 000 records, most commonly identified foreign languages were German (24 percent), Russian (16 percent), and Chinese (44 percent), comprising 84 percent of reports in language other than English. Other languages included Norwegian (4 percent), and Italian, Polish, Swedish, Dutch, and French (2 percent each). Because of uncertain applicability of Russian and Chinese language studies to the United States population and settings, the only foreign language considered to be eligible was German.

The list of relevant dietary supplements, rationale for the above-mentioned project scope amendments, and other details, are presented in the Table 3 below.

Table 3. Protocol amendments

Item	Amendment	Section of the Protocol Report Affected
Revision to the list of dietary supplements	Include only: Coenzyme Q10 *Echinacea* Garlic Ginger *Ginkgo biloba* Ginseng Hawthorn Magnesium (oral) Niacin (≤ 250 mg/day) Omega-3 fatty acids Red yeast rice extract Resveratrol Vitamin A Vitamin D ± calcium Vitamins E and K	Definition of intervention Method: Table 1 (intervention Key Questions1- 4)
Language of publication	Restriction to English and German for experimental and observational studies	Methods: criteria for inclusion; Table 1: report characteristics
Restriction of Key Questions	Elimination of Key Question 5	Key Question 5 Analytic framework Methods: criteria for inclusion, Table 1: grading the evidence

Abbreviation: mg = milligrams.

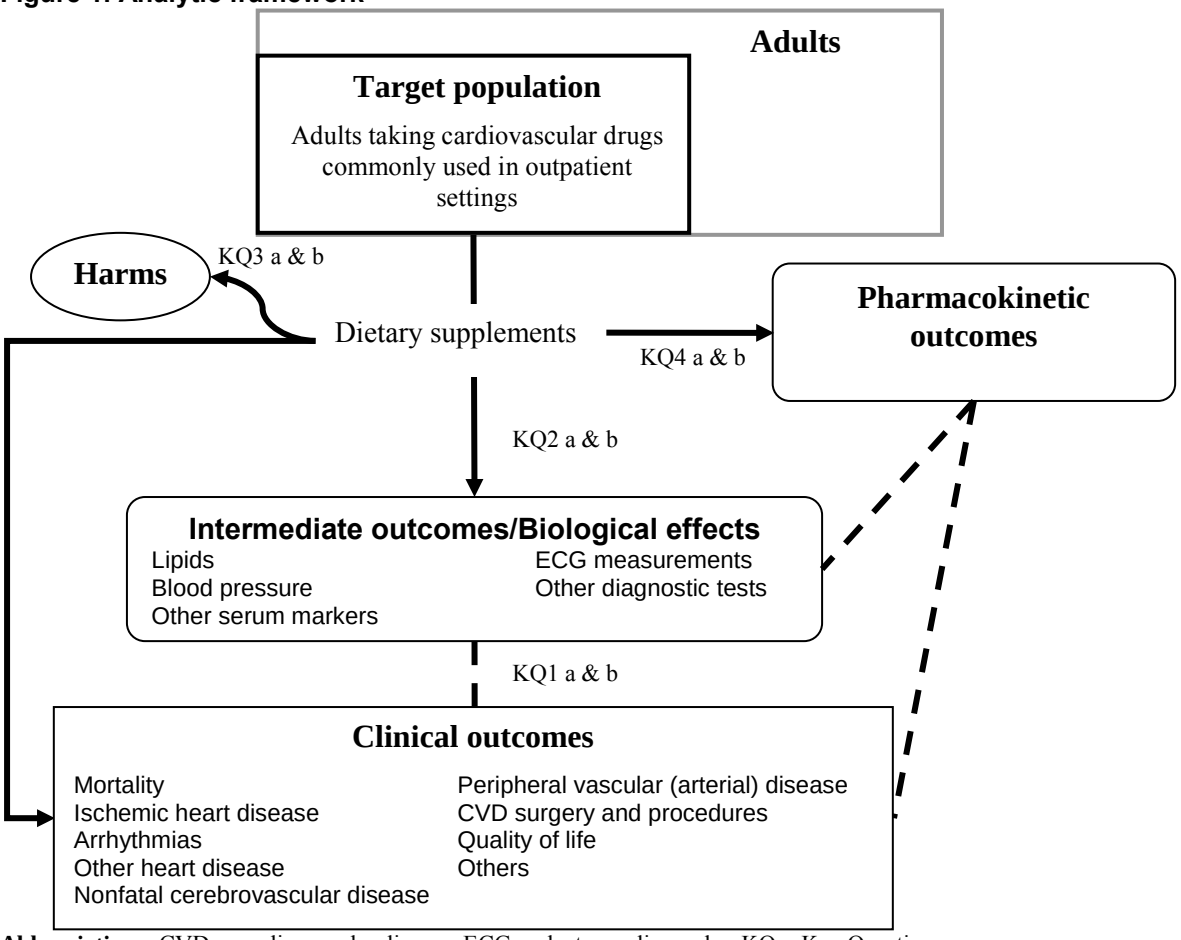
Development of the Analytic Framework

The analytic framework depicts the causal pathways forming the basis of the Key Questions (Figure 1). The framework outlines the conceptual basis or expectations for adding a dietary supplement to prescribed cardiovascular drugs. Expectations include improvement in efficacy and reduction in harms related to cardiovascular drugs. Outcomes that represent these changes may be clinical, surrogate (proxy for clinical), or pharmacokinetic. Altered outcomes may be a result of an add-on effect of the dietary supplement and/or supplement-drug interaction. Drug interactions may be seen as biologic (i.e., pharmacodynamic or pharmacokinetic interactions reflected in altered clinical and surrogate outcomes of benefit and harms) or statistical.[125] Statistical interactions measure biologic interactions in terms of a product term added to a linear model. The Key Questions posed therefore examine whether outcomes of benefit and harms change with the addition of a dietary supplement. In addition, they examine pharmacokinetic and statistical interactions.

In the context of the population of interest, the Key Questions are indicated along the corresponding arrows connecting treatment and outcomes of interest. The framework includes

seven sections. The first section represents the adult population, within which the target population is included. The remaining six sections are: (1) target population (adults taking cardiovascular drugs commonly used in the outpatient setting); (2) treatment (dietary supplements); (3) intermediate outcomes/biological effects (lipid levels, blood pressure, electrocardiogram measurements, other serum markers, and diagnostic tests); (4) clinical outcomes (mortality, ischemic heart disease, arrhythmias, cerebrovascular disease, peripheral arterial disease, cardiovascular disease surgery and procedures, and quality of life); (5) harms (allergic reactions, significant bleeding, and neurological and gastrointestinal adverse events); and (6) pharmacokinetic outcomes (measures of drug absorption, distribution, metabolism, and excretion).

Figure 1. Analytic framework



Abbreviations: CVD = cardiovascular disease; ECG = electrocardiography; KQ = Key Question.

Literature Search Strategy

An experienced medical information specialist developed and tested the electronic search strategies by using a combination of controlled vocabulary and free text, in consultation with the team. An independent information specialist peer-reviewed the search strategies according to the PRESS checklist.[126]

To identify primary study reports (see Appendix A), we searched the following electronic databases: Ovid MEDLINE® In-Process and other Non-Indexed Citations, and Ovid MEDLINE® (1950 to Sept 1, 2011); Embase (1980 to Sept 1, 2011); Cochrane Library via the Wiley interface

(Sept 1 2011) including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Health Technology Assessment Database and Cochrane Central Register of Controlled Trials; International Bibliographic Information on Dietary Supplements (IBIDS) on October 26, 2010; and Allied and Complementary Medicine Database (AMED) 1985 to September 1, 2011. We used controlled vocabulary (e.g., "Dietary Supplements," "Drugs, Chinese Herbal," "Phytotherapy") and keywords (e.g., nutritional supplements, garlic, ginger) in combination with controlled vocabulary and keywords related to cardiovascular agents. A broad range of controlled vocabulary was used to address the various synonyms associated with this topic, as well as to cover any evolutionary gaps associated with the introduction of certain vocabulary terms. Results were refined using filters for systematic reviews, RCTs, non-RCTs and observational studies, and safety. A more specific strategy related solely to herb–drug interactions was run in the same databases using only a systematic review filter.

To identify systematic reviews addressing research questions similar to the Key Questions outlined for this review, we used a slightly modified strategy from that indicated above, by including a systematic review filter (for MEDLINE and Embase) and limiting the search of the Cochrane Library to the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database (see Appendix Y). The identification of relevant systematic reviews addressing any one of the Key Questions would serve the purpose of replacing a de novo process involving primary synthesis with existing systematic reviews.

We restricted our searches to human studies without imposing any language or date restrictions. We attempted to identify unpublished literature (including abstracts and conference proceedings) through searches of trial registries (e.g., ClinicalTrials.gov, Current Controlled Trials, Clinical Study Results, World Health Organization Clinical Trials), the Cambridge Scientific Abstracts (CSA) Conference Papers Index, and Scopus. Additional references were identified by scanning bibliographies of relevant systematic reviews and clinical trials. We also contacted Technical Expert Panel (TEP) members.

Through the Scientific Resource Center, we contacted the industry (see Appendix B for list of drug manufacturers contacted) for scientific information packets (SIPs) on drug-supplement interaction and requested:

- a current product label;
- randomized controlled trials, published or unpublished; and
- observational studies, published or unpublished.

All identified citations were downloaded into a Reference Manager 12[127] database for duplicate removal and early analysis. The unique references were then uploaded into DistillerSR,[128] a review management Web application.

Study Selection

Process Description

The reviewers involved in initial screening attended a screening training session and pilot tested the screening forms. Titles were screened by one reviewer; all exclusions were independently screened by a second reviewer. A similar process of screening was followed to screen abstracts of studies that passed the title screen. Two reviewers independently screened the full text of all included records. Discrepancies were resolved by consensus.

Eligibility Criteria for Systematic Reviews

When available, topically relevant reviews were to be included to answer one or more of the Key Questions. As per the Cochrane Collaboration definition,[129] a systematic review includes: a specific research question; a search strategy (e.g., sources such as electronic databases, period covered by the search); and methods used to assess the risk of bias of studies included in the review. Narrative reviews were excluded. We limited our review to those systematic reviews judged to be of "Good" quality (see below for how quality of a review was assessed). Reasons for exclusion were noted. We planned to replace de novo evidence synthesis with good quality systematic review evidence only when it was deemed current, obviating the need to update.

Eligibility Criteria for Primary Studies

We aimed to include hypothesis-testing as opposed to hypothesis generating studies (case-reports and series). We thus included experimental and observational comparative studies (i.e., those with independent controls) evaluating the benefits or harms of concomitant dietary supplement use in adults taking cardiovascular medications versus no dietary supplement (or other dietary supplement). In a post hoc decision, we expanded the study design criteria to allow inclusion of single arm controlled before-after pharmacokinetic studies in which posttreatment values were compared with baseline values. This was because we considered such evidence as a reasonable comparison between drug-supplement and drug alone for pharmacokinetic outcomes when an adequate washout period was employed. This review was limited to human studies with specific eligibility criteria presented in Table 4.

Table 4. Study inclusion criteria

Population		
KQs 1–4	Adult participants (the majority of participants ≥16 years of age or with subgroup data presented for adults) taking at least one specific cardiovascular drug or one specific class of cardiovascular drugs such as α-adrenergic antagonists , antiarrhythmic drugs, anticoagulants, antilipemic agents, antiplatelet agents, β-adrenergic antagonists, calcium channel antagonists, diuretics, inotropic agents, renin-angiotensin-aldosterone system antagonists, and other vasodilators (e.g., centrally acting, phosphodiesterase inhibitors, prostaclyclin derivates, endothelin anatagonsts, etc)	The drugs were restricted to those commonly used in U.S. outpatient settings for treatment and prevention of cardiovascular disorders.
Intervention		
KQs 1–4	Coenzyme Q10 *Echinacea* Garlic Ginger *Ginkgo biloba* Ginseng Hawthorn Magnesium (oral)	Niacin (≤ 250 mg/d) Omega-3 fatty acids Red yeast rice extract Resveratrol Vitamin A Vitamin D ± calcium Vitamin E Vitamin K
Comparator		
KQs 1–4	No dietary supplement (placebo, no treatment) or another dietary supplement.	

Table 4. Study inclusion criteria (continued)

Outcomes		
KQ 1 Clinical outcomes	Mortality • All-cause mortality • Vascular death • Specific vascular death (e.g., fatal MI, fatal stroke) Ischemic Heart Disease (Coronary Artery Disease) • All myocardial infarction (MI, acute MI) • Nonfatal MI (MI, acute MI) • Unstable angina • Acute coronary syndrome • Coronary artery disease composite outcomes (combination) • Coronary (re)stenosis/graft occlusion/vasospasm (*post hoc*) Arrhythmias • Sudden death • Ventricular fibrillation • Ventricular tachycardia • Atrial fibrillation • Heart block Other heart disease • Congestive heart failure • Valvular disease Adherence to prescribed cardiovascular drug or regimen Hospitalization	Cerebrovascular disease • All stroke • Hemorrhagic stroke • Thrombotic stroke • Transient ischemia attack (TIA) • Carotid artery disease (not measured by IMT or Doppler) • Other Peripheral arterial disease (PAD) • Limb thrombosis/leg ischemia • Claudication (pain walking) • Mesenteric ischemia • Abdominal aortic aneurysm • Ankle-brachial index • Other reported clinical PAD CVD surgery and procedures • Coronary artery revascularization (coronary artery bypass graft [CABG], percutaneous transluminal coronary angioplasty [PTCA], stent) • Valve replacement • Carotid revascularization (± stent) • Peripheral revascularization (± stent) • Amputation Syncope Quality of life Renal replacement therapy
KQ 2 Intermediate outcomes (limited to established outcomes)	Lipids • Total cholesterol • Low-density lipoprotein cholesterol (LDL-C) • High-density lipoprotein cholesterol (HDL-C) • Triglycerides • Lipoprotein a (LP(a)) • Non–HDL-C Other serum markers • C-reactive protein (CRP) Blood pressure • Systolic (SBP) • Diastolic (DBP) • Hypertension (HTN), new or worsening (e.g., need for change in therapy) • Hypotension	Electrocardiographic (ECG) measurements (≥24 h Holter monitor, PR interval) other than established arrhythmias (based on context, this might be evaluated as a harms outcome rather than efficacy) Other diagnostic tests • Carotid intima-media thickness (IMT), as measured by Doppler ultrasound • Coronary/cerebral arterial calcification Platelet aggregability Bleeding and coagulation times Ejection fraction Incidence of metabolic syndrome and change in 10-year Framingham risk profile

Table 4. Study inclusion criteria (continued)

KQ 3 Harms	Clinical adverse events • Serious adverse events (composite outcome)[c] • Neurologic adverse events (e.g., neuropathy, seizure) • Allergic reactions (e.g., anaphylaxis, skin, transient acute airway disease) • Gastrointestinal adverse events (e.g., diarrhea, constipation, nausea/vomiting) • Clinically significant bleeding (e.g., intracerebral/intraventricular, gastrointestinal, hematuria) • Withdrawal due to adverse events • Other reported important clinical adverse events	Organ toxicity • Liver (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], or hepatitis) • Renal (blood urea nitrogen [BUN], creatinine, glomerular filtration rate [GFR]) • Bone marrow (e.g., leukopenia, anemia, neutropenia, thrombocytopenia) Fasting blood glucose Hemoglobin A_{1c} QT interval Other harms
KQ 4 Pharmacokinetic and pharmacodynamic outcomes	Absorption • Bioavailability (F), maximum drug concentration (C_{max}) and time to C_{max} (t_{max}) (latter two were added post hoc) Area under the concentration curve (AUC)	Distribution • Volume of distribution (Vd; e.g., in L/kg) Metabolism/Excretion • Clearance, elimination constant (K_{el}), half life ($t_{1/2}$)
Timing		
KQs 1–4	No restrictions have been prespecified based on the timing of an intervention and/or duration of length of followup of the studies.	This will be considered as a dose (or exposure) response modifier in the assessment of heterogeneity and applicability.
Setting		
KQs 1–4	No restrictions have been prespecified based on the setting of the studies.	This will be considered in the assessment of heterogeneity and applicability.
Study Design		
KQs 1–4	Experimental (randomized or nonrandomized controlled trial) and observational (cohort, case-control, cross-sectional) comparative studies with independent (concurrent or historical) control group including at least five participants.	For KQ 4, studies employing participants as their own control were also eligible (*post hoc* decision).
Report Characteristics		
KQs 1–4	No limits on publication year or status Publication language: Systematic reviews: limited to English	Primary studies: limited to the English language or German

Abbreviations: CVD = cardiovascular disease; KQ = Key Question.

Data Extraction and Data Management

Prior to data abstraction, we iteratively developed and pilot tested a standardized data extraction form. One reviewer extracted relevant data from each study and a second reviewer independently verified data from a 10 percent random sample of studies. In contrast with data pertaining to other Key Questions, where errors were few and sporadic (less than 0.5 percent), we noted some missed harms outcomes; therefore a second reviewer verified that all reported outcomes data of interest were extracted. Before this harms data verification was carried out, we clarified understanding of the reporting of harms. For example, we decided that when authors reported regular laboratory harms surveillance by testing for liver enzymes, glomerular filtration

rate, blood urea nitrogen and serum creatinine, and then disclosed that no adverse events were identified, zero patients with events of raised levels of these enzymes should be extracted. Likewise a statement that no thrombotic event was identified was extracted as zero patients with stroke, angina and myocardial infarction. We could not generate extractable harms data from reports stating for example, "no significant adverse events were observed," "no adverse effects of clinical importance occurred," or "all remaining adverse events were mild in severity." We extracted all harms data, not merely those thought to be drug related. Discrepancies in data extractions were resolved through discussions or with a help of third reviewer. Data extractors were not blinded to study information. If a study was reported in multiple publications, we extracted data from the latest and/or most complete publication and supplemented it with data from companion publications, as appropriate. We sought additional information from authors, when necessary. Data were input into DistillerSR.[128] During the data extraction process, one reviewer with clinical background rated study populations' 10-year CHD risk as per Table 5 below, according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP, ATP III) guidelines.[24] When all participants were healthy non-smokers, study level 10-year CHD risk was categorized as low.

Table 5. Ten-year coronary heart disease risk strata used to categorize study participants

Category		Details
High risk (10-year risk >20%)	A	Participants with established coronary heart disease, i.e., anyone or more of the following: *coronary death, acute coronary syndromes, myocardial infarction, angina, heart failure, and coronary artery procedures (angioplasty or bypass surgery)*
	B	Participants with noncoronary form of atherosclerotic disease, i.e., anyone or more of the following: *peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease (transient ischemic attacks or stroke of carotid origin or > 50% obstruction of a carotid artery)*
	C	Those diagnosed with diabetes or those reported in the paper as high risk according to NCEP ATP III criteria
Moderate to moderately high risk (10-year risk <10% to maximum of 20%)		Two or more of the following risk factors in >80% of participants: *cigarette smoking, hypertension (BP ≥140/90 mmHg or on antihypertensive medication), low HDL-C (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years), age (men ≥45 years; women ≥55 years)*
Low risk (0-1 risk factors)		Zero or just one of the above risk factors
Mixed risk		Participants clearly in more than one of the above categories
Unclear risk		Participants could be in one or a mix of the above categories

Abbreviations: BP = blood pressure; CHD = coronary heart disease; HDL-C = high density lipoprotein-cholesterol; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.

There was some additional attrition after studies were included during screening. Of the included studies, we extracted data when the following additional criteria were met:

- The dietary supplement was added to one or more cardiovascular drug(s) that were all taken by 100 percent or the majority (at least 80 percent) of participants in randomized controlled trials;
- Nonrandomized controlled trials, or observational studies reported effect estimates reflective of a supplement plus drug(s) versus drug(s) alone comparison (or with another supplement);

- Studies reported, or data could be obtained from authors, for at least one relevant outcome;
- The design of the study was lower in the hierarchy of evidence (i.e., nonrandomized experimental or observational study in presence of higher RCT evidence), and did not meaningfully add (by not being a longer-term or pragmatic study reporting conclusive results) to the already included evidence from a higher study design category;
- Studies were on a cardiovascular drug not marketed in the U.S.A.;
- Dosing of the dietary supplement was specified.

Remaining studies were transparently eliminated from data synthesis with reasons.

Extracted Data Elements

The following elements were extracted:

- Study and report characteristics (first author, study design, study setting, duration of followup, year and language of publication, funding source, treatment sequence generation, treatment allocation concealment, use of blinding)
- Population characteristics (inclusion/exclusion criteria, number of enrolled and analyzed participants, age, gender, ethnicity/race, health status, comorbidities, baseline nutrient exposures and/or background diet, methods used to assess baseline nutrient exposures, specific cardiovascular drugs and drug classes, drug doses, dose regimens, duration of treatment, potential confounders such as blood pressure, concomitant medication, smoking, lipid levels, number and reasons for withdrawals or drop-outs)
- Intervention characteristics (name, brand, and country of manufacturer of a dietary supplement or extract, license/registration of the product in the country of manufacture, source from which a dietary supplement or extract was manufactured, method of authentication, dosage regimen and quantitative description, dose form, qualitative testing for authenticity of herbal species, purity assessment for contamination/substitution, standardization, storage conditions and length, methods and instruments for assessing nutrient-intake exposures including validation by using nutrient biomarkers)
- Control (comparator) intervention characteristics
  - Placebo - description/definition in placebo-controlled trials, duration of treatment, similarity of treatments)
  - Other dietary supplement - same data as above
- Outcomes
  - Continuous measures (mean baseline and final values, within-treatment arm mean change, between-treatment arm mean difference, standard deviation, if reported means – the corresponding variance, standard error, 95 percent confidence interval)
  - Binary outcomes (number of participants with an event, risk of an event, odds of an event, risk ratio, odds ratio, hazard ratio, variance, standard error, 95 percent confidence interval, crude or adjusted measures of effect)
  - Definitions
  - Measurement method(s)
  - Timing of measurement
  - Data analysis details
  - Statistical test used

- Regression models (model type, covariates)

For systematic reviews, we planned to extract data on the research question, search strategy, design of individual studies included in a review, risk of bias assessment methods, population characteristics (inclusion and exclusion criteria, type of cardiovascular drug intake), and treatment characteristics (name and type of dietary of supplement).

Assessment of Study Risk of Bias and Quality of Systematic Reviews

Risk of bias of individual studies was assessed according to outcomes. One reviewer assessed risk of bias of all individual primary studies (randomized trials, nonrandomized controlled trials, cohort, and case-control studies). The risk of bias for gradable outcomes was verified by two reviewers, while a random ten percent of risk of bias assessment was verified for other outcomes. Disagreements were resolved by discussions with a third team member.

We used generic criteria to assess study risk of bias (Table 6). These criteria estimate risk of bias across five domains (selection bias, performance bias, attrition bias, detection bias, and other bias). The domains were tailored according to study design. For example, specific sub-domains such as randomization sequence generation were assessed only for randomized trials (parallel arm and crossover). Crossover randomized trials were assessed with the following additional criteria: appropriateness of crossover design; washout period (the length of time had to be at least 3 times the half life of drug elimination); and the report of appropriate data analysis (i.e., based on within-subject differences). The subdomain of blinding (within the Performance Bias domain) of participants, healthcare providers, and outcome assessors to treatment allocation was assessed only for experimental designs (i.e., randomized and non-randomized trials). We assessed the completeness of outcome data (i.e., attrition bias due to loss to followup or withdrawals) by comparing the number of participants who entered the study with the number of participants reported in outcome table(s). We then assessed whether there was complete followup of all participants, small lost to followup (less than 20 percent) or differential lost to followup.

Other forms of bias assessed included potential financial conflict of interest and selected criteria from the McMaster Quality Assessment Scale of Harms (McHarm).[25] All domains had response options of "Yes," "No," or "Unclear" with allowance for justifications of such judgments. For each gradable outcome in a study we provided an overall risk of bias rating designated as high, moderate, or low (Table 7). In order to be classified as high risk of bias, a study must have demonstrated some apparent and major flaw (within that study design category) that would invalidate results.

Table 6. Criteria for risk of bias assessment

Criteria	Experimental Controlled Trials (RCT and non-RCT)	Observational Controlled Studies	Uncontrolled Experimental Studies
Selection Bias			
Appropriateness of participant selection*		X	X
Randomization sequence generation†	X		
Allocation concealment	X		
Control for important baseline/prognostic factors‡: restriction, similarity of groups at baseline, matching, and/or adjustment in the analysis	X	X	
Performance Bias			
Purity/standardization of dietary supplement§	X	X	X
Blinding of subjects and providers to treatment allocation	X		
Attrition Bias			
Completeness of outcome data (attrition and exclusions) with focus on differential loss to followup or overall high loss to followup and potential for associated confounding‡	X	X	X
Detection Bias			
Blinding of outcome assessors to treatment or exposure status in experimental or cohort studies or blinding of exposure assessors to case/control status in case-control studies.	X	X	X
Extent to which valid outcomes were described¶	X	X	X
Other			
Financial conflict of interest	X	X	X
Criteria for assessment of harms (from the McHarm checklist[130]): prespecified and valid definition of harms, mode of harms collection (e.g., active or passive, standard tool)	X X	X	

Notes: *Appropriateness of participant selection included whether participants from each arm were from the same or different populations, the use of adequate definitions and measurements of exposed/nonexposed or case/control status and demonstration that outcomes were not present at beginning of prospective studies.
†For RCTs only.
‡Important baseline/prognostic factors evaluated: age, gender, race, baseline diet/nutrient exposures for dietary substance of interest, smoking, concomitant medications/supplements, and health status, including comorbidities and LDL-C and blood pressure if these measures were not included as study outcomes.
§Description of the source, methods of extraction, and constituents of the dietary supplement (e.g., quantification or quality assurance/standardization of dose/purity, stability and length of storage).
¶Definition and methods used to assess outcome including timing, and comparability of assessment across study arms.
Abbreviation: RCT = randomized controlled trial.

Table 7. Overall risk of bias ratings

Low risk of bias. These studies have the least bias and results are considered valid. Examples of characteristics of these studies include the following: a formal randomized controlled design; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; low dropout rate; and clear reporting of dropouts.
Moderate risk of bias. These studies are susceptible to some bias, but it is not sufficient to invalidate the results. They do not meet all the criteria required for a rating of low risk of bias because they have some deficiencies, but no flaw is likely to cause major bias. Study deficiency may be missing information, making it difficult to assess limitations and potential problems.
High risk of bias. These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Methodological quality of included systematic reviews was assessed using the AMSTAR tool,[131] which rates each systematic review with a "Yes," "No," "Cannot answer," or "Not applicable" across the 11 domains. The overall assessment of quality for each systematic review was based on a reviewer's overall judgment given their responses to the individual AMSTAR items, and had three overall ratings: "Good," "Fair," or "Poor." In general, "Good" quality systematic reviews were defined as those having few or no methodological/reporting shortcomings (low risk of bias). "Fair" quality systematic reviews were defined as those having some methodological flaws although not sufficient to seriously bias or invalidate the review results. "Poor" quality systematic reviews were defined as those having serious flaws sufficient to seriously bias or invalidate the review results, and were not eligible for inclusion in the evidence synthesis. An independent reviewer helped to resolve any discrepancies regarding the AMSTAR tool assessment between the reviewers.

Grading the Strength of the Body of Evidence

In principle, a body of evidence originating in randomized trials starts with a presumed high strength of evidence, and is downgraded across the domains when there is important overall risk of bias of contributing studies, inconsistency in direction of intervention effect, indirectness of the outcome of interest (e.g., a surrogate outcome, rather than a clinical health outcome) and imprecision in effect estimates of an extent that neither important benefit nor harm can be ruled out. For nonrandomized studies, the body of evidence starts with a presumed low strength of evidence but may be upgraded across certain domains. The strength of a body of evidence was graded based on the following four domains, per previously published guidance: overall risk of bias by outcome, consistency, directness, and precision.[26] A methodologist and a content expert graded the strength of the body of evidence as "High," "Moderate," "Low," or "Insufficient" (Table 8). A third methodologist with clinical background adjudicated to resolve disagreements. Given the results we found, optional domains such as dose-response association and existence of confounders were not applicable in this comparative effectiveness review. Given the uncertainties involved in interpreting asymmetry tests for publication bias in most reviews, especially in presence of heterogeneity in effect estimates, we did not plan to investigate publication bias in this review.[102,103]

The strength of evidence was graded insufficient when there was no evidence for an outcome, when direction of estimates were inconsistent between studies without an identifiable cause, or when the body of evidence from the contributing study/studies was underpowered for the outcome of interest (imprecise estimate). That is, when the effect estimate associated with

confidence intervals was not only nonsignificant, but wide enough such that the clinical action would differ if the upper versus the lower boundary of the CI represented the truth, we rated the estimate as imprecise, reflecting our uncertainty about clinically important benefits, harms or clinically unimportant differences in effect estimates between the contrasting interventions.

Customarily only a subset of important outcomes are chosen to grade the strength of evidence—outcomes that are most meaningful for decision making given a specific Key Question.[26] In consultation with the Technical Expert Panel (TEP), the review team chose the following outcomes for grading the strength of the body of evidence:

Key Question 1. Mortality (all-cause and vascular death), myocardial ischemic events (fatal myocardial infarction, nonfatal myocardial infarction, unspecified myocardial infarction, and acute coronary syndromes), cerebrovascular events (hemorrhagic/ischemic/unspecified stroke), quality of life, hospitalization, arrhythmia, and clinical outcomes of peripheral arterial disease

Key Question 2. Blood pressure (systolic and diastolic), lipid profile (low density lipoprotein, high density lipoprotein, and non–high density lipoprotein cholesterol; and triglycerides), international normalised ratio for coumarin derivatives, incidence of metabolic syndrome, and change in 10-year Framingham risk profile.

Key Question 3. Serious adverse events (composite outcome according to the Food and Drug Administration definition of serious adverse events),[27] withdrawal due to adverse events, clinical bleeding (intracranial, gastrointestinal, genitourinary, subretinal, etc.), renal dysfunction (e.g., proteinuria, elevated creatinine, need for transplant, glomerular filtration rate), hepatotoxicity (elevated enzymes or fulminant failure), and QT prolongation

Key Question 4. Area under the plasma cardiovascular drug concentration-time curve (AUC), maximum drug concentration (C_{max}), drug half-life($t_{1/2}$), and oral clearance.

Table 8. Strength of evidence grade and definition[26]

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect, and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect, and is likely to change the estimate.
Insufficient	Evidence is either unavailable or does not permit a conclusion.

Applicability

We followed previously published guidance, and summarized the population, intervention, comparator, outcome, timing and setting (PICOTS) to assess the applicability of the body of evidence for outcomes or categories of similar outcomes.[28] We considered age, race/ethnicity and gender representation; strictness of exclusion criteria; 10-year CHD risk; study setting; whether or not the cardiovascular drug(s) was administered in therapeutic doses; frequency of monitoring of adherence; surrogacy of outcomes; and short versus long-term treatment duration as important aspects determining applicability. Applicability is reported for all conclusive results. When direction of effect was indeterminate either because of lack of evidence or under powered evidence (with imprecise and nonsignificant data), applicability of evidence was not reported. Studies that evaluated representative patient populations in usual or routine care conditions lasting long enough to meaningfully measure health outcomes of both benefit and harm while comparing the intervention with standard of care were considered pragmatic or

effectiveness studies as opposed to efficacy studies examining intermediate efficacy outcomes in highly selected patients less likely to experience harms.[29]

Data Synthesis and Analysis

All analyses compared the combination of dietary supplement plus cardiovascular drug with cardiovascular drug alone (or plus placebo or another dietary supplement). The decision to meta-analyze or qualitatively synthesize outcome specific evidence from primary studies depended upon the presence or absence of homogeneity in clinical and methodological characteristics across studies, and the statistical format of outcome reporting. For pharmacokinetic outcomes in Key Question 4, we followed the FDA guidance for analysis and interpretation of drug interaction studies.[30] Because data are usually skewed, the guidance recommends that the pharmacokinetic outcomes in drug interaction studies be reported, after log transformation, as geometric mean ratios (GMR) with their 90 percent confidence intervals (CI) based on a procedure termed the 'two one-sided test procedure.' A conservative margin of bioequivalence for most drug interactions is recommended to be between the lower and upper bound 90 percent GMR CI of 0.8 and 1.25. We refer to this as the zone of clinical nonsignificance.

Meta-analysis was considered, or studies were considered suitable for pooling if they were randomized trials that included similar populations in terms of demographics, morbidity, and intake of cardiovascular drug(s) or classes of drugs (e.g., participants aged 65 years or younger, healthy or with diabetes or history of myocardial infarction, use of warfarin or nitrates), compared the same type of dietary supplement (e.g., niacin, oral magnesium, fish oil) versus comparator treatment (e.g., other dietary supplement, no treatment, placebo), and reported the same outcome measures in the same statistical format (e.g., mean difference or geometric mean ratios [GMR]). Where risk of bias differed across studies, this was explored by sensitivity analyses. We did not plan to meta-analyze observational and experimental studies; however, we pooled parallel with crossover randomized studies.[32] We did not consider pre-crossover data for synthesis except when it was judged that the treatment given to participants in a given crossover trial was not appropriate for the condition under consideration.[31,32] Similarly, we did not pool crossover trials that had not employed sufficient washout period between the two treatment periods because of bias arising from carryover treatment effects. We planned not to meta-analyze observational studies because of the differences in adjustment for confounders and residual confounding.

We used a DerSimonian and Laird random-effects model to generate pooled estimates of relative risk (RR) if an outcome was measured on a dichotomous scale, and weighted between-group mean difference (for end points and within group changes), if an outcome was measured on a continuous scale.[33] The measure of variability of the pooled estimates was a 95 percent confidence interval. Statistical heterogeneity was assessed using Cochran's Q (α=0.10) and the I^2 statistic. All analyses were performed using *Comprehensive Meta Analysis* version 2.2.057 (New Jersey, USA); StatsDirect Ltd. *StatsDirect* statistical software,[132] and *R: A Language and Environment for Statistical Computing*, Foundation for Statistical Computing.[133]

When studies failed to report summary statistics (e.g., mean score, standard deviation, standard error), we calculated the needed parameters if individual participant data were provided. If a study reported only a standard error of the mean response, we converted it into a standard deviation. Trials were not meta-analyzed if the mean and standard deviation could not be ascertained. Trials with obvious between-group baseline imbalance in a continuous outcome

were not pooled unless the mean change from baseline and corresponding standard deviation for the compared study groups were reported.

We used the Peto odds ratio method when event rates were less than1 percent.[32] For studies with zero events in some arms or sparse data overall, we pooled using the fixed effects Mantel-Haenszel method without continuity correction.[34] Studies with zero events in both arms were excluded from meta-analysis.[32]

Outcome results were considered inconclusive when the pooled estimate or the single contributing study estimate had confidence intervals wide enough to incorporate both important benefit and harm (i.e., type II error suggesting underpowered studies unable to precisely conclude benefit, harm or no difference between treatments). When studies could not be pooled, for example when similar outcomes were reported in different statistical formats, or study results pointed in opposite directions, results were also labelled as inconclusive. When inconclusive results were associated with a gradable outcome, strength of evidence was deemed insufficient.

Exploration of heterogeneity was planned to examine clinical and methodological diversity, to answer subquestion (a) of the four Key Questions by carrying out subgroup and sensitivity analyses, and/or meta-regression if there was a sufficient number of studies (4 studies for each categorical subgroup variable, and 6 to10 for a continuous subgroup variable).[32] This was not carried out because of a paucity of studies for each outcome.

Prespecified clinical subgroups included: gender (male, female), ethnicity (including Hispanic, Asian, African American, and Native American), age (those age 65 years and above, and 80 years and above), baseline health status (healthy volunteers, participants according to coronary heart disease risk category, participants at risk for cardiovascular disease, participants with known cardiovascular disease, participants with diabetes, participants with hepatic or renal dysfunction or end-stage renal disease, participants taking a cardiovascular drug for an indication other than cardiovascular disease), and genotypic polymorphisms (e.g., in CYP2D6, 2C9, 2C19).

Sensitivity analyses were to be conducted to explore whether the effect estimates of dietary supplement treatment were influenced by methodological variables such as overall study risk of bias, adequacy of participant selection, important confounding, blinding of outcome assessors, purity/dose/stability of a dietary supplement, or duration of treatment or followup.

Statistical interaction was to be investigated for all four Key Questions. To determine measureable interactions between cardiovascular drugs and dietary supplements, we followed the procedures described below:

- If a study explicitly examined interaction between cardiovascular drug and dietary supplement, then we extracted the study's findings along with the method for assessing interaction.
- When studies did not investigate statistical interaction between the dietary supplement plus cardiovascular drug group and the cardiovascular drug alone group, we carried out test for interactions when data for at least four groups were reported. These groups had to be supplement plus cardiovascular drug group, supplement alone group, cardiovascular drug alone group, and a common comparator placebo or no treatment group. For studies that presented dichotomous data we calculated the synergy index (S).[35]

$$\text{Synergy Index (S)} = \frac{1 - RR_{11}}{1\text{-}RR_{01}RR_{10}}$$

Where RR_{11} is the relative risk for subjects exposed to cardiovascular drug and dietary supplement, and RR_{01} and RR_{10} are the relative risks for subjects exposed to cardiovascular drug

alone and dietary supplement alone respectively. An S-index greater than 1 describes a positive interaction (synergism) and an S-index less than 1 indicates a negative interaction (antagonism).For continuous outcomes, individual patient data were needed to have been modeled in a linear regression with an interaction term.

Definitions

Pharmacokinetic Measurements: Absorption, Distribution, Metabolism, and Excretion. Adapted from Rowland and Tozer 1995[134]

Pharmacokinetics

The study of the mechanisms of absorption, distribution, metabolism and elimination of an administered drug in the living organism

Absorption

Absorption can refer to any route of administration except intravenous administration (i.e., enteral, subcutaneous, transdermal).

1. Fractional bioavailability (F): the fraction of a non-intravenously administered dose of a drug that reaches the systemic circulation (unit: percent)
2. Time to maximum concentration (t_{max}): the time at which the maximum plasma concentration of a drug occurs following administration of an extravascular dose (unit: minute or hour)
3. Maximum concentration (C_{max}): the highest drug concentration in plasma after an extravascular dose (unit: $\mu g\ mL^{-1}$)
4. The area under the plasma drug concentration-time curve (AUC_{0-t}): the measure of an exposure of plasma to a drug over a given time period. It is calculated as the area under the serum concentration-time curve which is based on multiple drug concentration measurements at various time points (unit: $\mu g\ mL^{-1}$hour)

Distribution

Volume of distribution (Vd) is the apparent volume into which a drug distributes in the body at equilibrium. Alternatively, it is the volume of plasma at the drug concentration required to account for the entire drug in the body (unit: L/kg) Volume is not limited to plasma. For example, volume of distribution will exceed plasma volume or total body water volume for highly lipophylic drugs.

Metabolism/Excretion

1. Clearance: the volume of plasma in the vascular compartment cleared of drug per unit time by the processes of metabolism and excretion (unit: mL/hour)
2. The elimination half-life ($t_{1/2}$): the time required to reduce the plasma concentration of a drug or the total amount of drug in the body to one half of its initial value (unit: hour)

Results

Screening and Inclusion of Records

Overall, 33,224 records were identified by searches of databases after removing all duplicates. The PRISMA diagram in Figure 2 depicts the flow of retrieved records through the phases of screening and inclusion.

A total of 169 English publication studies were included after title/abstract, and full text screening. None of the 68 German publications screened at full text level met the eligibility criteria. Eighty-nine studies were subsequently excluded from the data synthesis for the following reasons:

- Proportion of population taking cardiovascular drugs was less than 80 percent, preventing accurate analysis of interaction of supplement and cardiovascular drug (n=72);
- No outcome of interest was reported (n=6)[135-140]
- Cardiovascular drug was not used in U.S.A. (n=4)[141-144]
- Dose of supplement was not reported (n=1)[145]
- Outcome data were reported only for the first period crossover (n=1)[146]
- A sequential study was not included in synthesis of evidence because higher quality randomized controlled trial (RCT) evidence was available for the same pharmacokinetic outcome, for the same drug-supplement combination (n=1)[147]
- No response was received to a data request made to authors (n=1)[148]
- High quality systematic review was of limited utility because it was out of date. Inclusion would have necessitated a de novo process for the included studies; (n=1)[149] (In two separate records).
- Observational study reported outcomes where higher level of evidence was available from RCT for the same outcomes (n=1)[150]

As a result, 80 reports were included in the evidence synthesis of this review and entered the quality assessment and data extraction. Among these, seven studies were reported in more than one publication, amounting to 18 records (Table 9). We identified one of these records as the primary report of the study and other(s) as a companion; however, relevant data from all related reports were used in the evidence syntheses. With this approach, 70 primary studies were included and are referenced accordingly in this review (Table 9). One of the included studies was observational,[88] two were controlled clinical trials,[62,79] and the remaining 66 studies were RCTs.

Twenty two RCT studies contributed to meta-analyses and the remaining were included in the qualitative syntheses of evidence.[36,37,40,44,53,67,68,73,74,76,77,83-86,91,93-96,151,152]

We contacted authors of two records requesting additional data or seeking data clarification.[39,148] One of the authors,[39] responded to our query and provided additional data which was incorporated in the evidence syntheses.

Comprehensive individual study data and quality assessment are presented in Appendix C.

Figure 2. PRISMA flow chart of study identification, screening, eligibility, and inclusion

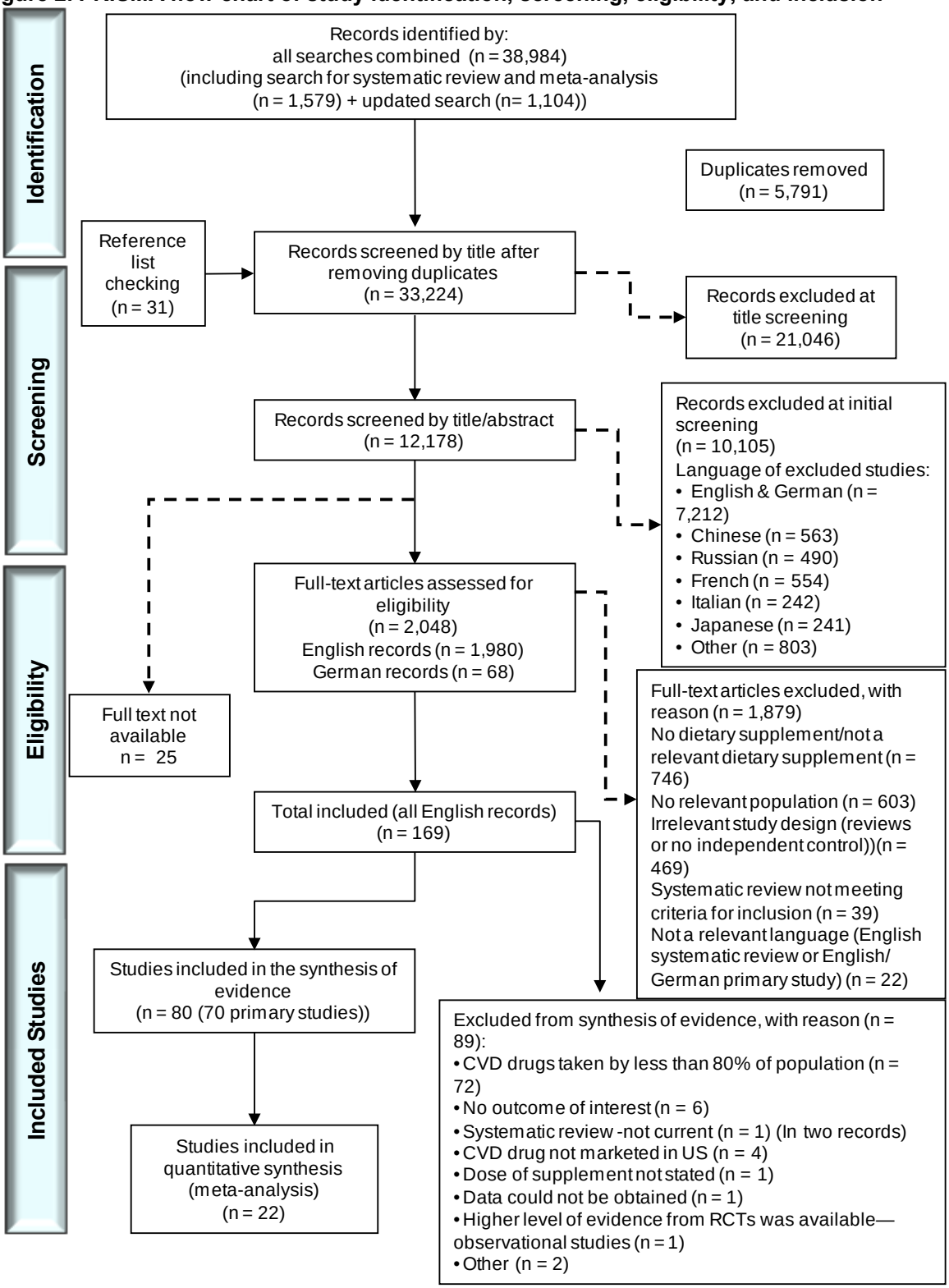


Table 9. Primary and companion records for studies with multiple reports

Primary Record	Companion Record(s)
Budoff 2004[63]	Budoff 2006[153]
Chan 2002[44]	Chan 2006, Chan 2003, Chan 2002, Chan 2010, Chan 2002, Chan 2002[138,154-158]
Davidson 2007[40]	Maki 2010[159]
Gardner 2007[66]	Chan 2002[157]
Nordøy 1998[160]	Nordøy 2000[76]
Nordøy 2003[92]	Nordøy 2001[161]
Roth 2009[56]	Bays 2009[162]

Key Question 1. In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared to cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement[s]) on clinical cardiovascular effectiveness/efficacy outcomes (e.g., mortality and specific cardiovascular or cerebrovascular conditions such as myocardial infarction [MI] and stroke)?
a. Do the effect estimates of clinical cardiovascular outcomes vary by age, ethnicity, gender, or health status?
b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for clinical cardiovascular outcomes?

Overview

Twenty-one RCTs addressed Key Question 1.[36-56] No relevant data were available from observational studies. No evidence on clinical outcomes was found for *Echinacea*, garlic, ginger, ginseng, hawthorn, niacin (not more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, and vitamin D with or without calcium supplementation (Table 10). There was insufficient evidence for the gradable outcomes of hospitalization and those related to peripheral arterial disease across all supplement-cardiovascular drug(s) combinations, due to lack of data. A paucity of studies for each supplement-drug combination of interest precluded exploration of heterogeneity in terms of pre-identified subgroups (Key Question 1a). No study examined any statistical interaction between supplement and drug on clinical outcomes (Key Question1b). Table 11 summarizes characteristics of included studies and Table 12 summarizes their risks of bias. Below we report results separately for each supplement and cardiovascular drug combination, by outcomes for which evidence was available. We then grade the evidence for the prestated gradable outcomes, and summarize the PICOTS determinants of applicability for conclusive results across all outcomes—that is, when results were not impacted by the possibility of type II error. In all analyses, the intervention was administration of a dietary supplement along with one or more cardiovascular drug or class of drugs, while the comparator was administration of the drug or its class alone. Details of individual study characteristics, risk of bias and outcomes data are reported in Appendix C.

Table 10. Overview of availability of evidence for clinical outcomes—Key Question 1

Supplement and Cardiovascular Drug(s)	Outcome	Number of Studies
Coenzyme Q10		
Statins (*Dm)*	Adherence	1
ACE inhibitor with other CV drugs (*Dm)*	Mortality	1*
ACE inhibitor with other CV drugs (*Cs)*	Quality of life	1*
Ginkgo biloba		
Aspirin (*Dm)*	Mortality	1
Aspirin (*Cs)*	Other clinical outcomes	1 (NRS)
Magnesium (oral)		
Beta-blocker (*Dm)*	Myocardial infarction	1*
Omega-3 fatty acids/fish oils		
Statins (*Dm)*	Adherence	3*
	Mortality	1*
	Arrhythmia	1
	Other clinical outcomes	1 (exacerbation of CHF)
Calcium channel antagonist plus aspirin (*Dm)*	Myocardial infarction	1
	Procedures	1 (CABG and PCI)
	Other clinical outcomes	1 (Restenosis)
Aspirin plus dipyridamole plus calcium channel antagonist (*Dm)*	Other clinical outcomes	1 (Restenosis)
Aspirin plus dipyridamole plus calcium channel antagonist (*Cs)*	Other clinical outcomes	1 (Restenosis)
Aspirin (*Dm)*	Other clinical outcomes	1 (Graft occlusion†)
Warfarin (*Dm)*	Other clinical outcomes	1 (Graft occlusion)
Calcium channel antagonist (*Cs)*	Other clinical outcomes	1 (induced coronary vasospasm)
Fibrates (*Dm)*	Mortality	1
Vitamin E		
Aspirin (*Dm)*	Composite outcome	1
	Stroke	1
	TIA	1
Statin (*Dm)*	Adherence	1
Calcium channel antagonist (*Cs)*	Unstable angina	2
Vitamin K		
W (*Dm)*	Adherence	1
	Mortality	1
	Stroke	1

Notes: *At least one crossover RCT; † omega-3 fatty acids supplement also contained α-tocopherol
Abbreviations: ACE = angiotensin converting enzyme; CABG = coronary artery bypass grafting; CHF = congestive heart failure; Cs = outcomes data were continuous; Dm = outcomes data were dichotomous; NRS = neurologic recovery score; PCI = percutaneous coronary intervention; QoL = quality of life; RCT = randomized controlled trial; TIA = transient ischemic attack; UA = unstable angina.

Table 11. Summary of study characteristics for studies addressing clinical outcomes

Study Characteristic	Distribution
Sample CHD risk	Low 4.8% Moderate to moderately high 4.8% High 43% Mixed 14% Unclear 33%
Geographical region	North America 33% Europe 24% Australia/New Zealand 10% East Asia 14% Rest of Asia 10% NR 9%
Setting	Primary care/community 38% Specialty care 24% NR 38%
Duration	Mean 41 weeks (SD 112), range 2 weeks to 10 years
Total N randomized	Mean 1043(SD 4330), range 11 to 19,934, total across studies = 21895
Age	Mean age 56 years (SD 9)
Gender	Two trials exclusively in males,[44,52] and one in females.[39] Of the mixed gender studies, 60% included females representing less than 40% of study sample.
Race/Ethnicity	Eight studies reported race/ethnicity distribution. Most included a majority of Caucasian participants. One study included all Asians and another majority Hispanics.[50,55]

Abbreviations: CHD = cardiovascular heart disease; SD = standard deviation.

Table 12. Risk of bias and potential for conflict of interest for studies addressing clinical outcomes

Items	% of Total RCTs		
All RCTs (N=21)	**Yes**	**No**	**Unclear**
Adequate generation of allocation sequence	38	0	62
Allocation concealment	5	0	95
Comparability of groups	19	19	62
Purity of supplement	71	19	10
Blinding of allocated intervention	43	5	52
Adequately addressed missing data	52	0	48
Freedom from potential conflict of interest	24	33	43
Crossover RCTs (N=4)			
Suitability of crossover design for the study condition	100	0	0
Freedom from carryover effect	50	25	25
Appropriateness of statistical analysis for crossover design	0	50	50
Comparability of groups between periods 1 and 2	25	0	75
Freedom from bias introduced by dropouts	100	0	0

Abbreviations: N = total number; RCTs = randomized controlled trials.

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Coenzyme Q10

Coenzyme Q10 Plus ACE Inhibitors Versus ACE Inhibitors Alone

All-cause mortality and quality of life. These outcomes were reported in one crossover randomized placebo-controlled trial with a duration of 3 months, in 30, mostly male patients with left ventricular dysfunction, at a specialty center. Coenzyme Q10 (33 mg three times daily) plus maximally tolerated doses of angiotensin-converting enzyme (ACE) inhibitors was compared with ACE inhibitors alone. The majority of patients (i.e., greater than 80 percent) were also taking digoxin, furosemide, hydralazine and/or nitrates. A single death in the placebo group was noted.[54] No significant differences were noted in quality of life scores using the Minnesota "Living with Heart Failure" questionnaire (mean sum of all scores posttreatment 26.7±17.9 versus 26.5±18.7).It is not clear whether the statistical analysis incorporated within patient differences in order to fully utilize the robustness of this crossover design. The strength of evidence is summarized in Table 13.

Table 13. Strength of evidence for ACE inhibitors with or without coenzyme Q10—Clinical outcomes

Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Conclusions
All-cause mortality					
Moderate	NA	Direct	Imprecise	Insufficient	The study was grossly underpowered for this outcome
Quality of life					
Moderate	NA	Direct	Imprecise	Insufficient	No significant differences were noted. Type II error could not be excluded.

Abbreviations: ACE = angiotensin converting enzyme; NA = not applicable.

Coenzyme Q10 Plus Statins Versus Statins Alone

Adherence. A 12-week pilot study of limited internal validity (unclear adequacy of sequence generation, allocation concealment and blinding) assessed adherence to statins. A select group of patients with moderate to high 10 year coronary heart disease (CHD) risk and self reported statin associated myalgia were included. The trial did not demonstrate any difference in rates of adherence to simvastatin (10 mg/day to 40 mg/day) between add-on coenzyme Q10 (200 mg/day) and statin alone in patients with previous statin related myalgia. Adherence to simvastatin was 98 percent in both groups, but it is not clear how adherence was assessed.[38]

Ginkgo Biloba

Ginkgo Biloba Plus Antiplatelets Versus Antiplatelets Alone

All-cause mortality and neurologic recovery score. These outcomes with *G.biloba* extract (40 mg every six hours) were investigated over 4 weeks in 62 South Asian patients with previous ischemic stroke, who were on regular aspirin and/or pentoxphilline.[48] Trial limitations included

unclear allocation concealment, attrition bias, and potential imbalance between groups in terms of the nature of neurologic deficits. The trial was clearly underpowered and of too short duration to detect differences in all-cause mortality and neurologic improvement in the modified Mathew's scale. There were no deaths and no significant differences in neurologic recovery score after one month of treatment. The mean relative change from baseline in linear transformed Mathew's scale averaged approximately 20 in both groups, and showed improvement over time (mean difference (MD)) 0.81 [95 percent confidence interval (CI) -9.12, 10.74]).[48] Strength of evidence is summarized in Table 14.

Table 14. Strength of evidence for aspirin and/or pentoxphilline with or without *Ginkgo biloba*—Clinical outcomes

Outcome	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Conclusions
All-cause mortality	Moderate	NA	Direct	Imprecise	Insufficient	The study was grossly underpowered for this outcome

Abbreviation: NA = not applicable.

Oral Magnesium

Magnesium Plus Beta-Blockers Versus Beta-Blockers Alone

Myocardial infarction. A single event of myocardial infarction was observed in a randomized crossover controlled trial of oral magnesium aspartate (365 mg daily) or placebo administered daily for 8 weeks to a selected group of 40 hypertensive patients with no comorbidities, on therapeutic doses of beta-blockers. The trial was underpowered to detect differences in clinical outcomes and lacked a clear description of several risk of bias items.[42] Strength of evidence is summarized in Table 15.

Table 15. Strength of evidence for beta-blockers with or without magnesium—Clinical outcomes

Outcome	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Conclusions
Myocardial Infarction	Moderate	NA	Direct	Imprecise	Insufficient	The study was grossly underpowered for this outcome

Abbreviations: NA = not applicable.

Omega-3 Fatty Acids/Fish Oils

Omega-3 Fatty Acids/Fish Oils Plus Statins Versus Statins Alone

Mortality, arrhythmia, and adherence to medication. These outcomes were assessed in five trials.

Zero mortality in one randomized crossover pharmacokinetic study of omega-3 fatty acids (4 g/day) with atorvastatin (80 mg/day) versus atorvastatin monotherapy, over 14 days in 50 healthy nonsmoking adults provided insufficient evidence.[36]

In another study, a single case of supraventricular tachycardia (in the add-on 4 g/day omega-3 fatty acid group) in an 8-week efficacy trial in 256 highly selected dyslipidemic patients on statin therapy constituted insufficient evidence for the arrhythmia outcome.[40] There was also one case of exacerbation of congestive heart failure in the add-on omega-3 fatty acid group.[40]

Rates of adherence to statin therapy were reported in three efficacy trials of 6 to 12 weeks duration in highly selected patient populations with dyslipidemia with or without add-on 4 to 9 g/day of omega-3 fatty acids. All studies had unclear risk of bias for adequacy of sequence generation and allocation concealment. Adherence to statin therapy was judged by pill count. No differences in statin adherence rates were noted between both groups – across all three studies, adherence rates in the two groups were equal to or greater than 95 percent.[37,44,53] Strength of evidence is summarized in Table 16.

Omega-3 Fatty Acids/Fish Oils Plus Cardiovascular Drugs Versus Cardiovascular Drugs Alone

Mortality, myocardial infarction, cardiovascular procedures, restenosis, coronary vasospasm, and graft occlusion. These outcomes were assessed with various cardiovascular drugs. Insufficient evidence from single efficacy trials with sparse events did not demonstrate a difference in the outcome of all-cause mortality when study cardiovascular drugs were either aspirin (291 high risk patients followed for 1 year, with nine deaths), warfarin (319 high risk patients followed for 1 year with 5 deaths), or fenofibrate (unclear 10 year CHD risk in 167 participants with hypertriglyceridemia followed for 8 weeks with no deaths) (Table 16).[47,56]

In a 6 month efficacy study of omega-3 fatty acids daily (1.8 g eicosapentaenoic acid plus 1.2 g docosahexaenoic acid) in addition to therapeutic doses of aspirin plus calcium channel antagonist versus the latter two drugs alone, six cases of acute myocardial infarction were identified among 58 patients who had undergone successful coronary angioplasty (relative risk [RR] 1.70 [95 percent CI 0.32, 8.84]) (Table 16).[51] The same study reported non-significant differences among 26 patients requiring subsequent angioplasty (RR 1.35 [95 percent CI 0.68, 2.70]) and four who underwent coronary artery bypass graft (RR 0.84 [95 percent CI 0.12, 5.78]).[51]

Table 16. Strength of evidence for cardiovascular drug(s)* with or without omega-3 fatty acids/fish oils—Clinical outcomes

	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Conclusions
Statins						
All-cause mortality and arrhythmia	Moderate	NA	Direct	Imprecise	Insufficient	Studies were grossly underpowered for both outcomes
Aspirin, warfarin or fenofibrate						
All-cause mortality	Moderate	NA	Direct	Imprecise	Insufficient	Studies were grossly underpowered. Aspirin+omega-3 fatty acids RR 1.29 (95% CI 0.35, 4.72) Warfarin+omega-3 fatty acids RR 1.25 (95% CI 0.21, 7.38) Fenofibrate+omega-3 fatty acids RR was not estimable because of zero deaths

Table 16. Strength of evidence for cardiovascular drug(s)* with or without omega-3 fatty acids/fish oils—Clinical outcomes (continued)

	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Conclusions
Aspirin and calcium channel antagonist						
Acute myocardial infarction	Moderate	NA	Direct	Imprecise	Insufficient	Single study, underpowered for clinical events

*Cardiovascular drugs were aspirin, warfarin, or fenofibrate
Abbreviations: CI = confidence interval; NA = not applicable; RR = relative risk

Coronary artery restenosis. Rates of restenosis were investigated with coronary angiography three to four months following successful angioplasty, in 82 highly selected male patients. Although it was not an a priori outcome for this review, we are reporting restenosis because of its clinical relevance.[52] Restenosis was defined as 50 percent narrowing of the luminal diameter. Outcome assessors were blinded to treatment allocation. In this randomized trial, patients were treated either with a daily dose of 3.2 grams of eicosapentaenoic acid added to therapeutic doses of the combination of aspirin, dipyridamole, and calcium channel antagonists, or the latter three drugs in combination. Significantly lower rates of restenosis were observed in the treatment group (RR 0.40 [95 percent CI 0.20, 0.82]); however, the mean percentage reduction in luminal diameter was not significantly different between the two groups. These results conflict with a similar trial conducted in India in 107 patients, that found no significant difference in rates of early restenosis (RR 1.33 [95 percent CI, 0.76, 2.30]).[51] Restenosis rates were not significantly influenced by gender or age (p greater than 0.05 for interaction).[51] Possible explanations for these differing trial results, besides differences in patient populations, include that in the Indian trial patients were not treated with dipyridamole, and in the same trial followup angiography was only conducted in those with angina symptoms or a positive exercise test (unlike the previously discussed trial that undertook followup angiography in all patients), thereby potentially biasing the results by excluding healthier individuals.

Coronary vasospasm induced by intracoronary acetylcholine was studied in 22 Japanese patients with variant angina randomized to 4 months treatment with therapeutic doses of diltiazem plus eicosapentaenoic acid (1.8 g/day), or diltiazem alone. Patients served as their own controls. Acetylcholine induced vasoconstriction, measured as percentage change in post nitrate coronary artery diameter compared to the baseline response, was significantly improved in those receivingomega-3 fatty acids but not in the control group.[50] The report was unclear as to how the randomization sequence was generated, allocation was concealed, and outcome assessors were blinded. Based on the reported data, our comparative analysis of posttreatment percentage change in coronary artery diameter following intracoronary acetylcholine injection showed nonsignificant differences between supplement plus diltiazem and diltiazem alone groups (percentage mean difference in spastic segment was -1.3 [95 percent CI-10.34, 7.74)] and in nonspastic segments was 0.9 [95 percent CI -4.56, 6.36])

Coronary bypass graft occlusion rates were evaluated after one year, in 610 participants on either aspirin (300 mg/day) or warfarin (target prothrombin International Normalized Ratio [INR] 2.5-4.2), in conjunction with placebo oromega-3 fatty acids (4 g/day) plus α-tocopherol (15 mg/day) as an anti-oxidant.[47] Graft occlusion was predefined as visualization of the lack of contrast flow on followup angiography. An important limitation of this randomized trial was its lack of clear reporting of adequate allocation concealment. No significant differences in graft occlusion rates were noted, but studies were underpowered to detect a difference (Table 17).

Table 17. Graft occlusion rates with omega-3 fatty acids/fish oils and α-tocopherol—Clinical outcomes

Occlusion Subtype	Drugs and Supplements	RR (95% CI)
Internal mammary artery graft occlusion		
	Warfarin+ omega-3 fatty acids+ α-tocopherol	1.25 (0.70, 2.23)
	Aspirin+ omega-3 fatty acids+ α-tocopherol	1.03 (0.50, 2.14)
Vein graft occlusion, distal anastomosis		
	Warfarin+ omega-3 fatty acids+ α-tocopherol	0.84 (0.66, 1.07)
	Aspirin+ omega-3 fatty acids+ α-tocopherol	0.83 (0.65, 1.06)
Patients with > 1 occluded vein graft		
	Warfarin+ omega-3 fatty acids+ α-tocopherol	0.79 (0.62, 1.01)
	Aspirin+ omega-3 fatty acids+ α-tocopherol	0.89 (0.69, 1.15)

Abbreviations: CI = confidence interval; RR = relative risk.

Vitamin E (α-Tocopherol)

Vitamin E Plus Cardiovascular Drug Versus Cardiovascular Drug Alone

Stroke, transient ischemic attacks, adherence, angina, myocardial infarction, and vascular death. These outcomes were assessed in five trials.

In an efficacy trial, 100 highly selected patients with previous reversible or irreversible ischemic neurologic deficit and good performance status presenting to a university hospital were randomized to vitamin E (0.4 g/day) plus aspirin (325 mg/day) versus aspirin alone for a period of two years. Nine patients experienced outcomes of stroke (seven ischemic, two hemorrhagic), and three experienced recurrent transient ischemic attack, precluding definitive conclusions (Table 18).[49]

Table 18. Strength of evidence for aspirin with or without vitamin E—Clinical outcomes

	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Conclusions
Aspirin						
All stroke, ischemic stroke, hemorrhagic stroke and transient ischemic attacks	Moderate	NA	Direct	Imprecise	Insufficient	Small efficacy trial clearly underpowered for clinical events

Abbreviation: NA = not applicable

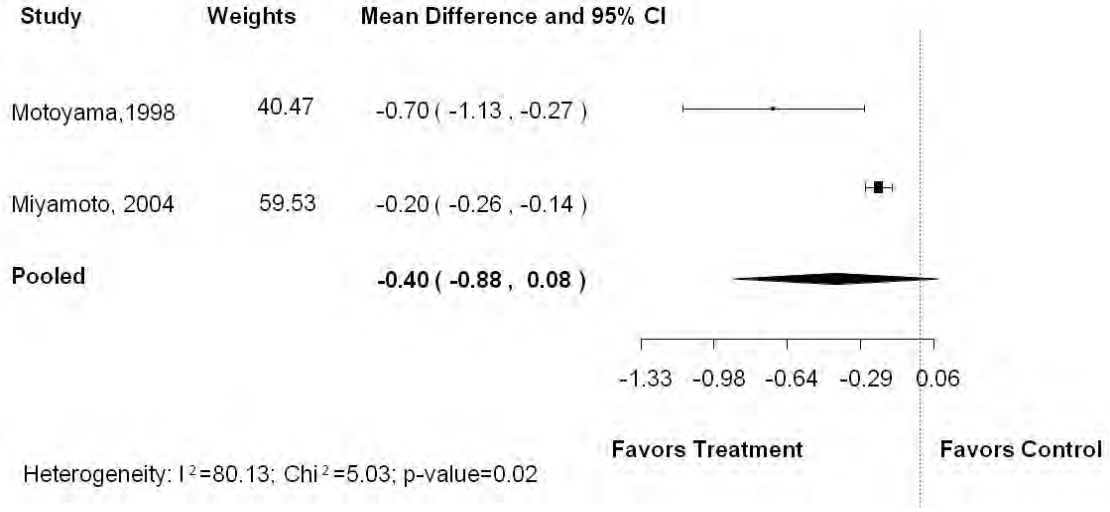
Adherence to a statin was reported in one trial that randomized a highly selected group of 220 hypercholestrolemic patients with normal triglycerides on a standardized diet of 100 mg/day of vitamin E plus 20 to 40 mg/day of pravastatin versus pravastatin alone.[46] Ninety-eight percent of all patients were compliant with their treatment.

In one pragmatic trial in 19,934 women randomized to vitamin E (600 IU/day) plus aspirin (100 mg/day) versus aspirin alone for 10 years, no significant differences were noted for the composite outcome of nonfatal myocardial infarction, nonfatal stroke, and vascular death (RR 0.95 [95 percent CI 0.79, 1.13]).[39] Data regarding the total number of participants randomized

into the two groups were obtained from the authors. Although components of the composite outcome were gradable, it was not possible to discern if shifts in incidence of stroke and heart attack might have been obscured in this composite outcome.

Two trials, each of one month duration, in a total of 60 highly selected Japanese patients with variant angina, were inconclusive for the mean number of angina attacks per patient following addition of vitamin E (400 mg/day) to therapeutic doses of diltiazem (MD -0.40 [95 percent CI -0.88, 0.08]) (Figure 3).[43,45]

Figure 3. Forest plot of the mean number of angina attacks for participants administered aspirin with or without vitamin E



Vitamin K

Vitamin K Plus Warfarin Versus Warfarin Alone

Mortality, stroke, and adherence to cardiovascular medication. Insufficient evidence was found for mortality and stroke. One 6 month efficacy trial in 70 selected patients with unstable INRs, anticoagulated with warfarin, reported no stroke and one death.[41] During the 6 month study period, two of 35 patients failed to take their warfarin and the supplement on a single occasion.[41] Strength of evidence is summarized in Table 19.

Table 19. Strength of evidence for warfarin with or without vitamin K—Clinical outcomes

Cardiovascular drug / Outcome	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence	Conclusions
All-cause mortality and stroke	Moderate	NA	Direct	Imprecise	Insufficient	Two small trials clearly underpowered for clinical events

Abbreviation: NA = not applicable

Key Question 1a. Do the effect estimates of clinical cardiovascular outcomes vary by age, ethnicity, gender, or health status?

A paucity of studies of supplement-drug combinations for which data were available precluded exploration of heterogeneity in terms of pre-identified subgroups.

Key Question 1b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for clinical cardiovascular outcomes?

No study analyzed statistical interaction between a supplement and a cardiovascular drug on clinical outcomes.

Main Points for Key Question 1: Clinical Outcomes

For Key Question 1, we compared dietary supplement(s) coadministered with cardiovascular drug(s), with the cardiovascular drug(s) alone, to investigate comparative clinical efficacy/effectiveness, subgroup effects and statistical interactions.

- Twenty-one randomized controlled trials contributed evidence.
- For all predetermined gradable clinical outcomes for which evidence was found, the strength of evidence of comparative efficacy or effectiveness was graded insufficient because type II error could not be excluded due to the low power of studies. When compared with the specific cardiovascular drug alone, insufficient evidence was found for an effect of coenzyme Q10 coadministered with ACE inhibitors on all-cause mortality and quality of life; *Ginkgo biloba* plus aspirin and/or pentoxyphilline on all-cause mortality; oral magnesium and beta-blockers on myocardial infarction; omega-3 fatty acids plus statins on all-cause mortality and arrhythmia; omega-3 fatty acids plus aspirin, warfarin or fenofibrate on all-cause mortality; omega-3 fatty acids plus aspirin and calcium channel antagonist on acute myocardial infarction; vitamin E plus aspirin on stroke and transient ischemic attacks; and vitamin K plus warfarin derivative on all-cause mortality and stroke.
- No differences in adherence to statins were noted with coadministration of coenzyme Q10, omega-3 fatty acids, and vitamin E, with adherence rates greater than 90 percent in both drug plus supplement and drug alone groups. Evidence supporting benefit of omega-3 fatty acids added to conventional antiplatelet therapy and calcium channel antagonists on rates of restenosis following successful coronary angioplasty is conflicting. Underpowered studies addressed all other outcomes such as exacerbation of congestive heart failure, number of patients undergoing cardiac procedures, graft occlusion, neurologic recovery score, coronary vasospasm, and number of angina attacks in patients with variant angina for various dietary supplement and cardiovascular drug combinations
- Most studies were short-term efficacy trials, except for one pragmatic trial on 19,934 women randomized to vitamin E (600 IU/day) plus aspirin (100 mg/day) versus aspirin alone for 10 years. In this trial, no significant difference was noted for the composite outcome of nonfatal myocardial infarction, nonfatal stroke, and vascular death (RR 0.95, 95 percent CI, 0.79, 1.13).
- With no data, there was insufficient evidence for the outcomes of hospitalization and those related to peripheral arterial disease across all supplement-cardiovascular drug(s) combinations.
- No evidence on clinical outcomes was found for *Echinacea*, garlic, ginger, ginseng, hawthorn, niacin (not more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, and vitamin D (with or without calcium supplementation) coadministered with a cardiovascular drug(s)

- A paucity of studies of supplement-drug combinations for which data were available precluded exploration of heterogeneity in terms of pre-identified subgroups, or documentation of any dose-response effect.
- No study analyzed statistical interaction between a supplement and a cardiovascular drug on clinical outcomes.

Key Question 2. In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared to cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement[s]) on intermediate cardiovascular efficacy outcomes (e.g., lipids, blood pressure, electrocardiographic measurements, serum markers, bleeding, and coagulation times)?

a. Do the effect estimates of intermediate cardiovascular outcomes vary by age, ethnicity, gender, or health status?

b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for intermediate cardiovascular outcomes?

Overview

Fifty-eight RCTs and one controlled clinical trial addressed Key Question 2. The availability of evidence is summarized in Table 20. The dietary supplements used in the studies were the following: coenzyme Q10 (five studies),[38,54,57,58,89] *Echinacea* (one study),[59] garlic (four studies),[60-63] ginger (one study),[64] *Ginkgo biloba* (five studies),[64-68] ginseng (three studies),[69-71] hawthorn (one study),[72] magnesium (three studies),[42,73,74] niacin (one study),[75] omega-3 fatty acids (24 studies),[37,40,44,50-53,55,56,76-78,91,92,94-99,151,152,163,164] vitamin E (11 studies),[46,49,79-87] and vitamin K (one study)[41]. No evidence was identified for effects of red yeast rice extract, resveratrol, vitamin A, or vitamin D in combination with cardiovascular drugs on intermediate outcomes. No study addressed the following outcomes: incidence of metabolic syndrome; incidence of hypotension; carotid-intima media thickness; or change in 10-year Framingham risk profile. Two studies examined statistical interaction.[44,78] One study used general linear modeling to assess interaction between fish/marine oils and atorvastatin on lipid parameters.[44] The other study used ANOVA to assess interaction between omega-3 fatty acids and niacin plus aspirin on triglyceride levels.[78] No relevant data were available from observational studies. One systematic review reporting the effectiveness of concomitant administration of omega-3 fatty acids plus statins compared with statins alone on lipid profiles in participants requiring lipid lowering therapy[149] was not included for synthesis because it was determined to be out of date. Details of individual study characteristics, risk of bias and outcomes data are reported in Appendix C.

Table 20. Overview of availability of evidence for intermediate outcomes—Key Question 2

Supplement and Cardiovascular Drug(s)	Outcome	Number of Studies
Coenzyme Q10		
ACE inhibitors*	Ejection Fraction	1
Fenofibrate	Lipid Profile Blood Pressure – Systolic	1
Statins	Lipid Profile	3

Table 20. Overview of availability of evidence for intermediate outcomes—Key Question 2 (continued)

Supplement and Cardiovascular Drug(s)	Outcome	Number of Studies
Echinacea		
Warfarin	INR Platelet Aggregation	1
Garlic		
Nitrates	Lipid Profile	1
Statins + Aspirin	Lipid Profile CRP Platelet Count Coronary Artery Calcification	1
Warfarin	Lipid Profile Blood Pressure – Systolic and Diastolic Platelet Count Platelet Aggregation	1
	INR	2
Ginger		
Warfarin	INR Platelet Aggregation	1
Ginkgo biloba		
Aspirin	Lipid Profile Blood Pressure – Systolic and Diastolic Clotting Time Platelet Count Partial Thromboplastin Time	1
	Platelet Aggregation	2
Antiplatelet drugs – thienopyridines	Blood Pressure – Systolic Clotting Time Platelet Count	1
	Platelet Aggregation Bleeding Time	2
Cilostazol	Blood Pressure – Systolic Platelet Aggregation Clotting Time Platelet Count	1
Warfarin	INR Platelet Aggregation	1
Ginseng		
Warfarin	INR	3
	Prothrombin Time Platelet Count Platelet Aggregation	1
Hawthorn		
Digoxin	PR Interval	1
Magnesium		
Beta-Adrenergic Antagonists	Blood Pressure – Systolic and Diastolic	1
Hydrochlorothiazide	Lipid Profile	1
	Blood Pressure – Systolic and Diastolic	2
Niacin ≤ 250 mg		
Propranolol	Lipid Profile	1

Table 20. Overview of availability of evidence for intermediate outcomes—Key Question 2 (continued)

Supplement and Cardiovascular Drug(s)	Outcome	Number of Studies
Omega-3 fatty acids/fish oils		
ACE inhibitors	Lipid Profile Blood Pressure – Systolic and Diastolic	2
	Urinary Protein Excretion Reduction in Proteinuria	1
Aspirin	Lipid Profile Platelet Count	2
	Blood Pressure – Systolic and Diastolic	1
Beta-Adrenergic Antagonists	Blood Pressure – Systolic and Diastolic	1
Calcium Channel Blockers	Lipid Profile	1
Calcium Channel Blockers with + Aspirin (with or without dipyridamole)	Lipid Profile	2
	Platelet Count	1
Fenofibrate	Lipid Profile Incidence of Hypertension	1
Niacin + Aspirin	Lipid Profile	1
Statins	Lipid Profile	11
	Blood Pressure – Systolic and Diastolic Platelet Count	3
	CRP Blood Coagulation	1
Warfarin	INR	1
Vitamin E		
Antiplatelets	Lipid Profile Platelet Aggregation	1
Furosemide	Blood Pressure – Systolic and Diastolic	1
Gemfibrozil	Lipid Profile Blood Pressure – Systolic and Diastolic	1
Nifedipine	Lipid Profile Blood Pressure – Systolic and Diastolic	1
Statins	Lipid Profile	6
	CRP Prothrombin Time Platelet Count	1
Vitamin K		
Anticoagulants	INR	2

Note: *Subjects were also taking digoxin, furosemide, hydralazine, or nitrates.
Abbreviations: ACE = angiotensin converting enzyme; CRP = C-reactive protein; INR = international normalized ratio

Participant and study characteristics are summarized in Table 21.

Table 21. Summary of study characteristics for studies addressing intermediate outcomes—Key Question 2

Characteristic	Distribution
Sample CHD risk	• Low 8.0% • Moderate to moderately high 2.3% • High 20.3% • Mixed 33.2% • Unclear 36.2%
Geographical region	• North America 15.3% • Europe 28.8% • Australia/New Zealand 10.2% • East Asia 6.8% • Rest of Asia 3.4% • NR 10.2%
Setting	• Primary care/community 34.0% • Specialty care 21.7% • NR 44.3%
Duration	Mean 10 weeks (SD 14.7) Range 1 week to 2 years
Total N randomized	Mean 50.6(SD 51.7), range 10 to 332, total across studies = 3,201
Age	Mean age 48.8 years (SD 14.4)
Gender	Ten all-male trials.[44,52,59,61,64,65,67,68,71,98] In 28.0% of the mixed gender studies, females were less than 40% of the study sample
Race/Ethnicity	Eighteen (31.0%) studies reported race/ethnicity distribution. Five studies included a majority of Caucasian participants. Three studies included all Asians[50,57,68] Two studies included majority of Hispanics[55,95]

Abbreviations: CHD = coronary heart disease; N = total number in trial; NR = not reported; SD = standard deviation.

Assessment of risks of bias is summarized in Table 22. Among all RCTs the purity of supplement was the item most frequently reported, while underreporting of generation and concealment of allocation represented the greatest potential for bias. In all crossover trials the study design was deemed to be suitable for the studied condition and a majority were judged to be free of carryover effect.

Table 22. Risk of bias and potential for conflict of interest—Key Question 2

Items	Yes	No	Unclear
All RCTs	**% of total studies (N=58)**		
Adequate generation of allocation sequence	20	2	78
Allocation concealment	9	0	91
Comparability of groups	9	46	46
Purity of supplement	81	12	7
Blinding of allocated intervention	22	24	53
Adequately addressed missing data	63	3	34
Freedom from potential for conflict of interest	24	31	47

Table 22. Risk of bias and potential for conflict of interest—Key Question 2 (continued)

Items	Yes	No	Unclear
Crossover RCTs	**% of total crossover studies (N=19)**		
Suitability of crossover design for the study condition	100	0	0
Free of carryover effect	26.3	63.2	10.5
Appropriateness of statistical analysis for crossover design	21.1	21.1	57.9
Comparability of groups between periods 1 and 2	10.5	0.0	89.5
Freedom from bias introduced by dropouts	5.3	78.9	15.8

Abbreviations: N = total number; RCTs = randomized controlled trials.

Coenzyme Q10

Five RCTs, including four parallel-arm trials,[38,57,58,89] and one crossover trial[54] examined cardiovascular drugs with and without coenzyme Q10. The trials were conducted in Australia,[38,54,58] North America,[89] and East Asia.[57] The number of included participants across these trials ranged from 30[54] to 49,[57] and they received statins (atorvastatin, simvastatin),[38,57] fenofibrate,[58] ACE inhibitors (specific agents not stated), or vitamin E[89] in addition to other cardiovascular drugs (digoxin, furosemide, hydralazine, nitrates, or statins).[54] According to the National Cholesterol Education Program, Adult Treatment Panel III,[165] the study participants were categorized as having a high,[54,58] unclear,[57,89] or mixed (moderate and high)[38] risk for CHD. The duration of treatment across the studies ranged from 4 [89] to 12 weeks.[38,54,57,58] Generally, these studies were reported to be double-blind and had moderate risk of bias across the outcomes of interest. The washout period in the one crossover trial was adequate to minimize or avoid a carryover treatment effect.[54] Further details on study, participant, and treatment characteristics are presented in Appendix C .

Summary of findings and strength of evidence data are presented in Table 23. No meta-analysis was possible for coenzyme Q10 studies because when more than one study reported a particular outcome,[38,57,89] the treatment effect was either not reported,[89] or it was reported as a median (interquartile range) change,[38] so the study results were in a format that is unsuitable for statistical pooling.

Coenzyme Q10 Plus Statins Versus Statins Alone

C-reactive protein (CRP). One placebo-controlled parallel-arm RCT examined CRP changes in participants with unclear CHD risk.[57] The 12-week mean CRP levels were not different between groups with add-on dietary supplement treatment (100 mg/day) versus the statin-only (10 mg/day) group.

High density lipoprotein-cholesterol. Two placebo-controlled parallel-arm randomized trials examined HDL-C changes in participants with unclear or mixed CHD risk.[38,57] In one trial, mean HDL-C levels after 12 weeks of treatment were not significantly different for those receiving coenzyme Q10 (100 mg/day) plus statins (10 mg/day) versus those receiving only statins.[57] Similarly, in the second trial (200 mg/day coenzyme Q10; 10-40 mg/day statins), there was no significant between-group difference for the median change in HDL-C.[38]

Low density lipoprotein-cholesterol, total cholesterol and triglycerides. Two trials in participants with mixed[38] or unclear CHD risk investigated changes in LDL-C.[57] Levels were not significantly different following treatment with coenzyme Q10 plus statins compared with plus statins alone after 12 weeks.[38,57] Mean differences [57] and between-group difference for the median change [38] were not significant for LDL-C, total cholesterol, or triglycerides.

Coenzyme Q10 Plus Statins Versus Vitamin E Plus Statins

Lipid profile, low density lipoprotein-cholesterol, total cholesterol and triglycerides. In one trial of 32 participants with unclear CHD risk, changes of LDL-C, TC, and TG levels were studied.[89] Results from this RCT indicated no differences in lipid profile (total cholesterol, LDL-C, triglycerides) after 30 days of treatment with coenzyme Q10 (100 mg/day) plus statins or vitamin E (400 IU/day) plus statin groups in participants with statin induced myopathic pain (numeric data were not provided).[89]

Coenzyme Q10 Plus ACE Inhibitors Versus ACE Inhibitors Alone

Participants were also taking digoxin, furosemide, hydralazine, and nitrates.

Ejection fraction. One randomized crossover trial reported ejection fraction in participants with heart failure (high CHD risk).[54] The 12 week posttreatment ejection fraction in the treatment (coenzyme Q10 [100 mg/day] plus ACE inhibitors) and control (ACE inhibitors alone) groups were not significantly different.

Coenzyme Q10 Plus Fenofibrate Versus Fenofibrate Alone

Lipid profiles and systolic blood pressure. One parallel arm randomized trial in participants with type II diabetes and high CHD risk reported changes in systolic blood pressure.[58] The 12 week posttreatment mean levels in the treatment (200 mg/day coenzyme Q10 plus 200 mg/day fenofibrate) and control (fenofibrate alone) groups did not significantly differ for any of the outcomes assessed (HDL-C, LDL-C, total cholesterol, triglycerides, non-HDL-C, and systolic blood pressure).

Applicability. Low grade evidence of no effect on HDL-C was found in a primarily (70 percent) male population, of mean age 53 years, with high risk for cardiovascular disease. Treatment was over 12 weeks, with fenofibrate and with or without coenzyme Q10.

Table 23. Strength of evidence for cardiovascular drugs with and without coenzyme Q10—Intermediate outcomes

Cardiovascular drug(s)/ Outcome	Risk of bias	Consistency	Directness	Precision	Grade	Treatment effect and conclusion* MD (95% CI)
Statins						
CRP[57]	-	-	-	-	-	No difference 0.02 mg/L (-0.64, 0.68)
HDL-C(mg/dL)[38,57]	Moderate	Consistent	Indirect	Imprecise	Insufficient	Inconclusive 5.02 mg/dL (-3.73, 13.77)[57] Arm-specific median change 0.39 versus -0.77, p=0.65[38 †]
LDL-C (mg/dL)[38,57]	Moderate	Consistent	Indirect	Imprecise	Insufficient	Inconclusive 8.12 mg/dL (-3.79, 20.03))[57] Arm-specific median change -65.73 versus -50.27, p=0.53[38]
TC (mg/dL) [38,57]	-	-	-	-	-	Inconclusive 11.9 (-3.55, 27.53)[57] Arm-specific median change -58.00 versus -61.87, p=0.57[38]
TG (mg/dL)[38,57]	Moderate	Consistent	Indirect	Imprecise	Insufficient	Inconclusive -21.26 (-48.88, 6.36) [57] Arm-specific median change -35.43 versus -26.57, p=0.90[38]
ACE inhibitors						
Ejection fraction (%)[54]	-	-	-	-	-	No difference 0 (-4.75, 4.75)
Fenofibrate						
HDL-C (mg/dL) [58]	Moderate	NA	Indirect	Precise	Low	No difference -1.55 (-6.78, 3.68)
LDL-C (mg/dL) [58]	Moderate	NA	Indirect	Imprecise	Insufficient	Inconclusive 3.87 (-19.30, 27.04)
TC (mg/dL) [58]	-	-	-	-	-	Inconclusive 0 (-23.17, 23.17)
TG (mg/dL) [58]	Moderate	NA	Indirect	Imprecise	Insufficient	Inconclusive 8.85 (-52.49, 70.19)
Non-HDL-C (mg/dL) [58]	Moderate	NA	Indirect	Imprecise	Insufficient	Inconclusive 0.87 (-22.30, 24.04)
SBP (mmHg) [58]	Moderate	NA	Indirect	Imprecise	Insufficient	Inconclusive -3.40 (-15.56, 8.76)

Notes: * Mean difference and 95 percent confidence interval; range for mean difference given only when evidence consists of multiple studies that were not pooled; (-) is indicated where non-gradable outcomes are reported (for example TC, or CRP)
† Arm-specific median change (from baseline) was not used to assess the domain of precision
Abbreviations: ACE = angiotensin-converting enzyme; CHD = coronary heart disease; CRP = C-reactive protein; HDL-C = high density lipoprotein-cholesterol; LDL-C = low density lipoprotein-cholesterol; NA = not applicable; NR = not reported; TC = total cholesterol; TG = triglycerides; RCT = randomized controlled trial; SBP = systolic blood pressure; wk(s) = week(s); yr(s) = year(s).

Echinacea

Echinacea Plus Warfarin Versus Warfarin Alone

One crossover RCT in 12 healthy male volunteers examined the effect of two weeks pre-treatment with *Echinacea* (600 mg of *E. angustifolia* root plus 675 mg of *E. purpurea* root daily) and a single dose of warfarin (25 mg) versus warfarin alone.[59]

There was no effect on blood pressure, maximum International Normalized Ratio (INR_{max}), geometric mean ratio [GMR] 1.04 [90 percent CI 0.95, 1.13]), AUC of INR (MD 2.50 [95 percent CI -17.72, 22.72] and GMR 1.09 [95 percent CI 0.91, 1.31]), or measures of platelet aggregation (using three different platelet agonists: adenosine diphosphate, arachidonic acid and collagen; data not shown). Strength of evidence is summarized in Table 24.

Table 24. Strength of evidence for warfarin with and without *Echinacea*—Intermediate outcomes

Cardio-vascular Drug(s)/ Outcome	Risk of Bias	Consistency	Directness	Precision	Grade	Treatment Effect and Conclusion MD (95% CI)
Warfarin						
Blood pressure	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	No difference Systolic blood pressure: 2.20 mm Hg (-8.98, 13.38) Diastolic blood pressure: -0.80 mm Hg (-8.21, 6.61)
INR_{max}	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	No difference INR_{max} 0.10 (-0.20, 0.40

Abbreviations: CI = confidence interval; MD = mean difference; mm Hg = millimetres of mercury.

Garlic

Four RCTs, including three parallel-arm trials,[60,62,63] and one crossover trial[61] examined cardiovascular drugs with and without garlic. The trials were conducted in Australia,[61] North America,[60,63] and Europe.[62] The number of included participants across these trials ranged from 12[61] to 60,[62] and they received statins plus aspirin,[63] warfarin,[60,61] or nitrates.[62] According to the National Cholesterol Education Program, Adult Treatment Panel III,[165] the study participants were categorized as having a high,[62,63] unclear,[60] or low [61] CHD risk. The duration of treatment across the studies ranged from one day[61] to 12 months.[63] The washout period in the one crossover trial was adequate to minimize or avoid a carryover treatment effect. Further details on study, participant, and treatment characteristics are presented in Appendix C. Strength of evidence is summarized in Table 25.

Garlic Plus Warfarin Versus Warfarin Alone

Two small RCTs, one parallel-group[60] and one crossover[61] trial, examined the effect of treating patients on warfarin with garlic extracts. Both studies concluded that supplementation with garlic in patients taking warfarin does not further affect INR, based on various measures including INR,[60] or INR_{max}, AUC of INR, or the number of participants with an INR greater than 4 (no events in either arm).[61]

One study[60] in 48 participants with prosthetic heart valves, or diagnosed with deep vein thrombosis, valvular heart disease, or atrial fibrillation assessed the effects of aged garlic extract

(AGE) (10 mL/day) plus warfarin. No significant effects were seen for total cholesterol, LDL-C, or triglycerides. However, there was a statistically significant increase in HDL-C in the combination group. Neither blood pressure, nor platelet count (data not shown) were significantly affected.

One crossover study[61] found no significant effect of pretreatment with garlic (4 g single dose) plus a single dose of warfarin (25 mg) on platelet aggregation (using four different agents: adenoside diphosphate, arachidonic acid, collagen and ristocetin; data not presented). Participants in this trial were 16 healthy male adults of known CYP2C9 and VKORC1 genotype.

All results for major review outcomes, aside from HDL-C, were considered to have insufficient strength of evidence (Table 25).The strength of evidence for HDL-C was initially rated as insufficient by one reviewer because the lower bound confidence interval of 0.19 mg/dL is not clinically meaningful. A second reviewer provided a rating of low because the estimate is statistically significant. Adjudication by a third reviewer led to a final rating of low.

Garlic Plus Nitrates Versus Nitrates Alone

One controlled clinical trial[62] recruited 60 participants with coronary artery disease to receive either garlic oil (4 g/day) or placebo in addition to their prescribed nitrates (specific drugs and doses were not reported). Compared with placebo, administration of garlic was found to significantly decrease total serum cholesterol, and increase serum HDL-C.[62] Serum triglycerides were also reduced but the comparison was not statistically significant. These results were considered to provide insufficient strength of evidence for triglycerides and low strength of evidence for HDL-C in favor of combination treatment (Table 25).

Garlic Plus Statins and Aspirin Versus Statins and Aspirin Alone

One small parallel group trial[63] randomly allocated 23 participants with, or at high risk for coronary artery disease to receive AGE (4 mL,305 g/L of extracted solids/day) or placebo in addition to their prescribed statins (10-40 mg/day) and aspirin (dose not specified) over a period of one year. Compared with placebo, administration of AGE was not found to have a significant effect on lipid parameters (total cholesterol (TC), TC/HDL-C, HDL-C, LDL-C, triglycerides), CRP, or platelet count.

This study also examined two measures of coronary artery calcification: volume calcium score (using isotropic interpolation method) and Agatston calcium score (multiplying the lesion area by a coefficient based on the peak density within plaque). The first measure was found to be lowered significantly by supplementation with garlic compared with placebo (change in volume calcium score: -83.80 mm^3 [95 percent CI -164.22, -3.38]; percent change in volume calcium score per year: -14.7 mm^3 [95 percent CI -28.93, -0.47]). No differences were found in the second measure.

Strength of evidence was insufficient for LDL-C, HDL-C, and triglycerides (Table 25).

Table 25. Strength of evidence for cardiovascular drugs with and without garlic—Intermediate outcomes

Cardio-vascular Drug(s)/ Outcome	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect MD (95% CI)
Warfarin						
Blood pressure (mmHg)	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** Systolic: 2.20 (-8.98, 13.38) Diastolic: -0.80 (-8.21, 6.61)
LDL-C (mg/dL)	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** 4.20 mg/dL (-12.01, 20.41)
HLD-C (mg/dL)	Moderate	NA	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** 4.50 mg/dL (0.19, 8.81)
Total cholesterol (mg/dL)	-	-	-	-	-	**No difference** 12.50 (-3.74, 28.74)
Triglycerides (mg/dL)	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** 31.90 (-23.66, 87.46)
INR	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** INR: -0.20 (-0.83, 0.43) INR_{max} :-0.10 (95% CI -0.63, 0.43) AUC of INR : 4.30 (-35.90, 44.50) INR > 4 No events in either arm
Nitrates						
HDL-C (mg/dL)	High	NA	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** 8.40 (1.91, 14.89)
Total cholesterol (mg/dL)	-	-	-	-	-	**In favor of combination treatment** -28.20 (-48.30, -8.10)
Triglycerides (mg/dL)	High	NA	Indirect(surrogate)	Imprecise	Insufficient	**No difference** -10.30 (-27.60, 7.00)

Table 25. Strength of evidence for cardiovascular drugs with and without garlic—Intermediate outcomes (continued)

Cardio-vascular Drug(s)/ Outcome	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect MD (95% CI)
Statins + Aspirin						
LDL-C (mg/dL)	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** -25.10 (-54.69, 4.49)
HLD-C (mg/dL)	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** 4.30 (-7.55, 16.15)
Triglycerides (mg/dL)	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**No difference** -21.20 (-93.42, 51.02)

Abbreviations: AUC = area under the curve; CI = confidence interval; HDL-C = high density lipoprotein-cholesterol; INR = international normalized ratio; LDL-C = low-density lipoprotein cholesterol; MD = mean difference; NA = not applicable; (-) is indicated where non-gradable outcomes (total cholesterol) are reported

Applicability. Garlic in addition to nitrates for 3 months was found to significantly improve total cholesterol and HDL-C compared with nitrates alone, in subjects with healed myocardial infarction with or without angina.[62] Garlic in addition to statins plus aspirin for 12 months significantly lowered a measure of coronary artery calcification in subjects with known coronary artery disease.[63]

Ginger

One crossover RCT compared a single dose of warfarin following seven days pre-treatment with ginger (3.6 g/day) with warfarin alone in 12 healthy male subjects (Table 26).[64] The study also included a warfarin plus *G. biloba* group (data for the comparison between warfarin plus ginger and warfarin plus *Ginkgo* is in the *G. biloba* section).

The same study reported AUC of INR for the combination of ginger plus warfarin versus warfarin alone.[64] One of the two analyses of the data suggests a possible effect of unknown clinical significance. The mean difference in platelet aggregation was not statistically significant (MD 0.6 [95 percent CI -0.42, 1.62]) but the geometric mean ratio was statistically significant. Given the inconsistency in findings, strength of evidence was graded as insufficient for INR (Table 26).

Table 26. Strength of evidence for warfarin with or without ginger—Intermediate outcomes

Cardio-vascular Drug(s) / Outcome	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
AUC of INR[64]	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** MD 1.00 (95% CI -43.68, 45.68) GMR 1.01 (90% CI 0.93, 1.15)

Abbreviations: AUC of INR = area under the curve of the international normalized ratio; CI = confidence interval; GMR = geometric mean ratio; MD = mean difference.

Ginkgo Biloba

Five RCTs investigated *G. biloba* with cardiovascular drugs (Table 27).[64-68] Four studies included subjects taking antiplatelet agents (aspirin,[65,66] clopidogrel,[67] or ticlopidine[68]). One study included subjects taking an anticoagulant (warfarin[64]) and one study included subjects taking a vasodilator (cilostazol[67]).

G. Biloba Plus Antiplatelet Agents Versus Antiplatelet Agents Alone

Aspirin was administered with *G. biloba* in two studies, of young healthy males (240 mg/day *G. biloba*)[65] or elderly subjects with peripheral arterial disease or risk factors for cardiovascular disease (300 mg/day *G. biloba*).[66] Although platelet aggregation was reported in both studies, meta-analysis could not be performed because different posttreatment effect estimates were reported (mean[65] and mean change from baseline[66]). Both studies reported nonsignificant differences in platelet aggregation. Nonsignificant differences were also reported in clotting time,[66] bleeding time,[65] partial thromboplastin time,[65] and platelet count.[65] No changes were found in lipid parameters and blood pressure (reported qualitatively only).[65]

In two studies, single doses of a thienopyridine antiplatelet drug (clopidogrel[67] or ticlopidine[68]) were administered with or without single doses of G. biloba(80 mg/day). The pooled estimates for platelet aggregation were statistically nonsignificant (Figures 4 and 5), as was the pooled estimate for bleeding time (Figure 6). There were no significant changes in clotting time, systolic blood pressure, or platelet count (reported qualitatively only).[67]

Strength of evidence was insufficient for blood pressure and lipid profile (Table 27).

Figure 4. Forest plot of posttreatment mean difference of platelet aggregation for clopidogrel/ticlopidine with or without *G. biloba* (induced by 5 µL of 10 µM ADP or 2.5 µL of 10 µM ADP)-(percent)

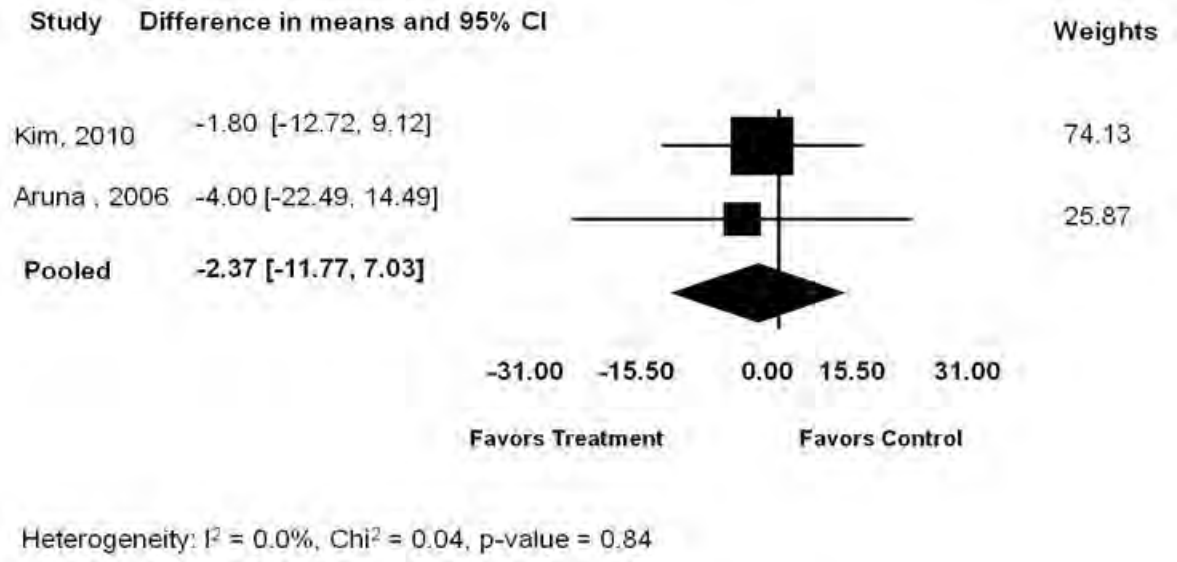


Figure 5. Forest plot of posttreatment mean of platelet aggregation for clopidogrel/ticlopidine with or without *G. biloba* (induced by 5 µL of 10 µM ADP or 2.5 µL of 5 µM ADP)-(percent)

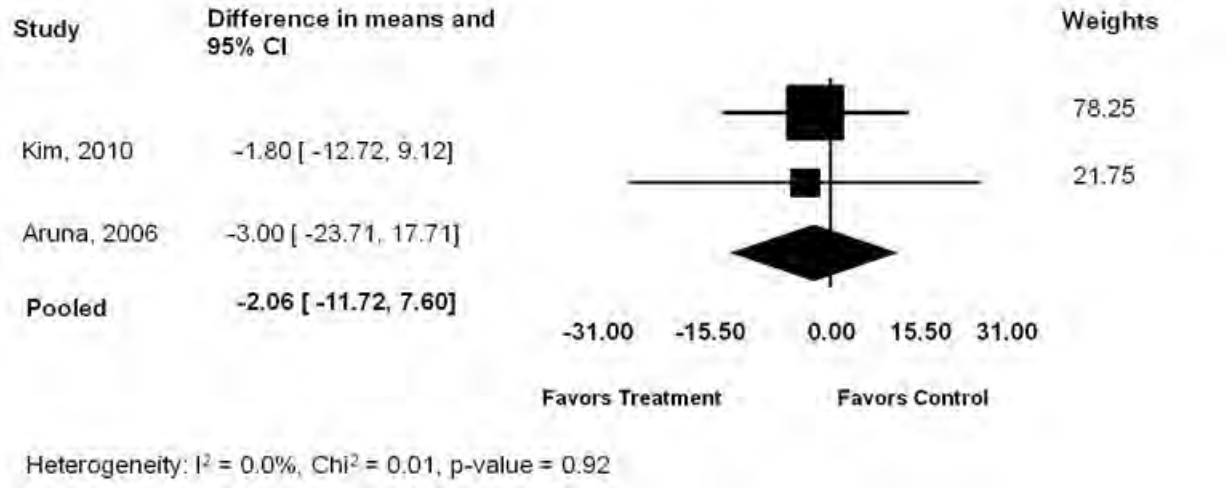
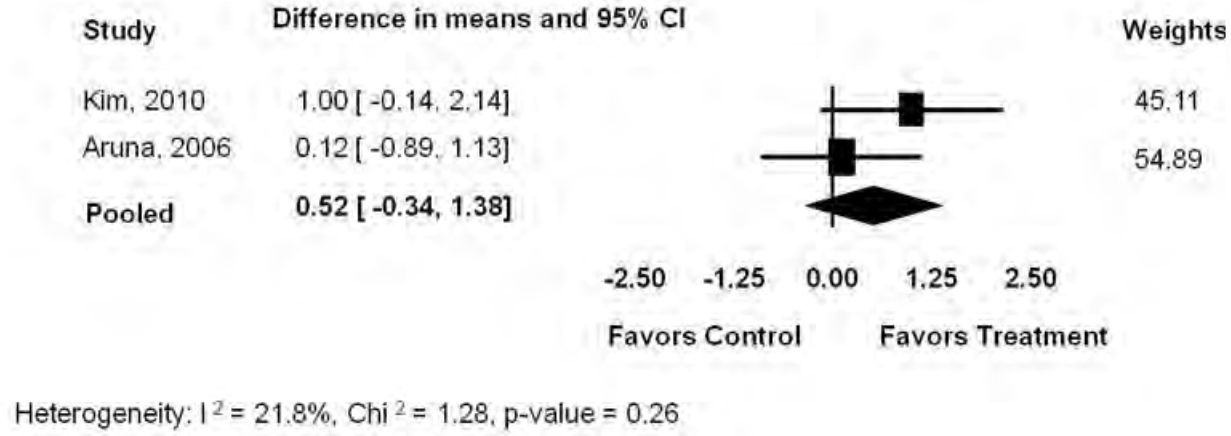


Figure 6. Forest plot of bleeding time for clopidogrel/ticlopidine with or without *G. biloba*- (minutes)



G. Biloba Plus Warfarin Versus Warfarin Alone

One crossover RCT examined single dose warfarin (25 mg/day) following either no pretreatment or seven days pretreatment with *G. biloba* (12 g/day) or ginger (3.6 g/day) in healthy subjects.[64] Compared with warfarin alone, there was a statistically significant increase in platelet aggregation (GMR 1.14 [90 percent CI 1.08, 1.20]). However, the difference in AUC of INR was not statistically significant. Compared with warfarin plus ginger, there were no statistically significant differences in platelet aggregation or AUC of INR.

Strength of evidence comparing *G. biloba* plus warfarin with warfarin alone or warfarin plus ginger was insufficient for INR (Table 27).

G. Biloba Plus Cilostazol Versus Cilostazol Alone

One crossover RCT examined single dose cilostazol (100 mg) with or without single dose *G. biloba* (120 mg) in healthy South Asian males.[67] Bleeding time was slightly prolonged in the *G. biloba* plus cilostazol group. One measure of platelet aggregation was statistically significant (MD 18.00 percent [95 percent CI 1.92, 34.08]).There was no significant change in clotting time, systolic blood pressure, or platelet count (reported qualitatively only).

Strength of evidence for systolic blood pressure was insufficient (Table 27).

Table 27. Summary and strength of evidence for cardiovascular drugs with or without *G. biloba*—Intermediate outcomes

Cardio-vascular Drug/ Outcome	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Antiplatelet drugs						
Bleeding Time (min)[67,68]	Moderate	-	-	-	-	**Inconclusive** Pooled 0.52 (95% CI -0.34, 1.38)
Blood Pressure – Systolic and Diastolic	Moderate	NA	Indirect (surrogate)	NA	Insufficient	**Inconclusive**
Lipid Profile (LDL-C, HDL-C, TG)[65]	Moderate	NA	Indirect (surrogate)	NA	Insufficient	**Inconclusive**
Warfarin						
AUC of INR (versus warfarin alone)	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** MD-3.00 (95% CI -62.00, 56.00) GMR 0.93 (90% CI 0.81, 1.05)
AUC of INR (versus warfarin plus ginger)	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** MD -4.00 (95% CI -62.84, 54.84)
Cilostazol						
Bleeding Time (min)[67]	Moderate	-	-	-	-	**Inconclusive** MD 1.02 (95% CI 0.10, 1.94)
Blood pressure - Systolic	Moderate	NA	Indirect (surrogate)	NA	Insufficient	**Inconclusive**

Abbreviations: AUC of INR = area under the curve of the International Normalized Ratio; CI = confidence interval; GMR = geometric mean ratio; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MD = mean difference; NA = not applicable; TG = triglycerides.

Ginseng

Three RCTs compared ginseng plus warfarin with warfarin alone (Table 28).[69-71]

Ginseng Plus Warfarin Versus Warfarin Alone

Reported outcomes included INR,[69-71], prothrombin time,[69] platelet aggregation,[71] and platelet count.[69]

Meta-analyses were not possible because of differences in patient populations (e.g., healthy versus postischemic stroke) and incompatible effect estimates (e.g., differences in means and differences in medians). One small study using *Panax ginseng* (1.5 g/day)in subjects with ischemic stroke reported no statistically significant differences in peak and AUC of INR, peak and AUC of prothrombin time, and platelet count.[69] A study in young, healthy subjects, however, reported significantly lower peak INR and AUC of INR in the American ginseng (2 g/day) plus warfarin group.[70] Another small study using single does of warfarin in 12 healthy males found no differences in AUC of INR and platelet aggregation after seven days pretreatment with ginseng (*Panax ginseng*, 3 g/day).[71]

Strength of evidence was graded as insufficient for peak INR and AUC of INR (Table 28).

Table 28. Strength of evidence for warfarin with or without ginseng—Intermediate outcomes

Cardio-vascular Drugs(s) / Outcome	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect*
Warfarin						
INR_{peak}	Moderate	Inconsistent	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** MD range 0.01-0.11 (95% CI -0.20 to -0.06, 0.08 to 0.42] $M_{ed}D$-0.19 (95% CI -0.36, -0.07]
AUC of INR MD	Moderate	Inconsistent	Indirect (surrogate)	Imprecise	Insufficient	Inconclusive MD range 0.03-0.49 (95% CI -39.10 to -0.28, 0.34 to 39.30] $M_{ed}D$-0.43 (95% CI -1.00, -0.09]

Note: * Range is provided when more than one study is being summarized.
Abbreviations: AUC of INR = area under the curve of the International Normalized Ratio; CI = confidence interval; GMR = geometric mean ratio; MD = mean difference; $M_{ed}D$ = difference of the medians; NA = not applicable; TG = triglycerides.

Hawthorn

In a randomized crossover trial, subjects were administered digoxin 0.25 mg/day for 10 days or digoxin 0.25 mg/day plus hawthorn 450 mg twice daily for 3 weeks.[72] Subjects were tested with a standard 12-lead electrocardiogram for PR interval measurements. The difference between groups was statistically nonsignificant.

Magnesium

Three RCTs investigated the use of oral magnesium with cardiovascular drugs: magnesium plus hydrochlorothiazide [73,74] and magnesium plus beta-adrenergic antagonists.[42] Reported outcomes included total cholesterol, triglycerides, and systolic and diastolic blood pressure.

Magnesium Plus Hydrochlorothiazide Versus Hydrochlorothiazide Alone

In an eight week trial of 18 elderly subjects with benign essential hypertension taking magnesium (365 mg/day), nonsignificant differences were found in total cholesterol, triglycerides, and supine systolic and diastolic blood pressure.[73] Nonsignificant differences for systolic and diastolic blood pressure (supine and standing) were also reported in a seven week trial using magnesium (365 mg/day) in 21 subjects with mild to severe uncomplicated essential hypertension.[74] These two studies were meta-analyzed for supine systolic and diastolic blood pressure and the pooled estimates were statistically nonsignificant (Figures 7 and 8).[73,74]

Strength of evidence was graded as insufficient for systolic and diastolic blood pressure and triglyceride level (Table 29).

Figure 7. Forest plot of supine systolic blood pressure for hydrochlorothiazide with or without magnesium (mmHg)

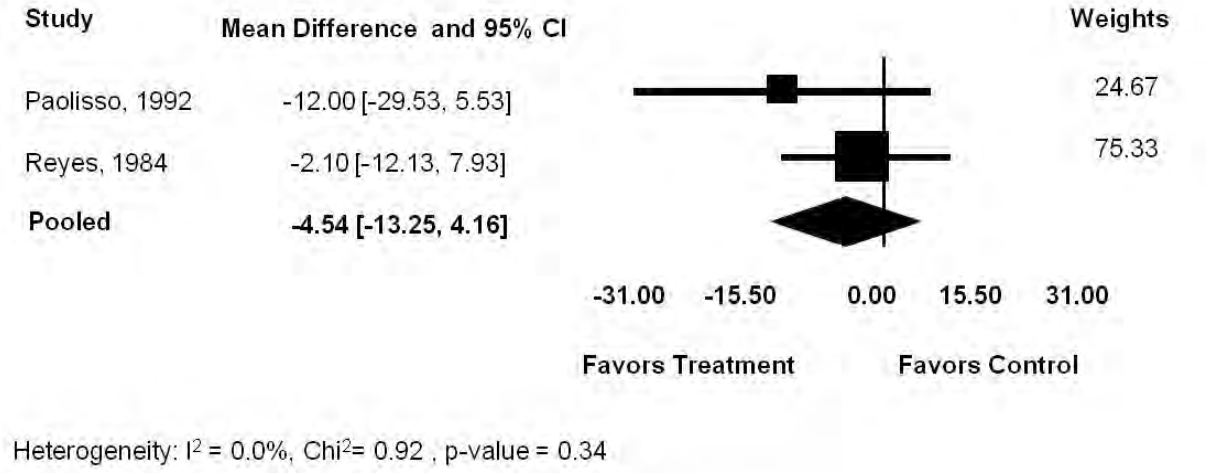
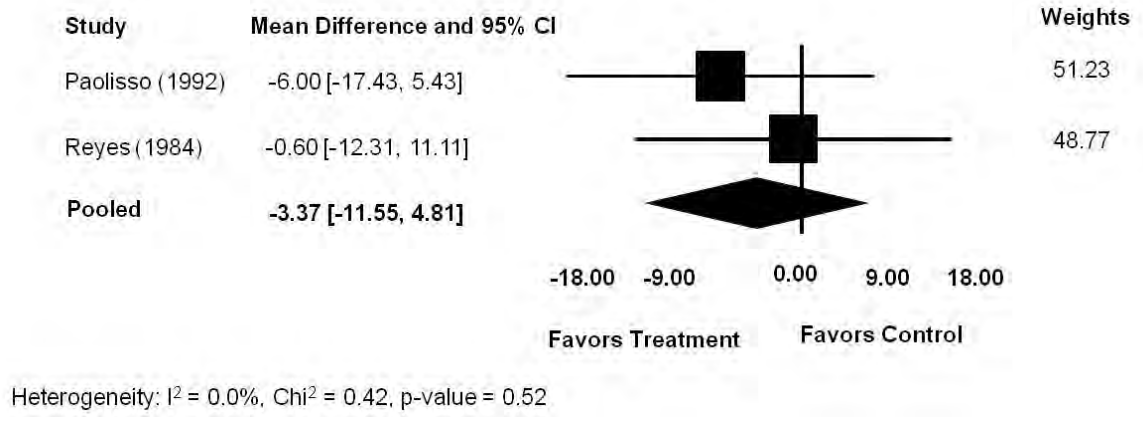


Figure 8. Forest plot of supine diastolic blood pressure for hydrochlorothiazide with or without magnesium (mmHg)



Magnesium Plus Beta-Adrenergic Antagonists Versus Beta-Adrenergic Antagonists Alone

In a crossover RCT, 39 subjects with essential hypertension on atenolol, metoprolol, pindolol, or propranolol were randomized to receive magnesium (365 mg/day) or placebo for eight weeks. Effect estimates for supine and standing systolic and diastolic blood pressures were statistically nonsignificant.[42]

Strength of evidence was graded as insufficient for systolic and diastolic blood pressure (Table 29).

Table 29. Strength of evidence for cardiovascular drugs with or without magnesium—Intermediate outcomes

Cardio-vascular Drug(s)/ Outcome	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect* MD (95% CI)
Hydrochloro-thiazide						
Blood pressure (mm Hg)	Moderate	Consistent	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** *Systolic* Supine: Pooled -4.54 (-13.25, 4.16) Standing: 0 (-5.94, 5.94) *Diastolic* Supine: Pooled -3.37 (-11.55, 4.81) Standing: 1.00 (-8.84, 10.84)
Triglycerides (mg/dL)	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** 1.77 (-103.19, 106.73)
Beta-adrenergic antagonists						
Blood pressure (mm Hg)	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** *Systolic* Supine: -4.26 (-12.56, 4.04) Standing: -4.34 (-13.90, 5.22) *Diastolic* Supine: -2.65 (-6.85, 1.55) Standing: -1.65 (-6.18, 2.88)

Note: * Range is provided when more than one study is being summarized; pooled data is from meta-analysis of more than one study.
Abbreviations: CI = confidence interval; MD = mean difference; mm Hg = millimetres of mercury; NA = not applicable.

Niacin (Not More Than 250 mg)

One parallel-arm RCT described the use of niacin with propranolol in 16 subjects with Type II or Type IV hyperlipoproteinemia (Table 30).[75] This study was rated as high risk of bias because groups were administered different dosages of propranolol (20 mg and 60 mg). Effect estimates for total cholesterol and triglycerides were statistically nonsignificant.

Strength of evidence was insufficient for triglycerides (Table 30).

Table 30. Strength of evidence for propranolol with or without niacin—Intermediate outcomes

Cardio-vascular Drug(s) / Outcome	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect MD (95% CI)
Triglycerides (mg/dL)	High	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** In Type II hyperlipoproteinemia: 8.40 (-114.22, 97.42) In Type IV hyperlipoproteinemia: -49.83 (-523.94, 424.28)

Abbreviations: CI = confidence interval; MD: mean difference; NA: not applicable

Omega-3 Fatty Acids/Fish Oil

Twenty-four RCTs, including 18 parallel-arm trials,[40,44,50-53,55,56,76-78,91,92,94,98,151,152,163] and six crossover trials[37,95-97,99,164] contributed evidence. The trials were conducted in North America,[37,40,52,55,56,78,94,95,99,163] Australia,[44,151,152,164] Europe,[53,76,77,91,92,96-98] and Asia.[50,51] The number of included participants in these trials ranged from 11[55] to 658.[91] The participants across studies received the following cardiovascular drugs: statins (atorvastatin, simvastatin, lovastatin),[37,40,44,53,76,91,92,94-97,151,163] calcium channel blockers,[50-52] niacin plus aspirin,[78] ACE inhibitors,[77,152] aspirin,[98,99] beta-blockers,[164] anticoagulation agents,[55] and fenofibrates.[56] In two trials, calcium channel blockers were used concomitantly with either aspirin,[51] or aspirin plus dipyridamole.[52] In most of the trials, participants were categorized as having unclear or mixed (different combinations of low, moderate/moderately high, and high) risk of coronary heart disease.[165] The duration of treatment ranged from 2 weeks[95,98] to 25 weeks.[151,152] Further details on study, participants and treatment characteristics are presented in Appendix C.

Generally, most of these studies were reported to be double blind and had a moderate risk of bias across the outcomes of interest. In crossover trials, the adequacy of washout period was not clear for one trial,[37] there was a potential of carryover in one trial (i.e., the treatment effect depended on the order of drug randomization),[99] and no washout period was employed for another trial.[164] The washout period length reported for three other trials was deemed to be adequate.[95-97]

Summary of findings and strength of evidence data are presented in Table 31. Meta-analyses were performed for the following outcome measures: HDL-C, LDL-C, total cholesterol, and triglycerides (Figures 9 to 14).

Omega-3 Fatty Acids/Fish Oils Plus Statins Versus Statins Alone

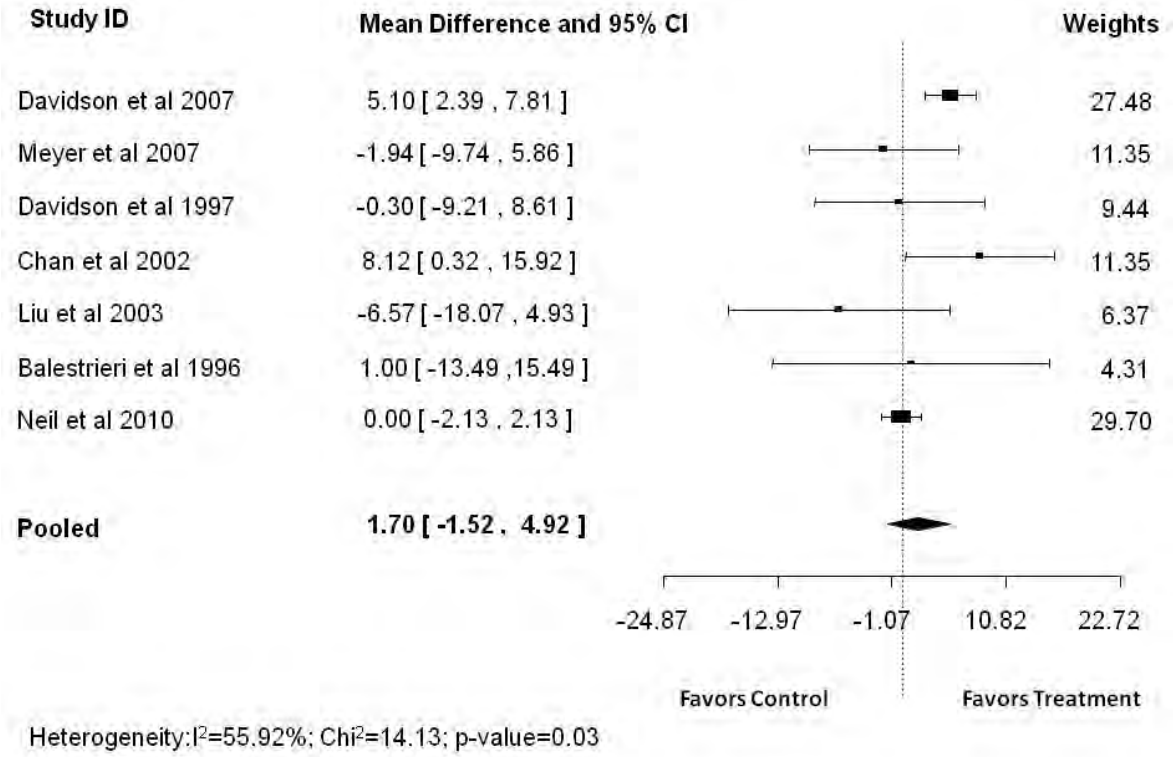
C-Reactive protein (CRP) was assessed in one placebo-controlled parallel arm randomized trial in participants at mixed CHD risk.[44] The six week posttreatment geometric mean CRP levels were not different between the omega-3 fatty acids (4 g/day) plus atorvastatin and control (atorvastatin alone) groups.

High density lipoprotein-cholesterol. Posttreatment HDL-C was reported in 11 randomized trials.[37,40,44,53,91,92,94,96,97,151,163] In five studies,[44,53,96,151,163] the mean endpoint differences in HDL-

C levels for participants with unclear or mixed CHD risk were not significantly different between the omega-3 fatty acids (2 to 10 g/day) combination and statins alone group. In one trial of participants at moderate CHD risk,[40] the eight week posttreatment mean HDL-C level was significantly greater in the dietary supplement versus control group (MD 5.10 [95 percent CI 2.36, 7.83]). A meta-analysis based on the results from seven studies (participants with unclear or mixed CHD risk),[40,44,53,91,96,151,163] indicated that the mean HDL-C levels did not differ between the omega-3 fatty acids (2.0 to 10.0 g/day) combination and statins alone group (Figure 9). Results from the remaining four trials reporting mean change,[92] percent change,[97] or percent median change[37,94] were not consistent. Specifically, one trial of participants with mixed CHD risk reported a significant difference in the five week posttreatment mean change in favor of the omega-3 fatty acids (2 g/day) combination (difference in mean change 2.32 [95 percent CI 0.18, 4.45]).[92] Similarly, two other trials of participants with unclear[94] and mixed[37] CHD risk reported significantly greater (i.e., improved) posttreatment percent increase in median HDL-C levels at 6 weeks (difference7.2 percent, p 0.001),[37] at eight weeks (difference of 2.4 percent, p less than 0.001)[94] or at 16 weeks (difference of 6.3 percent, p less than 0.001)[94] in favor of the dietary supplement intervention (4 g/day). In contrast, the percent change in HDL-C (from baseline) in one crossover trial of participants with mixed CHD risk was not significantly different between the dietary supplement (4 g/day) and control group at six weeks after the baseline (6.0 percent versus 14.0 percent).[97]

Overall, results indicated no difference in posttreatment HDL-C levels between the dietary supplement and control interventions (Table 31).

Figure 9. Posttreatment HDL-C levels in subjects taking statins with or without omega-3 fatty acids/fish oils (mg/dL)

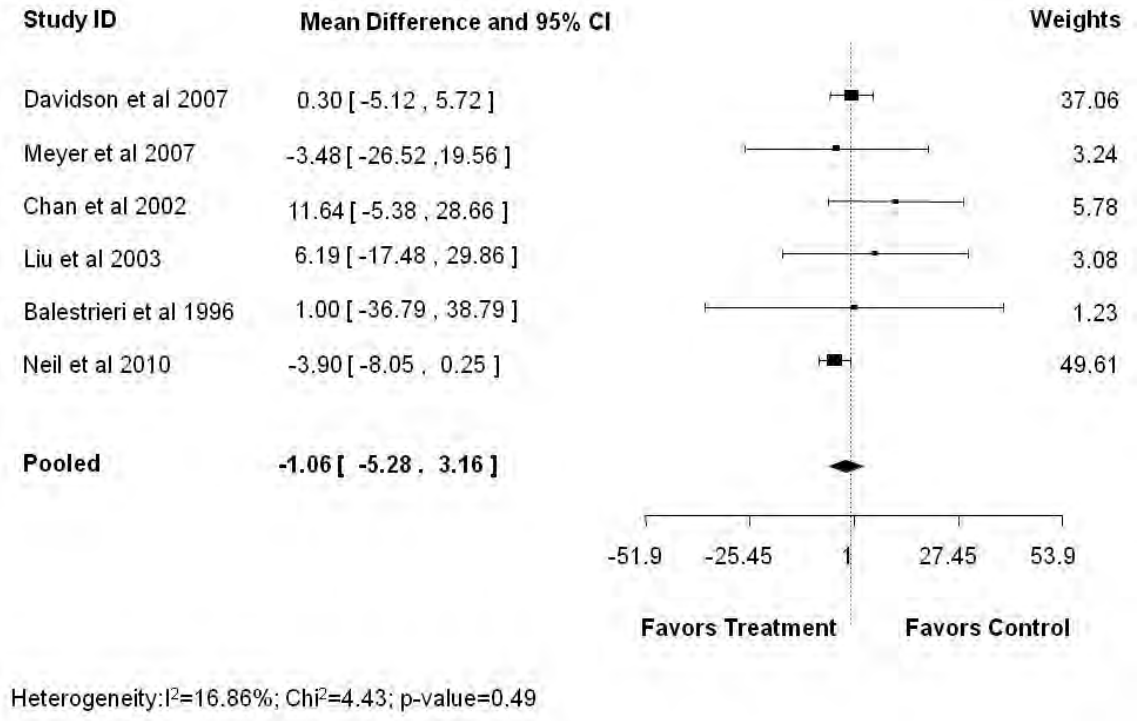


Low density lipoprotein-C. Posttreatment levels of levels of LDL-C were reported in 10 randomized trials.[37,40,44,53,91,92,94,96,97,151] In six trials,[40,44,53,91,96,151] the mean endpoint differences in LDL-C levels for participants with unclear or mixed CHD risk were not significantly different between the dietary supplement (2.0 to 9.2 g/day) and the control groups. Likewise, one trial found no significant difference in the mean change between the dietary supplement (2 g/day) and control groups (difference in mean change -5.84 mg/dL [95 percent CI -16.88, 5.20]).[92]

Our meta-analysis based on the results from 6 studies (participants with unclear or mixed CHD risk),[40,44,53,91,96,151] indicated that the mean LDL-C levels did not differ between the intervention (2.0 to 9.2 g/day) and control groups (Figure 10).

Two other trials of participants with unclear[94] and mixed[37] CHD risk reported that there was no significant difference in either posttreatment percent change in least squares mean (difference of 1.30 percent, p 0.43)[37] or percent change in median (difference at 8 weeks 2.2 percent, p 0.24; at 16 weeks 0.3 percent, p 0.64)[94] in LDL-C levels for the supplement(4 g/day) versus control groups. The percent change in LDL-C (from baseline) in one crossover trial of participants at low CHD risk was not significantly different between the dietary supplement (6 g/day) and control group at six weeks (-39.0 percent versus -37.0 percent, p greater than 0.05).[97]

Figure10. Posttreatment LDL-C levels in subjects taking statins with or without omega-3 fatty acids/fish oils (mg/dL)



Total cholesterol. Posttreatment levels of TC were reported for 11 trials.[37,40,44,53,76,91,92,94,96,97,151] The pooled results based on our meta-analysis of six trials in participants with unclear or mixed CHD risk [40,44,53,91,96,151] showed that the mean total cholesterol levels did not differ significantly between the intervention (2 to 9 g/day) and control groups (Figure 11; pooled mean difference: -3.86 [95 percent CI -10.69, 2.97])

In two other trials,[76,92] the mean endpoint/mean change differences in total cholesterol levels for participants with unclear or mixed CHD risk were not significantly different between the dietary supplement and the control groups.

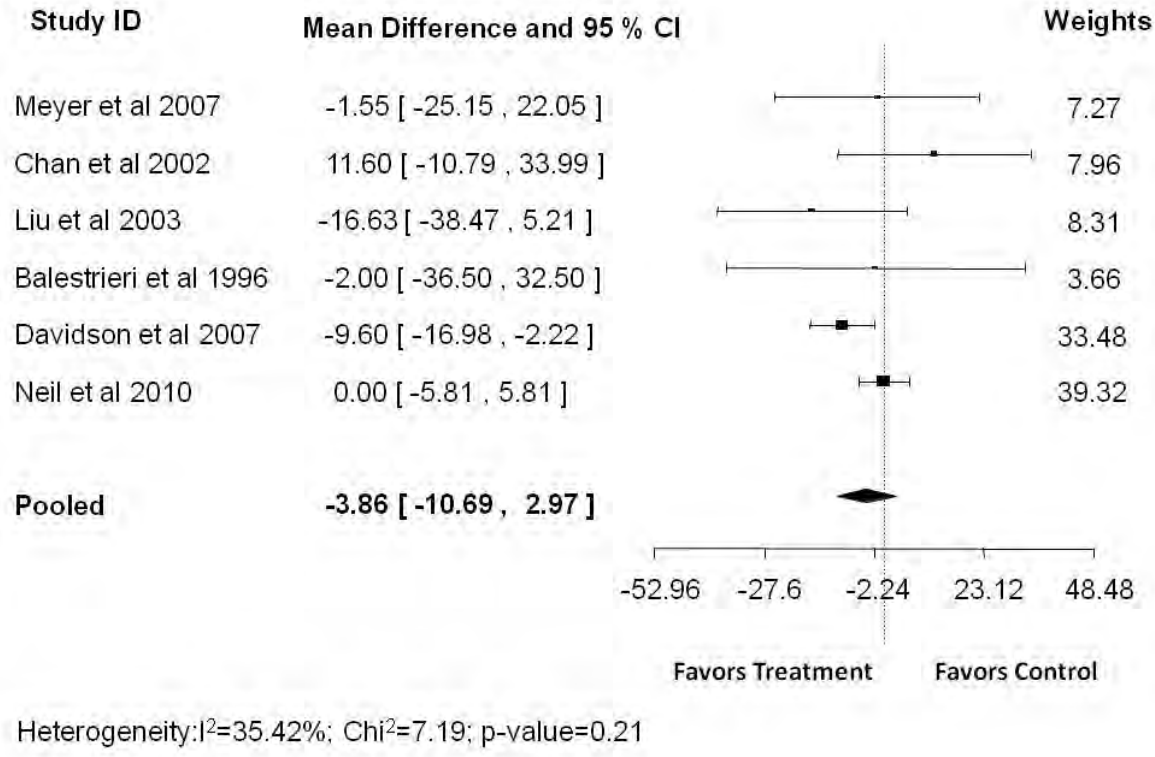
Similarly, one crossover trial[97] using 6 g/day omega-3 fatty acids did not find a significant difference for mixed CHD risk participants in the posttreatment total cholesterol percent change from baseline between the two treatment groups (-31.0 versus -27.0, p greater than 0.05).

In one trial of participants with unclear CHD risk,[40] the 8 week posttreatment mean total cholesterol level was significantly improved in the dietary supplement (4 g/day) versus control group (mean difference: -9.60 [95 percent CI -17.05, -2.14]). Two other trials reported significantly greater reductions in median total cholesterol percent change from baseline in the dietary supplement versus control groups for participants with mixed and unclear CHD risk (median percent change -2.7, p 0.006[37] and -5.8, p value less than 0.001[94]).

One trial in participants with mixed CHD risk did not report numerical data.[76]

The wide confidence intervals around the pooled estimate rendered the results regarding posttreatment total cholesterol levels as inconclusive (Table 31).

Figure 1. Posttreatment total cholesterol levels in subjects taking statins with or without omega-3 fatty acids/fish oils (mg/dL)



Triglycerides. Posttreatment levels of TG were reported for 12 trials which included participants with unclear or mixed CHD risk.[37,40,44,53,76,91,92,94,96,97,151,163]

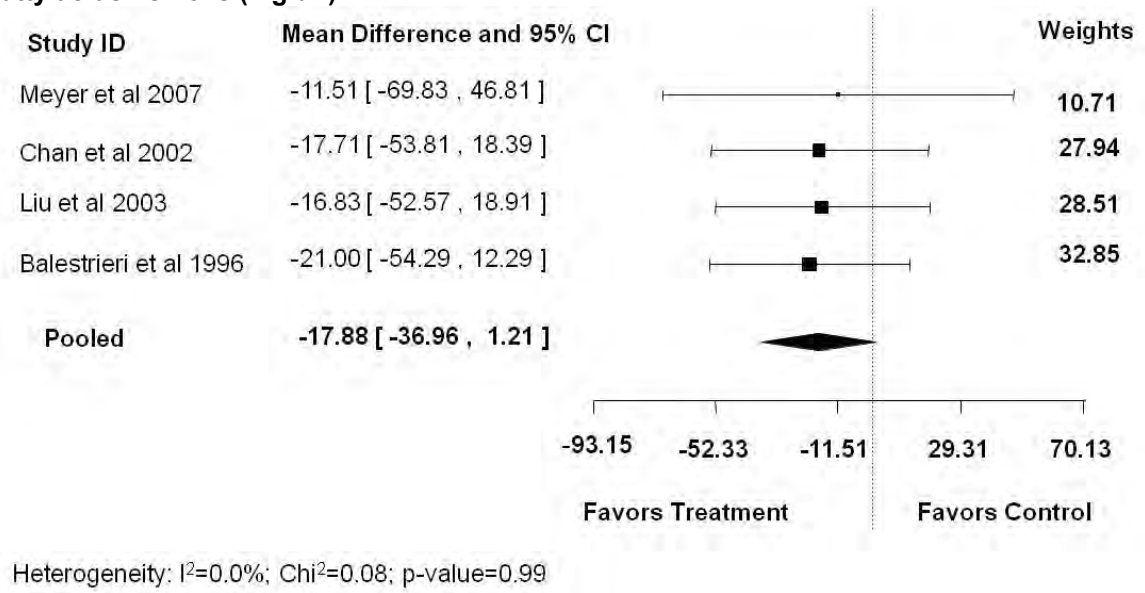
Initial pooling of six trials reporting posttreatment mean triglyceride levels revealed some degree of statistical heterogeneity (I^2 63.53 percent; Chi-squared statistic 15.95; p 0.01).[40,44,53,76,96,151] After careful examination of the study factors that could potentially explain this heterogeneity, we found that in two studies[40,76] which were conducted in specialty clinics,

the participants' baseline triglycerides levels were on average higher than those in other studies, thereby resulting in a greater magnitude of the observed mean differences in favor of the dietary supplement intervention (-73.50 mg/dL[40] and -91.23 mg/dL[76]). The meta-analysis of the two studies in participants with higher baseline levels of TG (greater than 200 mg/dL) resulted in a significant pooled estimate of mean difference in favor of adding the supplement to statins (I^2 0 percent, Chi-squared statistic 0.21) (Table 31). The meta-analysis based the remaining four studies in participants with lower baseline levels of TG (less than 200 mg/dL) showed a non-significant pooled mean difference (Figure 12) with no significant heterogeneity (I^2 0 percent; Chi-squared statistic 0.08; p 0.99).[44,53,96,151] Omega-3 fatty acid supplements ranged from 4 to 9.2 g/day, and participants were at mixed (moderate/moderately high[44], or low/moderate/high[96]) or unclear CHD risk. Information on clinical settings for these studies was not reported.

Three trials reporting median[37,94] or mean[97] percent change from baseline in triglyceride levels showed significantly reduced (i.e., improved) levels for the dietary supplement versus control groups of participants with mixed (low/moderate/high) CHD risk, using omega-3 fatty acids (4 to 6 g/day)[37,97] or unclear CHD risk, using omega-3 fatty acids (4 g/day).[94] In contrast 4 month posttreatment median triglyceride levels were numerically similar between omega-3 fatty acids (2 g/day) plus statins versus statin alone group in participants with type II diabetes (97.4 mg/dL versus 106.2 mg/dL, p value was not reported) in one trial.[91]

The wide confidence intervals around the pooled estimate rendered the results with regards to posttreatment triglyceride levels between the dietary supplement and control interventions as inconclusive (Table 31).

Figure 12. Posttreatment triglyceride levels in subjects taking statins with or without omega-3 fatty acids/fish oils (mg/dL)



Non-HDL-C. Posttreatment levels of non-HDL-C were reported for five trials, in which participants had mixed or unclear CHD risk.[37,40,44,94,163] Dose of supplements used were 4 g/day in three trials,[37,40,44,94] and 7.2 g/day in one trial.[163] Of three trials reporting mean non-HDL-C levels,[40,44,163] one trial in 254 participants with unclear CHD risk[40] indicated significantly lower (i.e., improved) posttreatment mean non-HDL-C in the dietary supplement group compared with the control group, whereas the remaining two trials (44 participants in both trials) showed no

significant between-group mean difference.[44,163] The pooling of results from the three trials[40,44,163] revealed statistical heterogeneity across the effect estimates (I^2 58.86 percent; Chi-squared statistic 4.96; p 0.08). There was no obvious explanation for this heterogeneity; the participants across these trials were of either unclear or mixed CHD risk. These studies were not pooled.

Trials reporting median percent change from baseline in non-HDL-C levels showed significantly greater (i.e., improved) reduction in non-HDL-C favoring the dietary supplement groups over the control groups in participants with unclear CHD risk[94] and mixed CHD risk.[37]

The overall results regarding posttreatment non-HDL-C levels between the treatment groups were determined to be inconclusive (Table 31).

TC/HDL-C ratio. Posttreatment levels of the TC/HDL-C ratio were reported for four trials.[37,40,94,163] Doses of supplement in these trials ranged from 4 to 7.2 g/day. Two trials in participants with unclear CHD risk [40,163] reporting posttreatment mean TC/HDL ratio levels yielded discrepant results, one in favor of the dietary supplement group,[40] and the other in favor of neither group.[163] This discrepancy in the results for TC/HDL-C ratio may have been due to differences between participants' CHD risk across the studies. Based on the differences in CHD risk and the different directions of the effect estimates, it was decided not to pool these studies.

Two other trials in participants with mixed[37] or unclear CHD risk[94] reported significant differences in posttreatment percent change in least squares mean[37] or percent change in median at eight weeks[94] in the TC/HDL-C ratio, favoring the dietary supplement over the control intervention.

The overall results regarding differences in posttreatment TC/HDL-C ratio levels between the treatment groups were inconclusive (Table 31).

Predefined thresholds of LDL-C and non-HDL-C. The proportion of participants reaching these thresholds was reported for one 16 week, parallel arm trial in participants with unclear CHD risk.[94] At the end of the treatment, there was no difference in the proportion of participants reaching pre-defined targets of either LDL-C (below 160, 130, or 100 mg/dL, or HDL-C (below 190, 160, or 130 mg/dL) between the supplement intervention (omega-3 fatty acids 4 g/day) and control groups (Table 31).

Lipoprotein A. Posttreatment levels of lipoprotein A were reported for one trial.[96] In this crossover randomized trial, participants with familial hypercholesterolemia (mixed CHD risk) were treated over 4 weeks, for each treatment period. The difference in the 4 week posttreatment mean lipoprotein A levels between the omega-3 fatty acids (5.1 g/day) and control groups was not significant (Table 31).

Blood pressure. Systolic and diastolic blood pressure levels posttreatment were reported for four trials; three parallel arm[91,92,151] and one crossover[37] trial. In the first parallel arm trial[92] participants with mixed CHD risk receiving omega-3 fatty acids (2 g/day) combined with statins (10 mg/day) for five weeks experienced significantly greater reductions in mean systolic blood pressure but not in diastolic blood pressure, compared with participants receiving statins alone. In two parallel arm trials with a treatment period of 16[91] and 25 weeks[151] in participants with unclear CHD risk there was no significant difference in the blood pressure between the omega-3

fatty acids(2 g/day in one trial, and 4 or 8 g/day in the other trial) in combination with statins versus statins alone. Statistical test results for the comparison were not provided.

In one crossover trial,[37] participants with mixed CHD risk receiving omega-3 fatty acids (4 g/day) and statins (20 mg/day) experienced significantly greater median reductions from baseline in systolic and diastolic blood pressure compared with those receiving the control intervention.

We were unable to perform a meta-analysis given the lack of data[151] and the differences in effect measures, reported as reductions in median[37] and mean levels.[92]

The overall results showed lower posttreatment systolic blood pressure levels for the combination of omega-3 fatty acids and statins versus statins alone group (Table 31).

Blood coagulation. This outcome was reported for a crossover randomized trial in healthy participants. [95] After 2 weeks of treatment, there was no difference between the groups of omega-3 fatty acids (4 g/day) in combination with statins (80 mg/day) versus statins alone in the following blood coagulation parameters: prothrombin time, activated partial thromboplastin time, platelet aggregation with adenosine diphosphate, or platelet aggregation with collagen.

Platelet count. Posttreatment platelet count was reported for three trials; one parallel arm[76] and two crossover trials.[95,97] Study participants in these trials had mixed CHD risk (healthy volunteers, and participants with combined or familial hyperlipidemia). The differences between posttreatment mean change[76,95] or percent change [97] in platelet counts between baseline and two to six weeks between the omega-3 fatty acids(4 to 6 g/day) and control groups was not significant. Two trials[76,95] reporting posttreatment mean change in platelet count were not pooled because standard deviations were not reported for one study.[95]

Bleeding time. Posttreatment bleeding time was reported for a crossover randomized trial that included participants with mixed CHD risk (familial hyperlipidemia).[97] There was no difference in percent change for bleeding time between the omega-3 fatty acids (6 g/day) and the control groups following 6 weeks of treatment.

Omega-3 Fatty Acids/Fish Oils Plus ACE Inhibitors Versus ACE Inhibitors Alone

Triglycerides. Posttreatment levels were reported for two parallel arm trials in participants with unclear CHD risk (Table 31).[77,152] In a 25 week trial [77] the difference in mean triglyceride levels between the omega-3 fatty acids (5 g/day) and control groups was not significant. In contrast, in a 6 week trial[152] the mean triglyceride reduction significantly favored the supplement (3 g/day) over the control group.[152] These trials were not pooled due to differences in the reported effect measures.

The overall results regarding posttreatment triglyceride levels between the treatment groups were inconclusive.

Blood Pressure. Systolic and diastolic blood pressure levels posttreatment were reported for two parallel arm trials in participants with unclear CHD risk, with supplementation with omega-3 fatty acids (3 to 5 g/day)[77,152] There was no significant between-group difference in either systolic blood pressure (mean difference 0 mm Hg[77] and -1.00 mm Hg[152]) or diastolic blood pressure (-1.40 mm Hg [77] and -2.00 mm Hg[152]).

The pooled analysis of these trials[77,152] indicated that there was no difference in either systolic (Figure 13) or diastolic (Figure 14) blood pressure between the intervention and control groups.

Figure 13. Posttreatment systolic blood pressure in subjects taking ACE inhibitors with or without omega-3 fatty acids/fish oils (mmHg)

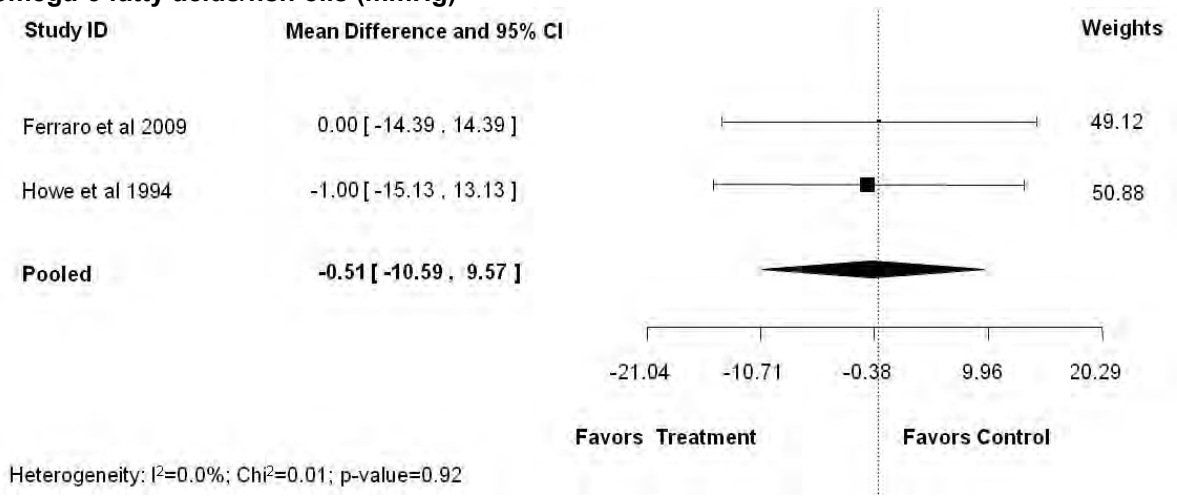
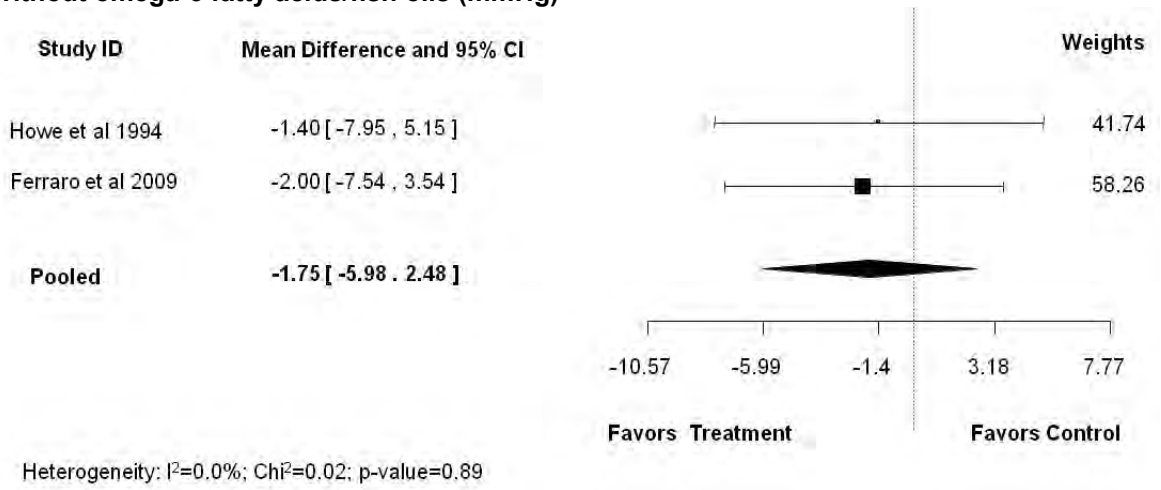


Figure 14. Posttreatment diastolic blood pressure in subjects taking ACE inhibitors with or without omega-3 fatty acids/fish oils (mmHg)



Urinary protein. Posttreatment data (protein excretion, and at least 50 percent reduction in proteinuria) was reported for one 25 week parallel arm trial in participants with unclear CHD risk.[77] The participants in the omega-3 fatty acids (3 g/day) plus ACE inhibitors (10 mg/day ramipril plus 300 mg/day irbersartan) combination group had significantly reduced (i.e., improved) mean urinary protein excretion compared with participants in the ACE inhibitor alone (367 mg/day versus 1353 mg/day). Similarly, the proportion of participants who achieved at least 50 percent reduction in proteinuria was significantly greater (i.e., improved) in the supplement versus control group (80 percent versus 20 percent).

Omega-3 Fatty Acids/Fish Oils Plus Fenofibrate Versus Fenofibrate Alone

One study[56] contributed evidence (Table 31). This was a parallel arm double blind placebo-controlled trial in 167 participants in whom the treatment allocation concealment was unclear (moderate risk of bias). Participants had unclear CHD risk and received treatment for eight weeks (4 g/day omega-3 fatty acids plus 130 mg/day fenofibrate versus 4 g/day placebo plus 130 mg/day fenofibrate). The percent change from baseline to week 8 was not significantly different between participants in the dietary supplement and control groups for HDL-C, total cholesterol/HDL-C ratio), total cholesterol, non-HDL-C, or triglycerides. In contrast, the percent change (i.e., reduction) from baseline in LDL-C levels was significantly greater in the dietary supplement versus control group. The incidence of hypertension was not significantly different between the two groups.

The overall results of this study on levels of LDL-C, HDL-C, TC/HDL-C ratio, total cholesterol, and non-HDL-C (reported as median percent change) were inconclusive.

Omega-3 Fatty Acids/Fish Oils Plus Calcium Channel Blockers Versus Calcium Channel Blockers Alone

One study[50] contributed evidence (Table 31). This 16 week parallel arm open label active treatment controlled trial was in 22 participants at high CHD risk (variant angina). The supplement treatment (1.8 g/day omega-3 fatty acids plus 90 to 120 mg/day diltiazem versus diltiazem) allocation concealment was unclear (moderate risk of bias). The posttreatment mean difference in total cholesterol, LDL-C, HDL-C, and triglycerides were not significantly different between participants in the dietary supplement and control groups. Due to wide confidence intervals, these results were inconclusive.

Omega-3 Fatty Acids/Fish Oils Plus Aspirin and Calcium Channel Blockers Versus Aspirin and Calcium Channel Blockers Alone

One study[51] contributed evidence (Table 31). This parallel arm single-blind (only assessors were blinded) active treatment (calcium channel blockers plus aspirin) controlled trial was in 107 participants for whom the randomization sequence was computer-generated and treatment allocation concealment was unclear (moderate risk of bias). Participants in this trial were at high CHD risk (pre-coronary angioplasty) and received their treatment for 6 weeks (3 g/day omega-3 plus calcium channel blockers and 150 mg/day aspirin versus calcium channel blockers and aspirin). The posttreatment mean triglycerides was significantly lower (i.e., improved) in the participants receiving the dietary supplement versus controls. The mean differences in total cholesterol, HDL-C, and LDL-C were not significantly different between the dietary supplement and control groups. The wide confidence intervals around these estimates rendered these results inconclusive (grade: insufficient).

Omega-3 Fatty Acids/Fish Oils Plus Calcium Channel Blockers, Aspirin, and Dipyridamole Versus Calcium Channel Blockers, Aspirin, and Dipyridamole

One study[52] contributed evidence (Table 31). This parallel arm single-blind controlled trial was in 82 male participants for whom the randomization sequence was computer-generated and treatment allocation concealment was unclear (moderate risk of bias). All men in this trial were

at high CHD risk (postcoronary angioplasty) and received their treatment for 12 weeks (3.2 g/day omega-3 plus calcium channel blockers,325 mg/day aspirin and 225 mg/day dipyridamole versus calcium channel blockers, aspirin and dipyridamole). Although the posttreatment mean LDL-C was significantly greater (i.e., worsened) in the participants receiving the dietary supplement versus controls, the mean triglyceride levels were significantly lower (i.e., improved) in the dietary supplement versus the control group. HDL-C, total cholesterol, and platelet count were not significantly different. The wide confidence intervals around these estimates rendered these results inconclusive (grade: insufficient).

Omega-3 Fatty Acids/Fish Oils Plus Niacin (More Than 250 mg), and Aspirin Versus Niacin (More Than 250 mg), and Aspirin

One study[78] contributed evidence (Table 31). This parallel arm placebo controlled active treatment (niacin plus aspirin) trial was in 14 participants for whom the randomization sequence and treatment allocation concealment were unclear (moderate risk of bias). The participants in this trial had unclear CHD risk (atherogenic dyslipidemia) and received their treatment for 12 weeks (4 g/day omega-3 plus 500 to 3000 mg/day niacin plus 325 mg/day aspirin versus niacin and aspirin).

The posttreatment mean differences in total cholesterol, HDL-C, LDL-C and triglycerides were not significantly different between the dietary supplement and control groups.

Omega-3 Fatty Acids/Fish Oils Plus Aspirin Versus Aspirin Alone

In two trials in healthy participants with low or mixed CHD risk, a single dose of aspirin (325 mg[99] or 100 mg[98]) was administered following two to three weeks of omega-3 fatty acids (8 to 10 g/day) or placebo pre-treatment.

Omega-3 Fatty Acids/Fish Oils Plus Beta-Adrenergic Antagonists Versus Beta-Adrenergic Antagonists

Blood Pressure. Systolic and diastolic blood pressure change posttreatment was reported for one trial.[164] This double-blind crossover trial was in 25 participants with unclear CHD risk, on beta-blocker monotherapy who were randomized to receive omega-3 fatty acids (4 g/day) or placebo for 6 weeks. No washout period was reported for this trial. The data for this study were not reported clearly, which precluded meaningful synthesis of the evidence.

Omega-3 Fatty Acids/Fish Oils Plus Warfarin Versus Warfarin Alone

One 4 week study[55] contributed evidence. This was a parallel double blind (blinding status of participants, care providers, or study assessors was unclear), placebo-controlled trial in 11 participants with unclear CHD risk, for whom the randomization sequence and treatment allocation concealment were unclear (high risk of bias – there was a baseline between-group imbalance in gender and age). Treatment was 3 g/day or 6 g/day omega-3 fatty acids plus warfarin versus placebo plus warfarin. There was no significant difference in posttreatment INR values between the dietary supplement and control groups (p 0.41; no additional numerical data were provided).

Table 31. Strength of evidence for cardiovascular drug(s) with and without omega-3 fatty acids—Intermediate outcomes

Cardio-vascular Drug(s)/ Outcome	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect*
Statins						
CRP[44,158] (mg/L)	-	-	-	-	-	**No difference** Geometric mean difference: 1.14 (95% CI 0.6, 2.4) versus 1.80 mg/L (95% CI 1.3, 3.2)
HDL-C[37,40,44,53,92,94,96,97,151,163] (mg/dL)	Moderate	Inconsistent	Indirect	Precise	Low	**No difference** Pooled mean difference: 2.26(95% CI -1.82, 6.34) [40,44,53,96,151,163]
LDL-C[37,40,44,53,92,94,96,97,151] (mg/dL)	Moderate	Inconsistent	Indirect	Precise	Low	**No difference** Pooled mean difference: 1.33 mg/dL (95% CI -3.56, 6.22)[40,44,53,96,151]
TC[37,40,44,53,76,92,94,96,97,151] (mg/dL)	Moderate	Inconsistent	Indirect	Imprecise	Insufficient	**Inconclusive** Pooled mean difference: -7.06 mg/dL (95% CI -14.50, 0.37)[40,44,53,96,151]
TG[40,76]	Moderate	Consistent	Indirect	Precise	Low	**In favour of combination** Pooled mean difference: -74.95 mg/dL (95% CI -95.80, -54.10)[40,76]
TG[37,40,44,53,76,92,94,96,97,151,163] (mg/dL)	Moderate	Consistent	Indirect	Imprecise	Insufficient	**Inconclusive** Pooled mean difference: -17.88 mg/dL (95% CI -36.96, 1.21) [44,53,96,151]
Non-HDL-C [37,40,44,94,163] (mg/dL)	Moderate	Inconsistent	Indirect	Imprecise	Insufficient	**Inconclusive** -14.70 (95% CI -21.77, -7.62) [40] 5.42 (95%CI -15.75, 26.59) [44] 5.60 (95% CI -34.06, 45.26) [163] Median changes -40.2% vs -33.7%, p <0.001[94] -40.0% vs -34.3%, p< 0.001[37]
TC/HDL-C ratio[37,40,94,163]	-	-	-	-	-	**Inconclusive** -0.60 (95% CI -0.83, -0.36) [40] 0.29 (95% CI -0.90, 1.48) [163] % change least squares means -6.5%, p<0.001[37] Median change -38.3% vs -34.5%, p less than 0.001

Table 31. Strength of evidence for cardiovascular drug(s) with and without omega-3 fatty acids—Intermediate outcomes (continued)

Cardio-vascular Drug(s)/ Outcome	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect*
LDL-C (<160/130/ 100 mg/dL) [94]	Moderate	NA	Indirect	Precise	Low	**No difference** RR 0.93 (95% CI 0.84, 1.03)
HDL-C (<190/160/ 130 mg/dL) [94]	Moderate	NA	Indirect	Precise	Low	**No difference** RR 1.00 (95% CI 0.91, 1.11)
Lipoprotein A [96] (mg/dL)	-	-	-	-	-	**Inconclusive** 2.00 (95% CI -34.40, 38.40)
Systolic Blood Pressure[37,92,151]	Moderate	Inconsistent	Indirect	Precise	Low	**In favor of supplement-CV drug combination** -8.50 mm Hg (95% CI -16.33, -0.66) [92] Median change from baseline -5.0 vs. +0.3 mmHg [37] No difference (data not given) [151]
Diastolic Blood Pressure[37,92,151] (mm Hg)	Moderate	Inconsistent	Indirect	Precise	Low	**No difference** 0.20 (95% CI -4.76, 5.16) [92] No difference (data not given) [151] **In favor of supplement-CV drug combination** Median change from baseline -23.3 vs. -1.8 mmHg [37]
Blood Coagulation [95] PT aPTT PA/AD PA/Collagen	-	-	-	-	-	**No difference** -0.10 sec (95% CI -0.28, 0.08) 0.10 sec (95% CI -0.62, 0.82) 1.10 % (95% CI -5.05, 7.25) 0.90 % (95% CI -5.70, 7.50)
Platelet Count[76,95,97]	-	-	-	-	-	**Inconclusive** -9.82 10^3/µL (95% CI -42.79, 23.15) [95] 6.00 10^3/µL (95% CI 1.74, 10.25) [76] 17.0% vs 20.0% change, p>0.05[97]
Bleeding Time[97]	-	-	-	-	-	**No difference** 1.0% (95% CI -0.59, 2.59)
ACE inhibitors						
TG[77,152] mg/dL	Moderate	Inconsistent	Indirect	Imprecise	Insufficient	**Inconclusive** -38.6 (95% CI -160.62, 83.42) [77] -24.35 mg/dL (95% CI -45.31, -3.38) [152]

Table 31. Strength of evidence for cardiovascular drug(s) with and without omega-3 fatty acids—Intermediate outcomes (continued)

Cardio-vascular Drug(s)/ Outcome	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect*
Systolic Blood Pressure[77,152] mm Hg	Moderate	Consistent	Indirect	Precise	Low	**No difference** Pooled mean difference: -0.51 (95% CI -10.59, 9.57)
Diastolic Blood Pressure[77,152] mm Hg	Moderate	Consistent	Indirect	Precise	Low	**No difference** Pooled mean difference: -1.75 (95% CI -5.98, 2.48)
Urinary Protein excretion[77] mg/d	-	-	-	-	-	**In favor of supplement-CV drug combination** -986.00 (95% CI -1763.43,-208.56)
≥50% Reduction in Proteinuria[77]	-	-	-	-	-	**In favor of supplement-CV drug combination** RR 4.00 % of participants (95%CI 1.40, 11.30)
Fenofibrate						
LDL-C[56]	Moderate	NA	Indirect	Unclear	Insufficient	**In favor of supplement-CV drug combination** 48.20% vs 39.00% change, p=0.03
HDL-C[56]	Moderate	NA	Indirect	Unclear	Insufficient	**Inconclusive** -1.90% vs 1.30% change, p>0.05
TC[56]	Moderate	NA	Indirect	Unclear	Insufficient	**Inconclusive** -8.00% vs -5.10% change, p>0.05
TC/HDL-C[56]	-	-	-	-	-	**Inconclusive** -4.80% vs -8.30% change, p>0.05
TG[56]	Moderate	NA	Indirect	Unclear	Insufficient	**Inconclusive** -60.80% vs -53.80% change, p=0.059
Non-HDL-C[56]	Moderate	NA	Indirect	Unclear	Insufficient	**Inconclusive** -8.20% vs -7.10% change, p>0.05
Incidence of hypertension (% of participants)	-	-	-	-	-	**Inconclusive** RR 0.98 (95% CI 0.14, 6.85)
Calcium Channel Blockers						
LDL-C[50] (mg/dL)	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** 0 (95% CI -94.30, 94.30)
HDL-C[50] (mg/dL)	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** -2.00 (95% CI -32.7, 28.70)
TC[50] (mg/dL)	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** 5.00 (95% CI -91.30, 101.30)
TG[50] mg/dL	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** -32.00 (95% CI -112.60, 176.60)

Table 31. Strength of evidence for cardiovascular drug(s) with and without omega-3 fatty acids—Intermediate outcomes (continued)

Cardio-vascular Drug(s)/ Outcome	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect*
Calcium Channel Blockers + Aspirin						
LDL-C[51] mg/dL	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** 1.00 (95% CI -10.90, 12.90)
HDL-C[51] mg/dL	Moderate	NA	Indirect	Precise	Insufficient	**Inconclusive** -2.00 (95% CI -32.70, 28.70)
TC[51] mg/dL	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** 9.00 (95% CI -6.40, 24.40)
TG[51] mg/dL	Moderate	NA	Indirect	Precise	Low	**In favor of supplement-CV drug combination** -54.00 (95% CI -94.1, -13.90)
Calcium Channel Blockers + Aspirin + Dipyridamole						
LDL-C[52] (mg/dL)	Moderate	NA	Indirect	Precise	Low	**In favor of CV drug alone** 21.00 (95% CI 3.30, 38.70)
HDL-C[52] (mg/dL)	Moderate	NA	Indirect	Precise	Insufficient	**Inconclusive** 0 (95% CI -4.00, 4.00)
TC[52] (mg/dL)	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** 19.00 (95% CI -1.70, 39.70)
TG[52] (mg/dL)	Moderate	NA	Indirect	Precise	Low	**In favor of supplement-CV drug combination** -81.0 (95% CI -125.30, -36.70)
Platelet count[52] ($10^3/\mu L$)	-	-	-	-	-	**Inconclusive** -2.80 (95% CI -56.20, 0.20)
Niacin + Aspirin						
LDL-C (mg/dL)	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** 17.00 (95% CI -6.60, 40.60)
HDL-C (mg/dL)	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** 1.00 (95% CI -13.20, 15.20)
TC (mg/dL)	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** 9.00 (95% CI -19.10, 37.10)
TG (mg/dL)	Moderate	NA	Indirect	Imprecise	Insufficient	**Inconclusive** -94.00 (95% CI -196.80, 8.80)
Warfarin						
INR	High	-	Indirect	-	-	No numeric data provided

Note: * Range for mean difference (or risk ratio) given only when evidence consists of multiple studies that were not pooled. Intervention denotes dietary supplement arm; Control denotes placebo or no treatment arm. Range given if evidence consists of multiple studies.

Abbreviations: ACE = angiotensin-converting enzyme; aPPT = activated partial prothrombin time; CHD = coronary heart disease; CRP = C-reactive protein; HDL-C = high density lipoprotein-cholesterol; LDL-C = low density lipoprotein-cholesterol; NA = not applicable; NR = not reported; PA/AD = platelet aggregation/adenosine diphosphate PT = prothrombin time; RCT = randomized controlled trial; RR=relative risk; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides; vs = versus; wk(s) = week(s); yr(s) = year(s).

Applicability. Statin combinations were examined in populations with 22 to 100 percent males, with unclear to mixed CHD risk, and mean age ranging from 30 years to 63 years. ACE inhibitors were examined in populations with 40 to 85 percent males, with unclear or high CHD

risk, and mean age 40 years to 60 years. Calcium channel blockers plus aspirin plus dipyridamole were examined in a male population, with high CHD risk, and mean age 56 years. Trial duration ranged from 4 to 25 weeks.

Vitamin E

Ten RCTs and one controlled clinical trial examined the use of Vitamin E with cardiovascular drugs. Subjects were concomitantly taking antiplatelet agents (aspirin or ticlopidine)[49,80], furosemide [81], gemfibrozil[79], nifedipine[82], or statins.[46,83-87]

Vitamin E Plus Antiplatelet Agents Versus Antiplatelet Agents Alone

Two parallel-arm RCTs examined the effect of concomitant use of vitamin E and antiplatelet agents.[49,80] In comparison with no treatment, 6 weeks of treatment with vitamin E (400 to 450 IU/day) was not found to effect total cholesterol in atherosclerotic plaque in 16 participants with high CHD risk taking aspirin or ticlopidine[80]. No changes in serum total cholesterol and triglyceride levels at followup were noted (reported qualitatively only). These results were potentially impacted by Type II error due to small sample size.

Platelet aggregation was assessed in a trial comparing vitamin E (400 IU/day) plus aspirin with aspirin alone in elderly, primarily white, subjects with transient ischemic attack, minor stroke, or residual neurologic deficits (unclear CHD risk).[49] Treatment was administered for 2 years. Platelet adhesion to collagen III was significantly decreased by vitamin E supplementation.

Strength of evidence was insufficient for triglycerides (Table 32).

Vitamin E Plus Furosemide Versus Furosemide Alone

One small parallel-arm RCT of 24 participants examined the concomitant use of Vitamin E and furosemide.[81] Participants were randomized to receive either Vitamin E (600 mg/day) and furosemide (25 mg/day) or furosemide (25 mg/day) with placebo for 4 weeks. No significant differences were found in systolic and diastolic blood pressure. Strength of evidence for blood pressure was insufficient (Table 32).

Vitamin E Plus Nifedipine Versus Nifedipine Alone

One small crossover RCT in 30 participants at high CHD risk examined vitamin E (900 mg/day) plus nifedipine versus placebo plus nifedipine.[82] Nifedipine long-acting formulation (average dose 88 plus/minus 11 mg/day) and Vitamin E were administered for four months.

Supplementation with Vitamin E was found to significantly lower total serum cholesterol, LDL-C, and triglycerides. HDL-C was slightly raised by administration of vitamin E, but the estimate was not statistically significant. There were no statistically significant differences in systolic and diastolic blood pressure.

The strength of evidence was insufficient for systolic and diastolic blood pressure, and HDL-C. Strength of evidence for improvement in LDL-C and triglyceride levels with combination treatment was low (Table 32).

Applicability. This study recruited elderly (mean age 73.8 plus/minus2.1 years), moderately obese subjects with stable effort angina and high CHD risk.

Vitamin E Plus Gemfibrozil Versus Gemfibrozil Alone

The combination of vitamin E (600 mg/day) and gemfibrozil was assessed in one controlled clinical trial in 67 participants.[79] Subjects were hyperlipidemic and were divided into young (mean age 29.5 plus/minus 4.9 years) and elderly (mean age 71.5 plus/minus 3.6 years) groups. No statistically significant effects were observed in lipid parameters or blood pressure. Effect estimates had very wide 95 percent confidence intervals, so this study was underpowered to detect statistically significant results. Strength of evidence for blood pressure and lipid parameters was insufficient (Table 32).

Vitamin E Plus Statins Versus Statins Alone

Six RCTs addressed combined use of vitamin E (400 to 1000 U/day) and statins, including atorvastatin[87], simvastatin[83-86], and pravastatin[46]. All studies included subjects with hypercholesterolemia. In some studies, subjects also had additional conditions, such as diabetes[87] and vascular disease.[86]

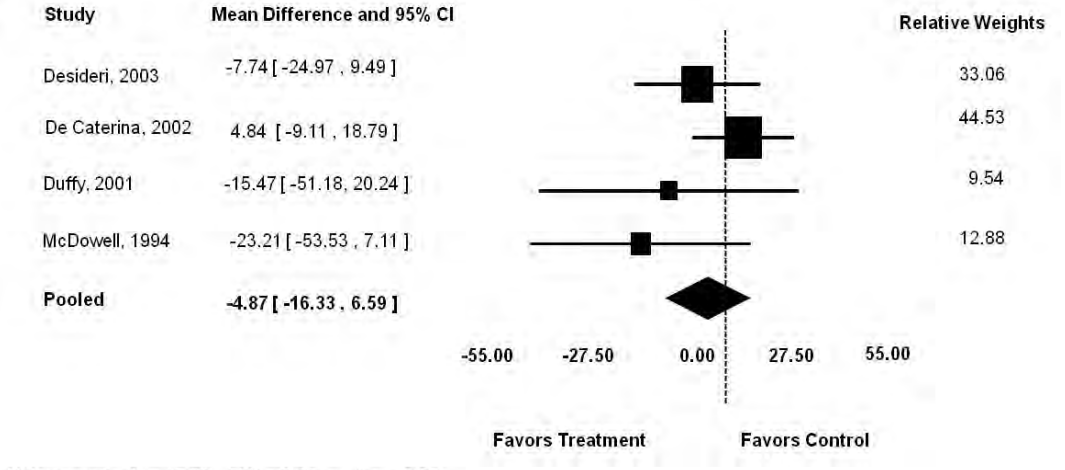
Lipid parameters were reported in all studies. Meta-analyses of total cholesterol, LDL-C, HDL-C, and triglycerides were undertaken for four trials.[83-86] Two trials could not be meta-analyzed because different effect estimates were reported (i.e., one trial reported serum lipid parameters in a qualitative manner only[87] and one trial reported lipid parameters as percent change from baseline[46]).

One study reported nonsignificant differences in cholesterol and triglyceride levels in non-HDL subfraction for combination vitamin E plus atorvastatin.[87] Another study reported nonsignificant differences for percent change in baseline for total cholesterol, LDL-C, HDL-C, and triglycerides for combination vitamin E plus pravastatin.[46]

The four trials that were pooled involved administration of vitamin E with simvastatin (total sample size 106).[83-86] Dosages of vitamin E and simvastatin ranged from 400 to 1000 U/day and 10 to 40 mg/day respectively. The pooled effect estimates for total cholesterol, LDL-C, HDL-C, and triglycerides were all statistically nonsignificant (Figures 15–18). Heterogeneity was minimal for all pooled estimates except for LDL-C (I^2 64.6 percent, p-value 0.04). The observed heterogeneity could not be explained by variation of doses of supplement or cardiovascular drug. The strength of evidence was insufficient for LDL-C, HDL-C, and triglycerides (Table 32).

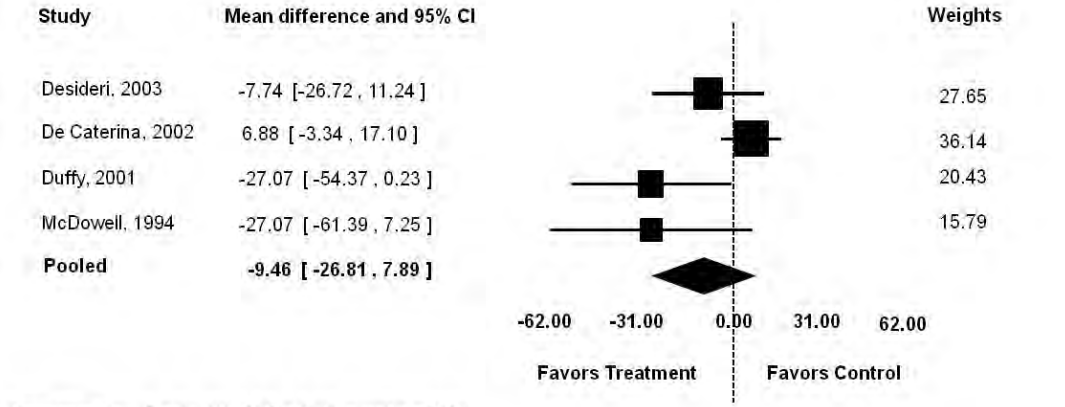
Other reported outcomes included C-reactive protein, prothrombin time, and platelet count. In a study of middle aged hypercholesterolemic subjects at low CHD risk, a statistically significant difference for C-reactive protein in favor of Vitamin E plus simvastatin was found (MD -0.40 mg/L (95 percent CI -0.66, -0.14]).[85] In another study of hypercholesterolemic subjects, no differences were found in prothrombin time and platelet count between Vitamin E plus pravastatin and pravastatin alone (reported qualitatively only).

Figure 15. Forest plot of total cholesterol for statins with or without vitamin E (mg/dL)



Heterogeneity: I^2 = 18.0%, Chi^2 = 3.66 p-value = 0.30

Figure 2. Forest plot of LDL-C for statins with or without vitamin E (mg/dL)



Heterogeneity: I^2 = 64.6%, Chi^2 = 8.49, p-value = 0.04

Figure 17. Forest plot of HDL-C for statins with or without vitamin E (mg/dL)

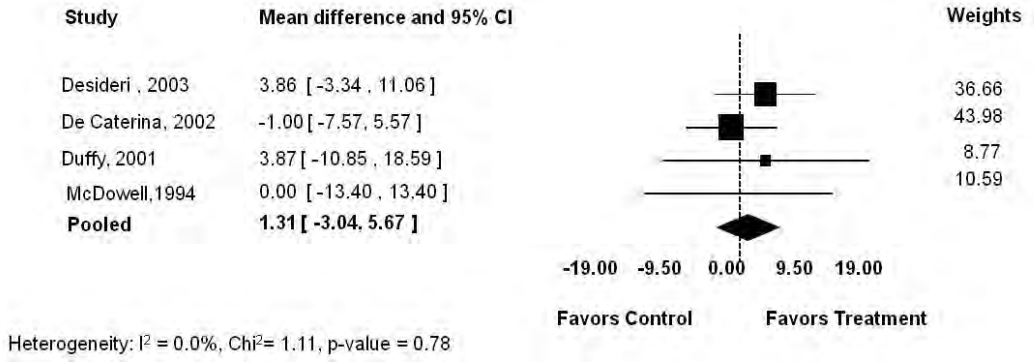


Figure 18. Forest plot of triglyceride levels for statins with or without vitamin E (mg/dL)

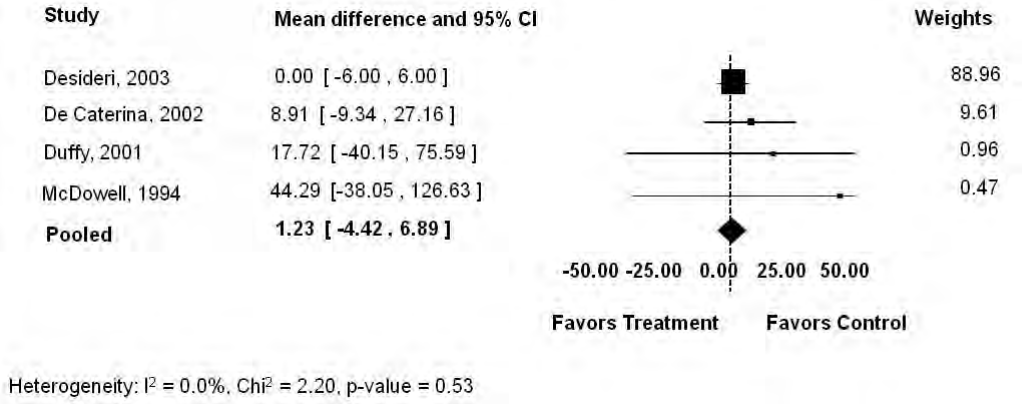


Table 32. Strength of evidence for cardiovascular drug(s) with and without vitamin E—Intermediate outcomes

Cardiovascular Drugs(s) / Outcome	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect* MD (95% CI)
Antiplatelet Agents						
Triglycerides	Moderate	NA	Indirect (surrogate)	NA	Insufficient	**Inconclusive** No changes observed at end of follow-up (reported qualitatively only)
Platelet adhesion to collagen III (/cm^2 x 10^5)	-	-	Indirect (surrogate)	-	-	**In favor of combination treatment** MD -1.70 (-2.06, -1.34]).

Table 32. Strength of evidence for cardiovascular drug(s) with and without vitamin E—Intermediate outcomes (continued)

Cardiovascular Drugs(s) / Outcome	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect* MD (95% CI)
Furosemide						
Blood pressure	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** Systolic -3.00 mmHg (-7.69, 1.69) Diastolic -2.00 mmHg (-6.36, 2.36)
Nifedipine						
Blood pressure	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** Systolic -2.00 mmHg (-19.55, 15.55) Diastolic -1.00 mmHg (-3.79, 1.79)
LDL-C	Moderate	NA	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** -39.83 mg/dL (-71.29, -8.37)
HDL-C	Moderate	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** 4.26 mg/dL (-2.02, 10.54)
Triglycerides	Moderate	NA	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** -23.91 mg/dL (-35.89, -11.93)
Total cholesterol(TC) (mg/dL)	-	-	Indirect (surrogate)	-	-	**In favor of combination treatment** MD-35.96 (-46.96, -24.96),
Gemfibrozil						
Blood Pressure	High	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** Systolic 7.00 mmHg (-14.07, 28.07) (elderly) -3.00 mmHg (-22.46, 16.46) (young) Diastolic 4.00 mmHg (-11.29, 19.29) (elderly) -1.00 mmHg (-13.00, 11.00) (young)
LDL-C	High	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** 6.96 (-132.08, 146.00) (elderly) -4.25 (-16.85, 8.35) (young)

Table 32. Strength of evidence for cardiovascular drug(s) with and without vitamin E—Intermediate outcomes (continued)

Cardiovascular Drugs(s) / Outcome	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect* MD (95% CI)
HDL-C	High	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** 0 (-4.42, 4.42) (elderly) 6.19 (-1.28, 13.66) (young)
Triglycerides	High	NA	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** -23.91 (-336.44, 288.62) (elderly) -7.97 (-45.23, 29.29) (young)
Statins						
HDL-C	Moderate	Inconsistent	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** Pooled MD 1.31 mg/dL (-3.04, 5.67)
LDL-C	Moderate	Consistent	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** Pooled MD -9.46 mg/dL (-26.81, 7.89)
Triglycerides	Moderate	Consistent	Indirect (surrogate)	Imprecise	Insufficient	**Inconclusive** Pooled MD 1.23 mg/dL (-4.42, 6.89)

Note: * Range for mean difference (or risk ratio) given only when evidence consists of multiple studies that were not pooled. Intervention denotes dietary supplement arm; Control denotes placebo or no treatment arm. Range given if evidence consists of multiple studies.
Abbreviations: CI = confidence interval; HDL-C = high density lipoprotein-cholesterol; LDL-C = low density lipoprotein-cholesterol; MD = mean difference; NA = not applicable.

Vitamin K

Vitamin K Plus Coumarin Derivatives Versus Coumarin Derivatives Alone

One parallel-group RCT examined the effect of concomitant use of Vitamin K (5 mL volume per dose with concentration of 30 μg/mL vitamin K) and warfarin.[41] One cohort study was also identified that assessed whether vitamin K intake in subjects taking anticoagulants is associated with subtherapeutic INR.[150] The results of this study have not been included in the evidence synthesis as it added no further insights to the existing randomized trial.

The percentage of time that INR remained in the therapeutic range was reported (defined as INR within 0.5 of 2.0 to 3.0). Patients receiving Vitamin K stayed in the INR therapeutic range for a statistically significant longer percentage of time than patients who received warfarin alone.

INR control was also examined in terms of the standard deviation of the INR[41] and the number of participants achieving improved INR control compared with six months prior to study.[41] Vitamin K was found to increase stability of anticoagulation treatment (Table 33). Furthermore, the number of participants achieving stable INR was higher in combination with warfarin (RR 2.56 [95 percent CI 1.24, 5.28]).[41]

Strength of evidence for the statistically significant INR measures was low (Table 33).

Applicability. Participants with atrial fibrillation being anticoagulated with warfarin for thromboembolic prophylaxis, but with unstable INR control.[41] The trial was of 6 months duration.

Table 33. Strength of evidence for coumarin derivatives with and without vitamin K—Intermediate outcomes

Cardiovascular Drugs(s) / Outcome	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect* (95% CI)
% time in INR therapeutic range	Moderate	Consistent	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** MD 9% (1.42, 16.57)
SD of INR	Moderate	NA	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** MD -0.12 (-0.20, -0.04)
N achieving INR control	Moderate	NA	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** N achieving INR control RR 1.30 (1.04, 1.62)
N achieving stable INR	Moderate	NA	Indirect (surrogate)	Precise	Low	**In favor of combination treatment** N achieving stable INR RR 2.56 (1.24, 5.28)

Note: * Range for mean difference (or risk ratio) given only when evidence consists of multiple studies that were not pooled. Intervention denotes dietary supplement arm; Control denotes placebo or no treatment arm. Range given if evidence consists of multiple studies.
Abbreviations: CI = confidence interval; INR = International Normalized Ratio; MD = mean difference; N = number; NA = not applicable; SD = standard deviation.

Key Question 2a. Do the effect estimates of intermediate cardiovascular outcomes vary by age, ethnicity, gender, or health status?

No studies for any supplement-drug combination of interest precluded exploration of heterogeneity in the effect estimates across preidentified subgroups for intermediate outcomes.

Key Question 2b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for intermediate cardiovascular outcomes?

Two studies contributed to the evidence regarding statistical interaction between cardiovascular drugs and dietary supplements for this section.[44,78] One study assessed statistical interaction using general linear modeling.[44] No significant interactions were observed between the combination of omega-3 fatty acids (4 g/day) and statins with regards to changes in lipid profile (HDL-C, LDL-C, total cholesterol, triglycerides, non-HDL-C) in 52 obese men with dyslipidaemia and insulin resistance (moderate/moderately high risk for CHD).[44] Authors of another trial[78] conducted a formal assessment of statistical interaction using ANOVA and found that the decrease in triglyceride levels resulting from the combination of omega-3 fatty acids (4

g/day) and niacin was more than twice the additive effect of either therapies alone in 29 participants with atherogenic dyslipidemia (unclear CHD risk).

Main Points for Key Question 2—Intermediate Outcomes

We compared a dietary supplement coadministered with a cardiovascular drug(s), with the cardiovascular drug(s) alone (or in conjunction with another supplement) to investigate comparative intermediate cardiovascular efficacy outcomes, subgroup effects and statistical interactions.

- Fifty-seven RCTs, two controlled clinical trials and no observational studies addressed this Key Question.
- No study addressed the following outcomes: incidence of metabolic syndrome; carotid-intima media thickness; and change in 10-year Framingham risk profile.
- Exploration of heterogeneity for preidentified subgroups (e.g., males/females, ethnic groups, and the elderly) was not possible due to sparse data found for each supplement-drug combination of interest.
- No evidence was found for intermediate outcomes for the following supplements in combination with cardiovascular drugs: red yeast rice extract; resveratrol; vitamin A; or vitamin D with or without calcium.
- Most evidence was from small, underpowered RCTs that provided inconclusive results.
- The strength of evidence for gradable outcomes was generally insufficient due to inconsistencies in the treatment effect direction and the wide confidence interval compatible to potential for both clinical benefits and harms.
- Low grade evidence indicated improvement in a few intermediate outcomes in the following dietary supplement plus cardiovascular drug versus cardiovascular drug alone:
  - HDL-C: garlic plus nitrates, garlic plus warfarin; coenzyme Q10 plus fenofibrate
  - Triglyceride: garlic plus nitrates, omega-3 fatty acids in addition to calcium channel blockers and aspirin, calcium channel blockers, statins plus aspirin and dipyridamole (in participants with mean baseline TG levels of 200 mg/dL or higher); vitamin E plus nifedipine;
  - LDL-C: vitamin E plus nifedipine;
  - Systolic blood pressure: omega-3 fatty acids plus statins;
  - INR (percentage of time INR in therapeutic range, proportion of subjects achieving INR, proportion of subjects with stable INR): vitamin K plus anticoagulant (warfarin, coumarin derivatives);
  - Bleeding time: *Ginkgo biloba* plus cilostazol;
  - Coronary artery calcification (volume calcium score): *Ginkgo biloba* plus cilostazol;
  - Proteinuria (participants with 50 percent or greater reduction): omega-3 fatty acids plus ACE inhibitors.
- Low grade evidence indicated no difference between omega-3 fatty acids plus statins compared with statins alone in the following measures: HDL-C, LDL-C, achieving LDL-C and HDL-C targets; diastolic blood pressure; C-reactive protein; blood coagulation parameters; and bleeding time.
- Evidence was insufficient (type II error could not be excluded due to the low power of studies) for the following supplement plus cardiovascular drug combinations compared with the cardiovascular drug alone:

- lipid profile: coenzyme Q10 plus statins; coenzyme Q10 plus fenofibrate; garlic plus statins and aspirin; *Ginkgo biloba* plus aspirin; magnesium plus hydrochlorothiazide;omega-3 fatty acids plus fenofibrates;omega-3 fatty acids plus calcium channel blockers;omega-3 fatty acids plus niacin and aspirin;omega-3 fatty acids plus aspirin; vitamin E plus gemfibrozil, or statins;
- HDL-C: vitamin E plus nifedipine;omega-3 fatty acids plus calcium channel blockers and aspirin, calcium channel blockers plus aspirin and dipyridamole;
- Triglycerides: niacin plus propranolol; garlic plus nitrates;omega-3 fatty acids plus ACE inhibitors; omega-3 fatty acids plus statins (in participants with lower baseline TG levels); magnesium-hydrochlorothiazide; magnesium plus beta-adrenergic antagonists; vitamin E plus antiplatelet agents;
- LDL-C: omega-3 fatty acids plus calcium channel blockers and aspirin;
- Blood pressure: garlic plus warfarin; *Ginkgo biloba* plus aspirin, or antiplatelet thienopyridines, or cilostazol; magnesium plus hydrochlorothiazide, or beta-adrenergic antagonists;omega-3 fatty acids plus aspirin, or beta-blockers; vitamin E plus furosemide; vitamin E plus nifedipine; vitamin E plus gemfibrozil;
- INR: *Echinacea* plus warfarin; garlic plus warfarin; ginger plus warfarin; *Ginkgo biloba* plus warfarin; ginseng plus warfarin (peak INR, AUC_{INR}); and omega-3 fatty acids plus warfarin.

- No statistical interaction was found for combination of omega-3 fatty acids plus statins for lipid parameters HDL-C, LDL-C, total cholesterol, triglycerides, and non-HDL-C.
- A positive interaction was found for the combination of omega-3 fatty acids plus niacin and aspirin for triglycerides. The decrease in triglycerides resulting from combination treatment was more than twice the additive effect of the therapies alone.

Key Question 3. In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared to cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement(s]) on clinical or intermediate harms outcomes (e.g., organ toxicity, serious adverse events, withdrawal due to adverse events)
a. Do the effect estimates of harms outcomes vary by age, ethnicity, gender, or health status?
b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for harms outcomes?

Overview

A total of 58 unique studies were included for Key Question 3 (Table 34).[39,44,46,47,49,51-53,55,56,78,81-84,86,87,91,92,96,97,99,100,36-38,40-42,48,54,57-69,71-77,88-90,93-95,98]

One of the included studies was a retrospective cohort study,[88] while the rest were RCTs. Summary characteristics of the study and population is shown in Table 35.

One study examined the statistical interaction between vitamin E and aspirin [100] on harms. The characteristics of included studies are summarized in Table 34. Overall, the studies were generally of moderate risk of bias across all gradable harms, as summarized in Table 36. The harms outcomes examined across the included studies ranged from minor (e.g., flatulence) to serious (e.g., major bleeding). Although a higher proportion of the harms outcomes were

reported as continuous data rather than dichotomous data, the dichotomous outcomes were the focus of the present work, as these are the most suitable type of data for examining harms. A carryover effect was not a major concern in the crossover trials because most of the studies incorporated adequate washout periods in their design – well over five times the half-life of the drug supplement under investigation. However, a carryover effect may have influenced the results of 5 of the included crossover studies because it was not clearly reported,[37] the washout period was only one week,[99] or there was no washout period.[42,75,86] Detailed study characteristics and data from each of the included studies are available in Appendix C. For each supplement examined, we compared the different cardiovascular drug and supplement combination(s) versus the cardiovascular drug alone. For most supplement-cardiovascular drug related harms outcomes, data were either absent or too sparse with occasional events, precluding meaningful synthesis (Appendix C). Where subgroup analysis could be carried out, we report subgroup results as an additional consideration under the corresponding supplement.

No data were found for the following supplements: red yeast rice, resveratrol, vitamin A, vitamin D (with or without calcium).

Table 34. Overview of availability of evidence for harms outcomes—Key Question 3

Dietary Supplement	N of Studies Included	Cardiovascular Drug(s)	Study Design(s)
Coenzyme Q10	5[38,54,57,58,89]	Atorvastatin, simvastatin, fenofibrate, ACE-Inhibitors	4 Parallel RCT, 1 crossover RCT
Echinacea	1[59]	Warfarin	Crossover RCT
Garlic	4[60-63]	Warfarin, nitrates, statin + aspirin	3 Parallel RCT, 1 crossover RCT
Ginger	1[64]	Warfarin (single dose)	1 Crossover RCT
Ginkgo biloba	7[48,64-68,90]	Warfarin, aspirin, aspirin and/or pentoxiphylline, digoxin, nitrates, statin + aspirin, ticlopidine	Parallel RCT (2), crossover RCT (5)
Ginseng	3[69-71]	Warfarin	1 crossover, and 2 parallel RCTs
Hawthorne	1[72]	Digoxin	Crossover RCT
Magnesium (oral)	3[42,73,74]	Hydrochlorthiazide, metoprolol, atenolol, pindolol, propanolol	2 Parallel RCTs and 1 crossover RCT
Niacin (≤ 250 mg/d)	1[75]	Propanolol	Crossover RCT
Omega- 3 fatty acids (or fish oils)	22[36,37,40,44,47,51-53,55,56,76-78,88,92-99]	Statins; Aspirin; Aspirin + Clopidogrel; Aspirin + Dipyridamole + Ca Channel Blockers; Warfarin; Ramipril and/or irbesartan; Fenofibrate	13 Parallel RCT, 8 crossover RCT, 1 retrospective cohort
Vitamin E	10[39,46,49,81-84,86,87,100]	Aspirin, simvastatin, atorvastatin, pravastatin, furosemide	8 Parallel RCT and 2 crossover RCT
Vitamin K	2[41,143]	Warfarin, phenprocoumon	Parallel RCT

Abbreviations: ACE-I = Angiotensin-converting enzyme inhibitors; N = total number; RCT = randomized controlled trial

Table 35. Summary of study characteristics—Key Question 3

Study Characteristic	Distribution
Sample CHD risk	Low 17.5% Moderate to moderately high 1.8% High 22.8% Mixed 25.3% Unclear 32.6%
Geographical region	North America 19.3% Europe 28.1% Australia/New Zealand 5.3% East Asia 4.3% Rest of Asia 5.3% NR/Other 37.8%
Setting	Primary care/community 36.1% Specialty care 24.6% NR 39.4%
Duration	Mean 21 weeks, range 1 day to 10 years
Total N randomized	Mean, 775.2, range 8 to 19,934, total across studies = 23,474
Age	Mean age 55 years
Gender	Ten trials exclusively in males,[44,52,59,61,64,65,67,68,71,98] and two in females.[39,100] Of the mixed gender studies, 77% included females representing less than 40% of study sample.
Race/Ethnicity	Seventeen studies reported race/ethnicity distribution. Eight included a majority of Caucasians.[36,37,39-41,49,65,74] Two studies included all Asians,[57,68] and two majority Hispanics.[55,95]

Table 36. Risk of bias and potential for conflict of interest—Key Question 3

Item			
All RCTs (N = 57)	**Yes**	**No**	**Unclear**
Adequate generation of allocation sequence	23	0	77
Allocation concealment	9	0	91
Comparability of groups	49	18	33
Purity of supplement	83	14	4
Blinding of allocated intervention	26	25	49
Adequately addressed missing data	61	4	35
Freedom from potential for conflict of interest	23	33	44
Crossover RCTs (N = 21)			
Suitability of crossover design for the study condition	100		
Freedom from carryover effect	19.0	71.4	9.5
Appropriateness of statistical analysis for crossover design	23.8	14.3	61.9
Comparability of groups between periods 1 and 2	9.5	0.0	90.5
Freedom from bias introduced by dropouts	76.2	9.5	14.3

Abbreviations: N = total number; RCTs = randomized controlled trials.

Coenzyme Q10

Four RCTs examined coenzyme Q10 plus statins, fenofibrate or angiotensin-converting enzyme (ACE) inhibitors versus statins, fenofibrate, or ACE inhibitors alone.[38,54,57,58] One study examined coenzyme Q10 plus statins compared with vitamin E plus statins.[89] The included patients ranged from those with ischemic or idiopathic dilated cardiomyopathy,[54] or diabetes, [58]

to individuals with myalgia,[38] or myopathic pain.[89] The majority of studies were parallel RCTs (one crossover RCT[54]) with moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes.

Coenzyme Q10 Plus Statins Versus Statins Alone

Insufficient evidence was noted across all of the gradable clinical adverse events and organ toxicity outcomes for coenzyme Q10 plus statins versus statins alone, including serious adverse events,[57] withdrawal due to adverse events,[38,57] hepatoxicity (elevated alanine transaminase,[38] or elevated aspartate aminotransferase[38]), and renal dysfunction (abnormal glomerular filtration rate[38]) (Table 36). None of the included studies examined the gradable outcome bleeding. One RCT examined adverse events in general and zero events were observed.[57] One small pilot RCT examined myalgia in 44 participants using visual Analogue Scale and did not find a statistically significant difference between coenzyme Q10 (200 mg/day) plus statins (simvastatin 10 to 40 mg/day) versus statins alone (median 6.0 [inter quartile range 2.1, 8.8] vs. 2.3 [interquartile range 0.0, 12.8], p 0.63).[38] Similarly, in this trial there was no statistically significant difference between coenzyme Q10 plus statin and statin alone groups in proportion of patients tolerating statin (16/22 versus 13/22, p 0.47; RR 1.23, 95 percent CI 0.80, 1.90). Note that this RCT[38] was powered to detect a 9 mm difference in myalgia scores between treatment groups. Study designers assumed that less than 10 percent of patients would tolerate high dose simvastatin (40 mg/day) alone compared with 50 percent tolerating combined therapy, and that 50 percent of patients would tolerate lower dose simvastatin (10 mg/day or more) compared with greater than 90 percent tolerating combination therapy at the comparable simvastatin dose.

Two RCTs examined fasting blood glucose as a continuous outcome; no differences were observed with 100 mg[57] or 200 mg[58] of coenzyme Q10 added to atorvastatin,[57] or fenofibrate[58] versus these cardiovascular drugs alone. Other continuous outcomes reported for the statins included myoglobin,[57] creatine kinase (CK), or creatine phosphokinase (CPK);[57] no statistically significant differences were observed.

Coenzyme Q10 Plus Statins Versus Vitamin E Plus Statins

One small pilot RCT found a higher frequency of decreased myopathic pain in the coenzyme Q10 (100 mg/day) plus statin group (16/18) versus the vitamin E (400 IU/day) plus statin group (3/14),and the relative risk (RR) was 4.18 (95 percentCI1.50, 11.46).[89] Similarly, significantly lower pain severity scores on the four pain intensity items of the Brief Pain Inventory Questionnaire,(MD -1.76 (95 percent CI -2.93, -0.58]) and lower average pain interference scores on the seven items of the Questionnaire (MD -1.43 (95 percent CI -2.76, -0.10]) were observed in the coenzyme Q10 plus statins versus the vitamin E plus statins group.[89] No statistically significant differences were observed in phosphokinase levels. Participants in this trial used various type of statins in varying doses.

Coenzyme Q10 Plus Fenofibrate Versus Fenofibrate Alone

Insufficient evidence was noted across all of the gradable clinical adverse events and organ toxicity outcomes for coenzyme Q10 plus fenofibrate versus fenofibrate alone, including withdrawal due to adverse events,[58] elevated alanine transaminase,[58] and elevated creatinine[58] (Table 36). None of the included studies examined the gradable outcomes serious adverse events or bleeding. RCTs also reported abnormal electrocardiogram (ECG)[58] and abnormal CK/CPK;[58] zero events were observed. In another RCT, frequency of retinopathy was the same with

coenzyme Q10 plus fenofibrates (5/20) versus fenofibrate alone (6/20).[58] One RCT examined fasting blood glucose as a continuous outcome; no differences were observed.[58]

Coenzyme Q10 Plus ACE Inhibitors Versus ACE Inhibitors Alone

Insufficient evidence was noted across all of the gradable clinical adverse events and organ toxicity outcomes for coenzyme Q10 (33 mg three times daily) plus ACE inhibitors versus ACE inhibitors alone, including hepatoxocity (elevated alanine transaminase,[54] aspartate aminotransferase[54]) and renal dysfunction (creatinine,[54] blood urea nitrogen [54]) (Table 37). None of the included studies examined the gradable outcomes serious adverse events, withdrawal due to adverse events or bleeding. One RCT also reported adverse events in general;[54] zero events were observed.

Table 37. Strength of evidence for coenzyme Q10 with or without cardiovascular drugs—Harms outcomes

Cardiovascular Drugs(s)/Harm	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Coenzyme Q10						
Serious adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Withdrawal due to adverse events [2 studies]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** Study 1: 0 events Study 2: no significant differences; 6/22 events in intervention group versus 4/22 events in placebo group
Renal dysfunction (glomerular filtration rate [1 study])	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Hepatotoxicity hepatoxicity (alanine transaminase, aspartate aminotransferase [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
Fenofibrate						
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 2 events total (not reported by group)
Renal dysfunction (creatinine [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No significant differences between groups, number of events not reported

Table 37. Strength of evidence for coenzyme Q10 with or without cardiovascular drugs—Harms outcomes (continued)

Cardiovascular Drugs(s)/Harm	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Hepatotoxicity (alanine transaminase [study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
ACE inhibitors						
Renal dysfunction (creatinine, blood urea nitrogen [n=1 study])						0 events observed in 1 study
Hepatotoxicity (alanine transaminase, aspartate aminotransferase [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	0 events observed in 1 study

Abbreviations: ACE = angiotensin-converting enzyme; NA = not applicable.

Echinacea

A randomized open-label crossover trial in 12 healthy, non-smoking males with known CYP2C9 genotype reported zero total adverse events and withdrawal due to adverse events. The participants in this trial received a single dose of warfarin (25 mg/day) alone or after two weeks of pre-treatment with of 600 mg of *Echinacea angustifolia* roots plus 675 mg of *E. purpurea* root given four times a day[59] Insufficient evidence was noted for the gradable outcome withdrawal due to adverse events (Table 38). Furthermore, this study did not report data on any of the other gradable outcomes (serious adverse events, bleeding, renal dysfunction or hepatotoxicity).[59].

Table 38. Strength of evidence for warfarin with or without *Echinacea*—Harms outcomes

Cardiovascular Drugs(s)/Harm	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed

Abbreviation: NA = not applicable.

Garlic

Four RCTs examined garlic (4 to10 g/day) plus warfarin, nitrates, or statins/aspirin versus warfarin, nitrates, or statins/aspirin alone.[60-63] The included patients ranged from healthy, non-smoking males [61] to individuals with cardiac conditions.[60,62,63] The majority of studies were parallel RCTs (one crossover RCT [61]) of moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes.

Garlic Plus Warfarin Versus Warfarin Alone

Insufficient evidence was available for the gradable harm bleeding for garlic (4 to 10 g/day) plus warfarin versus warfarin alone (Table 39).[60,61] In one study, bleeding was defined as hemorrhage, epistaxis, hemoptysis, hematuria, bloody stools, hemorrhage into organs, hemarthrosis, hematomas, or bruising.[60] The other study simply indicated major bleeding

episodes.[61] None of the included RCTs examined the gradable outcomes serious adverse events, withdrawal due to adverse events, renal dysfunction or hepatotoxicity. One RCT examined fasting blood glucose and anemia;[60] no statistically significant effects were observed.

Garlic Plus Nitrates Versus Nitrates Alone

One RCT examined garlic (4 g/day) plus nitrates versus nitrates alone and did not report the results for any of the gradable harms.[62] This RCT reported only one harm (fasting blood glucose as a continuous outcome) and found no statistically significant effects.[62]

Garlic Plus Statins/Aspirin Versus Statins/Aspirin Alone

Insufficient evidence was noted for the gradable outcomes renal dysfunction[63] and hepatoxocity[63] for garlic (4 mL/day) plus statins/aspirin versus statins/aspirin alone (Table 39). This RCT[63] also reported harms data related to leukopenia and fasting blood glucose; no statistically significant effects were observed.

Table 39. Strength of evidence for warfarin with or without garlic—Harms outcomes

Cardiovascular Drugs(s)/Harm	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Warfarin						
Bleeding [2 studies]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Aspirin						
Renal dysfunction* (creatinine, serum potassium [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences observed
Hepatotoxicity* (aspartate aminotransferase, alanine transaminase, alkaline phosphatase [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences observed

Note: * continuous data only (dichotomous data not available).
Abbreviation: NA = not applicable.

Ginger

No evidence of gradable outcomes was identified for this supplement. Mild diarrhea in 1/12 subjects was found in one RCT after two days of supplementation with ginger (3.6 g/day) plus a single dose of warfarin.[64]

Ginkgo Biloba

Seven RCTs examined *Ginkgo biloba* plus warfarin, aspirin, aspirin and/or pentoxiphylline, digoxin, statin/aspirin, cilostazol/clopidogrel or ticlopidine versus these cardiovascular medications alone.[48,64-68,90] Two of these studies included a single dose of a cardiovascular medication so their results should be interpreted with caution.[67,68] The included patients ranged from those at risk for peripheral artery disease[66] or stroke,[48] to healthy adults[65,90] and all

males.[64,67,68] The majority of studies were crossover RCTs (two parallel RCTs [48,66]) of moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes.

Ginkgo Biloba Plus Aspirin Versus Aspirin Alone

Insufficient evidence was noted across all of the gradable clinical adverse events and organ toxicity outcomes for *G. biloba*(240 mg/day,[65], or 300 mg/day[66]) plus aspirin versus aspirin alone, including withdrawal due to adverse events,[66] bleeding (nosebleeds and/or unusual bleeding),[66] renal dysfunction,[65] and hepatotoxicity[65] (Table 40). None of the included studies examined the gradable outcome serious adverse events. No statistically significant differences were observed across the total adverse events (11/34 combination group versus 15/33 control group) and upset stomach (6/34 combination group versus 5/33 aspirin alone group) harms.[66] One RCT reported anemia and white blood cell count using continuous data but found no significant differences between the groups taking *G. biloba* plus aspirin group and aspirin alone.[65]

Ginkgo Biloba Plus Aspirin and/or Pentoxiphylline Versus Aspirin and/or Pentoxiphylline Alone

Insufficient evidence was noted for the gradable harm withdrawal due to adverse events for *G. biloba*(40 mg every 6 hours)plus aspirin and/or pentoxiphylline versus aspirin and/or pentoxiphylline alone[48] (Table 40). This RCT reported 4/33 gastrointestinal events in the *G. biloba* plus aspirin and/or pentoxiphylline group compared with 3/29 events in the control group,[48] which was not statistically significant. There was no report of any of the gradable outcomes serious adverse events, bleeding, renal dysfunction or hepatotoxicity.

Ginkgo Biloba Plus Ticlopidine Versus Ticlopidine Alone

Insufficient evidence was noted for the gradable harms renal dysfunction (raised creatinine,[68] or abnormal blood urea nitrogen[68]) and hepatotoxicity (elevated aspartate aminotransaminase,[68] or elevated alkaline phosphatase[68]) for *G. biloba*(80 mg single dose) plus ticlopidine versus ticlopidine alone(Table 40). The included RCTs did not examine any of the gradable outcomes serious adverse events, withdrawal due to adverse events or bleeding. One RCT examined the effects of *G. biloba* plus ticlopidin versus ticlopidin alone on hypoglycemia, hyperglycemia, leukopenia, thrombocytopenia, anemia, and abnormal ECG; zero events were observed.[68]

Ginkgo Biloba Plus Warfarin Versus Warfarin Alone

Insufficient evidence was noted for the gradable harms serious adverse events and withdrawal due to adverse events for *G. biloba* (two tablets three times daily-each tablet with equivalent of 2 g of *Ginkgo biloba* leaf, 9.6 mg of ginkgo flavonglycosides, 2.4 mg of ginkgolides and bilobalide) plus warfarin versus warfarin alone (Table 40).[64] This RCTs did not examine any of the other gradable harms, including bleeding, renal dysfunction, and hepatotoxicity. Furthermore, zero events were observed for constipation and no statistically significant differences were reported for diarrhea (0/12 combination group versus 1/12 control group).[64]

Ginkgo Biloba Plus Digoxin Versus Digoxin Alone

Insufficient evidence was noted for *G. biloba*(80 mg three times daily) plus digoxin versus digoxin alone related to withdrawal due to adverse events (Table 40).[90] However, no data were

available on the other gradable harms, including serious adverse events, bleeding, renal dysfunction, and hepatotoxicity. Furthermore, zero events were reported for adverse events and no statistically significant differences were noted for gastrointestinal adverse events (1/8 combination group versus 0/8 control group).[90]

Ginkgo Biloba Plus Cilostazol/Clopidogrel Versus Cilostazol/Clopidogrel Alone

Insufficient evidence was noted for *Ginkgo biloba*(120, and 240 mg/day) plus cilostazol/clopidogrel versus cilostazol/clopidogrel alone across all gradable outcomes, as none of these were reported.[67] One RCT examined total adverse events; zero events were reported.[67]

Table 40. Strength of evidence for cardiovascular drugs with or without *G. biloba*—Harms outcomes

Cardiovascular Drugs(s)/Harm	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Aspirin						
Withdrawal due to adverse events [1 study]	Low	NA	Direct	Imprecise	Insufficient	**Inconclusive** No statistically significant differences, 3/34 intervention group versus 2/33 control group
Bleeding [1 study]	Low	NA	Direct	Imprecise	Insufficient	**Inconclusive** No statistically significant difference; 5/34 events intervention group versus 4/33 events control group
Renal dysfunction* (1 study)	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences observed
Hepatotoxicity* (1 study)	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences observed
Aspirin and/or pentoxiphylline						
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Ticlopidine						
Renal dysfunction (1 study)	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
Hepatotoxicity (1 study)	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
Warfarin						
Serious adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed

Table 40. Strength of evidence for cardiovascular drugs with or without *G. biloba* - Harms outcomes (continued)

Cardiovascular Drugs(s)/Harm	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Digoxin						
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed

Note: * continuous data only (dichotomous data not available).Renal dysfunction indication measures by creatinine, and or blood urea nitrogen levels; Hepatotoxicity measured by raised levels of aspartate aminotransaminase, and or alanine transaminase
Abbreviation: NA = not applicable.

Ginseng

One parallel RCT examined the effects of 1.5 g/day *Panax ginseng*(aqueous extract containing0.5 grams three times daily) plus warfarin versus warfarin alone among patients who had experienced a stroke.[69] Another parallel RCT examined the same comparison with 2 g/day American ginseng among healthy patients,[70] while a crossover RCT examined the same comparison but with 3 g/day Korean ginseng among healthy non-smoking males.[71] All three RCTs were of moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes. Insufficient evidence was noted across the gradable clinical adverse events, including withdrawal due to adverse events[71] and bleeding (no description provided)[69] (Table 41). None of the included RCTs examined the gradable outcome serious adverse events. Furthermore, insufficient evidence was noted for the organ toxicity outcomes (elevated creatinine,[69] abnormal blood urea nitrogen,[69] elevated aspartate aminotransaminase,[69] and elevated alanine transaminase[69]), yet these were based on continuous data only (dichotomous data were not available). One RCT also examined prothrombin time, total adverse events, headache, dizziness, indigestion, INR above 3.5, diarrhea, and constipation;[69] zero events were observed across all of these outcomes. Another RCT reported zero adverse events of clinical importance.[70] One RCT examined the outcomes hematocrit and anemia using continuous data;[69] no statistically significant differences were observed between intervention and control groups.

Table 41. Strength of evidence for warfarin with or without ginseng—Harms outcomes

Cardiovascular Drugs(s)/Harm	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Withdrawal due to adverse events	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Bleeding	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Renal dysfunction* (creatinine, blood urea nitrogen	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences observed
Hepatotoxicity* (aspartate aminotransamina se, alanine transaminase	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences observed

Note: * continuous data only (dichotomous data not available).
Abbreviation: NA = not applicable.

Hawthorn

Tankanow and colleagues investigated the occurrence of harms with hawthorn and digoxin in eight healthy male volunteers in an open-label, randomized crossover trial of digoxin 0.25 mg/day for a 10-day period plus 900 mg/day of extract of hawthorn leaves with flowers standardized to 84.3 mg of oligomeric procyanidines for a 21 day period, versus digoxin alone for 10 days.[72] This RCT did not report results for any of the gradable harms, including serious adverse events, withdrawal due to adverse events, bleeding, renal dysfunction, and hepatotoxicity. Furthermore, with sparse events, evidence was inconclusive for a difference between groups in flatulence, insomnia, headache, and dizziness.

Magnesium

One parallel RCT examined the effects of 4.5 g/day oral magnesium plus hydrochlorthiazide versus hydrochlorthiazide alone,[73] while another examined the same comparison with 15.78 mmol twice daily among hypertensive patients.[74] In addition, one crossover RCT examined the effects of 365 mg/day oral magnesium plus various beta adrenergic antagonists versus beta adrenergic antagonists alone among hypertensive patients.[42] All three RCTs had moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes.

Magnesium Plus Hydrochlorthiazide Versus Hydrochlorthiazide Alone

Insufficient evidence was noted across all of the gradable clinical adverse events and organ toxicity outcomes for magnesium plus hydrochlorthiazide versus hydrochlorthiazide alone, including withdrawal due to adverse events[73] and renal dysfunction (elevated creatinine [74]) (Table 42). None of the included RCTs examined the gradable outcomes serious adverse events, bleeding or hepatotoxicity. One RCT examining hydrochlorthiazide observed zero events across diarrhea, vomiting, nausea, adverse events, hypercalcemia, and fasting blood glucose harms.[73] Furthermore, no statistically significant differences were observed for abnormal ECG (number of events not reported).[73]

Magnesium Plus Beta Adrenergic Antagonists Versus Beta Adrenergic Antagonists Alone

Insufficient evidence was noted for magnesium (365 mg/day) plus beta adrenergic antagonists versus beta adrenergic antagonists alone for the gradable harms serious adverse events,[42] withdrawal due to adverse events,[42] and renal dysfunction (abnormal serum potassium[42]) (Table 42). None of the studies reported the gradable outcomes bleeding or hepatotoxicity.

Table 42. Strength of evidence for cardiovascular drugs with or without magnesium—Harms outcomes

Cardiovascular Drugs(s)/Harm	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Hydrochlor-thiazide						
Withdrawal due to adverse events	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Renal dysfunction (creatinine	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
Beta-adrenergic antagonists						
Serious adverse events	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Withdrawal due to adverse events	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Renal dysfunction* (serum potassium)	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences observed

Note: * continuous data only (dichotomous data not available).
Abbreviation: NA = not applicable.

Niacin (Not More Than 250 mg)

Harms were investigated among 20 patients with hyperlipoproteinemia in an open-label, randomized crossover trial of niacin (250 mg/day) plus propranolol (20 mg/day) versus propranolol alone for 1 month.[75] There was insufficient evidence for the gradable outcome withdrawals due to adverse events (Table 43).[75] This study did not report gradable harms, such as serious adverse events, bleeding, renal dysfunction or hepatotoxicity. Furthermore, there were no statistically significant differences in nausea plus flushing (zero events) or hypotension plus asthenia (0/10 intervention group versus 1/10 control group).

Table 43. Strength of evidence for propranolol with or without niacin—Harms outcomes

Cardiovascular Drugs(s)/Harm	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Withdrawal due to adverse events [n=1 study]	High	NA	Direct	Imprecise	Insufficient	**Inconclusive** No statistically significant differences; 0/10 intervention group versus 1/10 control group

Abbreviation: NA = not applicable.

Omega-3 Fatty Acids/Fish Oils

Twenty-two studies (21 RCTs, and one retrospective cohort study) examined omega-3 fatty acids plus statins,[36,37,40,53,92-97] aspirin,[47,52,78,98,99,99] aspirin and clopidogrel,[88] aspirin in

combination with dipyridamole and calcium channel blockers ,[52] warfarin,[47,55] rampril,[77] or fenofibrate,[56]. The included participants ranged from elderly patients with CHD,[82] to adults with diabetes [87] or stroke,[49] to healthy males [39] or adults.[36,93,95,99] The majority of studies were parallel RCTs, yet there were 7 crossover RCTs,[36,37,93,95-97,99] and one retrospective cohort study.[88] The majority were deemed as having moderate risk of bias, although two had low risk of bias [51,92] and one had high risk of bias.[55] Meta-analysis was only possible for the statins; for all other cardiovascular medications, low event rates across all of the harms outcomes precluded pooling.

Omega-3 Fatty Acids/Fish Oils Plus Statins Versus Statins Alone

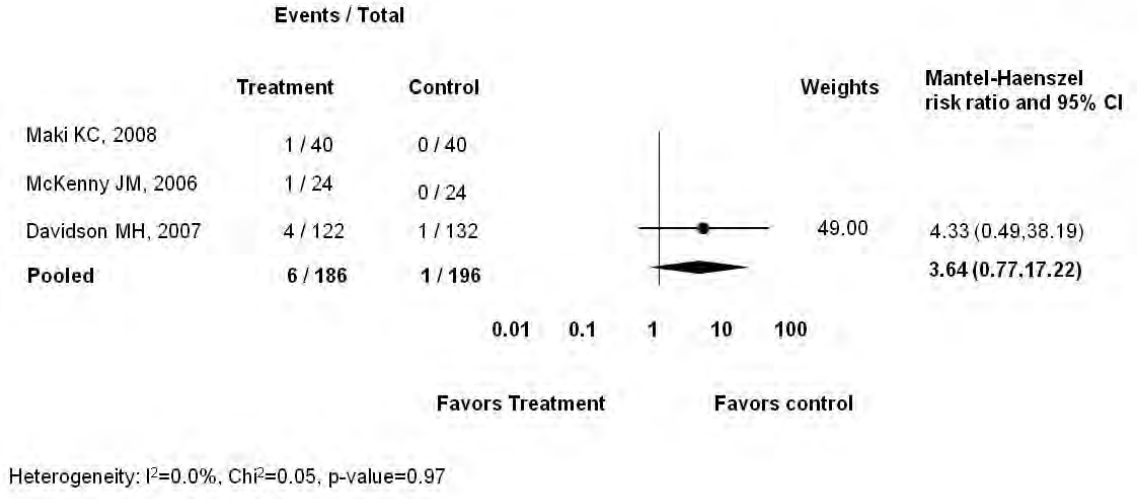
Eleven RCTs examined omega-3 fatty acids (2 to 9.2 g/day) plus statins versus statins alone.[36,37,40,53,91-97] One RCT had low risk of bias,[92] while the rest were of moderate risk of bias, including the seven RCTs included in the meta-analyses.[36,37,40,91,93-96] Insufficient evidence was noted across all gradable outcomes, including serious adverse events meta-analysis (Figure 19), withdrawal due to adverse events meta-analysis (Figure 20), aminotransaminase meta-analysis (Figure 21), and alanine transaminase meta-analysis (Figure 22, Table 44). None of the included RCTs examined the gradable outcome bleeding.

Meta-analysis was also possible for total adverse events (5 studies; RR 0.94 [95 percent CI 0.78, 1.12] Figure 23), dyspepsia (2 studies; odds ratio [OR] 1.61 [95 percent CI 0.46, 5.55] Figure 24), headache (2 studies; OR 0.76 [95 percent CI 0.25, 2.30] Figure 25), constipation (2 studies; RR 0.94 [95 percent CI 0.63, 1.39] Figure 26), upper respiratory infection (2 studies; RR 1.33 [95 percent CI 0.34, 5.21] Figure 27), and CK/CPK (3; RR 1.50 [95 percent CI 0.43, 5.25] Figure 28); no statistically significant effects were observed. Results were consistently not statistically significant despite differences in low [36,93,95] versus moderate [37,40,94,96] CHD risk, and healthy patients [36,93,95] versus those with hyperlipidemia or dyslipidemia [37,40,94,96].

We were unable to discern any effects of sex, ethnicity or age on the results, as these were not examined in the RCTs for which meta-analysis was deemed appropriate.

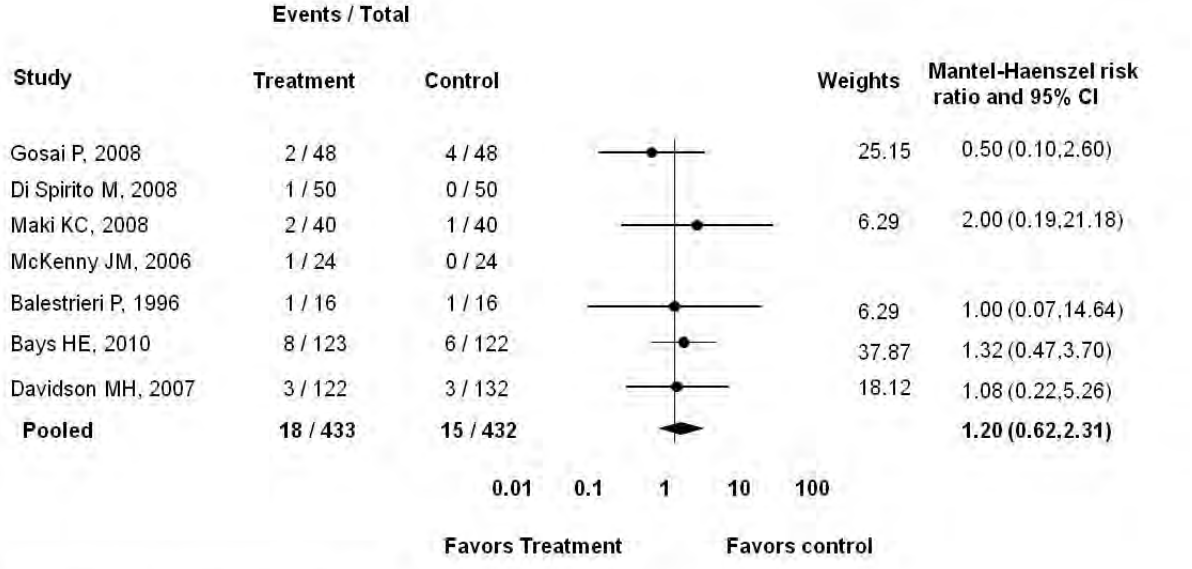
RCTs also reported many other harms outcomes for which no statistically significant differences were observed, such as diarrhea (3/122 intervention versus 3/132 control),[40] flatulence (5/50 intervention versus 5/50 control),[36] generalized edema (0/40 intervention versus 2/40 control),[37] hyperglycemia (2/40 intervention versus 1/40 control),[37] hypoglycemia (1/40 intervention versus 1/40 control),[37] infection (4/122 intervention versus 1/132 control),[40] myalgia (1/40 intervention versus 1/40 control),[37] and sinusitis (0/40 intervention versus 2/40 control).[37] The RCTs also examined harms outcomes as continuous variables, such as leukopenia,[97] anemia,[97] red blood cell count,[97] hematocrit,[97] glycosylated hemoglobin,[94] and fasting blood glucose;[37,40,44,53,76,91,92,94] and one RCT found a statistically significant elevated fasting blood glucose in the omega-3 fatty acids plus statins versus statins alone group.[40]

Figure 19. Forest plot of serious adverse events with statins, with or without omega-3 fatty acids



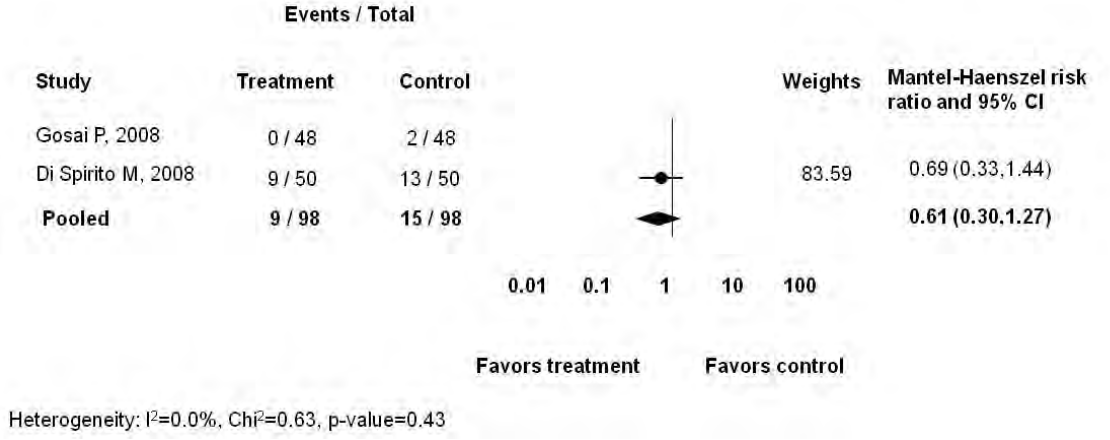
Heterogeneity: I^2=0.0%, Chi^2=0.05, p-value=0.97

Figure 20. Forest plot of withdrawal due to adverse events with statins, with or without omega-3 fatty acids



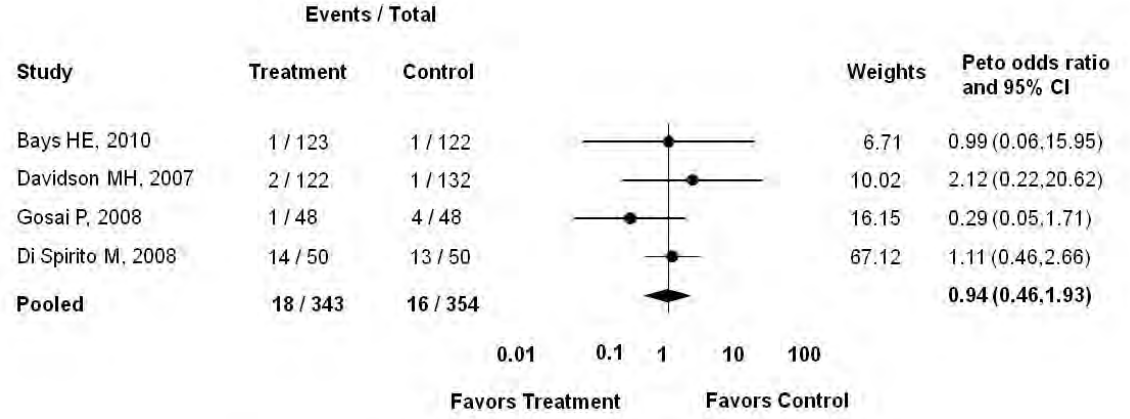
Heterogeneity: I^2=0.0%, Chi^2=1.98, p-value= 0.92

Figure 21. Forest plot of aminotransaminase with statins, with or without omega-3 fatty acids



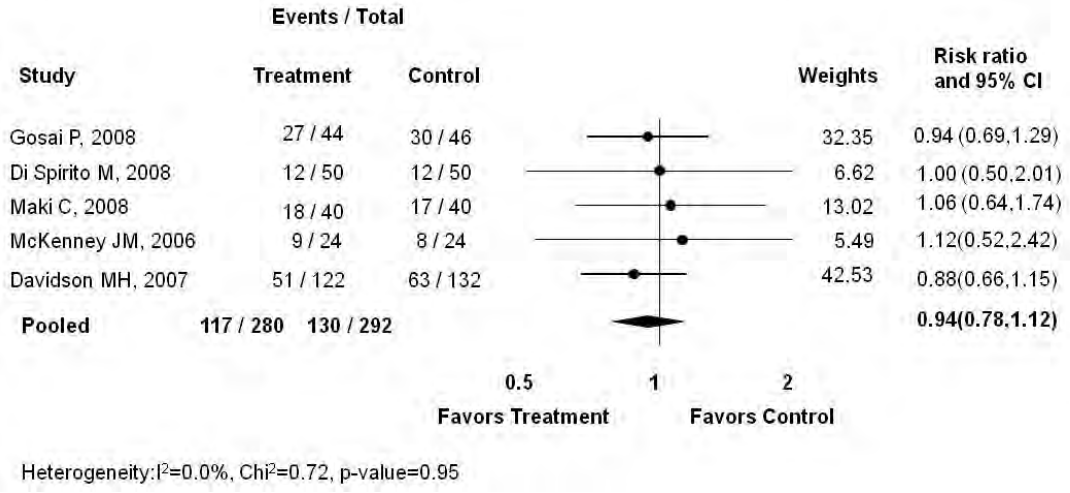
Heterogeneity: I^2=0.0%, Chi^2=0.63, p-value=0.43

Figure 22. Forest plot of alanine transaminase with statins, with or without omega-3 fatty acids



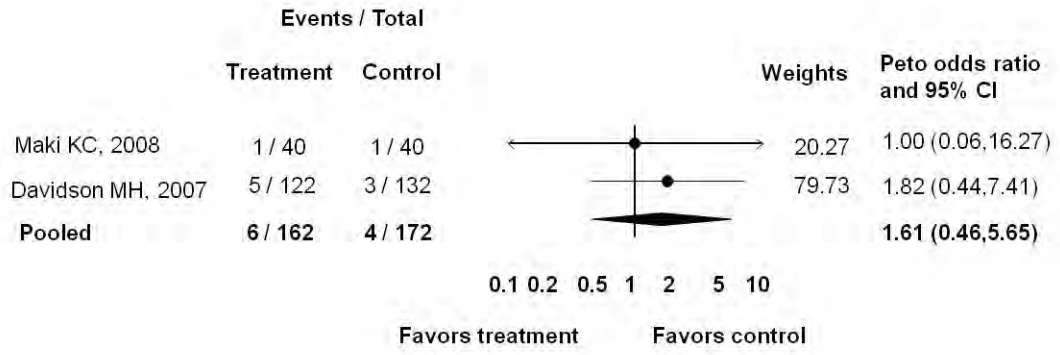
Heterogeneity: I^2=0.0%, Chi^2=2.32, p-value=0.51

Figure 23. Forest plot of total adverse events with statins, with or without omega-3 fatty acids



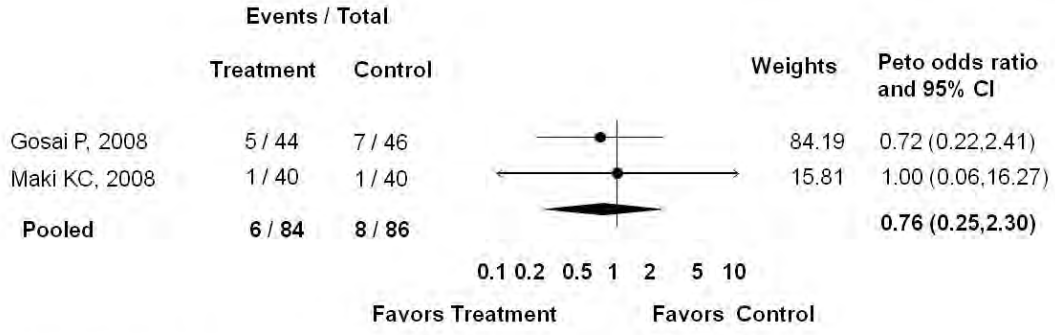
Heterogeneity: I^2=0.0%, Chi^2=0.72, p-value=0.95

Figure 24. Forest plot of dyspepsia with statins with or without omega-3 fatty acids



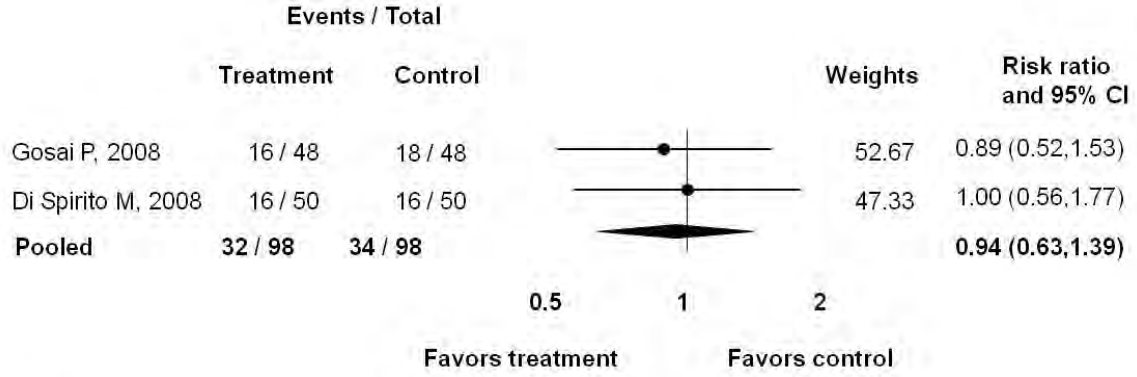
Heterogeneity: I^2=0.0%, Chi^2=0.14, p-value=0.71

Figure 25. Forest plot of headache with statins, with or without omega-3 fatty acids



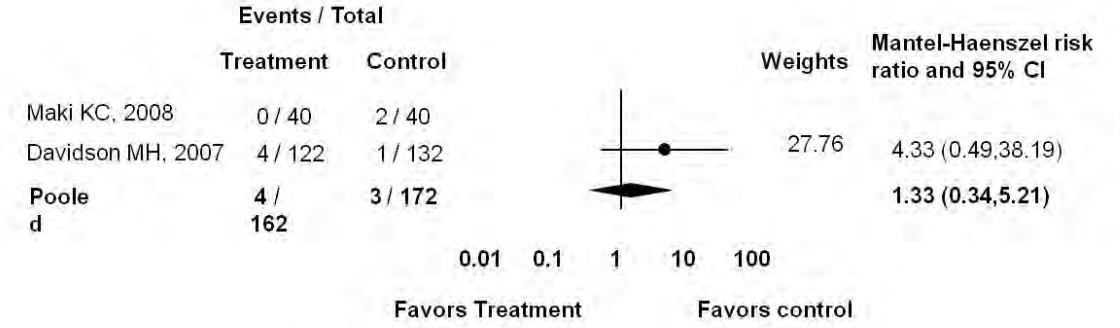
Heterogeneity:I^2=0.0%, Chi^2=0.04, p-value=0.83

Figure 26. Forest plot of constipation with statins, with or without omega-3 fatty acids



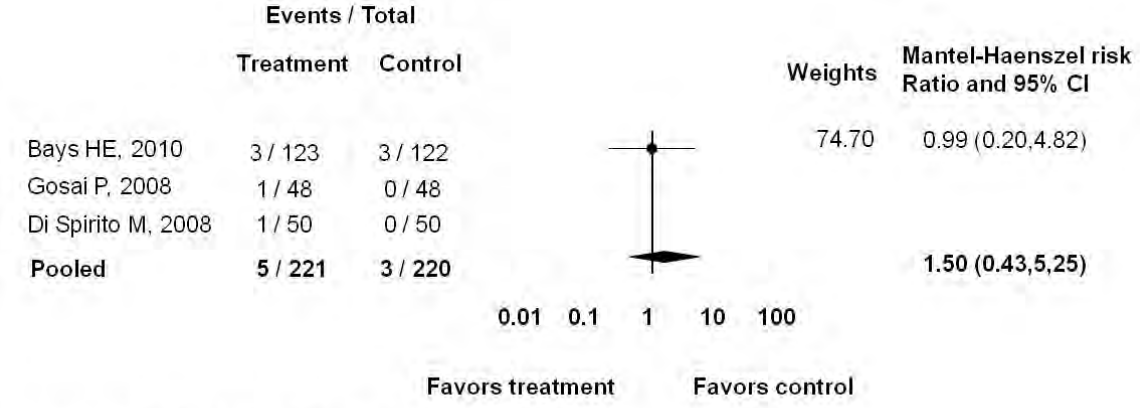
Heterogeneity: I^2=0.0%, Chi^2=0.09, p-value=0.77

Figure 27. Forest plot of upper respiratory infection with statins, with or without omega-3 fatty acids



Heterogeneity: I^2= 0.0%, Chi^2=2.66, p-value=0.10

Figure 28. Forest plot of CK/CPK with statins, with or without omega-3 fatty acids



Heterogeneity: I^2=0.0%, Chi^2=0.63, p-value=0.73

Omega-3 Fatty Acids/Fish Oils Plus Aspirin Versus Aspirin Alone

Six RCTs examined omega-3 fatty acids (4 to 10 mg/day) plus aspirin versus aspirin alone.[47,52,78,98,99,99] Two of these RCTs were conducted among males only.[52,98] Insufficient evidence was noted for all gradable outcomes, including withdrawal due to adverse events[78] and bleeding [47,99](Table 44). Bleeding in one study was defined as those episodes leading to deviation from the protocol (major and minor bleeding episodes: major bleeding defined as bleeding necessitating operation or blood transfusion; minor bleeding defined as all other episodes).[47] The second study reported bleeding episodes of any type.[99].

None of the included RCTs examined the gradable outcomes serious adverse events, renal dysfunction or hepatotoxicity. No significant differences were observed across all harms, including constipation (1/12 intervention group versus 0/12 control group),[99] diarrhea (0/12 intervention group versus1/12 control group),[99] fishy taste (4/12 intervention group versus 0/12 control group),[99] gastrointestinal adverse events (7/143 intervention group versus12/148 control group),[47] flatulence (0/12 intervention group versus 1/12 control group),[99] headache (1/12 intervention group versus 1/12 control group),[99] and nausea (3/12 intervention group versus 3/12 control group).[99] One RCT reported leukopenia as a continuous outcome, with no statistically significant differences observed.[99]

Omega-3 Fatty Acids/Fish Oils Plus Aspirin and Clopidogrel Versus Aspirin and Clopidogrel Alone

One retrospective cohort study examined the effect of fish oils (mean dose 3 g/day plus/minus 1.25 g/day) in combination with aspirin and clopidogrel in 182 elderly subjects with coronary artery disease.[88] An age and gender matched control group of subjects taking aspirin and clopidogrel alone was selected. Major and minor bleeding episodes were noted after a follow-up of 33 months. Major bleeding was defined as a decrease in hemoglobin of more than two grams, intracerebral hemorrhage, or any bleeding episode that required hospitalization. Minor bleeding was defined as epistaxis, abnormal bruising, and gastrointestinal bleeding that did not require hospitalization or lead to a decrease in hemoglobin of more than 2 grams. No significant differences were found between intervention and control groups. Strength of evidence for bleeding was insufficient (Table 44).

Omega-3 Fatty Acids/Fish Oils Plus Aspirin, Dipyridamole, and Calcium Channel Blockers Versus Aspirin, Dipyridamole, and Calcium Channel Blockers

One RCT also examined the effects of omega-3 fatty acids (eicosapentaenoic 3.2 g/day) plus aspirin, dipyridamole, and calcium channel blockers versus aspirin, dipyridamole, and calcium channel blockers alone.[52] Another RCT with a low risk of bias examined omega-3 fatty acids (3 g/day) plus aspirin and calcium channel blockers versus aspirin and calcium channel blockers alone.[51] Insufficient evidence was noted for the gradable outcomes bleeding (described as bleeding complications)[51,52] and withdrawal due to adverse events[51] (Table 44). None of the included RCTs examined serious adverse events, renal dysfunction or hepatotoxicity. No statistically significant differences were observed regarding gastrointestinal events (7/43 intervention group versus 3/39 control group[52]).

Omega-3 Fatty Acids/Fish Oils Plus Warfarin Versus Warfarin Alone

Two RCTs examined the effects of omega-3 fatty acids (3-6 g/day) plus warfarin versus warfarin alone.[47,55] Insufficient evidence was noted for the gradable outcomes bleeding [47,55] and withdrawals due to adverse events[55] (Table 44). Bleeding in one study was defined as those episodes leading to deviation from the protocol (major and minor bleeding episodes: major bleeding defined as bleeding necessitating operation or blood transfusion; minor bleeding defined as all other episodes).[47] The other study reported major bleeding (defined as bleeding episodes causing death or requiring hospitalization, vitamin K, or blood transfusion) and minor bleeding (defined as any bleeding episode that did not qualify as a major bleed but that required a change in warfarin dosage or referral).[55] None of the included studies examined the gradable outcomes serious adverse events, renal dysfunction or hepatotoxicity. Furthermore, three patients with an unstable international normalized ratio withdrew. Data were not reported by treatment groups.[55] One of the RCTs reported gastrointestinal events, which did not differ significantly between groups (9/174 intervention versus 0/145 control).[47]

Omega-3 Fatty Acids/Fish Oils Plus Ramipril and/or Irbesartan Versus Ramipril and/or Irbesartan Alone

One RCT with a moderate risk of bias examined the effects of fish or marine oils (3 g/day)plus ramipril among patients at low risk of CHD.[77] Insufficient evidence was noted for the gradable outcomes withdrawal due to adverse events, bleeding (erythrocyturia grade 3), and renal dysfunction (glomerular filtration rate) (Table 44). This RCT did not report the results for other gradable harms, such as serious adverse events and hepatotoxicity. Furthermore, zero events were observed for hypercalcemia.

Omega-3 Fatty Acids/Fish Oils Plus Fenofibrate Versus Fenofibrate Alone

One RCT with a moderate risk of bias examined the effects of omega-3 fatty acids (4 g/day)plus fenofibrate versus corn oil plus fenofibrate among patients with low CHD risk.[56] Insufficient evidence was noted for the gradable harms serious adverse events, withdrawal due to adverse events, and renal dysfunction (elevated creatinine) (Table 44). This RCT did not report results for the gradable harms bleeding or hepatotoxicity. Furthermore, no statistically significant differences were observed for constipation (1/84 intervention group versus 5/83 control group), diarrhea (4/84 intervention group versus 5/83 control group), flatulence (1/84 intervention group versus 3/83 control group), gastrointestinal adverse events (7/84 intervention group versus 5/83 control group) and nausea (5/84 intervention group versus 3/83 control group).

Table 44. Strength of evidence for cardiovascular drugs with or without omega-3 fatty acids/fish oils—Harms outcomes

Cardiovascular Drugs(s)/Harm	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Statins						
Serious adverse events [meta-analysis including 3 studies]	Moderate	Consistent	Direct	Imprecise	Insufficient	**Inconclusive** No statistically significant differences; 0/10 intervention group versus 1/10 control group
Withdrawal due to adverse events [meta-analysis including 7 studies]	Moderate	Inconsistent	Direct	Imprecise	Insufficient	**Inconclusive** No significant differences; RR 3.6 (95% CI 0.8, 17.2)
Renal dysfunction* (creatinine)	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences; OR 1.2 (95% CI 0.6, 2.4)
Hepatotoxicity: aminotransaminase [meta-analysis including 2 studies]	Moderate	Consistent	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No significant differences
Hepatotoxicity: alanine transaminase [meta-analysis including 4 studies]	Moderate	Inconsistent	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No statistically significant differences; RR 0.61 (95% CI 0.30, 1.27)
Aspirin						
Withdrawal due to adverse events	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Bleeding [n=2 studies]	High	NA	Direct	Imprecise	Insufficient	**Inconclusive** No significant differences: Study 1: 0 events observed Study 2: 3/143 intervention group versus 2/148 control group
Aspirin + clopidogrel						
Bleeding	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No significant differences: Major Bleeding: 1/182 intervention versus 0/182 control group Minor Bleeding: 4/182 intervention versus 7/182 control group

Table 44. Strength of evidence for cardiovascular drugs with or without omega-3 fatty acids/fish oils—Harms outcomes (continued)

Cardiovascular Drugs(s)/Harm	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Aspirin + dipridamole + calcium channel blockers						
Bleeding	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No significant differences: 3/43 intervention group versus 1/39 control group
Aspirin+ calcium channel blockers						
Withdrawal due to adverse events	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Bleeding [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Warfarin						
Withdrawal due to adverse events	High	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Bleeding [2 studies]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No significant differences: Study 1: 0 events observed Study 2: 2/174 intervention group versus 2/145 control group
Ramipril and/or irbesartan						
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	0 events observed
Bleeding (Grade 3 erythrocyturia)	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No significant differences: 4/15 intervention group versus 1/15 control group
Renal dysfunction* [glomerular filtration rate]	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	No statistically significant difference

Table 44. Strength of evidence for cardiovascular drugs with or without omega-3 fatty acids/fish oils—Harms outcomes (continued)

Cardiovascular Drugs(s)/Harm	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Fenofibrate						
Serious adverse events	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No significant differences; 3/84 intervention group versus 4/83 control group
Withdrawal due to adverse events	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No significant differences 4/84 intervention group versus 4/83 control group
Renal dysfunction (creatinine)	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** No significant differences 0/84 intervention group versus 1/83 control group

Note: * continuous data only (dichotomous data not available).
Abbreviation: NA = not applicable.

Vitamin E

Ten RCTs examined vitamin E plus aspirin, statins, or furosemide versus these cardiovascular medications alone.[39,46,49,81-84,86,87,100] The included participants ranged from the elderly with CHD,[82] to those with diabetes,[87] or stroke,[49] to healthy females.[39] The majority of studies were parallel RCTs (with two crossover RCTs [82,86]) of moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes.

Vitamin E Plus Aspirin Versus Aspirin Alone

Three RCTs examined vitamin E plus aspirin versus aspirin alone.[39,49,100] Insufficient evidence was noted for the gradable harms of bleeding (hemorrhagic events) after two years supplementation with vitamin E (400 IU/day) plus aspirin (325 mg/day) versus aspirin alone,[49] and for withdrawals due to adverse events after 10 days of vitamin E supplementation (200 mg/day) plus low dose aspirin (80 mg/day) or aspirin alone[100] (Table 45). None of the RCTs reported data related to the gradable harms serious adverse events, renal dysfunction or hepatotoxicity. No statistically significant differences were observed in the number of patients experiencing headache (28/121 intervention group versus 20/122 control group), gastrointestinal discomfort (14/121 intervention group versus 10/122 control group) or total adverse events (23/121 intervention group versus 24/122 control group) with 10 days of vitamin E supplementation (200 mg/day) plus low dose aspirin or aspirin alone.[100] One RCT examined the occurrence of cancer, and no statistically significant differences were observed (716/9966 intervention group versus 722/9968 control group)in a large sample of women (aged 45 years or older) supplemented with vitamin E (600 IU/day) plus low dose aspirin (100 mg/day) or aspirin alone over the period of 10 years.[39]

Vitamin E Plus Nifedipine Versus Nifedipine Alone

One crossover RCT examined the effects of vitamin E (900 mg/day) plus nifedipine versus nifedipine alone over four months in 30 elderly and moderately obese participants with stable effort angina. Insufficient evidence was noted across all of the gradable harms, including withdrawal due to adverse events, renal dysfunction, and hepatotoxicity (zero events were observed).[82] (Table 45) This RCT did not report on the gradable outcomes serious adverse events or bleeding. Furthermore, fasting plasma glucose was examined as a continuous outcome and no statistically significant difference was observed.[82]

Vitamin E Plus Furosemide Versus Furosemide Alone

One parallel RCT examined the effects of vitamin E (600 mg/day) plus furosemide versus furosemide alone over 4 weeks in 24 hypertensive participants, and did not report the results of any of the gradable outcomes. Fasting blood glucose was reported as a continuous outcome; no statistically significant effect was observed.[81]

Vitamin E Plus Statins Versus Statins Alone

Five RCTs examined the effects of vitamin E plus statins versus statins alone in hypercholesterolemic or hyperlipidemic,[46,83,84,86] or diabetic participants.[87] In one trial very low dose of vitamin E was administered (100 IU/day) over three months[46] in contrast to two other trials using higher doses (750 IU/day,[87] and 1000 IU/day[84])over six months. Insufficient evidence was noted across the gradable harms: organ toxicity (elevated alanine transaminase) with 100 IU/day vitamin E plus statins[46] or 1000 IU/day vitamin E plus statins over six months,[84] aspartate aminotransferase (100 IU/day),[46] abnormal alkaline phosphatase (100 IU/day),[46] elevated creatinine (100 IU/day),[46] abnormal blood urea nitrogen (100 IU/day)[46]) , and QT intervals (measured as continuous variable) with 400 IU/day over eight weeks[83] (Table 45). None of the RCTs reported data on the gradable harms serious adverse events, withdrawal due to adverse events or bleeding. Furthermore, glycosylated hemoglobin,[87] leukopenia,[46] and anemia,[46] were examined as continuous outcomes and no statistically significant difference was observed. Change in urinary creatinine levels were not significantly different after 1 month supplementation with vitamin E (600 mg/day) plus statins versus 1 month statins treatment alone in one trial reporting this outcomes as a continuous variable.[86]

Table 45. Strength of evidence for cardiovascular drugs with or without vitamin E—Harms outcomes

Cardiovascular Drugs(s)/Harm	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Aspirin						
Withdrawal due to adverse events [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No significant difference; 29/121 intervention group versus 19/122 control group
Bleeding [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No significant difference; 3/52 intervention group versus 3/48 control group
Nifedipine						
Withdrawal due to adverse events [n=1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed
Renal dysfunction (creatinine [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
Hepatotoxicity (alanine transaminase, aspartate aminotransferase [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
Statins						
Renal dysfunction (creatinine, blood urea nitrogen* [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
Hepatotoxicity (alanine transaminase [2 studies], aspartate aminotransferase, alkaline phosphatase [1 study])	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	**Inconclusive** 0 events observed
QT interval (continuous data)	Moderate	NA	Indirect Surrogate	Imprecise	Insufficient	**Inconclusive** No significant difference observed.

Note: * continuous data only (dichotomous data not available).
Abbreviation: NA = not applicable.

Vitamin K

One parallel RCT (moderate risk of bias) examined the effects of vitamin K plus warfarin versus warfarin alone.[41]

Vitamin K Plus Warfarin Versus Warfarin Alone

One RCT examined the effects of vitamin K (phytomenadione150 μg/day) plus warfarin versus warfarin alone.[41] Insufficient evidence was observed for the gradable harms of bleeding episodes (no further description provided) and withdrawals due to adverse events (Table 46). This RCT did not report the gradable harms serious adverse events, renal dysfunction or hepatotoxicity.

Table 46. Strength of evidence for anticoagulants with or without vitamin K—Harms outcomes

Cardiovascular Drugs(s)/Harm	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Phenprocoumon						
Bleeding [1 study]	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No statistically significant differences for minor bleeding; Minor bleeding: 7/94 intervention group versus 10/95 control group Major bleeding: 2/94 intervention group versus0/95 control group
Warfarin						
Withdrawal due to adverse events	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** No statistically significant differences; 0/35 intervention group versus 2/33 control group
Bleeding	Moderate	NA	Direct	Imprecise	Insufficient	**Inconclusive** 0 events observed

Abbreviation: NA = not applicable.

Key Question 3a. Do the effect estimates of harms outcomes vary by age, ethnicity, gender, or health status?

A lack of evidence precluded exploration of heterogeneity in the effect estimates for harms across preidentified subgroups.

Key Question 3b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for harms outcomes?

One RCT presented data that would allow examination of the interaction between vitamin E supplements and the cardiovascular medication aspirin. Participants in this study were 486 Norplant contraceptive implant receivers from five Asian centers. The main outcome of this study was vaginal bleeding, which is not discussed here (it was not an included outcome for the present review). This RCT found no significant difference in the rates of adverse events (headache, gastrointestinal discomfort, and withdrawal due to adverse events) among treatment regimes.[100]

Main Points for Key Question 3—Harms Outcomes

In this section we examined the evidence on harms outcomes, comparing dietary supplement(s) coadministered with cardiovascular drug(s), to cardiovascular drug(s) alone.

- Fifty-seven RCTs and one retrospective cohort study contributed to the evidence.
- Overall, the studies were of moderate risk of bias across all harms, which ranged from minor (e.g., flatulence) to severe (e.g., leukopenia, hemorrhaging).
- No evidence was identified for the effects of ginger, red yeast rice extract, resveratrol, vitamin A, or vitamin D in combination with cardiovascular drugs on clinical harms.
- No evidence for the following prespecified clinical harms were found: neurologic adverse events (e.g., neuropathy, seizure), and allergic reactions (anaphylaxis, skin, transient acute airway disease).
- Sparse evidence precluded exploration of heterogeneity in the effect estimates for harms across preidentified subgroups.
- Meta-analysis was not possible due to the low event rate across all of the reported harms outcomes for all supplements examined except for omega-3 fatty acids.
- A majority of the studies reported no events or no statistically significant differences across all harms and all supplements, including *Echinacea*, garlic, *G. biloba*, ginseng, hawthorn, oral magnesium, niacin (not more than 250 mg/day), omega-3 fatty acids, vitamin E, and vitamin K.
- For all gradable outcomes for which evidence was found, the strength of evidence was graded insufficient because type II error could not be excluded due to low power of studies to examine harms.
- Four RCTs examined the effects of coenzyme Q10 plus statins, fenofibrate or ACE-inhibitors versus these medications alone.
- The evidence for benefit of coenzyme Q10 in reducing myalgia, based on two small pilot studies, was inconclusive. One RCT found superior effect of coenzyme Q10 plus stain versus vitamin E plus statins in reducing myalgia. Another RCT found no significant difference in posttreatment myopathic pain between coenzyme Q10 plus statin and statin alone groups.
- Insufficient evidence was noted for meta-analyses for serious adverse events, withdrawal due to adverse events, and hepatic toxicity (abnormal levels of aminotransaminase, and alanine transaminase) for omega-3 fatty acids plus statins versus statins alone.
- No statistically significant effects were observed for meta-analyses of omega-3 fatty acids/statins for the following outcomes: dyspepsia, headache, constipation, upper respiratory tract infection, and creatine kinase. None of the other omega-3 fatty acids RCTs found statistically significant results across all harms, except for one RCT that found a statistically significant elevated fasting blood glucose level. Six other RCTs did not observe a statistically significant difference for the blood glucose levels.

Key Question 4. In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared to cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement[s]) on pharmacokinetic outcomes (e.g., half-life [t1/2], area under the concentration curve [AUC]) of cardiovascular drugs of interest?

a. Do the effect estimates of pharmacokinetic outcomes vary by age, ethnicity, gender, or health status?

b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for pharmacokinetic outcomes?

Overview

A total of 15 unique studies were screened in.[36,59,61,64,68,70-72,90,93,95,101,142,145,147] Three studies were removed from evidence synthesis because the dose of the dietary supplement was not reported,[145] a cardiovascular drug was used that is not marketed in the United States,[142] and finally a poorer study design sequential, single group before-after *Ginkgo biloba* and ticlopidine interaction study did not add to the available randomized controlled trial (RCT) evidence.[147] Thus, a total of 12 studies contributed evidence on exposure and pharmacokinetic outcomes (Table 47). Generally, these studies were open-label, crossover RCTs, of moderate risk of bias for outcomes of interest, and included between eight and 50 healthy volunteers (Table 48).

Seven studies investigated cardiovascular drug kinetics following a single dose.[59,61,64,68,71,90,101] In keeping with the United States Food and Drug Administration guidance,[30] seven studies reported pharmacokinetic outcomes potentially indicating cardiovascular drug interactions such as the area under the concentration curve (AUC) and maximum concentration (C_{max})as geometric mean ratios (dietary supplement plus cardiovascular drug: drug alone) with corresponding 90 percent confidence intervals.[36,59,61,64,68,71,93] Others reported data as posttreatment means or median changes from baseline or geometric mean ratio with 95 percent confidence intervals. Carryover effects in these crossover trials was not a major concern because all study designs incorporated adequate washout periods, that were well over five times the half-lives of the drugs and supplements under investigation. Detailed study characteristics and data are tabulated in Appendix C. Statistical analyses were undertaken to compare the combination of dietary supplement plus cardiovascular drug with the cardiovascular drug alone.

No evidence addressing Key Question 4 subquestions (a) or (b) was identified. No data were available on bioavailability and volume of distribution.

No studies were found examining pharmacokinetic interactions between coenzyme Q10, magnesium, niacin (not more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, vitamin D with or without calcium supplementation, vitamin E, or vitamin K, and a cardiovascular drug.

Table 47. Overview of included studies for pharmacokinetic outcomes—Key Question 4

Dietary Supplement	N of Studies Included for KQ 4	Cardio-vascular Drug(s)	Study Design(s)	Participants	Study Region	Race/Ethnicity	Industry Funding or Potential for Conflict of Interest
Echinacea	1[59]	Warfarin	Crossover RCT	Healthy non-smoking males	Australia/ New Zealand	Mixed – Caucasians and Asians/South Asians	Yes
Garlic	2[61,101]	Warfarin, simvastatin, and pravastatin	Crossover RCT	Healthy males	Australia/ New Zealand and Europe	Mixed – Caucasians and Asians	No Yes[101]
Ginger	1[64]	Warfarin	Crossover RCT	Healthy non-smoking males	Australia/ New Zealand	Mixed – Caucasians and Asians	No
Ginkgo biloba	3[64,68,90]	Ticlopidine, digoxin, and warfarin	Crossover RCT	Healthy adults	East Asia, North America and Australia/ New Zealand	Asians, NR, and Mixed – Caucasians and Asians	Yes[68] Unclear[90] No[64]
Ginseng	2[70,71]	Warfarin	1 crossover 1 parallel RCT	Healthy adults	Australia/ New Zealand and North America	Mixed – Caucasians Asians and Hispanics	No
Hawthorn	1[72]	Digoxin	Crossover RCT	Healthy non-smoking adults	North America	NR	Unclear
omega-3 fatty acids	3[36,93,95]	Rosuvastatin, atorvastatin, and simvastatin	Crossover RCT	Healthy adults	North America	Mostly Caucasians, or mostly Hispanics	Yes

Abbreviations: NR = not reported; RCT = randomized controlled trial.

Table 48. Risk of bias and potential for conflict of interest—Key Question 4

Item	% of Total RCT Studies		
All RCTs (N=12)	**Yes**	**No**	**Unclear**
Adequate generation of allocation sequence	18	0	91
Allocation concealment	0	0	109
Comparability of groups	91	0	18
Purity of supplement	82	18	9
Blinding of allocated intervention	109	0	0
Adequately addressed missing data	64	9	36
Freedom from potential for conflict of interest	45	45	18
Crossover RCTs (N=11)			
Suitability of crossover design for the study condition	109	0	0
Free of carryover effect	109	0	0
Appropriateness of statistical analysis for crossover design	27	10	70
Comparability of groups between periods 1 and 2	0	0	109
Freedom from bias introduced by dropouts	60	18	20

Abbreviations: N = total number; RCTs = randomized controlled trials.

Echinacea

A randomized open-label crossover trial investigated exposure and pharmacokinetic interactions between a mixture of 600 mg of *Echinacea angustifolia* root plus 675 mg of *E. purpurea* root given four times a day for a period of two weeks, with a single dose of 25 mg warfarin versus warfarin alone.[59] Both S- and R-warfarin enantiomer specific pharmacokinetic parameters were reported, including AUC_{∞}, C_{max}, half-life, clearance and volume of distribution in 12 healthy males of known CYP2C9 and VKORC1 genotype. The 90 percent CIs for the geometric means of all parameters were all within the bioequivalence range of 80 percent to 125 percent. Although not considered to be clinically significant, a statistically significant decrease in S-warfarin AUC_{∞}, and increases in drug clearance and apparent volume of distribution were noted with coadministration of the supplement (GMRs [90 percent CIs]: 0.92[0.85, 0.99]; 1.09[1.01, 1.18]; and 1.09 [1.03, 1.18] respectively).[59] Strength of evidence is summarized in Table 49.

Table 49. Strength of evidence for warfarin with or without *Echinacea*, for Key Question 4

Gradable Outcomes	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
AUC_{∞}, C_{max}, half-life, and clearance for S- and R-warfarin	Moderate	NA	Indirect surrogate	Precise	Low	No clinically significant interactions

Abbreviations: AUC_{∞} = area under the concentration curve extrapolated to infinity; C_{max}= maximum concentration; NA = not applicable.

Garlic

An open-label, randomized, crossover trial of allicin (7.4 mg/day) pretreatment for two weeks plus a single dose of 25 mg warfarin versus a single dose of warfarin alone was conducted in 16 healthy males.[61] Four participants were lost to followup or withdrew, so only 12 participants completed the study. GMRs of S- and R-warfarin AUC_{∞}, C_{max} , half-life and clearance for S- and R-warfarin were not statistically different; however, the 90 percent CIs went beyond the 0.8 to 1.25 clinical bioequivalence boundaries for C_{max} of both S- and R-warfarin (GMR [90 percent CI] S-warfarin 1.06 [0.77, 1.47]; R-warfarin 1.02 [0.8, 1.4]).[61] Strength of evidence is summarized in Table 50.

A crossover randomized trial investigated changes in baseline statin pharmacokinetics following coadministation with 3600µg of allicin given twice daily. The study randomized 10 healthy adults to single doses of simvastatin 20 mg and pravastatin 20 mg with a crossover after 24 hours.[101] Subsequently all patients were administered garlic tablet additionally continuing 12000µg of gamma glutamylcysteine and 3800µg of thiosulfinates for 21 days in the last 2 days randomized to single dose of one of the statins with a second crossover to the other. Hence, the investigation of change in statin pharmacokinetic with addition of garlic essentially originated in a nonrandomized before-after experimental study. Ninety-five percent geometric mean ratios of $AUC_{0\text{-}24\ h}$ and half-life of statins were reported which included but went beyond the FDA specified margins of bioequivalence based on 90 percent GMR. The difference in pre and postgarlic means in the outcomes of clearance, C_{max}, and time to the maximum concentration (t_{max}) were not statistically significant, however, the data were not analyzed GMR with 90 percent CIs.

Table 50. Strength of evidence for warfarin and statins with or without garlic, for Key Question 4

Gradable Outcomes	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Warfarin						
AUC_{∞}, half-life, and clearance for S- and R-warfarin	Moderate	NA	Indirect surrogate	Precise	Low	No clinically significant interactions
C_{max} S- and R-warfarin	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	Clinically significant interactions could not be ruled out in either direction
Simvastatin						
$AUC_{0\text{-}24\ h}$ and half-life	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	Clinically significant interactions could not be ruled out in either direction based on 95% CI of GMRs
Clearance, C_{max}	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	Inconclusive results because type II error could not be excluded
Pravastatin						
$AUC_{0\text{-}24\ h}$ and half-life	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	Clinically significant interactions could not be ruled out in either direction based on 95% CI of GMRs
Clearance, C_{max}	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	Inconclusive results because type II error could not be excluded

Abbreviations: AUC_{∞} = area under the concentration curve extrapolated to infinity; C_{max}= maximum concentration; NA = not applicable.

Ginger

Twelve healthy males participated in a study of ginger interaction with warfarin, in an open-label randomized crossover trial.[64] A single dose of 25 mg warfarin was preceded and followed by either no supplement or ginger (3.6 g of ginger rhizome per day) for 7 days. Statistically significant decreases in the t_{max} were observed for both S- and R-warfarin enantiomers (GMR [90 percent CI] S-warfarin 0.79 [0.73, 0.85]; R-warfarin 0.79 [0.73, 0.85]); the clinical significance of these findings is unclear. No interactions were noted for AUC_{∞}, C_{max}, half-life, clearance and volume of distribution; the GMR 90 percent CIs were not statistically significant, and were within the bioequivalence boundaries of 80 percent to 125 percent (Table 51).[64]

Table 51. Strength of evidence for ginger plus warfarin versus warfarin alone, for Key Question 4

Gradable Outcomes	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
AUC_{∞}, C_{max} , half-life, and clearance for S- and R-warfarin	Moderate	NA	Indirect surrogate	Precise	Low	No clinically significant interactions

Abbreviations: AUC_{∞} = area under the concentration curve extrapolated to infinity; C_{max}= maximum concentration; NA = not applicable.

Ginkgo Biloba

Three studies examined pharmacokinetic interaction of *Ginkgo biloba* and specific cardiovascular drugs.[64,68,90] All three studies were randomized crossover trials in healthy adults.

In a study of 24 young healthy Korean males, single doses of ticlopidine (250 mg) were administered with or without *G. biloba* (80 mg).[68] GMRs of AUC_{∞} and C_{max} of ticlopidine were not statistically different from unity, and were clinically nonsignificant (Appendix C). Ticlopidine mean half-life and median t_{max} were not significantly affected by coadministration with *G. biloba*.[68]

In eight healthy adults, digoxin mean AUC_{∞}, C_{max}, clearance, elimination rate constant, t_{max} and half-life were not statistically different with 7 day treatment with *G. biloba*(240 mg/day) plus a single dose of 0.5 mg of oral digoxin on the last day, versus a single dose of 0.5 mg digoxin alone.[90] GMRs were not reported, or could be calculated in the absence of individual patient data; therefore, we could not rule out clinical interaction based on the predefined GMR margins of bioequivalence.[90]

In 12 healthy male participants, no statistically or clinically significant differences were noted in geometric mean ratios of AUC_{∞}, C_{max}, half-life, clearance and volume of distribution of warfarin when administered as a 25 mg single dose with 7 day pre-treatment with *Ginkgo biloba* (12 g/day) or alone.[64] However, there was significant reduction in tmax of both S- and R-warfarin enantiomers (GMR [90 percent CI]: 0.68 [0.63, 0.73]; 0.72 [0.67, 0.77], respectively). Based on the available data by group, we estimated that this decrease amounted to approximately 33 percent and 23 percent decreases in t_{max} arithmetic means for S- and R-warfarin enantiomers respectively.[64]

Strength of evidence is summarized in Table 52.

Table 52. Summary and strength of evidence for ticlopidine, digoxin and warfarin with or without *G. biloba*, for Key Question 4

Gradable Outcomes	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Ticlopidine						
AUC_{∞}, Half-life and C_{max}	Moderate	NA	Indirect surrogate	Precise	Low	No clinically significant interactions
Clearance	-	-	-	-	Insufficient	Data not reported
Digoxin						
AUC_{∞}, C_{max}, half-life, and clearance	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	Inconclusive results because type II error could not be excluded
Warfarin						
AUC_{∞}, C_{max} , half-life, and clearance for S- and R-warfarin	Moderate	NA	Indirect surrogate	Precise	Low	No clinically significant interactions

Abbreviations: AUC_{∞} = area under the concentration curve extrapolated to infinity; C_{max}= maximum concentration; NA = not applicable.

Ginseng

Interactions between American ginseng (*Panax quinquefolius*, 2 g/day from weeks 2 to 4)and warfarin (5 mg/day for 3 consecutive days of weeks 1 and 4) given over 4 weeks were investigated in a parallel randomized double blind placebo controlled trial in 20 healthy volunteers.[70] Compared with controls administered warfarin alone, a statistically significant reduction in the warfarin AUC was noted when ginseng was coadministered (between group difference in median change between week 4 and week 1-0.64 µg/mL per day [95 percent CI, -1.25, -0.13]).[70] The clinical significance of this finding is unclear because analysis was not based on geometric mean ratios.

A second open-label randomized crossover trial in 12 healthy males of a single dose of 25 mg warfarin coadministered with a 7 day pretreatment with Korean ginseng (2 capsules 3 times a day, each capsule containing 0.5 g *Panax ginseng* root and 8.93 mg ginsenosides) or alone, found clinically interpretable results.[71] The geometric mean ratios of S- and R-warfarin AUC_{∞}, C_{max}, half-life, clearance and volume of distribution were neither statistically nor clinically different, indicating no interaction. The GMR for t_{max} of both S- and R-warfarins showed statistically nonsignificant results, but the lower and upper bounds of the 90 percent CI crossed the predefined bioequivalence boundaries (S- and R-warfarin tmax GMR [90 percent CI]: 1.20 [0.77, 1.62]; 1.11 [0.78, 1.44], respectively).[71]

Strength of evidence is summarized in Table 53.

Table 53. Summary and strength of evidence for warfarin with or without ginseng, for Key Question 4

Gradable Outcomes	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
C_{max} , half-life, and clearance for S- and R-warfarin	Moderate	NA	Indirect surrogate	Precise	Low	No clinically significant interactions for Korean and American ginseng
AUC_{∞}	Moderate	Inconsistent	Indirect surrogate	Imprecise	Insufficient	The evidence of American ginseng and warfarin interaction is unclear because statistically significant reduction in AUC of warfarin was noted, but clinical significance is unclear.

Abbreviations: AUC_{ss} = steady state area under the concentration curve; NA = not applicable.

Hawthorn

Pharmacokinetic interactions between hawthorn(*Craetagus oxycantha*) and digoxin were investigated in eight healthy male volunteers in an open-label, randomized crossover trial of digoxin 0.25 mg/day for a 10 day period plus 900 mg/day of extract of hawthorn leaves with flowers standardized to 84.3 mg of oligomeric procyanidins for a 21 day period, versus digoxin alone for ten days.[72] Using a paired analysis, the differences in means of AUC_{∞}, C_{max}, t_{max}, half-life, and clearance did not reach statistical significance.

Strength of evidence is summarized in Table 54.

Table 54. Strength of evidence for digoxin with or without hawthorn, for Key Question 4

Gradable Outcomes	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Digoxin AUC_{∞}, C_{max} , half-life, and clearance	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	Inconclusive results because type II error could not be excluded

Abbreviations: AUC_{ss} = steady state area under the concentration curve; NA = not applicable.

Omega-3 Fatty Acids/Fish Oils

Three open-label randomized crossover studies in 24 to 50 healthy adult volunteers investigated interactions between omega-3 fatty acids and various statins.[36,93,95] Each study compared statin (rosuvastatin 40 mg/day, atorvastatin 80 mg/day, or simvastatin 80 mg/day) coadministered with 4 g/day of omega-3 fatty acids, with statin alone over a 14 day period. Due to the differences in first pass metabolism among various statins,[166] we did not conduct meta-analysis of outcomes data. No statistically or clinically significant differences were noted for steady state AUC and C_{max} GMRs for rosuvastatin, atorvastatin, 2-hydroxyatorvastatin, and 4-hydroxyatorvastatin. No statistically significant changes were observed in steady state β-hydroxysimvastatin arithmetic means of AUC, C_{max}, t_{max}, clearance and half-life.[36,93,95]

Strength of evidence is summarized in Table 55.

Table 55. Strength of evidence for statins with or without omega-3 fatty acids/fish oil—Harms outcomes

Gradable Outcomes	Risk of Bias	Consistency	Directness	Precision	Grade	Conclusion Treatment Effect
Rosuvastatin, atorvastatin, 2-hydroxyatorvastatin and 4-hydroxyatorvastatin AUC_{ss}, C_{max}	Moderate	NA	Indirect surrogate	Precise	Low	No clinically significant interactions
Half-life, and clearance of rosuvastatin, atorvastatin, 2-hydroxyatorvastatin and 4-hydroxyatorvastatin Beta-hydroxy-simvastatin AUC_{ss}, C_{max} , half-life, and clearance	Moderate	NA	Indirect surrogate	Imprecise	Insufficient	Inconclusive results because type II error could not be excluded

Abbreviations: AUC_{ss} = steady state area under the concentration curve; C_{max}= maximum concentration; NA = not applicable.

Applicability. Evidence of interaction affecting pharmacokinetic outcomes may not translate into altered clinical effectiveness or harms. Evidence originating in healthy young adults is not representative of older patients taking cardiovascular drugs. Metabolism of cardiovascular drugs may differ between the populations studied in these trials and CHD patients.

Key Question 4a. Do the effect estimates of pharmacokinetic outcomes vary by age, ethnicity, gender, or health status?

A paucity of evidence for supplement-drug combinations precluded exploration of heterogeneity in terms of preidentified subgroups such as age and gender.

Key Question 4b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for pharmacokinetic outcomes?

Statistical interaction data were not reported in any pharmacokinetic study.

Main Points for Key Question 4—Pharmacokinetic Outcomes

In this section we examined the evidence on pharmacokinetics of cardiovascular drugs when coadministered with or without a dietary supplement. Clinical significance of interaction was evaluated using the FDA guidance. According to the guidance, a statistically significant interaction does not determine clinical significance of interactions unless the 90 percent confidence intervals of the geometric mean ratios fall outside of the defined no effect range of 0.80 to 1.25.

- Twelve randomized controlled trials contributed evidence on pharmacokinetic outcomes.
- All trials were conducted in small numbers of healthy participants.

- No studies were found examining pharmacokinetic interactions between coenzyme Q10, magnesium, niacin (not more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, vitamin D with or without calcium supplementation, vitamin E, or vitamin K, and a cardiovascular drug.
- No clinically significant interactions were noted when *Echinacea*, ginger, or *Ginkgo biloba* were coadministered with warfarin, and when *Ginkgo biloba* was coadministered with ticlopidine. The strength of evidence for these finding was graded as low because evidence was limited to single pharmacokinetic studies with moderate risk of bias. Available evidence was insufficient, precluding meaningful conclusions about interactions between garlic and warfarin, garlic and statins, *Ginkgo biloba* and digoxin, omega-3 fatty acids and simvastatin, and hawthorn and digoxin. Interactions between ginseng and warfarin, and omega-3 fatty acids and rosuvastatin or atorvastatin were unclear; for some of the pharmacokinetic outcomes there was low strength of evidence suggesting no clinically relevant interactions, and insufficient evidence for others.
- A paucity of studies of supplement-drug combinations for which data were available precluded exploration of heterogeneity in terms of preidentified subgroups such as age and gender. Statistical interaction was not investigated in any pharmacokinetic study.

Discussion

Key Findings and Strength of Evidence

Billions of dollars are spent annually in the United States on complementary and alternative medicine (CAM), and a large portion of this expenditure is spent directly on dietary supplements.[8] Given the high prevalence of cardiovascular disease and frequency of polypharmacy in this population, the risk of drug-supplement interactions deserves serious consideration primarily to avoid potential harm; either as a result of decreasing clinical effect of drugs, or increased toxicity. There is also a real possibility of drug interactions leading to synergistic effects and positive clinical outcomes. A more thorough understanding and knowledge of potential drug-supplement interactions is important to provide specific evidence-based recommendations that do not call for universal avoidance of all dietary supplements in conjunction with pharmaceutical treatments to treat or to prevent cardiovascular disease. Without such precision, recommendations may result in the avoidance of potentially beneficial supplements or more importantly might be more readily ignored, leading to greater likelihood for harm through negative interaction.

This systematic review identifies a considerable knowledge gap regarding the impact of combining dietary supplements with cardiovascular drugs in patients with cardiovascular disease. We sought to identify the direct and indirect evidence for cardiovascular drug-dietary supplement interactions and their outcomes, and found 69 unique studies contributed evidence for synthesis. With few exceptions there is insufficient evidence to draw any strong conclusions on particular interactions between dietary supplements and cardiovascular drugs. In addition to an overall lack of evidence, the studies that were included were generally not powered to assess the clinically relevant outcomes we pre-identified as being most relevant. In addition, many of the studies had important methodological limitations or were poorly generalizable to the population of relevance. The strength of the evidence found was frequently compromised by poor allocation concealment and issues related to blinding, study reporting, and potential for conflict of interest.

Evidence of direct impact (or lack thereof) on clinical outcomes such as heart attack or stroke is most useful for patients and providers. Twenty-two randomized controlled trials reported direct evidence of drug-supplement interactions on predetermined gradable clinical outcomes; however, most of the trials were grossly underpowered to demonstrate any real effect, and often were of moderate risk of bias, leading to insufficient grades for strength of evidence. We found evidence of impact on clinical outcomes from studies that evaluated two non-gradable outcomes. In one randomized controlled trial (RCT) postangiography restenosis rates were improved through consumption of 3.2 grams of eicosapentaenoic acid taken along with aspirin, dipyridamole, and calcium channel antagonists for a duration of six months.[52] This finding was not supported by a similar but lower quality trial in India.[51] The second non-gradable clinical outcome of note came from a large long-term pragmatic trial in which 19,934 women were randomized to 600 IU of vitamin E plus 100 mg/day of aspirin versus aspirin taken alone for 10 years. In this trial, no significant differences occurred between groups in a composite outcome consisting of nonfatal myocardial infarction, nonfatal stroke, and vascular death (RR 0.95 [95 percent confidence interval (CI) 0.79, 1.13]).[39]

Anticipating a paucity of evidence describing the influence of cardiovascular drug-dietary supplement interaction on meaningful clinical outcomes, we also sought indirect evidence of such interactions. Fifty-nine studies were identified that addressed intermediate cardiovascular

outcomes (blood pressure, lipid profile, International Normalized Ratio (INR), metabolic syndrome, change in 10-year Framingham risk profile, and QT prolongation).Again, these were mostly underpowered studies of highly selected individuals, with considerable risk of study bias attributed to inadequate blinding, and allocation concealment. As a result, the most frequently graded strength of the evidence was "insufficient," with a few outcomes graded as "low".

In our review, we found some of the richest evidence on the combination of omega-3 fatty acids with cardiovascular drugs. Out of a total of 24 RCTs that measured both gradable and non-gradable surrogate outcomes, 13 assessed the combination of omega-3 fatty acids with statins (atorvastatin, simvastatin, lovastatin). From pooled results of six trials[40,44,53,96,151,163] and five trials[40,44,53,96,151] respectively, no beneficial or harmful effect on HDL-C or LDL-C was found (low strength of evidence). While the evidence for total cholesterol and triglycerides was inconclusive (i.e., statistically non-significant pooled estimates with wide 95 percent confidence interval), there appeared to be some trend indicating possible improvement in these outcomes for patients taking omega-3 fatty acids with statins, which might not have reached the level of statistical significance due to low power of the meta-analyses. Results regarding non-HDL-C and total cholesterol/HDL-C ratio were inconsistent across studies. In addition, there was evidence of low strength from one parallel arm RCT[92] and one crossover RCT[37] that systolic blood pressure was improved when statins were taken with omega-3 fatty acids.

The addition of omega-3 fatty acids to statins (only in participants with high baseline levels of TG) or the combination of aspirin and a calcium channel blocker with or without dipyridamole appears to reduce triglyceride levels but not HDL-C or LDL-C.[40,51,52,76] It is likely that the triglyceride drop reflects the activity of omega-3 fatty acids alone rather than a synergistic or additive effect in combination with antiplatelet agents and calcium channel blockers. The combination of omega-3 fatty acids with ACE-inhibitors appears to have no significant effect on blood pressure and also demonstrates evidence consistent with omega-3 fatty acids having an independent benefit for triglyceride reduction.[152] In patients with biopsy proven IgA nephropathy, a single 6-month duration RCT found that the inclusion of omega-3 fatty acids with renin–angiotensin system blockers reduced the degree of proteinuria in comparison to the cardiovascular drugs.[77] In the only trial that assessed for pharmacodynamic interaction between warfarin and omega-3 fatty acids, there was no evidence of differences in coagulation based on INR; however this was a very small study (11 participants) and neither data nor confidence intervals were provided to evaluate this further.[55]

The inclusion of coenzyme Q10 with statin drugs seems to have no significant effect on any parameter of lipid profile predetermined to be a gradable outcome (high- or low-density lipoprotein-cholesterol (HDL-C or LDL-C), triglycerides, and non-HDL-C). Only one study explored the effect of coenzyme Q10 with fenofibrate on cholesterol levels and hypertension.[58] Although the trial failed to demonstrate any interaction, the RCT was underpowered to find any significant results. A similar situation applies to a small sized RCT comparing the combination of coenzyme Q10 with an angiotensin-converting enzyme (ACE) inhibitor on ejection fraction among patients with heart failure.[54] One RCT of 60 patients with coronary artery disease (CAD) suggests that the combination of 4 g/day of garlic oil taken with nitrates has a positive effect on HDL-C levels compared with nitrates taken alone.[62] This result, while statistically significant, may not be clinically meaningful and likely does not reflect an interaction between the two agents so much as an isolated effect of garlic, since nitrates are not known to affect HDL-C.

In a single RCT conducted in an elderly population (at least 65 years), platelet adhesion (a non-gradable outcome) decreased significantly through concomitant use of vitamin E with

aspirin.[49] In another RCT, supplementation with vitamin E in patients taking nifedipine led to a significant beneficial change in LDL-C (low strength of evidence).Again, we suspect this is an isolated effect of the dietary supplement rather than reflective of an interaction between vitamin E and nifedipine itself. Finally, supplementation with low doses of vitamin K (0.1 to 0.15 mg/day) in patients anticoagulated with warfarin appeared to provide stability to INR titration and increase time within the therapeutic range based one study in participants of unknown ethnicity.[41] The stabilizing effect of vitamin K was independent of pre-specified subgroup status including gender (male/female) and age (younger or older than 65 years) in one of the studies where this was evaluated.[159]

Outcomes related to harms associated with drug interactions between dietary supplement and cardiovascular drugs were reported in 57 unique studies, most of which were considered to be at moderate risk of bias. Gradable harms outcomes included serious adverse events, withdrawal due to adverse events, bleeding, renal dysfunction, and hepatotoxicity. Of the studies that assessed harms outcomes, reported adverse events ranged from mild (e.g., flatulence) to severe (e.g., leucopenia, major bleeding), but for all the gradable outcomes for which evidence was found, the strength of evidence was judged insufficient primarily due to a lack of power contributing to the possibility of a type II error. Furthermore, very few studies systematically screened for predefined adverse events. With respect to non-gradable harms outcomes, results on benefit of coenzyme Q10 in reducing statin induced myopathic pain were inconclusive. Two pilot trials with small sample sizes reported conflicting results regarding myopathic pain. One of these trials,[89] reported potential benefit of coenzyme (100 mg/day) added to statins (varying types and doses) compared with vitamin E added to statins. The other study,[38] reported no significant differences in reduction of myalgia or number of participants tolerating statin between groups treated with combination of coenzyme Q10 (200 mg/day) or simvastatin (10 to 40 mg/day) alone. In one RCT significantly elevated fasting blood glucose occurred in the omega-3 fatty acids plus statins group versus the statins alone group.[40]

Finally, evidence for interactions between cardiovascular drugs and dietary supplements was sought from studies that assessed for direct changes in drug pharmacokinetics when combined with any of the supplements in question. Gradable pharmacokinetic outcomes included area under the concentration curve (AUC), maximum concentration (C_{max}), clearance, and drug half-life. Eleven studies contributed pharmacokinetic evidence, all of which had moderate risk of bias. We found no clear evidence of drug-supplement pharmacokinetic interaction. Evidence was either low or insufficient to rule in or out clinically important pharmacokinetic interactions, or showed no clinically important interactions. The following findings were graded as having low strength of evidence. Coadministration of *Echinacea* with warfarin may reduce the AUC of warfarin with statistical significance, but warfarin was still within the range of clinical bioequivalence. Supplementation with *Ginkgo biloba*, garlic, *Panax ginseng* or ginger extracts in patients taking warfarin does not appear to change measurably any clinically relevant warfarin pharmacokinetics. American ginseng demonstrated a shift in AUC of warfarin; however the clinical significance of this shift is not clear. No pharmacokinetic interaction between *G.biloba* and ticlopidine was identified. Finally interactions between omega-3 fatty acids and statins (rosuvastatin, simvastatin, and atorvastatin) are unclear – while for some important pharmacokinetic outcomes there was evidence of no clinically important interactions (low strength of evidence), others remained inconclusive (insufficient evidence). No studies examined pharmacokinetic interactions between coenzyme Q10, magnesium, niacin (up to 250 mg/day),

red yeast rice extract, resveratrol, vitamin A, vitamin D (with or without calcium supplementation), vitamin E, and vitamin K with any of the cardiovascular drugs.

Clinical Context and Applicability of Evidence for Decisionmaking

The purpose of this review was to synthesise the available evidence regarding the clinical significance of drug interactions between dietary supplements and cardiovascular drugs, in order to provide recommendations for medication management to care providers and patients. Ideally, any such recommendations would arise from the synthesis of studies that evaluate meaningful clinical outcomes in the context of relevant drug interactions. In the absence of studies that provide enough data to make strong recommendations we employed a search for a hierarchy of outcomes including meaningful clinical outcomes (i.e., stroke, myocardial infarction), intermediate or surrogate outcomes (i.e., lipid profile, anticoagulation parameters), harms outcomes (i.e., bleeding, adverse drug effects) and finally, pharmacokinetic evidence of interaction (i.e., changes in AUC, drug clearance). Decision makers should be aware that when a strong recommendation cannot be supported by clinical outcome data, recommendations can still be made with intermediate, harms and pharmacokinetic outcomes but the strength of these recommendations cannot be considered to be equal. The correlation between surrogate and clinical outcomes relies on the clinical rationale that surrogate outcome measures truly predict the clinical outcome. Anticipating that the evidence linking drug interactions to clinical outcomes would be sparse, we were careful to ensure appropriate selection of intermediate, harms and pharmacokinetic outcomes by soliciting expert opinion and a strong clinical rationale for each chosen surrogate outcome. Our findings organised according to this hierarchy is provided in Table 56.

Furthermore, interpretation of this report and assessment of its clinical relevance requires acknowledgment of some of the limitations of the data within. The reader must recognize that dietary supplements in the US are not regulated in the same manner as prescription drugs. This has led to some fundamental barriers to conducting and interpreting clinical research with dietary supplements. Manufacturers of supplements are not held to the same standards as manufacturers of prescription and over-the-counter drugs with respect to providing evidence of efficacy and safety prior to marketing.[109] Dietary supplements do not require FDA approval, nor are there any FDA regulations that require evidence of purity, quality or composition prior to marketing. This has resulted in a lack of standardization of these products among manufacturers and even among products from a single manufacturer. Products that claim to have standardized composition of active ingredients (if known) most often cannot claim standardization of biologic activity. Furthermore, postmarketing assessment of "standardized" herbal preparations often reveal that claims on the product label are not true.[167-170] These products are available in pharmacies, grocery stores, health food stores, and via the internet, and are sold by many different vendors. Lack of manufacturing regulations, and labelling standards may result in significant differences between products, unbeknownst to the consumer, that limit the external validity of clinical trials. In addition to concerns over quality and quantity of active ingredients, concerns over purity can be troubling. Botanical products and herbal remedies can on occasion be contaminated with heavy metals or interact with other medications. If present, this interference puts patients at risk for toxicity and interactions from other substances that otherwise would be attributed to the supplement.[170-173] Finally, there is little reliable, published information regarding the safety of dietary supplements. Until only recently, manufacturers of dietary supplements were not obliged

to report serious adverse events. This represents a gross discrepancy compared with what is required of prescription drugs. Although, the FDA has recently taken steps to make serious adverse event reporting mandatory, most of the data in this report predates that mandate, and even since 2008 when the mandate was put in place, the FDA believes that adverse events are significantly underreported.[174]

Table 56. Summary and hierarchy of significant findings

Strength of Evidence	Dietary Supplement	Cardiovascular Drug(s)	Outcome	Findings
Clinical Outcomes – None with strength of evidence "Low" or better				
Intermediate Outcomes				
Low	CoEnzyme Q10	Fenofibrate	HDL-C	No additional benefit
Low	Garlic	Warfarin	HDL-C	In favor of combination
Low	Garlic	Nitrates	HDL-C	In favor of combination
Low	Omega-3 fatty acids	Statins	HDL-C	No additional benefit
Low	Omega-3 fatty acids	Statins	LDL-C	No additional benefit
Low	Omega-3 fatty acids	Statins	TG	In favor of combination
Low	Omega-3 fatty acids	Statins	Systolic blood pressure	In favor of combination
Low	Omega-3 fatty acids	Statins	Diastolic blood pressure	No additional benefit
Low	Omega-3 fatty acids	ACE inhibitors	Systolic blood pressure	No additional benefit
Low	Omega-3 fatty acids	ACE inhibitors	Diastolic blood pressure	No additional benefit
Low	Omega-3 fatty acids	Calcium channel blockers and ASA	Triglycerides	In favor of combination
Low	Omega-3 fatty acids	Calcium channel blockers and ASA and dipyridamole	LDL-C	In favor of combination
Low	Omega-3 fatty acids	Calcium channel blockers and ASA and dipyridamole	Triglycerides	In favor of combination
Low	Vitamin E	Nifedipine	LDL-C	In favor of combination
Low	Vitamin E	Nifedipine	Triglycerides	In favor of combination
Low	Vitamin K	Coumarin derivatives	% time in INR therapeutic range	In favor of combination
Low	Vitamin K	Coumarin derivatives	Variability (SD) of INR	In favor of combination
Low	Vitamin K	Coumarin derivatives	N in therapeutic range (INR) 100% of the time	In favor of combination
Low	Vitamin K	Coumarin derivatives	N achieving target INR	In favor of combination
Low	Vitamin K	Coumarin Derivatives	N achieving stable INR	In favor of combination

Table 56. Summary and hierarchy of significant findings (continued)

Strength of Evidence	Dietary Supplement	Cardiovascular Drug(s)	Outcome	Findings
Harms Outcomes – None with strength of evidence "Low" or better				
Pharmacokinetic Outcomes				
Low	*Echinacea*	Warfarin	AUC, Cmax, Half-life, clearance	No evidence of interaction
Low	Garlic	Warfarin	AUC, half-life, clearance	No evidence of interaction
Low	Ginger	Warfarin	AUC, Cmax, half-life, clearance	No evidence of interaction
Low	*Ginkgo biloba*	Ticlopidine	AUC, half-life, Cmax	No evidence of interaction
Low	*Ginkgo biloba*	Warfarin	AUC, Cmax, half-life, clearance	No evidence of interaction
Low	Ginseng	Warfarin	Cmax, half-life, clearance	No evidence of interaction
Low	Omega-3 fatty acids	Rosuvastatin, Atorvastatin	AUC, Cmax	No evidence of interaction

Abbreviations: AUC = area under the curve; Cmax = maximum concentration; HDL-C = high density lipoprotein-cholesterol; INR = International Normalized Ratio; LDL-C = low density lipoprotein cholesterol.

Most of the studies included in this review that measured clinical outcomes provided inconclusive findings, primarily due to limitations in study design (underpowered), and risk of bias (allocation concealment, randomization). The weakness of the evidence itself, and its clinical relevance is compounded by a general lack of evidence on dietary supplement-cardiovascular drug interactions in the literature overall. Ultimately this limited information makes it impossible to translate our findings into clear advice and tools for clinical decision-making. The limited evidence also did not permit an effective dose-response evaluation to distinguish dose thresholds at which interactions may result.

Without an adequate evidence base from the literature, variability in effects across clinically important subgroups (i.e., stratified by age, ethnicity, gender or health status) could not be assessed. The evidence on clinical outcomes was generally inconclusive and applicability of inconclusivity was meaningless. The trials were generally efficacy studies in highly selected cardiovascular populations lasting for a short period of observation, along with some single-dose studies in healthy individuals. Reported benefits or "lack of harm" from studies not powered to assess these outcomes, or those in healthy volunteers may not translate into efficacy or safety in the elderly population with cardiovascular disease. As such we are unfortunately left with the unsatisfying yet fundamentally important call for more research with focused consideration and evaluation of dietary supplement-drug interaction in both clinical and observational studies.

The limit of good clinical outcomes data on which to base recommendations, leads to predicting hypothetical interactions wherein indirect evidence is the most prevalent albeit least reliable information source. The study of pharmacokinetic outcomes and changes in these outcomes are best suited to address this area. However, evidence of pharmacokinetic alterations due to interaction may not translate into altered clinical effectiveness or harms even if well characterized. Pharmacokinetic studies are generally conducted in healthy volunteers and as such the evidence may not reflect the compromised physiologic processes of the elderly and the diseased.

With relatively limited findings given its scope, the value in this review is that it points out the need for further consideration of the question of interactions and comparative effectiveness

for dietary supplements when considered in conjunction with cardiovascular drugs. Aside from further research in the area of dietary supplement-drug interactions, better documentation of supplement use by cardiovascular patients is critical to better define where interactions may result in clinically relevant sequelae.

Review of Other Systematic Reviews

Recent systematic reviews related to the topic of dietary supplement-drug interactions do not address the same scope, are not comprehensive, or involve different populations of interest. Mills and colleagues published a systematic review in 2005 focused on the effect of natural health products on the metabolism of conventional medicines.[115] Their focus was not cardiovascular drugs or patients in particular, and they described the evidence for dietary supplement–drug interactions for any conventional drug category. The evidence in the review is compiled from 41 pharmacokinetic studies. Mills' review identified a lack of evidence supporting any interaction between coenzyme Q10 and warfarin, *Ginkgo biloba* and warfarin, and *G. biloba* and digoxin. These finding are consistent with those in our review. Both reviews identified a shift in AUC of INR when American ginseng was taken in conjunction with warfarin; however, we question the clinical significance of this finding.

Also in 2005, Desai and colleagues published a review of interactions between dietary supplements and antiplatelet agents.[175] The review included both clinical trials and case reports. With respect to the dietary supplements considered in our review, Desai concluded that omega-3 fatty acids given in conjunction with aspirin led to comparatively significant reductions in ADP induced platelet aggregation, blood platelet count, thromboxane B2, and restenosis rates, and also led to a prolongation in bleeding time. The addition of vitamin E to aspirin led to comparatively significant reductions in platelet adhesion, ischemic stroke, recurrent episodes of TIA, and prolonged dental bleeding time. Unlike our review, the Desai review did not attempt to grade the outcomes extracted and while findings are largely consistent, the graded evaluation we completed did not allow the same confidence in conclusions regarding the interactions from these agents based on the directness and overall strength of evidence.

In one of the more relevant reviews published by Izzo and colleagues in 2005, Pubmed was searched to Feb 2003 for drug interactions with cardiovascular drugs, and evidence was included from case reports (43 studies) and clinical trials (eight studies).[116] This review did not systematically evaluate the quality of evidence, nor was there any grading of the strength of their recommendations. For example, drug interactions between *Ginkgo*, garlic, and ginseng were identified based on few or single case reports while our review found low or insufficient evidence of any interaction from trials of both direct and indirect evidence. In a 2009 review by Izzo and Ernst, the evidence was again extracted from case reports (41 studies) and clinical studies (17 studies) but did not focus on drug interactions with cardiovascular drugs.[119] None of their 17 clinical studies provided evidence for dietary supplement-cardiovascular drugs within the scope of our review.

Skalli and colleagues published a review in 2007, wherein the majority of evidence for supplement-drug interactions was generated from case reports, and there was no focus on cardiovascular drugs.[176] The authors identified interactions between warfarin and all of the following: ginger; *Ginkgo biloba*; garlic; and ginseng. This was again primarily from single case reports or case series. Our review found no evidence of such interactions from clinical trials providing direct or indirect evidence (insufficient or low levels of evidence). The reviewers also

suggest that *G.biloba* can counteract the effect of thiazide diuretics by increasing blood pressure (based on case report data).We found insufficient evidence to support this claim.

The most recent systematic review on dietary supplement-drug interactions was published in 2010 by Kennedy and Seely, and examined herb-drug interactions identified from trials whereby herbal impact on hepatic metabolism via cytochrome P450 isoenzymes could be ascertained.[121] In this review, the target population was not specific to cardiovascular patients or drugs, and the review evaluated indirect evidence limited to herbs metabolized via the cytochrome P450 system. While the information from this review provides an evaluation of primarily indirect data regarding possible pharmacokinetic interactions, the results do not overlap meaningfully with the findings from our review, which addresses only direct evidence for pharmacokinetic interaction.

Limitations of the Review

Limitations of our systematic review process include our restriction of the number of dietary supplements of interest to 16 of the most commonly used; this was necessary given limitations of resources and review time. Up to 30 percent of included studies were assessed to have the potential for financial conflict of interest and approximately 45 percent did not report funding information. Given the uncertainties involved in interpreting asymmetry tests for publication bias in most reviews, especially in presence of heterogeneity in effect estimates, we did not plan to investigate publication bias in this review.[102,103] In fact, a recent recommendation is that tests for funnel plot asymmetry should be used only in a minority of meta-analyses including at least ten studies of unequal sizes per analysis without substantial heterogeneity in their effect sizes.[104] However, other means of evaluating publication bias and selective outcome reporting exist, such as comparing publications with study protocol, which we did not adopt because of time and resource limitations. Seemingly, another limitation could be the exclusion of indirect evidence of drug interactions derived from surrogate measures such as alterations in probe drug metabolism, that highlight effects on enzymes involved in drug metabolism.[121] As such, evidence traditionally originates in healthy volunteers; applicability of such evidence would have been as much of a concern as for the pharmacokinetic outcomes we examined, the applicability of which was restricted to healthy volunteers with uncompromised drug metabolism. In order to make causal inferences possible for translation into practice, we also excluded combinations of multiple dietary supplements with cardiovascular drugs. For example, a given combination of multivitamins coadministered with a cardiovascular drug(s) would be limited both in causal inference of supplement-drug(s) interactions and applicability to the specific doses and combinations of vitamins employed as intervention in the study.

Empiric evidence indicates that authors are more likely to report in an international English-language journal if results are positive, while publishing negative findings in German-language literature.[177] We restricted eligibility criteria to English and German language records. We are unsure as to the magnitude (if any) and direction of language bias introduced as a result of excluding Chinese language literature for several reasons. First, traditional Chinese, and Ayurvedic medications, which are often concoctions of many herbs, were not included in this review. Secondly, most reports of randomized controlled trials published in Chinese journals lack an adequate description of randomization, and many non-randomized controlled trials have been published as randomized controlled trials.[178] Thirdly, negative CAM findings are more likely to be published in mainstream medical journals (that is, English-language journals), while positive CAM findings are more likely to be published in CAM journals (which tend to be non–English-language journals).[179] Lastly, there is evidence that countries such as China, Japan,

Russia, and Taiwan publish more CAM studies with positive results than studies with negative results; this imbalance may reflect publication bias.[180]

Conclusions

With limited data to discern evidence on dietary supplement-drug interactions, it is difficult to provide clear guidance to clinicians and patients regarding advice on the choices to be made in this area. Drug interactions that may result in positive or negative outcomes likely exist, and occur, but the evidence available and identified in this review is insufficient to provide clinical recommendations with confidence. The strength of evidence that we did find was low at best, with poor grading resulting from risks of bias, and small sample sizes greatly increasing the risk of type II error. In addition, the etiology for results are difficult to determine effectively as changes in a measured outcome could be due to either a real therapeutic effect that comes from the dietary supplement itself or be due to an interaction between the drug and the supplement in question.

With these caveats in mind, and the fact that the most reliable data comes from indirect intermediate outcomes associated with clinical results, the following is a summary of the clearer indications of interactions from the evidence reviewed:

- Omega-3 fatty acids (2 to 4 g/day) from fish and/or supplements likely do not interfere with the efficacy of statin therapy or calcium channel blockers in presence of antiplatelet agents, and may provide independent benefit in resolving hypertriglyceridemia.
- Vitamin K (0.1 to 0.15 mg/day) may help to stabilize INR when given with warfarin.
- Garlic (4 to 10 g/day) may not interact negatively with nitrates and warfarin and may confer independent benefit in improving HDL and total cholesterol.

Our confidence, however, in the validity and reproducibility of these findings is low.

Limitations of the Evidence Base

The literature search applied in this review was comprehensive in exploring multiple sources for human level evidence, yet despite this, there was a decided lack of relevant evidence. The available literature came primarily from small trials of highly selected patients and subjects that limited external validity. While there was data from which we can derive a sense of lack of interaction in many cases, the small size of the trials made it impossible to ascertain the potential for a true clinical interaction. Had the trials been adequately powered, evidence of harm or interaction may have been seen.

The internal validity of most trials was compromised due to flawed designs, lack of appropriate allocation concealment, and risk of bias. There were very few examples where a formal assessment of statistical interaction was completed. One notable exception came from a trial whereby a decrease in triglyceride levels due to combination of omega-3 fatty acids with niacin led to twice the additive effect of the each therapy alone, indicating the possibility for synergy through concurrent use.[78] In the absence of corroborating pharmacokinetic evidence or assessment for interaction, it is often impossible to determine whether a difference in outcome was due to a true pharmacological interaction, or due to more independent combined, or possibly counteracting therapeutic effects. As the goal of this synthesis work was not to complete a comparative effectiveness analysis of dietary supplement versus drugs for cardiovascular disease we did not formally assess for these comparative therapeutic effects.

In terms of the pharmacokinetic evidence assessing Key Question 4, most of the research was conducted on healthy young adults. Thus this level of evidence may not be applicable to older patients taking cardiovascular drugs due to possible differences in metabolism and the existence of comorbidities.

One of the principal limitations of the trials we evaluated was the fact that they were very small and thus susceptible to type II error. A slimly reassuring corollary to this is that if there was a real and dramatic clinical impact due to an interaction then some clinical effect would likely have shown up despite being underpowered for smaller effect sizes. Of greater concern are possible interactions that could arise through polypharmacy of prescription drugs, a situation all too common, in particular for the elderly population.

Future Research Recommendations

Given the important gap in research in the area of dietary supplement-drug interactions there should be a strategic investment in building research capacity to address relevant questions. With the continued burden of cardiovascular disease in North America, this issue is not going to go away and will likely increase in magnitude if the public continues to increase their use of dietary supplements for self-care.

A focused research strategy regarding dietary supplement-cardiovascular drugs could consider a number of recommendations arising from this review:

1. First and foremost, future research with dietary supplements should involve substances for which the identity of the agents can be clearly ascertained and the chemical composition well characterized, and ideally standardized. If the active ingredients or biologic activity of these substances is not known then studies to characterize these variables, identify mechanisms of action and describe safety should precede clinical efficacy studies. According to the 2011–2015 strategic plan of the National Center for Complementary and Alternative Medicine (NCCAM), clinical trials of dietary supplements will not be supported without documentation of biology and mechanism of action[105];
2. As extant literature is largely based on few small size efficacy studies of limited internal validity examining intermediate outcomes, future supplement-cardiovascular drug interaction trials should focus on meaningful clinical outcomes, be appropriately powered and rigorously conducted and reported, and provide precise measurements of both clinical effectiveness and harms outcomes;
3. Most studies were conducted in speciality settings, excluded patients with comorbidities, or uncontrolled comorbidities, and did not include ethnic and racial minorities; prospective trials should be representative of the population taking cardiovascular drugs in terms of comorbidities, setting, and racial distribution. They should also collect data and undertake subgroup analysis for age, gender, race, comorbidities (e.g., liver or renal compromise), and genotypic polymorphisms of the cytochrome P450 enzyme;
4. A substantial number of pharmacokinetic interaction studies did not report and analyze pharmacokinetic outcomes as per Food and Drug Administration guidance for bioequivalence studies.[30] As such future experiments of drug interactions must evaluate pharmacokinetic outcomes as geometric mean ratios with predefined margins of bioequivalence. This would help in interpretation of statistically significant and nonsignificant outcomes in terms of clinical significance;

5. Given a dearth of studies examining interactions between specific supplements and cardiovascular drugs, future clinical trials and observational studies that explore the effect of cardiovascular drugs should additionally assess the use of dietary supplements, and include this in the reporting of results. One way to facilitate this would be to consider inclusion of inquiry for dietary supplement use and other CAM care in reporting guidelines such as CONSORT;
6. Phase I trials of cardiovascular drugs should include older populations, and if possible a pharmacokinetic assessment that includes dietary supplement usage;
7. As subgroups were underrepresented in existing studies, future studies investigating supplement-drug interactions should examine vulnerable subgroups such as the elderly, those with compromised renal and liver functions, and patients with multiple comorbidities;
8. Where possible, comparative effectiveness studies should include a statistical analysis for supplement drug interactions, and the trials should be powered accordingly;
9. Until well powered, experimental studies are conducted to examine dietary supplement-drug coadministration, evidence from well-conducted prospective observational studies should be sought. Observational studies compliant with STROBE guidelines should be powered appropriately to address predefined endpoints of both efficacy and safety in a naturalistic setting, where the population sampled is reflective of the population in whom this data would be meaningful;[106] and
10. Given the difficulty and resource intensive nature of clinical trials, other sources of data should be considered to derive information regarding drug-dietary supplement interactions. Possibilities include synthesis of reports of adverse events made to both FDA and the Pharmacovigilance program at Health Canada. In addition, electronic health record linkages between databases of dietary supplement use and cardiovascular drug prescription may also add to the sparse evidence of supplement-cardiovascular drug interaction that currently exist.

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Appendix A. Search Strategies

Appendix A lists the exact search strings used for each database included in the search of the literature for this review.

MEDLINE (1950 to September 1, 2011)

1. exp Dietary Supplements/

2. (Neutraceutical* or Nutraceutical* or (diet* adj1 supplement*) or (nutrition* adj1 supplement*) or (food$1 adj1 supplement*) or (botanic* adj1 supplement*)).ti,ab.

3. exp Vitamins/ or vitamin$1.ti,ab.

4. exp Minerals/ or exp Calcium/ or exp Chromium/ or exp Copper/ or exp Iron/ or exp Magnesium/ or exp Potassium/ or exp Selenium/ or (mineral$1 or bone meal or dicalcium or dolomite or chromium or copper or iron or magnesium or potassium or selenium).ti,ab.

5. (diet or diets or dietary or supplement*).ti,ab. or (dt or tu).fs.

6. (3 or 4) and 5

7. 1 or 2 or 6

8. exp Phytotherapy/

9. exp Plant Preparations/ or exp Plant Extracts/

10. exp Drugs, Chinese Herbal/ or exp Plants, Medicinal/

11. ((medicin* adj3 herb$2) or (medicin* adj3 plant$1) or (botanical* adj3 medicin*) or (botanical* adj3 drug$1) or (herb$2 adj3 drug$1) or (therapeutic* adj3 herb$2) or (therapeutic* adj3 plant$1) or (therapeutic* adj3 botanical*) or (plant$1 adj3 pharmacotherap*) or (plant$1 adj3 pharmaco-therap*) or (herb$2 adj3 pharmacotherap*) or (herb$2 adj3 pharmaco-therap*) or (botanical adj3 pharmacotherap*) or (botanical adj3 pharmaco-therap*) or (Chinese adj2 medicin*) or (Chinese adj2 medicin*) or (Chinese adj2 drug$1) or (Chinese adj2 pharmacotherap*) or (Chinese adj2 pharmaco-therap*) or phytochemical* or phyto-chemical* or phytonutrient* or phyto-nutrient* or phytotherap* or phyto-therap* or phytomedicin* or phyto-medicin*).ti,ab.

12. exp Folic Acid/

13. (folic acid$1 or folacin or folate or folvite or pteroylglutamic acid or "Vitamin M").ti,ab.

14. exp Glucosamine/ or glucosamin*.ti,ab.

15. exp Salvia miltiorrhiza/

16. (salvia miltiorrhiza or danshen or horse-racing grass$2 or rat-tail grass$2 or red-rooted sage$1 or red root$1 or red sage$1 or red sage root or (root$1 adj3 purple sage$1) or scarlet sage$1).ti,ab.

17. (Ch'ih shen or Chinese Salvia or dangshem or dan shen or dan-shen or danshensu or fufangdenshen or huang ken or hung ken or pin-ma ts'ao or Radix salviae miltiorrhizae or Salvia bowelyana or Salvia miltiorrhiza or Salvia przewalskii or Salvia root$1 or Salvia yunnanensis or sh'ih shen or shu-wei ts'ao or tan seng or tan-shen or tzu tan-ken or yunzhi-danshen).ti,ab.

18. exp Forskolin/ or (Forskolin or Coleus forskohlii or Indian Coleus or Coleonol).ti,ab.

19. exp Ruscus/ or (butcher$2 adj broom$1).ti,ab.

20. exp Cinnamomum zeylanicum/ or (Cinnamomum or Cinnamon*).ti,ab.

21. exp Taraxacum/ or (Taraxacum or dandelion* or blowball$1 or Irish daisy or Irish daisies or (pee adj3 bed) or (lion* adj2 tooth) or (lion* adj2 teeth) or (priest* adj2 crown$1)).ti,ab.

22. ((Dent adj2 lion$1) or huang hua di ding or yellow flower earth nail$1 or puffball$1 or swine snout$1).ti,ab.

23. exp Lycium/ or (wolfberr* or wolf berr* or gojiberr* or goji berr*).ti,ab.

24. exp Echinacea/ or (Echinacea or American coneflower$1 or purple coneflower$1 or Rudbeckia purpurea or Black Sampson or combflower$1 or Kansas snake root$1 or scurvy root$1).ti,ab.

25. exp Mentha piperita/ or exp Glycyrrhiza/ or (mentha piperita or peppermint$1 or glycyrrhiza or licorice$1 or liquorice$1).ti,ab.

26. exp Tanacetum parthenium/ or exp Tinospora/ or (Tanacetum parthenium or feverfew or (bachelor'* adj button$1) or featherfew or febrifuge plant$1 or featherfoil or tinospora or guduchi).ti,ab.

27. Chrysanthemum parthenium.ti,ab.

28. exp Garlic/

29. (garlic or allium or (nectar adj2 god$1) or pa-se-waa or poor man's treacle or stinking rose$1).ti,ab.

30. exp Ginkgo biloba/

31. (Ginkgo or Ginkgophyta or Maidenhair Tree$1 or Maiden Hair Tree$1 or Fossil Tree$1 or Duckfoot tree$1 or Duck foot tree$1 or Japanese silver apricot$1 or kew tree$1 or silver apricot$1).ti,ab.

32. exp Panax/

33. (Panax or Ginseng or Jen Shen or Ninjin or Renshen or Schinseng or Shinseng).ti,ab.

34. (Guggulipid$1 or guggul$1 or gugulipid$1 or gugulu or gugululipid$1 or guggulsterone$1 or yogaraj-guggulu).ti,ab.

35. (mukul or myrrh).ti,ab.

36. exp Gymnema/

37. (Gymnema or (Periploca adj3 wood$1) or small Indian ipecac or vishani or Sarpadarushtrika or Wakandi).ti,ab.

38. exp Crataegus/ or (hawthorn$2 or Crataegus oxycantha or (bread adj2 cheese tree$1) or cockspur thorn$1 or Chinese hawthorn$2 or May bush$2 or May tree$1 or May blossom$1 or May flower$1 or mayflower$1 or quickset or thorn-apple tree$1 or thornapple tree$1 or white thorn$1 or whitethorn$1).ti,ab.

39. exp Convallaria/

40. (Convallaria or (lily adj3 valley) or lady$2 tears or ladies tears or may lily or may lilies or may bell$1 or maybell$1 or conval lily or conval lilies or lily constancy or (ladder$1 adj2 heaven) or male lily or male lilies).ti,ab.

41. exp Leonurus/

42. (Motherwort* or Leonorus cardiaca or lion$2 tail$1 or lion$2 ear$1 or throwwort*).ti,ab.

43. exp Milk Thistle/

44. (Milk Thistle$1 or Silybum marianum or Carduus marianus or Holy thistle$1 or marythistle$1 or Mary$2 thistle$1 or Marian$2 thistle$1).ti,ab.

45. exp Rauwolfia/

46. (Rauwolfia or Rauvolfia or Indian snakeroot$1 or Sarpa-gandha or Nakuli or Chota-chand or Kanakachandrika).ti,ab.

47. (red yeast rice extract* or Monascus purpureus or (mould species adj3 rice$1) or (red adj2 yeast$1) or (red adj2 rice$1) or red koji or red leaven$1).ti,ab.

48. exp Eleutherococcus/

49. (Eleutherococcus or Siberian ginseng or Ci wu ju or Eleuthero or "touch-me-not" or "touch-me-nots" or devil$2 shrub$1).ti,ab.

50. ((Thorny bearer adj2 free) or ussurian thorny pepperbrush$2 or ussurian thorny pepper brush$2).ti,ab.

51. exp Hypericum/

52. (Hypericum or John$2 wort$1 or Johnswort$1 or Amber or (touch adj2 heal) or goat weed$1 or Hardhay$1 or Klamath weed$1 or Rosin rose$1 or Tipton weed$1 or (balm adj2 warrior$1)).ti,ab.

53. (Devil$2 scorge$1 or goatweed$1 or klammath weed$1).ti,ab.

54. exp Curcuma/

55. (Turmeric or curcuma or Indian saffron or Indian yellow root$1 or Zedoary zedoaria).ti,ab.

56. exp Valerian/

57. (Valerian* or vandal root$1 or all-heal$1 or setwall$1).ti,ab.

58. exp Selenoproteins/ or Selenoprotein$1.ti,ab.

59. exp Thioctic Acid/ or (thioctic acid$1 or Alpha lipoic acid$1 or Alpha-Lipogamma or Alpha-Lipon Stada or alpha-Liponaure Heumann or Alpha-Liponsaure or Alpha-Lippon or alpha-Vibolex or Alphaflam).ti,ab.

60. ("Coenzyme Q10" or "CoQ 10" or CoQ10 or idebenone or ubiquinone or ubidecarenone or ubisemiquinone or "vitamin q10").ti,ab.

61. exp Fish Oils/

62. (fish adj2 oil$1).ti,ab.

63. exp Fatty Acids, Omega-3/

64. ("omega 3" or "omega 3s" or omega three$1 or "n-3 Fatty Acid" or "n-3 Fatty Acids" or "n3 Fatty Acid" or "n3 Fatty Acids" or "n-3 Polyunsaturated Fatty Acid" or "n-3 Polyunsaturated Fatty Acids" or "n3 Polyunsaturated Fatty Acid" or "n3 Polyunsaturated Fatty Acids" or "n-3 PUFA" or "n3 PUFA").ti,ab.

65. (Eicosapentanoic acid$1 or decosahexanoic acid$1 or alpha linoleic acid$1).ti,ab.

66. (green tea$1 or black tea$1 or Camellia sinensis or Japanese tea$1 or Matsu-cha tea$1).ti,ab.

67. exp Phytosterols/

68. (Phytosterol$1 or plant sterol$1 or plant stanol$1 or Beta-sitosterol$1 or sterolin$1).ti,ab.

69. exp beta-Glucans/

70. beta-Glucan$1.ti,ab.

71. exp Kava/

72. (kava or kawa or Piper methysticum).ti,ab.

73. exp Psyllium/

74. (Psyllium or Plantago ovata or flea seed$1 or fleawort or hemicelluloses or plantago seed$1 or ispaghula husk$1 or ispagula husk$1 or ispaghula seed$1 or ispagula seed$1 or Plantago arenaria or Plantago isphagula or Plantago ispagula).ti,ab.

75. exp Soy Foods/

76. (soy or miso or natto or tempeh or tofu).ti,ab.

77. exp Arginine/

78. (Arginine or L-Arginine).ti,ab.

79. (Chia or Salvia columbariae or Salvia hispanica or salba).ti,ab.

80. exp Chitosan/

81. (Chitin or chitosan or "N-carboxybutyl" or Poliglusam).ti,ab.

82. exp Cynara/

83. (Cynara or globe artichoke$1 or cardoon$1).ti,ab.

84. exp Carnitine/

85. (Carnitine or Bicarnesine or "L-Carnitine" or Levocarnitine or "Vitamin BT" or "Acetyl-L-carnitine" or carnitene or carnitor or canitor or "D-carnitine" or "D,L-carnitine" or "L-acetyl-carnitine" or "L-carnitina" or "L-carnitine" or "L-tartrate" or "L-CARNIPURE" or levacecarnine or levocarnitine or "L-propionylcarnitine" or "propionil-L-carnitine" or "propionyl-L-carnitine" or ST261).ti,ab.

86. (Pantethine or "Vitamin B5" or bile acid sequestrant$1 or cyproheptadine or cysteamine or "D-pantethine" or pantetheine or pantetheinase or Pantetina or panthenol or pantomin or pantosin or pantothenic acid$1 or sulfopantetheine).ti,ab.

87. (Policosanol$1 or D003 or hexacontanol$1 or isopolicosanol$1 or "Octa-60" or octacosanoic acid$1 or octacosanol$1 or ricewax$2 or winteriser cake$1 or winterizer cake$1 or sugar cane policosanol$1 or sunflower seed policosanol$1 or triacontanol* or wheat germ policosanol$1).ti,ab.

88. exp Withania/ or (Withania or Ashwaganda or Indian ginseng or winter cherry or winter cherries or wintercherry or wintercherries or Ayurvedic ginseng).ti,ab.

89. exp Aesculus/ or exp Aloe/ or (aesculus or buckeye$1 or horse chestnut$1 or conqueror tree$1 or aloe vera or aloe barbadensis).ti,ab.

90. exp Ginger/ or (ginger or Zingiber officinale or Gamma oryzanol).ti,ab.

91. exp Ephedra/ or exp Trigonella/ or (ephedra or ginger trigonella or fenugreek or foenumgraecum or poenumgraecum).ti,ab.

92. (Gamma oryzanol or dong quai or tetrandrine or tetradrine or hanjisong).ti,ab.

93. exp Hydrastis/

94. (hydrastis or Golden Seal or Goldenseal).ti,ab.

95. or/7-94

96. exp Functional Food/

97. (functional food$1 or (therapeutic* adj2 food$1)).ti,ab.

98. Citrus paradisi/ or Vaccinium macrocarpon/ or Viburnum/ or Blueberry Plant/ or Punicaceae/

99. (Citrus paradisi or Vaccinium macrocarpon or Viburnum or Punicaceae or blueberr* or cranberr* or grapefruit* or Toronja* or pomegranate* or Punica granatum or bitter orange or citrus auranticum or kijitsu or shangzhou zhiqiao or zhi shi).ti,ab.

100. exp beverages/ or (beverage* or drink* or juice* or tea or teas).ti,ab.

101. (98 or 99) and 100

102. exp Plant oils/ or exp Olea/

103. ((botanic* or plant or plants or vegetable* or clove or cloves or corn or corns or cottonseed* or croton* or olive or olives or safflower* or sesame* or soybean* or teatree*) and (oil or oils)).ti,ab.

104. Linaceae/ or Flax/ or (Linaceae or flax or flaxseed* or Linum or linseed*).ti,ab.

105. exp Dietary Fiber/ or ((diet or diets or dietary) and (fibre or fibres or fiber or fibers or roughage or (wheat adj bran) or cereal*)).ti,ab.

106. exp Caffeine/ or caffein*.ti,ab.

107. or/102-106
108. 96 or 97 or 101 or 107
109. 95 or 108
110. exp Cardiovascular diseases/dt
111. exp Adrenergic beta-Antagonists/
112. (Adrenergic adj2 Antagonist*).ti,ab.
113. ((beta adj1 Adrenergic adj2 block*) or beta block*).ti,ab.
114. exp Acebutolol/
115. (acebutolol or acebutalol or Apo-Acebutolol or Apo-Acebulalol or Sectral or Prent).ti,ab.
116. exp Betaxolol/
117. (betaxolol or Kerlon or Kerlone).ti,ab.
118. exp Bisoprolol/
119. (bisoprolol or Concor or Concore or Zebeta or Monocor).ti,ab.
120. (carvedilol or Apo-carvedilol or Coreg or Dilatrend or Eucardic or Kredex).ti,ab.
121. exp Labetalol/
122. (labetalol or Labetolol or Normodyne or Trandate).ti,ab.
123. exp Metoprolol/
124. (metoprolol or Betaloc or Betalok or Lopressor or Seloken).ti,ab.
125. exp Nadolol/
126. (nadolol or Corgard or Solgol).ti,ab.
127. (nebivolol or Nebilet or Silostar).ti,ab.
128. exp Pindolol/
129. (pindolol or Visken).ti,ab.
130. exp Propranolol/
131. (propranolol or Avlocardyl or Deralin or Dociton or Inderal or Obsidan).ti,ab.
132. exp Sotalol/
133. (sotalol or Darob).ti,ab.
134. exp Timolol/
135. (timolol or Blocadren).ti,ab.
136. exp Calcium Channel Blockers/
137. ((calcium block* adj2 exogenous) or (calcium antagonist* adj2 exogenous) or (calcium inhibitor* adj2 exogenous) or calcium channel block*).ti,ab.
138. (Dihydropyridine or Lemildipine).ti,ab.
139. exp Amlodipine/
140. (amlodipine or Norvasc or Istin).ti,ab.
141. exp Felodipine/
142. (felodipine or Plendil or Renedil).ti,ab.
143. exp Isradipine/
144. (isradipine or DynaCirc or Lomir or Prescal).ti,ab.
145. exp Nicardipine/
146. (nicardipine or Cardene).ti,ab.
147. exp Nifedipine/
148. (nifedipine or Adalat or Cordipin or Nifediac or Nifedical or Procardia).ti,ab.
149. exp Nimodipine/
150. (nimodipine or Nimotop).ti,ab.

151. exp Nisoldipine/
152. (nisoldipine or Sular).ti,ab.
153. exp Diltiazem/
154. (diltiazem or Cardizem or Dilacor or Dilzem or Tiazac).ti,ab.
155. exp Verapamil/
156. (verapamil or Bosoptin or Calan or Cordilox or Covera-HS or Isoptin or Iproveratril or Verelan).ti,ab.
157. exp Angiotensin-Converting Enzyme Inhibitors/
158. ((Angiotensin-Converting Enzyme adj1 Inhibitor*) or ACE inhibitor* or (Angiotensin-Converting Enzyme adj1 antagonist*)).ti,ab.
159. (dipeptidyl carboxypeptidase inhibitor* or (Kininase II adj2 inhibitor*) or (Kininase II adj2 antagonist*)).ti,ab.
160. (benazepril or Cibacen or Lotensin).ti,ab.
161. exp Captopril/
162. (captopril or Capoten or Lopirin).ti,ab.
163. exp Enalapril/
164. (enalapril or Renitec or Renitek or Vasotec).ti,ab.
165. exp Fosinopril/
166. (fosinopril or Dynacil or Fozitec or Monopril or Staril or Tensocardil).ti,ab.
167. exp Lisinopril/
168. (lisinopril or Lysinopril or Prinivil or Zestril).ti,ab.
169. (moexipril or Perdix or Univasc).ti,ab.
170. exp Perindopril/
171. (perindopril or Aceon or Coversyl or Prestarium).ti,ab.
172. (Quinapril or Accupril).ti,ab.
173. exp Ramipril/
174. (Ramipril or Acovil or Altace or Triatec or Tritace or Vesdil).ti,ab.
175. (Trandolapril or Gopten or Mavik or Odrik).ti,ab.
176. (Candesartan or Atacand).ti,ab.
177. (eprosartan or Teveten).ti,ab.
178. (irbesartan or Aprovel or Avapro or Karvea).ti,ab.
179. exp Losartan/
180. (losartan or Cozaar).ti,ab.
181. (olmesartan or Benicar).ti,ab.
182. (telmisartan or Micardis or Pritor).ti,ab.
183. (valsartan or Diovan).ti,ab.
184. ((Renin adj1 Inhibit*) or Renin antagonist*).ti,ab.
185. (Aliskiren or Tekturna).ti,ab.
186. aldosterone receptor antagonist$1.ti,ab.
187. (Eplerenone or Inspra).ti,ab.
188. exp Spironolactone/
189. (Spironolactone or Aldactone or Verospirone).ti,ab.
190. exp Vasodilator Agents/
191. Vasodilator$1.ti,ab.
192. exp Clonidine/
193. (clonidine or Apo-Clonidine or Catapres or Duraclon).ti,ab.

194. exp Guanabenz/
195. (guanabenz or Wytensin).ti,ab.
196. exp Guanfacine/
197. (guanfacine or Intuniv or Tenex).ti,ab.
198. exp Methyldopa/
199. (Methyldopa or Apo-Methyldopa or Aldoril or Aldomet or Dopamet or Dopegyt).ti,ab.
200. exp Diazoxide/
201. (Diazoxide or Hyperstat or Proglycem).ti,ab.
202. exp Hydralazine/
203. (Hydralazine or Apo-Hydralazine or Apresoline or Dralzine).ti,ab.
204. exp Minoxidil/
205. (minoxidil or Loniten).ti,ab.
206. exp Isosorbide Dinitrate/
207. (Isosorbide Dinitrate or Dilatrate or Cedocard or Isoket or Isotrate or Isordil or Sorbitrate).ti,ab.
208. exp Nitroglycerin/
209. (nitroglycerin$1 or Natispray or Nitro-Dur or Nitromist or Nitrospan or Nitrostat or Nitro-Time or Transderm Nitro or Tridil or Trinipatch).ti,ab.
210. exp Phosphodiesterase inhibitors/
211. ((Phosphodiesterase adj1 Inhibit*) or (Phosphodiesterase adj1 antagonist*) or Antiphosphodiesterase$1 or Anti-phosphodiesterase$1 or (Phosphoric Diester Hydrolase adj1 Inhibit*) or (Phosphoric Diester Hydrolase adj1 antagonist*)).ti,ab.
212. (sildenafil or Revatio or tadalafil or vardenafil).ti,ab.
213. (Cilostazol or Pletal).ti,ab.
214. exp Alprostadil/
215. Alprostadil.ti,ab.
216. exp Epoprostenol/
217. (Epoprostenol or Flolan).ti,ab.
218. exp iloprost/
219. (iloprost or Ciloprost or Ventavis).ti,ab.
220. (Endothelin antagonist$1 or (Endothelin adj1 inhibit*)).ti,ab.
221. (treprostinil or Remodulin or bosentan or Tracleer or ambrisentan or Letairis).ti,ab.
222. exp Papaverine/
223. papaverine.ti,ab.
224. exp Isoxsuprine/
225. (isoxsuprine or Duvadilan).ti,ab.
226. exp Adrenergic alpha-Antagonists/
227. ((alpha-Adrenergic adj2 block*) or (Adrenergic alpha adj2 block*) or (alpha-Adrenergic adj2 antagonist*) or (Adrenergic alpha adj2 antagonist*) or (alpha block* adj2 adrenergic) or (alpha antagonist* adj2 adrenergic)).ti,ab.
228. exp Doxazosin/
229. (doxazosin or Cardura or Carduran or Diblocin or Doxazomerck or Doxazosin or Progandol).ti,ab.
230. exp Prazosin/
231. (prazosin or Minipress or Furazosin or Pratsiol).ti,ab.

232. (terazosin or Adecur or Apo-Terazosin or Deflox or Dysalfa or Flotrin or Heitrin or Hytrin or Hytrine or Magnurol).ti,ab.

233. exp Anti-Arrhythmia Agents/

234. ((Anti-Arrhythmia or Anti-Arrhythmic* or Antiarrhythmia or Antiarrhythmic* or Anti-fibrillatory or Antifibrillatory) and (drug or drugs or agent or agents or medication* or prescription*)).ti,ab.

235. exp Disopyramide/

236. (disopyramide or Norpace or Rhythmodan).ti,ab.

237. exp Procainamide/

238. (procainamide or Apo-Procainamide or Biocoryl or Novocainamide or Novocamid or Procamide or Pronestyl or Procan or Procanbid).ti,ab.

239. exp Quinidine/

240. (quinidine or Apo-Quinidine or Chinidin or Quinidex or Quinora).ti,ab.

241. exp Mexiletine/ or Mexiletine.ti,ab.

242. exp Encainide/

243. (encainide or Enkaid).ti,ab.

244. exp Flecainide/

245. (Flecainide or Tambocor).ti,ab.

246. exp Propafenone/

247. (propafenone or Apo-Propafenone or Arythmol or Baxarytmon or Fenoprain or Rythmol or Rytmonorm).ti,ab.

248. exp Amiodarone/

249. (amiodarone or Amiodarona or Cordarone or Cordarex or Pacerone or Trangorex).ti,ab.

250. (dofetilide or Tikosyn).ti,ab.

251. (dronedarone or Multaq).ti,ab.

252. exp Cardiotonic Agents/

253. ((Cardiotonic or Cardioprotective or Cardio-tonic or Cardio-protective) and (drug or drugs or agent or agents or medication$1 or prescription$1)).ti,ab.

254. (cardiotonics or cardio-tonics or cardiac stimulant* or myocardial stimulant* or inotropic agent*).ti,ab.

255. exp Digoxin/

256. (digoxin or Digacin or Digitek or Dilanacin or Lanacordin or Lanicor or Lanoxicaps or Lanoxin or Lenoxin).ti,ab.

257. exp Antilipemic Agents/

258. (Antilipemic$1 or anti-lipemic$1 or hypolipidemic$1 or hypo-lipidemic$1).ti,ab.

259. ((Antilipemic or anti-lipemic or antihyperlipemic or anti-hyperlipemic or antihyperlipidemic or anti-hyperlipidemic or hypolipidemic or hypo-lipidemic) and (drug or drugs or agent or agents or medication* or prescription*)).ti,ab.

260. (antihyperlipemics or anti-hyperlipemics or antihyperlipidemics or anti-hyperlipidemics).ti,ab.

261. exp Cholestyramine Resin/

262. (cholestyramin$1 or colestyramin$1 or Cuemid or Quantalan or Questran).ti,ab.

263. exp Colestipol/

264. (colestipol or Colestid).ti,ab.

265. (colesevelam or CholestaGel or Welchol).ti,ab.

266. (Bile acid sequestrant$1 or bile acid-binding drug$1 or bile acid-binding agent$1).ti,ab.

267. (Anticholesteremic$1 or Hypocholesteremic$1 or (cholesterol adj2 inhibitor$1) or cholesterol-lowering drug$1 or cholesterol-lowering agent$1 or cholesterol-lowering medication$1).ti,ab.

268. (ezetimibe or Zetia).ti,ab.

269. (fenofibrate or Antara or Fenoglide or Fibricor or Lipofen or Lofibra or TriCor or Triglide or Trilipix).ti,ab.

270. exp Gemfibrozil/

271. (Gemfibrozil or Apo-Gemfibrozil or Lopid or Trialmin).ti,ab.

272. ((Hydroxymethylglutaryl-CoA Reductase adj1 inhibit*) or (HMG-CoA Reductase adj1 inhibit*) or (Hydroxymethylglutaryl-CoA adj1 inhibit$) or (Hydroxymethylglutaryl-Coenzyme A adj1 inhibit$)).ti,ab.

273. (atorvastatin or Liptor).ti,ab.

274. (fluvastatin or Lescol).ti,ab.

275. exp Lovastatin/

276. (lovastatin or Altocor or Altoprev or Mevacor).ti,ab.

277. exp Pravastatin/

278. (pravastatin or Apo-Pravastatin or Lipostat or Pravasin$1 or Pravachol or Selektine).ti,ab.

279. (rosuvastatin or Crestor).ti,ab.

280. exp Simvastatin/

281. (simvastatin or Synvinolin or Zocor).ti,ab.

282. exp Niacin/

283. (niacin or Niacor or Niaspan or Nicobid or Nicolar or Nicotinex or Slo-Niacin).ti,ab.

284. exp Anticoagulants/

285. (Anticoagulant$1 or anti-coagulant$1 or bloodthinn* or blood-thinn*).ti,ab.

286. exp Warfarin/

287. (warfarin or Apo-Warfarin or Coumadin$1).ti,ab.

288. exp Dalteparin/

289. (dalteparin or Fragmin$1).ti,ab.

290. exp Heparin/

291. heparin.ti,ab.

292. (tinzaparin or Innohep).ti,ab.

293. exp Platelet Aggregation Inhibitors/

294. (antithrombocytic* or anti-thrombocytic* or (platelet$1 adj2 inhibit*) or Antiplatelet$1 or Anti-platelet$1 or Platelet Antagonist$1 or Platelet Antiaggregant$1).ti,ab.

295. exp Aspirin/

296. (Aspirin or Acetylsalicylic or Acylpyrin or Aloxiprimum or Aspergum or Bufferin or Colfarit or Dispril or Ecotrin or Easprin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin).ti,ab.

297. exp Ticlopidine/

298. (ticlopidine or Ticlid).ti,ab.

299. (clopidogrel or Plavix).ti,ab.

300. exp Diuretics/

301. (diuretic$1 or water pill$1).ti,ab.

302. exp Bumetanide/
303. (Bumetanide or bumex).ti,ab.
304. exp Ethacrynic Acid/
305. (etacrynic acid or ethacrynic acid or Edecrin).ti,ab.
306. exp Furosemide/
307. (furosemide or Errolon or Fursemide or Fusid or Lasix).ti,ab.
308. (torsemide or Demadex or torasemide).ti,ab.
309. (k-sparing or potassium-sparing).ti,ab.
310. exp Amiloride/
311. (Amiloride or Amidal or Amiduret or Kaluril or Midamor or Midoride or Modamide).ti,ab.
312. exp Triamterene/
313. (triamterene or Dyrenium).ti,ab.
314. thiazide diuretic$1.ti,ab.
315. exp Bendroflumethiazide/
316. (Bendroflumethiazide or Bendrofluazide).ti,ab.
317. exp Chlorothiazide/
318. (chlorothiazide or Chlotride or Diuril).ti,ab.
319. exp Hydrochlorothiazide/
320. (hydrochlorothiazide or Apo-Hydro or Dichlotride or Esidrex or HydroDIURIL or Microzide or Oretic).ti,ab.
321. exp Methyclothiazide/
322. (methyclothiazide or Aquatensen or Enduron).ti,ab.
323. exp Polythiazide/
324. (polythiazide or Renese).ti,ab.
325. exp Chlorthalidone/
326. (chlorthalidone or Apo-Chlorthalidone or Hygroton or Thalitone).ti,ab.
327. exp Indapamide/
328. (indapamide or Lozol or Metindamide).ti,ab.
329. exp Metolazone/
330. (metolazone or Mykrox or Zaroxolyn or Zytanix).ti,ab.
331. or/110-330
332. exp Herb-Drug Interactions/
333. exp Food-Drug Interactions/
334. exp Drug Synergism/
335. ad.fs.
336. ct.fs.
337. de.fs.
338. me.fs.
339. pk.fs.
340. to.fs.
341. ci.fs.
342. (interact* or react* or contraindicat* or contra-indicat* or chemically induce* or enhanc* or potentiat* or synergis* or toxic or toxicit*).ti,ab.
343. or/332-342
344. 109 and 331 and 343

345. limit 344 to human
346. limit 344 to ("in data review" or "in process" or "pubmednotmedline")
347. 345 or 346
348. limit 347 to "reviews (specificity)"
349. meta analysis.pt.
350. exp meta-analysis as topic/
351. (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).ti,ab.
352. (systematic review* or systematic overview* or technology assessment* or HTA or HTAs).ti,ab.
353. exp Technology assessment, biomedical/
354. health technology assessment winchester england.jn.
355. (evidence report technology assessment or evidence report technology assessment summary).jn.
356. or/349-355
357. 347 and 356
358. 348 or 357
359. (controlled clinical trial or randomized controlled trial).pt.
360. exp randomized controlled trials as topic/ or exp controlled clinical trials as topic/ or exp random allocation/ or exp double-blind method/ or exp single-blind method/ or exp placebos/
361. "controlled clinical trial".ti,ab.
362. (random* or RCT$1 or placebo*).ti,ab.
363. ((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)).ti,ab.
364. or/359-363
365. 347 and 364
366. 365 not 358
367. clinical trial.pt.
368. exp Clinical Trials as Topic/
369. "clinical trial".ti,ab.
370. evaluation studies.pt.
371. exp Evaluation Studies as Topic/
372. (volunteer or volunteers or open label* or nonrandom* or non random* or quasirandom* or quasi-random*).ti,ab.
373. exp Cohort Studies/ or exp Longitudinal Studies/ or exp Prospective Studies/ or exp Follow-Up Studies/ or exp Retrospective Studies/ or exp Case-Control Studies/
374. (cohort or cohorts or longitudinal or prospective or retrospective).ti,ab.
375. ((observational or follow-up or followup) adj stud*).ti,ab.
376. (population-based stud* or population-based analys* or population stud* or population analys*).ti,ab.
377. ((descriptive adj stud*) or (multidimensional adj stud*) or (multi-dimensional adj stud*) or (multicenter adj stud*) or (multi-center adj stud*) or (multicentr* adj stud*) or (multi-centr* adj stud*)).ti,ab.
378. exp Multicenter Study/ or exp Multicenter Studies as Topic/
379. Comparative Study.pt.

380. ((comparative adj study) or (comparative adj studies) or (case adj control*) or "case series" or (case adj comparison*) or (case adj history) or (case adj histories)).ti,ab.

381. or/367-380

382. 347 and 381

383. 382 not (358 or 365)

384. (ae or co or mo).fs.

385. exp Harm Reduction/ or exp Intraoperative Complications/ or exp Morbidity/ or exp Mortality/ or exp Postoperative Complications/ or exp Risk/ or exp Safety/ or exp Treatment Outcome/ or exp Teratogens/ or exp Abnormalities, Drug-Induced/

386. (adverse or complication* or harm or harms or harmful or harming or injurious or morbidit* or mortalit* or risk$1 or side effect$1 or undersirable or tolerability or teratogen* or safety).ti,ab.

387. or/384-386

388. 347 and 387

389. 388 not (358 or 365 or 382)

AMED (1985 to September 1, 2011)

1. exp Dietary supplements/

2. (Neutraceutical* or Nutraceutical* or (diet* adj1 supplement*) or (nutrition* adj1 supplement*) or (food$1 adj1 supplement*) or (botanic* adj1 supplement*)).ti,ab.

3. exp Vitamins/ or vitamin$1.ti,ab.

4. exp Minerals/ or exp Calcium/ or exp Chromium/ or exp Copper/ or exp Iron/ or exp Magnesium/ or exp Potassium/ or exp Selenium/ or (mineral$1 or bone meal or dicalcium or dolomite or chromium or copper or iron or magnesium or potassium or selenium).ti,ab.

5. (diet or diets or dietary or supplement*).ti,ab.

6. (3 or 4) and 5

7. 1 or 2 or 6

8. exp Phytotherapy/

9. exp plant extracts/ or exp plants medicinal/ or exp Herbal Drugs/

10. ((medicin* adj3 herb$2) or (medicin* adj3 plant$1) or (botanical* adj3 medicin*) or (botanical* adj3 drug$1) or (herb$2 adj3 drug$1) or (therapeutic* adj3 herb$2) or (therapeutic* adj3 plant$1) or (therapeutic* adj3 botanical*) or (plant$1 adj3 pharmacotherap*) or (plant$1 adj3 pharmaco-therap*) or (herb$2 adj3 pharmacotherap*) or (herb$2 adj3 pharmaco-therap*) or (botanical adj3 pharmacotherap*) or (botanical adj3 pharmaco-therap*) or (Chinese adj2 medicin*) or (Chinese adj2 medicin*) or (Chinese adj2 drug$1) or (Chinese adj2 pharmacotherap*) or (Chinese adj2 pharmaco-therap*) or phytochemical* or phyto-chemical* or phytonutrient* or phyto-nutrient* or phytotherap* or phyto-therap* or phytomedicin* or phyto-medicin*).ti,ab.

11. exp Folic Acid/

12. (folic acid$1 or folacin or folate or folvite or pteroylglutamic acid or "Vitamin M").ti,ab.

13. Glucosamin*.ti,ab.

14. exp Salvia/

15. (salvia miltiorrhiza or danshen or horse-racing grass$2 or rat-tail grass$2 or red-rooted sage$1 or red root$1 or red sage$1 or red sage root or (root$1 adj3 purple sage$1) or scarlet sage$1).ti,ab.

16. (Ch'ih shen or Chinese Salvia or dangshem or dan shen or dan-shen or danshensu or fufangdenshen or huang ken or hung ken or pin-ma ts'ao or Radix salviae miltiorrhizae or Salvia bowelyana or Salvia miltiorrhiza or Salvia przewalskii or Salvia root$1 or Salvia yunnanensis or sh'ih shen or shu-wei ts'ao or tan seng or tan-shen or tzu tan-ken or yunzhi-danshen).ti,ab.

17. (Forskolin or Coleus forskohlii or Indian Coleus or Coleonol).ti,ab.

18. (ruscus or (butcher$2 adj broom$1)).ti,ab.

19. exp Cinnamomum/ or (Cinnamomum or Cinnamon*).ti,ab.

20. exp Taraxacum/ or (Taraxacum or dandelion* or blowball$1 or Irish daisy or Irish daisies or (pee adj3 bed) or (lion* adj2 tooth) or (lion* adj2 teeth) or (priest* adj2 crown$1)).ti,ab.

21. ((Dent adj2 lion$1) or huang hua di ding or yellow flower earth nail$1 or puffball$1 or swine snout$1).ti,ab.

22. exp Lycium/ or (lycium or wolfberr* or wolf berr* or gojiberr* or goji berr*).ti,ab.

23. exp Echinacea/ or (Echinacea or American coneflower$1 or purple coneflower$1 or Rudbeckia purpurea or Black Sampson or combflower$1 or Kansas snake root$1 or scurvy root$1).ti,ab.

24. exp Mentha piperita/ or exp Glycyrrhiza/ or (mentha piperita or peppermint$1 or glycyrrhiza or licorice$1 or liquorice$1).ti,ab.

25. exp Tanacetum parthenium/ or (Tanacetum parthenium or feverfew or (bachelor'* adj button$1) or featherfew or febrifuge plant$1 or featherfoil or tinospora or guduchi).ti,ab.

26. Chrysanthemum parthenium.ti,ab.

27. exp Allium sativum/

28. (garlic or allium or (nectar adj2 god$1) or pa-se-waa or poor man's treacle or stinking rose$1).ti,ab.

29. exp Ginkgo biloba/

30. (Ginkgo or Ginkgophyta or Maidenhair Tree$1 or Maiden Hair Tree$1 or Fossil Tree$1 or Duckfoot tree$1 or Duck foot tree$1 or Japanese silver apricot$1 or kew tree$1 or silver apricot$1).ti,ab.

31. exp Panax/

32. (Panax or Ginseng or Jen Shen or Ninjin or Renshen or Schinseng or Shinseng).ti,ab.

33. (Guggulipid$1 or guggul$1 or gugulipid$1 or gugulu or gugululipid$1 or guggulsterone$1 or yogaraj-guggulu).ti,ab.

34. (mukul or myrrh).ti,ab.

35. (((Gymnema or Periploca) adj3 wood$1) or small Indian ipecac or vishani or Sarpadarushtrika or Wakandi).ti,ab.

36. (hawthorn$2 or Crataegus oxycantha or (bread adj2 cheese tree$1) or cockspur thorn$1 or Chinese hawthorn$2 or May bush$2 or May tree$1 or May blossom$1 or May flower$1 or mayflower$1 or quickset or thorn-apple tree$1 or thornapple tree$1 or white thorn$1 or whitethorn$1).ti,ab.

37. (Convallaria or (lily adj3 valley) or lady$2 tears or ladies tears or may lily or may lilies or may bell$1 or maybell$1 or conval lily or conval lilies or lily constancy or (ladder$1 adj2 heaven) or male lily or male lilies).ti,ab.

38. exp Leonurus/

39. (Motherwort* or Leonorus cardiaca or lion$2 tail$1 or lion$2 ear$1 or throwwort*).ti,ab.

40. exp Milk thistle/

41. (Milk Thistle$1 or Silybum marianum or Carduus marianus or Holy thistle$1 or marythistle$1 or Mary$2 thistle$1 or Marian$2 thistle$1).ti,ab.

42. (Rauwolfia or Rauvolfia or Indian snakeroot$1 or Sarpa-gandha or Nakuli or Chota-chand or Kanakachandrika).ti,ab.

43. (red yeast rice extract* or Monascus purpureus or (mould species adj3 rice$1) or (red adj2 yeast$1) or (red adj2 rice$1) or red koji or red leaven$1).ti,ab.

44. exp eleutherococcus senticosus/

45. (Eleutherococcus or Siberian ginseng or Ci wu ju or Eleuthero or "touch-me-not" or "touch-me-nots" or devil$2 shrub$1).ti,ab.

46. ((Thorny bearer adj2 free) or ussurian thorny pepperbrush$2 or ussurian thorny pepper brush$2).ti,ab.

47. exp Hypericum/

48. (Hypericum or John$2 wort$1 or Johnswort$1 or Amber or (touch adj2 heal) or goat weed$1 or Hardhay$1 or Klamath weed$1 or Rosin rose$1 or Tipton weed$1 or (balm adj2 warrior$1)).ti,ab.

49. (Devil$2 scorge$1 or goatweed$1 or klammath weed$1).ti,ab.

50. exp Curcuma/

51. (Turmeric or curcuma or Indian saffron or Indian yellow root$1 or Zedoary zedoaria).ti,ab.

52. (Valerian* or vandal root$1 or all-heal$1 or setwall$1).ti,ab.

53. Selenoprotein$1.ti,ab.

54. (thioctic acid$1 or Alpha lipoic acid$1 or Alpha-Lipogamma or Alpha-Lipon Stada or alpha-Liponaure Heumann or Alpha-Liponsaure or Alpha-Lippon or alpha-Vibolex or Alphaflam).ti,ab.

55. ("Coenzyme Q10" or "CoQ 10" or CoQ10 or idebenone or ubiquinone or ubidecarenone or ubisemiquinone or "vitamin q10").ti,ab.

56. exp Fish Oils/

57. (fish adj2 oil$1).ti,ab.

58. ("omega 3" or "omega 3s" or omega three$1 or "n-3 Fatty Acid" or "n-3 Fatty Acids" or "n3 Fatty Acid" or "n3 Fatty Acids" or "n-3 Polyunsaturated Fatty Acid" or "n-3 Polyunsaturated Fatty Acids" or "n3 Polyunsaturated Fatty Acid" or "n3 Polyunsaturated Fatty Acids" or "n-3 PUFA" or "n3 PUFA").ti,ab.

59. (Eicosapentanoic acid$1 or decosahexanoic acid$1 or alpha linoleic acid$1).ti,ab.

60. (green tea$1 or black tea$1 or Camellia sinensis or Japanese tea$1 or Matsu-cha tea$1).ti,ab.

61. (Phytosterol$1 or Plant sterol$1 or Plant stanol$1 or Beta-sitosterol$1 or sterolin$1).ti,ab.

62. beta-Glucan$1.ti,ab.

63. exp Kava/

64. (kava or kawa or Piper methysticum).ti,ab.

65. (Psyllium or Plantago ovata or flea seed$1 or fleawort or hemicelluloses or plantago seed$1 or ispaghula husk$1 or ispagula husk$1 or ispaghula seed$1 or ispagula seed$1 or Plantago arenaria or Plantago isphagula or Plantago ispagula).ti,ab.

66. exp soy foods/

67. (soy or miso or natto or tempeh or tofu).ti,ab.

68. (Arginine or L-Arginine).ti,ab.

69. (Chia or Salvia columbariae or Salvia hispanica or salba).ti,ab.

70. (Chitin or chitosan or "N-carboxybutyl" or Poliglusam).ti,ab.

71. exp Cynara/

72. (Cynara or globe artichoke$1 or cardoon$1).ti,ab.

73. exp Carnitine/

74. (Carnitine or Bicarnesine or "L-Carnitine" or Levocarnitine or "Vitamin BT" or "Acetyl-L-carnitine" or carnitene or carnitor or canitor or "D-carnitine" or "D,L-carnitine" or "L-acetyl-carnitine" or "L-carnitina" or "L-carnitine" or "L-tartrate" or "L-CARNIPURE" or levacecarnine or levocarnitine or "L-propionylcarnitine" or "propionil-L-carnitine" or "propionyl-L-carnitine" or ST261).ti,ab.

75. (Pantethine or "Vitamin B5" or bile acid sequestrant$1 or cyproheptadine or cysteamine or "D-pantethine" or pantetheine or pantetheinase or Pantetina or panthenol or pantomin or pantosin or pantothenic acid$1 or sulfopantetheine).ti,ab.

76. (Policosanol$1 or D003 or hexacontanol$1 or isopolicosanol$1 or "Octa-60" or octacosanoic acid$1 or octacosanol$1 or ricewax$2 or winteriser cake$1 or winterizer cake$1 or sugar cane policosanol$1 or sunflower seed policosanol$1 or triacontanol$1 or wheat germ policosanol$1).ti,ab.

77. exp Withania/

78. (Withania or Ashwaganda or Indian ginseng or winter cherry or winter cherries or wintercherry or wintercherries or Ayurvedic ginseng).ti,ab.

79. exp Aloe/ or (aesculus or buckeye$1 or horse chestnut$1 or conqueror tree$1 or aloe vera or aloe barbadensis).ti,ab.

80. (ginger or Zingiber officinale or Gamma oryzanol).ti,ab.

81. exp Ephedra/ or exp Trigonella/ or (ephedra or trigonella or fenugreek or foenumgraecum or poenumgraecum).ti,ab.

82. (Gamma oryzanol or dong quai or tetrandrine or tetradrine or hanjisong).ti,ab.

83. exp Hydrastis/

84. (hydrastis or Golden Seal or Goldenseal).ti,ab.

85. or/7-84

86. ((functional adj food$1) or (therapeutic* adj food$1)).ti,ab.

87. ((Citrus adj paradisi) or (Vaccinium adj macrocarpon) or Viburnum or Punicaceae or blueberr* or cranberr* or grapefruit* or Toronja* or pomegranate* or (Punica adj granatum) or (bitter adj orange) or (citrus adj auranticum) or kijitsu or (shangzhou adj zhiqiao) or (zhi adj shi)).ti,ab.

88. exp beverages/ or (beverage* or drink* or juice* or tea or teas).ti,ab.

89. 87 and 88

90. exp Plant oils/

91. exp Olea/

92. ((botanic* or plant or plants or vegetable* or clove or cloves or corn or corns or cottonseed* or croton* or olive or olives or safflower* or sesame* or soybean* or teatree*) and (oil or oils)).ti,ab.

93. (Linaceae or flax or flaxseed* or Linum or linseed*).ti,ab.

94. exp Dietary fiber/

95. ((diet or diets or dietary) and (fibre or fibres or fiber or fibers or roughage or (wheat adj bran) or cereal*)).ti,ab.

96. exp Caffeine/ or caffein*.ti,ab.

97. (or/89-96) or 85 or 86
98. exp cardiovascular disease/ and exp drug therapy/
99. (Adrenergic adj2 Antagonist*).ti,ab.
100. ((beta adj1 Adrenergic adj2 block*) or beta block*).ti,ab.
101. (acebutolol or acebutalol or Apo-Acebutolol or Apo-Acebulalol or Sectral or Prent).ti,ab.
102. (betaxolol or Kerlon or Kerlone).ti,ab.
103. (bisoprolol or Concor or Concore or Zebeta or Monocor).ti,ab.
104. (carvedilol or Apo-carvedilol or Coreg or Dilatrend or Eucardic or Kredex).ti,ab.
105. (labetalol or Labetolol or Normodyne or Trandate).ti,ab.
106. (metoprolol or Betaloc or Betalok or Lopressor or Seloken).ti,ab.
107. (nadolol or Corgard or Solgol).ti,ab.
108. (nebivolol or Nebilet or Silostar).ti,ab.
109. (pindolol or Visken).ti,ab.
110. (propranolol or Avlocardyl or Deralin or Dociton or Inderal or Obsidan).ti,ab.
111. (sotalol or Darob).ti,ab.
112. (timolol or Blocadren).ti,ab.
113. exp Calcium channel blockers/
114. ((calcium block* adj2 exogenous) or (calcium antagonist* adj2 exogenous) or (calcium inhibitor* adj2 exogenous) or calcium channel block*).ti,ab.
115. (Dihydropyridine or Lemildipine).ti,ab.
116. (amlodipine or Norvasc or Istin).ti,ab.
117. (felodipine or Plendil or Renedil).ti,ab.
118. (isradipine or DynaCirc or Lomir or Prescal).ti,ab.
119. (nicardipine or Cardene).ti,ab.
120. (nifedipine or Adalat or Cordipin or Nifediac or Nifedical or Procardia).ti,ab.
121. (nimodipine or Nimotop).ti,ab.
122. (nisoldipine or Sular).ti,ab.
123. (diltiazem or Cardizem or Dilacor or Dilzem or Tiazac).ti,ab.
124. (verapamil or Bosoptin or Calan or Cordilox or Covera-HS or Isoptin or Iproveratril or Verelan).ti,ab.
125. exp enzyme inhibitors/
126. ((Angiotensin-Converting Enzyme adj1 Inhibitor*) or ACE inhibitor* or (Angiotensin-Converting Enzyme adj1 antagonist*)).ti,ab.
127. (dipeptidyl carboxypeptidase inhibitor* or (Kininase II adj2 inhibitor*) or (Kininase II adj2 antagonist*)).ti,ab.
128. (benazepril or Cibacen or Lotensin).ti,ab.
129. (captopril or Capoten or Lopirin).ti,ab.
130. (enalapril or Renitec or Renitek or Vasotec).ti,ab.
131. (fosinopril or Dynacil or Fozitec or Monopril or Staril or Tensocardil).ti,ab.
132. (lisinopril or Lysinopril or Prinivil or Zestril).ti,ab.
133. (moexipril or Perdix or Univasc).ti,ab.
134. (perindopril or Aceon or Coversyl or Prestarium).ti,ab.
135. (Quinapril or Accupril).ti,ab.
136. (Ramipril or Acovil or Altace or Triatec or Tritace or Vesdil).ti,ab.
137. (Trandolapril or Gopten or Mavik or Odrik).ti,ab.

138. (Candesartan or Atacand).ti,ab.
139. (eprosartan or Teveten).ti,ab.
140. (irbesartan or Aprovel or Avapro or Karvea).ti,ab.
141. (losartan or Cozaar).ti,ab.
142. (olmesartan or Benicar).ti,ab.
143. (telmisartan or Micardis or Pritor).ti,ab.
144. (valsartan or Diovan).ti,ab.
145. ((Renin adj Inhibit*) or Renin antagonist*).ti,ab.
146. (Aliskiren or Tekturna).ti,ab.
147. aldosterone receptor antagonist$1.ti,ab.
148. (Eplerenone or Inspra).ti,ab.
149. (Spironolactone or Aldactone or Verospirone).ti,ab.
150. exp Vasodilator agents/
151. Vasodilator$1.ti,ab.
152. exp Clonidine/
153. (clonidine or Apo-Clonidine or Catapres or Duraclon).ti,ab.
154. (guanabenz or Wytensin).ti,ab.
155. (guanfacine or Intuniv or Tenex).ti,ab.
156. (Methyldopa or Apo-Methyldopa or Aldoril or Aldomet or Dopamet or Dopegyt).ti,ab.
157. (Diazoxide or Hyperstat or Proglycem).ti,ab.
158. (Hydralazine or Apo-Hydralazine or Apresoline or Dralzine).ti,ab.
159. (minoxidil or Loniten).ti,ab.
160. (Isosorbide Dinitrate or Dilatrate or Cedocard or Isoket or Isotrate or Isordil or Sorbitrate).ti,ab.
161. (nitroglycerin$1 or Natispray or Nitro-Dur or Nitromist or Nitrospan or Nitrostat or Nitro-Time or Transderm Nitro or Tridil or Trinipatch).ti,ab.
162. ((Phosphodiesterase adj1 Inhibit*) or (Phosphodiesterase adj1 antagonist*) or Antiphosphodiesterase$1 or Anti-phosphodiesterase$1 or (Phosphoric Diester Hydrolase adj1 Inhibit*) or (Phosphoric Diester Hydrolase adj1 antagonist*)).ti,ab.
163. (sildenafil or Revatio or tadalafil or vardenafil).ti,ab.
164. (Cilostazol or Pletal).ti,ab.
165. Alprostadil.ti,ab.
166. (Epoprostenol or Flolan).ti,ab.
167. (iloprost or Ciloprost or Ventavis).ti,ab.
168. (Endothelin antagonist$1 or (Endothelin adj1 inhibit*)).ti,ab.
169. (treprostinil or Remodulin or bosentan or Tracleer or ambrisentan or Letairis).ti,ab.
170. papaverine.ti,ab.
171. (isoxsuprine or Duvadilan).ti,ab.
172. ((alpha-Adrenergic adj2 block*) or (Adrenergic alpha adj2 block*) or (alpha-Adrenergic adj2 antagonist*) or (Adrenergic alpha adj2 antagonist*) or (alpha block* adj2 adrenergic) or (alpha antagonist* adj2 adrenergic)).ti,ab.
173. (doxazosin or Cardura or Carduran or Diblocin or Doxazomerck or Doxazosin or Progandol).ti,ab.
174. (prazosin or Minipress or Furazosin or Pratsiol).ti,ab.

175. (terazosin or Adecur or Apo-Terazosin or Deflox or Dysalfa or Flotrin or Heitrin or Hytrin or Hytrine or Magnurol).ti,ab.

176. ((Anti-Arrhythmia or Anti-Arrhythmic* or Antiarrhythmia or Antiarrhythmic* or Anti-fibrillatory or Antifibrillatory) and (drug or drugs or agent or agents or medication* or prescription*)).ti,ab.

177. (disopyramide or Norpace or Rhythmodan).ti,ab.

178. (procainamide or Apo-Procainamide or Biocoryl or Novocainamide or Novocamid or Procamide or Pronestyl or Procan or Procanbid).ti,ab.

179. (quinidine or Apo-Quinidine or Chinidin or Quinidex or Quinora).ti,ab.

180. Mexiletine.ti,ab.

181. (encainide or Enkaid).ti,ab.

182. (Flecainide or Tambocor).ti,ab.

183. (propafenone or Apo-Propafenone or Arythmol or Baxarytmon or Fenoprain or Rythmol or Rytmonorm).ti,ab.

184. (amiodarone or Amiodarona or Cordarone or Cordarex or Pacerone or Trangorex).ti,ab.

185. (dofetilide or Tikosyn).ti,ab.

186. (dronedarone or Multaq).ti,ab.

187. exp Cardiotonic agents/

188. ((Cardiotonic or Cardioprotective or Cardio-tonic or Cardio-protective) and (drug or drugs or agent or agents or medication$1 or prescription$1)).ti,ab.

189. (cardiotonics or cardio-tonics or cardiac stimulant* or myocardial stimulant* or inotropic agent*).ti,ab.

190. exp Digoxin/

191. (digoxin or Digacin or Digitek or Dilanacin or Lanacordin or Lanicor or Lanoxicaps or Lanoxin or Lenoxin).ti,ab.

192. exp Antilipemic agents/

193. (Antilipemic$1 or anti-lipemic$1 or hypolipidemic$1 or hypo-lipidemic$1).ti,ab.

194. ((Antilipemic or anti-lipemic or antihyperlipemic or anti-hyperlipemic or antihyperlipidemic or anti-hyperlipidemic or hypolipidemic or hypo-lipidemic) and (drug or drugs or agent or agents or medication* or prescription*)).ti,ab.

195. (antihyperlipemics or anti-hyperlipemics or antihyperlipidemics or anti-hyperlipidemics).ti,ab.

196. (cholestyramin$1 or colestyramin$1 or Cuemid or Quantalan or Questran).ti,ab.

197. (colestipol or Colestid).ti,ab.

198. (colesevelam or CholestaGel or Welchol).ti,ab.

199. (Bile acid sequestrant$1 or bile acid-binding drug$1 or bile acid-binding agent$1).ti,ab.

200. (Anticholesteremic$1 or Hypocholesteremic$1 or (cholesterol adj2 inhibitor$1) or cholesterol-lowering drug$1 or cholesterol-lowering agent$1 or cholesterol-lowering medication$1).ti,ab.

201. (ezetimibe or Zetia).ti,ab.

202. (fenofibrate or Antara or Fenoglide or Fibricor or Lipofen or Lofibra or TriCor or Triglide or Trilipix).ti,ab.

203. (Gemfibrozil or Apo-Gemfibrozil or Lopid or Trialmin).ti,ab.

204. ((Hydroxymethylglutaryl-CoA Reductase adj1 inhibit*) or (HMG-CoA Reductase adj1 inhibit*) or (Hydroxymethylglutaryl-CoA adj1 inhibit$) or (Hydroxymethylglutaryl-Coenzyme A adj1 inhibit$)).ti,ab.

205. (atorvastatin or Liptor).ti,ab.

206. (fluvastatin or Lescol).ti,ab.

207. (lovastatin or Altocor or Altoprev or Mevacor).ti,ab.

208. (pravastatin or Apo-Pravastatin or Lipostat or Pravasin$1 or Pravachol or Selektine).ti,ab.

209. (rosuvastatin or Crestor).ti,ab.

210. (simvastatin or Synvinolin or Zocor).ti,ab.

211. exp Niacin/

212. (niacin or Niacor or Niaspan or Nicobid or Nicolar or Nicotinex or Slo-Niacin).ti,ab.

213. exp Anticoagulants/

214. (Anticoagulant$1 or anti-coagulant$1 or bloodthinn* or blood-thinn*).ti,ab.

215. (warfarin or Apo-Warfarin or Coumadin$1).ti,ab.

216. (dalteparin or Fragmin$1).ti,ab.

217. exp Heparin/

218. heparin.ti,ab.

219. (tinzaparin or Innohep).ti,ab.

220. (antithrombocytic* or anti-thrombocytic* or (platelet$1 adj2 inhibit*) or Antiplatelet$1 or Anti-platelet$1 or Platelet Antagonist$1 or Platelet Antiaggregant$1).ti,ab.

221. exp Aspirin/

222. (Aspirin or Acetylsalicylic or Acylpyrin or Aloxiprimum or Aspergum or Bufferin or Colfarit or Dispril or Ecotrin or Easprin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin).ti,ab.

223. (ticlopidine or Ticlid).ti,ab.

224. (clopidogrel or Plavix).ti,ab.

225. exp Diuretics/

226. (diuretic$1 or water pill$1).ti,ab.

227. (Bumetanide or bumex).ti,ab.

228. (etacrynic acid or ethacrynic acid or Edecrin).ti,ab.

229. (furosemide or Errolon or Fursemide or Fusid or Lasix).ti,ab.

230. (torsemide or Demadex or torasemide).ti,ab.

231. (k-sparing or potassium-sparing).ti,ab.

232. (Amiloride or Amidal or Amiduret or Kaluril or Midamor or Midoride or Modamide).ti,ab.

233. (triamterene or Dyrenium).ti,ab.

234. thiazide diuretic$1.ti,ab.

235. (Bendroflumethiazide or Bendrofluazide).ti,ab.

236. (chlorothiazide or Chlotride or Diuril).ti,ab.

237. (hydrochlorothiazide or Apo-Hydro or Dichlotride or Esidrex or HydroDIURIL or Microzide or Oretic).ti,ab.

238. (methyclothiazide or Aquatensen or Enduron).ti,ab.

239. (polythiazide or Renese).ti,ab.

240. (chlorthalidone or Apo-Chlorthalidone or Hygroton or Thalitone).ti,ab.

241. (indapamide or Lozol or Metindamide).ti,ab.

242. (metolazone or Mykrox or Zaroxolyn or Zytanix).ti,ab.
243. or/98-242
244. 97 and 243
245. exp Herb drug interactions/
246. (interact* or react* or contraindicat* or contra-indicat* or chemically induce* or enhance* or potentiat* or synergis* or toxic or toxicit*).ti,ab.
247. 245 or 246
248. 244 and 247
249. meta analysis/
250. meta analysis.pt.
251. (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).ti,ab.
252. (systematic review* or systematic overview* or technology assessment* or HTA or HTAs).ti,ab.
253. health technol assess rep.ja.
254. evid rep technol assess summ.ja.
255. or/249-254
256. 248 and 255
257. (controlled clinical trial or controlled trial or randomised controlled trial or randomized controlled trial).pt.
258. exp Randomized controlled trials/
259. exp Random allocation/
260. exp Double blind method/
261. exp Placebos/
262. (random* or RCT$1 or placebo*).ti,ab.
263. ((singl* or doubl* or trebl* or tripl*) and (mask* or blind* or dumm*)).ti,ab.
264. controlled clinical trial.ti,ab.
265. or/257-264
266. 248 and 265
267. 266 not 256
268. clinical trial.pt.
269. exp Clinical trials/
270. "clinical trial".ti,ab.
271. (comparative studies or comparative study or evaluation studies or multicenter study or multicentre study).pt.
272. (volunteer or volunteers or open label* or nonrandom* or non random* or quasirandom* or quasi-random*).ti,ab.
273. exp cohort studies/ or exp longitudinal studies/ or exp prospective studies/ or exp Follow up studies/ or exp retrospective studies/ or exp case control studies/ or exp Comparative study/
274. (cohort or cohorts or longitudinal or prospective or retrospective).ti,ab.
275. ((observational or follow-up or followup) adj stud*).ti,ab.
276. (population-based stud* or population-based analys* or population stud* or population analys*).ti,ab.

277. ((descriptive adj stud*) or (multidimensional adj stud*) or (multi-dimensional adj stud*) or (multicenter adj stud*) or (multi-center adj stud*) or (multicentr* adj stud*) or (multi-centr* adj stud*)).ti,ab.

278. ((comparative adj study) or (comparative adj studies) or (case adj control*) or "case series" or (case adj comparison*) or (case adj history) or (case adj histories)).ti,ab.

279. or/268-278

280. 248 and 279

281. 280 not (256 or 266)

282. exp Mortality/ or exp Risk/ or exp Morbidity/

283. exp Adverse effects/ or exp Safety/ or exp Complications/

284. (adverse or complication* or harm or harms or harmful or harming or injurious or morbidit* or mortalit* or risk$1 or side effect$1 or undersirable or tolerability or teratogen* or safety).ti,ab.

285. or/282-284

286. 248 and 285

287. 286 not (256 or 266 or 280)

EMBASE (September 1, 2011)

1. exp diet supplementation/
2. exp cardiovascular agent/
3. 1 and 2
4. 3
5. limit 4 to human

Cochrane Library (September 1, 2011)

#1 MeSH descriptor Herb-Drug Interactions explode all trees

#2 ((herb or herbs or herbal or plant or plants or botanic*) and (drug or drugs or medication* or prescription* or pharmacotherap* or pharmaco-therap*) and (interact* or react* or contraindicat* or metabolis* or metaboliz* or pharmacokinetic* or pharmaco-kinetic*)):ti,ab,kw

#3 MeSH descriptor Food-Drug Interactions explode all trees

#4 ((food or foods) and (drug or drugs or medication* or prescription* or pharmacotherap* or pharmaco-therap*) and (interact* or react* or contraindicat* or metabolis* or metaboliz* or pharmacokinetic* or pharmaco-kinetic*)):ti,ab,kw

#5 (#1 OR #2 OR #3 OR #4)

#6 MeSH descriptor Dietary Supplements explode all trees

#7 (Neutraceutical* or Nutraceutical* or (diet* NEXT supplement*) or (nutrition* NEXT supplement*) or (food* NEXT supplement*) or (mineral* NEXT supplement*) or (vitamin* NEXT supplement*) or (botanic* NEXT supplement*)):ti,ab,kw

#8 MeSH descriptor Vitamins explode all trees

#9 (vitamin or vitamins):ti,ab,kw or (folic acid):ti,ab,kw

#10 MeSH descriptor Minerals explode all trees

#11 MeSH descriptor Copper explode all trees

#12 MeSH descriptor Iron explode all trees

#13 MeSH descriptor Magnesium explode all trees

#14 MeSH descriptor Potassium explode all trees

#15 MeSH descriptor Selenium explode all trees

#16 (copper or iron or magnesium or potassium or selenium):ti,ab,kw

#17 MeSH descriptor Plant Preparations explode all trees

#18 MeSH descriptor Plant Extracts explode all trees

#19 MeSH descriptor Drugs, Chinese Herbal explode all trees

#20 MeSH descriptor Plants, Medicinal explode all trees

#21 ((medicin* NEAR/3 herb*) or (medicin* NEAR/3 plant*) or (botanical* NEAR/3 medicin*) or (botanical* NEAR/3 drug*) or (herb* NEAR/3 drug*) or (therapeutic* NEAR/3 herb*) or (therapeutic* NEAR/3 plant*) or (therapeutic* NEAR/3 botanical*) or (plant* NEAR/3 pharmacotherap*) or (plant* NEAR/3 pharmaco-therap*)):ti,ab,kw or ((herb* NEAR/3 pharmacotherap*) or (herb* NEAR/3 pharmaco-therap*) or (botanical NEAR/3 pharmacotherap*) or (botanical NEAR/3 pharmaco-therap*) or (Chinese NEAR/2 medicin*) or (Chinese NEAR/2 medicin*) or (Chinese NEAR/2 drug*) or (Chinese NEAR/2 pharmacotherap*) or (Chinese NEAR/2 pharmaco-therap*)):ti,ab,kw or (phytochemical* OR phyto-chemical* OR phytonutrient* OR phyto-nutrient*):ti,ab,kw

#22 MeSH descriptor Glucosamine explode all trees

#23 (glucosamin*):ti,ab,kw

#24 MeSH descriptor Salvia miltiorrhiza explode all trees

#25 (salvia miltiorrhiza or danshen or horse-racing grass* or rat-tail grass* or red-rooted sage* or red root* or red sage* or red sage root or (root* NEAR/3 purple sage*) or scarlet sage*):ti,ab,kw or (Ch'ih shen or Chinese Salvia or dangshem or dan shen or dan-shen or danshensu or fufangdenshen or huang ken or hung ken or pin-ma ts'ao or Radix salviae miltiorrhizae or Salvia bowelyana or Salvia miltiorrhiza or Salvia przewalskii or Salvia root* or Salvia yunnanensis or sh'ih shen or shu-wei ts'ao or tan seng or tan-shen or tzu tan-ken or yunzhi-danshen):ti,ab,kw

#26 MeSH descriptor Forskolin explode all trees

#27 MeSH descriptor Ruscus explode all trees

#28 MeSH descriptor Cinnamomum zeylanicum explode all trees

#29 (Forskolin or Coleus forskohlii or Indian Coleus or Coleonol):ti,ab,kw or (ruscus or (butcher* NEXT broom*)):ti,ab,kw or (Cinnamomum or Cinnamon*):ti,ab,kw

#30 MeSH descriptor Taraxacum explode all trees

#31 (Taraxacum or dandelion* or blowball* or Irish daisy or Irish daisies or (pee NEAR/3 bed) or (lion* NEAR/2 tooth) or (lion* NEAR/2 teeth) or (priest* NEAR/2 crown*)):ti,ab,kw or (Dent NEAR/2 lion*) or huang hua di ding or yellow flower earth nail* or puffball* or swine snout*:ti,ab,kw

#32 MeSH descriptor Echinacea explode all trees

#33 (Echinacea or American coneflower* or purple coneflower* or Rudbeckia purpurea or Black Sampson or combflower* or Kansas snake root* or scurvy root*):ti,ab,kw

#34 MeSH descriptor Tanacetum parthenium explode all trees

#35 (Tanacetum parthenium or feverfew or (bachelor* NEXT button*) or featherfew or febrifuge plant* or featherfoil*):ti,ab,kw or (Chrysanthemum parthenium):ti,ab,kw

#36 MeSH descriptor Garlic explode all trees

#37 (garlic or allium or (nectar NEAR/2 god*) or pa-se-waa or poor man's treacle or stinking rose*):ti,ab,kw

#38 MeSH descriptor Ginkgo biloba explode all trees

#39 (Ginkgo or Ginkgophyta or Maidenhair Tree* or Maiden Hair Tree* or Fossil Tree* or Duckfoot tree* or Duck foot tree* or silver apricot* or kew tree*):ti,ab,kw

#40 MeSH descriptor Panax explode all trees

#41 (Panax or Ginseng or Jen Shen or Ninjin or Renshen or Schinseng or Shinseng):ti,ab,kw or (guggulipid* or guggul* or gugulipid* or gugulu or gugululipid* or guggulsterone* or yogaraj-guggulu):ti,ab,kw

#42 MeSH descriptor Lycium explode all trees

#43 (wolfberr* or (wolf NEXT berr*) or gojiberr* or (goji NEXT berr*)):ti,ab,kw

#44 MeSH descriptor Mentha piperita explode all trees

#45 MeSH descriptor Glycyrrhiza explode all trees

#46 MeSH descriptor Tinospora explode all trees

#47 (Chrysanthemum parthenium or gynura or gynuras or gulvel or gulvels):ti,ab,kw

#48 MeSH descriptor Gymnema explode all trees

#49 (Gymnema or (Periploca NEAR/3 wood*) or small Indian ipecac or vishani or Sarpadarushtrika or Wakandi):ti,ab,kw or (hawthorn* or Crataegus oxycantha or (bread NEAR/2 cheese tree*) or cockspur thorn* or Chinese hawthorn* or May bush* or May tree* or May blossom* or May flower* or mayflower* or quickset or thorn-apple tree* or thornapple tree* or white thorn* or whitethorn*):ti,ab,kw

#50 MeSH descriptor Convallaria explode all trees

#51 (Convallaria or (lily NEAR/3 valley) or (lady* NEXT tears) or ladies tears or may lily or may lilies or may bell or may bells or maybell* or conval lily or conval lilies or lily constancy or (ladder* NEAR/2 heaven) or male lily or male lilies):ti,ab,kw

#52 MeSH descriptor Leonurus explode all trees

#53 (Motherwort* or Leonorus cardiaca or (lion* NEXT tail*) or (lion* NEXT ear*) or throwwort*):ti,ab,kw

#54 MeSH descriptor Milk Thistle explode all trees

#55 (Milk Thistle* or Silybum marianum or Carduus marianus or Holy thistle* or marythistle* or (Mary* NEXT thistle*) or (Marian* NEXT thistle*)):ti,ab,kw

#56 MeSH descriptor Rauwolfia explode all trees

#57 (Rauwolfia or Rauvolfia or Indian snakeroot* or Sarpa-gandha or Nakuli or Chota-chand or Kanakachandrika):ti,ab,kw or (red yeast rice extract* or Monascus purpureus or (mould species NEAR/3 rice*) or (red NEAR/2 yeast*) or (red NEAR/2 rice*) or red koji or red leaven*):ti,ab,kw

#58 MeSH descriptor Eleutherococcus explode all trees

#59 (Eleutherococcus or Siberian ginseng or Ci wu ju or Eleuthero or "touch-me-not" or "touch-me-nots" or (devil* NEXT shrub*)):ti,ab,kw or ((Thorny bearer NEAR/2 free) or ussurian thorny pepperbrush* or ussurian thorny pepper brush*):ti,ab,kw

#60 MeSH descriptor Hypericum explode all trees

#61 (Hypericum or (John* NEXT wort*) or Johnswort* or Amber or (touch NEAR/2 heal) or goat weed* or goatweed* or Hardhay* or Klamath weed* or Klammath weed* or Rosin rose* or Tipton weed* or (balm NEAR/2 warrior*) or (Devil* NEXTscorge*)):ti,ab,kw

#62 MeSH descriptor Curcuma explode all trees

#63 MeSH descriptor Valerian explode all trees

#64 (Turmeric or curcuma or Indian saffron or Indian yellow root* or Zedoary zedoaria):ti,ab,kw or (Valerian* or vandal root* or all-heal* or setwall*):ti,ab,kw

#65 MeSH descriptor Selenoproteins explode all trees

#66 MeSH descriptor Thioctic Acid explode all trees

#67 (Selenoprotein*):ti,ab,kw or (Alpha lipoic acid* or Alpha-Lipogamma or Alpha-Lipon Stada or alpha-Liponaure Heumann or Alpha-Liponsaure or Alpha-Lippon or alpha-Vibolex or Alphaflam):ti,ab,kw or "Coenzyme Q10" or "CoQ 10" or CoQ10 or idebenone or ubiquinone or ubidecarenone or ubisemiquinone or "vitamin q10":ti,ab,kw

#68 MeSH descriptor Fish Oils explode all trees

#69 MeSH descriptor Fatty Acids, Omega-3 explode all trees

#70 (fish NEAR/2 oil) of (fish NEAR/2 oils):ti,ab,kw or ("omega 3" or "omega 3s" or omega three$1 or "n-3 Fatty Acid" or "n-3 Fatty Acids" or "n3 Fatty Acid" or "n3 Fatty Acids" or "n-3 Polyunsaturated Fatty Acid" or "n-3 Polyunsaturated Fatty Acids" or "n3 Polyunsaturated Fatty Acid" or "n3 Polyunsaturated Fatty Acids" or "n-3 PUFA" or "n3 PUFA"):ti,ab,kw

#71 (Eicosapentanoic acid* or decosahexanoic acid* or alpha linoleic acid*):ti,ab,kw or (green tea or green teas or black tea or black teas or Camellia sinensis or Japanese tea or Japanese teas or Matsu-cha tea or Matsu-cha teas):ti,ab,kw

#72 MeSH descriptor Phytosterols explode all trees

#73 MeSH descriptor beta-Glucans explode all trees

#74 (Phytosterol* or plant sterol* or plant stanol* or beta-sitosterol* or sterolin*):ti,ab,kw or (beta-Glucan or beta-Glucans):ti,ab,kw

#75 MeSH descriptor Calcium explode all trees

#76 MeSH descriptor Psyllium explode all trees

#77 (calcium or bone meal or dicalcium or dolomite):ti,ab,kw or (Psyllium or Plantago ovata or flea seed* or fleawort or hemicelluloses or plantago seed* or ispaghula husk* or ispaghula seed* or Plantago arenaria or Plantago isphagula):ti,ab,kw

#78 MeSH descriptor Soybeans explode all trees

#79 MeSH descriptor Arginine explode all trees

#80 (soy or soybean* or Glycine max):ti,ab,kw or (Arginine or L-Arginine):ti,ab,kw or (Chia or Salvia columbariae or Salvia hispanica or salba):ti,ab,kw

#81 MeSH descriptor Chitosan explode all trees

#82 MeSH descriptor Cynara explode all trees

#83 MeSH descriptor Carnitine explode all trees

#84 (Chitin or chitosan or "N-carboxybutyl" or Poliglusam):ti,ab,kw or (Cynara or globe artichoke* or cardoon*):ti,ab,kw or (Carnitine or Bicarnesine or "L-Carnitine" or Levocarnitine or "Vitamin BT" or "Acetyl-L-carnitine" or carnitene or carnitor or canitor or "D-carnitine" or "D,L-carnitine" or "L-acetyl-carnitine" or "L-carnitina" or "L-carnitine" or "L-tartrate" or "L-CARNIPURE" or levacecarnine or levocarnitine or "L-propionylcarnitine" or "propionil-L-carnitine" or "propionyl-L-carnitine" or ST261):ti,ab,kw

#85 (Pantethine or "Vitamin B5" or bile acid sequestrant* or cyproheptadine or cysteamine or "D-pantethine" or pantetheine or pantetheinase or Pantetina or panthenol or pantomin or pantosin or pantothenic acid* or sulfopantetheine):ti,ab,kw or (Policosanol* or D003 or hexacontanol* or isopolicosanol* or "Octa-60" or octacosanoic acid* or octacosanol* or ricewax* or winteriser cake* or winterizer cake* or sugar cane policosanol* or sunflower seed policosanol* or triacontanol* or wheat germ policosanol*):ti,ab,kw

#86 MeSH descriptor Withania explode all trees

#87 MeSH descriptor Aesculus explode all trees

#88 MeSH descriptor Aloe explode all trees

#89 (Withania or Ashwaganda or Indian ginseng or winter cherry or winter cherries or wintercherry or wintercherries or Ayurvedic ginseng):ti,ab,kw or (aesculus or buckeye* or horse chestnut* or conqueror tree* or aloe vera or aloe barbadensis):ti,ab,kw

#90 MeSH descriptor Ginger explode all trees

#91 MeSH descriptor Ephedra explode all trees

#92 MeSH descriptor Trigonella explode all trees

#93 (ginger or Zingiber officinale or Gamma oryzanol):ti,ab,kw or (ephedra or trigonella or fenugreek or foenumgraecum or poenumgraecum):ti,ab,kw or (Gamma oryzanol or dong quai or tetrandrine or tetradrine or hanjisong):ti,ab,kw

#94 (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)

#95 (#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60)

#96 (#61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR (#70 AND OF AND #71) OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93)

#97 MeSH descriptor Phytotherapy explode all trees

#98 (phytotherap* or phyto-therap* or phytomedicin* or phyto-medicin*)

#99 MeSH descriptor Cardiovascular Diseases explode all trees with qualifier: DT

#100 Any MeSH descriptor with qualifier: TU

#101 (#97 OR #98 OR #99 OR #100)

#102 (#94 OR #95 OR #96)

#103 (#101 AND #102)

#104 (#6 OR #7 OR #19 OR #20 OR #21)

#105 (#103 OR #104)

#106 (#97 OR #98 OR #105)

#107 MeSH descriptor Functional Food explode all trees

#108 (functional NEXT food*) or (therapeutic* NEXT food*):ti,ab,kw

#109 MeSH descriptor Citrus paradisi explode all trees

#110 MeSH descriptor Vaccinium macrocarpon explode all trees

#111 MeSH descriptor Viburnum explode all trees

#112 MeSH descriptor Blueberry Plant explode all trees

#113 MeSH descriptor Punicaceae explode all trees

#114 (citrus paradisi or vaccinium macrocarpon or viburnum or punicaceae or blueberr* or cranberr* or grapefruit* or toronja* or pomegranate* or punica granatum or bitter orange or citrus uranticum or kijitsu or shangzhou zhiqiao or zhi shi):ti,ab,kw

#115 MeSH descriptor Beverages explode all trees

#116 (beverage* or drink* or juice* or tea or teas):ti,ab,kw

#117 (#109 OR #110 OR #111 OR #112 OR #113 OR #114)

#118 (#115 OR #116)

#119 (#117 AND #118)

#120 MeSH descriptor Plant Oils explode all trees

#121 MeSH descriptor Olea explode all trees

#122 (botanic* or plant or plants or vegetable* or clove or cloves or corn or corns or cottonseed* or croton* or olive or olives or safflower* or sesame* or soybean* or teatree*):ti,ab,kw and (oil or oils):ti,ab,kw

#123 MeSH descriptor Linaceae explode all trees

#124 (Linaceae or flax or flaxseed* or Linum or linseed*):ti,ab,kw

#125 MeSH descriptor Dietary Fiber explode all trees

#126 (diet or diets or dietary):ti,ab,kw and (fibre or fibres or fiber or fibers or roughage or (wheat NEXT bran) or cereal*):ti,ab,kw

#127 MeSH descriptor Caffeine explode all trees

#128 (#120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127)

#129 (#107 OR #108 OR #119 OR #128)

#130 MeSH descriptor Cardiovascular Diseases explode all trees with qualifier: DT

#131 MeSH descriptor Adrenergic beta-Antagonists explode all trees

#132 MeSH descriptor Acebutolol explode all trees

#133 MeSH descriptor Betaxolol explode all trees

#134 MeSH descriptor Bisoprolol explode all trees

#135 (Adrenergic NEAR/2 Antagonist*) OR (beta NEXT block*) OR ((beta NEAR/1 Adrenergic) NEAR/2 block*):ti,ab,kw or (acebutolol or acebutalol or Apo-Acebutolol or Apo-Acebulalol or Sectral or Prent):ti,ab,kw or (betaxolol or Kerlon or Kerlone):ti,ab,kw or (bisoprolol or Concor or Concore or Zebeta or Monocor):ti,ab,kw or (carvedilol or Apo-carvedilol or Coreg or Dilatrend or Eucardic or Kredex):ti,ab,kw

#136 MeSH descriptor Labetalol explode all trees

#137 MeSH descriptor Metoprolol explode all trees

#138 MeSH descriptor Nadolol explode all trees

#139 MeSH descriptor Pindolol explode all trees

#140 MeSH descriptor Propranolol explode all trees

#141 (labetalol or Labetolol or Normodyne or Trandate):ti,ab,kw or (metoprolol or Betaloc or Betalok or Lopressor or Seloken):ti,ab,kw or (nadolol or Corgard or Solgol or nebivolol or Nebilet or Silostar):ti,ab,kw or (pindolol or Visken):ti,ab,kw or (propranolol or Avlocardyl or Deralin or Dociton or Inderal or Obsidan):ti,ab,kw

#142 MeSH descriptor Sotalol explode all trees

#143 MeSH descriptor Timolol explode all trees

#144 MeSH descriptor Calcium Channel Blockers explode all trees

#145 MeSH descriptor Amlodipine explode all trees

#146 (sotalol or Darob):ti,ab,kw or (timolol or Blocadren):ti,ab,kw or (calcium block* NEAR/2 exogenous) or (calcium antagonist* NEAR/2 exogenous) or (calcium inhibitor* NEAR/2 exogenous) or calcium channel block*:ti,ab,kw or (Dihydropyridine or Lemildipine):ti,ab,kw or (amlodipine or Norvasc or Istin):ti,ab,kw

#147 MeSH descriptor Felodipine explode all trees

#148 MeSH descriptor Isradipine explode all trees

#149 MeSH descriptor Nicardipine explode all trees

#150 MeSH descriptor Nifedipine explode all trees

#151 MeSH descriptor Nimodipine explode all trees

#152 (felodipine or Plendil or Renedil):ti,ab,kw or (isradipine or DynaCirc or Lomir or Prescal):ti,ab,kw or (nicardipine or Cardene):ti,ab,kw or (nifedipine or Adalat or Cordipin or Nifediac or Nifedical or Procardia):ti,ab,kw or (nimodipine or Nimotop):ti,ab,kw

#153 MeSH descriptor Nisoldipine explode all trees
#154 MeSH descriptor Diltiazem explode all trees
#155 MeSH descriptor Verapamil explode all trees
#156 (nisoldipine or Sular):ti,ab,kw or (diltiazem or Cardizem or Dilacor or Dilzem or Tiazac):ti,ab,kw or (verapamil or Bosoptin or Calan or Cordilox or Covera-HS or Isoptin or Iproveratril or Verelan):ti,ab,kw
#157 MeSH descriptor Angiotensin-Converting Enzyme Inhibitors explode all trees
#158 (Angiotensin-Converting Enzyme NEXT Inhibitor*) or ACE inhibitor* or (Angiotensin-Converting Enzyme antagonist*):ti,ab,kw or (Kininase II NEAR/2 inhibitor*) or (Kininase II NEAR/2 antagonist*):ti,ab,kw or (benazepril or Cibacen or Lotensin):ti,ab,kw
#159 MeSH descriptor Captopril explode all trees
#160 MeSH descriptor Enalapril explode all trees
#161 MeSH descriptor Fosinopril explode all trees
#162 MeSH descriptor Lisinopril explode all trees
#163 MeSH descriptor Perindopril explode all trees
#164 (captopril or Capoten or Lopirin):ti,ab,kw or (enalapril or Renitec or Renitek or Vasotec):ti,ab,kw or (fosinopril or Dynacil or Fozitec or Monopril or Staril or Tensocardil):ti,ab,kw or (lisinopril or Lysinopril or Prinivil or Zestril or moexipril or Perdix or Univasc):ti,ab,kw or (perindopril or Aceon or Coversyl or Prestarium or Quinapril or Accupril):ti,ab,kw
#165 MeSH descriptor Ramipril explode all trees
#166 MeSH descriptor Losartan explode all trees
#167 (Ramipril or Acovil or Altace or Triatec or Tritace or Vesdil):ti,ab,kw or (Trandolapril or Gopten or Mavik or Odrik or Candesartan or Atacand):ti,ab,kw or (eprosartan or Teveten or irbesartan or Aprovel or Avapro or Karvea):ti,ab,kw or (losartan or Cozaar or olmesartan or Benicar):ti,ab,kw or (telmisartan or Micardis or Pritor or valsartan or Diovan):ti,ab,kw
#168 (renin NEXT inhibit*) or renin antagonist*:ti,ab,kw or (Aliskiren or Tekturna):ti,ab,kw or (aldosterone receptor antagonist*):ti,ab,kw or (Eplerenone or Inspra):ti,ab,kw
#169 MeSH descriptor Spironolactone explode all trees
#170 MeSH descriptor Vasodilator Agents explode all trees
#171 MeSH descriptor Clonidine explode all trees
#172 MeSH descriptor Guanabenz explode all trees
#173 MeSH descriptor Guanfacine explode all trees
#174 (Spironolactone or Aldactone or Verospirone):ti,ab,kw or (Vasodilator*):ti,ab,kw or (clonidine or Apo-Clonidine or Catapres or Duraclon):ti,ab,kw or (guanabenz or Wytensin):ti,ab,kw or (guanfacine or Intuniv or Tenex):ti,ab,kw
#175 MeSH descriptor Methyldopa explode all trees
#176 MeSH descriptor Diazoxide explode all trees
#177 MeSH descriptor Hydralazine explode all trees
#178 MeSH descriptor Minoxidil explode all trees
#179 MeSH descriptor Isosorbide Dinitrate explode all trees
#180 (Methyldopa or Apo-Methyldopa or Aldoril or Aldomet or Dopamet or Dopegyt):ti,ab,kw or (Diazoxide or Hyperstat or Proglycem):ti,ab,kw or (Hydralazine or Apo-

Hydralazine or Apresoline or Dralzine):ti,ab,kw or (minoxidil or Loniten):ti,ab,kw or (Isosorbide Dinitrate or Dilatrate or Cedocard or Isoket or Isotrate or Isordil or Sorbitrate):ti,ab,kw

#181 MeSH descriptor Nitroglycerin explode all trees

#182 MeSH descriptor Phosphodiesterase Inhibitors explode all trees

#183 (nitroglycerin* or Natispray or Nitro-Dur or Nitromist or Nitrospan or Nitrostat or Nitro-Time or Transderm Nitro or Tridil or Trinipatch):ti,ab,kw or (Phosphodiesterase Inhibit* or Phosphodiesterase antagonist* or Antiphosphodiesterase* or Anti-phosphodiesterase* or Phosphoric Diester Hydrolase Inhibit* or Phosphoric Diester Hydrolase antagonist*):ti,ab,kw or (sildenafil or Revatio or tadalafil or vardenafil):ti,ab,kw or (Cilostazol or Pletal):ti,ab,kw

#184 MeSH descriptor Alprostadil explode all trees

#185 MeSH descriptor Epoprostenol explode all trees

#186 MeSH descriptor Iloprost explode all trees

#187 MeSH descriptor Papaverine explode all trees

#188 MeSH descriptor Isoxsuprine explode all trees

#189 (Alprostadil):ti,ab,kw or (Epoprostenol or Flolan or iloprost or Ciloprost or Ventavis):ti,ab,kw or (Endothelin antagonist* or (Endothelin NEAR/1 inhibit*)):ti,ab,kw or (treprostinil or Remodulin or bosentan or Tracleer or ambrisentan or Letairis):ti,ab,kw or (papaverine or isoxsuprine or Duvadilan):ti,ab,kw

#190 MeSH descriptor Adrenergic alpha-Antagonists explode all trees

#191 MeSH descriptor Doxazosin explode all trees

#192 MeSH descriptor Prazosin explode all trees

#193 ((alpha-Adrenergic NEAR/2 block*) or (adrenergic alpha NEAR/2 block*) or (alpha-adrenergic NEAR/2 antagonist*) or (adrenergic alpha NEAR/2 antagonist*) or (alpha block* NEAR/2 adrenergic) or (alpha antagonist* NEAR/2 adrenergic)):ti,ab,kw or (doxazosin or Cardura or Carduran or Diblocin or Doxazomerck or Doxazosin or Progandol):ti,ab,kw or (prazosin or Minipress or Furazosin or Pratsiol):ti,ab,kw or (terazosin or Adecur or Apo-Terazosin or Deflox or Dysalfa or Flotrin or Heitrin or Hytrin or Hytrine or Magnurol):ti,ab,kw

#194 MeSH descriptor Anti-Arrhythmia Agents explode all trees

#195 (Anti-Arrhythmia or Anti-Arrhythmic* or Antiarrhythmia or Antiarrhythmic* or Anti-fibrillatory or Antifibrillatory):ti,ab,kw and (drug or drugs or agent or agents):ti,ab,kw

#196 MeSH descriptor Disopyramide explode all trees

#197 MeSH descriptor Procainamide explode all trees

#198 MeSH descriptor Quinidine explode all trees

#199 MeSH descriptor Mexiletine explode all trees

#200 MeSH descriptor Encainide explode all trees

#201 (disopyramide or Norpace or Rhythmodan):ti,ab,kw or (procainamide or Apo-Procainamide or Biocoryl or Novocainamide or Novocamid or Procamide or Pronestyl or Procan or Procanbid):ti,ab,kw or (quinidine or Apo-Quinidine or Chinidin or Quinidex or Quinora):ti,ab,kw or (Mexiletine):ti,ab,kw or (encainide or Enkaid):ti,ab,kw

#202 MeSH descriptor Flecainide explode all trees

#203 MeSH descriptor Propafenone explode all trees

#204 MeSH descriptor Amiodarone explode all trees

#205 (Flecainide or Tambocor):ti,ab,kw or (propafenone or Apo-Propafenone or Arythmol or Baxarytmon or Fenoprain or Rythmol or Rytmonorm):ti,ab,kw or (amiodarone or Amiodarona or Cordarone or Cordarex or Pacerone or Trangorex):ti,ab,kw or (dofetilide or Tikosyn):ti,ab,kw or (dronedarone or Multaq):ti,ab,kw

#206 MeSH descriptor Cardiotonic Agents explode all trees

#207 MeSH descriptor Digoxin explode all trees

#208 (Cardiotonic or Cardioprotective or Cardio-tonic or Cardio-protective):ti,ab,kw and (drug or drugs or agent or agents or medication* or prescription*):ti,ab,kw

#209 (cardiotonics or cardio-tonics or cardiac stimulant* or myocardial stimulant* or inotropic agent*):ti,ab,kw or (digoxin or Digacin or Digitek or Dilanacin or Lanacordin or Lanicor or Lanoxicaps or Lanoxin or Lenoxin):ti,ab,kw

#210 MeSH descriptor Antilipemic Agents explode all trees

#211 (antilipemic* or anti-lipemic* or hypolipidemic* or hypo-lipidemic*):ti,ab,kw or (antihyperlipemics or anti-hyperlipemics or antihyperlipidemics or anti-hyperlipidemics):ti,ab,kw

#212 (Antilipemic or anti-lipemic or antihyperlipemic or anti-hyperlipemic or antihyperlipidemic or anti-hyperlipidemic or hypolipidemic or hypo-lipidemic):ti,ab,kw and (drug or drugs or agent or agents or medication* or prescription*):ti,ab,kw

#213 MeSH descriptor Cholestyramine Resin explode all trees

#214 MeSH descriptor Colestipol explode all trees

#215 (cholestyramin* or colestyramin* or Cuemid or Quantalan or Questran):ti,ab,kw or (colestipol or Colestid):ti,ab,kw or (colesevelam or CholestaGel or Welchol):ti,ab,kw or (Bile acid sequestrant* or bile acid-binding drug* or bile acid-binding agengt*):ti,ab,kw or (anticholesteremic* or hypocholesteremic* or (cholesterol NEAR/2 inhibitor*) or cholesterol-lowering drug* or cholesterol-lowering agent* or cholesterol-lowering medication*):ti,ab,kw

#216 MeSH descriptor Gemfibrozil explode all trees

#217 MeSH descriptor Lovastatin explode all trees

#218 MeSH descriptor Pravastatin explode all trees

#219 (ezetimibe or Zetia or fenofibrate or Antara or Fenoglide or Fibricor or Lipofen or Lofibra or TriCor or Triglide or Trilipix):ti,ab,kw or (Gemfibrozil or Apo-Gemfibrozil or Lopid or Trialmin):ti,ab,kw or (Hydroxymethylglutaryl-CoA Reductase inhibit*) or (HMG-CoA Reductase inhibit*) or (Hydroxymethylglutaryl-CoA inhibit*) or (Hydroxymethylglutaryl-Coenzyme A inhibit*):ti,ab,kw or (atorvastatin or Liptor or fluvastatin or Lescol or lovastatin or Altocor or Altoprev or Mevacor):ti,ab,kw or (pravastatin or Apo-Pravastatin or Lipostat or Pravasin* or Pravachol or Selektine or rosuvastatin or Crestor):ti,ab,kw

#220 MeSH descriptor Simvastatin explode all trees

#221 MeSH descriptor Niacin explode all trees

#222 MeSH descriptor Anticoagulants explode all trees

#223 MeSH descriptor Warfarin explode all trees

#224 MeSH descriptor Dalteparin explode all trees

#225 (simvastatin or Synvinolin or Zocor):ti,ab,kw or (niacin or Niacor or Niaspan or Nicobid or Nicolar or Nicotinex or Slo-Niacin):ti,ab,kw or (Anticoagulant* or bloodthinn* or blood-thinn*):ti,ab,kw or (warfarin or Apo-Warfarin or Coumadin*):ti,ab,kw or (dalteparin or Fragmin*):ti,ab,kw

#226 MeSH descriptor Heparin explode all trees

#227 MeSH descriptor Platelet Aggregation Inhibitors explode all trees

#228 MeSH descriptor Aspirin explode all trees

#229 MeSH descriptor Ticlopidine explode all trees

#230 (heparin or tinzaparin or Innohep):ti,ab,kw or (platelet* NEAR/2 inhibit*) or antiplatelet* or anti-platelet* or platelet antagonist*or platelet antiaggregant*:ti,ab,kw or

(Aspirin or Acetylsalicylic or Acylpyrin or Aloxiprimum or Aspergum or Bufferin or Colfarit or Dispril or Ecotrin or Easprin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin):ti,ab,kw or (ticlopidine or Ticlid):ti,ab,kw or (clopidogrel or Plavix):ti,ab,kw

#231 MeSH descriptor Diuretics explode all trees

#232 MeSH descriptor Bumetanide explode all trees

#233 MeSH descriptor Ethacrynic Acid explode all trees

#234 MeSH descriptor Furosemide explode all trees

#235 MeSH descriptor Amiloride explode all trees

#236 (diuretic* or water pill*):ti,ab,kw or (Bumetanide or bumex):ti,ab,kw or (ethacrynic acid or Edecrin):ti,ab,kw or (furosemide or Errolon or Fursemide or Fusid or Lasix or torsemide or Demadex or torasemide or k-sparing or potassium-sparing):ti,ab,kw or (Amiloride or Amidal or Amiduret or Kaluril or Midamor or Midoride or Modamide):ti,ab,kw

#237 MeSH descriptor Triamterene explode all trees

#238 MeSH descriptor Bendroflumethiazide explode all trees

#239 MeSH descriptor Chlorothiazide explode all trees

#240 MeSH descriptor Hydrochlorothiazide explode all trees

#241 MeSH descriptor Methyclothiazide explode all trees

#242 (triamterene or Dyrenium or thiazide diuretic*):ti,ab,kw or (Bendroflumethiazide or Bendrofluazide):ti,ab,kw or (chlorothiazide or Chlotride or Diuril):ti,ab,kw or (hydrochlorothiazide or Apo-Hydro or Dichlotride or Esidrex or HydroDIURIL or Microzide or Oretic):ti,ab,kw or (methyclothiazide or Aquatensen or Enduron):ti,ab,kw

#243 MeSH descriptor Polythiazide explode all trees

#244 MeSH descriptor Chlorthalidone explode all trees

#245 MeSH descriptor Indapamide explode all trees

#246 MeSH descriptor Metolazone explode all trees

#247 (polythiazide or Renese):ti,ab,kw or (chlorthalidone or Apo-Chlorthalidone or Hygroton or Thalitone):ti,ab,kw or (indapamide or Lozol or Metindamide):ti,ab,kw or (metolazone or Mykrox or Zaroxolyn or Zytanix):ti,ab,kw

#248 (#130 OR #131 OR #132 OR #133 OR #134 OR #135 OR #136 OR #137 OR #138 OR #139 OR #140 OR #141 OR #142 OR #143 OR #144 OR #145 OR #146 OR #147 OR #148 OR #149 OR #150 OR #151 OR #151 OR #152 OR #153 OR #154 OR #155 OR #156 OR #157 OR #158 OR #159 OR #160 OR #161 OR #162 OR #163 OR #164 OR #165 OR #166 OR #167 OR #168 OR #169 OR #170 OR #171 OR #172 OR #173 OR #174 OR #175 OR #176 OR #177 OR #176 OR #177 OR #178 OR #179 OR #180)

#249 (#181 OR #182 OR #183 OR #184 OR #185 OR #186 OR #187 OR #188 OR #189 OR #190 OR #191 OR #192 OR #193 OR #194 OR #195 OR #196 OR #197 OR #198 OR #199 OR #200 OR #201 OR #202 OR #203 OR #204 OR #205 OR #206 OR #207 OR #208 OR #209 OR #210 OR #211 OR #212 OR #213 OR #214 OR #215 OR #216 OR #217 OR #218 OR #219 OR #220 OR #221 OR #222 OR #223 OR #224 OR #225 OR #226 OR #227 OR #228 OR #229 OR #230)

#250 (#231 OR #232 OR #233 OR #234 OR #235 OR #236 OR #237 OR #238 OR #239 OR #240 OR #241 OR #242 OR #243 OR #244 OR #245 OR #246 OR #247)

#251 (#248 OR #249 OR #250)

#252 (#106 OR #129)

#253 (#251 AND #252)

#254 (#1 OR #3)
#255 Any MeSH descriptor with qualifiers: AD,CT,DE,ME,PK,TO
#256 MeSH descriptor Drug Synergism explode all trees
#257 (interact* or react* or contraindicat* or enhance* or metabolis* or metaboliz* or pharmacokinetic* or synergis* or toxic or toxicit*):ti,ab,kw
#258 (#254 OR #255 OR #256 OR #257)
#259 (#253 AND #258)
#260 (#5 OR #259)
#261 (#5 AND #251)
#262 (#259), from 2005 to 2010
#263 (#259), from 2000 to 2004
#264 (#259), from 1990 to 1999
#265 (#259), from 1950 to 1989
#266 (#5 AND NOT #261

Herb-Drug Interactions

MEDLINE (1950 to October 26, 2010)

1. exp Herb-Drug Interactions/
2. ((herb or herbs or herbal or plant or plants or botanic*) and (drug or drugs or medication$1 or prescription$1 or pharmacotherap* or pharmaco-therap*) and (interact* or react* or contraindicat* or metabolis* or metaboliz* or pharmacokinetic* or pharmaco-kinetic*)).ti,ab.
3. exp Food-Drug Interactions/
4. ((food or foods) and (drug or drugs or medication$1 or prescription$1 or pharmacotherap* or pharmaco-therap*) and (interact* or react* or contraindicat* or metabolis* or metaboliz* or pharmacokinetic* or pharmaco-kinetic*)).ti,ab.
5. or/1-4
6. limit 5 to human
7. limit 5 to ("in data review" or "in process" or "pubmednotmedline")
8. 6 or 7
9. limit 8 to "reviews (specificity)"
10. meta analysis.pt.
11. exp meta-analysis as topic/
12. (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).ti,ab.
13. (systematic review* or systematic overview* or technology assessment* or HTA or HTAs).ti,ab.
14. exp Technology assessment, biomedical/
15. health technology assessment winchester england.jn.
16. "cochrane database of systematic reviews".jn.
17. (evidence report technology assessment or evidence report technology assessment summary).jn.
18. or/10-17
19. 8 and 18

20. 9 or 19

EMBASE (1980 to October 26, 2010)

1. exp herb drug interaction/
2. ((herb or herbs or herbal or plant or plants or botanic*) and (drug or drugs or medication$1 or prescription$1 or pharmacotherap* or pharmaco-therap*) and (interact* or react* or contraindicat* or metabolis* or metaboliz* or pharmacokinetic* or pharmaco-kinetic*)).ti,ab.
3. exp food drug interaction/
4. ((food or foods) and (drug or drugs or medication$1 or prescription$1 or pharmacotherap* or pharmaco-therap*) and (interact* or react* or contraindicat* or metabolis* or metaboliz* or pharmacokinetic* or pharmaco-kinetic*)).ti,ab.
5. or/1-4
6. limit 5 to human
7. limit 6 to "reviews (2 or more terms high specificity)"
8. exp meta analysis/
9. (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).ti,ab.
10. (systematic review* or systematic overview* or technology assessment* or HTA or HTAs).ti,ab.
11. exp biomedical technology assessment/
12. health technology assessment winchester england.jn.
13. "cochrane database of systematic reviews".jn.
14. evidence report technology assessment.jn.
15. (evidence report technology assessment or evidence report technology assessment summary).jn.
16. or/8-15
17. 6 and 16
18. 7 or 17

AMED (1985 to October 26, 2010)

1. exp Herb drug interactions/
2. ((herb or herbs or herbal or plant or plants or botanic*) and (drug or drugs or medication$1 or prescription$1 or pharmacotherap* or pharmaco-therap*) and (interact* or react* or contraindicat* or metabolis* or metaboliz* or pharmacokinetic* or pharmaco-kinetic*)).ti,ab.
3. ((food or foods) and (drug or drugs or medication$1 or prescription$1 or pharmacotherap* or pharmaco-therap*) and (interact* or react* or contraindicat* or metabolis* or metaboliz* or pharmacokinetic* or pharmaco-kinetic*)).ti,ab.
4. or/1-3
5. meta analysis/
6. meta analysis.pt.
7. (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).ti,ab.

8. (systematic review* or systematic overview* or technology assessment* or HTA or HTAs).ti,ab.
9. health technol assess rep.ja.
10. evid rep technol assess summ.ja.
11. cochrane database syst rev.ja.
12. or/5-11
13. 4 and 12

International Bibliographic Information on Dietary Supplements (IBIDS)

(interact* react* contraindicat* enhanc* pharmacokinetic* synergis* toxic*) +(cardiovascular* "heart disease" "heart diseases") +(drug drugs agent* medication* prescription* prescribe*)

Appendix B. Scientific Information Packet Requests

Appendix B lists the names of the companies contacted from which to obtain scientific information packets.

Name of Company	
Abbott Laboratories	Lundbeck, Inc.
Actelion Pharmaceuticals US, Inc	Meda Pharmaceuticals
Alcon Laboratories, Inc.	Merck & Co., Inc.
Apothecon B.V.	Mutual Pharma (URL Pharma Inc)
AstraZeneca Pharmaceuticals, LP	Mylan Pharmaceuticals
AstraZeneca Pharmaceuticals, LP	Mylan Pharmaceuticals
Aton Pharma Inc.	NitroMed, Inc.
Bayer HealthCare Pharmaceuticals	NovaDel Pharma
Biovail Pharmaceuticals Inc.	Novartis Pharmaceuticals Corporation
Boehringer Ingelheim Pharmaceuticals, Inc.	Otsuka America Pharmaceutical, Inc.
Bristol-Myers Squibb	Paddock Laboratories, Inc.
Daiichi Sankyo, Inc	Pfizer Inc
Duramed Subsidiary of Barr Pharmaceuticals a.k.a. Teva	Prometheus Laboratories Inc.
Eisal Medical Research Inc.	Promius Pharma, LLC
EKR Therapeutics, Inc	Salix Pharmaceuticals
Eli Lilly & Co	Sandoz Inc
Ferndale	Sanofi Aventis US
Forest Pharmaceuticals	Santen Inc.
Forest Pharmaceuticals	Schering-Plough Corporation
G. Pohl-Boskamp GmbH & Co. KG	Shionogi Inc.
Gilead Sciences	Teva Pharmaceuticals USA
GlaxoSmithKline	Teva Pharmaceuticals USA
Graceway Pharmaceuticals, LLC	UCB, Inc
Hospira	United Therapeutics Corporation
Ivax Pharmaceuticals (Teva Pharmaceuticals)	Upsher-Smith Labratories, Inc
Johnson & Johnson Health Care Products & Pharmaceuticals	USL Pharmaceuticals
Key Pharmaceuticals	Validus Pharmaceuticals LLC
King Pharmaceuticals, Inc.	VIVUS, Inc.
LEO Pharma Inc.	Wyeth Pharmaceuticals Headquarters

Appendix C. Evidence Tables

The purpose of Appendix C is to provide detailed evidence tables that depict the criteria used to determine validity for each study and show the risk of bias assessment made to each study. Furthermore, the tables summarize the evidence described and reflect specific information discussed in the report. The tables are categorized and alphabetized. The categories are: General Characteristics; Interventions; Outcomes by Key Question and outcome; Risk of Bias.

Evidence Table 57. General characteristics of all studies

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Abdul 2010[1]	N screened: NR N included/randomized: 12 Age: 24 %female: 0 Ethnicity: - Caucasian (6) - Asian (6) Comorbidities (other than indication(s) for CVDs: NR CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: non-smokers and not taking any medication including any herbal medicines or dietary supplements (for at least 2 weeks) Exclusion Criteria: Subjects with any medical condition that could alter warfarin effects, including any clotting disorders, hepatic dysfunction or platelet dysfunction Brief Description: healthy male subjects of known CYP2C9 and VKORC1 genotype	Study Design: Crossover RCT Region: NR, likely Australia Setting: NR Industry Funded: Yes Treatment Duration supplement(s): 21 Treatment DurationCVD Drug(s): Single dose Duration of Followup: 7 Duration of Longest Followup: 7	Generic Name(s): warfarin Drug Category: Anticoagulants Mode of Administration: Oral Mean Daily Dose: 25mg- 1 dose Reason for taking CVD drug(s): Pharmacokinetics and pharmackodynamic study	N: 12 Supplement(s): Echinacea Form of Administration: Capsule/Tablet Daily Dose: 5100 mg	N1 = 12 No treatment N2 = 12 policosanol (non-relevant supplement)	Non-CVD Medications: NA Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Aruna 2007[2]	N screened: 16 N included/randomized: 10 Age: 27 %female: 0 Ethnicity: NR Comorbidities (other than indication(s) for CVDs: No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: NR Exclusion Criteria: subjects hypersensitive to study drugs, chronic smokers or alcoholics, and a history of gastrointestinal surgery that could interfere with absorption of study drugs Brief Description: healthy male subjects	Study Design: Crossover RCT Region: Rest of Asia Setting: General community Industry Funded: Unclear Treatment Duration supplement(s): 1 Treatment DurationCVD Drug(s): 1 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): cilostazol Drug Category: Vasodilator: Nitrates/PDE-5 Inhibitors Mode of Administration: Oral Mean Daily Dose: 150mg Reason for taking CVD drug(s): Pharmacokinetics and pharmackodynamic study Generic Name(s): clopidogrel Drug Category: Antiplatelets Mode of Administration: Oral Mean Daily Dose: 112.5mg Reason for taking CVD drug(s): Pharmacokinetics and pharmackodynamic study	N: 10 Supplement(s): Gingko biloba Form of Administration: Capsule/Tablet Daily Dose: 120mg single dose	N1 = 10 No treatment N2 = 10 No treatment	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Avogaro 1974[3]	N screened: NR N included/randomized: 20 Age: NR %female: NR Ethnicity: NR Comorbidities (other than indication(s) for CVDs): Not reported CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: suffering from hyperlipoproteinemia; high levels of cholesterol and/or serum triglycerides at least twice after being on a balanced diet for two weeks. Classified on the basis of lipids and lipoproteins levels according to the criteria of Fredrickson et al. and recommendations of the WHO Exclusion Criteria: NR Brief Description: Patients suffering from hyperlipoproteinemia	Study Design: Crossover RCT Region: Europe Setting: Primary care Industry Funded: Unclear Treatment Duration supplement(s): 28 Treatment DurationCVD Drug(s): 28 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): propranolol Drug Category: b-blockers Mode of Administration: Oral Mean Daily Dose: 20mg OR 60mg Reason for taking CVD drug(s): Cardiovascular indication	N: 20 Supplement(s): Niacin Form of Administration: Capsule/tablet Daily Dose: 250 mg (and non-relevant dose of 750mg/day)	N1 = 20 Placebo N2 = 20 No treatment N3 = 20 Intervention3: No treatment	Non-CVD Medications: NR Dietary Intervention(s): diet adjusted to bring each patient to ideal weight. The diet provided 45 % carbohydrates, 34 % fats, I5 % proteins and 6 % alcohol; 78% of carbohydrates was given as starches and 22% as sugars. For fats the P/S relationship was 1.87; the amount of dietary cholesterol did not exceed 200 mg. Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Balestrieri 1996[4]	N screened: NR N included/randomized: 16 Age: 42.5 %female: 44 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors) Inclusion Criteria: Heterozygous FH diagnosed according to the criteria of Brown and Goldstein; normal thyroid, renal and hepatic function Exclusion Criteria: diabetic, obese Brief Description: Group of heterozygous FH patients on long-term treatment with simvastatin	Study Design: Crossover RCT Region: Europe Setting: Not reported Industry Funded: Unclear Treatment Duration supplement(s): 28 Treatment DurationCVD Drug(s): 28 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): NR Simvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: range 10-40mg Reason for taking CVD drug(s): Cardiovascular indication	N: 8 Supplement(s): Fish oils/marine oils Form of Administration: Capsule/tablet Daily Dose: 5100mg	N1 = 8 Placebo	Non-CVD Medications: NA Dietary Intervention(s): lipid lowering diet (Step 1 AHA diet) Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Barbagallo 1999[5]	N screened: NR N included/randomized: 24 Age: 47.05 %female: 54 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): Not reported CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: Essential hypertension (outpatient blood pressure >140/90 mm Hg on >/=3 occasions and the absence of any history, physical examination, or laboratory evidence of secondary forms of hypertension) Exclusion Criteria: Patients with diabetes mellitus or glucose intolerance Brief Description: Patients with essential hypertension	Study Design: Parallel RCT Region: Europe Setting: Primary care Industry Funded: Unclear Treatment Duration supplement(s): 28 Treatment DurationCVD Drug(s): 28 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): furosemide Drug Category: Diuretic: Loop Mode of Administration: Oral Mean Daily Dose: 25mg Reason for taking CVD drug(s): Cardiovascular indication	N: 12 Supplement(s): Vitamin E Form of Administration: Capsule/Tablet Daily Dose: 600mg	N1 = 12 Placebo	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Bays 2010[6]	N screened: 585 N included/randomized: 245 Age: 56.15 %female: 42 Ethnicity: Caucasian (89) Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors) Inclusion Criteria: Between ages 18-79;medically stable; Lipid criteria: non-HDL-C level greater than 160mg/dL and triglycerides between 250 and 599 mg/dL Exclusion Criteria: Use of nonstudy lipid lowering therapy;omega3 supplements;or niacin dosages >400; known allergy to statins or omega3s; symptoms of muscle pain, tenderness or weakness 2mo before study; history of myopathy or rhabdomyolysis Brief Description: patients with combined hyperlipidemia	Study Design: Parallel RCT Region: North America Setting: Specialty clinic Industry Funded: Yes Treatment Duration supplement(s): 112 Treatment DurationCVD Drug(s): 112 Duration of Followup: End of treatment period Duration of Longest Followup: NR	Generic Name(s): atorvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: 10, 20 and 40mg Reason for taking CVD drug(s): Cardiovascular indication	N: 123 Supplement(s): Omega-3 Form of Administration: Capsule/Tablet Daily Dose:: 4000mg	N1 = 122 Placebo plus atorvastatin	Non-CVD Medications: none Dietary Intervention(s): National Cholesterol Education Program therapeutic lifestyle changes diet Exercise Intervention(s): No Other Lifestyle Intervention(s): No
Bays 2009[7]	N screened: 596 N included/randomized: 167 Age: 52.05 %female: 26.35 Ethnicity: - Caucasian (88) - African-American (1) - Hispanic (7) - Other (4)	Study Design: Parallel RCT Region: North America Setting: Not reported Industry Funded: Yes	Generic Name(s): fenofibrate Drug Category: Antilipidemic: Fibrate Mode of Administration: Oral Mean Daily Dose: 130mg Reason for taking	N: 75 Supplement(s): Omega-3 Form of Administration: Capsule/Tablet Daily Dose: 4000mg	N1 = 75 Placebo	Non-CVD Medications: NR Dietary Intervention(s): low saturated fat NCEP Therapeutic Lifestyle Changes (TLC) diet

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	Comorbidities (other than indication(s) for CVDs): overweight/obese; Type II Diabetes (20.5%) CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: men and women in good health between 18 and 79 years of age with a body mass index of >/=25 kg/m2 and </=43 kg/m2; mean fasting TG level of >/=500 mg/dL and <1300 mg/dL as determined by the average of the 2 TG values obtained at 2 weeks before and 1 week prior to randomization; met the criteria for Fredrickson type IV dyslipidemia Exclusion Criteria: use of warfarin, cyclic sex hormone therapy, or other agents known to affect lipid levels during the run-in or treatment period of the study; The use of cyclosporine, systemic corticosteroids, high-dose topical corticosteroids (1500 mg/d), androgens, phenytoin, isotretinoin, or thyroid hormones (except stable-dose replacement therapy for 2 months prior to week 6) during the study also was restricted. Subjects with a known sensitivity to seafood, EPA or DHA, in addition to any history of pancreatitis, significant renal, hepatic, biliary, or gastrointestinal disease, type 1 diabetes mellitus, or uncontrolled type 2 diabetes; Women who were pregnant, lactating, or were of childbearing potential and were not using a medically approved method of contraception	Treatment Duration supplement(s): 56 Treatment DurationCVD Drug(s): 56 Duration of Followup: 56 Duration of Longest Followup: End of treatment period	CVD drug(s): Cardiovascular indication			Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	Brief Description: 18-75 years old, overweight/obese, with dyslipidemia					
Bender 1998[8]	N screened: NR N included/randomized: 16 Age: 53.5 %female: 54.5 Ethnicity: - African-American (9) - Hispanic (91) Comorbidities (other than indication(s) for CVDs): Not reported CHD Risk Level: Unclear Inclusion Criteria: between the ages of 18 and 70years, stable anticoagulation status (i.e., INR change no greater than1.63 for at least the past 3 consecutive months, with no warfarin dosage adjustments). Exclusion Criteria: any new medication(s) other than the study medications within 1 month of the study, receiving concurrent therapy with salicylates or other nonsteroidal anti-inflammatory agents, baseline platelet count less than100,000, history of a major bleeding episode while receiving warfarin therapy within the past 5 years, had active peptic ulcer disease within the previous 6 months, or cerebrovascular disease, uncontrolled hypertension, or surgery/trauma within the previous 3 months. Women who	Study Design: Parallel RCT Region: North America Setting: Industry Funded: Unclear Treatment Duration supplement(s): 28 Treatment DurationCVD Drug(s): 28 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): warfarin Drug Category: Anticoagulants Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s): Cardiovascular indication	Supplement(s): Fish oils/marine oils Form of Administration: Capsule/Tablet Daily Dose: 3000 or 6000mg	Placebo (matching; R.P. Schering Pharmaceuticals Corporation)	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	were pregnant or of child-bearing potential who were not using an acceptable means of contraception Brief Description:Patients receiving chronic warfarin therapy for indications requiring oral anticoagulation					
Bordia 1998[9]	N screened: NR N included/randomized: 60 Age: NR %female: NR Ethnicity: NR Comorbidities (other than indication(s) for CVDs): Not reported CHD Risk Level: At high risk for CHD Inclusion Criteria: Patients with CAD and with old healed MI (> 6 months) with or without angina. Exclusion Criteria: NR Brief Description: Patients with CAD	Study Design: Controlled clinical trial (CCT) Region: Europe Setting: Not reported Industry Funded: No Treatment Duration supplement(s): 90 Treatment DurationCVD Drug(s): Unclear Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): NR Nitrates Drug Category: Vasodilator: Nitrates/PDE-5 Inhibitors Mode of Administration: NR Mean Daily Dose: NR Reason for taking CVD drug(s): Cardiovascular indication	N: 30 Supplement(s): Garlic Form of Administration: Capsule/Tablet Daily Dose: 4000mg	N1 = 30 Placebo	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Budoff 2004[10]	N screened: NR N included/randomized: 23 Age: 59.6 %female: 26 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At high risk for CHD Inclusion Criteria: known coronary artery disease or high risk for coronary artery disease, with a 10-year Framingham risk of developing coronary artery disease of >20% Exclusion Criteria: A contraindication to Aged Garlic Extract therapy including: known hypersensitivity to drug; Weight in excess of 300 lb; Serum creatinine >1.4 mg/d; Triglycerides >400 at visit; Drug or alcohol abuse, or current intake of more than 14 standard drinks per week; Concurrent enrollment in another placebo-controlled Trial; Presence of metal clips or stenting that preclude accurate measure of coronary calcification and angiographic disease by electron beam tomography; Partial ileal bypass or known gastrointestinal disease limiting drug absorption; Current intake of garlic supplement Brief Description: patients with known coronary artery disease or high risk for coronary artery disease	Study Design: Parallel RCT Region: NR, likely North America Setting: NR Industry Funded: Unclear Treatment Duration supplement(s): 365 Treatment DurationCVD Drug(s): 365 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): Statin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: NR Mean Daily Dose: Range of 10-40mg Reason for taking CVD drug(s): Cardiovascular indication	N: 9 Supplement(s): Garlic Form of Administration: Liquid Daily Dose: 4 ml	N1 = 10 Placebo N2 = NA NA	Non-CVD Medications: NR Dietary Intervention(s): All participants were educated on a low-cholesterol diet at entry to the study by the nurse coordinator Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Caso 2007[11]	N screened: NR N included/randomized: 32 Age: 60.63 %female: 47 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors) Inclusion Criteria: treated for hyperlipidemia with statin; under current NCEP guidelines and reporting myopathic symptoms (only if no other identifiable cause of myopathy could be determined) Exclusion Criteria: Clinical evidence of hepatic, vascular, renal or endocrine disease;coagulopathy; or other serious medical conditions; none were using CoQ10, Vit E or anticoagulants Brief Description: patients using statins with myopathic pain	Study Design: Parallel RCT Region: North America Setting: Speciality clinic Industry Funded: No Treatment Duration supplement(s): 30 Treatment DurationCVD Drug(s): 30 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): Simvastatin (22); Atorvastatin (7); Pravastatin (2); Lovastatin (1) Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: varying doses for all patients Reason for taking CVD drug(s): Cardiovascular indication	N: 18 Supplement(s): Coenzyme Q10 Form of Administration: Capsule/Tablet Daily Dose: 100mg	N1 = 14 Vitamin E, 400IU	Non-CVD Medications: nonsteroidal anti-inflammatory drugs taken by 9 patients Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): patients were already following Adult Treatment Panel III/National Cholesterol Education Program guidelines

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Chan 2002[12]	N screened: 52 N included/randomized: 52 Age: 53.23 %female: 0 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): obese CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors) Inclusion Criteria: obese (BMI>29kgm-2); dyslipidemia (LDL-C>2.6mmol L-1, non HDL-C>3.4mmolL-1 and triglycerides>1.2mmolL-1); weight-maintenance diet Exclusion Criteria: diabetes;apolipoprotein E2/D2 genotype;macroproteinuria;creatinaemia (>120umolL-1);hypothyroidism;abnormal liver and muscle enzymes; consumed fish oil supplements; more than 30g alcohol Brief Description: viscerally obese men	Study Design: Parallel RCT Region: NR Setting: Not reported Industry Funded: Yes Treatment Duration supplement(s): 42 Treatment DurationCVD Drug(s): 42 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): NR Atorvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: 40mg Reason for taking CVD drug(s): Cardiovascular indication	N: Supplement(s): Fish oils/marine oils Form of Administration: Capsule/Tablet Daily Dose: 4000mg	N1 = Placebo N2 = fish oil + atorvastatin placebo	Non-CVD Medications: NA Dietary Intervention(s): isocaloric diet Exercise Intervention(s): keep their physical activity constant Other Lifestyle Intervention(s): No
d'Arcangues 2004[13]	N screened: NR N included/randomized: 9297 Age: NR %female: NR Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At low risk for CHD (0-1 risk factors)	Study Design: Parallel RCT Region: Multiple (East Asia, Central & South America) Setting: Speciality clinic Industry Funded: Unclear	Generic Name(s): ASA Drug Category: Antiplatelets Mode of Administration: Oral Mean Daily Dose: 80mg Reason for taking CVD drug(s): Norplant-induced	N: 120 Supplement(s): Vitamin E Form of Administration: Capsule/Tablet Daily Dose: 200mg	N1 = 122 No treatment N2 = 123 Placebo	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	Inclusion Criteria: healthy, between 18 and 38 years old, nonpregnant and nonlactating and had been using the implantable contraceptive Norplant for 1 to 6 months. Able to keep a menstrual diary, willing to return to the clinic at prescribed intervals, agreed not to use vitamins, aspirin, anti-inflammatory drugs, steroids or any other drug that might affect the vaginal bleeding pattern (other than those prescribed in the trial) during the trial or for 3 weeks prior to admission. Exclusion Criteria: they had a last injection of DMPA within 6 months or a last injection of norethisterone enanthate (NET-EN) within 4 months, previous immediate use of Norplant or levonorgestrel-releasing intrauterine device, hemoglobin level lower than 8 g/dl,known hypersensitivity to aspirin or vitamin E or had participated in the pilot study of vitamin E previously conducted in Jakarta. Brief Description: healthy bleeding with Norplant-induced prolonged vaginal bleeding	Treatment Duration supplement(s): 10 Treatment DurationCVD Drug(s): 10 Duration of Followup: 360 Duration of Longest Followup: 360	prolonged vaginal bleeding			
Davidson 2007[14]	N screened: 690 N included/randomized: 256 Age: 59.8 %female: 42.5 Ethnicity: NR - Caucasian (95.7) - African-American (2) - Hispanic (1.6)	Study Design: Parallel RCT Region: North America Setting: Speciality clinic Industry Funded: Yes	Generic Name(s): simvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose:	N: 123 Supplement(s): Omega-3 Form of Administration: Capsule/Tablet Daily Dose: 4000mg	N1 = 133 Placebo	Non-CVD Medications: NA Dietary Intervention(s): NCEP Therapeutic Lifestyle Changes diet

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	- Asian (1.2) Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors) Inclusion Criteria: between ages 18-79;receiving stable does of statin for control of LDL-C levels for>8weeks;mean fasting T G level>200 and<500mg/dL, and a mean LDL-C level below or within 10% of the patient's NCEP ATP Exclusion Criteria: poorly controlled diabetes (HbA1c>8%); history of CV; revascularization procedure or aortic aneurysm within 6mo of screening; history of pancreatitis;sensitivity to statins or omega3s;poorly controlled hypertension (resting blood pressure>160mmHg systolic and/or_>100mm Hg; serum creatinine level_>2.0 mg/dL;serum transaminase>1.5 times the upper limit of normal;creatine kinase levels>2 times the ULN Brief Description: patients with persistent hypertriglyceridemia despite statin therapy	Treatment Duration supplement(s): 56 Treatment DurationCVD Drug(s): 112 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	40mg Reason for taking CVD drug(s): Cardiovascular indication			Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Davidson 1997[15]	N screened: 46 N included/randomized: 30 Age: NR %female: NR Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: Serum lipid values determined as mean values from 2 fasting measurements taken 1 week apart. Qualifying lipid concentrations were LDL cholesterol >/ 160 and </ 240 mg/dl, HDL </ 50mg/dl for men and </60 mg/dl for women, and fasting triglycerides of 200 to 600 mg/dl after >/ 4 weeks following a National Cholesterol Education Program Step I Diet. Exclusion Criteria: NR Brief Description: Hyperlipidemic subjects	Study Design: Parallel RCT Region: NR Setting: Not reported Industry Funded: Unclear Treatment Duration supplement(s): 84 Treatment DurationCVD Drug(s): 84 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): NR Simvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: 10mg Reason for taking CVD drug(s): Cardiovascular indication	N: 10 Supplement(s): Fish oils/marine oils Form of Administration: Capsule/Tablet Daily Dose: 10000mg	N1 = 10 No treatment N2 = 9 Fish oil	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
De, Caterina 2002[16]	N screened: NR N included/randomized: 43 Age: 63.1 %female: 51 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): diabetes (19%) CHD Risk Level: At high risk for CHD Inclusion Criteria: hypercholesterolemic subjects (Fredrickson IIa or IIb) with serum cholesterol 200 mg/dL and proven vascular (coronary, carotid, or peripheral arterial) disease. Exclusion Criteria: NR Brief Description: hypercholesterolemic subjects with proven vascular disease	Study Design: Crossover RCT Treatment Duration: 30 Region: NR Setting: Not reported Industry Funded: Yes Treatment Duration supplement(s): 30 Treatment DurationCVD Drug(s): 30 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): NR simvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: 10mg Reason for taking CVD drug(s): Cardiovascular indication	N: 21 Supplement(s): Vitamin E Form of Administration: Capsule/Tablet Daily Dose: 600mg	N1 = 22 No treatment	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Dehmer 1988[17]	N screened: 149 N included/randomized: 90 Age: 56 %female: 0 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): diabetes 28% in control groupl; 21% in treatment group CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors) Inclusion Criteria: male patients referred to laboratory for angioplasty Exclusion Criteria: age over 80 years, severe confounding medical problems, angioplasties for restenosis that had developed after an earlier procedure; acute MI or unstable ischemic symptoms that persisted despite all medical therapies. Brief Description: male patients undergoing angioplasty	Study Design: Parallel RCT Region: North America Setting: Speciality clinic Industry Funded: No Treatment Duration supplement(s): 187 Treatment DurationCVD Drug(s): 187 Duration of Followup: 270,360 Duration of Longest Followup: 360	Generic Name(s): ASA Drug Category: Antiplatelets Mode of Administration: Oral Mean Daily Dose: 325mg Reason for taking CVD drug(s): Cardiovascular indication Generic Name: dipyridamole Drug Category: Antiplatelets Mode of Administration: Oral Mean Daily Dose: 225mg Reason for taking CVD drug(s): Cardiovascular indication Generic Name: NR Drug Category: Calcium channel blockers Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s): Cardiovascular indication	N: 43 Supplement(s): Omega-3 Form of Administration: Capsule/Tablet Daily Dose: 3200mg	N1 = 39 No treatment	Non-CVD Medications: NA Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No
Desideri	N screened: 67	Study Design:	Generic Name(s):	N: 31	N1 = 19	Non-CVD

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
2003[18]	N included/randomized: 67 Age: 47.7 %female: 42 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: Serum LDL-cholesterol levels of more than 5.2 mmol/liter and less than 7.8 mmol/liter adn fasting triglycerdie levels of less than 1.7 mmol/liter after 30d on an American heart step I diet. Normal M-mode and B-mode echocardiograms and 12-lead electrocardiogram Exclusion Criteria: age of less than 25 year or higher than 55 year, pregnancy, concomitant diseases, personal history of previous cerebro-or cardiovascular disease, diabetes of either type I or II, hypertension, obesity, smoking, drug consumption (including vitamins, aspritin, birth control) alcohol intake of more than 10g, proteinuria, serum reatine of more than 100microM or atherosclerotic lesions of the neck and limb vessels, Patients with allergic diasthesis regaring both type I adn type II immune responses and/or reporting respiratory, GI or genotourinary tracts infections during the last 3 months. Brief Description: Hypercholesterolemic	Parallel RCT Region: Europe Setting: Not reported Industry Funded: Unclear Treatment Duration supplement(s): 180 Treatment DurationCVD Drug(s): 180 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	NR Simvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: 40mg Reason for taking CVD drug(s): Generic Name: NR Bezafibrate Drug Category: Antilipidemic: Fibrate Mode of Administration: Oral Mean Daily Dose: 800mg Reason for taking CVD drug(s): Cardiovascular indication	Supplement(s): Vitamin E Form of Administration: Capsule/Tablet Daily Dose: 400IU	No treatment N2 = 17 No treatment	Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	patients					
Di Spirito 2008[19]	N screened: 50 N included/randomized: 50 Age: 35 %female: 20 Ethnicity: - Caucasian (98) - African-American (2) Comorbidities (other than indication(s) for CVDs: No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: NR Exclusion Criteria: Women who were pregnant or lactating or who were planning a pregnancy; Individuals with a history of hypersensitivity or allergy to study medications Brief Description: healthy non-smoking men and women within 15% of ideal body weight	Study Design: Crossover RCT Region: North America Setting: Research Facility Industry Funded: Yes Treatment Duration supplement(s): 14 Treatment DurationCVD Drug(s): 14 Duration of Followup: 1 Duration of Longest Followup: 1	Generic Name(s): atorvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: 80mg Reason for taking CVD drug(s): pharmacokinetics of atorvastatin and P-OM3	N: 50 Supplement(s): Omega-3 (EPA, DHA or both) Form of Administration: Capsule/Tablet Daily Dose: 4000mg	N1 = 50 No treatment	Non-CVD Medications: hormonal contraceptives (portion NR) Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Duffy 2001[20]	N screened: NR N included/randomized: 29 Age: 28.7 %female: 54 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: hypercholesterolaemia (total cholesterol and LDL levels were above the 75th percentile for age and gender based on NHFA Risk Factor Prevalence Study) Exclusion Criteria: any other risk factor for CAD, cardiovascular disease, any other major disease; volunteers on CV medications or vitamin supplements Brief Description: young patients with hypercholesterolaemia	Study Design: Parallel RCT Region: NR (likely Australia) Setting: Not reported Industry Funded: No Treatment Duration supplement(s): 180 Treatment DurationCVD Drug(s): 180 Duration of Followup: End of treatment period Duration of Longest Followup: : End of treatment period	Generic Name(s): NA simvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: starting dose 10mg; ending dose 40mg Reason for taking CVD drug(s): Cardiovascular indication	N: 6 Supplement(s): Vitamin E Form of Administration: Capsule/Tablet Daily Dose: 1000 IU	N1 = 7 Placebo N2 = 7 No treatment N3 = 6 Intervention3: Vitamin E	Non-CVD Medications: estrogen-based oral contraceptives (portion of population) Dietary Intervention(s): dietary advice and information sheets on cholesterol lowering diets Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Eritsland 1996[21]	N screened: NR N included/randomized: 291 Age: 60.49 %female: 12.5 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): Diabetes CHD Risk Level: At high risk for CHD Inclusion Criteria: admitted for coronary artery bypass grafting without concomitant cardiac surgery. Exclusion Criteria: medical containdications to any of the treatment principles; refused participation; early (<2 days) perioperative death or complications; presumed lack of compliance; indication for anticoagulation; administrative reasons Brief Description: Subjects undergoing coronary artery bypass grafting without surgery	Study Design: Parallel RCT Region: Europe Setting: Specialty Clinic Industry Funded: Unclear Treatment Duration supplement(s): 365 Treatment DurationCVD Drug(s): 365 Duration of Followup: 365 Duration of Longest Followup: 365	Generic Name(s): ASA Drug Category: Antiplatelets Mode of Administration: Oral Mean Daily Dose: 300mg Reason for taking CVD drug(s):	N: 143 Supplement(s): Fish oils/marine oils Form of Administration: Capsule/Tablet Daily Dose: 4000mg	N1 = 148 No treatment	Non-CVD Medications: NR Dietary Intervention(s): Verbal and written dietary advice; decreased intake of saturated fatty acids advised; told to refrain from cod-liver oil and other fish oil products; dietary records obtained from a random sample. Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Eritsland 1996[21]	N screened: NR N included/randomized: 319 Age: 59.54 %female: 13.8 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): Diabetes CHD Risk Level: At high risk for CHD Inclusion Criteria: admitted for coronary artery bypass grafting without concomitant cardiac surgery. Exclusion Criteria: medical containdications to any of the treatment principles; refused participation; early (<2 days) perioperative death or complications; presumed lack of compliance; indication for anticoagulation; administrative reasons Brief Description: Subjects undergoing coronary artery bypass grafting without surgery	Study Design: Parallel RCT Region: Europe Setting: Specialty Clinic Industry Funded: Unclear Treatment Duration supplement(s): 365 Treatment DurationCVD Drug(s): 365 Duration of Followup: 365 Duration of Longest Followup: 365	Generic Name(s): warfarin Drug Category: Anticoagulants Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s): Cardiovascular indication	N: 174 Supplement(s): Fish oils/marine oils Form of Administration: Capsule/Tablet Daily Dose: 4000mg	N1 = 145 No treatment	Non-CVD Medications: NR Dietary Intervention(s): Verbal and written dietary advice; decreased intake of saturated fatty acids advised; told to refrain from cod-liver oil and other fish oil products; dietary records obtained from a random sample. Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Ferraro 2009[22]	N screened: NR N included/randomized: 30 Age: 45 %female: 36.6 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: patients with biopsy-proven IgAN and persistent proteinuria (>200 mg) despite treatment with ACE inhibitors and/or ARB. only patients with at least two positive determinations were included Exclusion Criteria: dialysis or kidney transplantation, diabetes mellitus, Henochâ€“Schoenlein purpura, systemic lupus erythematosus and an active or recent (<1 year) treatment with immunosuppressors and/or PUFA. Brief Description: patients with biopsy-proven IgAN and persistent proteinuria	Study Design: Parallel RCT Region: Europe Setting: Speciality clinic Industry Funded: Unclear Treatment Duration supplement(s): 180 Treatment DurationCVD Drug(s): 180 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): ramipril Drug Category: RAAS Antagonist: ACEI Mode of Administration: Oral Mean Daily Dose: 10mg Reason for taking CVD drug(s): IgA nephropathy	N: 15 Supplement(s): Fish oils/marine oils Form of Administration: Capsule/Tablet Daily Dose: 3000mg	N1 = 15 No treatment	Non-CVD Medications: Steroid 60 days prior to randomization in 1 vs. 2 pts (Irbesartan 300mg) Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Gardner 2007[23]	N screened: 188 N included/randomized: 67 Age: 68.5 %female: 40 Ethnicity: - Caucasian (75) - African-American (5) - Hispanic (13) - Asian (7) Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At high risk for CHD Inclusion Criteria: experienced leg pain during walking that was characteristic of the intermittent claudication symptom of PAD, or who might be at risk for PAD due to either a family history of cardiovascular disease (CVD) or elevated CVD risk factors.Older than 18 years of age, had not been taking (for at least 1 month prior to randomization) and did not plan to take (for the duration of the study) any medications or dietary supplements known to affect blood coagulation, and were able to tolerate daily use of aspirin for 6 weeks. Exclusion Criteria: NR Brief Description: adult patients at risk for PAD not taking any medications known to affect blood coagulation and able to tolerate aspirin for 6 weeks	Study Design: Parallel RCT Region:NR (likely North America) Setting: Not reported Industry Funded: Yes Treatment Duration supplement(s): 28 Treatment DurationCVD Drug(s): 42 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): ASA Drug Category: Antiplatelets Mode of Administration: Oral Mean Daily Dose: 325mg Reason for taking CVD drug(s): Cardiovascular indication	N: 29 Supplement(s): Gingko biloba Form of Administration: Capsule/Tablet Daily Dose: 300mg	N1 = 26 Placebo	Non-CVD Medications: NA Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Garg 1995[24]	N screened: 98 N included/randomized: 62 Age: 54.19 %female: 29.6 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): NR CHD Risk Level: At high risk for CHD Inclusion Criteria: acute ischemic stroke, either sex with sudden hemoplegia of either side with or without speech involvement, with cranial CT scan (non-contrast enhanced) showing a hypodense lesion (infarct) in the territory of either middle cerebral artery Exclusion Criteria: ischemia in posterior cerebral territory, overt systemic disease (e.g. recent myocardial infarction, renal failure, severe systemic infection, deeply comatose. Brief Description: patients with acute ischemic stroke	Study Design: Parallel RCT Region: Rest of Asia Setting: Primary care Industry Funded: Unclear Treatment Duration supplement(s): 7 Treatment DurationCVD Drug(s): Unclear Duration of Followup: 14 Duration of Longest Followup: 14	Generic Name(s): ASA Drug Category: Antiplatelets Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s): Cardiovascular indication	N: 29 Supplement(s): Gingko biloba Form of Administration: Capsule/Tablet Daily Dose: 240mg	N1 = 26 Placebo	Non-CVD Medications: antibiotics and short-term glucocorticoids Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Glynn 2007[25]	N screened: 453787 N included/randomized: 65169 Age: NR %female: 100 Ethnicity: - Caucasian (94.8) - African-American (2.3) - Hispanic (1.1) - Asian (1.4) - Other (0.4) Comorbidities (other than indication(s) for CVDs): Obesity (18%), Type II Diabetes (portion), women with deep vein thrombosis or pulmonary embolism were not excluded (portion NR) CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: age 45 years or older; no previous history of coronary heart disease, cerebrovascular disease, cancer (except nonmelanoma skin cancer), or other major chronic illnesses; no history of adverse effects from aspirin; no use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) more than once a week, or willingness to forgo their use; no use of anticoagulants or corticosteroids; and no use of individual supplements of vitamin A, E, or beta carotene more than once a week. Exclusion Criteria: women who currently used anticoagulants Brief Description: Healthy women not currently using anticoagulants	Study Design: Parallel RCT Region: North America Setting: General community Industry Funded: Unclear Treatment Duration supplement(s): 3650 Treatment DurationCVD Drug(s): 3650 Duration of Followup: 3650 Duration of Longest Followup: 3650	Generic Name(s): ASA Drug Category: Antiplatelets Mode of Administration: Oral Mean Daily Dose: 100mg/every other day Reason for taking CVD drug(s): prevention	N: 19,937 Supplement(s): Vitamin E Form of Administration: Capsule/Tablet Daily Dose: 600IU/every other day	N1 = 19,939 Placebo	Non-CVD Medications: Hormone therapy (30%) Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Gosai 2008[26]	N screened: NR N included/randomized: 48 Age: 37 %female: 25 Ethnicity: - Caucasian (42) - Other (arabic, african or undefined ethnicity) (6) Comorbidities (other than indication(s) for CVDs: NR CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: Healthy non-smoking men and women between the ages of 18 and 55 years who were within 15% of ideal body weight Exclusion Criteria: Women who were pregnant, lactating, or planning a pregnancy; individuals with a history of hypersensitivity or allergy to study medications Brief Description: healthy adult volunteers	Study Design: Crossover RCT Region: NR Setting: NR Industry Funded: Yes Treatment Duration supplement(s): 28 Treatment DurationCVD Drug(s): 28 Duration of Followup: 1 Duration of Longest Followup: 1	Generic Name(s): rosuvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: 40mg Reason for taking CVD drug(s):Pharmacokinetics and pharmackodynamic study	N: 48 Supplement(s): Omega-3 (EPA, DHA or both) Form of Administration: Capsule/Tablet Daily Dose: 4000mg	N1 = 48 No treatment	Non-CVD Medications: hormonal contraceptives (portion NR) Dietary Intervention(s): meal plans provided 4 and 9h after each dosing Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Govil 1979[27]	N screened: NR N included/randomized: 80 Age: NR %female: 31 Ethnicity: NR Comorbidities (other than indication(s) for CVDs: No CHD Risk Level: At high risk for CHD Inclusion Criteria: congestive cardiac failure Exclusion Criteria: renal insufficiency Brief Description: patients of congestive cardiac failure	Study Design: Controlled Clinical Trial Region: Rest of Asia Setting: Primary Care Industry Funded: Unclear Treatment Duration supplement(s): NR Treatment DurationCVD Drug(s): NR Duration of Followup: 8 Duration of Longest Followup: 8	Generic Name(s): Digoxin Drug Category: Inotropics Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s):Cardiovascular indication Generic Name(s): Diuretics Drug Category: Diuretic: Loop Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s):Cardiovascular indication	N: 20 Supplement(s): Magnesium Form of Administration: Liquid Capsule/Tablet Daily Dose: 396 mEq	N1 = 60 No treatment	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Hajda, 2010[28]	N screened: NR N included/randomized: 10 Age: 28.8 %female: 0 Ethnicity: Caucasian Comorbidities (other than indication(s) for CVDs: None CHD Risk Level: At low risk for CHD Inclusion Criteria: healthy male subjects (based on physical examinations, standard clinical chemistry and hematology analyses) Exclusion Criteria: NR Brief Description: patients of congestive cardiac failure	Study Design: Randomized cross over (the design may not fit the exact description of RCT for this review) Region: Europe Setting: Unclear Industry Funded: Yes Treatment Duration $_{supplement(s)}$: 21 days Treatment Duration$_{CVD\ Drug(s)}$: 21 days Duration of Followup: 21 days Duration of Longest Followup: 22 days	Generic Name(s): Statins (pravastatin, or simvastatin) Mode of Administration: Oral Daily Dose: 20 mg Reason for taking CVD drug(s):non-Cardiovascular indication Generic Name(s): Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s): non-Cardiovascular indication	N: 10 Supplement(s): Garlic Form of Administration: Capsule/Tablet Daily Dose: 600 mg bid (twice daily)	N_1 = 10 No treatment	Non-CVD Medications: No Dietary Intervention(s): standardized meals during the study period; all subjects were instrucete to abstain from taking any type of medication, including overthe-counter remedies and supplements, grapefruit, caffeine, or alcohol-containing food or beverages for at least 3 days prior to the start of the study and throughout the course of the study. Exercise Intervention(s): No Other Lifestyle Intervention(s): NR
Hansen 1993[29]	N screened: NR N included/randomized: 15 Age: 49 %female: 53.3 Ethnicity: NR	Study Design: Crossover RCT Region: Europe Setting: Primary care Industry	Generic Name(s): lovastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor	N=15 Supplement(s): Fish oils/marine oils Form of	N=15 Placebo (olive oil) + lovastatin	Non-CVD Medications: No Dietary Intervention(s): diet low in cholesterol

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	Comorbidities (other than indication(s) for CVDs): tendon xanthomas (3) CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: hypercholesterolemia, nonobese (within 15% of their ideal body weight) and had a total serum cholesterol level above 9.0 mmol/1 and a triglyceride level below 2.0 mmol/1 on two occasions after 8-20 weeks on a diet low in cholesterol and saturated fat (American Heart Association step I diet), normal thyroid, renal, and hepatic function, no diabetes, manifest cardiovascular disease, or other chronic illnesses Exclusion Criteria: peptic ulcers, gastrointestinal disorders likely to influence drug absorption, alcoholism, drug abuse, or mental illness Brief Description: hypercholesterolemic patients within 15% of their ideal body weight	Funded: Unclear Treatment Duration supplement(s): 42 Treatment DurationCVD Drug(s): 42 Duration of Followup: 84 Duration of Longest Followup: 84	Mode of Administration: Oral Mean Daily Dose: 40mg Reason for taking CVD drug(s): Cardiovascular indication	Administration: Capsule/Tablet Daily Dose: 6000mg	N=15 Placebo (olive oil) + lovastatin placebo	and saturated fat (American Heart Association step I diet) Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Howe 1994[30]	N screened: NR N included/randomized: 61 Age: 55 %female: 44.6 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): Not reported CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: Uncomplicated essential hypertension controlled by ACE inhibitor monnotherapy Exclusion Criteria: unstable heart, renal or liver disease, DBP >105mmHg, consumed more than 20 cigarettes or 40mg of alcohol per day, exercised erratically, institutionalized, or have no control over the preparation of their food Brief Description: Uncomplicated essential hypertension controlled by ACE inhibitor monnotherapy	Study Design: Parallel RCT Region: Australia/New Zealand Setting: Primary care Industry Funded: Unclear Treatment Duration supplement(s): 42 Treatment DurationCVD Drug(s): 42 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): Captopril Drug Category: RAAS Antagonist: ACEI Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s): Cardiovascular indication	N: 28 Supplement(s): Fish oils/marine oils Form of Administration: Capsule/Tablet Daily Dose: 5000mg	N1 = 28 Placebo	Non-CVD Medications: NR Dietary Intervention(s): low/vs/normal sodium diet Exercise Intervention(s): No Other Lifestyle Intervention(s): No
Isley 2007[31]	N screened: 100 N included/randomized: 36 Age: 49.93 %female: 31 Ethnicity: NR Comorbidities (other than indication(s) for CVDs: NR	Study Design: Parallel RCT Region: NR, likely North America Setting: NR	Generic Name(s): ASA Drug Category: Antiplatelets Mode of Administration: Oral Mean Daily Dose: 325mg Reason for taking	N: 8 Supplement(s): Omega-3 (EPA, DHA or both) Form of Administration: Capsule/tablet Daily Dose: 4000mg	N1 = 7 Omega-3 placebo (corn oil ethyl esters 4g/d) +- niacin placebo (Calcium	Non-CVD Medications: ibuprofen or acetaminophen were allowed as needed Dietary Intervention(s):

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors) Inclusion Criteria: Men and postmenopausal or surgically sterile women ages 21 to 70 years were studied; necessary for fasting serum triglyceride levels to be between 150 and 500 mg/dL; A normal chemistry screen was required to exclude secondary hypertriglyceridemia. HDL-C had to be 40 mg/dL for men and 50 mg/dL for women. LDL-C inclusion criteria were based on 1993 National Cholesterol Education Program guidelines: 130mg/dL with CHD; 160mg/dL with two or more risk factors; and 190 mg/dL with one risk factor Exclusion Criteria: Subjects with diabetes mellitus, peptic ulcer disease, gouty arthritis, or hyperuricemia; or known hepatic, renal, autoimmune, or gastrointestinal diseases; taking warfarin, chronic nonsteroidal anti-inflammatory agents, or any medication known to affect lipid metabolism Brief Description: patients with	Industry Funded: No Treatment Duration supplement(s): 135 Treatment DurationCVD Drug(s): 90 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	CVD drug(s): cardiovascular indication +/- Immediate-release niacin tablets (Rugby Laboratories, West Hempstead, NY). Patients Administration: Oral Mean Daily Dose: escalating dose 500-3000 mg x3 /d Reason for taking CVD drug(s): cardiovascular indication		gluconate USP; Roxane Laboratories, Columbus, OH).	Subjects were instructed to follow a low-fat, low-cholesterol diet per the National Cholesterol Education Program Exercise Intervention(s): maintain their usual exercise habits Other Lifestyle Intervention(s): abstain from alcohol excess

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	atherogenic dyslipidemia					
Jiang 2005[32]	N screened: NR N included/randomized: 12 Age: NR %female: 0 Ethnicity: - Caucasian (6) - Asian (6) Comorbidities (other than indication(s) for CVDs: NR CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: All subjects were nonsmokers and were selected on the basis of medical history, physical examination and clinical laboratory test results (including INR, platelet aggregation, creatinine, bilirubin, albumin and total protein) Exclusion Criteria: Subjects with current or past medical conditions that might affect the pharmacokinetic or pharmacodynamic response to warfarin; not taken any medication for at least 2 weeks before commencing the study Brief Description: healthy male subjects	Study Design: Crossover RCT Region: NR likely Australia Setting: Primary Care Industry Funded: No Treatment Duration supplement(s): 7 Treatment DurationCVD Drug(s): 1 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): warfarin Drug Category: Anticoagulants Mode of Administration: Oral Mean Daily Dose: 25mg – 1 dose Reason for taking CVD drug(s):Pharmacokinetics and pharmackodynamic study	N: 12 Supplement(s): Gingko biloba Form of Administration: Capsule/tablet Daily Dose: 12000mg N: 12 Supplement(s): Ginger Form of Administration: Capsule/Tablet Daily Dose: 3600mg	N1 = 12 No treatment	Non-CVD Medications: NA Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Jiang 2004[33]	N screened: NR N included/randomized: 12 Age: NR %female: 0 Ethnicity: - Caucasian (8) - Asian (4) Comorbidities (other than indication(s) for CVDs: NR CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: All subjects were nonsmokers and were selected on the basis of medical history, physical examination, and clinical laboratory test results (including INR, platelet aggregation, creatinine, bilirubin, albumin and total protein) Exclusion Criteria: Subjects with current or past medical conditions that might affect the pharmacokinetic or pharmacodynamic response to warfarin; had not taken any medication for at least 2 weeks before commencing the study Brief Description: healthy male subjects	Study Design: Crossover RCT Region: NR Setting: NR Industry Funded: No Treatment Duration supplement(s): 7 Treatment DurationCVD Drug(s): 1 Duration of Followup: 3 Duration of Longest Followup: 3	Generic Name(s): Warfarin Drug Category: Anticoagulants Mode of Administration: Oral Mean Daily Dose: 25mg – single dose Reason for taking CVD drug(s): Pharmacokinetics and pharmackodynamic study	N: 12 Supplement(s): Ginseng Form of Administration: Capsule/Tablet Daily Dose: 3000mg	N1 = 12 No treatment N2 = 12 non-relevant supplement	Non-CVD Medications: No Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Kaul 1992[34]	N screened: NR N included/randomized: 107 Age: 57.37 %female: 15 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): unstable angina 33.64% CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors) Inclusion Criteria: patients undergoing coronary angioplasty Exclusion Criteria: history of bleeding disorder;on oral anticoagulants;emergency angioplasty;recent MI;angioplasty of a saphenous vein bypass graft;angioplasty for restenosis;inability to perform treadmill test Brief Description: patients undergoing coronary angioplasty	Study Design: Parallel RCT Region: Rest of Asia Setting: Primary care Industry Funded: Unclear Treatment Duration supplement(s): 180 Treatment DurationCVD Drug(s): 180 Duration of Followup: 0 Duration of Longest Followup: 180	Generic Name(s): NR Drug Category: Calcium channel blockers Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s): Generic Name: ASA Drug Category: Antiplatelets Mode of Administration: Oral Mean Daily Dose: 150 mg Reason for taking CVD drug(s): Cardiovascular indication Generic Name: heparin Drug Category: anticoagulants Mode of administration: IV Mean daily dose: 1000 units/hour for 24 hours (max. 20,000 units)	N: 58 Supplement(s): Fish oils/marine oils Form of Administration: Capsule/Tablet Daily Dose: 10 capsules given to patients, daily dose NR	N1 = 49 No treatment	Non-CVD Medications: NA Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Kim 2010[35]	N screened: NR N included/randomized: 24 Age: 24.1 %female: 0 Ethnicity: Asian (100) Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: Unclear Inclusion Criteria: Healthy males, confirmed by physical exam and lab testing Exclusion Criteria: Those outside 80%-120% of ideal weight Brief Description: Healthy, adult, Korean males	Study Design: Crossover RCT Region: East Asia Setting: General community Industry Funded: Yes Treatment Duration supplement(s): single dose Treatment DurationCVD Drug(s): Single dose Duration of Followup: 2 Duration of Longest Followup: NA	Generic Name(s): Ticlopidine Drug Category: Antiplatelets Mode of Administration: Oral Mean Daily Dose: 250mg single dose Reason for taking CVD drug(s):Pharmacokinetics and pharmackodynamic study	N: 12 Supplement(s):Gingko Biloba Form of Administration: Capsule/Tablet Daily Dose: 80mg single dose	N1 = 12 No treatment	Non-CVD Medications: None Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No
Lee 2008[36]	N screened: 200 N included/randomized: 34 Age: 63.73 %female: 44 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): Hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia	Study Design: Parallel RCT Region: East Asia Setting: Primary Care Industry	Generic Name(s): Warfarin Drug Category: Anticoagulants Mode of Administration: Oral Mean Daily Dose: 3.5mg Reason for taking CVD	N: 12 Supplement(s): Ginseng Form of Administration: aqueous extracts Daily Dose: 1500mg	N1 = 13 No treatment	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	CHD Risk Level: high risk for CHD Inclusion Criteria: patients with ischemic stroke who received care between Mar 2007 and Aug 2007 in the Korean Medical Hospital, Kyung Hee University Medical Center; diagnosis of stroke was defined as an acute focal or global neurologic deficit lasting more than 24 hrs without an apparent cause other than one of vascular origin, subsequently confirmed by brain CT or MRI scan within 72 hours from onset of the symptoms; Subjects were required to have scores of 3 or more on the Glasgow Outcome Scale Exclusion Criteria: hepatic disease (alanine,aminotransferase and aspartate >2x the upper limit of laboratory normal range); history or presence of renal insufficiency (creatinine> 1.2mg/dL);hematologic abnormalities(thrombocytopenia,low granulocyte count, anemia, hypofibrinogenemia, hemophilia, vascularpurpura, hemopathy with prolongation of bleeding time, a baseline INR above the normal range [more than 1.4]); condition liable to interfere with the absorption, metabolism,or excretion of warfarin; positive test result for hepatitis (B and C) except for vaccinated patients; positive HIV test on admission lab; taking medications such as aspirin and clopidogrel Brief Description: patients with histories	Funded: No Treatment Duration supplement(s): 14 Treatment DurationCVD Drug(s): 14 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	drug(s):Pharmacokinetics and pharmackodynamic study			Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	of ischemic stroke					
Liu 2003[37]	N screened: NR N included/randomized: 88 Age: 60 %female: 69.3 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: Mixed - all participants were hyperlipidemic and subjects with obesity, high BMI, high blood pressure or insulin resistance were not excluded Inclusion Criteria: adults with hyperlipidemia, fasting TC > 6.2 mmol/L and/or fasting TG >1.8 mmol/L. Subjects with obesity, high BMI, high blood pressure or insulin resistance were not excluded Exclusion Criteria: Subjects with previously known lipid changes undergoing treatment; allergy to statins; diabetes mellitus; liver or renal disease; other diseases that might influence lipid metabolism; pregnant women; articipation in another drug study during the last month; treatment with antimycotic drugs or antibiotics that might interfere with the effects of statins; other drugs that may influence lipid metabolism; cancer or other serious diseases. Brief Description: Adults with hyperlipidemia	Study Design: Parallel RCT Region: NR (likely Europe) Setting: Industry Funded: Unclear Treatment Duration supplement(s): 84 Treatment DurationCVD Drug(s): 84 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): simvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: 10gmay Reason for taking CVD drug(s): Cardiovascular indication	N: 29 Supplement(s): Fish oils/marine oils Form of Administration: Capsule/Tablet Daily Dose: 9.2g	N1 = 18 No treatment N2 = 22 Low fat diet N3 = 19 Fish oil	Non-CVD Medications: NR Dietary Intervention(s): decrease intake of fat milk, cream, and fat cheese Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Lungershausen 1994[38]	N screened: NR N included/randomized: 43 Age: 61 %female: 69 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: Unclear Inclusion Criteria: uncomplicated essential hypertension being treated with monotherapy (b-blocker and/or diuretic) Exclusion Criteria: history of unstable heart, renal or liver disease, or DBP exceeding 105mmHg consumed more than 20 cigarettes or 40g alcohol per day or exercised erratically Brief Description: volunteers with uncomplicated essential hypertension controlled by monotherapy with beta-blocker or diuretic or combination of 2	Study Design: Crossover RCT Region: Australia/New Zealand Setting: Other (recruited by GP) Industry Funded: Yes Treatment Duration supplement(s): 42 Treatment DurationCVD Drug(s): 42 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): NR NR Drug Category: b-blockers Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s): Cardiovascular indication	N: 42 Supplement(s): Fish oils/marine oils Form of Administration: Capsule/Tablet Daily Dose: 4000mg	N1 = 42 Placebo	Non-CVD Medications: NA Dietary Intervention(s): told to maintain constant diet and avoid fatty fish Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Mabuchi 2007[39]	N screened: NR N included/randomized: 49 Age: 60.49 %female: 71 Ethnicity: Asian (100) Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors) Inclusion Criteria: hypercholesterolemic (above 220 mg/dL) Exclusion Criteria: pregnant or lactating women; patients with familial hypercholesterolemia; Patients taking other lipid-lowering drugs; patients taking antioxidants Brief Description: Japanese hypercholesterolemic	Study Design: Parallel RCT Region: East Asia Setting: Not reported Industry Funded: Yes Treatment Duration supplement(s): 112 Treatment DurationCVD Drug(s): 112 Duration of Followup: 28 Duration of Longest Followup: 28	Generic Name(s): atorvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: 10mg Reason for taking CVD drug(s): Cardiovascular indication	N: 24 Supplement(s): Coenzyme Q10 Form of Administration: Capsule/Tablet Daily Dose: 100mg	N1 = 25 Placebo	Non-CVD Medications: NA Dietary Intervention(s): less than 300 mg of low cholesterol diet Exercise Intervention(s): No Other Lifestyle Intervention(s): No
Macan 2006[40]	N screened: 66 N included/randomized: 52 Age: 55.4 %female: 66.6 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): Type II Diabetes, hypertension, hypercholesterolemia (portion NR) CHD Risk Level: At high risk for CHD	Study Design: Parallel RCT Region: NR (likely North America) Setting: Not reported Industry Funded: No Treatment Duration supplement(s): 84	Generic Name(s): Warfarin Drug Category: Anticoagulants Mode of Administration: NR Mean Daily Dose: NR Reason for taking CVD drug(s): Cardiovascular indication	N: 22 Supplement(s): Garlic Form of Administration: Liquid Daily Dose: 10ml	N1 = 26 Placebo	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	Inclusion Criteria: participants diagnosed with deep vein thrombosis, valvular heart disease, atrial fibrillation, or those with prosthetic heart valves. 18 years or older, on warfarin therapy. Exclusion Criteria: any significant medical conditions other than those mentioned, such as the presence of a terminal disease that could shorten the lifespan of the patient (e.g. cancer), a mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study, a history of hypersensitivity to garlic or study medication, the presence of anemia (<32 mg %) thrombocytopenia (platelets <75,000/mm3), current drug abuse, active bleeding, uncontrolled hypertension, prior treatment with garlic or any related products within 3 months, and treatment with any investigational drugs within 30 days prior to signing the consent. Brief Description: adults on warfarin therapy diagnosed with deep vein thrombosis, valvular heart disease, atrial fibrillation, or those with prosthetic heart valves	Treatment DurationCVD Drug(s): 84 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period				
Maki 2008[41]	N screened: 98 N included/randomized: 40 Age: 58 %female: 64 Ethnicity: - Caucasian (97) - Asian (3)	Study Design: Crossover RCT Region: North America Setting: Speciality clinic Industry Funded: Yes Treatment	Generic Name(s): Simvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose:	N: 20 Supplement(s): Omega-3 Form of Administration: Capsule/Tablet Daily Dose: 4000mg	N1 = 20 Placebo	Non-CVD Medications: NA Dietary Intervention(s): Therapeutic Lifestyle Changes diet

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors) Inclusion Criteria: Subjects with mixed dyslipidemia (defined as a mean fasting triglyceride level of 200 to 600 mg/dl and a non-HDL cholesterol level higher than the subject's National Cholesterol Education Program Third Adult Treatment Panel goal); Nonpregnant, nonlactating women who were not planning on becoming pregnant during study period Exclusion Criteria: Recent history of CV event, or revascularization procedure; presence or recent resection of an aortic aneurysm; a lipoprotein lipase impairment or deficiency,known apolipoprotein (apo) CII deficiency, or familial dysbetalipoproteinemia; significant renal (creatinine >=2.0 mg/dl), pulmonary, hepatic, biliary, or gastrointestinal disease;increased liver enzymes(1.5 times the upper limit of normal); history of pancreatitis; recent history of cancer (except nonmelanoma skin cancer); symptoms of unexplained muscle pain, tenderness or weakness, myopathy, or rhabdomyolysis; or a body mass index 40.0 kg/m2;poorly controlled hypertension; or poorly controlled diabetes Brief Description: Subjects with mixed dyslipidemia	Duration supplement(s): 42 Treatment DurationCVD Drug(s): 42 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	20mg Reason for taking CVD drug(s): Cardiovascular indication			Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Manuel 2004[42]	N screened: 32 N included/randomized: 24 Age: 51 %female: 13.7 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): T1DM CHD Risk Level: At high risk for CHD Inclusion Criteria: Inclusion criteria were total cholesterol > 4.9 and LDL cholesterol > 3.0 mmol/L but Triglycerides < 4.5 mmol/L) and normal blood levels of thyroxin (9.7-23.4 pmol/L) and TSH (0.4-4.0 uU/mL). Exclusion Criteria: NR Brief Description: T1DM patients with high cholesterol	Study Design: Parallel RCT Region: Europe Setting: Speciality clinic Industry Funded: Unclear Treatment Duration supplement(s): 183 Treatment DurationCVD Drug(s): 183 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): Atorvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: 20mg Reason for taking CVD drug(s): Cardiovascular indication	N: 11 Supplement(s): Vitamin E Form of Administration: Capsule/tablet Daily Dose: 750IU	N1 = 11 Placebo	Non-CVD Medications: NR Dietary Intervention(s): standard diet for diabetes recommending 7.5 to 8.5 MJ (50% of the energy as carbohydrates, 20% as protein and 30% as fats). This diet assures a daily intake of at least 3 mg Vitamin E, 3000mg Vitamin A, 150 mg Vitamin C and 26 mg flavonoids. Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Mauro 2003[43]	N screened: NR N included/randomized: 8 Age: 23 %female: 12.5 Ethnicity: NR Comorbidities (other than indication(s) for CVDs: No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: healthy adult volunteers aged 20 to 35 years willing to sign an informed consent document; All volunteers needed to pass a physical examination, have normal blood and urine chemistry results (SMA-20, CBC, coagulation panel, and urine analysis), a normal electrocardiogram, and, if female, a negative serum pregnancy test. Exclusion Criteria: a history of psychiatric, cardiovascular, renal, gastrointestinal, hepatic, thyroid, neurologic, hematologic, or pulmonary disease; were on medication, had a history of alcohol or drug abuse, a hypersensitivity to digoxin or herbal medications, or a history of chronic smoking or had smoked within the past year. Brief Description: young healthy adults	Study Design: Crossover RCT Region: North America Setting: Primary Care Industry Funded: Unclear Treatment Duration supplement(s): 8 Treatment DurationCVD Drug(s): 1 Duration of Followup: 1.5 Duration of Longest Followup: 1.5	Generic Name(s): Digoxin Drug Category: Inotropics Mode of Administration: Oral Mean Daily Dose:0.5mg – single dose Reason for taking CVD drug(s):Pharmacokinetics and pharmackodynamic study	N: 8 Supplement(s): Gingko Biloba Form of Administration: Capsule/Tablet Daily Dose: 240mg	N1 = 8 No treatment	Non-CVD Medications: Subjects not on any medications Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
McDowell 1994[44]	N screened: NR N included/randomized: 24 Age: 43.8 %female: 37.5 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): Not reported CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: Type IIa hyperlipidaemia Exclusion Criteria: Taking regular medication for angina or hypertension oxidation Brief Description: Patients with Type IIa hyperlipidaemia	Study Design: Parallel RCT Region: Europe Setting: Primary care Industry Funded: Unclear Treatment Duration supplement(s): 28 Treatment DurationCVD Drug(s): 28 Duration of Followup: 28 Duration of Longest Followup: 28	Generic Name(s): simvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: 20mg Reason for taking CVD drug(s): Cardiovascular indication	N: 8 Supplement(s): Vitamin E Form of Administration: Capsule/Tablet Daily Dose: 400IU	N1 = 8 Placebo N2 = 8 No treatment	Non-CVD Medications: NR Dietary Intervention(s): NR Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
McKenney 2006[45]	N screened: NR N included/randomized: 24 Age: 30 %female: 16.7 Ethnicity: - Caucasian (16.7) - Hispanic (83.3) Comorbidities (other than indication(s) for CVDs: No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: healthy male or female volunteers, aged 18 to 55 years and within 15% of ideal weight according to the 1983 Metropolitan Life Insurance Tables; nonsmokers for at least 3 months; Female subjects were required to be past menopause by more than 2 years, sexually abstinent, or using an acceptable method of birth control. Exclusion Criteria: Persons with a history of hypersensitivity or idiosyncratic reaction to HMG-CoA reductase inhibitors or lipid-regulating agents, or allergy or sensitivity to fish; Persons who had used drugs or substances known to be strong inhibitors or inducers of CYP enzymes within 10 days (inhibitors) or 28 days (inducers) of the first dose Brief Description: healthy adults	Study Design: Crossover RCT Region: NR, likely North America Setting: Research Unit Industry Funded: Yes Treatment Duration supplement(s): 14 Treatment DurationCVD Drug(s): 14 Duration of Followup: 1 Duration of Longest Followup: 1	Generic Name(s): Simvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: 80mg Reason for taking CVD drug(s): exploratory analysis of the effects of P-OM3 on blood coagulation and/or platelet aggregation	N: 24 Supplement(s): Omega-3 (EPA, DHA or both) Form of Administration: Capsule/Tablet Daily Dose: 4000mg	N1 = 24 No treatment	Non-CVD Medications: hormonal contraceptives; hormone replacement therapy allowed (portion NR) Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Meyer 2007[46]	N screened: NR N included/randomized: 45 Age: 56.66 %female: 33 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): Not reported CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: subjects on stable statin treatment for hypercholesterolaemia (i.e. already taking statin drug for at least 3 months and expecting to continue on the same dosage during the study period) who had persistent hypertriglyceridaemia (greater than 1.6 mmol/L). Exclusion Criteria: NR Brief Description: subjects on stable statin treatment for hypercholesterolaemia (i.e. already taking statin drug for at least 3 months	Study Design: Parallel RCT Region: Australia/New Zealand Setting: Not reported Industry Funded: Unclear Treatment Duration supplement(s): 183 Treatment DurationCVD Drug(s): 183 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): 19 pts were taking simvastatin, 13 atorvastatin, 4 pravastatin, 2 cerivastatin and 2 luvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s): Cardiovascular indication	N: 30 Supplement(s): Omega-3 Form of Administration: Capsule/Tablet Daily Dose: 4000mg or 8000mg	N1 = 15 Placebo	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Micheletta 2004[47]	N screened: NA N included/randomized: 16 Age: 60.9 %female: 35 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At high risk for CHD Inclusion Criteria: patients with carotid atherosclerosis having a lumen stenosis >70% and eligible for carotid endarterectomy Exclusion Criteria: acute and chronic liver disease, cancer, malabsorption syndrome, prior stomach surgery, renal failure, and the use of any supplements containing vitamin E, vitamin C, carotenoids, or iron in the 30 days before the study. Brief Description: patients with carotid atherosclerosis	Study Design: Parallel RCT Region: Europe Setting: Not reported Industry Funded: Yes Treatment Duration supplement(s): 42 Treatment DurationCVD Drug(s): 42 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): ASA or ticlopidin Drug Category: Antiplatelets Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s): Cardiovascular indication	N: 8 Supplement(s): Vitamin E Form of Administration: Capsule/tablet Daily Dose: 900mg	N1 = 8 No treatment	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Miyamoto 2004[48]	N screened: NR N included/randomized: 40 Age: 60.9 %female: 35 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): NR CHD Risk Level: At high risk for CHD Inclusion Criteria: patients with coronary spastic angina, in whom spontaneous angina occurred at rest. Exclusion Criteria: NR Brief Description: Patients with Coronary spastic angina	Study Design: Parallel RCT Region: East Asia Setting: Not reported Industry Funded: No Treatment Duration supplement(s): 30 Treatment DurationCVD Drug(s): 30 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): NR Diltiazem Drug Category: Calcium channel blockers Mode of Administration: Oral Mean Daily Dose: 100 OR 200 mg Reason for taking CVD drug(s): Cardiovascular indication	N: 20 Supplement(s): Vitamin E Form of Administration: Capsule/Tablet Daily Dose: 400mg	N1 = 20 Placebo	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Mohammed Abdul 2008[49]	N screened: 23 N included/randomized: 16 Age: 23 %female: 0 Ethnicity: - Caucasian (58.3) - Asian, including 3 Indians (41.7) Comorbidities (other than indication(s) for CVDs: No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: nonsmoking, not taking any medicines including herbal/vitamin supplements for at least 2 weeks and aged 18-34 years Exclusion Criteria: any medical condition that could alter warfarin effects, including any clotting disorders, hepatic dysfunction or platelet dysfunction Brief Description: healthy males	Study Design: Crossover RCT Region: Australia/New Zealand Setting: Primary Care Industry Funded: No Treatment Duration supplement(s): 21 Treatment DurationCVD Drug(s): 1 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): Warfarin Drug Category: Anticoagulants Mode of Administration: Oral Mean Daily Dose: 25mg – single dose Reason for taking CVD drug(s): pharmacokinetics and pharmacodynamics	N: 4 Supplement(s): Garlic Form of Administration: Capsule/Tablet Daily Dose: 4000mg	N1 = 4 No treatment N2 = 4 non-relevant supplement N3 = 4 Intervention3: non-relevant supplement	Non-CVD Medications: hormonal contraceptives; hormone replacement therapy allowed (portion NR) Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Motoyama 1998[50]	N screened: NR N included/randomized: 60 Age: 60.3 %female: 49 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): Not reported CHD Risk Level: At high risk for CHD Inclusion Criteria: Patients with coronary spastic angina in whom spontaneous angina occurred at rest Exclusion Criteria: NR Brief Description: Patients with angina	Study Design: Parallel RCT Region: East Asia Setting: Not reported Industry Funded: No Treatment Duration supplement(s): NR Treatment DurationCVD Drug(s): NR Duration of Followup: 30 Duration of Longest Followup: NR	Generic Name(s): NR Diltiazem Drug Category: Calcium channel blockers Mode of Administration: Oral Mean Daily Dose: 200mg Reason for taking CVD drug(s): Cardiovascular indication	Supplement(s): Vitamin E Form of Administration: Capsule/Tablet Daily Dose: 300mg	Placebo (not described)	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Mueller 1991[51]	N screened: NR N included/randomized: 12 Age: 29.67 %female: 41.7 Ethnicity: NR Comorbidities (other than indication(s) for CVDs: No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: healthy adult volunteers who provided informed consent Exclusion Criteria: Pregnant women, anyone with a known allergy to aspirin or fish, and those taking aspirin, NSAIDs, or oral anticoagulants for a concurrent medical condition; Subjects with known platelet or coagulation disorders and subjects with thrombocytopenia, defined as a platelet count of less than 150,000/mm3 at baseline; those receiving ethanol Brief Description: healthy adults	Study Design: Parallel RCT Region: NR Setting: NR Industry Funded: Unclear Treatment Duration supplement(s): 21 Treatment DurationCVD Drug(s): 1 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): ASA Drug Category: Antiplatelets Mode of Administration: Oral Mean Daily Dose: 325mg - single dose Reason for taking CVD drug(s): bleeding-time changes associated with aspirin in normal volunteers who ingest omega-3s	N: 6 Supplement(s): Omega-3 (EPA, DHA or both) Form of Administration: Capsule/tablet Daily Dose: 8000mg	N1 = 6 Placebo	Non-CVD Medications: NR Dietary Intervention(s): subjects asked not to change diet Exercise Intervention(s): subjects asked not to change exercise Other Lifestyle Intervention(s): subjects asked not to change lifestyle

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Napoli 1998[52]	N screened: NR N included/randomized: 220 Age: 37.2 %female: 36 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): Not reported CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: hypercholesterolemia and normal concentrations of triglycerides, Exclusion Criteria: evidence of renal, liver, or endocrine diseases, type I, IIb, III, IV, V, hyperlipoproteinemia, recent MI or apoplexy (<4 months), unstable angina pectoris, surgery within the previous 4 months, severe or mild heart failure, DM or fasting glycemia (blood glucose >150mg/dl), chronic pancreatitis, porphyria, lupus erythematosus, alcoholism, patients receiving active treatment with fish oil preparations, corticosteroid, estrogens, androgens, quinidine, coumarinic derivatives, theophylline, barbituates, aluminum salts, laxatives, thiazitic diuretics and other hypolipidemic drugs and any who were hypersensitive to drugs, potentially pregnant, or breast feeding Brief Description: hypercholesterolemic patients with normal concentrations of triglycerides	Study Design: Parallel RCT Region: Europe Setting: Primary care Industry Funded: Yes Treatment Duration supplement(s): 84 Treatment DurationCVD Drug(s): 84 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): Pravastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: 20-40mg Reason for taking CVD drug(s): Cardiovascular indication	N: 60 Supplement(s): Vitamin E Form of Administration: Capsule/Tablet Daily Dose: 100mg	N1 = 52 no treatment N2 = 52 Placebo	Non-CVD Medications: NR Dietary Intervention(s): American Heart Association Step I diet Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Neil (2010)[53]	N screened: NR N included/randomized: Age: 64 (SD 11.5) %female: 41.6 Ethnicity: NR Comorbidities (other than indication(s) for CVDs CHD Risk Level: at high risk of CHD Inclusion Criteria: Type 2 diabetes for at least 3 months; 18 years of age or older; no known CVD events; not thought by their general practitioner to be at high enough CVD risk to require immediate lipid-lowering therapy Exclusion Criteria: Taking lipid lowering therapy; plasma triglycerides > 8 mmol/L; impaired hepatic function (ALT > 2 times upper limit of normal range); uncontrolled diabetes (HbA1c > 10%); uncontrolled hypertension (bp > 160/100 mm Hg); elevated creatine kinase (> 3 times upper limit of normal) Brief Description: Patients with type 2 diabetes and no known CVD events.	Study Design: Parallel RCT Region: NR Setting: primary care Industry Funded: Yes (funded by Pfizer) Treatment Duration supplement(s): 120 days Treatment Duration$_{CVD\ Drug(s)}$: similar to dietary treatment Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): Lipitor/ atorvastatin Drug Category: Antilipidemic (HMG Co-A Reductase Inhibitor) Mode of Administration: Oral Mean Daily Dose: 20 mg/d Reason for taking CVD drug(s): cardiovascular indication	N: 163 Supplement(s): omega-3 fatty acids Form of Administration: Capsule/Tablet Daily Dose: 2 g/day	N_1 = 169 no treatment N_2 = None	Non-CVD Medications: NR Dietary Intervention(s): None Exercise Intervention(s): None Other Lifestyle Intervention(s): None **Note:** This study has four groups (double placebo; atorvastatin alone; omega-3 alone; and atorvastatin + omega-3. Only the atorvastatin alone and atorvastatin+omega-3 groups have been extracted.

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Nordoy 2000[54]	N screened: NR N included/randomized: 41 Age: 46.75 %female: 29.2 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): Type II diabetes (2) CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: combined hyperlipemia Exclusion Criteria: NR Brief Description: patients with combined hyperlipemia	Study Design: Parallel RCT Region: Europe Setting: Speciality clinic Industry Funded: Unclear Treatment Duration supplement(s): 35 Treatment DurationCVD Drug(s): 35 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): Drug Category: Mode of Administration: Oral Mean Daily Dose: Reason for taking CVD drug(s): Cardiovascular indication	N: 21 Supplement(s): Omega-3 Form of Administration: Capsule/Tablet Daily Dose: 4000mg	N1 = 20 Placebo	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Nordøy 2003[55]	N screened: NR N included/randomized: 42 Age: 49.8 %female: 28.5 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): Type II Diabetes (2) CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: patients with hyperlipemia Exclusion Criteria: NR Brief Description: patients with hyperlipemia	Design: Parallel RCT Region: Europe Setting: Speciality clinic Industry Funded: Unclear Treatment Duration supplement(s): 35 Treatment DurationCVD Drug(s): 35 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): atorvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: 10mg Reason for taking CVD drug(s): Cardiovascular indication	N: 22 Supplement(s): Omega-3 Form of Administration: Capsule/Tablet Daily Dose: 2g	N1 = 20 Placebo	Non-CVD Medications: NR Dietary Intervention(s): given dietary advice by a clinical dietician to adjust their macronutrient intake to comprise 30% (or less) of energy from fat, with no more than 10% of saturated fat, 55-60% from carbohydrate (preferably complex types) and 10-15% of energy from protein. Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Paolisso 1995[56]	N screened: NR N included/randomized: 30 Age: 73.8 %female: 40 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): obese CHD Risk Level: At high risk for CHD Inclusion Criteria: NR Exclusion Criteria: NR Brief Description: elderly patients with CHD	Study Design: Crossover RCT Region: NR Setting: Not reported Industry Funded: Unclear Treatment Duration supplement(s): 120 Treatment DurationCVD Drug(s): 120 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): NR nifedipine Drug Category: Calcium channel blockers Mode of Administration: Oral Mean Daily Dose: 88mg Reason for taking CVD drug(s): Cardiovascular indication	N: NR Supplement(s): Vitamin E Form of Administration: Capsule/Tablet Daily Dose: 900mg	N1 = NR Placebo	Non-CVD Medications: NA Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Paolisso 1992[57]	N screened: NR N included/randomized: 18 Age: 64 %female: 50 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: hypertensive patients receiving long term (>1 year) thiazide treatment, (benign essential hypertension) Exclusion Criteria: renal impairment, papilloedema, family history of diabetes or drug use known to interfere with glucose metabolism for at least 4 weeks. Brief Description: hypertensive patients receiving thiazide treatment	Study Design: Parallel RCT Region: NR (likely Europe) Setting: Not reported Industry Funded: Unclear Treatment Duration supplement(s): 56 Treatment DurationCVD Drug(s): 56 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): hydrochlorthiazide Drug Category: Diuretic: Thiazide/Thiazide-like Mode of Administration: Oral Mean Daily Dose: 25mg Reason for taking CVD drug(s): Cardiovascular indication	N: 9 Supplement(s): Magnesium Form of Administration: Capsule/Tablet Daily Dose: 4500mg	N1 = 9 Placebo	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Playford 2003[58]	N screened: NR N included/randomized: 40 Age: 53.1 %female: 30 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At high risk for CHD Inclusion Criteria: Patients with type 2 diabetes and dyslipidaenua (fasting triglycerdie > 1.8mmol/l or HDL-cholesterol < 1.0 mmol/l, totalcholesterol < 6.5 mmol/l, total cholesterol/HDL-cholesterol ratio >4 Exclusion Criteria: age > 75 years, BMI > 40kg/m2, history of CV event, insulin therapy, smloking, macroalbuminuria, creatinemia (> 150micromol/l), abnormal liver or muscle enzymes, use of antioxidants and lpid-regulators, hypertension (>160/90 mmHg), habitual alcohol intake > 3 standard drinks or treatment with angiotensin-converting-enzyme inhibitors and calcium antagonists. Brief Description: Diabetic subjects with dyslipidaemia	Study Design: Parallel RCT Region: Australia/New Zealand Setting: Not reported Industry Funded: No Treatment Duration supplement(s): 84 Treatment DurationCVD Drug(s): 84 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): NR Fenofibrate Drug Category: Antilipidemic: Fibrate Mode of Administration: Oral Mean Daily Dose: 200mg Reason for taking CVD drug(s): Cardiovascular indication	N: 20 Supplement(s): Coenzyme Q10 Form of Administration: NR Daily Dose: 200mg	N1 = 20 Placebo	Non-CVD Medications: NR Dietary Intervention(s): patients were on an isocalroic fat-modified diet for the 6 week run-in period Exercise Intervention(s): No Other Lifestyle Intervention(s): No
Reyes 1984[59]	N screened: NR N included/randomized: 21 Age: 56.7 %female: 80.9 Ethnicity:	Study Design: Parallel RCT Region: NR (likely Africa) Setting: NR Industry Funded:	Generic Name(s): hydrochlorothiazide Drug Category: Diuretic: Thiazide/Thiazide-like Mode of	N: 13 Supplement(s): Magnesium Form of Administration: Capsule/Tablet	N1 = 8 Placebo	Non-CVD Medications: NR Dietary Intervention(s): No Exercise

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	- Caucasian (100) Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: supine diastolic arterial pressures of 100 to 140 mmHg, recorded on at least two occasions separated by 7 days preceding the onset of therapy Exclusion Criteria: patients with one or more of the following: i) secondary or renal hypertension; ii) congestive cardiac failure; iii)a history or clinical evidence of cerebrovascular impairment, including retinal haemorrages; iv) evidence of renal impairment defined as a serum creatinine level of more than 1.5 mg/dl v) hyper- or hypokalemia, arbitrarily defined by limits of 5.5 and 3.5 mol/l with a history or clinical evidence of gout vii) a history or clinical evidence of hepatic insufficiency viii) coronary insufficiancy ix)diabetes mellitus x) rheumatic conditions requiring drug therapy xi) any severe systemic disease likely to interfere with objectives of the study xii) pregnant women xiii) lactating mothers xiv) patients considered uncooperative in terms of compliance. Brief Description: Caucasian ambulant patients with moderate to severe uncomplicated hypertension	Unclear Treatment Duration supplement(s): 21 Treatment DurationCVD Drug(s): 21 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Administration: Oral Mean Daily Dose:50mg Reason for taking CVD drug(s): Cardiovascular indication	Daily Dose: 15.78 mmol MgCl2		Intervention(s): No Other Lifestyle Intervention(s): No
Roth 2009[60]	N screened: 596	Study Design:	Generic Name(s):		N1 = 82	Non-CVD

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	N included/randomized: 167 Age: 52.04 %female: 73.6 Ethnicity: - Caucasian (88.6) - African-American (1.8) - Hispanic (7.2) - Other, not specified (6.6) Comorbidities (other than indication(s) for CVDs): DM, high BMI CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: Hypertriglyceridemic men and women (fasting TG </=500 - </= 1300 mg/dL) aged 18-79 years, with BMI >/= 25 kg/m2 and </=43 kg/m2 Exclusion Criteria: use of warfarin, cyclic sex hormone tx, or other agents known to affect lipid levels during the run-in or tx, use of cyclosporine, systemic or high dose topical corticosteroids, androgens, phenytoin, isotretinoin, or thyroid hormones (except stable-dose replacement tx- 60 days prior to day 42. While on tx also excluded pts with sensitivity to seafood/fish, fibrates, EPA or DHA in addition to any history of pancreatitis, sig. renal, hepatic, biliary, or GI disease, type 1 DM, or uncontrolled type 2 DM, pregnant women, lactating, or childbearing potential; a medically approved method of contraception were also excluded Brief Description: subjects with very high	Parallel RCT Region: North America Setting: NR Industry Funded: Yes Treatment Duration supplement(s): 56 Treatment DurationCVD Drug(s): 56 Duration of Followup: 56 Duration of Longest Followup: 56	fenofibrates Drug Category: Antilipidemic: Fibrate Mode of Administration: Oral Mean Daily Dose:130mg Reason for taking CVD drug(s): Cardiovascular indication	N: 81 Supplement(s): Omega-3 Form of Administration: NR Daily Dose: 4000mg	No treatment	Medications: NR Dietary Intervention(s): a diet run in period; reinforced NCEP TLC diet during the tx period Exercise Intervention(s): maintaining currect physical activity Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	TG levels (> or =500 mg/dL)					
Sconce 2007[61]	N screened: NR N included/randomized: 70 Age: NR %female: 50 Ethnicity: Caucasian(100) Comorbidities (other than indication(s) for CVDs): Not reported CHD Risk Level: At high risk for CHD Inclusion Criteria: target international normalized ratio (INR) range of 2.0 to 3.0, had been taking warfarin for at least 9 months, and were defined as having unstable control Exclusion Criteria: Those patients whose instability was deemed to be due to poor adherence to warfarin therapy, changes in concurrent medication, comorbidity, or irregular and excessive alcohol consumption Brief Description: Patients with atrial fibrillation anticoagulated with warfarin for thromboembolic prophylaxis	Study Design: Parallel RCT Region: Europe Setting: Speciality clinic Industry Funded: Unclear Treatment Duration supplement(s): 180 Treatment DurationCVD Drug(s): 180 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): warfarin Drug Category: anticoagulants Mode of Administration: Oral Mean Daily Dose: NR (various starting and ending dosages) Reason for taking CVD drug(s): Cardiovascular indication	N: 35 Supplement(s): Vitamin K Form of Administration: Capsule/Tablet Daily Dose: 0.15mg	N1 = 33 Placebo :	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No
Steiner 1995[62]	N screened: NR N included/randomized: 100 Age: 71 %female: 58 Ethnicity: NR Comorbidities (other than indication(s)	Study Design: Parallel RCT Region: NR (likely North America) Setting: Not reported Industry	Generic Name(s): ASA Drug Category: Antiplatelets Mode of Administration: Oral Mean Daily Dose: 325mg	N: 52 Supplement(s): Vitamin E Form of Administration: Capsule/Tablet Daily Dose: 400IU	N1 = 48 Placebo (not described)	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	for CVDs): Not reported CHD Risk Level: At high risk for CHD Inclusion Criteria: patients aged 18 y in whom any of the following conditions were diagnosed: 1) minor stroke, a focal ischemic cerebrovascular event that results in a less-than maximal neurologic deficit within the involved vascular distribution; 2) reversible ischemic neurologic deficit (RIND), a focal ischemic cerebrovascular event producing a neurologic deficit that persists for > 24 h but < 3 wk; 3) retinal ischemic event, an acute transient or permanent impairment of visual function caused by retinal ischemia; or 4) transient ischemic attack, a focal cerebrovascular event producing a neurologic deficit that resolves completely within 24 h of its onset. focal neurologic deficit had to occur within 8 wk of enrollment into the study, they had a performance status that allowed them to spend > 50% of their waking hours out of bed, they had no known allergy or contraindication to the use of aspirin or a-tocopherol, had no history of primary or secondary hypercoagulable state, were not using anticoagulants or platelet-active drugs other than aspirin, had no disorder other than atherosclerotic cerebrovascular disease;had no evidence of intracranial hemorrhage and no concurrent medical or signicifant psychiatric disease Exclusion Criteria: NR	Funded: Unclear Treatment Duration supplement(s): 730 Treatment DurationCVD Drug(s): 730 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Reason for taking CVD drug(s): Cardiovascular indication			Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	Brief Description: patients with transient ischemic attacks, minor strokes, or residual ischemic neurologic deficits					
Sutken 2006[63]	N screened: NR N included/randomized: 22 Age: 29.5 %female: 50 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: Hyperlipidemic subjects Exclusion Criteria:Acute illness or severe chronic disease, diabetes, hypertension, angina pectoris or previous MI or peripheral vascular disease, thyroid dysfunction, alcohol intake, smoking, hormonal treatment, lipid-lowering medication, or vitamin or iron supplementation in the last 6 months before admission. Brief Description: Young Hyperlipidemic	Study Design: Controlled clinical trial (CCT) Region: Middle East Setting: Speciality clinic Industry Funded: Unclear Treatment Duration supplement(s): 30 Treatment DurationCVD Drug(s): 30 Duration of Followup: 30 Duration of Longest Followup: NR	Generic Name(s): Gemfibrozil Drug Category: Antilipidemic: Fibrate Mode of Administration: Oral Mean Daily Dose: 1200 mg Reason for taking CVD drug(s): Cardiovascular indication	N: 12 Supplement(s): Vitamin E Form of Administration: NR Daily Dose: 600 mg	N1 = 10 No treatment N2 = 12 Vitamin E	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Sutken 2006[63]	N screened: NR N included/randomized: 45 Age: 71.5 %female: 46.7 Ethnicity: NR Comorbidities (other than indication(s) for CVDs: No CHD Risk Level: At low risk for CHD 90-1 risk factors) Inclusion Criteria: Hyperlipidemic subjects Exclusion Criteria: Acute illness or severe chronic disease, diabetes, hypertension, angina pectoris or previous MI or peripheral vascular disease, thyroid dysfunction, alcohol intake, smoking, hormonal treatment, lipid-lowering medication, or vitamin or iron supplementation in the last 6 months before admission. Brief Description: Elderly hyperlipidemic	Study Design: Controlled Clincal Trial Region: Middle East Setting: Specialty Clinic Industry Funded: Unclear Treatment Duration supplement(s): 30 Treatment DurationCVD Drug(s): 30 Duration of Followup: 30 Duration of Longest Followup: NR	Generic Name(s): Gemfibrozil Drug Category: Antilipidemic: Fibrate Mode of Administration: Oral Mean Daily Dose: 1200 mg Reason for taking CVD drug(s): Cardiovascular indication	N: 20 Supplement(s): Vitamin E Form of Administration: NR Daily Dose: 600 mg	N1 = 23 No treatment N2 = 22 Vitamin E	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Svaneborg 2002[64]	N screened: NR N included/randomized: 14 Age: 31 %female: 0 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: healthy, nonsmoking, nonobese men Exclusion Criteria: NR Brief Description: healthy, nonsmoking, nonobese men	Study Design: Parallel RCT Region: NR (likely Europe) Setting: Not reported Industry Funded: Unclear Treatment Duration supplement(s): 14 Treatment DurationCVD Drug(s): NA Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): ASA Drug Category: Antiplatelets Mode of Administration: Parenteral Mean Daily Dose: 100mg Reason for taking CVD drug(s): Aim was to test platelet function with ASA & n-3s	N: 12 Supplement(s): Fish oils/marine Form of Administration: Capsule/Tablet Daily Dose: 10000mg	N1 = 6 Placebo	Non-CVD Medications: NA Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Tankanow 2003[65]	N screened: 11 N included/randomized: 11 Age: 28 %female: 50 Ethnicity: NR Comorbidities (other than indication(s) for CVDs: No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: age > 18 years, serum creatinine < 1.2 mg/dL, and bilirubin < 1.5 mg/dL Exclusion Criteria: Individuals taking concurrent scheduled medications (excluding oral contraceptives), those with significant medical histories, and smokers and pregnant females Brief Description: Healthy subjects	Study Design: Crossover RCT Region: North America Setting: Primary Care Industry Funded: Unclear Treatment Duration supplement(s): 21 Treatment DurationCVD Drug(s): 10 Duration of Followup: 0.5 Duration of Longest Followup: 3	Generic Name(s): Digoxin Drug Category: Inotropics Mode of Administration: Oral Mean Daily Dose: 0.25mg Reason for taking CVD drug(s):Pharmacokinetics and pharmackodynamic study	N: 8 Supplement(s): Hawthorn Form of Administration: Capsule/Tablet Daily Dose: 900mg	N1 = 8 No treatment	Non-CVD Medications: oral contraceptives not excluded Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No
Watson 1999[66]	N screened: NR N included/randomized: 30 Age: 55 %female: 13 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): Not reported CHD Risk Level: At high risk for CHD	Study Design: Crossover RCT Region: Australia/New Zealand Setting Industry Funded: Unclear Treatment	Generic Name(s): ACE inhibitors (no description) Drug Category: RAAS Antagonist: ACEI Mode of Administration: Oral Mean Daily Dose: NR Reason for taking	N: NR Supplement(s): Coenzyme Q10 Form of Administration: Capsule/Tablet Daily Dose: 99mg	N1 = NR Placebo	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
	Inclusion Criteria: between 18 and 75 years of age with ischemic or idiopathic dilated cardiomyopathy Exclusion Criteria: obstructive valvular heart disease, renal (serum creatinine >0.18 mmol/liter-1) or hepatic (serum aspartate or alanine aminotransaminase > upper limit of normal) impairment, a history of alcohol or drug abuse or an inadequate echocardiographic study, or if they were pregnant Brief Description: between 18 and 75 years of age with ischemic or idiopathic dilated cardiomyopathy	Duration supplement(s): 84 Treatment DurationCVD Drug(s): 84 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	CVD drug(s): Cardiovascular indication Generic Name: Furosemide Drug Category: Diuretic: Loop Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s): Cardiovascular indication Generic Name:digoxin, also hydralazine and/or nitrates Drug Category: Inotropics Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s): Cardiovascular indication			

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Wirell 1994[67]	N screened: NR N included/randomized: 40 Age: 35.4 %female: 23 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: mild to moderate essential hypertension Exclusion Criteria: Patients treated with drugs containing magnesium, ACE-inhibitors, Ca antagonists, or potassium and magnesium sparing diuretics; s-creatinine >150 mmol L-1 or serum electrolyte disturbances (sodium and potassium) according to hospital normal values; Recent myocardial infarction less than 3 months before study start or cardiac failure class NYHA IV, AV block II or III; pregnancy, malignancies, diabetes mellitus, rheumatic diseases, collagenoses and patients unable to cooperate; DIastolic blood pressure exceeding 110 mmHg and systolic blood pressure exceeding 190 mmHg Brief Description: Patients with mild to moderate essential hypertension	Study Design: Crossover RCT Region: Europe Setting: Speciality clinic Industry Funded: Unclear Treatment Duration supplement(s): 56 Treatment DurationCVD Drug(s): 56 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): metoprolol Drug Category: b-blockers Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s): Cardiovascular indication Generic Name(s): atenolol Drug Category: b-blockers Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s): Cardiovascular indication Generic Name(s): pindolol & propanolol Drug Category: b-blockers Mode of Administration: Oral Mean Daily Dose: NR Reason for taking CVD drug(s): Cardiovascular indication	N: 19 Supplement(s): Magnesium Form of Administration: Powder mixed with water Daily Dose: 365mg	N1 = 20 Placebo	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Wolf 2006[68]	N screened: NR N included/randomized: 50 Age: 27.2 %female: 0 Ethnicity: - Caucasian (98) - Asian (2) Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: normal laboratory values, had not been taking any medication within the last 3 weeks Exclusion Criteria: Intake of medication containing ASA, anticoagulants,NSAIDs, sulfinpyrazone, ticlopidine and lipid-lowering agents Brief Description: healthy subjects	Study Design: Crossover RCT Region: Europe Setting: General community Industry Funded: Yes Treatment Duration supplement(s): 7 Treatment DurationCVD Drug(s): 7 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): ASA Drug Category: Antiplatelets Mode of Administration: Oral Mean Daily Dose: 500mg Reason for taking CVD drug(s): to determine the influence of EBg761 on the effects of ASA on bleeding time, coagulation parameters and platelet activity	N: 50 Supplement(s): Gingko biloba Form of Administration: Capsule/Tablet Daily Dose: 240mg	N1 = 50 No treatment	Non-CVD Medications: paracetamol (15) and Sinupret (4) Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Yamamoto 1995[69]	N screened: NR N included/randomized: NR Age: 59.6 %female: 22.7 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): No CHD Risk Level: At high risk for CHD Inclusion Criteria: variant angina, angiographically normal- appearing coronary artery after ISDM administration Exclusion Criteria: history of MI, DM, hypertension, heart failure or hyperlipidemia Brief Description: Participants with variant angina	Study Design: Parallel RCT Region: East Asia Setting: Primary care Industry Funded: Yes Treatment Duration supplement(s): 112 Treatment DurationCVD Drug(s): 112 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): diltiazem Drug Category: Calcium channel blockers Mode of Administration: Oral Mean Daily Dose: 90-120mg Reason for taking CVD drug(s): Cardiovascular indication	N: 12 Supplement(s): Omega-3 Form of Administration: Capsule/Tablet Daily Dose: 1800mg	N1 = 10 No treatment	Non-CVD Medications: NR Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Young 2007[70]	N screened: NR N included/randomized: 44 Age: 59 %female: 50 Ethnicity: NR Comorbidities (other than indication(s) for CVDs): Type II Diabetes (5) CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: patients with self-reported myalgia who had been unable to continue taking adequate doses of statin therapy Exclusion Criteria: acute myocardial infarction or cerebral vascular accident within 3 months, alanine aminotransferase or aspartate aminotransferase >3 times the upper level of normal, calculated glomerular filtration rate <45 ml/min, decompensated heart failure, warfarin treatment, and antioxidant vitamin supplementation. Brief Description: patients with self-reported myalgia who had been unable to continue taking adequate doses of statin therapy	Study Design: Parallel RCT Region:NR (likely Australia) Setting: Not reported Industry Funded: Unclear Treatment Duration supplement(s): 63 Treatment DurationCVD Drug(s): 63 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): simvastatin Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor Mode of Administration: Oral Mean Daily Dose: Staring 10mg, ending 40mg Reason for taking CVD drug(s): NR	N = 22 Supplement(s): Coenzyme Q10 Form of Administration: Capsule/Tablet Daily Dose: 200mg	N1 = 22 Placebo	Non-CVD Medications: Ezetimibe (4) Dietary Intervention(s): No Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 57. General characteristics of all studies (continued)

Author Year	Population	Study	CVD Drug	Dietary Supplements	Control Group(s)	Other Interventions
Yuan 2004[71]	N screened: NR N included/randomized: 21 Age: 27.84 %female: 55 Ethnicity: - Caucasian (10) - African-American (5) - Hispanic (3) - Asian (2) Comorbidities (other than indication(s) for CVDs: NR CHD Risk Level: At low risk for CHD (0-1 risk factors) Inclusion Criteria: NR Exclusion Criteria: NR Brief Description: Healthy patients	Study Design: Parallel RCT Region: North America Setting: Primary Care Industry Funded: No Treatment Duration supplement(s): 28 Treatment DurationCVD Drug(s): 6 Duration of Followup: End of treatment period Duration of Longest Followup: End of treatment period	Generic Name(s): Warfarin Drug Category: Anticoagulants Mode of Administration: Oral Mean Daily Dose: 5mg Reason for taking CVD drug(s): Pharmacokinetics and pharmackodynamic study	N: 12 Supplement(s): Ginseng Form of Administration: Capsule/Tablet Daily Dose: 2000mg	N1 = 8 Placebo	Non-CVD Medications: NA Dietary Intervention(s): Patients were instructed to eat a balanced diet to maintain a consistent amount of vitamin K and to avoid drastic changes in dietary habits Exercise Intervention(s): No Other Lifestyle Intervention(s): No

Evidence Table 58. Interventions listed in detail for all studies

Author Year	Supplement:	Latin or other names used in this study for the supplement	Supplement Composition	Is purity of the supplement reported?	Is the supplement licensed in the region used?	Does the paper report where the supplement was manufactured?	Have storage conditions for the supplement been reported?	Is the origin of the supplement reported?	What subtype of the supplement was administered?	Are nutrient levels or biomarkers of the supplement reported?
Abdul 2010[1]	Echinacea	E. angustifolia and E. purpurea	600 mg of E. angustifolia roots and 675 mg of E. purpurea root;	No	NR	QLD, Australia	No	roots of E. angustifolia and E. purpurea	NA	Echinacea alkamide content in plasma
Aruna 2007[2]	Gingko biloba	NR	NR	No	NR		No	No	NA	No
Avogaro 1974[3]	Niacin	nicotinic acid	NR	No	NR		No	No	NR	No
Balestrieri 1996[4]	Fish oils/marine oils	ethylester	85% n-3 fatty acids (EPA + DHA ratio 1:1)	No	NR	Esapent-Carlo Erba, Milano Italy	No	No	NR	No
Barbagallo 1999[5]	Vitamin E	NR	NR	No	NR		No	No	NR	plasma vit E
Bays 2009[7]	Omega-3 (EPA, DHA or both)	Lovaza	NR	No	NR	No	No	No	NA	No
Bays 2010[6]	Omega-3 (EPA, DHA or both)	P-OM3 (omega-3-acid ethyl esters)	465mg EHA;375mgDHA	No	NR	No	No	No	NA	No
Bender 1998[8]	Fish oils/marine oils	MaxEPA	NR	No	NR		No	No	NR	No
Bordia 1998[9]	Garlic	NR	NR	No	NR		No	Peeled garlic clves were crushed, extracted in ethyl acetate, the solvent evaporated and the resultant oil dissolved in soy oil. The oil extract of garlic was encapsulated. Each capsule contained oil equivalent of 1g raw garlic.	NR	No

Evidence Table 58. Interventions listed in detail for all studies (continued)

Author Year	Supplement:	Latin or other names used in this study for the supplement	Supplement Composition	Is purity of the supplement reported?	Is the supplement licensed in the region used?	Does the paper report where the supplement was manufactured?	Have storage conditions for the supplement been reported?	Is the origin of the supplement reported?	What subtype of the supplement was administered?	Are nutrient levels or biomarkers of the supplement reported?
Budoff 2004[10]	Garlic	Aged Garlic Extract (AGE), Kyolic	NR	No	NR		No	No	NR	No
Caso 2007[11]	Supp 1: Coenzyme Q10 Supp 2: Vitamin E	Supp 1: Q-Sorb softgel Supp 2: NR	Supp 1: NA Supp 2: NA	Supp 1: No Supp 2: No	Supp 1: NR Supp 2: NR	Supp 1: NY, USA Supp 2: NY, USA	Supp 1: No Supp 2: No	Supp 1: No Supp 2: No	Supp 1: NA Supp 2: NA	Supp 1: No Supp 2: No
Chan 2002[12]	Fish oils/marine oils	Omacor	45% EPA and 39% EHA	No	Yes	Oslo, Norway	No	No	NA	measurements of plasma EPA and DHA levels
d'Arcangues 2004[13]	Vitamin E	Evion	NA	tablets returned to the Merck laboratories for retesting at the end of the trial and their stability over the course of the study was confirmed	NR	Germany	No	No	NA	No
Davidson 1997[15]	Fish oils/marine oils	NR	The Omega FA content of 7.2g of the marine oil supplements used was 3.6g EPA: DHA ratio = 1.5	No	NR	SuperEPA 1200, Advanced Nutritional Technoligy, Inc., Dublin California	No	No	NR	No
Davidson, 2007[14]	Omega-3 (EPA, DHA or both)	omega 3-acid ethyl esters (P-OM3)	465mg EPA; 375mg DHA	No	NR	New Jersey, USA	No	No	NA	No
De, Caterina 2002[16]	Vitamin E	NA	NA	No	NR	Switzerland	No	No	NA	plasma vit E
Dehmer 1988[17]	Omega-3 (EPA, DHA or both)	MaxEPA	3.2g EPA 2.2g DHA in 18 capsules	No	NR	Michigan	No	No	NA	No

Evidence Table 58. Interventions listed in detail for all studies (continued)

Author Year	Supplement:	Latin or other names used in this study for the supplement	Supplement Composition	Is purity of the supplement reported?	Is the supplement licensed in the region used?	Does the paper report where the supplement was manufactured?	Have storage conditions for the supplement been reported?	Is the origin of the supplement reported?	What subtype of the supplement was administered?	Are nutrient levels or biomarkers of the supplement reported?
Desideri 2003[18]	Vitamin E	alpha-tocopherol	NR	No	NR	Roche Molecular Biochemicals, Milan, Italy	No	No	NR	Plasma Vit E concentrations were measured by HPLC according to the well-estalished method of Lee et al. Plamsa vitamin E leveers were expressed both in absolute concentrations and as the ratio of Vitmain E / (total cholesterol + triglycerdies)
Di, Spirito 2008[19]	Omega-3 (EPA, DHA or both)	P-OM3, Lovaza	465 mg of the ethyl ester of eicosapentaenoic acid and 375 mg of the ethyl ester of docosahexaenoic acid	No	NR	North Carolina US	No	No	NA	No
Duffy 2001[20]	Vitamin E	NR	NR	No	NR	Victoria, Australia	No	No	Acetylcholine for vasomotion study; Sodium nitroprusside to assess response to endothelial-independent vasodilator	tocopherol measured by high-performance liquid chromatography

Evidence Table 58. Interventions listed in detail for all studies (continued)

Author Year	Supplement:	Latin or other names used in this study for the supplement	Supplement Composition	Is purity of the supplement reported?	Is the supplement licensed in the region used?	Does the paper report where the supplement was manufactured?	Have storage conditions for the supplement been reported?	Is the origin of the supplement reported?	What subtype of the supplement was administered?	Are nutrient levels or biomarkers of the supplement reported?
Eritsland 1996[21]	Fish oils/marine oils	Omacor	Each soft gelatin capsule contains 1 g of fatty acids (51% eicosapentaenoic acid C20:5n-3 and 32% docosahexaenoic acid C22:6n-3 ethyl esters) and 3.7 mg o-tocopherol as an antioxidant.	No	NR	Pronova AS, Oslo, Norway	No	No	NR	No
Eritsland 1996[21]	Fish oils/marine oils	Omacor	each capsule contained 1 gram fatty acids (51% EPA and 32% DHA) and 3.7 mg alpha-tocopherol	No	NR	Pronova AS, Oslo, Norway	No	fish oil	NR	No
Eritsland 1996[21]	Fish oils/marine oils	n-3 fatty acids	each capsule contained 1 gram fatty acids (51% EPA and 32% DHA) and 3.7 mg alpha-tocopherol	No	NR	Norway	No	fish oil	NR	No
Ferraro 2009[22]	Fish oils/marine oils	PUFA	85% EPA + DHA	No	NR		No	No	NA	No
Gardner 2007 [23]	Gingko biloba	EGb 761	24% Ginkgo flavone glycosides and 6% terpene lactones	No	NR	Springville, Utah by Nature's Way	No	No	NA	No
Garg 1995[24]	Gingko biloba	Ginkgo Biloba Extract	NR	No	NR		No	No	NR	No
Glynn 2007[25]	Vitamin E	alpha-tocopherol	NR	No	NR		No	No	NR	No

Evidence Table 58. Interventions listed in detail for all studies (continued)

Author Year	Supplement:	Latin or other names used in this study for the supplement	Supplement Composition	Is purity of the supplement reported?	Is the supplement licensed in the region used?	Does the paper report where the supplement was manufactured?	Have storage conditions for the supplement been reported?	Is the origin of the supplement reported?	What subtype of the supplement was administered?	Are nutrient levels or biomarkers of the supplement reported?
Gosai 2008[26]	Omega-3 (EPA, DHA or both)	P-OM3	465 mg of the ethyl ester eicosapentaenoic acid and 375 mg of the ethyl ester docosahexaenoic acid	No	Yes	North Carolina, US	No	No	NA	No
Govil 1979[27]	Magnesium	magnesium hydroxide solution	NA	No	NR		No	No	NR	serum magnesium
Hansen 1993[29]	Fish oils/marine oils	fish oil ethyl ester (K-85)	EPA to DHA ratio 1.90	94% n-3 fatty acids	NR	Pronova A/S, Oslo, Norway)	No	No	NR	No
Hajda, J[28](2010)	Garlic extract	GaliPure	GarliPure®, 600mgcaplets from Natrol®, CA, USA containing gamma glutamylcysteines 12,000µg, 4800µg alliin, 3900µg sulfur and 3800µg thiosulfinates resulting in a allicin yield 3600µg	No	Yes	Yes, USA	No	Yes	NA	No
Howe 1994 [30]	Fish oils/marine oils	Lipitac Forte	NR	No	NR	Marker Pharma, Sydney Australia	No	No	NR	No
Isley 2007[31]	Supp 1: Omega-3 (EPA, DHA or both) Supp 2: Niacin	Supp 1: Omacor Supp 2: NR	Supp 1: 85% eicosapentaenoic (EPA) plus docosahexaenoic acids (DHA) Supp 2: NA	Supp 1: No Supp 2: No	Supp 1: NR Supp 2: NR	Supp 1: Norway Supp 2: NY, USA	Supp 1: No Supp 2: No	Supp 1: No Supp 2: No	Supp 1: NA Supp 2: NA	Supp 1: No Supp 2: No

Evidence Table 58. Interventions listed in detail for all studies (continued)

Author Year	Supplement:	Latin or other names used in this study for the supplement	Supplement Composition	Is purity of the supplement reported?	Is the supplement licensed in the region used?	Does the paper report where the supplement was manufactured?	Have storage conditions for the supplement been reported?	Is the origin of the supplement reported?	What subtype of the supplement was administered?	Are nutrient levels or biomarkers of the supplement reported?
Jiang 2004 [33]	Ginseng	Panax ginseng	8.93 mg ginsenosides as ginsenoside Rg1	No	NR		No	No	NA	No
Jiang 2005[32]	Supp 1: Gingko biloba Supp 2: Ginger	Supp 1: Tavonin Supp 2: NR	Supp 1: 2000mg of Ginkgo biloba leaf, 9.6 mg of ginkgo, avonglycosides, 2.4 mg of ginkgolides and bilobalide Supp 2: each capsule containing extract equivalent to 0.4 g of ginger rhizome powder	Supp 1: No Supp 2: No	Supp 1: NR Supp 2: NR	Supp 1: Germany Supp 2: Australia	Supp 1: No Supp 2: No	Supp 1: gingko leaf, avonglycosides and ginkgolides and bilobalide Supp 2: NR	Supp 1: NA Supp 2: NA	Supp 1: No Supp 2: No
Kaul 1992[34]	Fish oils/marine oils	Maxepa	1.8g EPA; 1.2g DHA	No	NR	Hull, UK	No	No	NA	No
Kim 2010[35]	Gingko biloba	NA	204% glycosidic flavonoids + 6% terpenoids	No	NR	Korea	No	No	NA	No
Lee 2008[36]	Ginseng	P. ginseng	NR	The quality was tested according to the Korea Food & Drug Administration and hospital standards (ginsenoside Rb1>0.20%, Rg1>0.10%)	NR	Korea	No	Root was air dried and crushed materials were added to distilled water, and extraction was performed by heating the solution for 4 hours at 100°C	NA	No

Evidence Table 58. Interventions listed in detail for all studies (continued)

Author Year	Supplement:	Latin or other names used in this study for the supplement	Supplement Composition	Is purity of the supplement reported?	Is the supplement licensed in the region used?	Does the paper report where the supplement was manufactured?	Have storage conditions for the supplement been reported?	Is the origin of the supplement reported?	What subtype of the supplement was administered?	Are nutrient levels or biomarkers of the supplement reported?
Liu 2003[37]	Fish oils/marine oils	Eskimo-3	18% eicosapentaenoic acid (EPA, 20:5n-3), 12% docosahexaenoic acid (DHA, 22:6n-3) and a total of 38% of long-chain omega-3 fatty acids and is stabilized by a mixture of natural antioxidants, Pufanox, such as vitamins C and E and lecithin.	No	NR	Cardinova, Uppsala, Sweden	No	No	NR	No
Lungershausen 1994[38]	Fish oils/marine oils	Omacor	1.9g EPA; 1.5g DHA	No	NR	Oslo, Norway	No	No	NR	No
Mabuchi 2007 [39]	Coenzyme Q10	NA	NA	No	NR	Kaneka Co., Osaka, Japan	No	No	NA	No
Macan2006[40]	Garlic	Kyolic (Aged Garlic Extract)	NR	No	NR	Wakunaga of America, Mission Viejo California	No	No	NR	No
Maki 2008[41]	Omega-3 (EPA, DHA or both)	P-OM3	NR	No	NR	New Jersey	No	No	NA	No
Manuel 2004[42]	Vitamin E	d-alpha-tocopherol	NR	No	NR	Omega Pharma, NV, Nazareth, Belgium	No	No	NR	serum vit E

Evidence Table 58. Interventions listed in detail for all studies (continued)

Author Year	Supplement:	Latin or other names used in this study for the supplement	Supplement Composition	Is purity of the supplement reported?	Is the supplement licensed in the region used?	Does the paper report where the supplement was manufactured?	Have storage conditions for the supplement been reported?	Is the origin of the supplement reported?	What subtype of the supplement was administered?	Are nutrient levels or biomarkers of the supplement reported?
Mauro 2003[43]	Gingko biloba	NR	containing 24% ginkgo flavone glycosides	Verification of the flavone content and a general fingerprint of the chemical constituents ethanolic, reversedphase high-performance liquid chromatography (HPLC) assay using UV detection according to a previously described procedure	NR	California	No	leaf extract	NA	No
McDowell 1994[44]	Vitamin E	RRR-alpha-tocopherol	NR	No	NR	Henkel Corporation, Cork, Ireland	No	No	NR	serum alpha-tocopherol
McKenney, 2006[45]	Omega-3 (EPA, DHA or both)	Omacor	NR	No	NR	New Jersey, US	No	No	NA	No
Meyer 2007[46]	Supp 1: Omega-3 (EPA, DHA or both) Supp 2: Omega-3 (EPA, DHA or both)	Supp 1: DHA Supp 2: DHA	Supp 1: 7% EPA, 27% DHA Supp 2: 7% EPA, 27% DHA	Supp 1: No Supp 2: No	Supp 1: NR Supp 2: NR	Supp 1: No Supp 2: No	Supp 1: No Supp 2: No	Supp 1: No Supp 2: No	Supp 1: NA Supp 2: NA	Supp 1: No Supp 2: No
Micheletta 2004[47]	Vitamin E	alpha-tocopherol	NR	No	NR		No	No	NA	serum vit E
Miyamoto 2004[48]	Vitamin E	alpha-tocopherol acetate	NR	No	NR		No	No	NR	No

Evidence Table 58. Interventions listed in detail for all studies (continued)

Author Year	Supplement:	Latin or other names used in this study for the supplement	Supplement Composition	Is purity of the supplement reported?	Is the supplement licensed in the region used?	Does the paper report where the supplement was manufactured?	Have storage conditions for the supplement been reported?	Is the origin of the supplement reported?	What subtype of the supplement was administered?	Are nutrient levels or biomarkers of the supplement reported?
Mohammed Abdul 2008[49]	Garlic	Garliplex 2000	equivalent to 3.71mg of allicin	No	NR	Australia	No	garlic bulb	NA	No
Motoyama 1998[50]	Vitamin E	Alpha-tocopherol acetate	NR	No	NR		No	No	NR	Measurement of flow-dependent vasodilation and blood sampling for assaysof thiobarbituric acid reactive substances (TBARS) and alpha-tocopherol weire performed before and 4 weeks after treatment
Mueller 1991 [51]	Omega-3 (EPA, DHA or both)	Promega	8 g of omega-3 fatty acids and 3.5 g of eicosapentaenoic	No	NR	New Jersey, US	No	No	NA	No
Napoli 1998 [52]	Vitamin E	DL-alpha-tocopherol	NR	No	NR	Walgreen Co., Deerfield Illinois	No	No	NR	No
Neil, HAW	Omega-3 (EPA, DHA or both)	NR	EPA=46%, DHA=38%	No	NR	Yes	No	No	NA	No
Nordoy 2000 [54]	Omega-3 (EPA, DHA or both)	Omacor	EHA=49%, DHA=39%	No	NR		No	No	NR	No
Nordøy 2003[55]	Omega-3 (EPA, DHA or both)	Omacor	ethyl esters of eicosapentaenoic acid (EPA) 45% and docosahexaenoic acid (DHA) 39%	No	NR	Pronova, A/S, Lysaker, Norway	No	No	NR	No
Paolisso 1992 [57]	Magnesium	MAG2	NR	No	NR	Lyrca Synthelabo, Italy	No	No	magnesium pidolate	erythrocyte magnesium
Paolisso 1995[56]	Vitamin E	DL-a-tocopherol acetate/d	NA	No	NR	Milan, Italy	No	No	NA	No

Evidence Table 58. Interventions listed in detail for all studies (continued)

Author Year	Supplement:	Latin or other names used in this study for the supplement	Supplement Composition	Is purity of the supplement reported?	Is the supplement licensed in the region used?	Does the paper report where the supplement was manufactured?	Have storage conditions for the supplement been reported?	Is the origin of the supplement reported?	What subtype of the supplement was administered?	Are nutrient levels or biomarkers of the supplement reported?
Playford 2003[58]	Coenzyme Q10	NR	NR	No	NR	Blackmores, Australia	No	No	NR	Serum CoQ was assayed by reverse-phase HPLC plasma fibrinogen by Clauss reaction adn homocysteine by immunoassay.
Reyes 1984[59]	Magnesium	Slow Mag	2.63 mmol Mg2+	No	NR		No	No	magnesium chloride	No
Roth 2009[60]	Omega-3 (EPA, DHA or both)	prescription Omega-3	NR	No	Yes	Ovaza (Omacor)- US	No	No	NA	No
Sconce 2007[61]	Vitamin K	phytomenadione	20:80 ethanol odeionized water solution	stability and quality control checks	NR	United Kingdom	No	No	NA	plasma vit K
Steiner 1995[62]	Vitamin E	alpha-tocopherol	NR	No	NR		No	No	NR	serum concentration of alpha-tocopherol
Sutken 2006[63]	Vitamin E	NR	NR	No	NR		No	No	NR	Vit E was measured in serum samples that were isolated and were determined according to the Hashim's method.
Svaneborg 2002[64]	Fish oils/marine oils	NR	NR	No	NR	Pronova Biocare, Norway, delivered as Pikasol by Lube, Denmark	No	No	NR	platelet levels of EPA & DHA
Tankanow 2003[65]	Hawthorn	Crataegus	one tablet contained 450 mg dry extract of hawthorn leaves with flowers standardized to 84.3 mg of oligomeric procyanidines	No	NR	Germany	No	hawthorn leaves with flowers	NA	No

Evidence Table 58. Interventions listed in detail for all studies (continued)

Author Year	Supplement:	Latin or other names used in this study for the supplement	Supplement Composition	Is purity of the supplement reported?	Is the supplement licensed in the region used?	Does the paper report where the supplement was manufactured?	Have storage conditions for the supplement been reported?	Is the origin of the supplement reported?	What subtype of the supplement was administered?	Are nutrient levels or biomarkers of the supplement reported?
Watson 1999[66]	Coenzyme Q10	Coenzyme Q	NR	No	NR	Health World Limited, Brisbane, Australia	No	No	NR	Plasma levels of Coenzyme Q
Wirell 1994[67]	Magnesium	Magnesiocard	NR	No	NR	Tutzing Germany	No	No	magnesium aspartate hydrochloride	serum magnesium, also in urine
Wolf 2006[68]	Gingko biloba	EGb761	NA	No	NR	Germany	No	dry extract from gingko biloba leaves	NA	No
Yamamoto 1995[69]	Omega-3 (EPA, DHA or both)	Epadel	NR	No	NR	Mochido Pharmacy, Japan	No	No	NR	plasma EPA levels
Young 2007[70]	Coenzyme Q10	Q-Gel	NR	No	NR		No	No	NR	total plasma levels of CoQ10
Yuan 2004[71]	Ginseng	Panax quinquefolius	total ginsenoside content was 5.19%	The constituent split was as follows: ginsenoside Rb1 , 1.93%; Rb2 , 0.20%; Rc, 0.61%; Rd, 0.42%; Re, 1.68%; and Rg1 , 0.35%	NR	Wisconsin US	No	root of American ginseng	NA	No

Outcomes Tables Categorized by Key Question and Outcome

Evidence Table 59. KQ1—Dichotomous data—Mortality

Author Year Study design	Definition of outcome (if relevant)	CHD risk category	CVD drug (dose mg/d)	Group 1: Supplement name (dose g/d)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
All cause mortality												
Sconce 2007 [61] Parallel	N/A	Unclear	Warfarin (3.3-4.4)	Vitamin K (0.15)	35	0	Placebo	33	1			Medium
Eritsland 1996 [21] Parallel	N/A	High	ASA (300)	Fish/marine oils (4)	143	5	No treatment	148	4			Medium
Eritsland 1996 [21] Parallel	N/A	High	Warfarin (NR)	Fish/marine oils (4)	174	3	No treatment	145	2			Medium
Garg 1995 [24] Parallel	N/A	High	ASA and/or pentoxiphylline (NR)	*Ginkgo biloba* (0.16)	29	0	Placebo	26	0			High
Roth 2009 [60] Parallel	N/A	Unclear	Fenofibrates (130)	Omega-3 (EPA, DHA or both) (4)	84	0	Placebo	83	0			Medium
Di Spirito 2008 [19] Cross-over	N/A	Low (healthy)	Atorvastatin (80)	Omega-3 (EPA, DHA or both) (4)	50	0	No treatment	50	0			Medium

Evidence Table 59. KQ1—Dichotomous data—Mortality

Author Year Study design	Definition of outcome (if relevant)	CHD risk category	CVD drug (dose mg/d)	Group 1: Supplement name (dose g/d)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Watson 1999 [66] Cross-over	N/A	High	Mixed: ACE inhibitors + furosemide, digoxin, hydralazine and/or nitrates (NR)	Coenzyme Q10 (0.1)	30	0	Placebo	30	1			Medium
Vascular death – *no outcome data*												
Specific vascular death – no outcome data												

Evidence Table 60. KQ1—Dichotomous data—Ischemic heart disease (coronary artery disease)

Author Year Study design	Definition of outcome (if relevant)	CHD risk category	CVD drug (dose mg/d)	Group 1: Supplement name (dose g/d)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
All myocardial infarction (MI, acute MI)												
Wirell 1994 [67] Cross-over	NR	Unclear	Beta Adrenergic Antagonists: metoprolol, atenolol, pindolol & propanolol (NR)	Magnesium (0.365)	19	1	Placebo	20	0			Medium
Nonfatal MI (MI, acute MI)												
Kaul 1992 [34] Parallel	Acute MI	High	Calcium channel blocker, ASA (NR)	Fish/marine oils	58	4	No treatment	49	2			Low
Unstable angina *(see also Cont. data)*												
Acute coronary syndrome - no outcome data												
(Re)stenosis – *see also Cont. data*												

Evidence Table 60. KQ1—Dichotomous data—Ischemic heart disease (coronary artery disease) (continued)

Author Year Study design	Definition of outcome (if relevant)	CHD risk category	CVD drug (dose mg/d)	Group 1: Supplement name (dose g/d)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Kaul 1992[34] Parallel	Angiopraphic restenosis: Patients with angina symptoms and/or positive exercise test who underwant repeat coronary angiography: loss of 50% of the gain in luminal diameter at angioplasty or recurrence of stenosis in only one of the two segments of vessel dilated – 6 months follow-up	High	Calcium channel blocker, ASA (NR)	Fish/marine oils	58	19	No treatment	49	13	-	4 patients with clinical restonosis refused repeat angiography.	-
Kaul 1992[34] Parallel	Clinical restenosis: presence of positive exercise test, new since the early post angioplasty study with or without anginal symptoms – 6 months follow-up	High	Calcium channel blocker, ASA (NR)	Fish/marine oils	58	22	No treatment	49	14	-	-	-
	Subgroup: male			*Fish/marine oils*	*50*	*18*	*No treatment*	*41*	*12*	-	-	-
	Subgroup: female			*Fish/marine oils*	*8*	*3*	*No treatment*	*8*	*1*	-	-	-
Kaul 1992[34] Parallel	Progression of disease: the presence of a new luminal narrowing > 70% in the non-dilated vessel – 6 months follow-up	High	Calcium channel blocker, ASA (NR)	Fish/marine oils	58	4	No treatment	49	3	-	-	-

Evidence Table 60. KQ1—Dichotomous data—Ischemic heart disease (coronary artery disease) (continued)

Author Year Study design	Definition of outcome (if relevant)	CHD risk category	CVD drug (dose mg/d)	Group 1: Supplement name (dose g/d)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Dehmer 1988[17] Parallel	Restenosis post-angioplasty (per patient): defined angiographically as recurrence of a lesion with more than 50% narrowing of the luminal diameter – 3 to 4 months follow-up	High	ASA (325) + dipyridamole (225) + calcium channel blockers (NR)	Omega-3 (EPA, DHA, or both) (3.2)	43	8	No treatment	39	18	-	-	-
Graft occlusion												
Eritsland 1996[21] Parallel	occluded vein graft (>/=1) per all patients	High	ASA (300)	Fish/marine oils (4)	134	57	Placebo	134	66	-	N presented per arm are number free of event at baseline (Total N1 = 134; N2 = 140)	-
Eritsland 1996[21] Parallel	occluded vein graft (>/=1) per all patients	High	Warfarin (NR)	Fish/marine oils (4)	164	69	Placebo	134	71		N presented per arm are number free of event at baseline (Total N1 = 168; N2 = 139)	

Evidence Table 61. KQ1—Dichotomous data—Composite cardiovascular outcome

Author Year Study design	Definition of outcome (if relevant)	CHD risk category	CVD drug (dose mg/d)	Group 1: Supplement name (dose g/d)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Glynn 2007[25] Parallel	Combination of major cardiovascular events, including nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes	Low and/or mod to high risk	ASA (100)	Vitamin E (0.1)	9966 included	232	Placebo	9968	245	Crude risk ratio (95% CI): 0.95 (0.79, 1.13) P-value: 0.55		Medium

Evidence Table 62. KQ1—Dichotomous data—Arrhythmia

Author Year Study design	Definition of outcome (if relevant)	CHD risk category	CVD drug (dose mg/d)	Group 1: Supplement name (dose g/d)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Sudden Death *– no outcome data*												
Ventricular fibrillation *– no outcome data*												
Ventricular tachycardia												
Davidson 2007[14] Parallel	Tachycardia	Unclear	Simvastatin (40)	Omega-3 (EPA, DHA, or both) (4)	122	1	Placebo	132	0	-	Also led to hospitalization	Medium
Atrial fibrillation – no outcome data												
Heart block – no outcome data												

Evidence Table 63. KQ1—Dichotomous data—Other heart disease

Author Year Study design	Definition of outcome (if relevant)	CHD risk category	CVD drug (dose mg/d)	Group 1: Supplement name (dose g/d)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Congestive heart failure												
Davidson 2007[14] Parallel	Exacerbation of CHF after 8 weeks	Unclear	Simvastatin (40)	Omega-3 (EPA, DHA, or both) (4)	122	1	Placebo	132	0	-	-	-
Valvular disease – no outcome data												

Evidence Table 64. KQ1 - Dichotomous data—Cerebrovascular disease

Author Year Study design	Definition of outcome (if relevant)	CHD risk category	CVD drug (dose mg/d)	Group 1: Supplement name (dose g/d)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
All Stroke												
Sconce 2007[61] Parallel	NR; 6 months follow-up	Unclear	warfarin (3.3-4.4)	Vitamin K (0.15)	35	0	Placebo	33	0	-	-	Medium
Steiner 1995[62] Parallel	Fatal or non-fatal – 2 years follow-up	High	ASA (325)	Vitamin E (400 IU/d)	52	3	Placebo	48	6	-	-	Medium
Hemorrhagic stroke												
Steiner 1995[62] Parallel	2 years follow-up	High	ASA (325)	Vitamin E (400 IU/d)	52	2	Placebo	48	0	-	-	Medium
Ischemic stroke												
Steiner 1995[62] Parallel	2 years follow-up	High	ASA (325)	Vitamin E (400 IU/d)	52	1	Placebo	48	6	-	-	Medium
Transient ischemia attack (TIA)												
Steiner 1995 [62] Parallel	Recurrent TIA - 2 years follow-up	High	ASA (325)	Vitamin E (400 IU/d)	52	1	Placebo	48	2	-	-	-
Carotid artery disease (not measured by IMT or Doppler) *– no outcome data*												

Evidence Table 65. KQ1—Dichotomous data—Peripheral arterial disease

Author Year Study design	Definition of outcome (if relevant)	CHD risk category	CVD drug (dose mg/d)	Group 1: Supplement name (dose g/d)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Limb thrombosis/leg ischemia *– no outcome data*												
Claudication (pain walking) *– no outcome data*												
Mesenteric ischemia *– no outcome data*												
Abdominal aortic aneurysm *- no outcome data*												
Ankle-brachial index *– no outcome data*												

Evidence Table 66. KQ1—Dichotomous data—CVD surgery and procedures

Author Year Study design	Definition of outcome (if relevant)	CHD risk category	CVD drug (dose mg/d)	Group 1: Supplement name (dose g/d)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Coronary artery bypass graft												
Kaul 1992 [34] Parallel	Late CABG – 6 months follow-up	High	Calcium channel blocker (NR) + ASA (NR)	Fish/marine oils	58	2	No treatment	49	2	-	-	-
Percutaneous transluminal coronary angioplasty												
Kaul 1992 [34] Parallel	Restenosis documented by repeat angioplasty– 6 months follow-up	High	Calcium channel blocker (NR) + ASA (NR)	Fish/marine oils	58	16	No treatment	49	10	-	Not significant between groups	-
Stent *– no outcome data*												
Valve replacement *– no outcome data*												
Carotid or peripheral vascularization *- no outcome data*												
Amputation *– no outcome data*												

Evidence Table 67. KQ1—Dichotomous data—Hospitalization

Author Year Study design	Definition of outcome (if relevant)	CHD risk category	CVD drug (dose mg/d)	Group 1: Supplement name (dose g/d)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Davidson 2007[14] Parallel	Hospitalization due to SAE (pneumonia, CHF, supraventricular tachycardia) – 8 weeks follow-up	Unclear	simvastatin (40)	Omega-3 (EPA, DHA, or both) (4)	122	3	Placebo	132	0	-	-	Medium

Evidence Table 68. KQ1—Dichotomous data—Adherence to cardiovascular drug

Author Year Study design	Definition of outcome (if relevant)	CHD risk category	CVD drug (dose mg/d)	Group 1: Supplement name (dose g/d)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Young 2007[70] Parallel	NR – 12 weeks follow-up	Mod and high risk	simvastatin (10-40)	Coenzyme Q10 (0.2)	22		Placebo	22			Both groups had 98% adherence to simvastatin	
Sconce 2007[61] Parallel	Score of 1 or lower out of 10 in the Brief Medication Questionnaire – 6 months follow-up	Unclear	warfarin (3.3-4.4)	Vitamin K (0.15)	35	35	Placebo	33	33	-	All participants were considered to have a 'high probable degree of adherence.	-
Napoli 1998[52] Parallel	Pill counts – 3 months follow-up	Unclear	Pravastatin (20-40)	Vitamin E (0.1)	-	-	-	-	-	-	Report states "...almost all patients (98%) followed their treatments and diet carefully.' No individual group data reported.	-

Evidence Table 68. KQ1—Dichotomous data—Adherence to cardiovascular drug (continued)

Author Year Study design	Definition of outcome (if relevant)	CHD risk category	CVD drug (dose mg/d)	Group 1: Supplement name (dose g/d)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Bender 1998[8] Parallel	compliance rate (study drug) - % - 4 weeks follow-up	Unclear	Warfarin (NR)	Omega-3 (EPA, DHA, or both) (3 or 6)	6	-	Placebo	5	-	-	Report states that compliance was >99.5%; no individual group data reported	-
Chan 2002 [12] Parallel	Pill counts – 3 and 6 weeks follow-up	Moderate/ moderately high risk for CHD (2+ risk factors)	atorvastatin (40)	Fish/marine oils (4)	11	-	Placebo	13	-	-	Report states that compliance was >95%; no individual group data reported	-
Liu 2003 [37] Parallel	Pill counts – 12 weeks follow-up	Unclear	simvastatin (10)	Fish/marine oils (9.2)	19	-	No treatment	18	-	-	Report states that compliance was >95%; no individual group data reported	
Maki 2008 [41] Cross-over	Pill counts and subject interview – 6 weeks follow-up/period	Low, Moderate and high risk	Simvastatin (20)	Omega-3 (EPA, DHA, or both) (4)	39	-	Placebo	39	-	-	Report states: 'Compliance with simvastatin was 97% during POM3 treatment and 96% during placebo treatment (p = 0.448)'	-

Evidence Table 69. KQ1—Continuous data—Ischemic heart disease (coronary artery disease)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change / % change from baseline / SD / P Value	Between group differences in Means/ medians SD / P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Unstable angina *(see also Dich. data)*										
Miyamoto 2004[48] Parallel	Number of anginal attacks recorded after before and after 1 month	High	Diltiazem (100-200)	Vitamin E (0.4)	20	Mean: 0.4 SE: 0.1	P: <0.01	P: NS		-
				Placebo	20	Mean: 0.6 SE: 0.1	P: <0.01			
Motoyama 1998[50] Parallel	Number of anginal attacks recorded after 1 month	High	Diltiazem (200)	Vitamin E (0.3)	30	Mean: 0.2 SD: 0.5	Mean: -6.7	$Mean_{diff:}$ 0.7		-
				Placebo	30	Mean: 0.9 SD: 1.1	Mean: -5.9			

Evidence Table 69. KQ1—Continuous data—Ischemic heart disease (coronary artery disease) (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD / P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
(Re)stenosis *– see also Dich. data)*										
Yamamoto 1995[69] Parallel	Coronary artery diameter- nonspastic segments: angiographically normal site where acetylcholine injection did not provoke coronary vasospasm (diameter [mm], expressed as a % after admin of ISDN was reduced by < 50% after intracoronary admin of acetylcholine) – 4 months follow-up	High	Diltiazem (90-120)	Omega-3 (EPA, DHA, or both) (3.6)	12	Mean: 3.0 SE: 0.1	-	-	-	-
				No treatment	10	Mean: 2.9 SE: 0.2	-			
Yamamoto 1995[69] Parallel	coronary artery diameter- spastic segments: spastic site = site of the most severe narrowing in the coronary vasospasm artery after injection of acetylcholine (mm) – 4 months follow-up	High	Diltiazem (90-120)	Omega-3 (EPA, DHA, or both) (3.6)	12	Mean: 2.9 SE: 0.1	-	-	-	-
				No treatment	10	Mean: 3.0 SE: 0.3	-			

Evidence Table 69. KQ1—Continuous data—Ischemic heart disease (coronary artery disease) (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD / P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Dehmer 1988[17] Parallel	Luminal narrowing (%) after angioplasty – 3-4 months follow-up	High	ASA (325) + dipyridamole (225) + calcium channel blockers (NR)	Omega-3 (EPA, DHA, or both) (3.2)	43	Mean: 25 SD: 15.1	-	-	-	-
				No treatment	39	Mean: 29 SD: 14	-			

Evidence Table 70. KQ1—Continuous data—Cerebrovascular disease

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Neurological recovery score										
[24] Parallel	Modified Mathew's score (scale: 0-100) – 4 weeks follow-up	High	ASA and/or pentoxiphylline (NR)	*Gingko biloba* (0.16)	29	Mean: 77.79 SD: 14.73	-	-	-	-
				Placebo	26	Mean: 78.57 SD: 12.47	-			

Evidence Table 71. KQ1—Continuous data—Quality of life

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline / SD / P Value	Between group differences in Means/ medians SD / P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
[66] Cross-over	Minnesota Living with Heart Failure questionnaire – 12 weeks follow-up	High	Mixed: ACE inhibitors + furosemide, digoxin, hydralazine and/or nitrates (NR)	Coenzyme Q10 (0.099)	27	Mean: 26.7 Median: 22 SD: 17.9	Mean: -2.7	$P\text{-value}_{adj}$: 0.22	Between group difference adjusted for order of treatment	Medium
				Placebo	27	Mean: 26.5 Median: 22 SD: 18.7	Mean: -2.9			

Evidence Table 72. KQ2—Continuous data—Bleeding time

Author Year Study Design	CHD Risk Category	CVD drug	Dose (mg/d)	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Svaneborg 2002[64] parallel	At low risk for CHD (0-1 risk factors)	ASA	100	Omega-3 (EPA, DHA, or both).	12	BP cuff 40 mm Hg- incisions with parallel to the fold of the elbow	Median 9.6 Lower: 7.6 Upper: 11	P: <0.05	NR	p value is for before the injection of ASA	medium
				Placebo	6		Median 7.9 Lower: 6.3 Upper: 11.5	P: <0.05			
Neil, HAW 2010[53]	At high risk for CHD	Statins	20	Omega-3	163	Total Cholesterol (mmol/l)	Mean: 3.4 SD: 0.7	NR	NR	No significant differences between groups.	NA
	At high risk for CHD	Statins	20	placebo	169		Mean: 3.4 SD: 0.7	NR	NR		
Neil, HAW 2010[53]	At high risk for CHD	Statins	20	Omega-3	163	LDL-C (mmol/l)	Mean: 1.7 SD: 0.5	NR	NR	No significant differences between groups.	Low
				Placebo	169		Mean: 1.8 SD: 0.5	NR	NR		
Neil, HAW 2010[53]	At high risk for CHD	Statins	20	Omega-3	163	HDL-C (mmol/L)	Mean: 1.1 SD: 0.3	NR	NR	No significant differences between groups.	Low
				Placebo	169		Mean: 1.1 SD: 0.2	NR	NR		

Evidence Table 72. KQ2—Continuous data—Bleeding time (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose (mg/d)	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Neil, HAW 2010[53]	At high risk for CHD	Statins	20	Omega-3	163	Triglyceride (mmol/l)	Median: 1.1 IQR, lower limit: 0.8 IQR, upper limit: 1.5	NR	NR	No significant differences between groups.	Low
				Placebo	169		Median: 1.5 IQR, lower limit: 1.1 IQR, upper limit: 2.3	NR	NR		
Neil, HAW 2010[53]	At high risk for CHD	Statins	20	Omega-3	163	Systolic blood pressure (mmHg)	Mean: 142 SD: 17	NR	NR	No significant differences between groups.	Low
				Placebo	169		Mean: 143 SD: 21	NR	NR		
Neil, HAW 2010[53]	At high risk for CHD	Statins	20	Omega-3	163	Diastolic blood pressure	Mean: 80 SD:11	NR	NR	No significant differences between groups.	NA
				Placebo	169		Mean: 80 SD: 12	NR	NR		
Wolf 2006[68] crossover	Low and/or Moderate	ASA	500	ginkgo biloba	50	Ivy method - bleeding time was the time between first and last extravasations and value was mean of three bleeding times	Mean: 6.3 SD: 3.1	Mean: .21	Mean: 1.01	ratio of means presented with 90% CI	low-medium
				Placebo	50		Mean: 6.2 SD: 3.8	Mean: 2.1			

Evidence Table 72. KQ2—Continuous data—Bleeding time (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose (mg/d)	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Hansen 1993[29] crossover	Low and/or Moderate	lovastatin	40	Fish/marine oils	14	NR	Mean: 390 Median SD: 150 SE: Lower: Upper:	NR	NR	Reported in graphical form only.	medium
				Placebo	14		Mean: 330 Median SD: 70 SE: Lower: Upper:	NR			
Kim 2010[35] crossover	Low and/or Moderate	Ticlopidine	250- single dose	ginkgo biloba	24	determined just before dosing and at 5, 12, and 48 hours after dosing. While applying 40 mm Hg of pressure on the upper arm, we made an incision using a bleeding-time measurement device (Surgicutt, International Technidyne Corp., Edison, New Jersey) on the volar surface of the forearm to measure the bleeding time.	Mean: 6.3 Median SD: 2.3 SE: Lower: Upper:	Mean:1.1 % mean: Median: SD: P:	NR	Range of mean: ginkgo group 3-11.5; To treatment group 2.5-8.5.	medium
				No treatment	24		Mean: 5.3 Median SD: 1.7 SE: Lower: Upper:	Mean:0.9 Median: SD: P: <0.05			

Evidence Table 72. KQ2—Continuous data—Bleeding time (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose (mg/d)	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Aruna 2007[2] crossover	At low risk for CHD (0-1 risk factors)	Cilostazol 100 mg	104 to 200 (cilostazol); 75 to 150 (clopidogrel)	ginkgo biloba	10	measured 0 and 6 h after drug administration by Ivy's method	Mean: 211 Median SD: 70 SE: 25 Lower: Upper:	NR	NR	95% CI of mean for individual group data: ginkgo group: 153.00-270.00; No treatment group: 118.00-182.00.	medium
				No treatment	10		Mean: 150 Median SD: 42 SE: 14 Lower: Upper:	NR			
Aruna 2007[2] crossover	At low risk for CHD (0-1 risk factors)	Clopidogrel 75 mg	105 to 200 (cilostazol); 75 to 150 (clopidogrel)	ginkgo biloba	10	measured 0 and 6 h after drug administration by Ivy's method	Mean: 148 Median SD: 78 SE: 28 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	95% CI of mean for individual group data: ginkgo group: 83.00-213.00; No treatment group: 91.00-190.00.	medium
				No treatment	10		Mean: 141 Median SD: 59 SE: 21	NR			

Evidence Table 72. KQ2—Continuous data—Bleeding time (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose (mg/d)	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Mueller 1991[51] crossover	Low and/or Moderate	aspirin	325 - single dose	Fish/marine oils	12	measured using a Simplate II system. By blinded operator.	Mean: 680 Median SD: 302.6 SE: Lower: Upper:	Mean: % mean: 18.6 Median: SD: P:	NR		medium
				Placebo	12		Mean: 633.8 Median SD: 339.8	Mean: % mean: 14.5			

Evidence Table 73. KQ2—Continuous data—Clotting time

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Gardner 2007[23] Parallel	moderate to high	ASA	325	ginkgo biloba	29	NR	NR	Mean: 1.5 SD:17	NR		low
				Placebo	26		NR	Mean: 6.5 SD: 16.7			

Evidence Table 74. KQ2—Continuous data—Coronary artery calcification

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD / P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Budoff 2004[10] parallel	At high risk for CHD	statins + aspirin	10 - 40	Garlic	9	volume calcuim score; volumetric score by the method of isotropic interpolation	Mean: Median SD: SE: Lower: Upper:	Mean: 45.2 % mean: Median: SD: 57.2 P:	Mean: Median: SD: P: 0.0445		medium
				Placebo	10		Mean: Median SD: SE: Lower: Upper:	Mean: 129 Median: SD: 102.1 P:			
Budoff 2004[10] parallel	At high risk for CHD	statins + aspirin	10 - 40	Garlic	9	% change (volume of calcium)	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: 7.5 Median: SD: 9.40 P:	Mean: Median: SD: P: 0.064		medium
				Placebo	10		Mean: Median SD: SE: Lower: Upper:	Mean: % mean 22.5 Median: SD: 18.50 P:			

Evidence Table 74. KQ2—Continuous data—Coronary artery calcification (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change / % change from baseline / SD / P Value	Between group differences in Means/ medians SD / P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Budoff 2004[10] parallel	At high risk for CHD	statins + aspirin	10 - 40	Garlic	9	Agatston caclium score; as described by Agatston et al. by multiplying the lesion area by a coefficient based on the peak density within that plaque. The total Agatston score was determined by summing the scores obtained for each lesion.	Mean: Median SD: SE: Lower: Upper:	Mean: 71.1 % mean: Median: SD: 95.8 P:	Mean: Median: SD: P: 0.1401		medium
				Placebo	10		Mean: Median SD: SE: Lower: Upper:	Mean: 151.6 Median: SD: 126.5			
Budoff 2004[10] parallel	At high risk for CHD	statins + aspirin	10 - 40	Garlic	9	% change of Agatston score	NR	Mean: 38 % mean: 11.5	Mean: Median: SD: P: 0.2628		medium
				Placebo	10		NR	Mean: % mean: 21.1 SD: 18.90P:			

Evidence Table 75. KQ2—Continuous data—C-reactive protein

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Mabuchi 2007[39] parallel	Unclear	atorvastatin	1	Coenzyme Q10.	24	NR	Mean: 799 Median SD: 1209 SE: Lower: Upper:	Mean: % mean: -46.8 Median: SD: 0.5408 P:	Mean: Median: SD: P:	There's no significant differences between groups (p=0.5943). Several other continuous outcomes, such as alkaline phosphatase, LDH, CoQ10/ total cholesterol and CoQ10/LDL were not extracted.	medium
				Placebo	25		Mean:777 Median SD: 1038 SE: Lower: Upper:	Mean: % mean: -14.6 Median: SD: P: 0.8743			

Evidence Table 75. KQ2—Continuous data—C-reactive protein (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Budoff 2004[10] parallel	At high risk for CHD	statins + aspirin	10-40	Garlic	9	measured after 12 hr fast at 800 hr	Mean: Median SD: SE: Lower: Upper:	Mean:-0.1 % mean: Median: SD: 0.22 P:	Mean: Median: SD: P: 0.8464		medium
				Placebo	10		Mean: Median SD: SE: Lower: Upper:	Mean:-0.13 Median: SD: 0.27 P:			
Chan 2002[12] parallel	At moderate/moderately high risk for CHD (2+ risk factors)	atorvastatin	40	Fish/marine oils.	11	12 hr fasting at 800hr	Mean: 1.14 Median SD: 1.97 SE: Lower: 0.6 Upper: 2.4	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	13		Mean: Median SD: SE: Lower: 1.1 Upper:4	Mean: Median: SD: P:			

Evidence Table 75. KQ2—Continuous data—C-reactive protein (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Desideri 2003[18] parallel	At low risk for CHD (0-1 risk factors)	Simvastatinstatin, Bezafibrate	simvastatinstatin: 40; Bezafibrate: 800	Vitamin E.		Measured after 12 hr fast	Mean: 1.5 Median SD: 0.4 SE: Lower: Upper:	Mean: % mean: Median: SD: P: <0.05	Mean: Median: SD: P:	I assumed no losses to follow-up although I did not see this explicitely stated. Baseline data also given.	medium
				No treatment (aside from CVD drug)			Mean:1.9 Median SD: 0.3 SE: Lower: Upper:	Mean: Median: SD: P: <0.05			
							Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Ferraro 2009[22] parallel	Unclear	ramipril	10	Omega-3 (EPA, DHA, or both).	15	NR	Mean: 73.5 Median SD: 20.3	NR	NR		medium
				No treatment (aside from CVD drug)	15		Mean:76.7 Median SD: 9.0	NR			
Meyer 2007[46] parallel	Unclear	simvastatinstatin, 13 atorvastatin, 4 pravastatin, 2 cerivastatin and 2 fluvastatin	81	Fish/marine oils.	13	Supine in clinic	NR	NR	NR	Report states that no changes were noted in DBP across groups and results are not shown	medium
				Fish/marine oils.	13		NR	NR			
				Placebo	14						
Sutken 2006[63] parallel	Low and/or Moderate	Gemfibrozil	1200	Vitamin E.	22	NR	Mean: 84 Median SD: SE: 4 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		high
				No treatment (aside from CVD drug)	23		Mean:80 Median SD: SE:6.4 Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Sutken 2006[63] parallel	Low and/or Moderate	Gemfibrozil	1200	Vitamin E.	12	NR	Mean: 80 Median SD: SE:3.9 Lower: Upper:	NR	NR		high
				No treatment (aside from CVD drug)	10		Mean:81 Median SD: SE:4.2 Lower: Upper:	NR			
Macan 2006[40] parallel	Low and/or Moderate	Warfarin	NR	Garlic.	22	NR	Mean: Median SD: SE: Lower: Upper:	Mean:-0.5 % mean: Median: SD: 11.8 P:	Mean: Median: SD: P: 0.829		medium
				Placebo	26		Mean: Median SD: SE: Lower: Upper:	Mean:0.3 Median: SD: 13.7 P:			
Barbagallo 1999[5] parallel	Unclear	furosemide	25	Vitamin E.	12	overnight fast, supine at rest, empty bladder	Mean:82 Median SD: 4 SE: Lower: Upper:	Mean:-8 % mean: Median: SD: P: <0.005	Mean: Median: SD: P:	calculation of mean change from baseline questionably as it won't be useable (SD cannot be inferred, I don't think.).	medium

Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	12		Mean:84 Median SD: 6 SE: Lower: Upper:	Mean:-9 Median: SD: P: <0.005			
Howe 1994[30] parallel	Unclear	Captopril	61	Fish/marine oils.	14	NR	Mean: 77 Median SD: SE:2 Lower: Upper:	Mean:3.1 % mean: Median: SD: P:	Mean: Median: SD: P:	outcomes in this study are reported as the average of three measurment during the treatment peiod.	medium
				Placebo	14		Mean:79 Median SD: SE:2 Lower: Upper:	Mean:2.3 Median: SD: P:			
				Fish/marine oils.	14		Mean:79 Median SD: 2 SE: Lower: Upper:	Mean:4.0 Median: SD: 1.1 P:			
				Placebo	14		Mean:77 Median SD: 2 SE: Lower: Upper:	Mean:4.4 Median: SD: 1.7 P:			

Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Paolisso 1992[57] parallel	Unclear	hydrochlorthiazide	25	Magnesium.	9	supine, fasted (12 h) and at rest for 30 minutes - measured over 60 minutes, mean of last 10 minutes of measurement included.	Mean: 95 Median SD: SE:3 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P: <0.05		medium
				Placebo	9		Mean:89 Median SD: SE:5 Lower: Upper:	Mean: Median: SD: P:			
Nordøy 2003[55] parallel	Mod and high risk	atorvastatin	10	Fish/marine oils.	22	NR	Mean: Median SD: SE: Lower: Upper:	Mean:-2.8 % mean: Median: SD: 7.2 P: <0.05	Mean: Median: SD: P: 0.92		medium
				Placebo	20		Mean: Median SD: SE: Lower: Upper:	Mean:-3.0 Median: SD: 8.1 P:			
Reyes 1984[59] parallel	Low and/or Moderate	hydrochlorothiazide	50	Magnesium.	13	Supine diastolic	Mean: 104.4 Median SD: SE:3.9 Lower: Upper:	Mean:-6 % mean: Median: SD: P: <0.05	Mean: Median: SD: P:	Data for % change measured from graph and verified with numerical data in abstract	medium

Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	8		Mean:1.5 Median SD: SE:4.2 Lower: Upper:	Mean: % mean: -3.4 Median: SD: P: <0.05			
Reyes 1984[59] parallel	Low and/or Moderate	hydrochlorothiazide	50	Magnesium.	13	Erect diastolic blood pressure	Mean: 106 Median SD: SE:2 Lower: Upper:	Mean:-5 % mean: Median: SD: P:	Mean: Median: SD: P:	Data extracted from bar charts - method of extraction verified for other variables that had corresponding numerical summary. In this case for final mean and SEM 1.9 cm = 40 mmHg and results rounded to nearest whole mmHg. For % change from time of randomization 1.1 cm = 2.5% and results rounded to nearest 0.5%	medium
				Placebo	8		Mean: 105 Median SD: SE:4 Lower: Upper:	Mean:-3 % mean: Median: SD: P:			
Dehmer 1988[17] parallel	At high risk for CHD	aspirin + Dipyridamole + ca channel blockers)	ASA: 325; dipyridamole: 225; Ca blocker: NR	Omega-3 (EPA, DHA, or both).	43	NR	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium

Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	39		Mean:36 Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Wolf 2006[68] crossover	Low and/or Moderate	ASA	500	ginkgo biloba	NR	NR	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	Study states that: Laboratory findings in all subjects were unremarkable and did not indicate any differences between the treatment groups. Similarly, no noteworthy changes of vital sign variables occurred during the study	low-medium
					NR		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Paolisso 1995[56] crossover	At high risk for CHD	nifedipine	88	Vitamin E	30	NR	Mean: 85 Median SD: SE:0.7 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	30		Mean:86 Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Lungershausen 1994[38] crossover	Unclear	b-blockers	NR	Fish/marine oils	25	Clinical diastolic BP - Resting for 5 min, empty bladder, fasted and no exercise for 2 hours; average of 3 or 4 readings after discarding initial reading; measured using automated oscillometric monitor	Mean: 72.5 Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P: <0.05	Data of mean measured from histogram (10 mmHg = 2.2 cm). Measure of dispersion not stated. This study is at risk of selective outcome reporting; p-values for crude difference also don't make sense in context of graph. I would approach this data with e	medium
				Placebo	25		Mean:75.5 Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Lungershausen 1994[38] crossover	Unclear	b-blockers	NR	Fish/marine oils	25	Ambulatory diastolic BP - Measured over next 24 hours using Spacelab 90207 instrument, same time of day; taken at 20 min intervals during wake and every 1 hour during sleep.	Mean: 76 Median SD: SE: Lower: Upper:	Mean:2.3 % mean: Median: SD: 0.8 P:	Mean: Median: SD: P: <0.01	Data of mean measured from histogram (10 mmHg = 2.2 cm). Measure of dispersion not stated. Data of mean difference in text. This study is at risk of selective outcome reporting; p-values for crude difference also don't make sense in context of graph.	medium
				Placebo	25		Mean:78 Median SD: SE: Lower: Upper:	Mean: Median: SD: 1 P:			

Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Mueller 1991[51] crossover	Low and/or Moderate	aspirin	325-single dose	Fish/marine oils	12	before and 90 minutes after a single oral 325-mg dose of aspirin. Done by blinded operator	Mean: 77.5 Median SD: 11.7 SE: Lower: Upper:	Mean:-2 % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	12		Mean:74.08 Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Maki 2008[41] crossover	Low and/or Moderate	simvastatin	20	Omega-3	39	At rest, seated	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -3.3 Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	40		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Wirell 1994[67] Crossover	Unclear	metoprolol, atenolol, pindolol & propanolol	NR	magnesium	39	standing	Mean: 100.84 Median SD: 9.48	NR	Mean: Median: SD: P:		medium
				Placebo	39		Mean:102.49	NR			

Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Wirell 1994[67] Crossover	Unclear	metoprolol, atenolol, pindolol & propanolol	NR	magnesium	39	supine	Mean: 93.03 Median SD: 9.37 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	NR		medium
				Placebo	39		Mean:95.68	NR			
							NR	NR			

Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Bays 2010[6] parallel	Unclear	atorvastatin	10-40	Omega-3 (EPA, DHA, or both).	122		Mean: Median 39.8 SD: 34 SE:48 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean:2.4 Median: SD: P:<0.001		medium
				Placebo	121		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Bays 2010[b] parallel	Unclear	atorvastatin	10-40	Omega-3 (EPA, DHA, or both).	122		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean:6.3 Median: SD: P:0.001		medium
				Placebo	121		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Mabuchi 2007[39] parallel	Unclear	atorvastatin	1	Coenzyme Q10.	24		Mean: 1.74 Median SD: 0.42 SE: Lower: Upper:	Mean: % mean: Median: SD: P: 0.0033	Mean: Median: SD: P:	"...no significant differences between the groups"	medium
				Placebo	25		Mean:1.61 Median SD: 0.34 SE: Lower: Upper:	Mean: Median: SD: P: 0.0583			
Young 2007[70] parallel	Mod and high risk	simvastatinstatin	10-40	Coenzyme Q10.	22		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P: 0.65	No difference in groups (p=0.65)	medium
				Placebo	22		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Davidson 2007[14] parallel	Unclear	simvastatinstatin	40	Omega-3 (EPA, DHA, or both).	122		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P: <0.001		medium
				Placebo	132		Mean:	Mean:			

Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
							Median SD: SE: Lower: Upper:	% mean: -1.10 Median: SD: P:			
Meyer 2007[46] parallel	Unclear	simvastatinstatin	81	Fish/marine oils.	13		Mean: 1.16 Median SD: SE:0.09 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Fish/marine oils. 8g/d	13		Mean: 1.21 Median SD: SE:0.05 Lower: Upper:	Mean: % mean: Median: SD: P:			
				Placebo	14		Mean:1.11 Median SD: SE:0.10 Lower: Upper:	Mean: Median: SD: P:			
Sutken 2006[63] parallel	Low and/or Moderate	Gemfibrozil	1200	Vitamin E.	22		Mean: 0.82 Median SD: SE:0.04 Lower: Upper:	Mean: % mean: Median: SD: P: <0.05	Mean: Median: SD: P:		high
				Placebo	23		Mean:0.82 Median	Mean: Median:			

Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
							SD: SE:0.04 Lower: Upper:	SD: P: <0.05			
Sutken 2006[63] parallel	Low and/or Moderate	Gemfibrozil	1200	Vitamin E.	12		Mean: 1.57 Median SD: SE:0.04 Lower: Upper:	Mean: % mean: Median: SD: P: <0.01	Mean: Median: SD: P:		high
				Placebo	10		Mean:1.41 Median SD: SE:0.08 Lower: Upper:	Mean: Median: SD: P: <0.01			
Macan 2006[40] parallel	Low and/or Moderate	Warfarin	NR	Garlic.	22		Mean: Median SD: SE: Lower: Upper:	Mean:2.9 % mean: Median: SD: 7.9 P:	Mean: Median: SD: P: 0.038	Other continous outcome assessed in this study: hemoglobin (weight also but I stated this in another comment as well)	medium
				Placebo	26		Mean: Median SD: SE: Lower: Upper:	Mean:-1.6 Median: SD: 6.7 P:			
Manuel	At high risk for CHD	Atorvastatin	20	Vitamin E.	11		Mean:	Mean:	Mean:	Data not	medium

Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
2004[42] parallel							Median SD: SE: Lower: Upper:	% mean: Median: SD: P:	Median: SD: P:	presented in paper - only provides baseline data per group and states that this outcome 'did not change in either group'.	
				Placebo	11		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Playford 2003[58] parallel	At high risk for CHD	Fenofibrate	200	Coenzyme Q10. 200 mg plus 200 mg fenofibrate	18		Mean: 1.07 Median SD: 0.05 SE: Lower: Upper:	Mean:0.14 % mean: Median: SD: P:	Mean:0.04 (group 1 vs. group 2 Median: SD: P:0.385 Mean:0.09 (group 1 vs. group 3 Median: SD: P:0.001		low-medium
				No treatment (aside from CVD drug)	17		Mean:1.11 Median SD: SE:0.04 Lower: Upper:	Mean:0.17 Median: SD: P:			
				Coenzyme Q10. 200 mg CoQ10 only	20		Mean:0.98 Median SD: SE:0.04 Lower: Upper:	Mean:0.03 Median: SD: P:			
				Placebo	18		Mean:0.98 Median	Mean:-0.05 Median:			

Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
							SD: SE:0.04 Lower: Upper:	SD: P:			
Svaneborg 2002[64] parallel	At low risk for CHD (0-1 risk factors)	ASA	100	Omega-3 (EPA, DHA, or both).	12		Mean: Median 1.18 SD: 0.73 SE:1.38 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	placebo= corn oil containing omega-6	medium
				Placebo	6		Mean:1.05 Median SD: SE: Lower: 0.88 Upper:1.45	Mean: Median: SD: P:			
Duffy 2001[20] parallel	Low and/or Moderate	simvastatinstatin	10-40	Vitamin E 1000 IU vitmain E plus simvastatin	6		Mean: 1.4 Median SD: 0.4 SE: Lower: Upper:	Mean:-0.1 % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)	7		Mean:1.3 Median SD: 0.3 SE: Lower: Upper:	Mean:0 Median: SD: P:			
				1000IU Vitamin E	6		Mean:1.4 Median	Mean:0.1 Median:			

Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
							SD: 0.3 SE: Lower: Upper:	SD: P:			
				Placebo	7		Mean: Median SD: SE: Lower: Upper:	Mean-0.1 Median: SD: P:			
Napoli 1998[52] parallel	Unclear	Pravastatin	20-40	Vitamin E.	52		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: 9 Median: SD: 3% P: <0.05	Mean: Median: SD: P:	Data not extracted but also available for VLDL-C, IDL-C, ApoB, Apo AI, Apo AII. Further, data not reported for routine laboratory tests and adverse effects. For these outcomes it is reported that “no differences in routine	medium
				No treatment (aside from CVD drug)	56		Mean: Median SD: SE: Lower: Upper:	Mean: % mean:10 Median: SD: 4% P: <0.05			

Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
										laboratory tests and adverse effects were registered during the study (data not shown); in particular, there were no differences between the values recorded in each individual after treatment compared with baseline values, and no differences between the treatment groups.	
Bordia 1998[9] parallel	At high risk for CHD	Nitrates	NR	Garlic.	30		Mean: 49.5 Median SD: SE:1.6	Mean:9 % mean22.3: Median: SD:	Mean: Median: SD: P:		high

Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
							Lower: Upper:	P: <0.05			
				Placebo	30		Mean:41.1 Median SD: SE:2.8 Lower: Upper:	Mean:0.1 Median: SD: P:			
Davidson 1997[15] parallel	Unclear	Simvastatinstatin	10	Fish/marine oils	9		Mean: 44.8 Median SD: SE:3.5 Lower: Upper:	Mean:4.5 % mean: 10.4 Median: SD: P: <0.05	Mean: Median: SD: P:		Medium
				No treatment (aside from CVD drug)	10		Mean:45.1 Median SD: SE:2.9 Lower: Upper:	Mean:2.7 % mean 7.2 Median: SD: P: <0.05			
Yamamoto 1995[69] parallel	At high risk for CHD	diltiazem	90-120	Omega-3 (EPA, DHA, or both).	12		Mean: 45 Median SD: SE:9 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				No treatment (aside from	10		Mean:47 Median	Mean: Median:			

Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				CVD drug)			SD: SE:12 Lower: Upper:	SD: P:			
McDowell 1994[44] parallel	Unclear	Simvastatinstatin	20	Vitamin E.	8		Mean: 1.3 Median SD: 0.3 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	8		Mean:1.3 Median SD: 0.4 SE: Lower: Upper:	Mean: Median: SD: P:			
Kaul 1992[34] parallel	At high risk for CHD	Calcium channel blocker, ASA	ASA: 150; heparin: 1000 U/d; ca blockers: NR	Fish/marine oils.	58		Mean: 37 Median SD: 10.5 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		low-medium
				No treatment (aside from CVD drug)	49		Mean:37 Median SD: 10.5 SE: Lower: Upper:	Mean: Median: SD: P:			
Nordøy 2003[55] parallel	Mod and high risk	atorvastatin	10	Fish/marine oils.	22		Mean: Median SD:	Mean:0.07 % mean: Median:	Mean: Median: SD:		medium

Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
							SE: Lower: Upper:	SD: 0.08 P:	P: 0.03		
				Placebo	20		Mean: Median SD: SE: Lower: Upper:	Mean:0.01 Median: SD: 0.09 P:			
Roth 2009[60] parallel	Unclear	fenofibrates by 100%	130	Omega-3 (EPA, DHA, or both).	81		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median : -1.9 SD: P:	Mean: Median: SD: P:	Not significant between groups	medium
				Placebo	82		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Isley 2007[31] parallel	Unclear	niacin	325	Omega-3	7		Mean: 49 Median SD: 5 SE: Lower: Upper:	Mean: % mean:33 Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	8		Mean:48 Median SD: 14 SE:	Mean: % mean: 18 Median: SD:			

Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
							Lower: Upper:	P:			
Budoff 2004[10] parallel	At high risk for CHD	statins + aspirin	10-40	Garlic	9		Mean: Median SD: SE: Lower: Upper:	Mean:3 % mean: Median: SD: 10.6 P:	Mean: Median: SD: P: 0.4611		medium
				Placebo	10		Mean: Median SD: SE: Lower: Upper:	Mean:-1.3 Median: SD: 13.8 P:			
Chan 2002[12] parallel	At moderate/moderately high risk for CHD (2+ risk factors)	atorvastatin	40	Fish/marine oils.	11		Mean: 1.25 Median SD: SE:0.09 Lower: Upper:	Mean: % mean: 13.5 Median: SD: 3.80% P:	Mean: Median: SD: P:		medium
				Placebo	13		Mean: 1.04 Median SD: SE: 0.05 Lower: Upper:	Mean: % mean:4.5 Median: SD: P:			
Liu 2003[37] parallel	Unclear	simvastatinstatin	10	Fish/marine oils.	19		Mean: 1.53 Median SD: 0.36 SE: Lower:	Mean:0.11 % mean: Median: SD: 0.21	Mean: Median: SD: P:		medium

Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
							Upper:	P:			
				No treatment (aside from CVD drug)	18		Mean:1.77 Median SD: 0.54 SE: Lower: Upper:7.1	Mean:0.12 Median: SD: 0.2 P:			
Dehmer 1988[17] parallel	At high risk for CHD	aspirin + Dipyridamole + ca channel blockers)	ASA: 325; dipyridamole: 225; Ca blocker: NR	Omega-3 (EPA, DHA, or both).	43		Mean: 36 Median SD: 8.7 SE: Lower: Upper:	Mean: % mean:7.4 Median: SD: P:	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)	39		Mean:36 Median SD: 9.4 SE: Lower: Upper:	Mean: Median: SD: P:			
Desideri 2003[18] parallel	At low risk for CHD (0-1 risk factors)	Simvastatinstatin, Bezafibrate	simvastatinstatin: 40; Bezafibrate: 800	Vitamin E.			Mean: 1.2 Median SD: 0.4 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	I assumed no losses to follow-up although I did not see this explicitely stated	medium
				No treatment (aside from CVD drug)			Mean:1.1 Median SD: 0.1 SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Wolf 2006[68] crossover	Low and/or Moderate	ASA	500	ginkgo biloba			Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	Study states that: Laboratory findings in all subjects were un-remarkable and did not indicate any differences between the treatment groups.	low-medium
							Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
De Caterina 2002[16] crossover	At high risk for CHD	simvastatinstatin	10-40	Vitamin E			Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	Values are presented in graphs, but difficult to read. Statement that "Neither LDL cholesterol nor triglycerides were affected by Vitamin E."	high
				No treatment (aside from CVD drug)			Mean:54 Median SD: 15.3 SE: Lower: Upper:	Mean:2.2 Median: SD: P:			
Balestrieri 1996[4] crossover	Low and/or Moderate	Simvastatinstatin	10-40	Fish/marine oils	14		Mean: 53 Median SD: 21 SE:	Mean:2 % mean: Median: SD:	Mean: Median: SD: P:		medium

Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
							Lower: Upper:	P:			
				Placebo	14		Mean:52 Median SD: 18 SE: Lower: Upper:	Mean:2 Median: SD: P:			
Paolisso 1995[56] crossover	At high risk for CHD	nifedipine	88	Vitamin E	30		Mean: 0.89 Median SD: SE:0.04 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P: <0.05		medium
				Placebo	30		Mean:0.78 Median SD: 0.07 SE: Lower: Upper:	Mean: Median: SD: P:			
Hansen1993[29] crossover	Low and/or Moderate	lovastatin	40	Fish/marine oils	14		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: 6 Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	14		Mean: Median SD: SE: Lower:	Mean: % mean:14 Median: SD: P:			

Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
							Upper:				
Mueller 1991[51] crossover	Low and/or Moderate	aspirin	325-single dose	Fish/marine oils	12		Mean: 46.17 Median SD: 11.56 SE: Lower: Upper:	Mean:3.34 % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	12		Mean:44.25 Median SD: 9.17 SE: Lower: Upper:	Mean:1.42 Median: SD: P:			
Maki 2008[41] crossover	Low and/or Moderate	simvastatin	20	Omega-3	39		Mean: Median 45 SD: SE: Lower: 27 Upper:106	Mean: % mean: Median: 16.4% SD: P:	Mean: Median: 7.2 SD: P: 0.001	The IQRs reported are actually ranges (low-high).	medium
				Placebo	39		Mean: Median 41 SD: SE: Lower: 29 Upper:93	Mean: Median:10.6% SD: P:			

Evidence Table 78. KQ2—Continuous data—INR

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Sconce 2007[61]	Unclear	wafarin	varying doses	Vitamin K	35	Standard deviation of INR (This is actually the standard deviation of the INR over a 6 month period after begining treatment with Vit K compared to 6 months prior to treatment with vit K)	Mean: 0.47 Median SD: 0.18 SE: Lower: Upper:	Mean:-0.24 % mean: Median: SD: 0.14 P: <0.001	Mean: Median: SD: P:	Some data (<1% in each arm) omitted from analysis due to known confounding factors	medium
				Placebo	33		Mean:0.59 Median SD: 0.15 SE: Lower: Upper:	Mean:-0.11 Median: SD: 0.18 P: <0.001			
Sconce 2007[61]	Unclear	wafarin	varying doses	Vitamin K	35	% of time in target INR range (within 0.5 U); within 0.5 U	Mean: 87 Median SD: 14 SE: Lower: Upper:	Mean:28 % mean: Median: SD: 20 P: <0.01	Mean: Median: SD: P:		medium
				Placebo	33		Mean:78 Median SD: 17 SE: Lower: Upper:	Mean:15 Median: SD: 20 P: <0.01			

Evidence Table 78. KQ2—Continuous data—INR (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Lee 2008[36]	At high risk for CHD	wafarin	3.5	Ginseng.	12	Peak INR	Mean: 1.16 Median SD: 0.09 SE: Lower: Upper:	Mean:0.15 % mean: Median: SD: P: <0.01	Mean:0.01 Median: SD: P:		medium
				No treatment (aside from CVD drug)	13		Mean:1.15 Median SD: 0.07 SE: Lower: Upper:	Mean:0.13 Median: SD: P: <0.01			
Lee 2008[36]	At high risk for CHD	wafarin	3.5	Ginseng.	12	Peak INR	Mean: 2.25 Median SD: 0.38 SE: Lower: Upper:	Mean:1.24 % mean: Median: SD: P: <0.01	Mean:0.11 Median: SD: P:		medium
				No treatment (aside from CVD drug)	13		Mean:2.14 Median SD: 0.38 SE: Lower: Upper:	Mean:1.12 Median: SD: P: <0.01			
Lee 2008[36]	At high risk for CHD	wafarin	3.5	Ginseng	12	AUC_{INR} Measured as area under the curve	Mean: 7.55 Median SD: 0.41 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean:0.04 Median: SD: P:		medium

Evidence Table 78. KQ2—Continuous data—INR (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	13		Mean:7.52 Median SD: 0.31 SE: Lower: Upper:	Mean: Median: SD: P:			
Lee 2008[36]	At high risk for CHD	phenprocoumon	3.5	Ginseng.	12	AUC_{INR} Measured as area under the curve	Mean: 22.18 Median SD: 1.85 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean:0.49 Median: SD: P:		medium
				No treatment (aside from CVD drug)	13		Mean:21.69 Median SD: 1.54 SE: Lower: Upper:	Mean: Median: SD: P:			
Macan 2006[40]	Low and/or mod to high risk	Warfarin	NR	Garlic.	22	NR - assessed after 12 hr fast	Mean: Median SD: SE: Lower: Upper:	Mean:0 % mean: Median: SD: 1.2 P:	Mean: Median: SD: P: 0.579		medium
				Placebo	26		Mean: Median SD: SE: Lower: Upper:	Mean:0.2 Median: SD: 0.09 P:			

Evidence Table 78. KQ2—Continuous data—INR (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Yuan 2004[71]	Low and/or Moderate	Warfarin	5.00	Ginseng	12	peak INR	Mean: Median SD: SE: Lower: -2.41 Upper:0.02	Mean: % mean: Median: :-0.16 SD: P:	Mean: Median SD: P: 0.019		low
				Placebo	8		Mean: Median SD: SE: Lower: -2.41 Upper:-0.07	Mean:-0.02 Median: SD: P:			
Yuan 2004[71]	Low and/or Moderate	Warfarin	5.00	Ginseng	12	AUC_{INR}	Mean: Median SD: SE: Lower: -6.36 Upper:0.36	Mean: % mean: Median:-0.46 SD: P:	Mean: Median: SD: P:		low
				Placebo	8		Mean: Median SD: SE: Lower: -0.51 Upper:0.72	Mean:-0.09 Median: SD: P:			
Wolf 2006[68]	Unclear	Warfarin	NR	Omega-3	6	no numeric data reported- data could not be obtained from the graph with an accaptable degree	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		high

Evidence Table 78. KQ2—Continuous data—INR (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	5	of accuracy	Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Jiang 2004[33]	At low risk for CHD (0-1 risk factors)	Warfarin	25 - single dose	Ginseng	12	AUC(0-168)	Mean: 111.1 Median SD: 43.1 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean:1.01 (Ginseng+ no treatment)	95% CI of mean for individual group data: Ginseng group: 83.9-138.7; St. Johns Wort group: 68.8-107.8; No treatment group: 79.6-142.3	medium
				St. John's	12		Mean:88.3 Median SD: 30.7 SE: Lower: Upper:	Mean:0.79 Median: SD: P:			
				No treatment	12		Mean: 111 Median SD: 49.3 SE: Lower: Upper:	Mean: Median: SD: P:			medium
Jiang 2005[32]	At low risk for CHD (0-1 risk factors)	Warfarin	25 - single dose	Gingko Biloba	12	AUC(0-168)	Mean: 121 Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean:0.93 (gingko biloba + no treatment) Median: SD:	95% CI of mean for individual group data: ginkgo group: 77-165; Ginger	medium

Evidence Table 78. KQ2—Continuous data—INR (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Ginger	12		Mean:125 Median SD: SE: Lower: Upper:	Mean: Median: SD: P:	P:	group: 91-160; No treatment group: 90-158	
				No treatment	12		Mean:124 Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Mohammed Abdul 2008[49]	At low risk for CHD (0-1 risk factors)	Warfarin	25 - single dose	Garlic	12	INR_{max} measured at each blood sampling time before and after warfarin dosing using a BFT II analyser	Mean: 2.5 Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: 0.95 Median: SD: P:	Post treatment mean 95% CI: Garlic group 2.10-2.80; No treatment group 2.30-3.00.	medium
				No treatment	12		Mean: 2.6 Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Mohammed Abdul 2008[49]	At low risk for CHD (0-1 risk factors)	Warfarin	25 - single dose	Garlic	12	AUC_{INR} measured at each blood sampling time before and after warfarin dosing using a	Mean: 100.3 Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean:0.98 Median: SD: P:	Post treatment mean 95% CI: Garlic group 70.90-129.80; No treatment group 72.10-	medium

Evidence Table 78. KQ2—Continuous data—INR (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment	12	BFT II analyser	Mean:96 Median SD: SE: Lower: Upper:	Mean: Median: SD: P:		119.80.	
Abdul 2010[1]	At low risk for CHD (0-1 risk factors)	Warfarin	25 - single dose	Echinacea	11	INR max samples were collected into sodium citrate - measured using a BFT II analyzerTM (Dade Behring Diagnostics Pty Ltd, Lane Cove, NSW, Australia) as previously reported (reference provided)	Mean: 1.8 Median SD: SE: Lower: Upper:	NR	Mean:1.04 Median: SD: P:	Post treatment mean 95% CI: Echinacea group 1.60-2.00; No treatment group 1.50-1.90.	medium
				No treatment	11		Mean:1.7 Median SD: SE: Lower: Upper:	NR			
Abdul 2010[1]	At low risk for CHD (0-1 risk factors)	Warfarin	25 - single dose	Echinacea	11	AUC_{INR} samples were collected into sodium citrate -	Mean: 55.2	NR	Mean:1.09 Median: SD: P:	Post treatment mean 95% CI: Echinacea group 42.80-	medium
				No treatment	11		NR	NR			

Evidence Table 78. KQ2—Continuous data—INR (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
						measured using a BFT II analyzerTM (Dade Behring Diagnostics Pty Ltd, Lane Cove, NSW, Australia) as previously reported (reference provided)	NR	NR		67.60; No treatment group 38.30-67.20.	

Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Bays 2010[6] parallel	Unclear	atorvastatin	10-40	Omega-3 (EPA, DHA, or both).	122	at week 8, end of 10 mg/d atorvastatin	Mean: Median 97 SD: SE: Lower: 82 Upper: 118	Mean: % mean: Median:-29.3% SD: P:	Mean: Median:2.2% SD: P:2.4		medium
				Placebo	121		Mean: Median 98 SD: SE: Lower: 81 Upper:111	Mean: Median:-31.5% SD: P:			
Bays 2010[6] parallel	Unclear	atorvastatin	10-40	Omega-3 (EPA, DHA, or both).	122	at week 16, end of 40 mg/d atorvastatin	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median:0.3% SD: P:0.64		medium
				Placebo	121		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Mabuchi 2007[39]	Unclear	atorvastatin	1	Coenzyme Q10.	24		Mean: 2.68 Median SD: 0.55 SE: Lower: Upper:	Mean: % mean: -43 Median: SD: P: <0.001	Mean: Median: SD: P:	"...there were no differences between the groups"	medium
				Placebo	25		Mean:2.47 Median SD: 0.49 SE: Lower: Upper:	Mean: % mean:-49 Median: SD: P: <0.0001			
Young 2007[70] parallel	Mod and high risk	simvastatinstatin	10-40	Coenzyme Q10.	22		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median:-1.7% SD: P: >0.001	Mean: Median: SD: P: 0.53	No difference in groups (p=0.53)	medium
				Placebo	22		Mean: Median SD: SE: Lower: Upper:	Mean: Median:-1.3% SD: P: >0.001			
Davidson 2007[14] parallel	Unclear	simvastatinstatin	40	Omega-3 (EPA, DHA, or both).	122		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: 3.4 Median:0.7 SD: 18.50% P:	Mean: Median: SD: P: 0.53		medium

Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	132		Mean: Median SD: SE: Lower: Upper:	Mean: Median:-1.9% SD: 12.40% P:			
Caso 2007[11]	Unclear	Simvastatinstatin (22); Atorvastatin (7); Pravastatin (2); Lovastatin (1)	varying doses	Coenzyme Q10.	18	fasting plasma	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median:-2.8 SD: P:	Mean: Median: SD: P:	No final outcome data presented. Study reports baseline data and that the values did not change during the intervention period. Mean +/- SEM - Baseline CoQ10: 96 +/- 3; Baseline Vit E: 115 +/- 13	low
				Vit E	14		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Meyer 2007[46]	Unclear	simvastatinstatin, 13 atorvastatin, 4 pravastatin, 2 cerivastatin and 2 fluvastatin 81	81	Fish/marine oils	13	For all participants at 6 months: Blood plasma LDL-C under overnight fasted condition	Mean: 2.4 Median SD: SE:0.21 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	also measured in a subset of participants with higher	medium

Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Fish/marine oils	13		Mean:2.35 Median SD: SE:0.21 Lower: Upper:	Mean: Median: SD: P:		TC baseline levels (will be extracted separately)	
				Placebo	14		Mean:2.49 Median SD: SE:0.22 Lower: Upper:	Mean: Median: SD: P:			
Meyer 2007[46]	Unclear	simvastatinstatin, 13 atorvastatin, 4 pravastatin, 2 cerivastatin and 2 fluvastatin 81	81	Fish/marine oils	13	Blood plasma LDL-C in subjects with baseline Total cholesterol levels >= 3.8 mmol/L as reduction is total cholesterol was associated with baseline values	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	Data presented in bar graph with Means and SEs	medium
				Fish/marine oils	13		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
				Placebo	14						
Sutken 2006[63] parallel	Low and/or Moderate	Gemfibrozil	1200	Vitamin E.	22	Serum for elderly sub-group	Mean: 5.99 Median SD: SE:1.22 Lower: Upper:	Mean: % mean: Median: SD: P: <0.01	Mean: Median: SD: P:		high

Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	23		Mean:5.81 Median SD: SE:1.3 Lower: Upper:	Mean: Median: SD: P: <0.05			
Sutken 2006[63] parallel	Low and/or Moderate	Gemfibrozil	1200	Vitamin E.	22	Serum for younger sub-group	Mean: 4.61 Median SD: SE:0.12 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		high
				No treatment (aside from CVD drug)	23		Mean:4.72 Median SD: SE:0.1 Lower: Upper:	Mean: Median: SD: P:			
Macan 2006[40] parallel	Low and/or Moderate	Warfarin	NR	Garlic.	22	12 hour fasting blood sample	Mean: Median SD: SE: Lower: Upper:	Mean:2.6 % mean: Median: SD: 25.8 P:	Mean: Median: SD: P: 0.626		medium
				Placebo	26		Mean: Median SD: SE: Lower: Upper:	Mean:-1.6 Median: SD: 30 P:			

Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Manuel 2004[42] parallel	At high risk for CHD	Atorvastatin	20	Vitamin E.	11	serum, fasting	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P: <0.001	Mean: Median: SD: P:	Data not presented in paper - only combined data for both groups across time and for groups separately at baseline only. Report states that changes were 'same in both groups (the between-group comparison of change over time was not significant)	medium
				Placebo	11		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P: <0.001			
Playford 2003[58]	At high risk for CHD	Fenofibrate	200	Coenzyme Q10: 200 mg C0Q10 plus 200mg fenofibrate	18	measured after 14 hr fast;	Mean: 3.0 Median SD: SE:0.2 Lower: Upper:	Mean:-0.1 % mean: Median: SD: P:	Mean:0.4 Median: SD: P: 0.353 or 0.014		low-medium

Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	17		Mean:2.9 Median SD: SE:0.2 Lower: Upper:	Mean:-0.4 Median: SD: P:			
				200 mg CoQ10 only	20		Mean:3.4 Median SD: SE:0.2 Lower: Upper:	Mean:-0.2 Median: SD: P:			
				Placebo	18		Mean:3.2 Median SD: SE:0.2 Lower: Upper:	Mean: 0 Median: SD: P:			
Svaneborg 2002[64] parallel	At low risk for CHD (0-1 risk factors)	ASA	100	Omega-3 (EPA, DHA, or both).	12		Mean: Median 2.55 SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	placebo= corn oil containing omega-6	medium
				Placebo	6		Mean: Median 2.95 SD: SE: Lower:2.15 Upper:3.8	Mean: Median: SD: P:			

Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Duffy 2001[20] parallel	Low and/or Moderate	simvastatin	10-40	Vitamin E.	6		Mean: 2.6 Median SD: 0.7 SE: Lower: Upper:	Mean:-1.5 % mean: Median: SD: P: 0.02	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)	7		Mean:3.3 Median SD: 0.6 SE: Lower: Upper:	Mean:-2.1 Median: SD: P: 0.01			
				1000IU Vitamin E	6		Mean:4.9 Median SD: 2.3 SE: Lower: Upper:	Mean:0.2 Median: SD: P:			
				Placebo	7		Mean:4.3 Median SD: 0.9 SE: Lower: Upper:	Mean:-0.6 Median: SD: P: 0.02			
Napoli 1998[52] parallel	Unclear	Pravastatin	20-40	Vitamin E.	52	12-14 hr fasting determined enzymatically by Boehringer test kit	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -34 Median: SD: P: <0.05	Mean: Median: SD: P: <0.05		medium

Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	56		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P: <0.05			
Yamamoto 1995[69] parallel	At high risk for CHD	diltiazem	90-120	Omega-3 (EPA, DHA, or both).	12		Mean: 118 Median SD: SE:36 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)	10		Mean:118 Median SD: SE:24 Lower: Upper:	Mean: Median: SD: P:			
McDowell 1994[44] parallel	Unclear	Simvastatinstatin	20	Vitamin E.	8	overnight fasting measurement	Mean: 4.1 Median SD: 1.0 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	8		Mean:4.8 Median SD: 0.8 SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Kaul 1992[34] parallel	At high risk for CHD	Calcium channel blocker, ASA	ASA: 150; heparin: 1000 U/d; ca blockers: NR	Fish/marine oils.	58		Mean: 132 Median SD: 31.7 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		low-medium
				No treatment (aside from CVD drug)	49		Mean:131 Median SD: 30.1 SE: Lower: Upper:	Mean: Median: SD: P:			
Nordøy 2003[55] parallel	Mod and high risk	atorvastatin	10	Fish/marine oils.	22	Blood sample taken after 12 hr fasting, within 6 days of end of study	Mean: Median SD: SE: Lower: Upper:	Mean:-0.12 % mean: Median: SD: 0.51 P:	Mean: Median: SD: P: 0.28		medium
				Placebo	20		Mean: Median SD: SE: Lower: Upper:	Mean:-0.27 Median: SD: 0.37 P:			
Roth 2009[60] parallel	Unclear	fenofibrates by 100%	130	Omega-3 (EPA, DHA, or both).	81		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median:48.2% SD: P:	Mean: Median: SD: P: 9.0 or 0.03	Significant p = 0.030	medium

Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	82		Mean: Median SD: SE: Lower: Upper:	Mean: Median:39% SD: P:			
Isley 2007[31] parallel	Unclear	niacin	325	Omega-3	7		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: 11 Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	8		Mean: Median SD: SE: Lower: Upper:	Mean: % mean -4 Median: SD: P:			
Budoff 2004[10] parallel	At high risk for CHD	statins + aspirin	10-40	Garlic	9	Measured after 12 hr fast	Mean: Median SD: SE: Lower: Upper:	Mean:-3.2 % mean: Median: SD: 16.2 P:	Mean: Median: SD: P: 0.0932		medium
				Placebo	10		Mean: Median SD: SE: Lower: Upper:	Mean:21.9 Median: SD: 39.4 P:			

Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Chan 2002[12] parallel	At moderate/moderately high risk for CHD (2+ risk factors)	atorvastatin	40	Fish/marine oils.	11	collected after an overnight fast (14 h) in a semirecumbent position for all biochemical measurements.	Mean: 2.15 Median SD: SE:0.19 Lower: Upper:	Mean: % mean:-42.5 Median: SD: 3.50% P:	Mean: Median: SD: P:		medium
				Placebo	13		Mean:1.84 Median SD: SE:0.12 Lower: Upper:	Mean: % mean:-54 Median: SD: P:			
Liu 2003[37] parallel	Unclear	simvastatinstatin	10	Fish/marine oils.	19	Fasting blood samples	Mean: 3.21 Median SD: 1.15 SE: Lower: Upper:	Mean:-1.29 % mean: -28.7 Median: SD: 1.05 P:	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)	18		Mean:3.05 Median SD:0.7 SE: Lower: Upper:-31.6	Mean:-1.41 Median: SD: 0.76 P:			
Dehmer 1988[17] parallel	At high risk for CHD	aspirin + Dipyridamole + ca channel blockers)	ASA: 325; dipyridamole: 225; Ca blocker: NR	Omega-3 (EPA, DHA, or both).	43	Fasting blood samples; standard automated techniques	Mean: 140 Median SD: 54.3 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium

Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	39		Mean:221 Median SD: 127.7 SE: Lower: Upper:	Mean: Median: SD: P:			
Desideri 2003[18] parallel	At low risk for CHD (0-1 risk factors)	Simvastatinstatin, Bezafibrate	simvastatinstatin: 40; Bezafibrate: 800	Vitamin E.		12 hr fasting at 800hr - serum	Mean: 3.9 Median SD: 0.4 SE: Lower: Upper:	Mean: % mean: Median: SD: P: <0.0001	Mean: Median: SD: P:	I assumed no losses to follow-up although I did not see this explicitely stated	medium
				No treatment (aside from CVD drug)			Mean:4.1 Median SD: 0.9 SE: Lower: Upper:	Mean: Median: SD: P: <0.0001			
Wolf 2006[68] crossover	Low and/or Moderate	ASA	500	ginkgo biloba	50		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	Study states that: Laboratory findings in all subjects were un-remarkable and did not indicate any differences between the treatment groups.	low-medium
				Placebo	50		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
De Caterina 2002[16] crossover	At high risk for CHD	simvastatinstatin	10-40	Vitamin E		at 1 mo after treatment started - like a parallel RCT (treatment lasted two months)	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	Values are presented in graphs, but difficult to read.	High
				No treatment (aside from CVD drug)			Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Balestrieri 1996[4] crossover	Low and/or Moderate	Simvastatinstatin	10-40	Fish/marine oils	14	12 hour fast, anti-tubectal vein	Mean: 228 Median SD: 50 SE: Lower: Upper:	Mean:0 % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	14		Mean:227 Median SD: 52 SE: Lower: Upper:	Mean:-5 Median: SD: P:			
Paolisso 1995[56] crossover	At high risk for CHD	nifedipine	88	Vitamin E	30	Fasting; at 2 months at end of treatment	Mean: 4.94 Median SD: SE:0.34 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P: <0.05		medium

Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	30		Mean:5.97 Median SD: SE:0.22 Lower: Upper:	Mean: Median: SD: P:			
Hansen1993[29] crossover	Low and/or Moderate	lovastatin	40	Fish/marine oils	14		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -39 Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	14		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -37 Median: SD: P:			
Mueller 1991[51] crossover	Low and/or Moderate	aspirin	325 - single dose	Fish/marine oils	12	Fasting	Mean: 135.58 Median SD: 34.94 SE: Lower: Upper:	Mean:-1 % mean: Median: SD: P: <0.06	Mean:-15 Median: SD: P:		medium
				Placebo	12		Mean:121.58 Median SD: 33.81 SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Maki 2008[41] crossover	Low and/or Moderate	simvastatin	20	Omega-3	39	Least square mean (SEM)	Mean: 103 Median SD: SE:5.2 Lower: Upper:	Mean: % mean:-37.2 Median: SD: P:	Mean:1.3 Median: SD: P: 0.433		medium
				Placebo	40		Mean:98 Median SD: SE:5. 3 Lower: Upper:	Mean:-38.4% Median: SD: P:			

Evidence Table 80. KQ2—Continuous data—Non-HDL-C

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Bays 2010[6] parallel	Unclear	atorvastatin	10-40	Omega-3 (EPA, DHA, or both).	122	The follow up was at the end of 10 mg atorvastatin at week 8	Mean: Median 133 SD: SE: Lower: 114.5 Upper:153.5	Mean: % mean: Median:-40.2 SD: P:	Mean: Median: SD: P: <0.001	there are 90%CIs reported instead of 95% CI	medium
				Placebo	121		Mean: Median 142.5 SD: SE: Lower:123.5 Upper:162.5	Mean: Median:-33.7 SD: P:			
Bays 2010[6] parallel	Unclear	atorvastatin	10-40	Omega-3 (EPA, DHA, or both).	122	At week 16, end of 40 mg atorvastatin	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: -50 SD: P:	Mean: Median: SD: P: <0.001	The 95% CIs reported are actually 90% CIs. The difference in % medians reported for individual group data were read from a graph.	medium
				Placebo	121		Mean: Median SD: SE: Lower: Upper:	Mean: Median:-45 SD: P:			

Evidence Table 80. KQ2—Continuous data—Non-HDL-C (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Davidson 2007[14] parallel	Unclear	simvastatinstatin	40	Omega-3 (EPA, DHA, or both).	122		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -7.9% Median:-9 SD: P:	Mean: Median: SD: P: <0.001		medium
				Placebo	132		Mean: Median SD: SE: Lower: Upper:	Mean: % mean -1.5 Median:-2.2 SD: P:			
							Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Playford 2003[58] parallel	At high risk for CHD	Fenofibrate	200	Coenzyme Q10. 200 mg plus 200 mg fenofibrate	18	measured after 14 hr fast;	Mean: 3.7 Median SD: 0.2 SE: Lower: Upper:	Mean:-0.6 % mean: Median: SD: P:	Mean:0.1 Median: SD: P:0.496		low-medium

Evidence Table 80. KQ2—Continuous data—Non-HDL-C (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	17		Mean: 3.6 Median SD: SE:0.2 Lower: Upper:	Mean:-0.8 % mean: Median: SD: P:			
				Coenzyme Q10. 200 mg CoQ10 only	20		Mean: 4.3 Median SD: SE:0.2 Lower: Upper:	Mean:0 % mean: Median: SD: P:			
				Placebo	18		Mean:4.4 Median SD: SE:0.2 Lower: Upper:	Mean:0.1 Median: SD: P:			
Davidson 1997[15] parallel	Unclear	Simvastatinstatin	10	Fish/marine oils.	9	fasting blood sample	Mean: 170.4 Median SD: SE:15.8 Lower: Upper:	Mean:-61.9 % mean: -24.8% Median: SD: P: <0.001	Mean:5.6 Median: SD: P:		Medium

Evidence Table 80. KQ2—Continuous data—Non-HDL-C (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	10		Mean: 164.8 Median SD: SE:6.8 Lower: Upper:	Mean:- 57.9 % mean: -25.8 Median: SD: P: <0.001			
				7.2 g/day marine oil	10		Mean:226.4 Median SD: SE:10.2 Lower: Upper:	Mean:- 9.8 % mean: -3.5% Median: SD: P:			
Roth 2009[60] parallel	Unclear	fenofibrates by 100%	130	Omega-3 (EPA, DHA, or both).	81		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median:- 8.2 SD: P:	Mean: Median: SD: P: 0.767		medium
				Placebo	82		Mean: Median SD: SE: Lower: Upper:	Mean: Median:- 7 SD: P:			

Evidence Table 80. KQ2—Continuous data—Non-HDL-C (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Chan 2002[12]	At moderate/moderately high risk for CHD (2+ risk factors)	atorvastatin	40	Fish/marine oils.	11	collected after an overnight fast (14 h) in a semirecumbent position for all biochemical measurements.	Mean: 2.72 Median SD: SE:0.22 Lower: Upper:	Mean: % mean: -48 Median: SD: 3% P:	Mean: Median: SD: P:		medium
				Placebo	13		Mean:2.58 Median SD: SE:0.11 Lower: Upper:	Mean: % mean: -43 Median: SD: P:			
Maki 2008[41] crossover	Low and/or Moderate	simvastatin	20	Omega-3	39	10-14 hour fast; Centers for Disease Control and Prevention lipid standardization program	Mean: Median 133 SD: SE: Lower: 70 Upper:288	Mean: % mean: Median:-40 SD: P:	Mean: Median: SD: P: <0.001	The IQRs reported are actually ranges (low-high).	medium
				Placebo	40		Mean: Median 139 SD: SE: Lower: 45 Upper:260	Mean: Median:-34.3 SD: P:			
							Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 81. KQ2—Continuous data—Platelet aggregability

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Gardner 2007[23] Parallel	moderate to high	ASA	325	ginkgo biloba	29		Mean: Median SD: SE: Lower: Upper:	Mean: % mean:1.3 Median: SD: 6.00% P:	Mean: Median: SD: P:	No difference in groups (p=0.2)	low
				Placebo	26		Mean: Median SD: SE: Lower: Upper:	Mean: % mean:-2.7 Median: SD: 10.00% P:			
Gardner 2007[23] Parallel	moderate to high	ASA	325	ginkgo biloba	29		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -1.3 Median: SD: 12.00% P:	Mean: Median: SD: P:	No difference in groups (p=0.15)	low
				Placebo	26		Mean: Median SD: SE: Lower: Upper:	Mean: % mean4.2 Median: SD: 12.60% P:			

Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Gardner 2007[23] Parallel	moderate to high	ASA	325	ginkgo biloba	29		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -4.1 Median: SD: 14.90% P:	Mean: Median: SD: P:	No difference in groups (p=0.7)	low
				Placebo	26		Mean: Median SD: SE: Lower: Upper:	Mean: % mean - 6 Median: SD: 19.60% P:			
Gardner 2007[23] Parallel	moderate to high	ASA	325	ginkgo biloba	29		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -1.5 Median: SD: 18.70% P:	Mean: Median: SD: P:	No difference in groups (p=0.3)	low-medium
				Placebo	26		Mean: Median SD: SE: Lower: Upper:	Mean: % mean - 6.3 Median: SD: 18.70% P:			

Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Steiner 1995[62] Parallel	At high risk for CHD	ASA	325	Vitamin E	25	platelet adhesion to collagen III	Mean: 2.7 Median SD: 0.4 SE: Lower: Upper:	Mean: % mean: 40 Median: SD: P: <0.0001	Mean: Median: SD: P:	please ensure about the unit. the difference is reported for change from baseline in the vit E group only.	medium
				Placebo	48		Mean:4.4 Median SD: 0.8 SE: Lower: Upper:	Mean: Median: SD: P:			
Kim 2010[35] crossover	Low and/or Moderate	Ticlopidine	250- single dose	ginkgo biloba	24	5µl of 10 µM ADP	Mean: 63 Median SD: 18.9 SE: Lower: Upper:	Mean:-3.6 % mean: Median: SD: P:	Mean: Median: SD: P:	Mean ratio of ginkgo/No treatment: 1.02	medium medium
				No treatment	24		Mean:64.8 Median SD: 19.7 SE: Lower: Upper:	Mean:-3.5 Median: SD: P:			

Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Kim 2010[35] crossover	Low and/or Moderate	Ticlopidine	250- single dose	ginkgo biloba	24	1 µL of 2 µg/mL collagen	Mean: 80.4 Median SD: 11.2 SE: Lower: Upper:	Mean:3.5 % mean: Median: SD: P:	Mean: Median: SD: P:	Mean ratio of ginkgo/No treatment: 1.03	medium
				No treatment	24		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Jiang 2004[33]	At low risk for CHD (0-1 risk factors)	Warfarin	25 - single dose	Ginseng	12	Arachidonic acid 10 ml of 50 mM concentration	Mean: 7.1 Median SD: 1.4 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean:1 Median: SD: P:	95% CI of mean for individual group data: Ginseng group: 6-7.8; St. Johns Wort: 6.5-8.2; No treatment group: 5.6-9.1	medium
				St. John's	12		Mean: 7.5 Median SD: 1.1 SE: Lower: Upper:	Mean: % mean: Median: SD: P:			

Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment	12		Mean:7.7 Median SD: 2.2 SE: Lower: Upper:	Mean: Median: SD: P:			
Jiang 2005[32]	At low risk for CHD (0-1 risk factors)	Warfarin	25 - single dose	Gingko Biloba	12	Arachidonic acid	Mean: 8.4 Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean:1.14 Median: SD: P:	95% CI of mean for individual group data: ginkgo group: 7.60-9.20; Ginger group: 7.50-8.70; No treatment group: 6.50-8.40	medium
				Ginger	12		Mean: 8.1 Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:			
				No treatment	12		Mean:7.5 Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Aruna 2007[2] crossover	At low risk for CHD (0-1 risk factors)	Cilostazol 100 mg	104 to 200 (cilostazol); 75 to 150 (clopidogrel)	ginkgo biloba	10	2.5µl of 10µM ADP	Mean: 77 Median SD: 20 SE:7 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	95% CI of mean for individual group data: ginkgo group: 39.00-73.00;	medium

Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment	10		Mean:59 Median SD: 13 SE:10 Lower: Upper:	Mean: Median: SD: P:		No treatment group: 36.00-82.00	
Aruna 2007[2] crossover	At low risk for CHD (0-1 risk factors)	Cilostazol 100 mg	104 to 200 (cilostazol); 75 to 150 (clopidogrel)	ginkgo biloba	10	2.5µl of 10µM ADP	Mean: 56 Median SD: 19 SE:7 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	95% CI of mean for individual group data: ginkgo group: 61.00-92.00; No treatment group: 41.00-79.00.	medium
				No treatment	10		Mean:60 Median SD: 23 SE:8 Lower: Upper:	Mean: Median: SD: P:			
Aruna 2007[2] crossover	At low risk for CHD (0-1 risk factors)	Cilostazol 100 mg	104 to 200 (cilostazol); 75 to 150 (clopidogrel)	ginkgo biloba	10	2.5µl of 5µM ADP	Mean: 57 Median SD: 22 SE:8 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	95% CI of mean for individual group data: ginkgo group: 39.00-75.00 p-value <0.05; No treatment group: 23.00-72.00, p-value <0.05.	medium
				No treatment	10		Mean:47 Median SD:32 SE:11 Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Aruna 2007[2] crossover	At low risk for CHD (0-1 risk factors)	Cilostazol 100 mg	104 to 200 (cilostazol); 75 to 150 (clopidogrel)	ginkgo biloba	10	2.5µl of 5µM ADP	Mean: 49 Median SD: 21 SE:8 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	95% CI of mean for individual group data: ginkgo group: 31.00-67.00, p-value <0.05; No treatment group: 30.00-73.00, p-value < 0.05.	medium
				No treatment	10		Mean:52 Median SD: 26 SE:9 Lower: Upper:	Mean: Median: SD: P:			
Mohammed Abdul 2008[49] Crossover	At low risk for CHD (0-1 risk factors)	Warfarin	25 - single dose	Garlic	12	assessed on blood samples (within 3 h of blood collection) collected 24 h	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	"…2 weeks of pretreatment with garlic…had no effect on platelet	medium

Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment	12	prior to warfarin administration (24 h) in each treatment period using a whole blood aggregometer (Chrono-par; Chrono-log Corp., Havertown, Pennsylvania, USA; Edward Keller Australia Pty Ltd, Hallam, VIC, Australia). Method described further but not extracted	Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:		aggregation."	
McKenney 2006[45] Crossover	Low and/or Moderate	simvastatin	80	Omega-3	24	ADP	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -3.4 Median: SD: P:	Mean: Median: SD: P:		medium

Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment	23		Mean: Median SD: SE: Lower: Upper:	Mean: % mean -4.5 Median: SD: P:			
McKenney 2006[45] Crossover	Low and/or Moderate	simvastatin	80	Omega-3	24	Collagen	Mean: Median SD: SE: Lower: Upper:	Mean: % mean:-5.1 Median: SD: P:	Mean: Median: SD: P:		medium
				No treatment	23		Mean: Median SD: SE: Lower: Upper:	Mean: % mean -6 Median: SD: P:			
Abdul 2010[1]	At low risk for CHD (0-1 risk factors)	Warfarin	25 - single dose	Echinacea	11	10µM ADP	Mean: 7.5 Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean:0.84 Median: SD: P:	Post treatment mean 95% CI: Echinacea group 4.1-10.8; No treatment group 5.5-10.	medium
				No treatment	11		Mean:7.8 Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Abdul 2010[1]	At low risk for CHD (0-1 risk factors)	Warfarin	25 - single dose	Echinacea	11	Arachidonic acid 0.5mM	Mean: 12.1 Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean:1.06 Median: SD: P:	Post treatment mean 95% CI: Echinacea group 9.3-15; No treatment group 9.6-12.5.	medium
				No treatment	11		Mean:11 Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Abdul 2010[1]	At low risk for CHD (0-1 risk factors)	Warfarin	25 - single dose	Echinacea	11	Collagen-induced 2µg/ml	Mean:15.8 Median SD: SE: Lower: Upper:	Mean: Median: SD: P:	Mean:1 Median: SD: P:	Post treatment mean 95% CI: Echinacea group 12.2-19.5; No treatment group 11.5-14.6.	medium
				No treatment	11		Mean:13 Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Wolf 2006[68] crossover	Low and/or Moderate	ASA	500	ginkgo biloba	50	Collagen-induced at 7 days after treatment	Mean: 81 Median SD: 8.6 SE: Lower: Upper:	Mean: % mean: -5.6 Median: SD: P:	Mean: Median: SD: P:	ratio of means presented with 90% CI	medium
				Placebo	50		Mean:81 Median SD: 12.7 SE: Lower: Upper:	Mean: % mean: -3.5 Median: SD: P:			
Wolf 2006[68] crossover	Low and/or Moderate	ASA	500	ginkgo biloba	50	Adenosine diphosphate-induced at day 7 after treatment	Mean: 44.8 Median SD: 18.1 SE: Lower: Upper:	Mean: % mean: -26.9 Median: SD: P:	Mean:0.95 Median: SD: P:	ratio of means reported with 90% CI	low-medium
				Placebo	50		Mean:47.2 Median SD: 15.1 SE: Lower: Upper:	Mean: % mean: -25.4 Median: SD: P:			

Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Wolf 2006[68] crossover	Low and/or Moderate	ASA	500	ginkgo biloba	50	Arachidonate-induced at day 7 after treatment	Mean: 2.2 Median SD: 2.1 SE: Lower: Upper:	Mean: % mean: -76 Median: SD: P:	Mean:0.65 Median: SD: P:	ratio of means reported with 90% CI; 100 put in as top of 90% CI but actually infinity	low-medium
				Placebo	50		Mean:3.4 Median SD: 10.4 SE: Lower: Upper:	Mean: % mean:-75.1 Median: SD: P:			
Wolf 2006[68] crossover	Low and/or Moderate	ASA	500	ginkgo biloba	50	Ristocetin-induced at 7 days, after treatment	Mean: 90 Median SD: 10.5 SE: Lower: Upper:	Mean: % mean: -6.5 Median: SD: P:	Mean:0.98 Median: SD: P:	ratio of means reported with 90% CI	low-medium
				Placebo	50		Mean:92.2 Median SD: 12.3 SE: Lower: Upper:	Mean: % mean:-4.1 Median: SD: P:			

Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Wolf 2006[68] crossover	Low and/or Moderate	ASA	500	ginkgo biloba	50	Epinephrine-induced at 7 days after treatment	Mean: 13.7 Median SD: 7.7 SE: Lower: Upper:	Mean:-7.1 % mean: Median: SD: P:	Mean:0.99 Median: SD: P:	ratio of means reported with 90% CI	low-medium
				Placebo	50		Mean:13.8 Median SD: 6.8 SE: Lower: Upper:	Mean: % mean:-6.5 Median: SD: P:			
Wolf 2006[68] crossover	Low and/or Moderate	ASA	500	ginkgo biloba	50	Platelet-activating factor-induced at day 7 after treatment	Mean: 4.8 Median SD: 3.7 SE: Lower: Upper:	Mean: % mean: -22.3 Median: SD: P:	Mean:0.69 Median: SD: P:	ratio of means reported with 90% CI	low-medium
				Placebo	50		Mean:6.9 Median SD: 11.5 SE: Lower: Upper:	Mean: % mean:-23.2 Median: SD: P:			

Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	50		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:			

Evidence Table 82. KQ2—Continuous data—Platelet count

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Lee 2008[36]	At high risk for CHD	wafarin	3.5	Ginseng.	12		Mean: 265.5 Median SD: 66.35 SE: Lower: Upper:	Mean:0.8 % mean: Median: SD: P:	Mean: Median: SD: P:	"There were no statistically significant differences between the ginseng group and control group."	medium
				No treatment (aside from CVD drug)	13		Mean:278.3 Median SD: 88.67 SE: Lower: Upper:	Mean:11.6 Median: SD: P:			
Macan 2006[40] parallel	Low and/or Moderate	Warfarin	NR	Garlic.	22	12 hr fasting blood measurement	Mean: Median SD: SE: Lower: Upper:	Mean:0.1 % mean: Median: SD: 72.1 P:	Mean: Median: SD: P: 0.887		medium
				Placebo	26		Mean: Median SD: SE: Lower: Upper:	Mean:2.4 Median: SD: 35.4 P:			

Evidence Table 82. KQ2—Continuous data—Platelet count (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Svaneborg 2002[64] parallel	At low risk for CHD (0-1 risk factors)	ASA	100	Omega-3 (EPA, DHA, or both).	12		Mean: Median 198 SD: SE: Lower: 156 Upper:240	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	6		Mean: Median 201 SD: SE: Lower: 169 Upper:254	Mean: Median: SD: P:			
Nordøy 2000[54] Parallel	Low and/or mod to high risk	simvastatinstatin	20	Omega-3 (EPA, DHA, or both).	21		Mean: Median SD: SE: Lower: Upper:	Mean:9 % mean: Median: SD: 7 P:	Mean: Median: SD: P:	Crude difference between groups in mean change from baseline (omega-3 vs. placebo): 6 (p=0.5)	medium
				Placebo	20		Mean: Median SD: SE: Lower: Upper:	Mean:3 Median: SD: 6 P:			
Napoli 1998[52] parallel	Unclear	Pravastatin	20-40	Vitamin E.	52		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	"..no differences in routine laboratory tests or adverse	medium

Evidence Table 82. KQ2—Continuous data—Platelet count (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	56		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:		events were registered during the study (data not shown); in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups."	
Budoff 2004[10] parallel	At high risk for CHD	statins + aspirin	10 -40	Garlic	9	Measured after 12 hr fast	Mean: Median SD: SE: Lower: Upper:	Mean:3.2 % mean: Median: SD: 17.4 P:	Mean: Median: SD: P: 0.9269		medium

Evidence Table 82. KQ2—Continuous data—Platelet count (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	10		Mean: Median SD: SE: Lower: Upper:	Mean:1.8 Median: SD: 42.6 P:			
Dehmer 1988[17] parallel	At high risk for CHD	aspirin + Dipyridamole + ca channel blockers)	ASA: 325; dipyridamole: 225; Ca blocker: NR	Omega-3 (EPA, DHA, or both).	43	Fasting blood samples; standard automated techniques	Mean: 259 Median SD: 55 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)	39		Mean:287 Median SD: 73 SE: Lower: Upper:	Mean: Median: SD: P:			
Wolf 2006[68] crossover	Low and/or Moderate	ASA	500	ginkgo biloba	50		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	Study data are in forest plot with point estimates and 90% CIs	low-medium

Evidence Table 82. KQ2—Continuous data—Platelet count (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	50		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:		for the ratio acetylsalicylic acid (ASA) + EGb 761®/ASA - difficult to extract (can certainly do this with a ruler..but have not yet.. - can say that point estimate is close to 1 (between 1 an	
Hansen 1993[29] crossover	Low and/or Moderate	lovastatin	40	Fish/marine oils	14		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: 17 Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	14		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: 20 Median: SD: P:			

Evidence Table 82. KQ2—Continuous data—Platelet count (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Aruna 2007[2] crossover	At low risk for CHD (0-1 risk factors)	Cilostazol 100 mg	104 to 200 (cilostazol); 75 to 150 (clopidogrel)	ginkgo biloba	10	measured 0 and 6 h after drug administration	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	"There were no significant changes in…platelet count in any of the treatment groups."	medium
				No treatment	10		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
McKenney 2006[45] Crossover	Low and/or Moderate	simvastatin	80	Omega-3	24		Mean: Median SD: SE: Lower: Upper:	Mean:-6.92 % mean: Median: SD: 55.6 P:	Mean: Median: SD: P:		medium
				No treatment	23		Mean: Median SD: SE: Lower: Upper:	Mean:2.9 Median: SD: 53.4 P:			

Evidence Table 82. KQ2—Continuous data—Platelet count (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Mueller 1991[51] crossover	Low and/or Moderate	aspirin	325 - single dose	Fish/marine oils	12	Fasting	Mean: 251.83 Median SD: 52.51 SE: Lower: Upper:	Mean:-36.34 % mean: Median: SD: P: <0.05	Mean: Median: SD: P:		medium
				Placebo	12		Mean: 253.67 Median SD: 51.46 SE: Lower: Upper:	Mean:-34.5 Median: SD: P:			

Evidence Table 83. KQ2—Continuous data—Prothrombin time (PT)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Lee 2008[36]	At high risk for CHD	wafarin	3.5	Ginseng.	12	Peak PT After 2 mg warfarin phase (after 1 week)	Mean: 14.75 Median SD: 0.8 SE: Lower: Upper:	Mean:1.59 % mean: Median: SD: P: <0.001	Mean:0.08 Median: SD: P:		medium
				No treatment (aside from CVD drug)	13		Mean:14.67 Median SD: 0.71 SE: Lower: Upper:	Mean:1.41 Median: SD: P: <0.001			
Lee 2008[36]	At high risk for CHD	wafarin	3.5	Ginseng.	12	Peak PT After 5 mg warfarin phase (after 2 weeks)	Mean: 24.23 Median SD: 3.25 SE: Lower: Upper:	Mean:11.07 % mean: Median: SD: P: <0.001	Mean:0.8 Median: SD: P:		medium
				No treatment (aside from CVD drug)	13		Mean:23.42 Median SD: 3.2 SE: Lower: Upper:	Mean:10.16 Median: SD: P: <0.001			

Evidence Table 83. KQ2—Continuous data—Prothrombin time (PT) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Lee 2008[36]	At high risk for CHD	wafarin	3.5	Ginseng.	12	Measured as area under the curve After 5 mg warfarin phase (after 2 weeks)	Mean: 97.33 Median SD: 4.03 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean:0.34 Median: SD: P:		medium
				No treatment (aside from CVD drug)	13		Mean:96.99 Median SD: 3.16 SE: Lower: Upper:	Mean: Median: SD: P:			
Lee 2008[36]	At high risk for CHD	wafarin	3.5	Ginseng.	12	Measured as area under the curve After 5 mg warfarin phase (after 2 weeks)	Mean: 142.67 Median SD: 14.24 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean:3.55 Median: SD: P:		
				No treatment (aside from CVD drug)	13		Mean:139.12 Median SD: 12.88 SE: Lower: Upper:	Mean: Median: SD: P:			
Napoli 1998[52] parallel	Unclear	Pravastatin	20-40	Vitamin E.	52	NR	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	"..no differences in routine laboratory tests or adverse	medium

Evidence Table 83. KQ2—Continuous data—Prothrombin time (PT) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	56		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:		events were registered during the study (data not shown); in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups."	
McKenney 2006[45] Crossover	Low and/or Moderate	simvastatin	80	Omega-3	24	partial PT	Mean: Median SD: SE: Lower: Upper:	Mean:0.1 % mean: Median: SD: 0.3 P:	Mean: Median: SD: P:		medium

Evidence Table 83. KQ2—Continuous data—Prothrombin time (PT) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment	23		NR	Mean:0.2 SD:0.3			

Evidence Table 84. KQ2—Continuous data—Proteinuria

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Ferraro 2009[22] parallel	Unclear	ramipril	10	Omega-3 (EPA, DHA, or both).	15	UPE (urinary protein excersion) baseline was considered a mean of the positive measurements obtained before the final period.	Mean: 367 Median SD: 520 SE: Lower: Upper:	Mean: % mean: -77.9 Median: SD: P:	Mean:-61.6 Median: SD: P:<0.01		medium
				No treatment (aside from CVD drug)	15		Mean:1353 Median SD: 1304	Mean: % mean: -11.3			

Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Ferraro 2009[22] parallel	Unclear	ramipril	10	Omega-3 (EPA, DHA, or both).	15		Mean: 123 Median SD: 23 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)	15		Mean:123 Median SD: 19.9 SE: Lower: Upper:	Mean: Median: SD: P:			
Meyer 2007[46]	Unclear	simvastatinstatin, 13 atorvastatin, 4 pravastatin, 2 cerivastatin and 2 fluvastatin 81	81	Fish/marine oils	13	Supine in clinic	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	Report states that no changes were noted in SBP across groups and results are not shown	medium
				Fish/marine oils	13						
				Placebo	14		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Sutken 2006[63] parallel	Low and/or Moderate	Gemfibrozil	1200	Vitamin E.	22	Data for elderly sub-group	Mean: 132 Median SD: SE:8 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	Other continuous outcomes also measured in this study: BMI, Height , Weight, Glutathione - whole blood, Malondialdehyde - plasma, Vitamin E, Erythrocyte GPx and SOD activities	high
				No treatment (aside from CVD drug)	23		Mean:125 Median SD: SE:6.7 Lower: Upper:	Mean: Median: SD: P:			
Sutken 2006[63] parallel	Low and/or Moderate	Gemfibrozil	1200	Vitamin E.	22	For young sub-group	Mean: 125 Median SD: SE:5 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		high
				No treatment (aside from CVD drug)	23		Mean:128 Median SD: SE:7.7 Lower: Upper:	Mean: Median: SD: P:			
Macan 2006[40] parallel	Low and/or Moderate	Warfarin	NR	Garlic.	22		Mean: Median SD: SE: Lower: Upper:	Mean:2.9 % mean: Median: SD: 18.7 P:0.697	Mean: Median: SD: P: 0.697	This study also assesses the continuous outcome: weight	medium

Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	26		Mean: Median SD: SE: Lower: Upper:	Mean:0.7 Median: SD: 19.7 P:			
Playford 2003[58] parallel	At high risk for CHD	Fenofibrate	200	Coenzyme Q10. 200 mg plus 200 mg fenofibrate	18	measured after 14 hr fast; measured after resting in supine for 10 minutes, at 2 minute intervals for 10 minutes	Mean: 127.4 Median SD: SE:3.8 Lower: Upper:	Mean:-4.4 % mean: Median: SD: P:	Mean:3.4 Median: SD: P:0.033		low-medium
				No treatment (aside from CVD drug)	17		Mean:130.8 Median SD: SE:4.3 Lower: Upper:	Mean:0.4 Median: SD: P:			
				Coenzyme Q10. 200 mg CoQ10 only	20		Mean:124.8 Median SD: SE:3.4 Lower: Upper:	Mean:-4 Median: SD: P:			
				Placebo	18		Mean:137.8 Median SD: SE:4 Lower: Upper:	Mean:1.2 Median: SD: P:			

Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Barbagallo 1999[5] parallel	Unclear	furosemide	25	Vitamin E.	12	supine, overnight fasted, empty bladder	Mean: 132 Median SD: 6 SE: Lower: Upper:	Mean:26 % mean: Median: SD: P: <0.001	Mean:3 Median: SD: P:	calculation of mean change from baseline questionably as it won't be useable (SD cannot be inferred, I don't think.).	medium
				No treatment (aside from CVD drug)	12		Mean:135 Median SD: 5 SE: Lower: Upper:	Mean:22 Median: SD: P: <0.001			
Howe 1994[30] parallel	Unclear	Captopril	61	Fish/marine oils.	14		Mean: 139 Median SD: SE:6 Lower: Upper:	Mean:4.3 % mean: Median: SD: P:	Mean:4.2 Median: SD: P:0.05		medium
				Placebo	14		Mean:140 Median SD: SE:4 Lower: Upper:	Mean:5.3 Median: SD: P:			
				Fish/marine oils.	14		Mean:138 Median SD: SE:4 Lower: Upper:	Mean:7.7 Median: SD: 1.8 P:			

Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	14		Mean:135 Median SD: SE:5 Lower: Upper:	Mean: Median: SD: P:			
Paolisso 1992[57] parallel	Unclear	hydrochlorthiazide	25	Magnesium.	9	supine, fasted (12 h) and at rest for 30 minutes - measured over 60 minutes, mean of last 10 minutes of measurement included.	Mean: 171 Median SD: SE:8 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P: <0.04		medium
				Placebo	9		Mean:159 Median SD: SE:4 Lower: Upper:	Mean: Median: SD: P:			
Nordøy 2003[55] parallel	Mod and high risk	atorvastatin	10	Fish/marine oils.	22		Mean: Median SD: SE: Lower: Upper:	Mean:-5.5 % mean: Median: SD: 11.3 P:	Mean: Median: SD: P: 0.03		medium
				Placebo	20		Mean: Median SD: SE: Lower: Upper:	Mean:3 Median: SD: 12.8 P:			

Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Reyes 1984[59] parallel	Low and/or Moderate	hydrochlorothiazide	50	Magnesium.	13	Patients rested supine for 10 minutes prior to measurement - an average of 3 measurements rounded to nearest 10 mmHg - 900-1100hr readings	Mean: 145.4 Median SD: SE:3.3 Lower: Upper:	Mean: % mean: -7 Median: SD: <0.02 P: <0.005	Mean: Median: SD: P:	Percent change data taken from graph - 2.5% = 1.1 cm, rounded to the nearest 0.5%	medium
				Placebo	8		Mean:147.5 Median SD: SE:3.7 Lower: Upper:	Mean: % mean:-8 Median: SD: P:			
Reyes 1984[59] parallel	Low and/or Moderate	hydrochlorothiazide	50	Magnesium.	13	Erect systolic blood pressure Patients rested erect for 10 minutes prior to measurement - an average of 3 measurements rounded to nearest 10 mmHg	Mean: 145 Median SD: SE:2 Lower: Upper:	Mean: % mean: -7 Median: SD: <0.01 P: <0.01	Mean: Median: SD: P:	Data extracted from bar charts - method of extraction verified for other variables that had corresponding numerical summary. In this case for final mean and SEM 1.9 cm = 40 mmHg and results rounded to nearest whole mmHg. For % change from time of randomization 1.1 cm = 2.5% and results rounded to nearest 0.5%	medium
				Placebo	8		Mean:145 Median SD: SE:2 Lower: Upper:	Mean: % mean:-6.5 Median: SD: P:			

Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Dehmer 1988[17] parallel	At high risk for CHD	aspirin + Dipyridamole + ca channel blockers)	ASA: 325; dipyridamole: 225; Ca blocker: NR	Omega-3 (EPA, DHA, or both).	43		Mean: Median SD: SE: Lower: Upper:	Mean:6 % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)	39		Mean:36 Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Wolf 2006[68] crossover	Low and/or Moderate	ASA	500	ginkgo biloba	NR		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	Study states that: Laboratory findings in all subjects were un-remarkable and did not indicate any differences between the treatment groups. Similarly, no noteworthy changes of vital sign variables occurred during the study	low-medium
					NR		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Paolisso 1995[56] crossover	At high risk for CHD	nifedipine	88	Vitamin E	30		Mean: 147 Median SD: SE:6.3 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium

Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	30		Mean:149 Median SD: SE:6.1 Lower: Upper:	Mean: Median: SD: P:			
Lungershausen 1994[38] crossover	Unclear	b-blockers	NR	Fish/marine oils	25	Clinical systolic BP (no exercise or eating for 2hr before, empty bladder, resting for 5 minutes); taken by averaving 3 or 4 consecutive readings after discarding initial reading	Mean: 127 Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	Data of mean measured from histogram (10 mmHg = 2.2 cm). Measure of dispersion not stated. This study is at risk of selective outcome reporting; p-values for crude difference also don't make sense in context	medium
				Placebo	25		Mean:131 Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Lungershausen 1994[38] crossover	Unclear	b-blockers	NR	Fish/marine oils	25	Ambulatory systolic BP - Measured over next 24 hours using Spacelab 90207 instrument, same time of day; taken at 20 min intervals during wake and every 1 hour during sleep.	Mean: 128 Median SD: SE: Lower: Upper:	Mean:2.5 % mean: Median: SD: 1 P:	Mean: Median: SD: P: <0.05	Data of mean measured from histogram (10 mmHg = 2.2 cm). Measure of dispersion not stated. Data of mean difference in text. This study is at risk of selective outcome reporting; p-values for crude difference	medium
				Placebo	25		Mean:131 Median SD: SE: Lower: Upper:	Mean:3.3 Median: SD: 1.8 P:			

Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Aruna 2007[2] crossover	At low risk for CHD (0-1 risk factors)	Clopidogrel 75 mg	105 to 200 (cilostazol); 75 to 150 (clopidogrel)	ginkgo biloba	10		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	"There was no significant change in systolic BP in any of the groups…"	medium
				No treatment	10		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Mueller 1991[51] crossover	Low and/or Moderate	aspirin	325 - single dose	Fish/marine oils	12	before and 90 minutes after a single oral 325-mg dose of aspirin. Done by blinded operator	Mean: 117 Median SD: 12.47 SE: Lower: Upper:	Mean:-0.6 % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	12		Mean:117.08 Median SD: 11.54 SE: Lower: Upper:	Mean:-0.52 Median: SD: P:			
Maki 2008[41] crossover	Low and/or Moderate	simvastatin	20	Omega-3	39	At rest, seated	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium

Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	40		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: 0.3 Median: SD: P:			
Wirell 1994[67] Crossover	Unclear	metoprolol, atenolol, pindolol & propanolol	NR	magnesium	39	standing	Mean: 141.62 Median SD: 18.4 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	39		Mean:145.96 Median SD: 23.62 SE: Lower: Upper:	Mean: Median: SD: P:			
Wirell 1994[67] Crossover	Unclear	metoprolol, atenolol, pindolol & propanolol	NR	magnesium	39	supine	Mean: 145.05 Median SD: 18.2 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium

Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	39		Mean:149.31 Median SD: 18.61 SE: Lower: Upper:	Mean: Median: SD: P:			
							Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 86. KQ2—Continuous data—TD: HDL-C

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Bays 2010[6] parallel	Unclear	atorvastatin	10-40	Omega-3 (EPA, DHA, or both).	122	TC: HDL-C ratio at week 8, end of 10 mg/d atorvastatin	Mean: Median 4.3 SD: SE: Lower: 3.5 Upper:5.2	Mean: % mean: Median:-38.3 SD: P:	Mean: Median:-3.8% SD: P:0.001		medium
				Placebo	121		Mean: Median 4.7 SD: SE: Lower: 3.9 Upper:5.7	Mean: Median:-34.5 SD: P:			
Davidson 2007[14] parallel	Unclear	simvastatinstatin	40	Omega-3 (EPA, DHA, or both).	122	TC: HDL-C ratio	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -8 Median:-9.6 SD: P:	Mean: Median:-3.8 SD: P:0.001	*TC:HDL-C ratio was signifincantly lower in omega group compared withthe placebo group (p = 0.012)	medium
				Placebo	132		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -0.1 Median:-0.7 SD: P:			

Evidence Table 86. KQ2—Continuous data—TD: HDL-C (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Davidson 1997[15] parallel	Unclear	Simvastatinstatin	10	Fish/marine oils.	9	TC/HDL-C ratio fasting blood sample	Mean: 5.06 Median SD: SE:0.46 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)	10		Mean:4.77 Median SD: SE:0.24 Lower: Upper:	Mean: % mean: -25.6 Median: SD: P:			
Roth 2009[60] parallel	Unclear	fenofibrates by 100%	130	Omega-3 (EPA, DHA, or both).	81	TC/HDL-C ratio	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median:-4.8 SD: P:	Mean: Median: SD: P:	Not significant between groups	medium
				Placebo	82		Mean: Median SD: SE: Lower: Upper:	Mean: Median:-8.3 SD: P:			

Evidence Table 86. KQ2—Continuous data—TD: HDL-C (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Budoff 2004[10] parallel	At high risk for CHD	statins + aspirin	10 - 40	Garlic	9	TC: HDL Measured after 12 hr fast	Mean: Median SD: SE: Lower: Upper:	Mean:-0.15 % mean: Median: SD: 1.04 P:	Mean: Median: SD: P: 0.0763		medium
				Placebo	10		Mean: Median SD: SE: Lower: Upper:	Mean:0.79 Median: SD: 1.13 P:			
Maki 2008[41] crossover	Low and/or Moderate	simvastatin	20	Omega-3	39	Least square mean (SEM)	Mean: 4.1 Median SD: SE:0.2 Lower: Upper:	Mean: % mean: -39 Median: SD: P:	Mean:-6.5 Median: SD: P: <0.001		medium
				Placebo	40		Mean:4.5 Median SD: SE:0.2 Lower: Upper:	Mean: % mean: -33 Median: SD: P:			

Evidence Table 87. KQ2—Continuous data—Total cholesterol

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Bays 2010[6] parallel	Unclear	atorvastatin	10-40	Omega-3 (EPA, DHA, or both).	122		Mean: Median 172.5 SD: SE: Lower:157.5 Upper:194.5	Mean: % mean: Median: SD: P:	Mean: Median:-4.1; -2.7 SD: P: <0.001		medium
				Placebo	121		Mean: Median 181.5 SD: SE: Lower:164.5 Upper:206	Mean: Median:-27.4 SD: P:			
Bays 2010[6] parallel	Unclear	atorvastatin	10-40	Omega-3 (EPA, DHA, or both).	122		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P: <0.001		medium
				Placebo	121		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Mabuchi 2007[39] parallel	Unclear	atorvastatin	1	Coenzyme Q10.	24		Mean: 4.99 Median SD: 0.68 SE: Lower: Upper:	Mean:-30 % mean: Median: SD: P: <0.0001	Mean: Median: SD: P:	"There were no significant differencs between the 2 groups". NOTE: For all outcomes, data is also presented for followup 4 weeks after end of treatment (none of this data was extracted).	medium
				Placebo	25		Mean:4.68 Median SD: 0.68 SE: Lower: Upper:	Mean: % mean: -36 Median: SD: P: <0.0001			

Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Young 2007[70] parallel	Mod and high risk	simvastatinstatin	10-40	Coenzyme Q10.	22		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P: <0.001	Mean: Median: SD: P: 0.57	No difference in groups (p=0.57).	medium
				Placebo	22		Mean: Median SD: SE: Lower: Upper:	Mean: Median:-1.6% SD: P: <0.001			
Caso 2007[11]	Unclear	Simvastatinstatin (22); Atorvastatin (7); Pravastatin (2); Lovastatin (1)	varying doses	Coenzyme Q10.	18	Fasting plasma	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	No final outcome data presented. Study reports baseline data and that the values did not change during the intervention period. Mean +/- SEM - Baseline CoQ10: 183 +/- 10; Baseline Vit E: 189 +/- 14	low
				Vit E	14		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Meyer 2007[46]	Unclear	simvastatinstatin, 13 atorvastatin, 4 pravastatin, 2 cerivastatin and 2 fluvastatin 81	81	Fish/marine oils	13	Blood plasma TC after overnight fast	Mean: 4.43 Median SD: SE:0.23 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	significant correlation between dosage of fish oil and extent of cholesterol reduction (r = –0.344, P < 0.05); The reduction of plasma total cholesterol correlated with initial cholesterol levels (r = –0.44, P < 0.05).	medium
				Fish/marine oils	13		Mean:4.18 Median SD: SE:0.23 Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	14		Mean:4.47 Median SD: SE:0.21 Lower: Upper:	Mean: Median: SD: P:			
Sutken 2006[63] parallel	Low and/or Moderate	Gemfibrozil	1200	Vitamin E.	22	serum for elderly sub-group	Mean: 7.3 Median SD: SE:1.07 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		high
				No treatment (aside from CVD drug)	23		Mean:7.1 Median SD: SE:2.3 Lower: Upper:	Mean: Median: SD: P:			
Sutken 2006[63] parallel	Low and/or Moderate	Gemfibrozil	1200	Vitamin E.	12	Serum For younger sub-group	Mean: 6.58 Median SD: SE:0.18 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		high
				No treatment (aside from CVD drug)	10		Mean:6.55 Median SD: SE:0.07 Lower: Upper:	Mean: Median: SD: P:			
Macan 2006[40] parallel	Low and/or Moderate	Warfarin	NR	Garlic.	22	NR - other than 12 hr fasting measurement	Mean: Median SD: SE: Lower: Upper:	Mean:8.4 % mean: Median: SD: 28.0 P:	Mean: Median: SD: P: 0.128		medium

Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	26		Mean: Median SD: SE: Lower: Upper:	Mean:-4.1 Median: SD: 27.6 P:			
Manuel 2004[42] parallel	At high risk for CHD	Atorvastatin	20	Vitamin E.	11	serum, fasting	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P: <0.0001	Mean: Median: SD: P:	Data not presented in paper - only combined data for both groups across time	medium
				Placebo	11		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P: <0.0001			
Manuel 2004[42] parallel	At high risk for CHD	Atorvastatin	20	Vitamin E.	11	total cholesterol in non-HDL subfraction	Mean: 2.57 Median SD: 0.81 SE: Lower: Upper:	Mean: % mean: Median: SD: P: <0.001	Mean: Median: SD: P:	Other outcomes reported but not extracted for this study: serum tocopherol, TBARS - Copper-induced production of thiobarbituric reactive substances in LDL and VLDL sub-fractions (lag-time, propagation phase and saturation phase), Plasma malondialdehyde, Blood count, Creatinephosphokinase, Oxidant-antioxidant balance (concentrations of Vit A and E in serum), non-HDL-fraction of Vit E, non-HDL fraction of Vit A, 7 bands in LDL subfraction	medium
				Placebo	11		Mean:2.69 Median SD: 1.11 SE: Lower: Upper:	Mean: Median: SD: P: <0.001			

Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Micheletta 2004[47] Parallel	At high risk for CHD	ASA or ticlopidine	NR	Vitamin E.	8	Total cholesterol in atherosclerotic plaque tissue excised during endarterectomy	Mean: 34.8 Median SD: 24.5 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	This study also assesses TG and TC (relevant but with no data to extract, only noted that there were no differences between baseline and follow-up - to fill out separate form after) and the following non-relevant outcomes: Plasma alphatocopherol, 7-beta hydroxycholesterol, 7-ketocholesterol	medium
				No treatment (aside from CVD drug)	8		Mean:40.6 Median SD: 28.7 SE: Lower: Upper:	Mean: Median: SD: P:			
Micheletta 2004[47] Parallel	At high risk for CHD	ASA or ticlopidine	NR	Vitamin E.	8	Plasma - 12hr fast at 800-900hr	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:		Total cholesterol outcome data reported. Study states only baseline data and that 'no changes of cholesterol and triglyceride concentrations were observed at the end of follow-up. Baseline values for total cholesterol given for both groups together... (mean +/- SD): 5.9 +/- 1.2	medium
				No treatment (aside from CVD drug)	8		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Playford 2003[58] parallel	At high risk for CHD	Fenofibrate	200	Coenzyme Q10. 200 mg plus 200 mg fenofibrate	18	measured after 14 hr fast;	Mean: 4.7 Median SD: SE:0.2 Lower: Upper:	Mean:-0.5 % mean: Median: SD: P:	Mean: Median: SD: P: 0.455 or 0.001		low-medium
				No treatment (aside from CVD drug)	17		Mean: 4.7 Median SD: SE:0.2 Lower: Upper:	Mean:-0.8 % mean: Median: SD: P:			
				Coenzyme Q10. 200 mg CoQ10 only	20		Mean: 5.3 Median SD: SE:0.2 Lower: Upper:	Mean:0 % mean: Median: SD: P:			
				Placebo	18		Mean:5.4 Median SD: SE:0.2 Lower: Upper:	Mean:0.1 Median: SD: P:			
Svaneborg 2002[64] parallel	At low risk for CHD (0-1 risk factors)	ASA	100	Omega-3 (EPA, DHA, or both).	12		Mean: Median 3.85 SD: SE: Lower:3.25 Upper:5.2	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	baseline is 14 days prior to the second IV dose of ASA.--- vs. placebo (corn oil containing 61% omega-6)	medium
				Placebo	6		Mean: Median 4.65 SD: SE: Lower:3.57 Upper:6.08	Mean: Median: SD: P: <0.05			

Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Duffy 2001[20] parallel	Low and/or Moderate	simvastatinstatin	10-40	Vitamin E.	6		Mean: 4.7 Median SD: 0.9 SE: Lower: Upper:	Mean:-1.6 % mean: Median: SD: P: 0.01	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)	7		Mean:5.1 Median SD: 0.8 SE: Lower: Upper:	Mean:-2.2 Median: SD: P: 0.01			
				1000IU Vitamin E	6		Mean:6.8 Median SD: 1.7 SE: Lower: Upper:	Mean:0 Median: SD: P:			
				Placebo	7		Mean:6.4 Median SD: 1 SE: Lower: Upper:	Mean:0.6 Median: SD: P: 0.01			
Nordøy 2000[54] Parallel	Low and/or mod to high risk	simvastatinstatin	20	Omega-3 (EPA, DHA, or both).	21		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	"Simvastatin and w-3 FA compared with simvastatin and placebo reduced seum concentrations of total cholesterol (p=0.05). No data provided.	medium
				Placebo	20		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Napoli 1998[52] parallel	Unclear	Pravastatin	20-40	Vitamin E.	52	Fasting 12-14 hrs; determined enzymatically using Boehringer test kit	Mean: Median SD: SE: Lower: Upper:	Mean:-25 % mean: Median: SD: 4 P:0.05	Mean: 0.225 Median: SD: P: <0.05		medium
				No treatment (aside from CVD drug)	56		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -26 Median: SD: 5% P: <0.05			
Bordia 1998[9] parallel	At high risk for CHD	Nitrates	NR	Garlic.	30		Mean: 220.5 Median SD: SE:7 Lower: Upper:	Mean:-32.4 % mean: -12.8 Median: SD: P: <0.01	Mean:28.2 Median: SD: P:		high
				Placebo	30		Mean:248.7 Median SD: SE:7.2 Lower: Upper:	Mean:-4.6 Median: SD: P:			
Yamamoto 1995[69] parallel	At high risk for CHD	diltiazem	90-120	Omega-3 (EPA, DHA, or both).	12		Mean: 185 Median SD: SE:37 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium

Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	10		Mean:180 Median SD: SE:24 Lower: Upper:	Mean: Median: SD: P:			
McDowell 1994[44] parallel	Unclear	Simvastatinstatin	20	Vitamin E.	8	overnight fast	Mean: 5.9 Median SD: 0.8 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	Other continuous outcomes not extracted: Vascular forearm bloodflow response to 3 agents (possibly to come back to after discussion with Michelle Turek); Apo A1; Apo B; serum alpha-tocopherol; serum probucol; serum TBARS	medium
				Placebo	8		Mean:6.5 Median SD: 0.8 SE: Lower: Upper:	Mean: Median: SD: P:			
Paolisso 1992[57] parallel	Unclear	hydrochlorthiazide	25	Magnesium.	9	plasma measurement after overnight fast	Mean: 6.28 Median SD: SE:0.21 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	9		Mean:6.31 Median SD: SE:0.18 Lower: Upper:	Mean: Median: SD: P:			
Kaul 1992[34] parallel	At high risk for CHD	Calcium channel blocker, ASA	ASA: 150; heparin: 1000 U/d; ca blockers: NR	Fish/marine oils.	58		Mean: 224 Median SD: 39.8 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		low-medium

Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	49		Mean:215 Median SD: 40.2 SE: Lower: Upper:	Mean: Median: SD: P:			
Nordøy 2003[55] parallel	Mod and high risk	atorvastatin	10	Fish/marine oils.	22	Blood sample taken after 12 hr fasting, within 6 days of end of study	Mean: Median SD: SE: Lower: Upper:	Mean:-0.07 % mean: Median: SD: 0.42 P:	Mean:2.9 Median:-16.9 SD: P: 0.13		medium
				Placebo	20		Mean: Median SD: SE: Lower: Upper:	Mean:-0.36 Median: SD: 0.74 P:			
Roth 2009[60] parallel	Unclear	fenofibrates by 100%	130	Omega-3 (EPA, DHA, or both).			Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:2.9		medium
				Placebo			Mean: Median SD: SE: Lower: Upper:	Mean: Median:-5.1 SD: P:			
Isley 2007[31] parallel	Unclear	niacin	325	Omega-3		measured enzymatically on a Cobas Fara II (Roche) using enzymatic reagents and procedures	Mean: 194 Median SD: 29 SE: Lower: Upper:	Mean:-5 % mean: Median: SD: P:	Mean:-16.9 Median: SD: P:<0.001		medium

Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo		standardized by the Lipid Standardization Program of the Centers for Disease Control and Prevention/National Institutes of Health.	Mean:185 Median SD: 18 SE: Lower: Upper:	Mean:12.8 % mean:-6 Median: SD: P:			
Budoff 2004[10] parallel	At high risk for CHD	statins + aspirin	10-40	Garlic		Measured after 12 hr fast	Mean: Median SD: SE: Lower: Upper:	Mean:7 % mean: Median: SD: 21.8 P:	Mean: Median: SD: P: 0.6065		medium
				Placebo			Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: 25.9 P:			
Chan 2002[12] parallel	At moderate/moderately high risk for CHD (2+ risk factors)	atorvastatin	40	Fish/marine oils.		collected after an overnight fast (14 h) in a semirecumbent position for all biochemical measurements.	Mean: 3.9 Median SD: SE:0.27 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo			Mean:3.6 Median SD: SE:0.12 Lower: Upper:	Mean: Median: SD: P:			
Liu 2003[37] parallel	Unclear	simvastatinstatin	10	Fish/marine oils.		Fasting blood samples	Mean: 5.13 Median SD: 0.95 SE: Lower: Upper:	Mean:-1.56 % mean:-23.3 Median: SD: 0.95 P:	Mean: Median: SD: P:		medium

Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)			Mean:5.56 Median SD: 0.8 SE: Lower: Upper:	Mean:-1.48 Median: SD: 0.8 P:			
Dehmer 1988[17] parallel	At high risk for CHD	aspirin + Dipyridamole + ca channel blockers)	ASA: 325; dipyridamole: 225; Ca blocker: NR	Omega-3 (EPA, DHA, or both).		Fasting blood samples; standard automated techniques	Mean: 236 Median SD: 50.3 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)			Mean:217 Median SD: 42.9 SE: Lower: Upper:	Mean: Median: SD: P:			
Desideri 2003[18] parallel	At low risk for CHD (0-1 risk factors)	Simvastatinstatin, Bezafibrate	simvastatinstatin: 40; Bezafibrate: 800	Vitamin E.		12 hr fasting at 800hr – serum;	Mean: 5.8 Median SD: 0.7 SE: Lower: Upper:	Mean: % mean: Median: SD: P: <0.0001	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)			Mean:5.6 Median SD: 0.6 SE: Lower: Upper:	Mean: Median: SD: P: <0.0001			
Wolf 2006[68] crossover	Low and/or Moderate	ASA	500	ginkgo biloba	50		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	Study states that: Laboratory findings in all subjects were un-remarkable and did not indicate any differences between the treatment	low-medium

Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	50		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:		groups.	
De Caterina 2002[16] crossover	At high risk for CHD	simvastatinstatin	10-40	Vitamin E		20% reduction in TC for each patient	Mean: Median SD: SE: Lower: Upper:	Mean: % mean:26.5 Median: SD: P:	Mean: Median: SD: P:	Values are presented in graphs, but difficult to read.	high
				No treatment (aside from CVD drug)			Mean: Median SD: SE: Lower: Upper:	Mean: % mean:26.5 Median: SD: P:			
Balestrieri 1996[4] crossover	Low and/or Moderate	Simvastatinstatin	10-40	Fish/marine oils	14	12 hour fast, anti-tubectal vein	Mean: 300 Median SD: 49 SE: Lower: Upper:	Mean:2 % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	14		Mean:302 Median SD: 44 SE: Lower: Upper:	Mean:-1 Median: SD: P:			
Paolisso 1995[56] crossover	At high risk for CHD	nifedipine	88	Vitamin E	30	Fasting; at 2 months after treatment start	Mean: 6.03 Median SD: SE:0.09 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P: <0.05		medium

Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	30		Mean:6.96 Median SD: SE:0.11 Lower: Upper:	Mean: Median: SD: P:			
Hansen 1993[29] crossover	Low and/or Moderate	lovastatin	40	Fish/marine oils	14		Mean: Median SD: SE: Lower: Upper:	Mean: % mean:-31 Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	14		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -27 Median: SD: P:			
Avogaro 1974[3] Crossover	Unclear	propranolol	20 or 60	Niacin	10	at end of 1 mo treatment	Mean: 316.2 Median SD: SE:12.1 Lower: Upper:	Mean:-30 % mean: Median: SD: P:	Mean:-10.8 Median: SD: P:	Type II hyperlipoproteinemia	high
				No treatment (aside from CVD drug)	10		Mean:327 Median SD: SE:50.29 Lower: Upper:	Mean:-19.2 Median: SD: P:			
Avogaro 1974[3] Crossover	Unclear	propranolol	20 or 60	Niacin	10	at end of 1 mo treatment	Mean: 241.67 Median SD: SE:41.79 Lower: Upper:	Mean:-12.5 % mean: Median: SD: P:	Mean:-5.83 Median: SD: P:	Type IV hyperlipoproteinemia	high

Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	10		Mean:247.5 Median SD: SE:37.38 Lower: Upper:	Mean:-6.67 Median: SD: P:			
Mueller 1991[51] crossover	Low and/or Moderate	aspirin	325 - single dose	Fish/marine oils	12	Fasting	Mean: 198.75 Median SD: 34.45 SE: Lower: Upper:	Mean:-3.92 % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	12		Mean:188.83 Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Maki 2008[41] crossover	Low and/or Moderate	simvastatin	20	Omega-3	39	10-14 hour fast; Centers for Disease Control and Prevention lipid standardization program	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P: 0.006	The IQRs reported are actually ranges (low-high).	medium
				Placebo	40		Mean: Median SD: SE: Lower: Upper:	Mean:-13.84 Median: SD: P:			
Maki 2008[41] crossover	Low and/or Moderate	simvastatin	20	Omega-3	39	Hour fast	Mean:37.25 Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium

Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	40		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:			

Evidence Table 88. KQ2—Continuous data—Triglycerides

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Bays 2010[6] parallel	Unclear	atorvastatin	10-40	Omega-3 (EPA, DHA, or both).	122	at week 8, end of 10 mg/d atorvastatin	Mean: Median 184.5 SD: SE: Lower: 154.5 Upper:232	Mean: % mean: -45.4 Median: SD: P:	Mean: Median:-18.6(-19.2) SD: P:<0.001		medium
				Placebo	121		Mean: Median 233.5 SD: SE: Lower: 186.5 Uppe325r:	Mean: Median:-26.9 SD: P:			
Bays 2010[6] parallel	Unclear	atorvastatin	10-40	Omega-3 (EPA, DHA, or both).	122	at week 16, end of 40 mg/d atorvastatin	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median:-19.1 SD: P:<0.001		medium
				Placebo	121		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Ferraro 2009[22] parallel	Unclear	ramipril	10	Omega-3 (EPA, DHA, or both).	15		Mean: 145.7 Median SD: 143.4 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)	15		Mean:184.3 Median SD:167.3 SE: Lower: Upper:	Mean: Median: SD: P:			
Mabuchi 2007[39]	Unclear	atorvastatin	1	Coenzyme Q10.	24		Mean: 1.13 Median SD: 0.46 SE: Lower: Upper:	Mean: % mean: -18.7 Median: SD: P: <0.0001	Mean: Median: SD: P:	"...no significant differences between the groups."	medium
				Placebo	25		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -25.9 Median: SD: P: <0.0001			

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Young 2007[70] parallel	Mod and high risk	simvastatinstatin	10-40	Coenzyme Q10.	22		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median:-0.4 SD: P:	Mean: Median SD: P: 0.90	No difference in groups (p=0.90)	medium
				Placebo	22		Mean: Median SD: SE: Lower: Upper:	Mean: Median:-0.3 SD: P: <0.05			
Davidson 2007[14] parallel	Unclear	simvastatinstatin	40	Omega-3 (EPA, DHA, or both).	122		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -28.2 Median:-29.5 SD: 18.7 P:	Mean: Median: SD: P: <0.001		medium
				Placebo	132		Mean: Median SD: SE: Lower: Upper:	Mean: %mean: -3.5 Median:-6.3 SD: 22.1 P:			

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Caso 2007[11]	Unclear	Simvastatinstatin (22); Atorvastatin (7); Pravastatin (2); Lovastatin (1)	varying doses	Coenzyme Q10.	18	fasting plasma measurement	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	No final outcome data presented. Study reports baseline data and that the values did not change during the intervention period. Mean +/- SEM - Baseline CoQ10: 196 +/- 30; Baseline Vit E: 155 +/- 18 ata analysis performed on log-transformed data as data were not normally distributed	low
				Vit E	14		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Meyer 2007[46] parallel	Unclear	simvastatinstatin, 13 atorvastatin, 4 pravastatin, 2 cerivastatin and 2 fluvastatin	81	Fish/marine oils.	13	Blood plasma TG after overnight fast	Mean: 1.9*2 Median SD: SE:0.27 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Fish/marine oils.	13		Mean: 1.72 Median SD: SE:0.2 Lower: Upper:	Mean: % mean: Median: SD: P:			
				Placebo	14		Mean:2.05 Median SD: SE:0.2 Lower: Upper:	Mean: Median: SD: P:			
Sutken 2006[63] parallel	Low and/or Moderate	Gemfibrozil	1200	Vitamin E.	22	serum for elderly sub-group	Mean: 2.23 Median SD: SE:0.07 Lower: Upper:	Mean: % mean: Median: SD: P: <0.001	Mean: Median: SD: P:		high
				No treatment (aside from CVD drug)	23		Mean:2.5 Median SD: SE:1.7 Lower: Upper:	Mean: Median: SD: P: <0.001			
Sutken 2006[63] parallel	Low and/or Moderate	Gemfibrozil	1200	Vitamin E.	12	serum for younger sub-group	Mean: 1.88 Median SD: SE:0.07 Lower: Upper:	Mean: % mean: Median: SD: P: <0.001	Mean: Median: SD: P:		high

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	10		Mean:1.97 Median SD: SE:0.18 Lower: Upper:	Mean: Median: SD: P: <0.001			
Macan 2006[40] parallel	Low and/or Moderate	Warfarin	NR	Garlic.	22	12 hr fasting blood sample	Mean: Median SD: SE: Lower: Upper:	Mean:27.9 % mean: Median: SD: 115.3 P:	Mean: Median: SD: P: 0.279		medium
				Placebo	26		Mean: Median SD: SE: Lower: Upper:	Mean:-4 Median: SD: 59.4 P:			
Manuel 2004[42] parallel	At high risk for CHD	Atorvastatin	20	Vitamin E.	11	serum, fasting	Mean: 0.59 Median SD: 0.24 SE: Lower: Upper:	Mean: % mean: Median: SD: P: ~0.005	Mean: Median: SD: P:	Data not presented in paper - only combined data for both groups across time	medium

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	11		Mean:0.75 Median SD: 0.37 SE: Lower: Upper:	Mean: Median: SD: P: ~0.005		and for groups separately at baseline only. Report states that changes were 'same in both groups (the between-group comparison of change over time was not significant)	
Manuel 2004[42] parallel	At high risk for CHD	Atorvastatin	20	Vitamin E.	11	Triglycerides in non-HDL fraction	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	11		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Micheletta 2004[47] Parallel	At high risk for CHD	ASA or ticlopidine	NR	Vitamin E.	8	fasting plasma (12 hr) taken at 800-900hr	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	This is not likely usable data and should likely be excluded or authors	medium

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	8		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:		contacted...Triglyceride outcome data reported. Study states only baseline data and that 'no changes of cholesterol and triglyceride concentrations were observed at the end of follow-up. Baseline values for triglyceride given for both groups together... (mean +/- SD): 1.55 +/-0.9	
Playford 2003[58] parallel	At high risk for CHD	Fenofibrate	200	Coenzyme Q10. 200 mg plus 200 mg fenofibrate	18	measured after 14 hr fast;	Mean: 1.4 Median SD: SE: Lower: Upper:	Mean:-1.2 % mean: Median: SD: P:	Mean:0.1 Median: SD: P: 0.369 or .001		low-medium

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	17		Mean:1.3 Median SD: SE: Lower: Upper:	Mean:-1.1 Median: SD: P:			
				Coenzyme Q10. 200 mg CoQ10 only	20		Mean: 1.9 Median SD: SE: Lower: Upper:	Mean:-0.1 % mean: Median: SD: P:			
				Placebo	18		Mean: 2.4 Median SD: SE: Lower: Upper:	Mean:0.1 % mean: Median: SD: P:			
Svaneborg 2002[64] parallel	At low risk for CHD (0-1 risk factors)	ASA	100	Omega-3 (EPA, DHA, or both).	12	used TG PAP	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P: <0.05	Mean: Median: SD: P: 0.05		medium
				Placebo	6		Mean: Median 0.9 SD: SE: Lower: 0.65 Upper:2.42	Mean: Median: SD: P:			

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Duffy 2001[20] parallel	Low and/or Moderate	simvastatinstatin	10-40	Vitamin E.	6		Mean: 1.4 Median SD: 0.7 SE: Lower: Upper:	Mean:-0.4 % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)	7		Mean: 1.2 Median SD: 0.5 SE: Lower: Upper:	Mean:-0.1 % mean: Median: SD: P:			
				1000IU Vitamin E	6		Mean: 1.8 Median SD: 1.6 SE: Lower: Upper:	Mean:0.2 % mean: Median: SD: P:			
				Placebo	7		Mean:1.4 Median SD: 0.6 SE: Lower: Upper:	Mean:0.6 Median: SD: P:			
Nordøy 2000[54] Parallel	Low and/or mod to high risk	simvastatinstatin	20	Omega-3 (EPA, DHA, or both).	21	Measured area under the curve, integrated incremental (AUCi)	Mean: 8.8 Median SD: 4.7 SE: Lower: Upper:	Mean:-5.8 % mean: Median: SD: P: <0.05	Mean: Median: SD: P:		medium

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	20		Mean:15.2 Median SD: 9.6 SE: Lower: Upper:	Mean:4.5 Median: SD: P: <0.05			
Nordøy 2000[54] Parallel	Low and/or mod to high risk	simvastatinstatin	20	Omega-3 (EPA, DHA, or both).	21	Measured as area under the curve, intergrated absolute (AUC)	Mean: 23.9 Median SD: 9.1 SE: Lower: Upper:	Mean:-23 % mean: Median: SD: P: <0.01	Mean: Median: SD: P:	Crude difference between groups in mean change from baseline (omega-3 vs. placebo): -10.3 (p=0.003)	medium
				Placebo	20		Mean:36.8 Median SD: 18.4 SE: Lower: Upper:	Mean:-9 Median: SD: P:			
Nordøy 2000[54] Parallel	Low and/or mod to high risk	simvastatinstatin	20	Omega-3 (EPA, DHA, or both)	21	Measured as triglyceride response: defined as average of the 2 highest postprandial triglyceride concentrations	Mean: 1.77 Median SD: 0.8 SE: Lower: Upper:	Mean:-1.37 % mean: Median: SD: P: <0.001		Crude difference between groups in mean change from baseline (omega-3 vs. placebo): -14.1 (p=0.087)	medium

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	20	minus the baseline concentration	Mean: 2.8 Median SD: 1.56 SE: Lower: Upper:	Mean:0.6 % mean: Median: SD: P:		Crude difference between groups in mean change from baseline (omega-3 vs. placebo): -1.96 (p=0.001)	
Napoli 1998[52] parallel	Unclear	Pravastatin	20-40	Vitamin E	52	12 -14 hr fasting determined enzymatically using Boehringer test kit	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -15 Median: SD: 4% P: <0.05	Mean:0.013 Median: SD: P: <0.05		medium
				No treatment (aside from CVD drug)	56		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: -16 Median: SD: 4% P: <0.05			

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Bordia 1998[9] parallel	At high risk for CHD	Nitrates	NR	Garlic.	30		Mean: 110.2 Median SD: SE:4.2 Lower: Upper:	Mean:- 19.8 % mean: -15.2 Median: SD: P: <0.01	Mean:10.3 Median: SD: P:		high
				Placebo	30		Mean:120.5 Median SD: S7.5E: Lower: Upper:	Mean:- 4.5 Median: SD: P:			
Davidson 1997[15] parallel	Unclear	Simvastatinstatin	10	Fish/marine oils.	9	fasting blood sample	Mean: 190.6 Median SD: SE: Lower: Upper:	Mean: % mean:- 28.8 Median: SD: P: <0.01	Mean:74.5 Median: SD: P:		Medium
				No treatment (aside from CVD drug)	10		Mean:265.1 Median SD: SE: Lower: Upper:	Mean: % mean:- 18.5 Median: SD: P: <0.05			

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Marine Oil	10		Mean:211.5 Median SD: SE: Lower: Upper:	Mean: % mean: -25.3 Median: SD: P: <0.01			
Yamamoto 1995[69] parallel	At high risk for CHD	diltiazem	90-120	Omega-3 (EPA, DHA, or both).	12		Mean: 105 Median SD: SE:56 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)	10		Mean:73 Median SD: SE:35 Lower: Upper:	Mean: Median: SD: P:			
McDowell 1994[44] parallel	Unclear	Simvastatinstatin	20	Vitamin E.	8	overnight fasting measurement	Mean:1.7 Median SD: 1.2 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	8		Mean:1.2 Median SD: 0.6 SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Howe 1994[30] parallel	Unclear	Captopril	61	Fish/marine oils.	14		Mean: Median SD: SE: Lower: Upper:	Mean:0.4 % mean: Median: SD: P:	Mean: Median: SD: P: <0.05	the study stated that plasma total cholestrol were unaffected by intervention. no further data provided.	medium
				Placebo	14		Mean: Median SD: SE: Lower: Upper:	Mean:0.12 % mean: Median: SD: P:			
				Fish/marine oils.	14		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:			
				Placebo	14		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
Paolisso 1992[57] parallel	Unclear	hydrochlorthiazide	25	Magnesium.	9	fasting (overnight) plasma measurement	Mean: 2.33 Median SD: SE:0.38 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	Many other outcomes assessed but not extracted - if not noted elsewhere,	medium

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	9		Mean:2.31 Median SD: SE:0.41 Lower: Upper:	Mean: Median: SD: P:		look to JMT's excel file	
Kaul 1992[34] parallel	At high risk for CHD	Calcium channel blocker, ASA	ASA: 150; heparin: 1000 U/d; ca blockers: NR	Fish/marine oils.	58		Mean: 161 Median SD: 95.5 SE: Lower: Upper:	Mean: % mean: Median: SD: P: <0.01	Mean: Median: SD: P:		low-medium
				No treatment (aside from CVD drug)	49		Mean: 215 Median SD: 113.5 SE: Lower: Upper:	Mean: % mean: Median: SD: P:			
Nordøy 2003[55] parallel	Mod and high risk	atorvastatin	10	Fish/marine oils.	22	Blood sample taken after 12 hr fasting, within 6 days of end of study	Mean: Median SD: SE: Lower: Upper:	Mean:-0.04 % mean: Median: SD: 0.6 P:	Mean: Median: SD: P: 0.59		medium

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	20		Mean: Median SD: SE: Lower: Upper:	Mean:0.26 Median: SD: 1.71 P:			
Roth 2009[60] parallel	Unclear	fenofibrates by 100%	130	Omega-3 (EPA, DHA, or both).	81		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median:-60.8 SD: P:	Mean:7 Median: SD: P:0.059	P = 0.059	medium
				Placebo	82		Mean: Median SD: SE: Lower: Upper:	Mean: Median:-53.8 SD: P:			
Isley 2007[31] parallel	Unclear	niacin	325	Omega-3	7	measured enzymatically on a Cobas Fara II (Roche) using enzymatic	Mean: 128 Median SD: 72 SE: Lower: Upper:	Mean: % mean: -52 Median SD: P:	Mean: Median: SD: P:		medium

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	8	reagents and procedures standardized by the Lipid Standardization Program of the Centers for Disease Control and Prevention/ National Institutes of Health.	Mean:222 Median SD: 102 SE: Lower: Upper:	Mean: % mean:-17 Median SD: P:			
Budoff 2004[10] parallel	At high risk for CHD	statins + aspirin	10-40	Garlic	9	Measured after 12 hr fast	Mean: Median SD: SE: Lower: Upper:	Mean: 8.3 % mean: Median: SD: 42.6 P:	Mean: Median: SD: P: 0.55		medium
				Placebo	10		Mean: Median SD: SE: Lower: Upper:	Mean:29.5 Median: SD: 95.7 P:			

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Chan 2002[12] parallel	At moderate/ moderately high risk for CHD (2+ risk factors)	atorvastatin	40	Fish/marine oils.	11	collected after an overnight fast (14 h) in a semirecumbent position for all biochemical measurements.	Mean: 1.2 Median SD: SE:0.17 Lower: Upper:	Mean: % mean: -43 Median: SD: 3% P:	Mean: Median: SD: P:		medium
				Placebo	13		Mean:1.4 Median SD: SE:0.12 Lower: Upper:	Mean: % mean: -26 Median: SD: P:			
Liu 2003[37] parallel	Unclear	simvastatinstatin	10	Fish/marine oils.	19	Fasting blood samples	Mean: 1.21 Median SD: 0.46 SE: Lower: Upper:	Mean:-0.55 % mean:-31.2 Median: SD: 0.58 P: <0.0001	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)	18		Mean:1.4 Median SD: 0.75 SE: Lower: Upper:	Mean:-0.14 Median: SD: 0.63 P: <0.0001			

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Dehmer 1988[17] parallel	At high risk for CHD	aspirin + Dipyridamole + ca channel blockers)	ASA: 325; dipyridamole: 225; Ca blocker: NR	Omega-3 (EPA, DHA, or both).	43	Fasting blood samples; standard automated techniques	Mean: 158 Median SD: 42.9 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)	39		Mean:137 Median SD: 36.8 SE: Lower: Upper:	Mean: Median: SD: P:			
Desideri 2003[18] parallel	At low risk for CHD (0-1 risk factors)	Simvastatinstatin, Bezafibrate	simvastatinstatin: 40; Bezafibrate: 800	Vitamin E.		12 hr fasting at 800hr - serum	Mean: 1.1 Median SD: 0.1 SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	I have assumed no losses to follow-up although I did not see this explicitely stated	medium
				No treatment (aside from CVD drug)			Mean:1.1 Median SD: 0.1 SE: Lower: Upper:	Mean: Median: SD: P:			
Wolf 2006[68] crossover	Low and/or Moderate	ASA	500	ginkgo biloba	50		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	Study states that: Laboratory findings in all subjects were un-remarkable	low-medium

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	50		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:		and did not indicate any differences between the treatment groups.	
De Caterina 2002[16] crossover	At high risk for CHD	simvastatinstatin	10-40	Vitamin E	NR		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:	Values are presented in graphs, but difficult to read. Statement that "Neither LDL cholesterol nor triglycerides were affected by Vitamin E."	high
				No treatment (aside from CVD drug)	NR		Mean: Median SD: SE: Lower: Upper:	Mean:28.5 % mean: Median: SD: P:			
Balestrieri 1996[4] crossover	Low and/or Moderate	Simvastatinstatin	10-40	Fish/marine oils	14	12 hour fast, anti-tubectal vein	Mean: 90 Median SD: 26 SE: Lower: Upper:	Mean:-7 % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	14		Mean:111 Median SD: 58 SE: Lower: Upper:	Mean:5 Median: SD: P:			

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Paolisso 1995[56] crossover	At high risk for CHD	nifedipine	88	Vitamin E	30	Fasting at end of 2 mo treatment	Mean: 1.07 Median SD: SE:0.03 Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P: <0.05		medium
				Placebo	30		Mean:1.34 Median SD: SE:0.06 Lower: Upper:	Mean: Median: SD: P:			
Hansen1993 [29] crossover	Low and/or Moderate	lovastatin	40	Fish/marine oils	14		Mean: Median SD: SE: Lower: Upper:	Mean:-41 % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	14		Mean: Median SD: SE: Lower: Upper:	Mean:-18 Median: SD: P:			
Avogaro 1974[3] Crossover	Unclear	propranolol	20 or 60	Niacin	10	at end of 1 mo treatment	Mean: 122.4 Median SD: SE:34.26 Lower: Upper:	Mean:- 12.6 % mean: Median: SD: P:	Mean:-8.4 Median: SD: P:	Type II hyper-lipoproteinemia	high

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				No treatment (aside from CVD drug)	10		Mean:130.8 Median SD: S E:36.92 Lower: Upper:	Mean:-4.2 Median: SD: P:			
Avogaro 1974[3] Crossover	Unclear	propranolol	20 or 60	Niacin	10	at end of 1 mo treatment	Mean: 240 Median SD: SE:150.02 Lower: Upper:	Mean:-119.83 % mean: Median: SD: P:	Mean:-49.83 Median: SD: P:	Type IV hyper-lipoproteinemia	high
				No treatment (aside from CVD drug)	10		Mean:289.83 Median SD: SE150.9: Lower: Upper:	Mean:-70 Median: SD: P:			
Mueller 1991[51] crossover	Low and/or Moderate	aspirin	325 - single dose	Fish/marine oils	12	Fasting	Mean: 82.58 Median SD: 40.98 SE: Lower: Upper:	Mean:-31.5 % mean: Median: SD: P:	Mean: Median: SD: P:		medium

Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
				Placebo	12		Mean:112.5 Median S67.37D: SE: Lower: Upper:	Mean:-1.58 Median: SD: P:			
Maki 2008[41] crossover	Low and/or Moderate	simvastatin	20	Omega-3	39	10-14 hour fast; Centers for Disease Control and Prevention lipid standardizatio n program	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P: <0.001	The IQRs reported are actually ranges (low-high).	medium
				Placebo	40		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 89. KQ2—Continuous data—Activated partial thromboplastin time (aPTT)

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Wolf 2006[68] crossover	Low and/or Moderate	ASA	500	ginkgo biloba	50		Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	50		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			
McKenney 2006[45] Crossover	Low and/or Moderate	simvastatin	80	Omega-3	24		Mean: Median SD: SE: Lower: Upper:	Mean: –0.3 % mean: Median: SD: 1.2 P:	Mean: Median: SD: P:		medium
				No treatment	23		Mean: Median SD: SE: Lower: Upper:	Mean: –0.4 Median: SD: 1.2 P:			

Evidence Table 90. KQ2—Continuous data—Ejection fraction

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
36585	At high risk for CHD	ACE inhibitors (no description); furosemide; digoxin, also hydralazine and/or nitrates	NR	Coenzyme Q10	27	at 12 wks of treatment	Mean: 31 Median SD: 9 SE: Lower: Upper:	Mean:5 % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	27		Mean:31 Median SD: 9 SE: Lower: Upper:	Mean:5 Median: SD: P:			

Evidence Table 91. KQ2—Continuous data—Lipoprotein A

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Balestrieri 1996[4] crossover	Low and/or Moderate	Simvastatinstatin	10-40	Fish/marine oils	14	12 hour fast, anti-tubectal vein	Mean: Median SD: SE: Lower: Upper:	Mean: % mean: Median: SD: P:	Mean: Median: SD: P:		medium
				Placebo	14		Mean: Median SD: SE: Lower: Upper:	Mean: Median: SD: P:			

Evidence Table 92. KQ2—Continuous data—PR interval

Author Year Study Design	CHD Risk Category	CVD drug	Dose	Supplement/. Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Summary of Results	Overall Risk of Bias (ROB) Assessment
Tankanow 2003[65]	At low risk for CHD (0-1 risk factors)	digoxin	0.25	Hawthorn	8	PR Interval (ECG measurement)	Mean: 152 Median SD: 14 SE: Lower: Upper:	Mean:1 % mean: Median: SD:13 P:	Mean: Median: SD: P:		medium
				No treatment (aside from CVD drug)	8		Mean:156 Median SD: 24 SE: Lower: Upper:	Mean:6.5 Median: SD:11 P:			

Evidence Table 93. KQ2—Dichotomous outcomes

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose)	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Bays 2010[6] parallel	Low-density lipoprotein cholesterol (LDL-C) (above/below threshold). <160 mg/dL, <130 mg/dL, or <100 mg/dL	Unclear	Atorvastatin (10-40mg/d)	Omega-3 (EPA, DHA, or both).	105	90	Placebo	106	97	NR	p value =0.20	Medium
Bays 2010[6] parallel	non-HDL-C. <190 mg/dL, <160 mg/dL, or <130 mg/dL	Unclear	Atorvastatin (10-40mg/d)	Omega-3 (EPA, DHA, or both).	106	94	Placebo	107	94	NR	p value >0.99	Medium
Ferraro 2009[22] parallel	Proteinuria reduction; % of patients acheiving reduction of >/= 50% from baseline	Unclear	ramipril (10mg/d)	Omega-3 (EPA, DHA, or both).	15	12	No treatment (aside from CVD drug)	15	3	4 (4.1; adjusted event risk ratio)	5 (33.3%) of ptas in tx group vs. 0 in control showed a completed negativizatioon of proteinuria (p=0.042)	Medium
Mohammed Abdul 2008[49] Crossover	International normalized ratio (INR) (above/below threshold). Indicate threshold. INR > 4	At low risk for CHD (0-1 risk factors)	Wafarin (26mg - single dose)	Garlic	12	0	No treatment (aside from CVD drug)	12	0	NR		Medium

Evidence Table 93. KQ2—Dichotomous outcomes (continued)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose)	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Sconce 2007[61] Parallel	INR; Number achieving improved control of anticoagulation	Unclear	Wafarin (3.8-4.4 vs. 3.3-3.4 mg/d)	Vitamin K. Other details if needed (e.g. dose).	35	33	Placebo	33	24	NR	Some data (<1% in each arm) omitted from analysis due to known confounding factors	Medium
Sconce 2007[61] Parallel	INR; Number reaching target for stable anticoagulation (SD of INR values below 0.5)	Unclear	Wafarin (3.8-4.4 vs. 3.3-3.4 mg/d)	Vitamin K. Other details if needed (e.g. dose).	35	19	Placebo	33	7	NR	Some data (<1% in each arm) omitted from analysis due to known confounding factors	Medium
McKenney 2006[45] Crossover	Platelet aggregability (above/below threshold). Indicate outcome and threshold. adenosine diphosphate, collagen; threshold not reported	Low and/or Moderate	Simvastatin (20mg/d)	Omega-3 (EPA, DHA, or both)	NR	0	No treatment (aside from CVD drug)	NR	0	NR		Medium
Bender 1998[8] Parallel	Hypertension (HTN), new or worsening (e.g. need for change in therapy)	Unclear	warfarin (NR)	Omega-3 (EPA, DHA, or both).	6	0	Placebo	5	0	NR		High
Bender 1998[8] Parallel	Hypotension	Unclear	warfarin (NR)	Omega-3 (EPA, DHA, or both).	6	0	Placebo	5	0	NR		High

Evidence Table 93. KQ2—Dichotomous outcomes (continued)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose)	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Roth 2009[60] parallel	Hypertension (HTN), new or worsening (e.g. need for change in therapy)	Unclear	fenofibrates (130 mg/d)	Omega-3 (EPA, DHA, or both).	84	2	Placebo	83	2	NR		Medium

Evidence Table 94. KQ3—Continuous Alanine transaminase (ALT)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Lee 2008[36] Parallel	At high risk for CHD	Warfarin	3.5	Ginseng	12	NR Unit: U/L	Mean: 22.09 SD: 7.19	Mean:0.18	NR	There were no statistically significant differences between the two groups.	N/A
				No treatment	13		Mean:23.15 SD: 5.61	Mean:1.8			
Mabuchi 2007[39] Parallel	Unclear	Atorvastatin	10	CoQ10	24	NR Unit: IU/L	Mean: 31.6 SD: 26.1	Mean:18.4 P: 0.0219	NR	There were no significant differences between the two groups.	Medium
				Placebo	25		Mean:32.6 SD: 14.9	Mean:21.6 P:0.0147			
Davidson 2007[14] Parallel	Unclear	Simvastatin	40	Omega 3	122	NR Unit: U/L	NR	Mean:5.7	Mean:6.4 P: <0.001	N/A	Medium
				Placebo	132		NR	Mean: -0.7			
Nordøy 2000[54] Parallel	Mixed: Low and/or mod to high risk	Simvastatin	20	Omega 3		laboratory tests perfomed for liver function Unit: NR	NR	NR	NR	No significant changes were observed in serum ALT	Medium
				Placebo			NR	NR			

Evidence Table 94. KQ3—Continuous Alanine transaminase (ALT) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Napoli 1998[52] Parallel	Unclear	Pravastatin	20-40	Vitamin E		alanine aminotransferase Unit: NR	NR	NR	NR	No differences in routine laboratory tests or adverse events were registered during the study. In particular, there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups.	Medium
				No treatment			NR	NR			
Budoff 2004[10] Parallel	At high risk for CHD	Satins + aspirin	10-40	Garlic	9	Measured after 12 hr fast Unit: mg/dl	NR	Mean:0.11 SD:7.25	P:0.5876	N/A	Medium
				Placebo	10		NR	Mean: -2.6 SD:13			
Lui 2003[37] Parallel	Unclear	Simvastatin	10	Omega3	19	Narratively reported for post treatment Unit: NR	NR:	NR	NR	N/A	Medium
				Control	18		NR	NR			

Evidence Table 94. KQ3—Continuous Alanine transaminase (ALT) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Wolf 2008[68] Crossover	Mixed: Low and/or Moderate	ASA	500	Gingko biloba		NR Unit: NR	NR	NR	NR	Study states that: Laboratory findings in all subjects were un-remarkable and did not indicate any differences between the treatment groups.	Medium
							NR	NR			

Evidence Table 95. KQ3—Continuous—Alkaline phosphatase

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Mabuchi 2007[39] Parallel	Unclear	Atorvastatin	10	Co Q10	24	NR Unit: IU/L	Mean: 256 SD: 76	NR	P: 0.3409	There's no significant differences between groups (p=0.5943).	Medium
				Placebo	25		Mean:235 SD: 58	NR			
Playford 2003[58] Parallel	At high risk for CHD	Fenofibrate	200	Co Q10 + Fenofibrate	18	NR Unit: U/L	Mean: 52.5 Lower: 44.0 Upper: 62.6	NR	NR	N/A	Low-medium
				No Treatment	17		Mean:58.5 Lower: 52.7 Upper:65.1	NR			
				CoQ 10	20		NR	NR			
				Placebo	18		NR	NR			

Evidence Table 95. KQ3—Continuous—Alkaline phosphatase (continued)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Napoli 1998[52] Parallel	Unclear	Pravastatin	20-40	Vitamin E		NR Unit: NR	NR	NR	NR	No differences in routine laboratory tests or adverse events were registered during the study. In particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups."	Medium
				No Treatment			NR	NR			
Budoff 2004[10] Parallel	At high risk for CHD	Statins + aspirin	10-40	Garlic	9	NR Unit: mg/dl	NR	Mean:4 Median: SD:12.1	P: 0.1452	N/A	Medium
				Placebo	10		NR	Mean:-10.1 SD:25.2			

Evidence Table 95. KQ3—Continuous—Alkaline phosphatase (continued)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Wolf 2008[68] Crossover	Mixed: Low and/or Moderate	ASA	500	Gingko biloba		NR Unit: NR	NR	NR	NR	Study states that: Laboratory findings in all subjects were un-remarkable and did not indicate any differences between the treatment groups.	Low-medium
							NR	NR			

Evidence Table 96. KQ 3—Continuous Anemia: Other parameter (e.g. ferritin, MCV, MCH). Specify outcome—Hemoglobin

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Macan 2006[40] Parallel	Unclear	Warfarin	NR	Garlic	22	NR Unit: g/dl	NR	Mean:-0.2 SD:0.6	NR	p-value for comparison of changes of mean from baseline between two groups: 0.210	Medium
				Placebo	26		NR	Mean:0.0 SD:0.8			
Napoli 1998[52] Parallel	Unclear	Pravastatin	20-40	Vitamin E		NR Unit: NR	NR	NR	NR	No differences in routine laboratory tests or adverse events were registered during the study. In particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups."	Medium
				No Treatment			NR	NR			

Evidence Table 96. KQ 3—Continuous Anemia: Other parameter (e.g. ferritin, MCV, MCH). Specify outcome—Hemoglobin (continued)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Lee 2008[36] Parallel	At high risk for CHD	Warfarin	3.5	Ginseng	12	NR Unit: g/dl	Mean: 13.1 SD: 1.03	Mean: -0.25	NR	There were no statistically significant differences between the ginseng group and control group.	N/A
				No Treatment	13		Mean:14.05 SD: 1.41	Mean:-0.26			
Wolf 2008[68] Crossover	Mixed: Low and/or Moderate	ASA	500	Gingko biloba		NR Unit: NR	NR	NR	NR	Study states that: Laboratory findings in all subjects were un-remarkable and did not indicate any differences between the treatment groups.	Low-medium
							NR	NR			
Hansen 1993[29] Crossover	Mixed: Low and/or Moderate	Lovastatin	40	Omega-3	14	NR Unit: % change	NR	% Mean: 0 SD: 1 P: NS	NR	N/A	Medium
				No treatment	14		NR	% Mean: 0 SD: 1 P: NS			

Evidence Table 97. KQ 3—Continuous Aspartate aminotransferase (AST)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Nordøy 2000[54] Parallel	Mixed: Low and/or mod to high risk	Simvastatin	20	Omega-3		laboratory tests perfomed for liver function Unit: NR	NR	NR	NR	no significant changes were observed in serum AST	Medium
				Placebo			NR	NR			
Napoli 1998[52] Parallel	Unclear	Pravastatin	20-40	Vitamin E		NR Unit: NR	NR	NR	NR		Medium
				No Treatment			NR	NR			
McDowell 1994[44] Parallel	Unclear	Simvastatin	20	Vitamin E	8	Serum levels Unit: NR	NR	NR	NR	report states 'there was no change in serum levels of aspartate transaminase	Medium
				Placebo	8		NR	NR			
Budoff 2004[10] Parallel	At high risk for CHD	Statins + aspirin	10-40	Garlic	9	Measured after 12 hr fast Unit: mg/dl	NR	Mean:1.89 SD:7.85	P: 0.262	N/A	Medium
				Placebo	10		NR	Mean:-4.6 SD:15			
Lui 2003[37] Parallel	Unclear	Simvastatin	10	Omega-3	19	narratively reported for post treatment Unit: U/L	NR	NR	NR	N/A	Medium
				No Treatment	18		NR	NR			

Evidence Table 97. KQ 3—Continuous Aspartate aminotransferase (AST) (continued)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Lee 2008[36] Parallel	At high risk for CHD	Warfarin	3.5	Ginseng	12	NR Unit: U/L	Mean: 24.45 SD: 7.10	Mean:-1.10	NR	There were no statistically significant differences between the two groups.	N/A
				No Treatment	13		Mean:26.88 SD: 7.8	Mean:1.69			
Mabuchi 2007[39] Parallel	Unclear	Atorvastatin	10	Co Q10	24	NR Unit: IU/L	Mean: 28.8 SD: 13.4	% mean: 12.5 P:0.0205	NR	There were no significant differences between the two groups.	Medium
				Placebo	25		Mean:27.9 SD: 7.4	% mean: 10.7 P:0.0184			
Davidson 2007[14] Parallel	Unclear	Simvastatin	40	Omega-3	122	NR Unit: U/L	NR	Mean:1.9	Mean: 1.7 P: <0.032	N/A	Medium
				Placebo	132		NR	Mean:0.2			
Wolf 2008[68] Crossover	Mixed: Low and/or Moderate	ASA	500	Gingko biloba		NR Unit: NR	NR	NR	NR	Study states that: Laboratory findings in all subjects were un-remarkable and did not indicate any differences between the treatment groups.	Low-medium
							NR	NR			

Evidence Table 98. KQ 3—Continuous Blood urea nitrogen (BUN)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome / Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Lee 2008[36] Parallel	At high risk for CHD	Warfarin	3.5	Ginseng	12	NR Unit: mg/dl	Mean:9.45 SD: 5.16	Mean:-2.28	NR	There were no statistically significant differences between the two groups.	N/A
				No Treatment	13		Mean:13.46 SD: 4.44	Mean:0.46			
Napoli 1998[52] Parallel	Unclear	Pravastatin	20-40	Vitamin E		NR Unit: NR	NR	NR	NR	No differences in routine laboratory tests or adverse events were registered during the study. In particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups.	Medium
				No Treatment			NR	NR			

Evidence Table 99. KQ 3—Continuous CK or CPK

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome / Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Mabuchi 2007[39] Parallel	Unclear	Atorvastatin	10	Co Q10	24	NR Unit: IU/L	Mean: 145 SD: 73	% mean:14.2 P:0.2423	NR	There's no significant difference between groups (p=1182)	Medium
				Placebo	25		Mean:192 SD: 196	% mean:23.9 P:0.1081			
Young 2007[70] Parallel	Mixed: Mod and high risk	Simvastatin	10-40	Co Q10	22	NR Unit: U/L	NR	NR	P:0.85	No difference in groups (p=0.85)	Medium
				Co Q10	22		NR	NR			
Caso 2007[11] Parallel	Unclear	Simvastatin (22); Atorvastatin (7); Pravastatin (2); Lovastatin (1)	Varying Doses	Co Q10	18	Fasting Unit: U/L	Mean: 157 SE:23	NR	NR	The report states 'there was no change in serum levels of aspartate transaminase	Low
				Other dietary supplement – Vitamin E	14		Mean:103 SE:14	NR			

Evidence Table 99. KQ 3—Continuous CK or CPK (continued)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome / Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Manuel 2004[42] Parallel	At high risk for CHD	Atorvastatin	20	Vitamin E	11	NR Unit: U/L	NR	Mean:1.89 SD:7.85	NR	Creatine phosphokinase tended to increase in both groups and to the same extent (from 132 ± 69 U/L before treatment to 136 ± 70 U/L after 3 months and 171 ± 113 U/L after 6 months, P = 0.07 when comparing inclusion and 6 months).	Medium
				Placebo	11		NR	Mean:-4.6 SD:15			

Evidence Table 99. KQ 3—Continuous CK or CPK (continued)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome / Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Napoli 1998[52] Parallel	Unclear	Pravastatin	20-40	Vitamin E No Treatment	19 	NR Unit: NR	NR NR	NR NR	NR	..no differences in routine laboratory tests or adverse events were registered during the study (data not shown); in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups.	Medium
McDowell 1994[44] Parallel	Unclear	Simvastatin	20	Vitamin E Placebo	8 8	NR Unit: NR	Mean: 24.45 SD: 7.10 Mean:26.88 SD: 7.8	Mean:-1.10 Mean:1.69	NR	Study reports: "There was no change in serum levels of...creatine kinase	Medium

Evidence Table 99. KQ 3—Continuous CK or CPK (continued)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome / Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Lui 2003[37] Parallel	Unclear	Simvastatin	10	Omega-3	19	narratively reported for post treatment Unit: NR	Mean: 28.8 SD: 13.4	% mean: 12.5 P:0.0205	NR	N/A	Medium
				No Treatment	18		Mean:27.9 SD: 7.4	% mean: 10.7 P:0.0184			

Evidence Table 100.KQ 3—Continuous Creatinine

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome / Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD / P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Lee 2008[36] Parallel	At high risk for CHD	Warfarin	3.5	Ginseng	12	NR Unit: mg/dl	Mean: 0.74 SD: 0.19	Mean:-0.04	NR:	There were no statistically significant differences between the ginseng group and control group.	N/A
				No Treatment	13		Mean:0.86 SD: 0.21	Mean:-0.01 SD:0.8			
Nordøy 2000[54] Parallel	Mixed: Low and/or mod to high risk	Simvastatin	20	Omega-3		NR Unit: NR	NR	NR	NR	no significant changes were observed in serum creatinine levels	Medium
				Placebo			NR	NR			
Napoli 1998[52] Parallel	Unclear	Pravastatin	20-40	Vitamin E		NR Unit: NR	NR	NR	NR	No differences in routine laboratory tests or adverse events were registered during the study (data not shown); in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups."	Medium
				No Treatment			NR	NR			
Reyes 1984[59] Parallel	Mixed: Low and/or Moderate	Hydrochlorothiazide	50	Magnesium	13	NR Unit: NR	NR	P: NS	NR	Results state only that 'no statistically significant changes affected the electrocardiogram or the plasma variables studied during the trial'.	Medium
				Placebo	8		NR	P: NS			
Budoff 2004[10] Parallel	At high risk for CHD	Statins + aspirin	10-40	Garlic	9	Measured after 12 hr fast Unit: mg/dl	NR	Mean: 0 SD: 0	P:0.9152	N/A	Medium
				Placebo	10		NR	Mean: 0.01 SD: 0.14			

Evidence Table 100.KQ 3—Continuous Creatinine (continued)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome / Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD / P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Wolf 2008[68] Crossover	Mixed: Low and/or Moderate	ASA	500	Gingko biloba		NR Unit: NR	NR	NR	NR	Study states that: Laboratory findings in all subjects were un-remarkable and did not indicate any differences between the treatment groups.	Low-medium
							NR	NR			
De Caterina 2002[16] Crossover	At high risk for CHD	Simvastatin	10-40	Vitamin E		NR Unit: pg/mg	Mean: 237 SD: 122	NR	NR	N/A	High
				No treatment			Mean: 240 SD: 124	NR			

Evidence Table 101. KQ 3—Continuous Fasting blood glucose

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Bays 2010[6] Parallel	Unclear	Atorvastatin	10-40	Omega-3	122	NR Unit: mg/dL	NR	Mean: 6.18 SD:24.29	NR	N/A	Medium
				Placebo	121		NR	Mean:4.39 SD: 18.67			
Mabuchi 2007[39] Parallel	Unclear	Atorvastatin	10	Co-Q10	24	NR Unit: NR	NR	NR	NR	no significant changes in both groups	Medium
				Placebo			NR	NR			
Neil 2010[53] Parallel	High	Atorvastatin	20	Omega-3	163	HbA_{1C} %	Mean: 7.3 SD: 1.2	NR	NR	No significant changes between groups	Low
				Placebo	169		Mean: 7.4 SD: 1.2	NR	NR		
Davidson 2007[14] Parallel	Unclear	Simvastatin	40	Omega-3	122	NR Unit: mg/dL	NR	Mean:5.5	P: 0.002	N/A	Medium
				Placebo	132		NR	Mean:-0.1			
Macan 2006[40] Parallel	Unclear	Warfarin	NR	Garlic	22	Blood draw after 12 hour fast. Samples centrifuged and serum separated Unit: mg/dL	NR	Mean:7.4 SD:34.9	P: 0.788	N/A	Medium
				Placebo	26		NR	Mean:9.9 SD:29.6			
Playford 2003[58] Parallel	At high risk for CHD	Fenofibrate	200	Co-Q10 + Fenofibrate	18	NR Unit: NR	NR	NR	NR	N/A	Low-medium
				No Treatment	17		NR	NR			
				Co-Q10	20		NR	NR			
				Placebo	18		NR	NR			

Evidence Table 101. KQ 3—Continuous Fasting blood glucose (continued)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Duffy 2001[20] Parallel	Mixed - Low and/or Moderate	Simvastatin	10-40	Vitamin E + Simvastatin	6	NR Unit: mmol/L	Mean: 5.2 SD: 0.6	Mean:0.3	NR	N/A	Medium
				No Treatment	7		Mean:4.9 SD: 0.5	Mean:0			
				Vitamin E	6		Mean:5.7 SD: 2.1	Mean:0.2			
				Placebo	7		Mean:4.6 SD: 0.4	Mean:- 0.2			
Nordøy 2000[54] Parallel	Mixed - Low and/or mod to high risk	Simvastatin	20	Omega-3	15	Measured in a fasted state 4 and 8 hours after meal Unit: mmol/h/L	Mean: 42.3 SD: 5.0	Mean:1.1 P: NS	NR	Crude difference between groups in mean change from basline (omega-2 vs. placebo): -3.2 (p=0.312)	Medium
				Placebo	15		Mean: 48.2 SD: 10.2	Mean:4.2 P: NS			
Barbagallo 1999[5] Parallel	Unclear	Flurosemide	25	Vitamin E	12	fasting plasma glucose Unit: mmol/L	Mean: 4.9 SD: 0.5	P: NS	P: NS	Outcomes addressed in study but not extracted: Body fat, Fasting plasma insulin, Vitamin E, Blood (e.g. red blood cell) Mg, Plasma glutathione, Total Glutathione, GSH, GSSG	Medium
				Placebo	12		Mean:5.0 SD: 0.3	P: NS			

Evidence Table 101. KQ 3—Continuous Fasting blood glucose (continued)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Napoli 1998[52] Parallel	Unclear	Pravastatin	20-40	Vitamin E		NR Unit: NR	NR:	NR	NR:	no differences in routine laboratory tests or adverse events were registered during the study (data not shown); in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups."	Medium
				No Treatment			NR	NR			
Bordia 1998[9] Parallel	At high risk for CHD	Nitrates	NR	Garlic	30	fasting blood sugar Unit: mg/dL	Mean: 100.8 SE:2.5	Mean:4 P: NS	NR	N/A	High
				Placebo			NR	NR			
Paolissa 1992[57] Parallel	Unclear	Hydrochlorothiazide	25	??		Fasting plasma glucose Unit: NR	NR	NR	NR	N/A	Medium
				Placebo			NR	NR			

Evidence Table 101. KQ 3—Continuous Fasting blood glucose (continued)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Nordøy 2003[55] Parallel	Mixed - Mod and high risk	Atorvastatin	10	Omega-3	22	Blood sample taken after 12 hr fasting, within 6 days of end of study Unit: mmol/L	NR	Mean: 0.1 SD: 0.5	P:0.23	N/A	Low
				Placebo	20		NR	Mean: 0.1 SD: 0.7			
Reyes 1984[59] Parallel	Mixed - Low and/or Moderate	Hydrochlorothiazide	50	Magnesium	13	measured between 900-1100hrs Unit: NR	NR	P: NS	NR	Blood glucose measured. Results state only that 'no statistically significant changes affected the electrocardiogram or the plasma variables studied during the trial'.	Medium
				Placebo	8		NR	P: NS			
Budoff 2004[10] Parallel	At high risk for CHD	Statins + aspirin	10-40	Garlic	9	Measured after 12 hr fast Unit: mg/dL	NR	Mean:14.3 SD: 55.1	P: 0.9666	N/A	Medium
				Placebo	10		NR	Mean:13.3 SD:50.8			

Evidence Table 101. KQ 3—Continuous Fasting blood glucose (continued)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Chan 2002[12] Parallel	At moderate/moderately high risk for CHD (2+ risk factors)	Atorvastatin	40	Omega-3	11	narratively reported for post treatment Unit: NR	NR	NR	NR	N/A	Medium
				No Treatment	13		NR	NR			
Lui 2003[37] Parallel	Unclear	Simvastatin	10	Omega-3	19	narratively reported for post treatment Unit: NR	NR	NR	NR	N/A	Medium
				No Treatment	18		NR	NR			
Maki 2008[41] Crossover	Mixed: Low, Moderate and high risk	Simvastatin	20	Omega-3	39	NR Unit: mg/dl	NR	Median: 5	NR	N/A	Medium
				No treatment	39		NR	Median: 1			

Evidence Table 102. KQ 3—Continuous Fasting plasma glucose

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Paolissa 1995[56] Crossover	At high risk for CHD	Nifedipine	88	Vitamin E	30	NR Unit: mmol/L	Mean:5.7 SE: 0.6	NR	NR	N/A	Medium
				Placebo	30		Mean:5.7 SE: 0.4	NR			

Evidence Table 103. KQ 3—Continuous Glomeluar filtration rate

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome / Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Ferraro 2009[22] Parallel	Unclear	Ramipril	10	Omega-3	15	Estimated GFR Unit: ml/min	Mean: 93.9 SD: 35.4	NR	NR	N/A	Medium
				No Treatment	15		Mean:67.7 SD: 35.0	NR			

Evidence Table 104. KQ 3—Continuous Glycosylated hemoglobin (HbA1c)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Manuel 2004[42] Parallel	At high risk for CHD	Atorvastatin	20	Vitamin E	11	Fasting, measured using a HPLC cation exchange column Unit: measured as percentage	NR	P: NS	P: NS	N/A	Medium
				Placebo	11		NR	P: NS			
Playford 2003[58] Parallel	At high risk for CHD	Fenofibrate	200	Co-Q10 + Fenofibrate	18	Measured after 14 hr fast; Unit: measured as percentage	Mean: 7.2 SE:0.2	Mean:-0.3	Mean:0.2 P:0.032 Crude difference in means: 0.2 P:0.832	N/A	Low-medium
				No Treatment	17		Mean:7.4 SE:0.4	Mean:0.3			
				Co-Q10	20		Mean: 7.0 SE:0.3	Mean:0.1			
				Placebo	18		Mean:6.6 SE:0.2	Mean:0.3			
Bays 2010[6] Parallel	Unclear	Atorvastatin	10-40	Omega-3	122	NR Unit: measured as percentage	NR	Mean: 0.18 SD: 0.45	NR	N/A	Medium
				Placebo	121		NR	Mean: 0.10 SD: 0.33			

Evidence Table 10. KQ 3—Continuous Hematocrit

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD / P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Lee 2008[36] Parallel	At high risk for CHD	Warfarin	3.5	Ginseng	12	Average rating of the interference items of Pain Inventory questionnaire Unit: measured as percentage	Mean: 39.36 SD: 3.03	Mean: -0.06	NR	There were no statistically significant differences between the ginseng group and control group.	N/A
				No Treatment	13		Mean: 42.11 SD: 4.12	Mean: -0.54			
Hansen 1993[29] Crossover	Mixed: Low and/or Moderate	Lovastatin	40	Omega-3	14	NR Unit: % change	NR	% Mean: 7 SD: 3 P: <0.001	NR	N/A	Medium
				No Treatment	14		NR	% Mean: 5 SD: 3 P: <0.01			

Evidence Table 106. KQ 3 Continuous Leukopenia: WBC count

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Napoli 1998[52] Parallel	Unclear	Pravastatin	20-40	Vitamin E		NR Unit: NR	NR	NR	NR	No differences in routine laboratory tests or adverse events were registered during the study. In particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups."	Medium
				No Treatment			NR	NR			
Budoff 2004[10] Parallel	At high risk for CHD	Statins + aspirin	10-40	Garlic	9	Measured after 12 hr fast Unit: NR	NR	Mean: -0.2 SD: 1.9	P:0.396	N/A	Medium
				Placebo	10		NR	Mean: -0.95 SD: 1.85			
Wolf 2008[68] Crossover	Mixed: Low and/or Moderate	ASA	500	Gingko biloba		NR Unit: NR	NR	NR	NR	Study states that: Laboratory findings in all subjects were un-remarkable and did not indicate any differences between the treatment groups.	Low-medium
							NR	NR			
Hansen 1993[29] Crossover	Mixed: Low and/or Moderate	Lovastatin	40	Omega-3	14	NR Unit: % change	NR	% Mean: 49 SD: 29 P: <0.001	NR	N/A	Medium
				No treatment	14		NR	% Mean: 50 SD: 31 P: <0.001			
Mueller 1991[51] Crossover	Mixed: Low and/or Moderate	Aspriin	325	Omega-3	12	NR Unit: x 103/mm3	Mean:5.36 SD:1.44	Mean: -1.02	NR		Medium
				Placebo	12		Mean:5.68 SD:1.61	P: <0.05			

Evidence Table 107. KQ 3—Continuous Myalgia

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Young 2007[70] Parallel	Mixed - Mod and high risk	Simvastatin	10-40	Co Q10	22	Patients documented the number of sites affected by myalgia and rated the intensity of pain on the scale. UnIt: Visual analogue scale with intensity of pain rated from 0 to 100mm	NR	Median:6.0 P:0.001	NR	No difference in groups (p=0.63). An adjusted analysis has also been presented for individual group data (myalgia score adjusted for no. of affected sites).	Medium
				Placebo	21		NR	Median:2.3 P:0.001			
Caso 2007[11] Parallel	Unclear	Simvastatin (22); Atorvastatin (7); Pravastatin (2); Lovastatin (1)	Varying Doses	Co Q10	18	Pain severity score: averaging scores of the 4 pain intensity items of Brief Pain Inventory questionnaire Unit: Score on questionnaire	Mean: 2.97 SE:0.48	Mean: -2.03 SE: 0.44 P: <0.001 % mean: 40 SE: 11	P: 0.001	N/A	Low
				Other dietary supplement – Vitamin E	14		Mean:4.73 SE:0.68	Mean: 0.34 SE: 0.33 P: NS % mean: 9 SE: 14			

Evidence Table 107. KQ 3—Continuous Myalgia (continued)

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Caso 2007[11] Parallel	Unclear	Simvastatin (22); Atorvastatin (7); Pravastatin (2); Lovastatin (1)	Varying Doses	Co Q10	18	averaging ratings of the 7 interference items of Brief Pain Inventory questionnaire Unit: Score on questionnaire	Mean: 2.82 SE:0.61	P: <0.02 % mean: 38 SE: 14	NR	N/A	Low
				Other dietary supplement – Vitamin E	14		Mean:4.25 SE:0.70	P: NS			

Evidence Table 108. KQ 3—Continuous Myoglobin

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Mabuchi 2007[39] Parallel	Unclear	Atorvastatin	10	Co-Q10	24	NR Unit: ng/ml	Mean: 59.7 SD: 28.3	% mean: 17.5 P:0.0713	NR	There's no significant differences between groups (p=0.1453)	Medium
				Placebo	25		Mean: 66.9 SD: 39.4	% mean: 0.75 P:0.7405			

Evidence Table 109. KQ 3—Continuous QT interval

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
McDowell 1994[44] Parallel	Unclear	Simvastatin	20	Vitamin E	8	At rest using Siemens Minograf 470 which computes QT interval corrected to a heart rate of 60/min using formula - QTc = QT + 1.75(HR-60) Unit: m/sec	Mean: 413 SD: 22	P: NS	NR	N/A	Medium
				Placebo	8		Mean: 399 SD: 16	P: NS			

Evidence Table 110. KQ 3—Continuous RBC count

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Hansen 1993[29] Crossover	Mixed: Low and/or Moderate	Lovastatin	40	Omega-3	14	NR Unit: % change	NR	% Mean: 8 SD: 4 P: <0.001	NR	N/A	Medium
				No treatment	14		NR	% Mean: 5 SD: 2 P: <0.001			

Evidence Table 111. KQ 3—Continuous Serum potassium

Author Year Study Design	CHD Risk Category	CVD drug	CVD Dose (mg/d)	Supplement/ Control	N	Definition of outcome/ Unit of outcome	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional Comments	Overall Risk of Bias (ROB) Assessment
Budoff 2004[10] Parallel	At high risk for CHD	Statins + aspirin	10-40	Garlic	9	Unit: mg/dl	NR	Mean: -0.01 SD: 1.15	P:0.7464	N/A	Medium
				Placebo	10		NR	Mean: -0.15 SD: 0.64			
Wirell 1994[67] Crossover	Unclear	metoprolol, atenolol, pindolol & propanolol	NR	Magnesium	39	NR mmol/L	Mean: 4 SD: 0.3	NR	P: 0.045 Crude difference	N/A	Medium
				Placebo	39		Mean: 3.9 SD: 0.3	NR			

Evidence Table 112. KQ3—Dichotomous outcomes—Abnormal ECG

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Reyes 1984[59] Parallel	N/A	Mixed: Low and/or Moderate	Hydrochlorothiazide (50)	Magnesium	13	NR	Placebo	8	NR	NR	Results state only that 'no statistically significant changes affected the electrocardiogram or the plasma variables studied during the trial'. Methods do not state which electrocardiographic measurements were taken.	Medium
Playford 2003[58] Parallel	N/A	At high risk for CHD	Fenofibrate (200)	Co-Q10	18	NR	No Treatment	17	NR	NR		Low-medium
Di Spirito 2008[19] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Atorvastatin (80)	Omega-3	50		No Treatment	50		NR	No treatment related trends regarding ECG or other clinical or laboratory markers were found (no specific data)	Medium
McKenney 2006[45] Crossover	N/A	Mixed: Low and/or Moderate	Simvastatin (80)	Omega-3	24		No Treatment	24		NR		Medium
Kim 2010[35] Crossover	N/A	Mixed: Low and/or Moderate	Ticlopidine (250 – single dose)	Gonkgo Biloba	24	0	No Treatment	24	0	NR		Medium

Evidence Table 113. KQ3—Dichotomous outcomes—Adverse event other (other than neurologic, allergic, gastrointestinal, bleeding, withdrawal due to adverse event)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
McDowell 1994[44] Parallel	N/A	Unclear	Simvastatin (20)	Vitamin E	8	0	Placebo	8	0	NR	It is unclear if this was measured actively or in a standard manner - it is not reported for these two groups, only for the third, non-relevant group and no indication that this was actively sought.	Medium
Wolf 2006[68] Crossover	N/A	Mixed: Low and/or Moderate	ASA (500)	Ginkgo biloba	50	50	Placebo	50	49	NR		Low-medium
Wolf 2006[68] Crossover	N/A	Mixed: Low and/or Moderate	ASA (500)	Ginkgo biloba	50	49	Placebo	50	48	NR		Low-medium
Wolf 2006[68] Crossover	N/A	Mixed: Low and/or Moderate	ASA (500)	Ginkgo biloba	50	19	Placebo	50	19	NR		Low-medium
Wolf 2006[68] Crossover	N/A	Mixed: Low and/or Moderate	ASA (500)	Ginkgo biloba	50	17	Placebo	50	20	NR		Low-medium
Hansen 1993[29] Crossover	N/A	Mixed: Low and/or Moderate	Lovastatin (40)	Omega-3	14	0	No Treatment	14	0	NR		Medium

Evidence Table 114. KQ3—Dichotomous outcomes—Adverse events general

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Watson 1999[66] Crossover	N/A	At high risk for CHD	ACE inhibitors (no description), furosemide, digoxin, also hydralazine and/or nitrates (NR)	Co-Q10		0	Placebo	0	0	NR		Medium
Kim 2010[35] Crossover	N/A	Mixed: Low and/or Moderate	Ticlopidine (250 – single dose)	Ginkgo biloba	24	7	No Treatment	24	7	NR		Medium

Evidence Table 115. KQ3—Dichotomous—Alanine transaminase (ALT) (raised)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Bays 2010[6] Parallel		Unclear	Atorvastatin (10-40)	Omega-3		NR	Placebo		NR	NR		Medium
Young 2007[70] Parallel	> 3 times the upper level of normal	Mixed: Mod and high risk	Simvastatin (10-40)	Co-Q10	22	1	Placebo	22	1	NR	Exclusion criteria included: alanine aminotransferase or aspartate aminotransferase > 3 times the upper level of normal and results state: "Liver... function, …[was] not altered with either regime." Thus, counts of 0 and 0 were added for each arm	Medium
Davidson 2007[14] Parallel	mild elevation of ALT	Unclear	Simvastatin (40)	Omega-3	122	0	Placebo	132	0	NR	p=NS	Medium
Davidson 2007[14] Parallel	ALT >3.0 x ULN	Unclear	Simvastatin (40)	Omega-3	122	2	Placebo	132	1		Study reports: no cases of clinically significant increases in hepatic transaminase levels (>3.0 x ULN) in either group.	Medium

Evidence Table 115. KQ3—Dichotomous—Alanine transaminase (ALT) (raised) (continued)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Duffy 2001[20] Parallel		Mixed: Mod and high risk.	Simvastatin (10-40)	Vitamin E	6	0	No Treatment	7	0			Medium
Napoli 1998[52] Parallel	NR	Unclear	Pravastatin (20-40)	Vitamin E		0	No Treatment		0		"..no differences in routine laboratory tests or adverse events were registered during the study (data not shown); in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups."	Medium
Chan 2002[12] Parallel		At moderate/moderately high risk for CHD (2+ risk factors)	Atorvastatin (40)	Omega-3	11	0	No Treatment	13	0			Medium
Liu 2003[37] Parallel	tested for liver function	Unclear	Simvastatin (10)	Omega-3	19	0	No Treatment	18	0			Medium
Playford 2003[58] Parallel		At high risk for CHD	Fenofibrate (200)	Co-Q10	18	0	No Treatment	17	0			Low-medium

Evidence Table 115. KQ3—Dichotomous—Alanine transaminase (ALT) (raised) (continued)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Gosai 2008[26] Crossover	reference range males: 0-46 U/L; females: 0-36 U/L	At low risk for CHD (0-1 risk factors)	Rosuvastatin (40)	Omega-3	48	1	No Treatment	48	4		N/A	Medium
Di Spirito 2008[19] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Atorvastatin (80)	Omega-3	50	14	No Treatment	50	13		N/A	Medium
Balestrieri 1996[4] Crossover	N/A	Mixed: Low and/or mod to high risk	Simvastatin (10-40)	Omega-3	14	0	Placebo	16	0		N/A	Medium
Paolissa 1992[56] Crossover	N/A	At high risk for CHD	Nifedipine (88)	Vitamin E		0	Placebo		0		N/A	Medium
Watson 1999[66] Crossover	N/A	At high risk for CHD	ACE inhibitors (no description), furosemide, digoxin, also hydralazine and/or nitrates (NR)	Co-Q10		0	Placebo	0	0	NR	N/A	Medium
Kim 2010[35] Crossover	N/A	Mixed: Low and/or Moderate	Ticlopidine (250 – single dose)	Ginkgo biloba	24	0	No Treatment	24	0	NR	N/A	Medium

Evidence Table 11. KQ3- Dichotomous – Alkaline phosphatase

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Napoli 1998[52] Parallel	NA	Unclear	Pravastatin (20-40)	Vitamin E		0	No Treatment		0		No differences in routine laboratory tests or adverse events were registered during the study. In particular, there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups.	Medium
Chan 2002[12] Parallel	NA	At moderate/moderately high risk for CHD (2+ risk factors)	Atorvastatin (40)	Omega-3	11	0	No Treatment	13	0			Medium
Kim 2010[35] Crossover	N/A	Mixed: Low and/or Moderate	Ticlopidine (250 –single dose)	Ginkgo biloba	24	0	No Treatment	24	0	NR	N/A	Medium

Evidence Table 117. KQ3—Dichotomous—Anemia

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Balestrieri 1996[4] Crossover	N/A	Mixed: Low and/or mod to high risk	Simvastatin (10-40)	Omega-3	14	0	Placebo	16	0	NR	N/A	Medium
Kim 2010[35] Crossover	N/A	Mixed: Low and/or Moderate	Ticlopidine (250 –single dose)	Ginkgo biloba	24	0	No Treatment	24	0	NR	N/A	Medium

Evidence Table 118. KQ3—Dichotomous—Any adverse event

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Maki 2008[41] Crossover	N/A	Mixed: Low, Moderate and high risk	Simvastatin (20)	Omega-3		18	Placebo		17	NR	N/A	Medium

Evidence Table 119. KQ3—Dichotomous—Asparatate aminotransaminase (AST) raised

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Kim 2010[35] Crossover	N/A	Mixed: Low and/or Moderate	Ticlopidine (250 – single dose)	Ginkgo biloba	24	0	No Treatment	24	0	NR	N/A	Medium

Evidence Table 120. KQ3—Dichotomous—Asparatate aminotransferase (AST) raised

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Davidson 2007[14] Parallel	> 3.0 x ULN	Unclear	Simvastatin (40)	Omega-3	122	0	Placebo	132	0	NR		Medium
Napoli 1998[52] Parallel	Data imputed-there were no differences between baseline and post treatment values.	Unclear	Pravastatin (20-40)	Vitamin E		0	No Treatment		0		No differences in routine laboratory tests or adverse events were registered during the study in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups.	Medium
Chan 2002[12] Parallel	thresholds not specified	At moderate/moderately high risk for CHD (2+ risk factors)	Atorvastatin (40)	Omega-3	11	0	No Treatment	13	0			Medium
Liu 2003[37] Parallel	thresholds not specified	Unclear	Simvastatin (10)	Omega-3	19	0	No Treatment	18	0			Medium

Evidence Table 120. KQ3—Dichotomous—Asparatate aminotransferase (AST) raised (continued)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Young 2007[70] Parallel	> 3 times the upper level of normal	Mixed: Mod and high risk	Simvastatin (10-40)	Co-Q10	22	0	Placebo	22	0	NR	Exclusion criteria included: alanine aminotransferase or aspartate aminotransferase > 3 times the upper level of normal and results state: "Liver... function, …[was] not altered with either regime." Thus, counts of 0 and 0 were added for each arm	Medium
Gosai 2008[26] Crossover	reference range males: 0-46 U/L; females: 0-36 U/L	At low risk for CHD (0-1 risk factors)	Rosuvastatin (40)	Omega-3	48	0	No Treatment	48	2		N/A	Medium
Di Spirito 2008[19] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Atorvastatin (80)	Omega-3	50	9	No Treatment	50	13		N/A	Medium
Balestrieri 1996[4] Crossover	N/A	Mixed: Low and/or mod to high risk	Simvastatin (10-40)	Omega-3	14	0	Placebo	16	0		N/A	Medium
Paolissa 1992[56] Crossover	N/A	At high risk for CHD	Nifedipine (88)	Vitamin E		0	Placebo		0		N/A	Medium
Watson 1999[66] Crossover	N/A	At high risk for CHD	ACE inhibitors (no description), furosemide, digoxin, also hydralazine and/or nitrates (NR)	Co-Q10		0	Placebo		0	NR	N/A	Medium

Evidence Table 121. KQ3—Dichotomous—Bleeding

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Ferraro 2009[22] Parallel	Bleeding: Erythrocyturia Class1	Unclear	Ramipril (10)	Omega-3	15	5	No Treatment	15	0		2 vs. 10 at baseline were at level 1 erythrocyturia.	Medium
Ferraro 2009[22] Parallel	Bleeding: CE (erythocyturia 2	Unclear	Ramipril (10)	Omega-3	15	-4	No Treatment	15	0			Medium
Ferraro 2009[22] Parallel	Bleeding: CE (erythocyturia 3	Unclear	Ramipril (10)	Omega-3	15	-1	No Treatment	15	0			Medium
Lee 2008[36] Parallel		At high risk for CHD	Warfarin (3.5)	Ginseng	12		No Treatment	13	0		No events occurred. No data reported.	Medium
Gardner 2007[23] Parallel	Nosebleed and/or unusual bleeding	Mixed : Moderate to high	ASA (325)	Gingko baloba	30	5	Placebo	30	4			Low
Whitlock 2007[72] Parallel		At high risk for CHD	Warfarin (2)	Vitamin K	12	0	Placebo	16	0			
Sconce 2007[61] Parallel		Unclear	Warfarin (3.8-4.4 vs. 3.3-3.4)	Vitamin K	35	0	Placebo	33	0			Medium
Macan 2006[40] Parallel	Incidence of hemorrhager	Unclear	Warfarin (NR)	Garlic	22	0	Placebo	26	0	P: 1.000 (Crude event risk ratio)	N included is unclear: Unclear (66 enrolled, 52 randomized total)	Medium

Evidence Table 121. KQ3—Dichotomous—Bleeding (continued)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Macan 2006[40] Parallel	Epitaxis	Unclear	Warfarin (NR)	Garlic	22	0	Placebo	26	0		Other dichotomous outcomes assessed in this study (not specifically relevant): change in warfarin dosage	Medium
Macan 2006[40] Parallel	Clinically relevant bleeding: Hemoptysis	Unclear	Warfarin (NR)	Garlic	22	0	Placebo	26	0			Medium
Macan 2006[40] Parallel	Clinically relevant bleeding: bloody stools	Unclear	Warfarin (NR)	Garlic	22	0	Placebo	26	0		Total included per arm is unclear (66 enrolled, 52 randomized total)	Medium
Macan 2006[40] Parallel	hemorrhage into organs	Unclear	Warfarin (NR)	Garlic	22	0	Placebo	26	0		Total included per arm is unclear (66 enrolled, 52 randomized total)	Medium
Macan 2006[40] Parallel	Clinically relevant bleeding: hemarthrosis	Unclear	Warfarin (NR)	Garlic	22	0	Placebo	26	0		Total included per arm is unclear (66 enrolled, 52 randomized total)	Medium

Evidence Table 121. KQ3—Dichotomous—Bleeding (continued)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Macan 2006[40] Parallel	Clinically relevant bleeding: hematomas	Unclear	Warfarin (NR)	Garlic	22	0	Placebo	26	0		Total included per arm is unclear (66 enrolled, 52 randomized total)	Medium
Macan 2006[40] Parallel	Clinically relevant bleeding?: brusing	Unclear	Warfarin (NR)	Garlic	22	0	Placebo	26	0		Total included per arm is unclear (66 enrolled, 52 randomized total)	Medium
Steiner 1995[62] Parallel	Hemorrhagic event	At high risk for CHD	ASA (325)	Vitamin E	52	3	Placebo	48	3			Low-medium
Kaul 1992[34] Parallel	bleeding complications (non-specific)	At high risk for CHD	Calcium channel blocker, ASA (NR)	Omega-3	58	0	No Treatment	49	0			Low-medium
Bender 1998[8] Parallel	Bleeding	Unclear	Warfarin (NR)	Omega-3	6	0	No Treatment	5	0			High
Bender 1998[8] Parallel	minor brusing	Unclear	Warfarin (NR)	Omega-3	6		No Treatment	5			numeric data is not separated by groups. One episode of bruising occured but no group designation reported.	High
Dehmer 1988[17] Parallel	bleeding complications	At high risk for CHD	Aspirin (325)+ Dipyridamole (225) + Calcium channel blockers (NR)	Omega-3	43	0	No Treatment	39	0			Medium

Evidence Table 121. KQ3—Dichotomous—Bleeding (continued)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Dehmer 1988[17] Parallel	serious passive hematoams	At high risk for CHD	Aspirin (325)+ Dipyridamole (225) + Calcium channel blockers (NR)	Omega-3	43	3	No Treatment	39	1			Medium
Eritsland 1996[21] Parallel	bleeding complications (major and minor)	At high risk for CHD	Warfarin (NR)	Omega-3	174	2	No Treatment	145	2			Medium
Eritsland 1996[21] Parallel	bleeding complications (major and minor)	At high risk for CHD	Aspirin (300)	Omega-3	143	3	No Treatment	148	2			Medium
Mueller 1991[51] Crossover	N/A	Mixed: Low and/or Moderate	ASA (325 – single dose)	Omega-3		0	Placebo		0			Medium

Evidence Table 122.KQ3—Dichotomous—Bloating

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Mueller 1991[51] Crossover	N/A	Mixed: Low and/or Moderate	ASA (325 – single dose)	Omega-3		2	Placebo		0			Medium

Evidence Table 123. KQ3—Dichotomous—Blood urea nitrogen (BUN) (raised)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Watson 1999[66] Crossover	N/A	At high risk for CHD	ACE inhibitors (no description), furosemide, digoxin, also hydralazine and/or nitrates (NR)	Co-Q10		0	Placebo		0	NR	N/A	Medium
Kim 2010[35] Crossover	N/A	Mixed: Low and/or Moderate	Ticlopidine (250 –single dose)	Ginkgo biloba	24	0	No Treatment	24	0	NR	N/A	Medium

Evidence Table 124. KQ3—Dichotomous—Parallel—CK or CPK

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Bays 2010[6] Parallel	Creatine kinase greater than 3 times the upper limit of normal	Unclear	Atorvastatin (10-40)	Omega-3		3	Placebo		3	NR		Medium
Davidson 2007[14] Parallel	AE-myopathy	Unclear	Simvastatin (40)	Omega-3	122	0	Placebo	132	0		described as no AEs involved myopathy	Medium
Duffy 2001[20] Parallel	Threshold not specified	Mixed: Low and/or moderate	Simvastatin (10-40)	Vitamin E	6	0	No Treatment	7	0			Medium

Evidence Table 124. KQ3—Dichotomous—Parallel—CK or CPK (continued)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Napoli 1998[52] Parallel	Data imputed-there were no differences between baseline and post treatment values.	Unclear	Pravastatin (20-40)	Vitamin E		0	No Treatment		0		"..no differences in routine laboratory tests or adverse events were registered during the study (data not shown); in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups."	Medium
Chan 2002[12] Parallel	thresholds not specified	At moderate/ moderately high risk for CHD (2+ risk factors)	Atorvastatin (40)	Omega-3	11	0	No Treatment	13				Medium
Liu 2003[37] Parallel	thresholds not specified	Unclear	Simvastatin (10)	Omega-3	19	0	No Treatment	18				Medium
Playford 2003[58] Parallel	NR	At high risk for CHD	Fenofibrate (200)	Co-Q10	18	0	No Treatment	17				Low-medium

Evidence Table 124. KQ3—Dichotomous—Parallel—CK or CPK (continued)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Gosai 2008[26] Crossover	reference range males: 0-46 U/L; females: 0-36 U/L	At low risk for CHD (0-1 risk factors)	Rosuvastatin (40)	Omega-3	48	1	No Treatment	48	0		N/A	Medium
Di Spirito 2008[19] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Atorvastatin (80)	Omega-3	50	1	No Treatment	50	0		N/A	Medium
Balestrieri 1996[4] Crossover	N/A	Mixed: Low and/or mod to high risk	Simvastatin (10-40)	Omega-3	14	0	Placebo	16	0		N/A	Medium

Evidence Table 125. KQ3—Dichotomous—Constipation

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Lee 2008[36] Parallel	NR	At high risk for CHD	Warfarin (3.5)	Ginseng	12		No Treatment	13	0		No events occurred. No data reported.	Medium
Roth 2009[60] Parallel	NR	Unclear	Fenofibrates (130)	Omega-3	84	1	Placebo	83	5			Medium
Gosai 2008[26] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Rosuvastatin (40)	Omega-3	44	16	No Treatment	46	18		N/A	Medium
Di Spirito 2008[19] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Atorvastatin (80)	Omega-3	50		No Treatment	50	0		N/A	Medium
Jiang 2005[32] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Warfarin (25 single dose)	Ginkgo biloba		1	No Treatment		0		N/A	Medium
Jiang 2005[32] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Warfarin (25 single dose)	Ginger		0	No Treatment		0			Medium
Mueller 1991[51] Crossover	N/A	Mixed: Low and/or Moderate	ASA (325 – single dose)	Omega-3		1	Placebo		0			Medium
Kim 2010[35] Crossover	N/A	Mixed: Low and/or Moderate	Ticlopidine (250 – single dose)	Ginkgo biloba	24	1	No Treatment	24	0	NR	N/A	Medium

Evidence Table 126. KQ3—Dichotomous—Creatinine (raised)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Davidson 2007[14] Parallel	creatinine levels (also creatnie phosphokinase, or homocysteine)	Unclear	Simvastatin (40)	Omega-3	122		Placebo			NR	no numeric data reported. no significant effect of omega 3 + statin during the course of the trial	Medium
Napoli 1998[52] Parallel	Data imputed-there were no differences between baseline and post treatment values.	Unclear	Pravastatin (20-40)	Vitamin E		0	No Treatment		0		No differences in routine laboratory tests or adverse events were registered during the study in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups.	Medium
Reyes 1984[59] Parallel	NR	Mixed: Low and/or Moderate	Hydrochlorothiazide (50)	Magnesium		0	Placebo	8	0			Medium

Evidence Table 126. KQ3—Dichotomous—Creatinine (raised) (continued)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Roth 2009[60] Parallel	blood CPK increase	Unclear	Fenofibrate (130)	Omega-3	13	0	Placebo	83	1			Medium
Playford 2003[58] Parallel	Unclear if this is the correct def.: creatinemia (/150 mmol/l)	At high risk for CHD	Fenofibrate (200)	Co-Q10	84		No Treatment	17				Low-medium
Watson 1999[66] Crossover	N/A	At high risk for CHD	ACE inhibitors (no description), furosemide, digoxin, also hydralazine and/or nitrates (NR)	Co-Q10		0	Placebo		0	NR	N/A	Medium
Kim 2010[35] Crossover	N/A	Mixed: Low and/or Moderate	Ticlopidine (250 – single dose)	Ginkgo biloba	24	0	No Treatment	24	0	NR	N/A	Medium
Balestrieri 1996[4] Crossover	N/A	Mixed: Low and/or mod to high risk	Simvastatin (10-40)	Omega-3	14	0	Placebo	16	0		N/A	Medium
Paolissa 1992[56] Crossover	N/A	At high risk for CHD	Nifedipine (88)	Vitamin E		0	Placebo		0		N/A	Medium

Evidence Table 127. KQ3—Dichotomous—Parallel—Diarrhea

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Lee 2008[36] Parallel	NR	At high risk for CHD	Warfarin (3.5)	Ginseng	12		No Treatment	13	0		No events occurred. No data reported.	Medium
Davidson 2007[14] Parallel	NR	Unclear	Simvastatin (40)	Omega-3	122	3	Placebo	132	3			Medium
McDowell 1994[44] Parallel	NR	Unclear	Simvastatin (20)	Vitamin E	8	0	Placebo	8	1			Medium
McDowell 1994[44] Parallel	NR	Unclear	Simvastatin (20)	Vitamin E	8	1	Placebo	8	0			Medium
Paolissa 1992[57] Parallel	NR	Unclear	Hydrochlorthiazide (25)	Magnesium	9	0	Placebo	9	0			Medium
Roth 2009[60] Parallel	NR	Unclear	Fenofibrates (130)	Omega-3	84	4	Placebo	83	5			Medium
Kim 2010[35] Crossover	N/A	Mixed: Low and/or Moderate	Ticlopidine (250 – single dose)	Ginkgo biloba	24	3	No Treatment	24	1	NR	N/A	Medium
Jiang 2005[32] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Warfarin (25 single dose)	Ginkgo biloba		0	No Treatment		0			Medium
Mueller 1991[51] Crossover	N/A	Mixed: Low and/or Moderate	ASA (325 – single dose)	Omega-3		0	Placebo		1		N/A	Medium
Maki 2008[41] Crossover	N/A	Mixed: Low, Moderate and high risk	Simvastatin (20)	Omega-3	40	3		40	1			Medium
Jiang 2005[32] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Warfarin (25 single dose)	Ginger		1	No Treatment		0			Medium

Evidence Table 128. KQ3—Dichotomous—Dizziness

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Lee 2008[36] Parallel	NR	At high risk for CHD	Warfarin (3.5)	Ginseng	12		No Treatment	13	0		No events occurred. No data reported.	Medium
Tankanow 2003[65] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Digoxin (0.25)	Hawthorn	8	1	No Treatment	8	0			Medium

Evidence Table 129. KQ3—Dichotomous—Fasting blood glucose

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Napoli 1998[52] Parallel	Data imputed-there were no differences between baseline and post treatment values.	Unclear	Pravastatin (20-40)	Vitamin E		0	No Treatment		0		No differences in routine laboratory tests or adverse events were registered during the study in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups.	Medium
Reyes 1984[59] Parallel	NR	Mixed: Low and/or Moderate	Hydrochlorothiazide (50)	Magnesium	13	0	Placebo	8	0			Medium

Evidence Table 130. KQ3-Dichotomous—Fishy taste

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Mueller 1991[51] Crossover	N/A	Mixed: Low and/or Moderate	ASA (325 – single dose)	Omega-3		4	Placebo		0			Medium

Evidence Table 12. KQ3—Dichotomous—Flatulence

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Roth 2009[60] Parallel	NR	Unclear	Fenofibrates (130)	Omega-3	84	1	Placebo	83	3			Medium
Di Spirito 2008[19] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Atorvastatin (80)	Omega-3	50		No Treatment	50		NR	No treatment related trends regarding ECG or other clinical or laboratory markers were found (no specific data)	Medium
Tankanow 2003[65] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Digoxin (0.25)	Hawthorn	8	1	No Treatment	8	0			Medium
Mueller 1991[51] Crossover	N/A	Mixed: Low and/or Moderate	ASA (325 – single dose)	Omega-3		0	Placebo		1			Medium

Evidence Table 132. KQ3—Dichotomous—Flushing

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Isley 2007[31] Parallel	NR	Unclear	Niacin (500); ASA (325)	Omega-3	8		No Treatment	7			no data reported. Difference between groups in flushing is not significant.	Medium

Evidence Table 133. KQ3—Dichotomous—Gastrointestinal adverse events

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Davidson 2007[14] Parallel	NR	Unclear	Simvastatin (40)	Omega-3	122	5	Placebo	132	3			Medium
D'Arcangues 2004[13] Parallel	NR	Mixed: Low and/or Moderate	ASA (80)	Vitamin E	121		No Treatment	122			Treatment course was for 10 days. But followup went on for up to 1 year.	Medium
Garg 1995[24] Parallel	NR	At high risk for CHD	ASA and/or pentoxiphylline (NR)	Ginkgo biloba	29	4	Placebo	26	3			Medium-high
Roth 2009[60] Parallel	NR	Unclear	Fenofibrate (130)	Omega-3	84	7	Placebo	83	5			Medium
Dehmer 1988[17] Parallel	belching, dyspepsia flatulence in tx group vs. Dyspepsia in control group	At high risk for CHD	Aspirin (325)+ Dipyridamole (225) + Calcium channel blockers (NR)	Omega-3	43	7	No Treatment	39	3			Medium
Eritsland 1996[21] Parallel	NR	At high risk for CHD	Warfarin (NR)	Omega-3	174	9	No Treatment	145	0			Medium
Eritsland 1996[21] Parallel	NR	At high risk for CHD	Aspirin (300)	Omega-3	143	7	No Treatment	148	12			Medium
Maki 2008[41] Crossover	N/A	Mixed: Low, Moderate and high risk	Simvastatin (20)	Omega-3	40	1	Placebo	40	1			Medium

Evidence Table 133. KQ3—Dichotomous—Gastrointestinal adverse events (continued)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Wolf 2006[68] Crossover	N/A	Mixed: Low and/or Moderate	ASA (500)	Ginkgo biloba	50	6	Placebo	50	9			Low-medium
Mauro 2003[43] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Digoxin (0.5 single dose)	Ginkgo biloba		1	No Treatment					Medium

Evidence Table 134. KQ3—Dichotomous—Generalized edema

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Maki 2008[41] Crossover	N/A	Mixed: Low, Moderate and high risk	Simvastatin (20)	Omega-3	40	0	Placebo	40	2			Medium

Evidence Table 135. KQ3—Dichotomous—Glomerular filtration rate (GFR)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Young 2007[70] Parallel	calculated glomerular filtration rate < 45/min	Mixed: Mod and high risk	Simvastatin (10-40)	Co-Q10	22	0	Placebo	22	0		Exclusion criteria included: calculated glomerular filtration rate <45 ml/min' and results state: "renal function, …[was] not altered with either regime." Thus, counts of 0 and 0 were added for each arm	Medium

Evidence Table 13. KQ3—Dichotomous—Headache

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Lee 2008[36] Parallel	N/A	At high risk for CHD	Warfarin (3.5)	Ginseng	12		No Treatment	13	0		No events occurred. No data reported.	Medium
D'Arcangues 2004[13] Parallel	N/A	Mixed: Low and/or Moderate	ASA (80)	Vitamin E	121		No Treatment	122			Treatment course was for 10 days. But followup went on for up to 1 year.	Medium
Gosai 2008[26] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Rosuvastatin (40)	Omega-3	44	5	No Treatment	46	7			Medium
Di Spirito 2008[19] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Atorvastatin (80)	Omega-3	50		No Treatment	50				Medium
Maki 2008[41] Crossover	N/A	Mixed: Low, Moderate and high risk	Simvastatin (20)	Omega-3	40	1	Placebo	40	1			Medium
Tankanow 2003[65] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Digoxin (0.25)	Hawthorn	8	1	No Treatment	8	0			Medium
Mueller 1991[51] Crossover	N/A	Mixed: Low and/or Moderate	ASA (325 – single dose)	Omega-3		1	Placebo		1			Medium
Kim 2010[35] Crossover	N/A	Mixed: Low and/or Moderate	Ticlopidine (250 – single dose)	Ginkgo biloba	24	2	No Treatment	24	0			Medium

Evidence Table 14. KQ3—Dichotomous—Hematuria

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Macan 2006[40] Parallel	NR	Unclear	Warfarin (NR)	Garlic	22	0	Placebo	26	0			Medium

Evidence Table 138. KQ3—Dichotomous—Hyperglycemia

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Maki 2008[41] Crossover	N/A	Mixed: Low, Moderate and high risk	Simvastatin (20)	Omega-3	40	2	Placebo	40	1			Medium
Kim 2010[35] Crossover	N/A	Mixed: Low and/or Moderate	Ticlopidine (250 – single dose)	Ginkgo biloba	24	0	No Treatment	24	0			Medium

Evidence Table 139. KQ3—Dichotomous—Hypoglycemia

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Kim 2010[35] Crossover	N/A	Mixed: Low and/or Moderate	Ticlopidine (250 – single dose)	Ginkgo biloba	24	0	No Treatment	24	0			Medium

Evidence Table 140. KQ3—Dichotomous—Hyperkalaemia

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Ferraro 2009[22] Parallel	serum potassium > 5.5 mEq/l)	Unclear	Ramipril (10)	Omega-3	15	0	No Treatment	15	0			Medium
Reyes 1984[59] Parallel	NR	Mixed: Low and/or Moderate	Hydrochlorothiazide (50)	Magnesium	13	0	Placebo	8	0			Medium

Evidence Table 141. KQ3—Dichotomous—Hypokalaemia

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Maki 2008[41] Crossover	N/A	Mixed: Low, Moderate and high risk	Simvastatin (20)	Omega-3	40	1	Placebo	40	1			Medium

Evidence Table 142. KQ3—Dichotomous—Indigestion

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Lee 2008[36] Parallel	NR	At high risk for CHD	Warfarin (3.5)	Ginseng	12		No Treatment	13	0		No events occurred. No data reported.	Medium

Evidence Table 143. KQ3—Dichotomous—Infection

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Davidson 2007[14] Parallel	NR	Unclear	Simvastatin (40)	Omega-3	122	4	Placebo	132	1			Medium

Evidence Table 144. KQ3—Dichotomous—INR

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Bender 1998[8] Parallel	NR	Unclear	Warfarin (NR)	Omega-3	6		No Treatment	5			numeric data is not separated by groups. Three patients with unstable INR withdrew but no group designation reported.	High

Evidence Table 145. KQ3—Dichotomous—INR > 3.5

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Lee 2008[36] Parallel	NR	At high risk for CHD	Warfarin (3.5)	Ginseng	12		No Treatment	13	0		No events occurred. No data reported.	Medium

Evidence Table146. KQ3—Dichotomous—Insomnia

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Tankanow 2003[65] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Digoxin (0.25)	Hawthorn	8	1	No Treatment	8	0			Medium

Evidence Table 147. KQ3—Dichotomous outcomes—Leukopenia

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Balestrieri 1996[4] Crossover	N/A	Mixed: Low and/or mod to high risk	Simvastatin (10-40)	Omega-3	14	0	Placebo	16	0			Medium
Kim 2010[35] Crossover	N/A	Mixed: Low and/or Moderate	Ticlopidine (250 – single dose)	Ginkgo biloba	24	0	No Treatment	24	0			Medium

Evidence Table 148. KQ3—Dichotomous outcomes—Major bleeding

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Mohammed Abdul 2008[49] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Warfarin (26 – single dose)	Garlic	12	0	No Treatment	12	0			Medium

Evidence Table 149. KQ3—Dichotomous outcomes—Myalgia

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Mabuchi 2007[39] Parallel	NR	Unclear	Atorvastatin (10)	Co-Q10			Placebo				"There were no complaints of myalgia or muscle weakness". Data not reported.	Medium
Caso 2007[11] Parallel	NR	Unclear	Simvastatin (22); Atorvastatin (7); Pravastatin (2); Lovastatin (1)	Co-Q10	18	16	Other dietary supplement – Vitamin E	14	3			Low
Maki 2008[41] Crossover	N/A	Mixed: Low, Moderate and high risk	Simvastatin (20)	Omega-3	40	1	Placebo	40	1			Medium

Evidence Table 150. KQ3—Dichotomous—Nausea

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Paolissa 1992[57] Parallel	NR	Unclear	Hydrochlorthiazide (25)	Magnesium	9	0	Placebo	9	0		"There were no complaints of myalgia or muscle weakness". Data not reported.	Medium
Roth 2009[60] Parallel	NR	Unclear	Fenofibrate (130)	Omega-3	84	5	Placebo	83	3			Medium
Tankanow 2003[65] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Digoxin (0.25)	Hawthorn	8	2	No Treatment	8	1			Medium
Mueller 1991[51] Crossover	N/A	Mixed: Low and/or Moderate	ASA (325 – single dose)	Omega-3		3	Placebo		3			Medium
Kim 2010[35] Crossover	N/A	Mixed: Low and/or Moderate	Ticlopidine (250 – single dose)	Ginkgo biloba	24	2	No Treatment	24	0			Medium

Evidence Table 151. KQ3—Dichotomous—Other adverse events

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Mabuchi 2007[39] Parallel	General Adverse events Vital signs, urinalysis, serum chemical values or hematological values	Unclear	Atorvastatin (10)	Co-Q10			Placebo				No clinically significant changes in vital signs, urinalysis, serum chemical values or hematological values." No data presented.	Medium
Gardner 2007[23] Parallel	Upset stomach	Mixed: Moderate to high	ASA (325)	Ginkgo biloba	30	6	Placebo	30	5			Low

Evidence Table 151. KQ3—Dichotomous—Other adverse events (continued)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Davidson 2007[14] Parallel	Nasopharyngitis	Unclear	Simvastatin (40)	Omega-3	122	4	Placebo	132	3		Note: specific AEs were those reported by >/= 1% of patients receiving simva + omega-3 that occurred with higher frequency that in those receiving simva + placebo. They include Nasopharyngitis, URT infection, diarrhea, dyspepsia, bronchitis, cystitis, alanine aminotransferase elevation and gastroenteritis	Medium
Davidson 2007[14] Parallel	Bronchitis	Unclear	Simvastatin (40)	Omega-3	122	2	Placebo	132	2			Medium
Davidson 2007[14] Parallel	Cystitis	Unclear	Simvastatin (40)	Omega-3	122	2	Placebo	132	1			Medium
Davidson 2007[14] Parallel	Rhabdomyolysis	Unclear	Simvastatin (40)	Omega-3	122	0	Placebo	132	0		described as no AEs involved rhabdomyolysis	Medium
Davidson 2007[14] Parallel	Pneumonia	Unclear	Simvastatin (40)	Omega-3	122	1	Placebo	132	0			Medium
McDowell 1994[44] Parallel	Malaise	Unclear	Simvastatin (20)	Vitamin E	8	1	Placebo	8	1			Medium
McDowell 1994[44] Parallel	Abdominal discomfort	Unclear	Simvastatin (20)	Vitamin E	8	0	Placebo	8	2			Medium
Paolissa 1992[57] Parallel	Adverse events (general)	Unclear	Hydrochlorthiazide (25)	Magnesium	9	0	Placebo	9	0			Medium

Evidence Table 151. KQ3—Dichotomous—Other adverse events (continued)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Roth 2009[60] Parallel	diabetes	Unclear	Fenofibrate (130)	Omega-3	84	1	Placebo	83	0			Medium
Liu 2003[37] Parallel	Adverse events (general) (Not defined)	Unclear	Simvastatin (10)	Omega-3	19	0	No Treatment	18	0			Medium
Glynn 2007[25] Parallel	Cancer	Mixed: Low and/or moderate	ASA (100)	Vitamin E		716	Placebo		722	Crude event risk ratio: 0.99 95%CI Lower: 0.89 95%CI Upper: 1.1 P: 0.86		Medium
Yuan 2004[71] Parallel	AE of clinical importance	Mixed: Low and/or moderate	Warfarin (5)	Ginseng	12	0	No Treatment	8	0			Low
Eritsland 1996[21] Parallel	dysphagia	At high risk for CHD	Warfarin (NR)	Omega-3	174	3	No Treatment	145	0			Medium
Eritsland 1996[21] Parallel	dysphagia	At high risk for CHD	Aspirin (300)	Omega-3	143	3	No Treatment	148	0			Medium
Playford 2003[58] Parallel	retinopathy	At high risk for CHD	Fenofibrate (200)	Co-Q10	18	5	No Treatment	17	6			Low-medium
Chan 2002[12] Parallel	N/A	At moderate/moderately high risk for CHD (2+ risk factors)	Atorvastatin (40)	Omega-3	11	0	No Treatment	13	0			Medium
Avogaro 1974[3] Crossover	Nausea+ flushing	Unclear	Propranolol (20 or 60)	Niacin	10	0	No Treatment	10	0			High
Avogaro 1974[3] Crossover	Hypotension + asthma	Unclear	Propranolol (20 or 60)	Niacin	10	0	No Treatment	10	1			High

Evidence Table 152. KQ3—Dichotomous—Prothrombin time (above/below threshold)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Lee 2008[36] Parallel	N/A	At high risk for CHD	Warfarin (3.5)	Ginseng	12		No Treatment	13	0		No events occurred. No data reported.	Medium
Napoli 1998[52] Parallel	N/A	Unclear	Pravastatin (20-40)	Vitamin E			No Treatment				No differences in routine laboratory tests or adverse events were registered during the study (data not shown); in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups."	Medium

Evidence Table 153. KQ3—Dichotomous—Serious adverse events (composite outcome)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Bays 2010[6] Parallel	N/A	Unclear	Atorvastatin (10-40)	Omega-3			Placebo				<5% in Omega-3 group and <5% in Placebo group	Medium
Mabuchi 2007[39] Parallel	N/A	Unclear	Atorvastatin (10)	Co-Q10			Placebo				"There were no serious adverse events" Data not reported.	Medium
Davidson 2007[14] Parallel	N/A	Unclear	Simvastatin (40)	Omega-3	122	4	Placebo	132	1			Medium
Roth 2009[60] Parallel	N/A	Unclear	Fenofibrate (130)	Omega-3	84	3	Placebo	83	1			Medium
Maki 2008[41] Crossover	N/A	Mixed: Low, moderate and high risk	Simvastatin (20)	Omega-3		1	Placebo		0			Medium
McKenney 2006[45] Crossover	N/A	Mixed: Low and/or moderate	Simvastatin (80)	Omega-3	24	1	No Treatment	24	0			Medium
Wolf 2006[68] Crossover	N/A	Mixed: Low and/or moderate	ASA (500)	Gingko Biloba	50	0	Placebo	50	0		Other outcomes (both dichotomous and continuous) assessed in this study but not extracted:fibrinogen, D-dimers, quick value, coagulation factors (a mix), Protein C activity, Protein S activity, Platelet morphological assessment, Platelet orbitometric asse	Low-medium

Evidence Table 153. KQ3—Dichotomous—Serious adverse events (composite outcome)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Jiang 2005[32] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Warfarin (25 single dose)	Gingko Biloba		0	No Treatment		0			Medium
Wirell 1994[67] Crossover	N/A	Unclear	metoprolol, atenolol, pindolol & propanolol (NR)	Magnesium	19		Placebo	20	0			Medium

Evidence Table 154. KQ3—Dichotomous—Sinusitis

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Maki 2008[41] Crossover	N/A	Mixed: Low, Moderate and high risk	Simvastatin (20)	Omega-3	40	0	Placebo	40	2			Medium

Evidence Table 155. KQ3—Dichotomous—Thrombocytopenia

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Balestrieri 1996[4] Crossover	N/A	Mixed: Low and/or mod to high risk	Simvastatin (10-40)	Omega-3	14	0	Placebo	16	0			Medium
Kim 2010[35] Crossover	N/A	Mixed: Low and/or Moderate	Ticlopidine (250 – single dose)	Ginkgo biloba	24	0	No Treatment	24	0			Medium

Evidence Table 156. KQ3—Dichotomous—Total adverse events

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Lee 2008[36] Parallel	N/A	At high risk for CHD	Warfarin (3.5)	Ginseng	12		No Treatment	13	0		No events occurred. No data reported.	Medium
Gardner 2007[23] Parallel	N/A	Mixed: Moderate to high	ASA (325)	Ginkgo biloba	30	11	Placebo	3	15	P: 0.4	No difference between groups	Low
Davidson 2007[14] Parallel	N/A	Unclear	Simvastatin (40)	Omega-3	122	51	Placebo	132	63			Medium
Sconce 2007[61] Parallel	N/A	Unclear	Warfarin (3.8-4.4 vs. 3.3-3.4)	Vitamin K	35	0	Placebo	33	2			Medium
D'Arcangues 2004[13] Parallel	N/A	Mixed: Low and/or Moderate	ASA (80)	Vitamin E	121		No Treatment	122		P: 0.0584	The difference in the occurance of any side effect between the two groups was not significant.	Medium
Abdul 2010[1] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Warfarin (25-single dose)	Echinacea	12	0	No Treatment	12	0			Medium
Gosai 2008[26] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Rosuvastatin (40)	Omega-3	44	27	No Treatment	46	30		N/A	Medium
Di Spirito 2008[19] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Atorvastatin (80)	Omega-3	50	12	No Treatment	50	12		N/A	Medium
McKenney 2006[45] Crossover	N/A	Mixed: Low and/or Moderate	Simvastain (80)	Omega-3	24	9	No Treatment	23	8			Medium
Mauro 2003[43] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Digoxin (0.5 single dose)	Ginkgo biloba		1	No Treatment		0			Medium

Evidence Table 157. KQ3—Dichotomous—Upper respiratory infection

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Maki 2008[41] Crossover	N/A	Mixed: Low, Moderate and high risk	Simvastatin (20)	Omega-3	40	0	Placebo	40	2			Medium

Evidence Table 158. KQ3—Dichotomous—Vomiting

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Paolissa 1992[57] Parallel	NR	Unclear	Hydrochlorthiazide (25)	Magnesium	9	0	Placebo	9	0			Medium

Evidence Table 159. KQ3—Dichotomous—Withdrawal due to adverse events

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Bays 2010[6] Parallel	N/A	Unclear	Atorvastatin (10-40)	Omega-3	123	8	Placebo	122	6			Medium
Ferraro 2009[22] Parallel	N/A	Unclear	Ramipril (10)	Omega-3	15	0	No Treatment	15	0			Medium
Mabuchi 2007[39] Parallel	N/A	Unclear	Atorvastatin (10)	Co-Q10			Placebo				"There were no serious adverse events". Data not reported.	Medium
Gardner 2007[23] Parallel	N/A	Mixed: Moderate to high	ASA (325)	Ginkgo biloba		3	Placebo		2			Low
Young 2007[70] Parallel	N/A	Mixed: Moderate and high risk	Simvastatin (10 - 40)	Co-Q10		6	Placebo		4			Medium
Davidson 2007[14] Parallel	N/A	Unclear	Simvastatin (40)	Omega-3	122	3	Placebo	132	3		no description	Medium
D'Arcangues 2004[13] Parallel	discontinuation due to side effects of treatment	Mixed: Low and/or Moderate	ASA (80)	Vitamin E	121	30	No Treatment	122	19		Treatment course was for 10 days. But followup went on for up to 1 year.	Medium
Nordøy 2000[54] Parallel	N/A	Mixed: Low and/or Moderate	Simvastatin (20)	Omega-3	21	0	Placebo	20	0			Medium
Garg 1995[24] Parallel	N/A	At high risk for CHD	ASA and/or pentoxiphylline (20)	Ginkgo biloba	29	0	Placebo	26	0			Medium-high
Paolissa 1992[57] Parallel	N/A	Unclear	Hydrochlorthiazide (25)	Magnesium	9	0	Placebo	9	0			Medium
Kaul 1992[34] Parallel	GI intolerance--stopped capsules of fish oil	At high risk for CHD	Calcium channel blocker, ASA (NR)	Omega-3	58	2	No Treatment	49	0			Low-medium

Evidence Table 159. KQ3—Dichotomous—Withdrawal due to adverse events (continued)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Nordøy 2003[55] Parallel	N/A	Mixed: Moderate and high risk	Atorvastatin (10)	Omega-3	22	0	Placebo	20	0			Low
Roth 2009[60] Parallel	N/A	Unclear	Fenofibrate (130)	Omega-3	84	4	Placebo	83	4			Medium
Isley 2007[31] Parallel	N/A	Unclear	Niacin (500); ASA (325)	Omega-3	8		No Treatment	7				Medium
Bender 1998[8] Parallel	N/A	Unclear	Warfarin (NR)	Omega-3	6	0	No Treatment	5	0			High
Chan 2002[12] Parallel	N/A	At moderate/moderately high risk for CHD (2+ risk factors)	Atorvastatin (40)	Omega-3	11	0	No Treatment	13	0			Medium
Playford 2003[58] Parallel	N/A	At high risk for CHD	Fenofibrate (200)	Co-Q10	18		No Treatment	17				Low-medium
Abdul 2010[1] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Warfarin (25 single dose)	Echinacea	12	0	No Treatment	12	0			Medium
Gosai 2008[26] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Rosuvastatin (40)	Omega-3	48	2	No Treatment	48	4			Medium
Di Spirito 2008[19] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Atorvastatin (80)	Omega-3	50	1	No Treatment	50	0		This one is the same patient who had an elevated CK	Medium
Maki 2008[41] Crossover	N/A	Mixed: Low, Moderate and high risk	Simvastatin (20)	Omega-3		2	Placebo		1			Medium
McKenney 2006[45] Crossover	N/A	Mixed: Low and/or Moderate	Simvastatin (80)	Omega-3	24	1	No Treatment	24	0			Medium

Evidence Table 159. KQ3—Dichotomous—Withdrawal due to adverse events (continued)

Author Year Study Design	Definition of outcome (if relevant)	CHD Risk Category	CVD drug (dose mg/d))	Group 1: Name (supplement)	N1	N1 with event	Group 2: Name	N2	N2 with event	Estimates of Group Differences	Additional comments	Overall Risk of Bias (ROB) Assessment
Jiang 2005[32] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Warfarin (25 single dose)	Gingko biloba		0	No Treatment		0			Medium
Jiang 2004[33] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Warfarin (25 single dose)	Ginseng		0	No Treatment		0			Medium
Mauro 2003[43] Crossover	N/A	At low risk for CHD (0-1 risk factors)	Digoxin (0.5 single dose)	Gingko biloba		0	No Treatment		0			Medium
Balestrieri 1996[4] Crossover	N/A	Mixed: Low and/or mod to high risk	Simvastatin (10 to 40)	Omega-3	16	1	Placebo	16	1		Two patients (one in each group) interrupted the study in the first month. One suffered from acute myocardial infarction, another one underwent a resection of abdominal aortic aneurysm.	Medium
Paolissa 1992[56] Crossover	N/A	At high risk for CHD	Nifedipine (88)	Vitamin E		0	Placebo		0			Medium
Mueller 1991[51] Crossover	N/A	Mixed: Low and/or Moderate	ASA (325 single dose)	Omega-3		0	Placebo		0			Medium
Wirell 1994[67] Crossover	N/A	Unclear	metoprolol, atenolol, pindolol & propanolol (NR)	Magnesium	19		Placebo	20	0			Medium
Avogaro 1974[3] Crossover	N/A	Unclear	Propranolol (20 or 60)	Niacin	10	0	No Treatment	10	1			High

Evidence Table 160. KQ4—Continuous data—Absorption

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change / % change from baseline / SD / P Value	Between group differences in Means / medians SD / P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Bioavailability (F) *– no outcome data*										

Evidence Table 161. KQ4—Cmax

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change / % change from baseline / SD / P Value	Between group differences in Means / medians SD / P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Kim 2010[35] Cross-over	ng/mL – measured after single dose of ticlopidine and single dose Ginkgo biloba	Low and/or Moderate	Ticlopidine (250; single dose)	Ginkgo biloba (0.08; single dose)	24	Mean: 1071.6 SD: 484.1	GMR: 963.7	GMR_{diff}: 1.03 Lower: 0.92 Upper: 1.16	Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	24	Mean: 1027.0 SD: 437.2	GMR: 932.6			
Hadja 2010[28] Cross-over	µg/L	Low (healthy men)	Simvastatin (20)	Garlic (600 mg twice daily)	10	Mean: 5.25 SD: 6.32	-	-	-	Medium
				No treatment	10	Mean: 3.85 SD: 1.99	-	-	-	Medium
Hadja 2010[28] Cross-over	µg/L	Low (healthy men)	Pravastatin (20)	Garlic (600 mg twice daily)	10	Mean: 14.2 SD: 6.7	-	-	-	Medium
				No treatment	10	Mean: 18.8 SD: 12.2	-	-	-	Medium
Tankanow 2003[65] Cross-over	ng/mL: Measured after 10 days digoxin or 21 days digoxin + hawthorn	Low (healthy)	Digoxin (0.25)	Hawthorn (0.9)	8	Mean: 1.80 SD: 0.20	-	-	-	Medium
				No treatment	8	Mean: 2.10 SD: 0.60	-			
Mauro 2003[43] Cross-over	ng/mL; Measured after single-dose administration of digoxin following 7 days pre-treatment with Ginkgo biloba or no pre-treatment	Low (healthy)	Digoxin (0.5; single dose)	*Ginkgo biloba* (0.24)	8	Mean: 1.4 SD: 0.5	-	-	-	Medium
				No treatment	8	Mean: 1.6 SD: 0.3	-			

Evidence Table 161. KQ4—Cmax (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Jiang 2004[33] Cross-over	R-Warfarin: µg/mL; measured after single dose warfarin following 1 week pretreatment with ginseng or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginseng (3)	12	Mean: 1.89 SD: 0.29 Lower: 1.70 Upper: 2.00	-	GMR_{diff}: 0.98 Lower: 0.88 Upper: 1.09	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean: 1.92 SD: 0.32 Lower: 1.70 Upper: 2.10	-			
	S-Warfarin: µg/mL; measured after single-dose warfarin following 1 wk pretreatment with ginseng or no pretreatment. Subjects followed for 1 wk post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginseng (3)	12	Mean: 1.93 SD: 0.31 Lower: 1.70 Upper: 2.10	-	GMR_{diff}:1.01 Lower: 0.90 Upper: 1.12	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean: 1.89 SD: 0.26 Lower: 1.70 Upper: 2.00	-			

Evidence Table 161. KQ4—Cmax (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Jiang 2005[32] Cross-over	R-Warfarin: µg/mL; measured after single dose warfarin following 1 week pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginger (3.6)	12	Mean:1.70 Lower: 1.50 Upper: 1.90	-	Ginger GMR_{diff}: 1.02 Lower: 0.95 Upper: 1.07 Ginkgo biloba GMR_{diff}: 1.03 Lower: 0.97 Upper:1.10	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				Ginkgo biloba (12)	12	Mean: 1.80 Lower: 1.50 Upper: 2.00	-			
				No treatment	12	Mean: 1.70 Lower: 1.40 Upper: 2.00	-			
	S-Warfarin: µg/mL; measured after single-dose warfarin following 1 wk pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for 1 wk post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginger (3.6)	12	Mean: 1.70 Lower: 1.50 Upper: 2.00	-	Ginger GMR_{diff}:1.01 Lower: 0.94 Upper:1.07 Ginkgo biloba GMR_{diff}:1.04 Lower: 0.97 Upper:1.09	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				Ginkgo biloba (12)	12	Mean:0.12 Lower: 0.11 Upper: 0.13	-			

Evidence Table 161. KQ4—Cmax (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
				No treatment	12	Mean:0.12 Lower: 0.11 Upper: 0.14				
Gosai 2008[26] Cross-over	ng/mL; 2 weeks treatment	Low (healthy)	Rovustatin (40)	Omega-3 fatty acids (EPA, DHA or both) (4)	42	Mean: 25.51 SD: 11.75	-	GMR_{diff}: 1.01 Lower: 0.94 Upper: 1.09	% coefficient of variation: Omega-3: 46.08 Control: 34.85 Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	41	Mean: 24.3 SD: 8.47	-			
Di Spirito 2008[19] Cross-over	Atorvastatin; Day 14 steady state (ng/mL); 2 weeks treatment	Low (healthy)	Atorvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	49	Mean: 52.1 SD: 62	-	GMR_{diff}: 1.03 Lower: 0.93 Upper: 1.14	Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	49	Mean: 50.9 SD: 51	-			
	2-hydroxytorvastatin; Day 14 steady state; (ng/mL); 2 weeks treatment	Low (healthy)	Atorvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	49	Mean: 45 SD: 59.3	-	GMR_{diff}: 0.95 Lower: 0.85 Upper: 1.06	Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	49	Mean: 47.6 SD: 50	-			
Mohammed Abdul 2008[49]	R-Warfarin: µg/mL; measured after single dose warfarin	Low (healthy)	Warfarin (25; single dose)	Garlic (4; 7.42 mg allicin)	12	Mean: 1.9 Lower: 1.5 Upper: 2.2	-	GMR_{diff}: 1.02 Lower: 0.80 Upper:1.40	Upper and lower limits of individual group	Medium

Evidence Table 161. KQ4—Cmax (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Cross-over	following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose.			No treatment	12	Mean: 1.8 Lower: 1.7 Upper: 2.0	-		data = 95% CI; Upper and lower limits of between group difference = 90% CI	
	S-Warfarin: µg/mL; measured after single dose warfarin following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose	Low (healthy)	Warfarin (25; single dose)	Garlic (4; 7.42 mg allicin)	12	Mean: 1.9 Lower: 1.5 Upper: 2.2	-	GMR_{diff}: 1.06 Lower: 0.70 Upper:1.47	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean: 1.8 Lower: 1.7 Upper: 1.9	-			
McKenney 2006[45] Cross-over	Simvastatin; C_{max} over final dosing interval (ng/mL); 2 wk treatment.	Low and/or Moderate	Simvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	24	Mean: 15.4 SD: 7.6	-	-	-	Medium
				No treatment	23	Mean: 13.5 SD: 6.1	-			
	Beta-hydroxy simvastatin; C_{max} over final dosing interval (ng/mL); 2 wk treatment.	Low and/or Moderate	Simvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	24	Mean: 6.1 SD: 3.6	-	-	-	Medium
				No treatment	23	Mean: 6.1 SD: 3.2	-			
Abdul 2010[1] Cross-over	R-Warfarin: µg/mL (1 hour); measured after single dose warfarin following 2 wks pretreatment with	Low (healthy)	Warfarin (25; single dose)	*Echinacea* (5.1; 23 mg total alkamides)	12	Mean:1.20 Lower: 1.10 Upper: 1.40	-	GMR_{diff}: 0.98 Lower: 0.88 Upper: 1.10	Upper and lower limits of individual group data = 95% CI; Upper and lower	Medium

Evidence Table 161. KQ4—Cmax (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
	Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose.			No treatment	12	Mean: 1.30 Lower: 1.10 Upper: 1.50	-		limits of between group difference = 90% CI	
	S-Warfarin: µg/mL (1 hour); measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	*Echinacea* (5.1; 23 mg total alkamides)	12	Mean: 1.30 Lower: 1.10 Upper: 1.43	-	GMR_{diff}: 0.97 Lower: 0.86 Upper: 1.10	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean: 1.30 Lower: 1.10 Upper: 1.60	-			

Evidence Table 162. KQ4—Tmax (hours)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change / % change from baseline / SD / P Value	Between group differences in Means / medians SD / P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Kim 2010[35] Cross-over	Hours – measured after single dose of ticlopidine and single dose Ginkgo biloba	Low and/or Moderate	Ticlopidine (250; single dose)	Ginkgo biloba (0.08; single dose)	24	Median: 1.50 Range – L: 1.00 H: 3:00	-	GMR_{diff}: 0.27 Lower: NR Upper: NR	Upper and lower limits of between group difference = 90% CI	-
				No treatment	24	Median: 1.75 Range – L: 1.00 H: 3:00	-			
Tankanow 2003[65] Cross-over	hours: Measured after 10 days digoxin or 21 days digoxin + hawthorn	Low (healthy)	Digoxin (0.25)	Hawthorn (0.9)	8	Mean: 1.00 SD: 0.50	-	-	-	-
				No treatment	8	Mean: 1.30 SD: 0.50	-			
Mauro 2003[43] Cross-over	hours; Measured after single-dose administration of digoxin following 7 days pre-treatment with Ginkgo biloba or no pre-treatment.	Low (healthy)	Digoxin (0.5; single dose)	*Ginkgo biloba* (0.24)	8	Mean: 1.30 SD: 0.50	-	-	-	-
				No treatment	8	Mean: 1.40 SD: 0.60	-			
Hajda 2010[28] Cross-over	Hours	Low (healthy)	Pravastatin (20)	Garlic extract (600 mg twice daily)	10	Mean: 1.1 SD: 0.4	-	-	-	Medium
				No treatment (before)	10	Mean: 1.0 SD:0.5	-	-	-	
Jiang 2004[33] Cross-over	R-Warfarin: hours; measured after single dose warfarin following 1 week pretreatment with ginseng or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginseng (3)	12	Mean: 1.30 SD: 0.52 Lower: 0.95 Upper: 1.65	-	GMR_{diff}: 1.11 Lower: 0.78 Upper: 1.44	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	-
				No treatment	12	Mean: 1.34 SD: 0.48 Lower: 1.02 Upper: 1.66	-			

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change / % change from baseline / SD / P Value	Between group differences in Means / medians SD / P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
	S-Warfarin: hours; measured after single-dose warfarin following 1 wk pretreatment with ginseng or no pretreatment. Subjects followed for 1 wk post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginseng (3)	12	Mean: 1.30 SD: 0.55 Lower: 0.95 Upper: 1.65	-	GMR_{diff}:1.20 Lower: 0.77 Upper: 1.62	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	-
				No treatment	12	Mean: 1.29 SD: 0.51 Lower: 0.97 Upper: 1.62	-			
Jiang 2005[32] Cross-over	R-Warfarin: hours; measured after single dose warfarin following 1 week pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginger (3.6)	12	Mean:1.60 Lower: 1.10 Upper: 2.10	-	<u>Ginger</u> GMR_{diff}: 0.72 Lower: 0.67 Upper: 0.77 <u>Ginkgo biloba</u> GMR_{diff}: 0.79 Lower: 0.73 Upper:0.85	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	-
				Ginkgo biloba (12)	12	Mean: 1.60 Lower: 0.60 Upper: 2.70	-			
				No treatment	12	Mean: 2.10 Lower: 1.40 Upper: 2.80	-			
	S-Warfarin: hours; measured after single-dose warfarin following 1 wk pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for 1 wk post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginger (3.6)	12	Mean: 1.60 Lower: 1.10 Upper: 2.10	-	<u>Ginger</u> GMR_{diff}:0.68 Lower: 0.63 Upper:0.73 <u>Ginkgo biloba</u> GMR_{diff}:0.79 Lower: 0.73 Upper:0.85	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	-
				Ginkgo biloba (12)	12	Mean: 1.40 Lower: 0.90 Upper: 1.90	-			
				No treatment	12	Mean: 2.10 Lower: 1.40 Upper: 2.80				
Gosai 2008[26] Cross-over	hours; 2 weeks treatment	Low (healthy)	Rovustatin (40)	Omega-3 fatty acids (EPA, DHA or both) (4)	42	Mean: 4.50 Median: 4.50 Median Range – L: 1.00 H: 6.00	-	-	-	-

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change / % change from baseline / SD / P Value	Between group differences in Means / medians SD / P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
				No treatment	41	Mean: 4.47 Median: 4.50 Median Range – L: 2.00 H: 6.00	-			
Di Spirito 2008[19] Cross-over	Atorvastatin; over the final dosing interval (hours); 2 weeks treatment	Low (healthy)	Atorvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	49	Mean: 1.43 SD: 1.09 Median: 1.00 Median range – L: 0.36 H: 4.10	-	-	-	-
				No treatment	49	Mean: 1.35 SD: 0.97 Median: 1.00 Median range – L: 0.50 H: 4.00	-			
	2-hydroxytorvastatin; Day 14 steady state; (ng/mL); 2 weeks treatment	Low (healthy)	Atorvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	49	Mean: 2.10 SD: 1.10 Median: 1.67 Median range – L: 0.50 H: 6.00	-	-	-	-

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change / % change from baseline / SD / P Value	Between group differences in Means / medians SD / P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
				No treatment	49	Mean: 1.88 SD: 0.95 Median: 1.67 Median range – L: 0.75 H: 4.00	-			
Mohammed Abdul 2008[49] Cross-over	R-Warfarin: hours; measured after single dose warfarin following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Garlic (4; 7.42 mg allicin)	12	Mean: 1.8 Lower: 0.70 Upper: 2.90	-	-	Upper and lower limits of individual group data = 95% CI;	-
				No treatment	12	Mean: 1.40 Lower: 1.10 Upper: 1.60	-			
	S-Warfarin: hours; measured after single dose warfarin following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose	Low (healthy)	Warfarin (25; single dose)	Garlic (4; 7.42 mg allicin)	12	Mean: 1.30 Lower: 1.10 Upper: 1.60	-	-	Upper and lower limits of individual group data = 95% CI	-
				No treatment	12	Mean: 1.40 Lower: 1.10 Upper: 1.60	-			
McKenney 2006[45] Cross-over	Simvastatin; over final dosing interval (hours); 2 wk treatment.	Low and/or Moderate	Simvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	24	Mean: 2.40 SD: 2.60	-	-	-	-
				No treatment	23	Mean: 2.60 SD: 1.90	-			

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change / % change from baseline / SD / P Value	Between group differences in Means / medians SD / P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
	Beta-hydroxy simvastatin; over final dosing interval (hours); 2 wk treatment.	Low and/or Moderate	Simvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	24	Mean: 5.50 SD: 2.30	-	-	-	-
				No treatment	23	Mean: 5.60 SD: 2.00	-			
Abdul 2010[1] Cross-over	R-Warfarin: hours; measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	*Echinacea* (5.1; 23 mg total alkamides)	12	Mean: 2.00 Lower: 1.50 Upper: 2.40	-	GMR_{diff}: 0.98 Lower: 0.88 Upper: 1.10	Upper and lower limits of individual group data = 95% CI	-
				No treatment	12	Mean: 2.00 Lower: 1.30 Upper: 2.60	-			
	S-Warfarin: hours; measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	*Echinacea* (5.1; 23 mg total alkamides)	12	Mean: 1.70 Lower: 1.10 Upper: 2.20	-	-	Upper and lower limits of individual group data = 95% CI	-
				No treatment						

Evidence Table 163. KQ4—Continuous data—Distribution

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change / % change from baseline / SD / P Value	Between group differences in Means / medians SD / P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Volume of distribution (Vd)										
Jiang 2004 [33] Cross-over	R-Warfarin: V/F (L/kg); measured after single dose warfarin following 1 week pretreatment with ginseng or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginseng (3)	12	Mean: 0.10 SD: 0.02 Lower: 0.10 Upper:0.12	-	GMR_{diff}:1.03 Lower: 0.95 Upper: 1.10	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	-
				No treatment	12	Mean:0.10 SD: 0.02 Lower: 0.09 Upper: 0.13	-			
	S-Warfarin: V/F (L/kg); measured after single-dose warfarin following 1 wk pretreatment with ginseng or no pretreatment. Subjects followed for 1 wk post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginseng (3)	12	Mean: 0.13 SD: 0.03 Lower: 0.11 Upper:0.15	-	GMR_{diff}:1.04 Lower: 0.94 Upper:1.14	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	-
				No treatment	12	Mean:0.12 SD: 0.03 Lower: 0.11 Upper: 0.14	-			

Evidence Table 163. KQ4—Continuous data—Distribution (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change / % change from baseline / SD / P Value	Between group differences in Means / medians SD / P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Jiang 2005[32] Cross-over	R-Warfarin: V/F (L/kg); measured after single dose warfarin following 1 week pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginger (3.6)	12	Mean:0.11 Lower: 0.10 Upper: 0.12	-	Ginger GMR_{diff}:0.97 Lower: 0.93 Upper:1.00 Ginkgo biloba GMR_{diff}:0.98 Lower: 0.95 Upper:1.01	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	-
				Ginkgo biloba (12)	12	Mean:0.11 Lower: 0.10 Upper: 0.11	-			
				No treatment	12	Mean:0.12 Lower: 0.10 Upper: 0.13	-			
	S-Warfarin: V/F (L/kg); measured after single-dose warfarin following 1 wk pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for 1 wk post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginger (3.6)	12	Mean:0.12 Lower: 0.11 Upper: 0.13	-	Ginger GMR_{diff}:1.03 Lower: 0.99 Upper:1.07 Ginkgo biloba GMR_{diff}:1.03 Lower: 0.99 Upper:1.08	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	
				Ginkgo biloba (12)	12	Mean:0.12 Lower: 0.11 Upper: 0.13	-			
				No treatment	12	Mean:0.12 Lower: 0.11 Upper: 0.14				
Abdul 2010[1] Cross-over	R-Warfarin: V/F (L/kg); measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	*Echinacea* (5.1; 23 mg total alkamides)	12	Mean:0.20 Lower: 0.13 Upper: 0.26	-	GMR_{diff}:1.03 Lower: 0.93 Upper:1.14	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	-
				No treatment	12	Mean:0.19 Lower: 0.13 Upper: 0.25	-			

Evidence Table 163. KQ4—Continuous data—Distribution (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change / % change from baseline / SD / P Value	Between group differences in Means / medians SD / P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Abdul 2010[1] Cross-over	S-Warfarin: V/F (L/kg); measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	*Echinacea* (5.1; 23 mg total alkamides)		Mean:0.23 Lower: 0.16 Upper: 0.30	-	GMR_{diff}:1.09 Lower: 1.03 Upper:1.18	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	-
				No treatment		Mean:0.21 Lower: 0.16 Upper: 0.27	-			

Evidence Table 164. KQ4—Continuous data—Clearance

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Clearance (V/time)										
Jiang 2004[33] Cross-over	R-Warfarin: CL/F (mL/min); measured after single dose warfarin following 1 wk pretreatment with ginseng or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginseng (3)	12	Mean: 119 SD: 20 Lower: 106 Upper:131	-	GMR_{diff}:1.10 Lower: 1.01 Upper: 1.20	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean:110 SD: 25 Lower: 94 Upper: 126	-			
	S-Warfarin: CL/F (mL/min); measured after single dose warfarin following 1 wk pretreatment with ginseng or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginseng (3)	12	Mean: 220 SD: 29 Lower: 201 Upper:238	-	GMR_{diff}:1.12 Lower: 1.03 Upper:1.22	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean:198 SD: 38 Lower: 174 Upper: 223	-			
Hajda 2010[28]	Clearance (CL/F) of statin (L/h)	Low (healthy men)	Simvastatin (20)	Garlic extract (600 mg twice daily)	10	Mean: 2146 SD: 1660	-	-	-	Medium
				No treatment	10	Mean: 2349 SD: 1340	-	-	-	

Evidence Table 164. KQ4—Continuous data—Clearance (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Hajda 2010[28]	Clearance (CL/F) of statin (L/h) (details not reported)	Low (healthy men)	Pravastatin (20)	Garlic extract (600 mg twice daily)	10	Mean: 722 SD:440	-	-	-	Medium
				No treatment	10	Mean: 834 SD: 928	-	-	-	
Jiang 2005[32] Cross-over	R-Warfarin: CL/F (mL/min); measured after single dose warfarin following 1 week pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginger (3.6)	12	Mean:131 Lower: 106 Upper: 156	-	<u>Ginger</u> GMR_{diff}:1.02 Lower: 0.95 Upper:1.10 <u>Ginkgo biloba</u> GMR_{diff}:1.00 Lower: 0.93 Upper:1.08	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				Ginkgo biloba (12)	12	Mean:126 Lower: 111 Upper: 141	-			
				No treatment	12	Mean:127 Lower: 106 Upper: 149	-			
	S-Warfarin: CL/F (mL/min); measured after single-dose warfarin following 1 wk pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for 1 wk post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginger (3.6)	12	Mean:201 Lower: 171 Upper: 231	-	<u>Ginger</u> GMR_{diff}:1.05 Lower: 0.97 Upper:1.13 <u>Ginkgo biloba</u> GMR_{diff}:1.05 Lower: 0.98 Upper:1.12	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	
				Ginkgo biloba (12)	12	Mean:200 Lower: 173 Upper: 227	-			
				No treatment	12	Mean:189 Lower: 167 Upper: 210				
Abdul 2010[1] Cross-over	R-Warfarin: mL/h; measured after single dose warfarin following 2 wks pretreatment with	Low (healthy)	Warfarin (25; single dose)	*Echinacea* (5.1; 23 mg total alkamides)	12	Mean:186.4 Lower: 140.5 Upper: 232.2	-	GMR_{diff}:1.10 Lower: 0.97 Upper:1.14	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of	Medium

Evidence Table 164. KQ4—Continuous data—Clearance (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
	Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose.			No treatment	12	Mean:178.3 Lower: 132.7 Upper: 223.4	-		between group difference = 90% CI	
	S-Warfarin: mL/h; measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	*Echinacea* (5.1; 23 mg total alkamides)	12	Mean:289.7 Lower: 218.2 Upper: 361.1	-	GMR_{diff}:1.09 Lower: 1.01 Upper:1.18	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean:267.3 Lower198.4 Upper: 336.3	-			
Mohammed Abdul 2008[49] Cross-over	R-Warfarin: mL/h; measured after single dose warfarin following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Garlic (4; 7.42 mg allicin)	12	Mean: 121 Lower: 112 Upper: 131	-	GMR_{diff}: 0.96 Lower: 0.84 Upper:1.11	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean: 123 Lower: 106 Upper: 140	-			
	S-Warfarin: mL/h; measured after single dose warfarin	Low (healthy)	Warfarin (25; single dose)	Garlic (4; 7.42 mg allicin)	12	Mean: 202 Lower: 175 Upper: 229	-	GMR_{diff}: 1.05 Lower: 0.94 Upper:1.17	Upper and lower limits of individual group data = 95%	Medium

Evidence Table 164. KQ4—Continuous data—Clearance (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
	following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose			No treatment	12	Mean: 213 Lower: 193 Upper: 232	-		CI; Upper and lower limits of between group difference = 90% CI	
McKenney 2006[45] Cross-over	CL/F (L/h) Total body clearance at steady state vs. time curve over the final dosing interval (0-24 h)	Low and/or Moderate	Simvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	21	Mean: 838 SD: 477	-	-	-	Medium
				No treatment	18	Mean: 872 SD: 402	-			
Tankanow 2003[65] Cross-over	mL/min; Measured after 10 days digoxin or 21 days digoxin + hawthorn	Low (healthy)	Digoxin (0.25; single dose)	Hawthorn (0.9)	8	Mean: 81 SD: 22	-	-	-	Medium
				No treatment	8	Mean: 74 SD: 10	-			
Mauro 2003[43] Cross-over	Oral clearance (L/h); Measured after single-dose administration of digoxin following 7 days pre-treatment with Ginkgo biloba or no pre-treatment	Low (healthy)	Digoxin (0.5; single dose)	*Ginkgo biloba* (0.24)	8	Mean: 26.6 SD: 18.1	-	-	-	Medium
				No treatment	8	Mean: 31.7 SD: 24.9	-			
Gosai 2008[26] Cross-over	Total body clearance at steady state (L/h); 2 weeks treatment	Low (healthy)	Rovustatin (40)	Omega-3 fatty acids (EPA, DHA or both) (4)	42	Mean: 204 SD: 88.5	-	-	% coefficient of variation: Omega-3: 43.36 Control: 36.25	Medium
				No treatment	41	Mean: 208 SD: 75.3	-			

Evidence Table 164. KQ4—Continuous data—Clearance (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Di Spirito 2008[19] Cross-over	Total body clearance at steady state vs. Time curve over the final dosing interval (0-24 h)	Low (healthy)	Atorvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	49	Mean: 413 SD: 179	-	-	-	Medium
				No treatment	49	Mean: 423 SD: 183	-			

Evidence Table 165. KQ4 Outcomes—Elimination rate

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/ % change from baseline/ SD/ P Value	Between group differences in Means/medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Mauro 2003 [43]	Elimination rated of single-dose administration of digoxin following 7 days pre-treatment with Ginkgo biloba or no pre-treatment	Low (healthy)	Digoxin (0.5; single dose)	*Ginkgo biloba* (0.24)	6	Mean: 0.02 SD: 0.01	-	-	-	Medium
				No treatment	6	Mean: 0.03 SD: 0.02	-			

Evidence Table 166. KQ4 Outcomes—Half life (T1/2)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Kim 2010[35] Cross-over	hours – measured after single dose of ticlopidine and single dose Ginkgo biloba	Low and/or Moderate	Ticlopidine (250; single dose)	Ginkgo biloba (0.08; single dose)	24	Mean: 13.5 SD: 5.6	-	GMR_{diff}: 0.27		Medium
				No treatment	24	Mean: 11.2 SD: 4.8	-			
Tankanow 2003[65] Cross-over	hours: Measured after 10 days digoxin or 21 days digoxin + hawthorn	Low (healthy)	Digoxin (0.25)	Hawthorn (0.9)	8	Mean: 48 SD: 6	-	-	-	Medium
				No treatment	8	Mean: 50 SD: 15	-			
Mauro 2003[43] Cross-over	hours; Measured after single-dose administration of digoxin following 7 days pre-treatment with Ginkgo biloba or no pre-treatment.	Low (healthy)	Digoxin (0.5; single dose)	*Ginkgo biloba* (0.24)	6	Mean: 44.0 SD: 19.6	-	-	-	Medium
				No treatment	6	Mean: 26.0 SD: 11.1	-			

Evidence Table 166. KQ4 Outcomes—Half life (T1/2) (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Jiang 2004[33] Cross-over	R-Warfarin: hours; measured after single dose warfarin following 1 week pretreatment with ginseng or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginseng (3)	12	Mean: 47.9 SD: 7.8 Lower: 42.9 Upper: 52.9	-	GMR_{diff}: 0.93 Lower: 0.88 Upper: 0.99	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean: 51.7 SD: 9.6 Lower: 45.6 Upper: 57.8	-			
	S-Warfarin: hours; measured after single-dose warfarin following 1 wk pretreatment with ginseng or no pretreatment. Subjects followed for 1 wk post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginseng (3)	12	Mean: 29.2 SD: 5.2 Lower: 25.9 Upper: 32.4	-	GMR_{diff}: 0.92 Lower: 0.85 Upper: 0.99	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean: 31.7 SD: 4.5 Lower: 28.8 Upper: 34.5	-			
Jiang 2005[32] Cross-over	R-Warfarin: hours; measured after single dose warfarin following 1 week pretreatment with Ginger,	Low (healthy)	Warfarin (25; single dose)	Ginger (3.6)	12	Mean:47.7 Lower: 42.6 Upper: 52.8	-	<u>Ginger</u> GMR_{diff}: 0.94 Lower: 0.90 Upper: 1.01	Upper and lower limits of individual group data = 95% CI; Upper and lower limits	Medium

Evidence Table 166. KQ4 Outcomes—Half life (T1/2) (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
	Ginkgo biloba or no pretreatment. Subjects followed for one more week post warfarin dose.			Ginkgo biloba (12)	12	Mean: 48.6 Lower: 44.7 Upper: 52.4	-	Ginkgo biloba GMR_{diff}: 0.97 Lower: 0.92 Upper:1.02	of between group difference = 90% CI	
				No treatment	12	Mean: 50.3 Lower: 45.8 Upper: 54.9	-			
	S-Warfarin: hours; measured after single-dose warfarin following 1 wk pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for 1 wk post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginger (3.6)	12	Mean: 35.7 Lower: 30.0 Upper: 41.3	-	Ginger GMR_{diff}: 0.99 Lower: 0.94 Upper:1.04 Ginkgo biloba GMR_{diff}: 0.98 Lower: 0.93 Upper:1.04	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				Ginkgo biloba (12)	12	Mean: 35.1 Lower: 30.9 Upper: 39.3	-			
				No treatment	12	Mean: 35.8 Lower: 31.1 Upper: 40.3				
Hajda 2010[28]	Statin half time.	Low (healthy)	Simvastatin (20)	Garlic extract (600 mg twice daily)	10	Mean: 5.0 SD: 1.9	-	GMR (95% CI): 1.02 (0.81, 1.27)	-	Medium
				No treatment	10	Mean: 4.92 SD: 0.93	-		-	

Evidence Table 166. KQ4 Outcomes—Half life (T1/2) (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Hajda 2010[28]	Statin half time.	Low (healthy)	Pravastatin (20)	Garlic extract (600 mg twice daily)	10	Mean: 3.57 SD: 1.11	-	GMR (95% CI): 0.92 (0.5, 1.13)	-	Medium
				No treatment	10	Mean: 3.75 SD: 0.66	-	-	-	
Di Spirito 2008[19] Cross-over	Atorvastatin; hours; 2 weeks treatment	Low (healthy)	Atorvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	49	Mean: 6.39 SD: 1.69	-	-		Medium
				No treatment	49	Mean: 6.66 SD: 3.81	-			
	2-hydroxytorvastatin; hours; 2 weeks treatment	Low (healthy)	Atorvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	49	Mean: 7.17 SD: 3.44	-	-		Medium
				No treatment	49	Mean: 6.75 SD: 2.72	-			
Mohammed Abdul 2008[49] Cross-over	R-Warfarin: hours; measured after single dose warfarin following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Garlic (4; 7.42 mg allicin)	12	Mean: 52.6 Lower: 47.4 Upper: 57.9	-	GMR_{diff}: 0.98 Lower: 0.84 Upper:1.14	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean: 55.6 Lower: 46.2 Upper: 65.0	-			

Evidence Table 166. KQ4 Outcomes—Half life (T1/2) (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
	S-Warfarin: hours; measured after single dose warfarin following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose	Low (healthy)	Warfarin (25; single dose)	Garlic (4; 7.42 mg allicin)	12	Mean: 41.2 Lower: 35.1 Upper: 47.3	-	GMR_{diff}: 0.99 Lower: 0.83 Upper: 1.18	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean: 38.6 Lower: 35.7 Upper: 41.5	-			
McKenney 2006[45] Cross-over	Simvastatin; hours; 2 wk treatment.	Low and/or Moderate	Simvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	23	Mean: 7.4 SD: 1.6	-	-	-	Medium
				No treatment	23	Mean: 9.9 SD: 5.5	-			
	Beta-hydroxy simvastatin; hours; 2 wk treatment.	Low and/or Moderate	Simvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	18	Mean: 9.5 SD: 5.8	-	-	-	Medium
				No treatment	18	Mean: 9.4 SD: 5.9	-			
Abdul 2010[1] Cross-over	R-Warfarin: hours; measured after single dose warfarin following 2 wks pretreatment with	Low (healthy)	Warfarin (25; single dose)	*Echinacea* (5.1; 23 mg total alkamides)	12	Mean: 49.2 Lower: 44.3 Upper: 54.2	-	GMR_{diff}: 0.98 Lower: 0.88 Upper: 1.10	Upper and lower limits of individual group data = 95% CI; Upper and lower limits	Medium

Evidence Table 166. KQ4 Outcomes—Half life (T1/2) (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
	Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose.			No treatment	12	Mean: 50.6 Lower: 44.9 Upper: 56.2	-		of between group difference = 90% CI	
	S-Warfarin: hours; measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	*Echinacea* (5.1; 23 mg total alkamides)	12	Mean: 36.5 Lower: 34.1 Upper: 38.8	-	GMR_{diff}: 0.95 Lower: 0.84 Upper: 1.08	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean: 38.6 Lower: 34.3 Upper: 43.0				

Evidence Table 167. KQ4—Continuous data—Area under the curve (AUC)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Kim 2010[35] Cross-over	ng*h/mL (0 - ∞); measured after single dose of ticlopidine and single dose Ginkgo biloba	Low and/or Moderate	Ticlopidine (250; single dose)	Ginkgo biloba (0.08; single dose)	24	Mean: 3466.00 SD: 1548.80	GMR: 3145.00	GMR_{diff}: 1.10 Lower: 1.00 Upper: 1.20	Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	24	Mean: 3240.00 SD: 1592.3	GMR: 2568.00			
Tankanow 2003[65] Cross-over	ng*h/mL (0 - ∞); Measured after 10 days digoxin or 21 days digoxin + hawthorn	Low (healthy)	Digoxin (0.25)	Hawthorn (0.9)	8	Mean: 73.00 SD: 20.00	-	-	-	Medium
				No treatment	8	Mean: 79.00 SD: 26.00	-			
Mauro 2003[43] Cross-over	ng*h/mL (0 - ∞); Measured after single-dose administration of digoxin following 7 days pre-treatment with Ginkgo biloba or no pre-treatment	Low (healthy)	Digoxin (0.5; single dose)	*Ginkgo biloba* (0.24)	8	Mean: 25.6 SD: 13.2	-	-	-	Medium
				No treatment	8	Mean: 21.00 SD: 8.6	-			

Evidence Table 167. KQ4—Continuous data—Area under the curve (AUC) (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Jiang 2004[33] Cross-over	R-Warfarin: µg/mL*hr (0 - ∞); measured after single dose warfarin following 1 week pretreatment with ginseng or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginseng (3)	12	Mean: 108.1 SD: 18.3 Lower: 95.9 Upper:120.2	-	GMR_{diff}: 0.91 Lower: 0.84 Upper: 0.99	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean: 120.9 SD: 32.9 Lower: 99.0 Upper: 142.7	-			
	S-Warfarin: µg/mL*hr (0 - ∞); measured after single-dose warfarin following 1 wk pretreatment with ginseng or no pretreatment. Subjects followed for 1 wk post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginseng (3)	12	Mean: 57.8 SD: 7.4 Lower: 53.1 Upper: 62.5	-	GMR_{diff}:0.89 Lower: 0.82 Upper: 0.98	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean: 65.4 SD: 13.8 Lower: 56.6 Upper: 74.1	-			
Jiang 2005[32]	R-Warfarin: µg*h/mL (0 - ∞); measured after	Low (healthy)	Warfarin (25; single dose)	Ginger (3.6)	12	-	-	Ginger GMR_{diff}: 1.00	Upper and lower limits of between	Medium
				Ginkgo biloba (12)	12	-	-			

Evidence Table 167. KQ4—Continuous data—Area under the curve (AUC) (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Cross-over	single dose warfarin following 1 week pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for one more week post warfarin dose.			No treatment	12	-	-	Lower: 0.92 Upper:1.07 <u>Ginkgo biloba</u> GMR_{diff}: 0.98 Lower: 0.91 Upper:1.06	group difference = 90% CI	
	S-Warfarin: µg*h/mL (0 - ∞); measured after single-dose warfarin following 1 wk pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for 1 wk post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Ginger (3.6)	12	-	-	<u>Ginger</u> GMR_{diff}: 0.95 Lower: 0.89 Upper:1.03 <u>Ginkgo biloba</u> GMR_{diff}: 0.97 Lower: 0.89 Upper:1.03	Upper and lower limits of between group difference = 90% CI	Medium
				Ginkgo biloba (12)	12	-	-			
				No treatment	12	-	-			
Hajda 2010[28] Cross over	ng*h/mL (0-24 hours)	Low (healthy)	Simvastatin (20)	Garlic extract (600 mg twice daily)	10	Mean: 22.1 SD: 25.7	-	GMR (95% CI): 1.37 (0.88, 2.12)	-	Medium
				No treatment	10	Mean: 11.2 SD: 5.7	-			
Hajda 2010[28] Cross over	ng*h/mL (0-24 hours)	Low (healthy)	Pravastatin (20)	Garlic extract (600 mg twice daily)	10	Mean: 35.4 SD: 15.5	-	GMR (95% CI): 0.94 (0.65, 1.36)	-	Medium
				No treatment	10	Mean: 41.8 SD: 24.1	-		-	

Evidence Table 167. KQ4—Continuous data—Area under the curve (AUC) (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Gosai 2008[26] Cross-over	ng*h/ml; 2 weeks treatment; Day 14 steady state	Low (healthy)	Rovustatin (40)	Omega-3 fatty acids (EPA, DHA or both) (4)	42	Mean: 231.35 SD: 93.15	GMR = 213.73	GMR_{diff}: 1.05 Lower: 0.99 Upper: 1.10	% coefficient of variation: Omega-3: 40.26 Control: 33.18 Intra % coefficient of variation (Omega-3): 14.5 Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	41	Mean: 215.77 SD: 71.60	GMR = 204.19			
Yuan 2004[71]	Change from wk1 to w4 (µg/mL/d); steady state: assessed after 3 days warfarin treatment before and after 3 weeks 3 weeks treatment with ginseng or placebo	Low and/or Moderate	Warfarin (5)	Ginseng (2)	12	-	$Median_{change}$: -0.40 Range L: -1.20 H: 0.20	$Median_{diff}$: -0.64 Range: L: -1.25 H: -0.13	-	Medium
				Placebo	8	-	$Median_{change}$: 0.18 Range L: -0.35 H: 1.40			

Evidence Table 167. KQ4—Continuous data—Area under the curve (AUC) (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
Di Spirito 2008[19] Cross-over	Atorvastatin; Day 14 steady state (ng*h/mL) over final dosing interval; 2 weeks treatment	Low (healthy)	Atorvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	49	Mean: 212.50 SD: 46.70	-	GMR_{diff}: 1.03 Lower: 0.97 Upper: 1.09	Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	49	Mean: 207.20 SD: 45.70	-			
	2-hydroxytorvastatin; Day 14 steady state; (ng*h/mL); 2 weeks treatment	Low (healthy)	Atorvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	49	Mean: 275.00 SD: 37.90	-	GMR_{diff}: 0.95 Lower: 0.85 Upper: 1.06	Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	49	Mean: 273.02 SD: 35.90	-			
Mohammed Abdul 2008[49] Cross-over	R-Warfarin: µg/mL*h (0 - ∞); measured after single dose warfarin following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	Garlic (4; 7.42 mg allicin)	12	Mean: 105.00 Lower: 96.30 Upper: 113.70	-	GMR_{diff}: 0.99 Lower: 0.87 Upper:1.13	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean: 108.70 Lower: 90.00 Upper: 127.30	-			
	S-Warfarin: µg/mL*h (0 - ∞); measured after single dose warfarin following 2 wks	Low (healthy)	Warfarin (25; single dose)	Garlic (4; 7.42 mg allicin)	12	Mean: 65.50 Lower: 55.30 Upper: 75.60	-	GMR_{diff}: 1.06 Lower: 0.95 Upper:1.19	Upper and lower limits of individual group data = 95% CI;	Medium

Evidence Table 167. KQ4—Continuous data—Area under the curve (AUC) (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
	pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose			No treatment	12	Mean: 60.30 Lower: 54.50 Upper: 66.10	-		Upper and lower limits of between group difference = 90% CI	
McKenney 2006[45] Cross-over	Simvastatin; AUCss over final dosing interval (ng*h/mL); 2 wk treatment.	Low and/or Moderate	Simvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	21	Mean: 125.10 SD: 62.90	-	-	-	Medium
				No treatment	18	Mean: 116.60 SD: 64.00	-			
	Beta-hydroxy simvastatin: AUCss over final dosing interval (ng*h/mL); 2 wk treatment.	Low and/or Moderate	Simvastatin (80)	Omega-3 fatty acids (EPA, DHA or both) (4)	20	Mean: 83.00 SD: 42.20	-	-	-	Medium
				No treatment	17	Mean: 83.90 SD: 44.40	-			
Abdul 2010[1] Cross-over	R-Warfarin: mg*h/mL (0 - ∞); measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	*Echinacea* (5.1; 23 mg total alkamides)	12	Mean: 74.9 Lower: 62.5 Upper: 87.2	-	GMR_{diff}: 0.95 Lower: 0.88 Upper: 1.03	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean: 79.4 Lower: 65.4 Upper: 93.4	-			

Evidence Table 167. KQ4—Continuous data—Area under the curve (AUC) (continued)

Author Year Study Design	Definition of outcome	CHD Risk Category	CVD drug (dose mg/d)	Supplement/ Control	N	Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI)	Mean change/% change from baseline/ SD/ P Value	Between group differences in Means/ medians SD/ P Value	Additional comments	Overall Risk of Bias (ROB) Assessment
	S-Warfarin: mg*h/mL (0 - ∞); measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose.	Low (healthy)	Warfarin (25; single dose)	*Echinacea* (5.1; 23 mg total alkamides)	12	Mean: 49.0 Lower: 40.0 Upper: 57.9	-	GMR_{diff}: 0.92 Lower: 0.85 Upper: 1.99	Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI	Medium
				No treatment	12	Mean: 53.9 Lower: 42.9 Upper: 64.8				

Evidence Table 168. Risk of bias assessment for all studies

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Coenzyme Q10									
Mabuchi 2007[39] KQ 2, 3	Unclear/Unclear	No major imbalance Unclear: smoking, comorbidities, blood pressure Other: glucose levels sign. higher in placebo group	Yes	All unclear double-blind, placebo controlled	Yes	No	Unclear/Unclear/Unclear	N/A	Medium
Young 2007[70] KQ 1, 2, 3	Unclear/Unclear	No major imbalance Unclear: Race, Baseline diet	Unclear	All unclear double-blind, placebo controlled	Unclear	Yes	Yes/Unclear/Yes	N/A	Medium
Caso 2007[11] KQ 2, 3	Unclear/Yes	No major imbalance Unclear: Race, baseline diet, smoking, concomitant medications/supplements, comorbidities, HDL-c, blood pressure Minor imbalance: > proportion of women in Vit E group vs. CoQ10	Yes	Yes/Yes/Yes	Yes	Yes	Yes/Yes/Yes	N/A	Low
Playford 2003[58] KQ 2, 3	Unclear/Unclear	No major imbalance Unclear: Race	Unclear	All unclear double-blind	Yes	Unclear	No/Unclear/Unclear	N/A	Low-medium

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Watson 1999[66] KQ 1, 2, 3	Unclear/Unclear	Unclear	No	All unclear double-blind, placebo controlled	Unclear	Unclear	No/Unclear/Unclear	Yes/Yes/Unclear	Medium
Echinacea									
Abdul 2010[1] KQ 2, 3, 4	Unclear/Unclear	No major imbalance/Unclear	Yes	No/No/No Open label trial	Unclear	No	No/Unclear/Unclear	Yes/Yes/Unclear	Medium
Garlic									
Macan 2006[40] KQ 2, 3	Unclear/Unclear	Major imbalance: for: Gender - proportion of men higher in placebo (77%) vs. AGE (45%) group. No other major imbalance Unclear: Race, Baseline diet, smoking	Yes	All unclear double-blind, placebo controlled	Unclear	No	Unclear/Unclear/Unclear	N/A	Medium
Bordia 1998[9] KQ 2, 3	Unclear/Unclear	All unclear	Yes	All unclear placebo-controlled	Unclear	Yes	Unclear/Unclear/Unclear	N/A	High
Hajda, 2010[28] KQ 4	No/No	Yes	Yes	No/No/No	Unclear	No	No/No/Unclear	Yes/Yes/Unclear	Medium

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Budoff 2004[10] KQ 1, 2, 3	Unclear/Unclear	No major imbalance Unclear: Race, Baseline diet, concomitant medications/supplements, blood pressure	Yes	All unclear double-blind, placebo controlled	Yes	No	Unclear/Unclear/Unclear	N/A	Medium
Mohammed Abdul 2008[49] KQ 2, 3, 4	Unclear/Unclear	Unclear	Yes	No/No/No Open label trial	No	Yes	Yes/Yes/Unclear	Yes/Yes/Unclear	Medium
Ginger									
Jiang 2005[32] KQ 3, 4	Unclear/Unclear	Unclear	Yes	No/No/No Open label trial	Yes	Yes	No/Unclear/Unclear	Yes/Yes/Unclear	Medium
Gingko biloba									
Gardner 2007[23] KQ 2, 3	Yes/Yes	No major imbalance Unclear: Baseline diet, smoking, LDL-c/HDL-c	Yes	Yes/Yes/Yes	Yes	Yes	Yes/Yes/Yes	N/A	Low

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Garg 1995[24] KQ 1, 3	Yes/Unclear	No major imbalance for pre-specified variables Unclear: Race, Baseline diet/nutrient status, comorbidity based on laboratory variables, LDL-c/HDL-c, Blood pressure Other imbalance - speech problems between groups (GB 44.8% vs. Placebo 23.1%) and comorbidities such as DM	No	Unclear/Unclear/Yes double-blind, placebo controlled	Yes	Unclear	No/No/Unclear	N/A	Medium-High
Wolf 2006[68] KQ 2, 3	Yes/Unclear	Unclear	Yes	All unclear, double-blind, placebo controlled	Yes	Yes	No/Unclear/Yes	Yes/Yes/No	Low-medium
Kim 2010 [35] KQ 2, 3, 4	Yes/Unclear	Unclear	Yes	No/No/No Open label trial	Yes	No	Unclear/Unclear/Unclear	Yes/Yes/Unclear	Medium
Jiang 2005[32] KQ 2, 3, 4	Unclear/Unclear	Unclear	Yes	No/No/No Open label trial	Yes	Yes	No/Unclear/Unclear	Yes/Yes/Unclear	Medium
Aruna 2007[2] KQ 2	Unclear/Unclear	Unclear	No	No/No/No Open label trial	Unclear	Unclear	No/Unclear/Unclear	Yes/Unclear/Unclear	Medium

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Mauro 2003[43] KQ 3, 4	Unclear/unclear	Unclear	Yes	No/No/No Open label trial	Yes	Yes	No/Yes/Unclear	Yes/Yes/Unclear	Medium
Ginseng									
Lee 2008[36] KQ 2, 3	Unclear/Unclear	No major imbalance Unclear: Race, baseline diet, smoking, some concomitant medications, LDL-c/HDL-c, Blood pressure	Yes	No/No/No Open label trial	Yes	Yes	No/Unclear/Unclear	N/A	Medium
Yuan 2004[71] KQ 2, 3, 4	Yes/Yes	No major imbalance Unclear: Comorbidities as assessed by lab values (restriction for clinical assessment of comorbidities), LDL-c/HDL-c, blood pressure	Yes	Yes/Yes/Yes	Yes	Yes	No/Yes/Unclear	N/A	Low
Jiang 2004[33] KQ 2, 3, 4	Unclear/unclear	Yes	Yes	No/No/No Open label trial	Yes	Unclear	No/Unclear/Unclear	Yes/Yes/Unclear	Medium
Hawthorne									

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Tankanow 2003[65] KQ 2, 3, 4	Unclear/Unclear	Unclear	Yes	No/No/No Open label trial	Unclear	Unclear	No/Yes/Yes	Yes/Yes/Yes	Medium
Magnesium									
Paolisso 1992[57] KQ 2, 3	Unclear/Unclear	All unclear	Unclear	Yes/Unclear/Unclear double-blind, placebo controlled	Yes	Unclear	Unclear/Unclear/Unclear	N/A	Medium
Reyes 1984[59] KQ 2, 3	Unclear/Unclear	Potential confounding/imbalance: Gender - more females in treatment group but small sample size No major imbalance noted for other prespecified variables Unclear: Smoking, concomitant supplements (medications controlled by restriction), LDL-c/HDL-c	Yes	All unclear double-blind, placebo controlled	Yes	Unclear	Unclear/Unclear/Unclear	N/A	Medium
Wirell 1994[67] KQ 1, 2, 3	Unclear/Unclear	Unclear	Yes	Unclear/Yes/Yes double-blind, placebo controlled	Yes	No	No/Unclear/Unclear	Yes/No/No	Medium

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Niacin									
Avogaro 1974[3] KQ 2, 3	Unclear/Unclear	Unclear for pre-specified variables Other: Propranolol dosage is different in the two groups: Supplement + CVD phase = 20 mg/day; CVD only phase = 60 mg/day	No	All unclear matching placebo	No	Unclear	No/Unclear/Unclear	Yes/No/Unclear	High
Omega-3 fatty acids/fish oils									
Bays 2010[6] K2, 3	Unclear/Unclear	No major imbalances Unclear: Comorbidities, Blood pressure.	Yes	All unclear double-blind, placebo controlled	Yes	No	Yes/Unclear/Yes	N/A	Medium

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Ferraro 2009[22] KQ 2, 3	Yes/Unclear	No major imbalance for pre-specified variables Unclear: Race, Baseline diet, smoking, some concomitant medications/supplements, comorbidities, LDL-c Other - Class of erythrocyturia; Control group significantly more likely to be lower class than intervention group	Yes	No/No/No no blinding	Yes	Unclear	Unclear/Unclear/Unclear	N/A	Medium
Davidson 2007[14] KQ 1, 2, 3	Yes/Yes	No major imbalance Unclea: Baseline diet, smoking	Yes	All unclear double-blind, placebo controlled	Yes	Unclear	Unclear/Yes/Yes	N/A	Medium
Meyer 2007[46] KQ 2	Yes/Unclear	No major imbalance Unclear: Race, Baseline diet, smoking, concomitant medications/supplements, lab values associated with comorbidities (but clinical presentation of comorbidities restricted/balanced), blood pressure	Yes	All unclear placebo controlled	Unclear	Yes	N/A	N/A	Medium

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Neil 2010[53] KQ2, 3	Yes/Unclear	Unclear	Yes	Yes/Yes/Double blind Placebo controlled	Yes	No	No/No/No	NA	Low with respect to KQ2 outcomes
Svaneborg 2002[64] KQ 2	Unclear/Unclear	Unclear for all	Yes	All unclear double-blind, placebo controlled	Unclear	Unclear	N/A	N/A	Medium
Nordoy 2000[54] KQ 2, 3	Unclear/Unclear	No major imbalance Unclear: Race, smoking, comorbidities as assessed by lab variables (considered balanced by clinical variables), Blood pressure	Yes	All unclear double-blind, placebo controlled	Yes	Unclear	Unclear/Unclear/Unclear	N/A	Medium
Davidson 1997[15] KQ 2	Unclear/Unclear	No major imbalance Unclear: Race, smoking, Concomitant medications/supplements, comorbidities, Blood pressure	Yes	All unclear double-blind, placebo controlled	Yes	Unclear	N/A	N/A	High

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Eritsland 1996[21] KQ 1, 3	Yes/Unclear	No major imbalance Unclear: Race, Baseline diet/nutrient status, comorbidities as assessed by laboratory variables (balanced as assessed by clinical variables)	Yes	No/No/No	Yes	No	Yes/Yes/Yes	N/A	Medium
Yamamoto 1995[69] KQ 1, 2	Unclear/Unclear	No major imbalance Unclear: Baseline diet/nutrient exposure, smoking, Concomitant medications/supplements, comorbidities as assessed by laboratory values, Blood pressure	Yes	No/No/No	Unclear	Unclear	N/A	N/A	Medium
Howe 1994[30] KQ 2	Unclear/Unclear	No major imbalance Unclear: Race, Baseline diet/nutrient status, smoking, Comorbidities as assessed by laboratory variables (balance/restriction based on clinical variables), Blood pressure	Yes	All unclear double-blind, placebo controlled	Yes	Unclear	N/A	N/A	Medium

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Kaul 1992[34] KQ 1, 2, 3	Yes/Unclear	No major imbalance for prespecified variables Unclear: Race, Baseline diet/nutrient status, Concomitant medications supplement (medications by restriction), Comorbidities, LDL-c/HDL-c, Blood pressure Other: higher N of dilations in circumflex artery in controls vs. treatment group	Yes	Yes/No/No	Yes	Unclear	No/Yes/Yes	N/A	Low-Medium
Nordøy 2003[55] KQ 2, 3	Unclear/Unclear	No major imbalance Unclear: Smoking, Comorbidities as assessed by laboratory measures (balanced/restriction based on clinical measures of comorbidity)	Yes	All unclear double-blind, placebo-controlled	Yes	Unclear	No/Unclear/Unclear	N/A	Low
Roth 2009[60] KQ 1, 2, 3	Unclear/Unclear	No major imbalance Unclear: Smoking, Blood pressure	Yes	All unclear double-blind, placebo-controlled	Yes	No	Unclear/Unclear/Yes	N/A	Medium

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Isley 2007[31] KQ 2, 3	Unclear/Unclear	No major imbalance Unclear: Race, smoking, Comorbidities as assessed by laboratory measures (balanced/restriction based on clinical measures of comorbidity), blood pressure	Yes	All unclear placebo-controlled	Yes	Yes	No/Yes/Unclear	N/A	Medium
Bender 1998[8] KQ 1, 2, 3	Unclear/Unclear	Potential confounding: Gender and age are imbalanced No major imbalance noted for other prespecified variables Unclear: Baseline diet/nutrient status, smoking, comorbidities as assessed clinically, LDL-c/HDL-c, Blood pressure	Yes	All unclear double-blind, placebo controlled	Unclear	No	Unclear/Unclear/Unclear	N/A	High
Chan 2002[12] KQ 1, 2, 3	Unclear/Unclear	No major imbalance Unclear: Race	Yes	All unclear double-blind, placebo-controlled	Yes	Unclear	No/Unclear/Unclear	N/A	Medium

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Liu 2003[37] KQ 1, 2, 3	Unclear/Unclear	No major imbalance Unclear: Race, Baseline diet/nutrient status, smoking, Concomitant medications supplement (medications by restriction), Comorbidities as assessed by laboratory measures (restriction based on clinical measures of comorbidity), Blood pressure	Yes	Yes/Unclear/No	Unclear	Unclear	Unclear/Unclear/Unclear	N/A	Medium
Dehmer 1988[17] KQ 1, 2, 3	Yes/Unclear	No major imbalance Unclear/not stated: Race, Baseline diet/nutrient status, Concomitant medications/supplement, Blood pressure	Yes	Yes/Unclear/No	Yes	Yes	No/Unclear/Unclear	N/A	Medium
Balestrieri 1996[4] KQ 2, 3	Unclear/Unclear	Unclear	Yes	All unclear double-blind, placebo-controlled	Yes	Unclear	Yes/Unclear/Unclear	Yes/Yes/Yes	Medium
Lungershausen 1994[38] KQ 2	Unclear/Unclear	Unclear	Yes	All unclear double-blind, placebo-controlled	Unclear	Unclear	N/A	Yes/No/Yes	Medium

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	**Selection bias** Appropriate sequence generation/ allocation concealment	**Comparable groups at baseline or control for imbalance**	**Purity/ standardization of supplement described**	**Blinding** Outcome Assessors/Care Provider/Patient	**Attrition bias** Completeness of outcome data	**Free of financial conflict of interest**	**Harms** Pre-specification/ active data collection/ appropriateness of harms data collection	**Cross-over trials** Appropriate design/ absence of carry-over effect/ appropriate analysis	**Overall risk of bias for gradable outcomes**
Hansen 1993[29] KQ 2, 3	Unclear/Unclear	Unclear	Yes	All unclear double-blind, placebo-controlled	Unclear	No	No/Unclear/Unclear	Yes/Yes/No	Medium
McKenney 2006[45] KQ 2, 3, 4	Unclear/Unclear	Unclear	No	No/No/No Open label trial	Yes	No	No/Unclear/Unclear	Yes/Yes/Yes	Medium
Mueller 1991[51] KQ 2, 3	Yes/Unclear	Unclear	Yes	Yes/Yes/Yes, double-blind, placebo-controlled	Unclear	No	No/Unclear/Unclear	Yes/No/Unclear	Medium
Maki 2008[41] KQ 1, 2, 3	Unclear/Unclear	No major imbalance	No	Yes/Yes/Yes	Yes	No	No/Unclear/Unclear	Yes/Unclear/Unclear	Medium
Gosai 2008[26] KQ 3, 4	Unclear/Unclear	Unclear	Yes	No/No/No Open label trial	Unclear	No	No/Unclear/Unclear	Yes/Yes/Unclear	Medium
Di Spirito 2008[19] KQ 1, 3, 4	Unclear/Unclear	Unclear	Yes	No/No/No Open label trial	Unclear	No	No/Unclear/Unclear	Yes/Yes/No	Medium
Red yeast rice extract – no included studies									

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Resveratrol – no included studies									
Vitamin A - no included studies									
Vitamin D (with or without calcium) – no included studies									
Vitamin E									
Glynn 2007[25] KQ 1, 3	Yes/Unclear	No major imbalance Unclear: Race, Baseline diet/nutrient status, Smoking, Concomitant medications (but restriction for anticoagulants and some supplements), Comorbidities, LDL-c/HDL-c, Blood pressure	Yes	Yes/Yes/Yes	Yes	Yes	Unclear/Yes/Yes	N/A	Medium

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Sutken 2006[63] KQ 2	No/Unclear	No major imbalance Unclear: Race, Baseline diet, comorbidity as assessed by laboratory measures (but restriction/balance for clinical measures of comorbidity).	Unclear	No/No/No	Yes	Unclear	N/A	N/A	High
d'Arcangues 2004[13] KQ 3	Unclear/Yes	No major imbalance Unclear: Age, Race, Baseline diet/nutrient status, smoking, Comorbidities as assessed by laboratory measures (restriction based on clinical variables), LDL-c/HDL-c, blood pressure	Yes	Yes/Yes/Yes	Unclear	Unclear	No/Yes/Unclear	N/A	Medium
Manuel 2004[42] KQ 2, 3	Yes/Unclear	No major imbalance Unclear: Race, smoking, concomitant medications/supplements Other - neuropathy; significantly greater in placebo group at baseline	Yes	All unclear matched placebo-control	Yes	Unclear	Unclear/Unclear/Unclear	N/A	Medium

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Miyamoto 2004[48] KQ 1	Yes/Unclear	No major imbalance Unclear: Race, baseline diet/nutrient intake, confounding as assessed by laboratory measures (restriction w.r.t. clinical assessment of confounding), blood pressure	Yes	All unclear double-blind, placebo-controlled	Yes	Yes	N/A	N/A	N/A
Micheletta 2004[47] KQ 2	Unclear/Unclear	No major imbalance. Study states that no significant differences were present between the groups for the following variables, with no data reported: Age, gender, smoking, clinical assessment of comorbidity Unclear: Race, baseline diet/nutrient intake, concomitant medications (supplements restricted), confounding as assessed by laboratory measures, LDL-c/HDL-c, blood pressure.	Yes	No/No/No	Yes	Yes	N/A	N/A	Medium

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Duffy 2001[20] KQ 2, 3	Unclear/Unclear	No major imbalance Unclear: Race, Baseline diet, smoking, comorbidities as assessed by lab variables (considered balanced by clinical variables)	Yes	Unclear/Unclear/Yes double-blind, placebo-controlled	Yes	Yes	No/Unclear/Unclear	N/A	Medium
Barbagallo 1999[5] KQ 2, 3	Unclear/Unclear	No major imbalance Unclear: Race, Baseline diet/nutrient statues, smoking, LDL-c/HDL-c	Unclear	All unclear double-blind, placebo-controlled	Unclear	Unclear	Unclear/Unclear/Unclear	N/A	Medium
Motoyama 1998[50] KQ 1	Yes/Unclear	No major imbalance Unclear: Race, Baseline diet/nutrient statues, comorbidities as assessed by laboratory variables (balanced as assessed by clinical variables)	Yes	Yes/Unclear/Unclearplacebo-controlled	Unclear	Unclear	N/A	N/A	Medium

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Napoli 1998[52] KQ 1, 2, 3	Unclear/Unclear	No major imbalance Unclear: Gender, Race, Concomitant medications/supplements, comorbidities as assessed by clinical variables (balanced as assessed by laboratory variables), Blood pressure	Yes	All unclear	Unclear	Yes	Yes/Yes/Yes	N/A	Medium
Steiner 1995[62] KQ 1, 2, 3	Unclear/Unclear	No major imbalance Unclear: Race, Baseline diet/nutrient status, concomitant medications/supplements, comorbidity based on laboratory variables.	No	All unclear double-blind, placebo-controlled	Unclear	No	No/Unclear/Unclear	N/A	Low-Medium
McDowell 1994[44] KQ 2, 3	Unclear/Unclear	No major imbalance Unclear: Age, Gender, Race, smoking, Comorbidities, Blood pressure	Yes	All unclear double-blind, placebo-controlled	Yes	No	No/Unclear/Unclear	N/A	Medium

Evidence Table 168. Risk of bias assessment for all studies (continued)

Author year Key question	Selection bias Appropriate sequence generation/ allocation concealment	Comparable groups at baseline or control for imbalance	Purity/ standardization of supplement described	Blinding Outcome Assessors/Care Provider/Patient	Attrition bias Completeness of outcome data	Free of financial conflict of interest	Harms Pre-specification/ active data collection/ appropriateness of harms data collection	Cross-over trials Appropriate design/ absence of carry-over effect/ appropriate analysis	Overall risk of bias for gradable outcomes
Desideri 2003[18] KQ 2	Unclear/Unclear	No major imbalance Unclear: Race, comorbidities as assessed by laboratory measures (clinical measures balanced by restriction)	Yes	All unclear double-blind, no placebo	Yes	Unclear	N/A	N/A	Medium
De 2002[16] KQ 2, 3	Unclear/Unclear	Unclear	Yes	No/No/No Open label study	Unclear	No	No/No/No	Yes/No/Unclear	High
Paolisso 1995[56] KQ 2, 3	Unclear/Unclear	Unclear	Yes	All unclear double-blind, placebo-controlled	Unclear	Unclear	No/Unclear/Unclear	Yes/Yes/No	Medium
Vitamin K									
Sconce 2007[61] KQ 1, 2, 3	Unclear/Unclear	No major imbalance Unclear: Baseline diet, smoking, LDL-c/HDL-c, blood pressure	Yes	Yes/Yes/Yes	Yes	Unclear	Unclear/Unclear/Unclear	N/A	Medium

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80. Whitlock RP, Crowther MA, Warkentin TE, et al. Warfarin cessation before cardiopulmonary bypass: lessons learned from a randomized controlled trial of oral vitamin K. Ann Thorac Surg 2007 Jul;84(1):103-8. [PMID: 17588394].

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Appendix D. Excluded Studies

Appendix D lists all of the studies that were excluded from this review, categorized by reason for exclusion and alphabetized.

Not Relevant Intervention(s)/Exposure(s) and Comparator(s)

Eligibility: Relevant dietary supplement VS. no dietary supplement (e.g. no treatment or placebo) OR Relevant dietary supplement VS. other relevant dietary supplement.

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Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. Homocysteine Lowering Trialists' Collaboration. BMJ 1998 Mar 21;316(7135):894-8. [PMID: 9569395].

Cholesterol-lowering margarines. Med Lett Drugs Ther 1999 Jun 18;41(1055):56-8. [PMID: 10436768].

Dietary supplements: (2) green tea. Pharmaceutical Journal 267 (7177) ()(pp 823), 2001 Date of Publication: 08 Dec 2001 2001;(7177):823

HMG-CoA reductase inhibitors (STATINS). Med Lett Drugs Ther 2001;43(1105):44-8.

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Not Relevant Study Design

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Appendix E. Data Extraction Forms

Appendix E outlines in detail all of the questions that were used in screening the literature and ultimately determined whether a study was included or excluded. Furthermore, all data extracted from each study are also listed in this appendix.

DSCI: Level 1, Broad Screen Form

Is this:

a systematic review or comparative primary study assessing the benefits or harms of dietary supplement use in a population of adults taking cardiovascular drugs

OR

a systematic review or primary study assessing the pharmacokinetics/dynamics of the shortlist of supplements relevant to Key Question 5?

- ❑ No
- ❑ Possibly/Yes

DSCI: Level 2, Abstract Screen Form

- *If the article meets at least one exclusion criterion (i.e., the record should be excluded) -SELECT ONLY THE FIRST RELEVANT EXCLUSION CRITERIA IN ORDER OF LIST.*
- If the article does not meet any of the exclusion criteria (i.e., it is eligible for inclusion) OR if it is unclear based on the title and abstract if certain criteria are met (i.e., full text required) - SELECT 'YES/POSSIBLY'.
- If eligibility is unclear based on need for content expertise - SELECT 'CONTENT EXPERTISE NEEDED' and briefly explain where guidance is needed. (CVD, DS, other with detail)

---

1. Does this report discuss the use of relevant dietary supplements[1]?

❑ No - no dietary supplement(s) (SUBMIT FORM)

❑ Yes/Possibly - at least one relevant dietary supplement or Unclear based on title abstract (Respond to question 2)

❑ No - non-relevant dietary supplement(s) only (please state) (SUBMIT FORM)

_____

2. Does this report describe a study which is potentially relevant for KQ 1-4?

❑ No (study design)-not a SR, experimental/observational comparative study with independent control group (i.e., narrative review, commentary or uncontrolled empirical study) (exclude)

❑ No (intervention/ctrl)-not comparing benefit/harms/PD/PK of relevant DS vs. relevant ctrl (see footnote 2) (exclude)

❑ No (population) - not in adult taking CV drugs in outpatient setting (see footnote 3)(exclude)

❑ Yes/Possibly (State: Study design; supplement(s); CV drug(s))

_____

❑ Unclear - need clinical content expertise (please specify: supplement, CV drug, other?)

❑ No (language) - Non-English SR or Exp/Obsv not in English, Chinese or German (state if probable SR or primary study; language)

_____

3. If you answered "NO" to question 2, does this study contain relevant information (e.g. clinical/SR studies providing indirect evidence: PK, PD) important for Introduction or Discussion sections? (non-consequential)

❑ No

❑ Yes/Possibly

DSCI: Level 3, Full Text Screening Form for Key Questions 1 to 4

PLEASE NOTE THE FOLLOWING:

If you have excluded a record for eligibility for KQ 1-4 (as stated with a response of 'No' to any of questions 1-5), please respond to the remaining unanswered questions 1-5 with 'NO RESPONSE - EXCLUDED IN OTHER QUESTION' and respond to question 6 accordingly. You must respond to all questions for each record.

1. Relevant INTERVENTION/EXPOSURE(S) and COMPARATOR(S) (see footnotes 1 & 2)**?**

- **Relevant dietary supplement VS. no dietary supplement** (e.g. no treatment or placebo) **OR**
- **Relevant dietary supplement VS. other relevant dietary supplement**

❑ Yes (Please specify [name] dietary supplement(s) - if many [e.g. review] state 'mixed')

_____

❑ No - no supplement or no appropriate comparator (EXCLUDE)

❑ Details present but content expertise requested (please describe)

_____

❑ NO RESPONSE - EXCLUDED IN OTHER QUESTION

❑ No - non-relevant supplement and/or comparator (please state) (EXCLUDE)

_____

2. Full study, subgroup results or regression analysis in relevant POPULATION for KQ 1-4**?**

- **Adults (majority ≥ 16 years old) taking one or more specific cardiovascular drugs or class of cardiovascular drugs commonly used in outpatient setting** (see footnote 3)

❑ Yes (Please state which CVD(s) or which class(es) of CVD)

_____

❑ No or unclear (specific CVD(s) or class(es) of CVDs not explicit) (EXCLUDE)

❑ Details available but content expertise requested (please describe)

❑ _____

❑ NO RESPONSE – EXCLUDED IN OTHER QUESTION

3. Relevant STUDY DESIGN?

- **Systematic review <u>meeting minimum eligibility requirements</u>** (see footnote 4) **OR**
- **Experimental or observational comparative study** (RCT, non-RCT, cohort, case-control, cross-sectional) **with independent (concurrent or historical) control group** including at least 5 participants.

❑ Yes - Systematic review meeting minimum criteria for review eligibility (see footnote 3)

❑ Yes - Experimental or observational comparative study with independent control and at least 5 participants

❑ No - likely a RELEVANT, THOROUGH (w.r.t. search methods) systematic review but does NOT meet minimum criteria for review eligibility (EXCLUDE)

❑ No - experimental study without independent control (before and after study)

❑ None of the above (EXCLUDE)

❑ NO RESPONSE - EXCLUDED IN OTHER QUESTION

4. Relevant OUTCOME(S) for at least one of Key questions 1-4**?**

- KQ 1: Clinical efficacy/effectivess cardiovascular outcomes
- KQ 2: Intermediate efficacy/effectivess cardiovascular outcomes
- KQ 3: Clinical or intermediate harms outcomes
- KQ 4: Pharmacokinetic/pharmacodynamic outcomes

Note: for list of relevant outcomes, please see review protocol

❑ Yes

❑ No (EXCLUDE)

❑ NO RESPONSE - EXCLUDED IN OTHER QUESTION

5. Relevant LANGUAGE?

- **SR** published in **English**
- **Experimental or observational comparative study** published in **English or German**

❑ Yes - SR in English

❑ Yes - Exp/Obs study in English

❑ Yes - Exp/Obs study in German

❑ No - SR in other language (please state which)

_____

❑ No - Exp/Obs study in other language (please state which)

_____

❑ NO RESPONSE - EXCLUDED IN OTHER QUESTION

6. Does this report include Mix of CVD drugs that are used by <80% of the population or the % of

patients using CVD drugs are not described? (Such studies will not be used in the evidence synthesis of the report--May 16)

❑ Yes (please describe)

_____

❑ No

DSCI: General Characteristics Form for Experimental Studies

Indicate NR if not reported and NA if not applicable. For percentages, just indicate the number without the percentage sign.

---

1. RefID: _____

2. Is subgroup data available?

Please see supplemental guidance for data extraction.
If the answer is yes, please also fill out a separate form for each subgroup for which data have been presented.

❑ Yes

3. If yes, **ONLY ANSWER IF THIS IS A <u>SUBGROUP FORM</u>:** Check the subgroup to which this form applies.

- ❑ Age >= 65
- ❑ Age >= 80
- ❑ Ethnicity
- ❑ Gender
- ❑ Healthy Adults
- ❑ Participants with disorders of the liver (e.g., hepatitis, cirrhosis)
- ❑ Diabetes
- ❑ Participants with disorders of the kidney (e.g., reduced GFR, end stage renal disease)
- ❑ CVD drug for non-CVD indication
- ❑ Genetic polymorphisms

4. If yes, **ONLY ANSWER IF THIS IS A <u>SUBGROUP FORM</u>:** Indicate the CHD risk level of the subgroup.

Please refer to supplemental guidance for data extraction.

- ❑ At low risk for CHD (0-1 risk factor)
- ❑ At moderate/moderately high risk for CHD (2+ risk factors)
- ❑ At high risk for CHD
- ❑ Mixed (please specify)

- ❑ Unclear

❑ No

5. Does the study contain subgroups of subjects with either low, moderate, or high CHD risk?

Please see supplemental guidance for data extraction.
If the answer is yes, please also fill out a separate form for each CHD risk level subgroup presented.

❑ Yes

6. If yes, **ONLY ANSWER IF THIS IS A <u>CHD RISK LEVEL SUBGROUP FORM</u>: Check the CHD risk subgroup to which this form applies.**

- ❑ At low risk for CHD (0-1 risk factor)
- ❑ At moderate/moderately high risk for CHD (2+ risk factors)
- ❑ At high risk for CHD

❑ No

7. Are any of the following presented as study-level covariates? (DO NOT ANSWER IF THIS IS A SUBGROUP FORM)

Please see supplemental guidance for data extraction.

- ❑ Age >= 65 years
- ❑ Age >=80 years
- ❑ Ethnicity
- ❑ Gender
- ❑ Healthy adults
- ❑ Participants with disorders of the liver (e.g. hepatitis, cirrhosis)
- ❑ Diabetes
- ❑ Participants with disorders of the kidney (e.g. reduced GFR, end stage renal disease)
- ❑ CVD drug for non-CVD indication
- ❑ Genetic polymorphisms
- ❑ None

8. Indicate the CHD risk level of the entire study population: (DO NOT ANSWER IF THIS IS A SUBGROUP FORM)

Please see supplemental guidance for data extraction.

- ❑ At low risk for CHD (0-1 risk factors)
- ❑ At moderate/moderately high risk for CHD (2+ risk factors)
- ❑ At high risk for CHD
- ❑ Mixed (please specify)
- ❑ Unclear

9. Author (Smith, JA): _____

10. Year of Publication _____

11. Ref IDs of Companions _____

12. Source of Funding (was the study supported by industry?)

Please see supplemental guidance for data extraction.

- ❑ Yes
- ❑ No
- ❑ Unclear

13. Region

- ❑ North America
- ❑ Central & South America
- ❑ Europe
- ❑ East Asia
- ❑ Rest of Asia
- ❑ Africa
- ❑ Australia/New Zealand
- ❑ Middle East
- ❑ Multiple regions (please describe)

  _____
- ❑ Other (please describe)

  _____
- ❑ Not reported

14. Setting

- ❑ General community
- ❑ Primary care
- ❑ Speciality clinic
- ❑ Mixed or other (please describe)

  _____
- ❑ Not reported

15. List of inclusion criteria

_____

16. List of Exclusion Criteria

_____

17. Brief Summary of Population (include important risk factors): E.g. Elderly diabetic subjects with angina.

18. Study Design

- ❑ Parallel randomized-controlled trial (RCT)
- ❑ Crossover RCT
- ❑ Pre-crossover RCT
- ❑ Controlled clinical trial (CCT)

19. Run-in Period (days): _____

20. Duration of Treatment (days) _____

21. Duration of Treatment in Period 2 (days) *FOR CROSSOVER TRIALS ONLY* _____

22. Wash-Out Period (days) *FOR CROSSOVER TRIALS ONLY* _____

23. Duration of Followup - measured from end of intervention (days) _____

24. Duration of Longest Followup (days) (i.e., the last followup point, which may include a long-term followup in the same study or a secondary publication)
Please refer to supplemental guidelines for data extraction _____

25. With respect to intention-to-treat, select the statement that best describes the method used in the study.

- ❑ Intention-to-treat analysis (all randomized or initially enrolled)
- ❑ Only subjects who received treatment at start of the study
- ❑ Only subjects with followup data (who completed the study)
- ❑ Other (please describe)

_____

- ❑ Unclear

❑ Not reported

26. Number screened (number of subjects screened initially using eligibility criteria)- NR if no data: _____

27. Number included (CCTs) or randomized _____

28. Number analyzed (number of subjects included in the analysis of results) _____

29. Was the number of dropouts or withdrawals reported?

- ❑ Yes (If yes, answer the next two questions below)

30. If yes, total number of dropouts or withdrawals:

Intervention Group 1 _____

Intervention Group 2 _____

Control Group _____

All Groups Combined _____

31. If yes, dropouts or withdrawals due to adverse events:

Intervention Group 1 _____

Intervention Group 2 _____

Control Group _____

All Groups Combined _____

❑ No

DETAILED POPULATION CHARACTERISTICS

AGE

Please see supplemental guidelines for data extraction and refer to formulas for calculating pooled means and SDs.

32. Pooled mean age (years) _____
33. Pooled age SD (years) _____
34. Pooled age SE (years) _____
35. Median age (years) _____
36. Age: IQR-low (years) _____
37. Age: IQR-high (years) _____
38. Age: lower 95% CI (years) _____
39. Age: upper 95% CI (years) _____
40. Age range (min-max) (years) _____

GENDER

41. Percentage of female subjects _____

ETHNICITY

42. Select the ethnicities that were included in the study, and provide percentages.
    - ❑ Caucasian _____
    - ❑ African-American _____
    - ❑ Hispanic _____
    - ❑ Asian _____
    - ❑ Native American _____
    - ❑ African _____
    - ❑ Other (please describe and provide percentage) _____
    - ❑ Not reported _____

MORBIDITIES

43. Indicate why subjects were taking CVD drug(s)
    - ❑ Cardiovascular indication
    - ❑ Non-cardiovascular indication(s) (please specify)
    - ❑ Both (please describe)

      _____
    - ❑ Other (please describe)

44. Did subjects have other comorbidities?

- ❑ Yes (please list)

_____

- ❑ No
- ❑ Not reported

OTHER CO-INTERVENTIONS

45. List of concomitant non-CVD medications taken by participants.

_____

46. Was a dietary modification intervention administered?

- ❑ Yes (please describe)

_____

- ❑ No
- ❑ Not reported

47. Was an exercise intervention administered?

- ❑ Yes (please describe)

_____

- ❑ No
- ❑ Not reported

48. Was any other type of lifestyle intervention administered?

- ❑ Yes (please describe)

_____

- ❑ No
- ❑ Not reported

DESCRIPTION OF CONTROL GROUP

49. What did the control group receive?

- ❑ Placebo. If the study provides further description of the placebo, please describe.

_____

- ❑ No treatment
- ❑ Another type of dietary supplement (please specify)

_____

DESCRIPTION OF INTERVENTION GROUP: DIETARY SUPPLEMENT(S)

50. Supplement (select one)

- ❑ Omega -3 (EPA, DHA or both)
- ❑ Fish oils/marine oils
- ❑ Magnesium
- ❑ Garlic

- ❑ Ginko biloba
- ❑ Ginseng
- ❑ Vitamin E
- ❑ Vitamin K
- ❑ Vitamin A
- ❑ Vitamin D
- ❑ Vitamin D + Calcium
- ❑ Hawthorn
- ❑ Echinacea
- ❑ Coenzyme Q10
- ❑ Red yeast rice
- ❑ Niacin
- ❑ Resveratrol

51. Latin or other names used in this study for the supplement (e.g., Crataegus oxyacantha for Hawthorn)

_____

52. Supplement Composition (e.g., % DHA + %EPA)

_____

53. Is purity of the supplement reported?

- ❑ Yes (please describe - Please see supplemental guidance)

_____

- ❑ No

54. Is the supplement licensed in the region used?

- ❑ Yes
- ❑ No
- ❑ Not reported

55. Does the paper report where the supplement was manufactured?

- ❑ Yes (please describe)

_____

- ❑ No

56. Have storage conditions (e.g., temperature) for the supplement been reported?

- ❑ Yes (please describe - Please see supplemental guidance)

_____

- ❑ No

56. Is the origin of the supplement reported (e.g. plant leaves)?

- ❑ Yes (please describe)

_____

- ❑ No

58. Administered dosage of the supplement (indicate units, e.g. IU/day or mg/day)

_____

59. What form was the supplement administered in?

- ❑ Capsule/Tablet
- ❑ Liquid
- ❑ Topical
- ❑ Mixed (please describe)

_____

- ❑ Other (please describe)
- ❑ _____
- ❑ Not reported

60. What subtype of the supplement was administered? (e.g., carotenoid for Vitamin A; salt-form such as citrate for magnesium)

_____

61. Are nutrient levels or biomarkers of the supplement reported (e.g., in blood or urine)?
Please see supplemental guidance

- ❑ Yes (please describe)

_____

- ❑ No

62. Is there a second intervention group?

- ❑ Yes (If yes, provide details of this supplement by answering the questions below.)

63. Supplement 2 (select one)

- ❑ Omega-3 (EPA, DHA or both)
- ❑ Fish oils/marine oils
- ❑ Magnesium
- ❑ Garlic
- ❑ Ginko biloba
- ❑ Ginseng
- ❑ Ginger
- ❑ Vitamin E
- ❑ Vitamin K
- ❑ Vitamin A
- ❑ Vitamin D
- ❑ Vitamin D + Calcium
- ❑ Hawthorn
- ❑ Echinacea
- ❑ Coenzyme Q10

- ❑ Red yeast rice
- ❑ Niacin
- ❑ Resveratrol

64. Latin or other names used in this study for supplement 2 (e.g., Crataegus oxyacantha for Hawthorn)

_____

65. Supplement 2 Composition (e.g., % DHA + %EPA)

_____

66. Is purity of supplement 2 reported?

- ❑ Yes (please describe - Please see supplemental guidance)

  _____
- ❑ No

67. Is supplement 2 licensed in the region used?

- ❑ Yes
- ❑ No
- ❑ Not reported

68. Does the paper report where supplement 2 was manufactured?

- ❑ Yes (please describe)

  _____
- ❑ No

69. Have storage conditions (e.g., temperature) for supplement 2 been reported?

- ❑ Yes (please describe - Please see supplemental guidance)

  _____
- ❑ No

70. Is the origin of supplement 2 reported (e.g. plant leaves)?

- ❑ Yes (please describe)

  _____
- ❑ No

71. Administered dosage of supplement 2 (indicate units, e.g. IU/day or mg/day)

72. What form was supplement 2 administered in?

- ❑ Capsule/Tablet
- ❑ Liquid
- ❑ Topical
- ❑ Mixed (please describe)

_____

- ❑ Other (please describe)
- ❑ _____
- ❑ Not reported

73. What subtype of supplement 2 was administered? (e.g., carotenoid for Vitamin A; salt-form such as citrate for magnesium)

_____

74. Are nutrient levels or biomarkers of supplement 2 reported (e.g., in blood or urine)? *Please see supplemental guidance*

- ❑ Yes (please describe)

_____

- ❑ No

❑ No

CVD DRUG(S) (Control and Intervention Groups)

75. Brand name of CVD drug (used by >80% of study sample)

_____

76. Chemical name of CVD drug (used by >80% of study sample):

_____

77. Drug Category/Class:

- ❑ b-blockers
- ❑ Calcium channel blockers
- ❑ Alpha-blockers
- ❑ Antiarrhythmics
- ❑ Inotropics
- ❑ Anticoagulants

- ❑ Antiplatelets
- ❑ RAAS Antagonist: ACEI
- ❑ RAAS Antagonist: ARB
- ❑ RAAS Antagonist: Renin Inhibitor
- ❑ RAAS Antagonist: Aldosterone-Receptor Antagonist
- ❑ Antilipidemic: HMG Co-A Reductase Inhibitor
- ❑ Antilipidemic: Fibrate
- ❑ Antilipidemic: Bile acid sequestrant
- ❑ Antilipidemic: Other
- ❑ Diuretic: Thiazide/Thiazide-like
- ❑ Diuretic: Loop
- ❑ Diuretic: Other
- ❑ Vasodilator: Central/Direct
- ❑ Vasodilator: Nitrates/PDE-5 Inhibitors
- ❑ Vasodilator: Other

78. Mode of administration of CVD drug:

- ❑ Oral
- ❑ Parenteral
- ❑ Patch
- ❑ Other (please indicate)

_____

79. Starting administered dosage of CVD drug (mg/day): _____

80. Final administered dosage of CVD drug (mg/day): _____

81. Mean administered dosage of CVD drug (mg/day): _____

82. Is the duration of treatment with this CVD drug the same as the supplement?

- ❑ Yes
- ❑ No
- ❑ Unclear

83. Was a second CVD drug administered to > 80% of the study sample?

- ❑ Yes (If yes, provide details of this drug by answering the questions below)

84. Brand name of CVD drug 2 (used by >80% of study sample)

85. Chemical name of CVD drug 2 (used by >80% of study sample):

86. Drug Category/Class (for CVD drug 2):

- ❑ b-blockers
- ❑ Calcium channel blockers
- ❑ Alpha-blockers
- ❑ Antiarrhythmics
- ❑ Inotropics
- ❑ Anticoagulants
- ❑ Antiplatelets
- ❑ RAAS Antagonist: ACEI
- ❑ RAAS Antagonist: ARB
- ❑ RAAS Antagonist: Renin Inhibitor
- ❑ RAAS Antagonist: Aldosterone-Receptor Antagonist
- ❑ Antilipidemic: HMG Co-A Reductase Inhibitor
- ❑ Antilipidemic: Fibrate
- ❑ Antilipidemic: Bile acid sequestrant
- ❑ Antilipidemic: Other
- ❑ Diuretic: Thiazide/Thiazide-like
- ❑ Diuretic: Loop
- ❑ Diuretic: Other
- ❑ Vasodilator: Central/Direct
- ❑ Vasodilator: Nitrates/PDE-5 Inhibitors
- ❑ Vasodilator: Other

87. Mode of administration of CVD drug 2:

- ❑ Oral
- ❑ Parenteral
- ❑ Patch
- ❑ Other (please indicate)

88. Starting administered dosage of CVD drug 2 (mg/day):

89. Final administered dosage of CVD drug 2 (mg/day): _____

90. Mean administered dosage of CVD drug 2 (mg/day): _____

91. Is the duration of treatment with this CVD drug 2 the same as the supplement?

- ❑ Yes
- ❑ No
- ❑ Unclear

❑ No

92. Was a third CVD drug administered to > 80% of the study sample?

❑ Yes (If yes, provide details of this drug by answering the questions below)

93. Brand name of CVD drug 3 (used by >80% of study sample)

_____

94. Chemical name of CVD drug 3 (used by >80% of study sample):

_____

95. Drug Category/Class (for CVD drug 3):

- ❑ b-blockers
- ❑ Calcium channel blockers
- ❑ Alpha-blockers
- ❑ Antiarrhythmics
- ❑ Inotropics
- ❑ Anticoagulants
- ❑ Antiplatelets
- ❑ RAAS Antagonist: ACEI
- ❑ RAAS Antagonist: ARB
- ❑ RAAS Antagonist: Renin Inhibitor
- ❑ RAAS Antagonist: Aldosterone-Receptor Antagonist
- ❑ Antilipidemic: HMG Co-A Reductase Inhibitor
- ❑ Antilipidemic: Fibrate
- ❑ Antilipidemic: Bile acid sequestrant
- ❑ Antilipidemic: Other
- ❑ Diuretic: Thiazide/Thiazide-like
- ❑ Diuretic: Loop
- ❑ Diuretic: Other
- ❑ Vasodilator: Central/Direct

- ❑ Vasodilator: Nitrates/PDE-5 Inhibitors
- ❑ Vasodilator: Other

96. Mode of administration of CVD drug 3:

- ❑ Oral
- ❑ Parenteral
- ❑ Patch
- ❑ Other (please indicate)

_____

97. Starting administered dosage of CVD drug 3 (mg/day): _____

98. Final administered dosage of CVD drug 3 (mg/day): _____

99. Mean administered dosage of CVD drug 3 (mg/day): _____

100. Is the duration of treatment with this CVD drug 3 the same as the supplement?

- ❑ Yes
- ❑ No
- ❑ Unclear

❑ No

101. **OTHER COMMENTS**

DSCI: Statistical Interaction Form

RefID: _____

1. Does the study examine statistical interaction between cardiovascular drug and supplement?

❑ Yes. If yes, describe method and conclusions.

_____

_____

_____

_____

❑ No

2. Does the study include the following groups:
1. supplement only,
2. drug only,

3. supplement and drug combined and
4. a common control group

❑ Yes. If yes, answer the following questions.

Indicate Outcome	
Supplement Only Group (n/N):	
Drug Only Group (n/N):	
Supplement + Drug Group (n/N):	
Control Group (n/N):	
RR (Supplement vs. Control):	
RR (Drug vs. Control)	
RR (Supplement + Drug vs. Control)	
OR (Supplement vs. Control)	
OR (Drug vs. Control)	
OR (Supplement + Drug vs. Control)	

❑ No

DSCI: Continuous Outcomes Form

PLEASE READ BEFORE STARTING:

- N(included) refers to either the number of participants <u>included</u> in a group of a controlled-clinical trial (CCT) or the number of participants <u>randomized</u> in a group in a randomized-controlled trial (RCT).

-Please do not indicate any units (including percentage signs) in the table cells. Numbers may be inputted to 2 decimal places, if that is the precision level reported in a study.

Select the outcome:
Complete a separate form for each relevant outcome reported in the study.

❑ Activated partial thromboplastin time (aPTT)

❑ Aggregation time

❑ Alanine transaminase (ALT)

❑ Anemia: Other parameter (e.g. ferritin, MCV, MCH). Specify outcome.

❑ Anemia: Serum iron level

❑ Ankle-brachial index

❑ Area under the concentration curve (AUC)

❑ Arterial blood pressure

- ❑ Aspartate aminotransferase (AST)
- ❑ Bioavailability (F)
- ❑ Bleeding time
- ❑ Blood urea nitrogen (BUN)
- ❑ Body mass index (BMI)
- ❑ Carotid intima-media thickness (IMT), as measured by Doppler ultrasound
- ❑ Change in 10-year Framingham risk profile
- ❑ Clearance (Cl: volume of blood cleared of drug per unit time)
- ❑ Clotting time
- ❑ Concentration of drug transport proteins
- ❑ Coronary/cerebral arterial calcification score
- ❑ C-reactive protein (CRP)
- ❑ Creatinine
- ❑ Diastolic blood pressure (DBP)
- ❑ Ejection fraction
- ❑ Elimination rate constant (Kel) or Fraction of drug eliminated per unit time
- ❑ Fasting blood glucose
- ❑ Glomerular filtration rate (GFR)
- ❑ Glycosylated hemoglobin (HbA1c)
- ❑ Half-life (T1/2)
- ❑ High-density lipoprotein cholesterol (HDL-C)
- ❑ International normalized ratio (INR)
- ❑ Leukpenia: WBC count
- ❑ Lipoprotein A (Lp(a))
- ❑ Low-density lipoprotein cholesterol (LDL-C)
- ❑ Lymphopenia: Lymphocyte level
- ❑ Maximum concentration (Cmax)
- ❑ Neutropenia: Neutrophilic granulocyte count (ANC)
- ❑ Non-HDL-C
- ❑ Platelet aggregability. Specify outcome.
- ❑ Platelet count
- ❑ Prothrombin time (PT)
- ❑ Quality of Life
- ❑ Ratio of BUN/creatinine
- ❑ Systolic blood pressure (SBP)
- ❑ Time to reach maximum concentration (Tmax)
- ❑ Total cholesterol

- ❑ Triglycerides
- ❑ Volume of distribution (Vd)
- ❑ Other. Please specify.

_____

Definition of outcome if reported:

_____

Other description of outcome:

_____

Units _____

Length of longest randomized followup (from baseline)
(days-- each week = 7 days; each month = 30 days) _____

INDIVIDUAL GROUP DATA (Longest randomized post treatment followup)

Group 1 (select one)

- ❑ Coenzyme Q10. Other details if needed (e.g. dose). _____
- ❑ Echinacea. Other details if needed (e.g. dose). _____
- ❑ Fish/marine oils. Other details if needed (e.g. dose). _____
- ❑ Garlic. Other details if needed (e.g. dose). _____
- ❑ Ginger. Other details if needed (e.g. dose). _____
- ❑ Gingko biloba. Other details if needed (e.g. dose). _____
- ❑ Ginseng. Other details if needed (e.g. dose). _____
- ❑ Hawthorn. Other details if needed (e.g. dose). _____
- ❑ Magnesium. Other details if needed (e.g. dose). _____
- ❑ Niacin. Other details if needed (e.g. dose). _____
- ❑ Omega-3 (EPA, DHA, or both). Other details if needed (e.g. dose). _____
- ❑ Red yeast rice. Other details if needed (e.g. dose). _____
- ❑ Resveratrol. Other details if needed (e.g. dose). _____
- ❑ Vitamin A. Other details if needed (e.g. dose). _____
- ❑ Vitamin D. Other details if needed (e.g. dose). _____
- ❑ Vitamin D + Calcium. Other details if needed (e.g. dose). _____
- ❑ Vitamin E. Other details if needed (e.g. dose). _____
- ❑ Vitamin K. Other details if needed (e.g. dose). _____

- ❑ Other supplement (intervention group). Please specify. _____
- ❑ CONTROL: No treatment (aside from CVD drug)
- ❑ CONTROL: Placebo
- ❑ CONTROL: Other dietary supplement. Please specify. _____

N(included)		Mean		Median	
N(analyzed)		SD		IQR – low	
		SE		IQR – high	

Mean Change from baseline		% change in mean		Difference in median OR Difference in median %	
SD		SD		IQR – lower	
SE		SE		IQR - upper	
95% CI – lower		95% CI – lower		95% CI – lower	
95% CI – upper		95% CI – upper		95% CI – upper	
p-value		p-value		p-value	

Group 2 (select one)

- ❑ Coenzyme Q10. Other details if needed (e.g. dose). _____
- ❑ Echinacea. Other details if needed (e.g. dose). _____
- ❑ Fish/marine oils. Other details if needed (e.g. dose). _____
- ❑ Garlic. Other details if needed (e.g. dose). _____
- ❑ Ginger. Other details if needed (e.g. dose). _____
- ❑ Gingko biloba. Other details if needed (e.g. dose). _____
- ❑ Ginseng. Other details if needed (e.g. dose). _____
- ❑ Hawthorn. Other details if needed (e.g. dose). _____
- ❑ Magnesium. Other details if needed (e.g. dose). _____
- ❑ Niacin. Other details if needed (e.g. dose). _____
- ❑ Omega-3 (EPA, DHA, or both). Other details if needed (e.g. dose). _____
- ❑ Red yeast rice. Other details if needed (e.g. dose). _____
- ❑ Resveratrol. Other details if needed (e.g. dose). _____
- ❑ Vitamin A. Other details if needed (e.g. dose). _____
- ❑ Vitamin D. Other details if needed (e.g. dose). _____
- ❑ Vitamin D + Calcium. Other details if needed (e.g. dose). _____
- ❑ Vitamin E. Other details if needed (e.g. dose). _____
- ❑ Vitamin K. Other details if needed (e.g. dose). _____
- ❑ Other supplement (intervention group). Please specify. _____

- ❑ CONTROL: No treatment (aside from CVD drug)
- ❑ CONTROL: Placebo
- ❑ CONTROL: Other dietary supplement. Please specify. _____

N(included)		Mean		Median	
N(analyzed)		SD		IQR – low	
		SE		IQR – high	

Mean Change from baseline		% change in mean		Difference in median OR Difference in median %	
SD		SD		IQR – lower	
SE		SE		IQR - upper	
95% CI – lower		95% CI – lower		95% CI – lower	
95% CI – upper		95% CI – upper		95% CI – upper	
p-value		p-value		p-value	

Group 3 (select one)

- ❑ Coenzyme Q10. Other details if needed (e.g. dose). _____
- ❑ Echinacea. Other details if needed (e.g. dose). _____
- ❑ Fish/marine oils. Other details if needed (e.g. dose). _____
- ❑ Garlic. Other details if needed (e.g. dose). _____
- ❑ Ginger. Other details if needed (e.g. dose). _____
- ❑ Gingko biloba. Other details if needed (e.g. dose). _____
- ❑ Ginseng. Other details if needed (e.g. dose). _____
- ❑ Hawthorn. Other details if needed (e.g. dose). _____
- ❑ Magnesium. Other details if needed (e.g. dose). _____
- ❑ Niacin. Other details if needed (e.g. dose). _____
- ❑ Omega-3 (EPA, DHA, or both). Other details if needed (e.g. dose). _____
- ❑ Red yeast rice. Other details if needed (e.g. dose). _____
- ❑ Resveratrol. Other details if needed (e.g. dose). _____
- ❑ Vitamin A. Other details if needed (e.g. dose). _____
- ❑ Vitamin D. Other details if needed (e.g. dose). _____
- ❑ Vitamin D + Calcium. Other details if needed (e.g. dose). _____
- ❑ Vitamin E. Other details if needed (e.g. dose). _____
- ❑ Vitamin K. Other details if needed (e.g. dose). _____

- ❑ Other supplement (intervention group). Please specify. _____
- ❑ CONTROL: No treatment (aside from CVD drug)
- ❑ CONTROL: Placebo
- ❑ CONTROL: Other dietary supplement. Please specify. _____

N(included)	_____	Mean	_____	Median	_____
N(analyzed)	_____	SD	_____	IQR – low	_____
		SE	_____	IQR – high	_____

Mean Change from baseline	_____	% change in mean	_____	Difference in median OR Difference in median %	_____
SD	_____	SD	_____	IQR – lower	_____
SE	_____	SE	_____	IQR - upper	_____
95% CI – lower	_____	95% CI – lower	_____	95% CI – lower	_____
95% CI – upper	_____	95% CI – upper	_____	95% CI – upper	_____
p-value	_____	p-value	_____	p-value	_____

Group 4 (select one)

- ❑ Coenzyme Q10. Other details if needed (e.g. dose). _____
- ❑ Echinacea. Other details if needed (e.g. dose). _____
- ❑ Fish/marine oils. Other details if needed (e.g. dose). _____
- ❑ Garlic. Other details if needed (e.g. dose). _____
- ❑ Ginger. Other details if needed (e.g. dose). _____
- ❑ Gingko biloba. Other details if needed (e.g. dose). _____
- ❑ Ginseng. Other details if needed (e.g. dose). _____
- ❑ Hawthorn. Other details if needed (e.g. dose). _____
- ❑ Magnesium. Other details if needed (e.g. dose). _____
- ❑ Niacin. Other details if needed (e.g. dose). _____
- ❑ Omega-3 (EPA, DHA, or both). Other details if needed (e.g. dose). _____
- ❑ Red yeast rice. Other details if needed (e.g. dose). _____
- ❑ Resveratrol. Other details if needed (e.g. dose). _____
- ❑ Vitamin A. Other details if needed (e.g. dose). _____
- ❑ Vitamin D. Other details if needed (e.g. dose). _____
- ❑ Vitamin D + Calcium. Other details if needed (e.g. dose). _____
- ❑ Vitamin E. Other details if needed (e.g. dose). _____
- ❑ Vitamin K. Other details if needed (e.g. dose). _____

❑ Other supplement (intervention group). Please specify. _____

❑ CONTROL: No treatment (aside from CVD drug)

❑ CONTROL: Placebo

❑ CONTROL: Other dietary supplement. Please specify. _____

N(included)		Mean		Median	
N(analyzed)		SD		IQR – low	
		SE		IQR – high	

Mean Change from baseline		% change in mean		Difference in median OR Difference in median %	
SD		SD		IQR – lower	
SE		SE		IQR - upper	
95% CI – lower		95% CI – lower		95% CI – lower	
95% CI – upper		95% CI – upper		95% CI – upper	
p-value		p-value		p-value	

ESTIMATES OF GROUP DIFFERENCES

Has an adjusted analysis been presented for this outcome?

❑ Yes. If yes, list the variables that were adjusted for. _____

❑ No

Crude Estimates

Group 1 (select one)	***VS.***	***Group 2 (select one)***	*Other details if needed (e.g., dose)*
❑ Coenzyme Q10		❑ Coenzyme Q10	
❑ Echinacea		❑ Echinacea	
❑ Fish/marine oils		❑ Fish/marine oils	
❑ Garlic		❑ Garlic	
❑ Ginger		❑ Ginger	
❑ Gingko biloba		❑ Gingko biloba	
❑ Ginseng		❑ Ginseng	
❑ Hawthorn		❑ Hawthorn	
❑ Magnesium		❑ Magnesium	
❑ Niacin		❑ Niacin	

❑ Omega-3 (EPA / DHA / both)	❑ Omega-3 (EPA / DHA / both)	
❑ Red yeast rice	❑ Red yeast rice	
❑ Resveratrol	❑ Resveratrol	
❑ Vitamin A	❑ Vitamin A	
❑ Vitamin D	❑ Vitamin D	
❑ Vitamin D + Calcium	❑ Vitamin D + Calcium	
❑ Vitamin E	❑ Vitamin E	
❑ Vitamin K	❑ Vitamin K	
❑ Other supplement (intervention group)	❑ Other supplement (intervention group)	
❑ CONTROL: No treatment (aside from CVD drug)	❑ CONTROL: No treatment (aside from CVD drug)	
❑ CONTROL: Placebo	❑ CONTROL: Placebo	
❑ CONTROL: Other dietary supplement. Please specify.	❑ CONTROL: Other dietary supplement. Please specify.	

Crude Difference in Means		Crude Difference in % mean change		Crude difference in medians OR crude difference in median %	
SD		SD		IQR – low	
SE		SE		IQR – high	
95% CI - lower		95% CI – lower		95% CI – lower	
95% CI - upper		95% CI – upper		95% CI – upper	
p-value		p-value		p-value	

Group 1 (select one) VS.	***Group 3 (select one)***	*Other details if needed (e.g., dose)*
❑ Coenzyme Q10	❑ Coenzyme Q10	
❑ Echinacea	❑ Echinacea	
❑ Fish/marine oils	❑ Fish/marine oils	
❑ Garlic	❑ Garlic	
❑ Ginger	❑ Ginger	
❑ Gingko biloba	❑ Gingko biloba	
❑ Ginseng	❑ Ginseng	
❑ Hawthorn	❑ Hawthorn	
❑ Magnesium	❑ Magnesium	
❑ Niacin	❑ Niacin	

❑ Omega-3 (EPA / DHA / both)	❑ Omega-3 (EPA / DHA / both)	
❑ Red yeast rice	❑ Red yeast rice	
❑ Resveratrol	❑ Resveratrol	
❑ Vitamin A	❑ Vitamin A	
❑ Vitamin D	❑ Vitamin D	
❑ Vitamin D + Calcium	❑ Vitamin D + Calcium	
❑ Vitamin E	❑ Vitamin E	
❑ Vitamin K	❑ Vitamin K	
❑ Other supplement (intervention group)	❑ Other supplement (intervention group)	
❑ CONTROL: No treatment (aside from CVD drug)	❑ CONTROL: No treatment (aside from CVD drug)	
❑ CONTROL: Placebo	❑ CONTROL: Placebo	
❑ CONTROL: Other dietary supplement. Please specify.	❑ CONTROL: Other dietary supplement. Please specify.	

Crude Difference in Means		Crude Difference in % mean change		Crude difference in medians OR crude difference in median %	
SD		SD		IQR – low	
SE		SE		IQR – high	
95% CI - lower		95% CI – lower		95% CI – lower	
95% CI - upper		95% CI – upper		95% CI – upper	
p-value		p-value		p-value	

Group 2 (select one) VS.	***Group 3 (select one)***	*Other details if needed (e.g., dose)*
❑ Coenzyme Q10	❑ Coenzyme Q10	
❑ Echinacea	❑ Echinacea	
❑ Fish/marine oils	❑ Fish/marine oils	
❑ Garlic	❑ Garlic	
❑ Ginger	❑ Ginger	
❑ Gingko biloba	❑ Gingko biloba	
❑ Ginseng	❑ Ginseng	
❑ Hawthorn	❑ Hawthorn	
❑ Magnesium	❑ Magnesium	
❑ Niacin	❑ Niacin	

❑ Omega-3 (EPA / DHA / both)	❑ Omega-3 (EPA / DHA / both)	
❑ Red yeast rice	❑ Red yeast rice	
❑ Resveratrol	❑ Resveratrol	
❑ Vitamin A	❑ Vitamin A	
❑ Vitamin D	❑ Vitamin D	
❑ Vitamin D + Calcium	❑ Vitamin D + Calcium	
❑ Vitamin E	❑ Vitamin E	
❑ Vitamin K	❑ Vitamin K	
❑ Other supplement (intervention group)	❑ Other supplement (intervention group)	
❑ CONTROL: No treatment (aside from CVD drug)	❑ CONTROL: No treatment (aside from CVD drug)	
❑ CONTROL: Placebo	❑ CONTROL: Placebo	
❑ CONTROL: Other dietary supplement. Please specify.	❑ CONTROL: Other dietary supplement. Please specify.	

Crude Difference in Means		Crude Difference in % mean change		Crude difference in medians OR crude difference in median %	
SD		SD		IQR – low	
SE		SE		IQR – high	
95% CI - lower		95% CI – lower		95% CI – lower	
95% CI - upper		95% CI – upper		95% CI – upper	
p-value		p-value		p-value	

Adjusted Estimates

Group 1 (select one)	***VS.***	***Group 2 (select one)***	*Other details if needed (e.g., dose)*
❑ Coenzyme Q10		❑ Coenzyme Q10	
❑ Echinacea		❑ Echinacea	
❑ Fish/marine oils		❑ Fish/marine oils	
❑ Garlic		❑ Garlic	
❑ Ginger		❑ Ginger	
❑ Gingko biloba		❑ Gingko biloba	
❑ Ginseng		❑ Ginseng	
❑ Hawthorn		❑ Hawthorn	

❑	Magnesium	❑	Magnesium	
❑	Niacin	❑	Niacin	
❑	Omega-3 (EPA / DHA / both)	❑	Omega-3 (EPA / DHA / both)	
❑	Red yeast rice	❑	Red yeast rice	
❑	Resveratrol	❑	Resveratrol	
❑	Vitamin A	❑	Vitamin A	
❑	Vitamin D	❑	Vitamin D	
❑	Vitamin D + Calcium	❑	Vitamin D + Calcium	
❑	Vitamin E	❑	Vitamin E	
❑	Vitamin K	❑	Vitamin K	
❑	Other supplement (intervention group)	❑	Other supplement (intervention group)	
❑	CONTROL: No treatment (aside from CVD drug)	❑	CONTROL: No treatment (aside from CVD drug)	
❑	CONTROL: Placebo	❑	CONTROL: Placebo	
❑	CONTROL: Other dietary supplement. Please specify.	❑	CONTROL: Other dietary supplement. Please specify.	

Adjusted Difference in Means		Adjusted Difference in % mean change		Adjusted difference in medians OR adjusted difference in median %	
SD		SD		IQR – low	
SE		SE		IQR – high	
95% CI - lower		95% CI – lower		95% CI – lower	
95% CI - upper		95% CI – upper		95% CI – upper	
p-value		p-value		p-value	

Group 1 (select one)	***VS.***	***Group 3 (select one)***	*Other details if needed (e.g., dose)*
❑	Coenzyme Q10	❑ Coenzyme Q10	
❑	Echinacea	❑ Echinacea	
❑	Fish/marine oils	❑ Fish/marine oils	
❑	Garlic	❑ Garlic	
❑	Ginger	❑ Ginger	
❑	Gingko biloba	❑ Gingko biloba	
❑	Ginseng	❑ Ginseng	
❑	Hawthorn	❑ Hawthorn	

❑	Magnesium	❑	Magnesium	
❑	Niacin	❑	Niacin	
❑	Omega-3 (EPA / DHA / both)	❑	Omega-3 (EPA / DHA / both)	
❑	Red yeast rice	❑	Red yeast rice	
❑	Resveratrol	❑	Resveratrol	
❑	Vitamin A	❑	Vitamin A	
❑	Vitamin D	❑	Vitamin D	
❑	Vitamin D + Calcium	❑	Vitamin D + Calcium	
❑	Vitamin E	❑	Vitamin E	
❑	Vitamin K	❑	Vitamin K	
❑	Other supplement (intervention group)	❑	Other supplement (intervention group)	
❑	CONTROL: No treatment (aside from CVD drug)	❑	CONTROL: No treatment (aside from CVD drug)	
❑	CONTROL: Placebo	❑	CONTROL: Placebo	
❑	CONTROL: Other dietary supplement. Please specify.	❑	CONTROL: Other dietary supplement. Please specify.	

Adjusted Difference in Means		Adjusted Difference in % mean change		Adjusted difference in medians OR adjusted difference in median %	
SD		SD		IQR – low	
SE		SE		IQR – high	
95% CI - lower		95% CI – lower		95% CI – lower	
95% CI - upper		95% CI – upper		95% CI – upper	
p-value		p-value		p-value	

Group 2 (select one) VS.		***Group 3 (select one)***		*Other details if needed (e.g., dose)*
❑	Coenzyme Q10	❑	Coenzyme Q10	
❑	Echinacea	❑	Echinacea	
❑	Fish/marine oils	❑	Fish/marine oils	
❑	Garlic	❑	Garlic	
❑	Ginger	❑	Ginger	
❑	Gingko biloba	❑	Gingko biloba	
❑	Ginseng	❑	Ginseng	

❑	Hawthorn	❑	Hawthorn	
❑	Magnesium	❑	Magnesium	
❑	Niacin	❑	Niacin	
❑	Omega-3 (EPA / DHA / both)	❑	Omega-3 (EPA / DHA / both)	
❑	Red yeast rice	❑	Red yeast rice	
❑	Resveratrol	❑	Resveratrol	
❑	Vitamin A	❑	Vitamin A	
❑	Vitamin D	❑	Vitamin D	
❑	Vitamin D + Calcium	❑	Vitamin D + Calcium	
❑	Vitamin E	❑	Vitamin E	
❑	Vitamin K	❑	Vitamin K	
❑	Other supplement (intervention group)	❑	Other supplement (intervention group)	
❑	CONTROL: No treatment (aside from CVD drug)	❑	CONTROL: No treatment (aside from CVD drug)	
❑	CONTROL: Placebo	❑	CONTROL: Placebo	
❑	CONTROL: Other dietary supplement. Please specify.	❑	CONTROL: Other dietary supplement. Please specify.	

Adjusted Difference in Means		Adjusted Difference in % mean change		Adjusted difference in medians OR adjusted difference in median %	
SD		SD		IQR – low	
SE		SE		IQR – high	
95% CI - lower		95% CI – lower		95% CI – lower	
95% CI - upper		95% CI – upper		95% CI – upper	
p-value		p-value		p-value	

Comments

DSCI: Dichotomous Outcomes Form

PLEASE READ BEFORE STARTING:

- N(included) refers to either the number of participants <u>included</u> in a group of a controlled-clinical trial (CCT) or the number of participants randomized in a group in a randomized-controlled trial (RCT).

- Please do not indicate any units (including percentage signs) in the table cells. Numbers may be inputted to 2 decimal places, if that is the precision level reported in a study.

RefID: _____

Select the outcome:
Complete a separate form for each relevant outcome reported in the study.

- ❑ Abdominal aortic aneurysm
- ❑ Activated partial thromboplastin time (aPTT) (above/below threshold). Indicate threshold. _____
- ❑ Acute coronary syndrome
- ❑ Adherence to prescribed cardiovascular drug regimen
- ❑ Adverse Event Other (other than neurologic, allergic, gastrointestinal, bleeding, withdrawal due to adverse event). Please specify. _____
- ❑ Alanine transaminase (ALT) (Raised)
- ❑ Allergic reactions (All types)
- ❑ Amputation
- ❑ Analphylaxis/allergic shock
- ❑ Anemia
- ❑ Ankle-brachial index (above/below threshold). Indicate threshold. _____
- ❑ Arrhythmia (All types)
- ❑ Aspartate aminotransferase (AST) (Raised)
- ❑ Asthma
- ❑ Atrial fibrillation
- ❑ Bleeding time (above/below threshold). Indicate threshold. _____
- ❑ Blood urea nitrogen (BUN) (Raised)
- ❑ Carotid artery disease (not measured by IMT or Doppler). Please specify. _____
- ❑ Carotid dilation/stenting
- ❑ Carotid intima-media thickness (IMT), as measured by Doppler ultrasound (above/below threshold). Indicate threshold. _____
- ❑ Claudication (pain walking)

- ❑ Clotting time (above/below threshold). Indicate threshold. _____
- ❑ Composite cardiovascular outcome (e.g. MI + Stroke + Vascular Death). Please specify. _____
- ❑ Congestive heart/cardiac failure
- ❑ Constipation
- ❑ Coronary artery bypass graft (CABG)
- ❑ Coronary/cerebral arterial calcification score (above/below threshold). Indicate threshold. _____
- ❑ C-reactive protein (above/below threshold). Indicate threshold. _____
- ❑ Creatinine (Raised)
- ❑ Diarrhea
- ❑ Ejection fraction (above/below threshold). Indicate threshold. _____
- ❑ Electrocardiographic (ECG) measurements or 24 hr ambulatory ECG/Holter monitoring. Please specify outcome. _____
- ❑ Fasting blood glucose (above/below threshold). Indicate threshold. _____
- ❑ Flatulence
- ❑ Gastrointestinal (GI) adverse events (All types)
- ❑ Gastrointestinal bleed (All types)
- ❑ Gastrointestinal bleed (Lower)
- ❑ Gastrointestinal bleed (Upper)
- ❑ Glycosylated hemoglobin (above/below threshold). Indicate threshold. _____
- ❑ Heart block
- ❑ Heartburn
- ❑ Hematologic abnormality. Please specify outcome. _____
- ❑ Hematuria
- ❑ Hemorrhagic stroke
- ❑ High-density lipoprotein cholesterol (HDL-C) (above/below threshold). Indicate threshold. _____
- ❑ Hospitilization
- ❑ Hospitilization (Prolonged)
- ❑ Hypertension (HTN), new or worsening (e.g. need for change in therapy)
- ❑ Hypotension
- ❑ Internal bleed (All types)
- ❑ International normalized ratio (INR) (above/below threshold). Indicate threshold.
- ❑ Intracerebral bleed
- ❑ Intracranial bleed
- ❑ Intraventricular bleed

- ❑ Leukopenia
- ❑ Limb thrombosis/Leg ischemia
- ❑ Lipoprotein A (Lp(a)) (above/below threshold). Indicate threshold. _____
- ❑ Liver damage/hepatitis
- ❑ Low-density lipoprotein cholesterol (LDL-C) (above/below threshold). Indicate threshold. _____
- ❑ Lymphopenia
- ❑ Mesenteric ischemia
- ❑ Metabolic syndrome
- ❑ Mortality (All-cause)
- ❑ Myocardial infarction (All types)
- ❑ Myocardial infarction (Fatal)
- ❑ Myocardial infarction (Non-fatal)
- ❑ Nausea
- ❑ Nausea and Vomiting (combined)
- ❑ Neurologic adverse events (All types)
- ❑ Neuropathy
- ❑ Neutropenia
- ❑ Non-HDL-C. specify threshold _____
- ❑ Obesity
- ❑ Organ toxicity
- ❑ Percutaneous transluminal coronary angioplasty (PTCA/PCI/stenting)
- ❑ Peripheral revascularization (+/- stent)
- ❑ Platelet aggregability (above/below threshold). Indicate outcome and threshold. _____
- ❑ Prolonged QT interval
- ❑ Prothrombin time (above/below threshold). Indicate threshold. _____
- ❑ Quality of Life
- ❑ Rash
- ❑ Ratio of BUN/creatinine (Raised)
- ❑ Renal replacement therapy (e.g. dialysis)
- ❑ Seizures
- ❑ Serious adverse events (composite outcome)
- ❑ Stroke (All types)
- ❑ Stroke (Fatal)
- ❑ Subretinal hemorrhage
- ❑ Sudden death

- ❑ Syncope
- ❑ Thrombocytopenia
- ❑ Thrombotic/Ischemic stroke
- ❑ Total cholesterol (above/below threshold). Indicate threshold. _____
- ❑ Transient ischemic attack (TIA)
- ❑ Triglycerides (above/below threshold). Indicate threshold. _____
- ❑ Unstable angina
- ❑ Valve replacement
- ❑ Valvular disease. Please specify outcome. _____
- ❑ Vascular death
- ❑ Ventricular fibrillation
- ❑ Ventricular tachycardia
- ❑ Vomiting
- ❑ Withdrawal due to adverse events
- ❑ Other. Please specify _____

Definition of outcome if reported:

_____

Other description of outcome:

_____

Length of longest randomized followup (from baseline) (days)
(1 week = 7 days and 1 month = 30 days) _____

INDIVIDUAL GROUP DATA (Longest randomized post treatment followup)

Group 1 (select one)

- ❑ Coenzyme Q10. Other details if needed (e.g. dose). _____
- ❑ Echinacea. Other details if needed (e.g. dose). _____
- ❑ Fish/marine oils. Other details if needed (e.g. dose). _____
- ❑ Garlic. Other details if needed (e.g. dose). _____
- ❑ Ginger. Other details if needed (e.g. dose). _____
- ❑ Gingko biloba. Other details if needed (e.g. dose). _____
- ❑ Ginseng. Other details if needed (e.g. dose). _____
- ❑ Hawthorn. Other details if needed (e.g. dose). _____
- ❑ Magnesium. Other details if needed (e.g. dose). _____
- ❑ Niacin. Other details if needed (e.g. dose). _____
- ❑ Omega-3 (EPA, DHA, or both). Other details if needed (e.g. dose). _____

- ❑ Red yeast rice. Other details if needed (e.g. dose). _____
- ❑ Resveratrol. Other details if needed (e.g. dose). _____
- ❑ Vitamin A. Other details if needed (e.g. dose). _____
- ❑ Vitamin D. Other details if needed (e.g. dose). _____
- ❑ Vitamin D + Calcium. Other details if needed (e.g. dose). _____
- ❑ Vitamin E. Other details if needed (e.g. dose). _____
- ❑ Vitamin K. Other details if needed (e.g. dose). _____
- ❑ Other supplement (intervention group). Please specify. _____
- ❑ CONTROL: No treatment (aside from CVD drug)
- ❑ CONTROL: Placebo
- ❑ CONTROL: Other dietary supplement. Please specify. _____

N(included) _____

N(analyzed) _____

n1(subjects free of event at baseline) _____

n2(subjects with event) _____

n3(events) _____

n2/N(analyzed) (%)
Complete only if reported in the study (do not calculate). Only report the percentage number (without the % sign). _____

Event Risk (n2/n1)(%)
Complete only if reported in the study (do not calculate). Only report the percentage number (without the % sign). _____

Group 2 (select one)

- ❑ Coenzyme Q10. Other details if needed (e.g. dose). _____
- ❑ Echinacea. Other details if needed (e.g. dose). _____
- ❑ Fish/marine oils. Other details if needed (e.g. dose). _____
- ❑ Garlic. Other details if needed (e.g. dose). _____
- ❑ Ginger. Other details if needed (e.g. dose). _____
- ❑ Gingko biloba. Other details if needed (e.g. dose). _____
- ❑ Ginseng. Other details if needed (e.g. dose). _____
- ❑ Hawthorn. Other details if needed (e.g. dose). _____
- ❑ Magnesium. Other details if needed (e.g. dose). _____
- ❑ Niacin. Other details if needed (e.g. dose). _____
- ❑ Omega-3 (EPA, DHA, or both). Other details if needed (e.g. dose). _____
- ❑ Red yeast rice. Other details if needed (e.g. dose). _____

- ❑ Resveratrol. Other details if needed (e.g. dose). _____
- ❑ Vitamin A. Other details if needed (e.g. dose). _____
- ❑ Vitamin D. Other details if needed (e.g. dose). _____
- ❑ Vitamin D + Calcium. Other details if needed (e.g. dose). _____
- ❑ Vitamin E. Other details if needed (e.g. dose). _____
- ❑ Vitamin K. Other details if needed (e.g. dose). _____
- ❑ Other supplement (intervention group). Please specify. _____
- ❑ CONTROL: No treatment (aside from CVD drug)
- ❑ CONTROL: Placebo
- ❑ CONTROL: Other dietary supplement. Please specify. _____

N(included) _____

N(analyzed) _____

n1(subjects free of event at baseline) _____

n2(subjects with event) _____

n3(events) _____

n2/N(analyzed) (%)
Complete only if reported in the study (do not calculate).
Only report the percentage number (without the % sign). _____

Event Risk (n2/n1)(%)
Complete only if reported in the study (do not calculate).
Only report the percentage number (without the % sign). _____

Group 3 (select one)

- ❑ Coenzyme Q10. Other details if needed (e.g. dose). _____
- ❑ Echinacea. Other details if needed (e.g. dose). _____
- ❑ Fish/marine oils. Other details if needed (e.g. dose). _____
- ❑ Garlic. Other details if needed (e.g. dose). _____
- ❑ Ginger. Other details if needed (e.g. dose). _____
- ❑ Gingko biloba. Other details if needed (e.g. dose). _____
- ❑ Ginseng. Other details if needed (e.g. dose). _____
- ❑ Hawthorn. Other details if needed (e.g. dose). _____
- ❑ Magnesium. Other details if needed (e.g. dose). _____
- ❑ Niacin. Other details if needed (e.g. dose). _____
- ❑ Omega-3 (EPA, DHA, or both). Other details if needed (e.g. dose). _____
- ❑ Red yeast rice. Other details if needed (e.g. dose). _____
- ❑ Resveratrol. Other details if needed (e.g. dose). _____
- ❑ Vitamin A. Other details if needed (e.g. dose). _____
- ❑ Vitamin D. Other details if needed (e.g. dose). _____
- ❑ Vitamin D + Calcium. Other details if needed (e.g. dose). _____
- ❑ Vitamin E. Other details if needed (e.g. dose). _____

- ❑ Vitamin K. Other details if needed (e.g. dose). _____
- ❑ Other supplement (intervention group). Please specify. _____
- ❑ CONTROL: No treatment (aside from CVD drug)
- ❑ CONTROL: Placebo
- ❑ CONTROL: Other dietary supplement. Please specify. _____

N(included) _____

N(analyzed) _____

n1(subjects free of event at baseline) _____

n2(subjects with event) _____

n3(events) _____

n2/N(analyzed) (%)
Complete only if reported in the study (do not calculate).
Only report the percentage number (without the % sign). _____

Event Risk (n2/n1)(%)
Complete only if reported in the study (do not calculate).
Only report the percentage number (without the % sign). _____

Group 4 (select one)

- ❑ Coenzyme Q10. Other details if needed (e.g. dose). _____
- ❑ Echinacea. Other details if needed (e.g. dose). _____
- ❑ Fish/marine oils. Other details if needed (e.g. dose). _____
- ❑ Garlic. Other details if needed (e.g. dose). _____
- ❑ Ginger. Other details if needed (e.g. dose). _____
- ❑ Gingko biloba. Other details if needed (e.g. dose). _____
- ❑ Ginseng. Other details if needed (e.g. dose). _____
- ❑ Hawthorn. Other details if needed (e.g. dose). _____
- ❑ Magnesium. Other details if needed (e.g. dose). _____
- ❑ Niacin. Other details if needed (e.g. dose). _____
- ❑ Omega-3 (EPA, DHA, or both). Other details if needed (e.g. dose). _____
- ❑ Red yeast rice. Other details if needed (e.g. dose). _____
- ❑ Resveratrol. Other details if needed (e.g. dose). _____
- ❑ Vitamin A. Other details if needed (e.g. dose). _____
- ❑ Vitamin D. Other details if needed (e.g. dose). _____
- ❑ Vitamin D + Calcium. Other details if needed (e.g. dose). _____
- ❑ Vitamin E. Other details if needed (e.g. dose). _____
- ❑ Vitamin K. Other details if needed (e.g. dose). _____
- ❑ Other supplement (intervention group). Please specify. _____
- ❑ CONTROL: No treatment (aside from CVD drug)

❑ CONTROL: Placebo

❑ CONTROL: Other dietary supplement. Please specify. _____

N(included) _____

N(analyzed) _____

n1(subjects free of event at baseline) _____

n2(subjects with event) _____

n3(events) _____

n2/N(analyzed) (%)
Complete only if reported in the study (do not calculate).
Only report the percentage number (without the % sign). _____

Event Risk (n2/n1)(%)
Complete only if reported in the study (do not calculate).
Only report the percentage number (without the % sign). _____

ESTIMATES OF GROUP DIFFERENCES

Group 1 (select one)	***VS.***	***Group 2 (select one)***	*Other details if needed (e.g., dose)*
❑	Coenzyme Q10	❑ Coenzyme Q10	
❑	Echinacea	❑ Echinacea	
❑	Fish/marine oils	❑ Fish/marine oils	
❑	Garlic	❑ Garlic	
❑	Ginger	❑ Ginger	
❑	Gingko biloba	❑ Gingko biloba	
❑	Ginseng	❑ Ginseng	
❑	Hawthorn	❑ Hawthorn	
❑	Magnesium	❑ Magnesium	
❑	Niacin	❑ Niacin	
❑	Omega-3 (EPA / DHA / both)	❑ Omega-3 (EPA / DHA / both)	
❑	Red yeast rice	❑ Red yeast rice	
❑	Resveratrol	❑ Resveratrol	
❑	Vitamin A	❑ Vitamin A	
❑	Vitamin D	❑ Vitamin D	
❑	Vitamin D + Calcium	❑ Vitamin D + Calcium	
❑	Vitamin E	❑ Vitamin E	
❑	Vitamin K	❑ Vitamin K	
❑	Other supplement	❑ Other supplement	

(intervention group)		(intervention group)	
❑ CONTROL: No treatment (aside from CVD drug)		❑ CONTROL: No treatment (aside from CVD drug)	
❑ CONTROL: Placebo		❑ CONTROL: Placebo	
❑ CONTROL: Other dietary supplement. Please specify.		❑ CONTROL: Other dietary supplement. Please specify.	

Crude Event Risk Ratio		Adjusted Event Risk Ratio	
95% CI - lower		95% CI – lower	
95% CI - upper		95% CI – upper	
p-value		p-value	
Crude Event Odds Ratio		Adjusted Event Odds Ratio	
95% CI – lower		95% CI – lower	
95% CI – upper		95% CI – upper	
p-value		p-value	

Group 1 (select one) VS.	***Group 3 (select one)***	*Other details if needed (e.g., dose)*
❑ Coenzyme Q10	❑ Coenzyme Q10	
❑ Echinacea	❑ Echinacea	
❑ Fish/marine oils	❑ Fish/marine oils	
❑ Garlic	❑ Garlic	
❑ Ginger	❑ Ginger	
❑ Gingko biloba	❑ Gingko biloba	
❑ Ginseng	❑ Ginseng	
❑ Hawthorn	❑ Hawthorn	
❑ Magnesium	❑ Magnesium	
❑ Niacin	❑ Niacin	
❑ Omega-3 (EPA / DHA / both)	❑ Omega-3 (EPA / DHA / both)	
❑ Red yeast rice	❑ Red yeast rice	
❑ Resveratrol	❑ Resveratrol	
❑ Vitamin A	❑ Vitamin A	
❑ Vitamin D	❑ Vitamin D	
❑ Vitamin D + Calcium	❑ Vitamin D + Calcium	
❑ Vitamin E	❑ Vitamin E	
❑ Vitamin K	❑ Vitamin K	

❑ Other supplement (intervention group)	❑ Other supplement (intervention group)	
❑ CONTROL: No treatment (aside from CVD drug)	❑ CONTROL: No treatment (aside from CVD drug)	
❑ CONTROL: Placebo	❑ CONTROL: Placebo	
❑ CONTROL: Other dietary supplement. Please specify.	❑ CONTROL: Other dietary supplement. Please specify.	

Crude Event Risk Ratio		Adjusted Event Risk Ratio	
95% CI - lower		95% CI – lower	
95% CI - upper		95% CI – upper	
p-value		p-value	
Crude Event Odds Ratio		Adjusted Event Odds Ratio	
95% CI – lower		95% CI – lower	
95% CI – upper		95% CI – upper	
p-value		p-value	

Group 2 (select one) VS.	***Group 3 (select one)***	*Other details if needed (e.g., dose)*
❑ Coenzyme Q10	❑ Coenzyme Q10	
❑ Echinacea	❑ Echinacea	
❑ Fish/marine oils	❑ Fish/marine oils	
❑ Garlic	❑ Garlic	
❑ Ginger	❑ Ginger	
❑ Gingko biloba	❑ Gingko biloba	
❑ Ginseng	❑ Ginseng	
❑ Hawthorn	❑ Hawthorn	
❑ Magnesium	❑ Magnesium	
❑ Niacin	❑ Niacin	
❑ Omega-3 (EPA / DHA / both)	❑ Omega-3 (EPA / DHA / both)	
❑ Red yeast rice	❑ Red yeast rice	
❑ Resveratrol	❑ Resveratrol	
❑ Vitamin A	❑ Vitamin A	
❑ Vitamin D	❑ Vitamin D	
❑ Vitamin D + Calcium	❑ Vitamin D + Calcium	

❑	Vitamin E	❑	Vitamin E
❑	Vitamin K	❑	Vitamin K
❑	Other supplement (intervention group)	❑	Other supplement (intervention group)
❑	CONTROL: No treatment (aside from CVD drug)	❑	CONTROL: No treatment (aside from CVD drug)
❑	CONTROL: Placebo	❑	CONTROL: Placebo
❑	CONTROL: Other dietary supplement. Please specify.	❑	CONTROL: Other dietary supplement. Please specify.

Crude Event Risk Ratio		Adjusted Event Risk Ratio	
95% CI - lower		95% CI – lower	
95% CI - upper		95% CI – upper	
p-value		p-value	
Crude Event Odds Ratio		Adjusted Event Odds Ratio	
95% CI – lower		95% CI – lower	
95% CI – upper		95% CI – upper	
p-value		p-value	

COMMENTS

DSCI: Continuous Outcomes Form for Cross-Over Studies

PLEASE READ BEFORE STARTING:

- N(included) refers to either the number of participants <u>included</u> in a group of a controlled-clinical trial (CCT) or the number of participants <u>randomized</u> in a group in a randomized-controlled trial (RCT).

- Please do not indicate any units (including percentage signs) in the table cells. Numbers may be inputted to 2 decimal places, if that is the precision level reported in a study.

RefID: _____

1. Select the outcome:
Complete a separate form for each relevant outcome reported in the study.

- ❑ Activated partial thromboplastin time (aPTT)
- ❑ Aggregation time
- ❑ Alanine transaminase (ALT)

- ❑ Anemia: Other parameter (e.g. ferritin, MCV, MCH). Specify outcome. _____
- ❑ Anemia: Serum iron level
- ❑ Ankle-brachial index
- ❑ Area under the concentration curve (AUC)
- ❑ Arterial blood pressure
- ❑ Aspartate aminotransferase (AST)
- ❑ Bioavailability (F)
- ❑ Bleeding time
- ❑ Blood urea nitrogen (BUN)
- ❑ Body mass index (BMI)
- ❑ Carotid intima-media thickness (IMT), as measured by Doppler ultrasound
- ❑ Change in 10-year Framingham risk profile
- ❑ Clearance (Cl: volume of blood cleared of drug per unit time)
- ❑ Clotting time
- ❑ Concentration of drug transport proteins
- ❑ Coronary/cerebral arterial calcification score
- ❑ C-reactive protein (CRP)
- ❑ Creatinine
- ❑ Diastolic blood pressure (DBP)
- ❑ Ejection fraction
- ❑ Elimination rate constant (Kel) or Fraction of drug eliminated per unit time
- ❑ Fasting blood glucose
- ❑ Glomerular filtration rate (GFR)
- ❑ Glycosylated hemoglobin (HbA1c)
- ❑ Half-life (T1/2)
- ❑ High-density lipoprotein cholesterol (HDL-C)
- ❑ International normalized ratio (INR)
- ❑ Leukpenia: WBC count
- ❑ Lipoprotein A (Lp(a))
- ❑ Low-density lipoprotein cholesterol (LDL-C)
- ❑ Lymphopenia: Lymphocyte level
- ❑ Maximum concentration (Cmax)
- ❑ Neutropenia: Neutrophilic granulocyte count (ANC)
- ❑ Non-HDL-C
- ❑ Platelet aggregability. Specify outcome. _____
- ❑ Platelet count
- ❑ Prothrombin time (PT)

- ❑ Quality of Life
- ❑ Ratio of BUN/creatinine
- ❑ Systolic blood pressure (SBP)
- ❑ Time to reach maximum concentration (Tmax)
- ❑ Total cholesterol
- ❑ Triglycerides
- ❑ Volume of distribution (Vd)
- ❑ Other. Please specify.

_____

2. Definition of outcome (optional – if reported):

_____

3. Other description of outcome:

_____

4. Units: _____

5. Pooled Data (Pre + Post cross over)

Pooled Supplement (select one)

❑ Coenzyme Q10	❑ Ginseng	❑ Resveratrol
❑ Echinacea	❑ Hawthorn	❑ Vitamin A
❑ Fish/marine oils	❑ Magnesium	❑ Vitamin D
❑ Garlic	❑ Niacin	❑ Vitamin D + Calcium
❑ Ginger	❑ Omega-3 (EPA, DHA, or both)	❑ Vitamin E
❑ Gingko biloba	❑ Red yeast rice	❑ Vitamin K

❑ Other supplement (intervention group). Please specify. _____

N(included)	_____	Mean Change	_____	% change in mean	_____
N(analyzed)	_____	SD	_____	SD	_____
Mean	_____	SE	_____	SE	_____
SD	_____	95% CI – lower	_____	95% CI – lower	_____
SE	_____	95% CI – upper	_____	95% CI – upper	_____
		p-value	_____	p-value	_____

Pooled Control (select one)

- ❑ No treatment (aside from CVD drug)
- ❑ Placebo
- ❑ Other dietary supplement. Please specify. _____

N(included)	_____	Mean Change	_____	% change in mean	_____
N(analyzed)	_____	SD	_____	SD	_____
Mean	_____	SE	_____	SE	_____
SD	_____	95% CI – lower	_____	95% CI – lower	_____
SE	_____	95% CI – upper	_____	95% CI – upper	_____
		p-value	_____	p-value	_____

ESTIMATES OF GROUP DIFFERENCES

6. Has an adjusted analysis been presented for this outcome?
   - ❑ Yes. If yes, list the variables that were adjusted for. _____
   - ❑ No

7. Mean between group differences: Crude estimates

Supplement *(select one)* ***VS.***

- ❑ Coenzyme Q10
- ❑ Echinacea
- ❑ Fish/marine oils
- ❑ Garlic
- ❑ Ginger
- ❑ Gingko biloba
- ❑ Ginseng
- ❑ Hawthorn
- ❑ Magnesium
- ❑ Niacin
- ❑ Omega-3 (EPA / DHA / both)
- ❑ Red yeast rice
- ❑ Resveratrol
- ❑ Vitamin A

Control *(select one)*

- ❑ No treatment (aside from CVD drug)
- ❑ Placebo
- ❑ Other dietary supplement. Please specify. _____

- ❑ Vitamin D
- ❑ Vitamin D + Calcium
- ❑ Vitamin E
- ❑ Vitamin K
- ❑ Other. Please specify.

_____

Crude Difference in Means[+]	_____	Crude Difference in % mean change[+]	_____	Crude mean ratio[+]*	_____
SD	_____	SD	_____	SD	_____
SE	_____	SE	_____	SE	_____
95% CI - lower	_____	95% CI – lower	_____	95% CI – lower	_____
95% CI - upper	_____	95% CI – upper	_____	95% CI – upper	_____
p-value	_____	p-value	_____	p-value	_____

[+] Pre + post cross over
* Mean(treatment)/Mean(control) *Indicate as a ratio, not a fraction.*

8. Mean between group differences: Adjusted estimates

Supplement *(select one)* ***VS.***

- ❑ Coenzyme Q10
- ❑ Echinacea
- ❑ Fish/marine oils
- ❑ Garlic
- ❑ Ginger
- ❑ Gingko biloba
- ❑ Ginseng
- ❑ Hawthorn
- ❑ Magnesium
- ❑ Niacin
- ❑ Omega-3 (EPA / DHA / both)
- ❑ Red yeast rice
- ❑ Resveratrol
- ❑ Vitamin A
- ❑ Vitamin D
- ❑ Vitamin D + Calcium

Control *(select one)*

- ❑ No treatment (aside from CVD drug)
- ❑ Placebo
- ❑ Other dietary supplement. Please specify. _____

- ❑ Vitamin E
- ❑ Vitamin K
- ❑ Other. Please specify.

_____

Adjusted Difference in Means[+]	_____	Adjusted Difference in % mean change[+]	_____	Adjusted mean ratio[+]*	_____
SD	_____	SD	_____	SD	_____
SE	_____	SE	_____	SE	_____
95% CI - lower	_____	95% CI – lower	_____	95% CI – lower	_____
95% CI - upper	_____	95% CI – upper	_____	95% CI – upper	_____
p-value	_____	p-value	_____	p-value	_____

[+] Pre + post cross over
* Mean(treatment)/Mean(control) *Indicate as a ratio, not a fraction.*

9. Do the measures of dispersion (SE/SD/95%CI) reported for this outcome include within patient differences?

- ❑ Yes _____
- ❑ No
- ❑ Unclear

COMMENTS

DSCI: Dichotomous Outcomes Form for Cross-Over Studies

PLEASE READ BEFORE STARTING:

- N(included) refers to either the number of participants <u>included</u> in a group of a controlled-clinical trial (CCT) or the number of participants <u>randomized</u> in a group in a randomized-controlled trial (RCT).

-Please do not indicate any units (including percentage signs) in the table cells. Numbers may be inputted to 2 decimal places, if that is the precision level reported in a study.

RefID: _____

1. Select the outcome:
Complete a separate form for each relevant outcome reported in the study.

- ❑ Abdominal aortic aneurysm
- ❑ Activated partial thromboplastin time (aPTT) (above/below _____

threshold). Indicate threshold. _____

- ❑ Acute coronary syndrome
- ❑ Adherence to prescribed cardiovascular drug regimen
- ❑ Adverse Event Other (other than neurologic, allergic, gastrointestinal, bleeding, withdrawal due to adverse event). Please specify. _____
- ❑ Alanine transaminase (ALT) (Raised)
- ❑ Allergic reactions (All types)
- ❑ Amputation
- ❑ Analphylaxis/allergic shock
- ❑ Anemia
- ❑ Ankle-brachial index (above/below threshold). Indicate threshold.
- ❑ Arrhythmia (All types)
- ❑ Aspartate aminotransferase (AST) (Raised)
- ❑ Asthma
- ❑ Atrial fibrillation
- ❑ Bleeding time (above/below threshold). Indicate threshold.
- ❑ Blood urea nitrogen (BUN) (Raised)
- ❑ Carotid artery disease (not measured by IMT or Doppler). Please specify. _____
- ❑ Carotid dilation/stenting
- ❑ Carotid intima-media thickness (IMT), as measured by Doppler ultrasound (above/below threshold). Indicate threshold. _____
- ❑ Claudication (pain walking)
- ❑ Clotting time (above/below threshold). Indicate threshold.
- ❑ Composite cardiovascular outcome (e.g. MI + Stroke + Vascular Death). Please specify. _____
- ❑ Congestive heart/cardiac failure
- ❑ Constipation
- ❑ Coronary artery bypass graft (CABG)
- ❑ Coronary/cerebral arterial calcification score (above/below threshold). Indicate threshold. _____
- ❑ C-reactive protein (above/below threshold). Indicate threshold. _____
- ❑ Creatinine (Raised)
- ❑ Diarrhea
- ❑ Ejection fraction (above/below threshold). Indicate threshold. _____
- ❑ Electrocardiographic (ECG) measurements or 24 hr ambulatory ECG/Holter monitoring. Please specify outcome. _____
- ❑ Fasting blood glucose (above/below threshold). Indicate threshold. _____
- ❑ Flatulence

- ❑ Gastrointestinal (GI) adverse events (All types)
- ❑ Gastrointestinal bleed (All types)
- ❑ Gastrointestinal bleed (Lower)
- ❑ Gastrointestinal bleed (Upper)
- ❑ Glycosylated hemoglobin (above/below threshold). Indicate threshold.
- ❑ Heart block
- ❑ Heartburn
- ❑ Hematologic abnormality. Please specify outcome. _____
- ❑ Hematuria
- ❑ Hemorrhagic stroke
- ❑ High-density lipoprotein cholesterol (HDL-C) (above/below threshold). Indicate threshold. _____
- ❑ Hospitilization
- ❑ Hospitilization (Prolonged)
- ❑ Hypertension (HTN), new or worsening (e.g. need for change in therapy)
- ❑ Hypotension
- ❑ Internal bleed (All types)
- ❑ International normalized ratio (INR) (above/below threshold). Indicate threshold.
- ❑ Intracerebral bleed
- ❑ Intracranial bleed
- ❑ Intraventricular bleed
- ❑ Leukopenia
- ❑ Limb thrombosis/Leg ischemia
- ❑ Lipoprotein A (Lp(a)) (above/below threshold). Indicate threshold. _____
- ❑ Liver damage/hepatitis
- ❑ Low-density lipoprotein cholesterol (LDL-C) (above/below threshold). Indicate threshold. _____
- ❑ Lymphopenia
- ❑ Mesenteric ischemia
- ❑ Metabolic syndrome
- ❑ Mortality (All-cause)
- ❑ Myocardial infarction (All types)
- ❑ Myocardial infarction (Fatal)
- ❑ Myocardial infarction (Non-fatal)
- ❑ Nausea
- ❑ Nausea and Vomiting (combined)

- ❑ Neurologic adverse events (All types)
- ❑ Neuropathy
- ❑ Neutropenia
- ❑ Non-HDL-C. specify threshold _____
- ❑ Obesity
- ❑ Organ toxicity
- ❑ Percutaneous transluminal coronary angioplasty (PTCA/PCI/stenting)
- ❑ Peripheral revascularization (+/- stent)
- ❑ Platelet aggregability (above/below threshold). Indicate outcome and threshold. _____
- ❑ Prolonged QT interval
- ❑ Prothrombin time (above/below threshold). Indicate threshold. _____
- ❑ Quality of Life
- ❑ Rash
- ❑ Ratio of BUN/creatinine (Raised)
- ❑ Renal replacement therapy (e.g. dialysis)
- ❑ Seizures
- ❑ Serious adverse events (composite outcome)
- ❑ Stroke (All types)
- ❑ Stroke (Fatal)
- ❑ Subretinal hemorrhage
- ❑ Sudden death
- ❑ Syncope
- ❑ Thrombocytopenia
- ❑ Thrombotic/Ischemic stroke
- ❑ Total cholesterol (above/below threshold). Indicate threshold. _____
- ❑ Transient ischemic attack (TIA)
- ❑ Triglycerides (above/below threshold). Indicate threshold. _____
- ❑ Unstable angina
- ❑ Valve replacement
- ❑ Valvular disease. Please specify outcome. _____
- ❑ Vascular death
- ❑ Ventricular fibrillation
- ❑ Ventricular tachycardia
- ❑ Vomiting
- ❑ Withdrawal due to adverse events
- ❑ Other. Please specify _____

2. Definition of outcome if reported:

_____

3. Other description of outcome:

_____

4. Pooled Data (Pre + Post cross over)

Pooled Supplement (select one)

❑ Coenzyme Q10	❑ Ginseng	❑ Resveratrol
❑ Echinacea	❑ Hawthorn	❑ Vitamin A
❑ Fish/marine oils	❑ Magnesium	❑ Vitamin D
❑ Garlic	❑ Niacin	❑ Vitamin D + Calcium
❑ Ginger	❑ Omega-3 (EPA, DHA, or both)	❑ Vitamin E
❑ Gingko biloba	❑ Red yeast rice	❑ Vitamin K

❑ Other supplement (intervention group). Please specify. _____

N(included)	_____
N(analyzed)	_____
n1(subjects free of event at baseline)	_____
n2(subjects with event)	_____
n3(events)	_____
n2/N(analyzed) (%) *Complete only if reported in the study (do not calculate). Only report the percentage number (without the % sign).*	_____
Event Risk (n2/n1)(%) *Complete only if reported in the study (do not calculate). Only report the percentage number (without the % sign).*	_____

Pooled Control (select one)

❑ No treatment (aside from CVD drug)

❑ Placebo

❑ Other dietary supplement. Please specify.

_____

N(included) _____

N(analyzed) _____

n1(subjects free of event at baseline) _____

n2(subjects with event) _____

n3(events) _____

n2/N(analyzed) (%)
Complete only if reported in the study (do not calculate). Only report the percentage number (without the % sign). _____

Event Risk (n2/n1)(%)
Complete only if reported in the study (do not calculate). Only report the percentage number (without the % sign). _____

ESTIMATES OF GROUP DIFFERENCES

5. Has an adjusted analysis been presented for this outcome?

- ❑ Yes. If yes, list the variables that were adjusted for. _____
- ❑ No

6. Pre + Post cross over: Mean between group comparisons

Supplement *(select one)* ***VS.***	***Control*** *(select one)*
❑ Coenzyme Q10	❑ No treatment (aside from CVD drug)
❑ Echinacea	❑ Placebo
❑ Fish/marine oils	❑ Other dietary supplement. Please specify. _____
❑ Garlic	
❑ Ginger	
❑ Gingko biloba	
❑ Ginseng	
❑ Hawthorn	
❑ Magnesium	
❑ Niacin	
❑ Omega-3 (EPA / DHA / both)	
❑ Red yeast rice	
❑ Resveratrol	
❑ Vitamin A	
❑ Vitamin D	
❑ Vitamin D + Calcium	
❑ Vitamin E	

- ❑ Vitamin K
- ❑ Other. Please specify.

_____

Crude Event Risk Ratio	_____	Adjusted Event Risk Ratio	_____
95% CI - lower	_____	95% CI – lower	_____
95% CI - upper	_____	95% CI – upper	_____
p-value	_____	p-value	_____
Crude Event Odds Ratio	_____	Adjusted Event Odds Ratio	_____
95% CI – lower	_____	95% CI – lower	_____
95% CI – upper	_____	95% CI – upper	_____
p-value	_____	p-value	_____

COMMENTS

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