AHRQ Comparative Effectiveness Review Surveillance Program

CER #51:
Dietary Supplements in Adults Taking Cardiovascular Drugs

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Surveillance Report:
April, 2013

Key Findings:

- A small number of new studies were identified on the interaction between omega-3 fatty acids, both over-the-counter and prescription-grade, on the effects of statins, clopidogrel, and aspirin. All of the original conclusions regarding omega-3 fatty acids remain valid.
- One new study was found on the interaction between a resveratrol-containing supplement and angiotensin converting enzyme inhibitors and angiotensin II receptor blockers; however all of the conclusions regarding resveratrol also remained valid.

Summary Decision

This CER's priority for updating is **Low**

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Dietary Supplements in Adults Taking Cardiovascular Drugs

1. Introduction

Comparative Effectiveness Review (CER) #51, Dietary Supplements in Adults Taking Cardiovascular Drugs, was released in April 2012.[1] It was therefore due for a surveillance assessment in October, 2012. At that time, we contacted experts involved in the original CER and subject matter experts to get their opinions as to whether the conclusions had changed and the report needed to be updated. We also conducted an update electronic literature search. Every month since the CER's original release, we received any FDA updates on the included treatments and tests.

2. Methods

2.1 Literature Searches

Using the search strategy employed for the original report, we conducted a limited literature search of Medline for the years January 2011-November 29, 2012. This search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and seven specialty journals (American Journal of Cardiology, American Journal of Clinical Nutrition, Atherosclerosis, British Journal of Clinical Pharmacology, Circulation: Cardiovascular Quality and Outcomes, Journal of Clinical Pharmacology, and Thrombosis Research). The specialty journals were those most highly represented among the references for the original report. Appendix A includes the search methodology for this topic.

2.2 Study selection

In general we used the same inclusion and exclusion criteria as the original CER.

2.3 Expert Opinion

We shared the conclusions of the original report with 15 experts in the field (including the original project leader, all original technical expert panel (TEP) members, key informants, and peer reviewers for their assessment of the need to update the report and their recommendations of any relevant new studies; 9 subject matter experts responded, including the project lead. Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative signals

After abstracting the study conditions and findings for each new included study into an evidence table, we assessed whether the new findings provided a signal according to the Ottawa

Method and/or the RAND Method, suggesting the need for an update. The criteria are listed in the table below.[2, 3]

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

2.5 Compilation of Findings and Conclusions

For this assessment, we constructed a summary table that included the key questions, the original conclusions, and the findings of the new literature search, the expert assessments, and any FDA reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.

- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

The literature search identified 132 titles. After title and abstract review, 123 titles were rejected because they did not address the key questions. The remaining 9 journal articles went on for further review. In addition to the searches, we also reference-mined articles that met inclusion criteria as well as non-systematic reviews identified by the literature searches but found no other articles. Twenty-one additional articles were reviewed at the suggestion of the experts

Thus, through literature searches and expert recommendations, 30 articles went on to full text review. Of these, 23 articles were rejected because they were non-systematic reviews or did not address a key question. Thus, 7 articles were abstracted into an evidence table (Appendix B).[4-10]

The FDA MedWatch, Health Canada, and MHRA UK searches identified one FDA notification of relevance. This notification pertained to a prescription form of a dietary supplement (omega-3 fatty acids) that was approved after the release of the original report.

3.2 Expert Opinion

The eight reviewers were in agreement that new evidence that might change a conclusion did not exist for most of the dietary supplements. The exceptions are as follows.

Two reviewers cited newly published or ongoing studies on the impact of interactions between omega-3 fatty acids and statins on intermediate cardiovascular outcomes. Miller cited the GO-FISH Trial by his research group, which found that omega -3 fatty acids increased albumin excretion in patients with Type 2 diabetes taking ARBs or ACE inhibitors.[7] Chung cited completed and ongoing studies of the effects of new prescription omega-3 fatty acids on lipid status in patients with normal or elevated triglycerides who were taking statins: none of the completed studies changed the conclusions.

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update, and qualitative signals.

Table 1: Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Key Question 1. Clinical cardiovascular effectiveness/ efficacy outcomes (e.g., mortality and specific cardiovascular or cerebrovascular conditions such as myocardial infarction and stroke)?				
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.	No new studies were identified.	No information found	5 reviewers stated the conclusion is still supported by the evidence. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
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.	No new studies were identified.	No information found	5 reviewers stated the conclusion is still supported by the evidence. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Magnesium In a crossover trial of oral magnesium aspartate or placebo administered daily for 8 weeks to 40 hypertensive patients with no comorbidities on therapeutic doses of beta-blockers, a single event of myocardial infarction was noted.	No new studies were identified.	No information found	Four reviewers stated the conclusion is still supported by the evidence. One reviewer said (and we corroborated) that the study referred to in this conclusion did not report this adverse event. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Omega-3 Fatty Acids In three short-term efficacy trials of omega-3 fatty acid and statin coadministration, effects on mortality and arrhythmia were insignificant.	No new studies were identified.	No information found	5 reviewers stated the conclusion is still supported by the evidence. Although two reviewers cited potentially relevant studies,	Original conclusion is still valid and this portion of the original report

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
acids with aspirin, warfarin, and fenofibrate had no significant effects on mortality or 10-year risk. 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 provided insufficient evidence on the outcome of acute myocardial infarction.			3 reviewers said they did not know.	
Vitamin E An efficacy trial of vitamin E plus aspirin versus aspirin alone in patients with previous neurologic deficit provided insufficient evidence with sparse events of stroke and transient ischemic attack.	No new studies were identified.	No information found	3 reviewers stated the conclusion is still supported by the evidence. Four reviewers said they did not know. One reviewer cited a study but this study did not address the key question (no interaction with CVD drugs assessed).	Original conclusion is still valid and this portion of the original report does not need updating
Vitamin K One 6-month efficacy trial in 70 selected groups of patients with unstable international normalized ratios (INRs) anticoagulated with warfarin with coadministered vitamin K resulted in no strokes and 1 death.	No new studies were identified.	No information found	4 reviewers stated the conclusion is still supported by the evidence. 2 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Other Supplement-Cardiovascular Drug Combinations and Outcomes Three notable trials reported outcomes that were not gradable. 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	No new studies were identified.	No information found	4 reviewers stated the conclusion is still supported by the evidence. 1 reviewer cited two studies of potential relevance on red yeast rice but these studies did not address the key question. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
death Omega-3 fatty acids daily along with therapeutic doses of aspirin, dipyridamole, and calcium channel antagonists, resulted in significantly lower rates of restenosis compared with the cardiovascular drugs alone; however, the mean percentage reduction in luminal diameter was not significantly different between the two groups. No differences were noted in rates of restenosis in a similar but lower quality trial among men not taking dipyridamole. 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 pre-identified subgroups or documentation of any dose-response effect.	No new studies were identified.	No information found	5 reviewers stated the conclusion is still supported by the evidence. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
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.	No new studies were identified.	No information found	5 reviewers stated the conclusion is still supported by the evidence. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
				does not need updating
Key Question 2. Intermediate cardiovascular efficacy outcomes of cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement				
No studies reported outcomes evaluating incidence of metabolic syndrome, incidence of hypotension, carotid-intima media thickness, or change in 10-year Framingham risk profile.	No new studies were identified.	No information found	2 reviewers stated the conclusion is still supported by the evidence. 4 said they did not know. 2 did not respond.	Original conclusion is still valid and this portion of the original report does not need updating
Coenzyme Q10 Among patients with mixed CVD risk, no significant differences were seen between the combination of coenzyme Q10 plus a cardiovascular drug and the 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)	No new studies were identified.	No information found	5 reviewers stated the conclusion is still supported by the evidence, although 1 reviewer cited a study rejected in the original report, and another reviewer cited a study that did not address the key question. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Echinacea In one small study of patients with low CHD risk, post-treatment levels of INR and platelet aggregation were not significantly different in the combination of *Echinacea* plus warfarin than with warfarin alone.	No new studies were identified.	No information found	3 reviewers stated the conclusion is still supported by the evidence. 5 said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Garlic Four studies examined the effects of garlic in combination with warfarin (48 participants with unclear CHD risk and 16 males with low CHD risk61), nitrates (60 participants with high CHD risk), and statins plus aspirin (19 participants with high CHD risk). Garlic plus warfarin versus warfarin alone on post-treatment lipid profile, blood pressure, INR, platelet aggregability, and platelet count: no significant difference (insufficient) Garlic plus warfarin versus warfarin alone: significant improvement of HDL-C levels for garlic plus warfarin versus warfarin alone. Garlic plus nitrates significantly improved total cholesterol (MD, -28.20 mg/dL [95% CI, -48.30 to -8.10]) and HDL-C levels, but not triglyceride levels (MD, -10.30 mg/dL [95% CI, 27.60 to 7.00]) in patients with high CVD risk. Garlic plus statins plus aspirin had no different effect on lipid profile, C-reactive protein, platelet count, and Agatston calcium score than statins plus aspirin in participants with CAD.	No new studies were identified.	No information found	4 reviewers stated the conclusion is still supported by the evidence. 1 did not respond. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Ginger Ginger plus warfarin vs. warfarin alone: no significant difference in post-treatment INR (inconclusive; grade: insufficient) or platelet aggregability.	No new studies were identified.	No information found	5 reviewers stated the conclusion is still supported by the evidence. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
				updating
Ginkgo biloba Five RCTs investigated this supplement in combination with antiplatelet agents (acetylsalicylic acid, clopidogrel, or ticlopidine), an anticoagulant (warfarin), or a vasodilator (cilostazol). For *G. biloba* plus antiplatelet agents (104 participants in total, mixed CHD risk), 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). *G. biloba* plus antiplatelet combination versus antiplatelet-only (2 trials, mixed-low risk): no significant differences in platelet aggregation and bleeding time. *G. biloba* plus warfarin versus warfarin: no significant difference in post-treatment levels of platelet aggregability or INR (result for INR inconclusive). *G. biloba* plus cilostazol combination group improved platelet aggregability (MD, 18.00 percent [95% CI, 1.92 to 34.08]) and bleeding time (MD, 1.02 minutes [95% CI, 0.10 to 1.94]) versus cilostazol only.	No new studies were identified.	No information found	4 reviewers stated the conclusion is still supported by the evidence. 4 said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Ginseng Ginseng plus warfarin vs. warfarin alone: conflicting results for INR (3 studies) no significant differences for PT time, platelet count, or platelet aggregability.	No new studies were identified.	No information found	4 reviewers stated the conclusion is still supported by the evidence. 4 said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Hawthorn Hawthorn plus digoxin vs. digoxin alone: no significant difference in an ECG measure (PR interval) in 1 small trial of low-risk patients.	No new studies were identified.	No information found	3 reviewers stated the conclusion is still supported by the evidence. 4 said they did not know. 1 cited 2 SRs and said the question deserves a new look, but neither of the SRs (by the same authors) address drug interactions.	Original conclusion is still valid and this portion of the original report does not need updating
Magnesium Oral magnesium plus hydrochlorothiazide vs. hydrochlorthiazide alone: no significant difference in SBP and DBP in small studies of patients with unclear or participants with low/moderate CHD risk. No difference in post-treatment total cholesterol and triglyceride levels. Oral magnesium plus beta-adrenergic antagonists vs. beta-adrenergic antagonists alone: no significant difference in SBP or DBP.	No new studies were identified.	No information found	3 reviewers stated the conclusion is still supported by the evidence. 4 said they did not know. 1 cited a study but it was uncontrolled so interaction could not be assessed.	Original conclusion is still valid and this portion of the original report does not need updating
Niacin (no more than 250 mg/day) Niacin plus propranolol vs. propranolol alone: no significant difference in post-treatment levels of triglycerides and total cholesterol 1 small trial of patients with hyperlipoproteinemia (unclear CHD risk).	No new studies were identified.	No information found	3 reviewers stated the conclusion is still supported by the evidence. 4 said they did not know. 1 did not respond.	Original conclusion is still valid and this portion of the original report does not need updating
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	6 new studies were identified by the search and/or experts. 3 of the studies reported on prescription-grade omega-3s and 4 reported on over-the-counter	In April 2009, FDA Medwatch reported the following change to the boxed warning for Lovaza (prescription-grade omega-3 fatty acids): ADVERSE REACTIONS	2 reviewers stated the conclusion is still supported by the evidence. 1 reviewer cited a completed trial, the GO FISH Trial that looked at the interaction of omega-3s with ACEs and	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
anticoagulation agent) versus cardiovascular drugs alone. **Omega-3s plus statins vs. statins alone**: The effect on post-treatment triglyceride (TG) levels of adding the supplement to statins differed by baseline triglyceride levels. For baseline TG >200 mg/dL, post-treatment TG levels were significantly lower in the combination arm (two trials) than in the statin arm. However, a meta-analysis of four studies with participants with lower baseline levels of TG (< 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 (PTT, activated partial thromboplastin time [aPTT], platelet aggregation), there were no significant differences between combination and control groups. Conflicting findings in trials of elderly males undergoing angioplasty for post-treatment levels of non-HDL-C, total	products. The 3 prescription studies (1 on Vascepa and 2 on Lovaza/Omacor) assessed the interaction of these products with statins. Vascepa decreased triglycerides, non-HDL, LDL, CRP more in those on higher-efficacy statins that in those on lower-efficacy statins.[9] Lovaza increased mean bleeding time in a dose-dependent manner in persons taking either clopidogrel or aspirin.[6] A study of individuals taking statins with or without Omacor found that Omacor had no effect on von Willebrand Factor or any other outcomes.[5] In individuals taking Icosapentethyl (IPE, pure EPA) along with statins, IPE (4g/d but not 2g/d) decreased median concentrations of large VLDL, LDL, and	Postmarketing Experience The following events have been reported: anaphylactic reaction, hemorrhagic diathesis In October, 2009, FDA reported that Lovaza did not affect the extent (area under the curve [AUC]) or Cmax (rate of exposure) to statins. (drug-drug interactions) In August 2012, FDA reported an association between Lovaza and recurrent atrial fibrillation (AF) in a RCT (Warnings and Precautions). In October 2012, a possible association was reported between Lovaza and recurrent AF and this inforrmation was added to the patient information. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm186892.htm	ARBs in persons with Type 2 diabetes (included, although not totally related),[7] and 1 reviewer cited a number of ongoing studies and 1 completed study (Ballantyne, included) of prescription omega-3 supplements. 1 did not respond. 3 reviewers said they did not know.	

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
cholesterol/HDL-C ratio, and platelet count **Omega-3 fatty acids+ACE inhibitors**: no changes in blood pressure compared with ACE inhibitors alone, but significantly more participants experienced at least 50 percent reduction in proteinuria in favor of the combination treatment. **Omega-3 fatty acids+fenofibrate**: Incidence of hypertension among participants with high triglyceride levels was not significantly different in the combination versus control group. **Omega-3 fatty acids+calcium channel blockers:** 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. These trials were not pooled because dipyridamole was an additional drug in one trial and not in another. **Omega-3 fatty acids+niacin and aspirin versus niacin and aspirin alone**: one underpowered trial (14 participants with atherogenic dyslipidemia, unclear CHD risk) showed no difference in post-treatment lipid profile. **Omega-3 fatty acids+warfarin vs. warfarin**: no significant difference in post-treatment INR values between	HDL.[10] The GO FISH trial found that 3g/d mixture of omega-3s decreased albumin excretion in participants on ACEs or ARBs.[7] A study that assessed the effect of combining fish oil with statins found that the combination decreased triglycerides more than omega-3s alone; omega-3s increased oxidative stress(superoxide dismutase [SOD] and malondialdehyde [MDA]), which was not counterbalanced by statins.[4]			

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
groups.				
Vitamin E Ten RCTs and one controlled clinical trial examined the use of vitamin E with antiplatelet agents (aspirin or ticlopidine), diuretics (furosemide), fibrates (gemfibrozil), Ca-channel blockers (nifedipine), or statins. Vitamin E+antiplatelet agent (aspirin or ticlopidine) versus aspirin or ticlopidine alone: no difference in post-treatment total cholesterol and triglyceride levels in pts with atherosclerosis, but platelet aggregation was significantly decreased. Vitamin E+furosemide: no significant effect on BP in pts. with essential hypertension Vitamin E+nifedipine significant decrease in total cholesterol, LDL-C, and triglycerides, but not HDL-C or SBP in elderly pts at high risk for CHD. Vitamin E+gemfibrozil or vitamin E+statins: no significant difference in lipid profile. No significant difference in BP for vitamin E+gemfibrozil, and no significant difference in C-reactive protein, PT time, and platelet count for vitamin E+statins compared with drugs alone.	No new studies were identified.	No information found	5 reviewers stated that the conclusions are still supported by the evidence. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Vitamin K Vitamin K+coumarin derivative (warfarin): increase in percent of time INR was in therapeutic range and in percent of patients achieving stable INR compared with warfarin alone (1 trial).	No new studies were identified.	No information found	4 reviewers stated that the conclusions are still supported by the evidence. 4 reviewers did not know.	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Vitamin K may improve the stability of anticoagulant therapy.				
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.	A small RCT (n=75) assessed the effects of Stilvid resveratrol-enriched grape extract against grape extract alone or placebo in patients taking statins found that the resveratrol-containing product decreased LDL, ApoB, LDLox and the LDLox/ApoB ratio compared to grape extract alone which decreased LDLonly, and the placebo.[8]	No information found	3 reviewers stated that the conclusion is still supported by the evidence. 1 reviewer cited a study of the interaction of a commercial preparation of resveratrol and statins on intermediate risk factors for CVD that showed a significantly greater cholesterol lowering effect of the combination compared with statins alone or statins plus grape juice.[8]. Another study cited by this reviewer, on the combination of vitamin D and statins, was rejected for lack of a control group. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Key Question 2a. Do the effect estimates of intermediate cardiovascular outcomes vary by age, ethnicity, gender, or health status?				
Insufficient evidence was found to assess subgroup differences.	No new studies were identified	No information found	5 reviewers stated that the conclusion is still supported by the evidence. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
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	No new studies were identified	No information found	3 reviewers stated that the conclusions are still supported by the evidence.	Original conclusion is still valid and this

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
supplements. One study that assessed statistical interaction using general linear modeling found no significant interactions 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. Another trial 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.			1 reviewer described new ongoing studies of prescription-grade omega-3s (Lovaza, Superba, Vascepa, Epanova) but did not cite actual studies or findings. 4 reviewers did not know.	portion of the original report does not need updating

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

A total of 58 studies assessed harms. 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. **Coenzyme Q + statins, fenofibrate, ACE inhibitors, or statins**: No statistically significant differences were observed for total adverse events, abnormalities in fasting blood glucose, myoglobin, creatine phosphokinase (CPK), electrocardiogram (ECG), or retinopathy.	No new studies were identified	No information found	5 reviewers stated that the conclusions are still supported by the evidence. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
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.	No new studies were identified	No information found	3 reviewers stated that the conclusions are still supported by the evidence. 5 said they do not know.	Original conclusion is still valid and this portion of the original report does not need updating
Garlic Four small short-term RCTs examined garlic in combination with warfarin, nitrates, or statins plus aspirin in healthy males or those with cardiovascular conditions. No significant between-group differences were observed across outcomes such as fasting blood glucose, anemia, and leukopenia. Wide confidence intervals for differences in bleeding and fasting blood glucose precluded drawing any meaningful conclusions.	No new studies were identified	No information found	5 reviewers stated that the conclusions are still supported by the evidence. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Ginkgo biloba Seven small RCTs examined *G. biloba* plus warfarin, digoxin, aspirin, aspirin and/or pentoxiphylline, nitrates, cilostazol or clopidogrel, or ticlopidine. Across all cardiovascular medications, nonsignificant results were observed for 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, upset stomach, anemia, abnormal white blood cell count, gastrointestinal events, diarrhea, constipation, hypoglycemia,	No new studies were identified	No information found	5 reviewers stated that the conclusions are still supported by the evidence. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
hyperglycemia, leukopenia, thrombocytopenia, and abnormal ECG.				
Ginseng Three RCTs examined the effects of *Panax ginseng*, American ginseng, and Korean ginseng plus warfarin versus warfarin alone. No statistically significant effects were observed in withdrawal due to adverse events, bleeding, renal dysfunction, hepatotoxicity, PT time, total adverse events, headache, dizziness, indigestion, INR above 3.5, diarrhea, constipation, hematocrit, and anemia.	No new studies were identified	No information found	4 reviewers stated that the conclusions are still supported by the evidence. 4 said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Hawthorn Hawthorn + digoxin versus digoxin alone: no statistically significant differences in incidence of flatulence, nausea, insomnia, headache, and dizziness (8 healthy participants).	No new studies were identified	No information found	4 reviewers stated that the conclusions are still supported by the evidence. 4 said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Magnesium Magnesium + hydrochlorothiazide or beta-adrenergic antagonists.: no statistically significant differences in withdrawal due to adverse events, renal dysfunction, serious adverse events, diarrhea, vomiting, nausea, adverse events, hypercalcemia, abnormal fasting blood glucose, or abnormal ECG.	No new studies were identified	No information found	4 reviewers stated that the conclusions are still supported by the evidence. 4 said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Niacin (not more than 250 mg/day) Niacin plus propranolol versus propranolol alone (in patients with hyper lipoproteinemia): No statistically significant differences in nausea, flushing or hypotension.	No new studies were identified	No information found	4 reviewers stated that the conclusions are still supported by the evidence. 4 said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Omega-3 Fatty Acids Twenty-two studies (21 RCTs and 1 retrospective cohort study) examined the effect of combining omega-3 fatty acids plus CVD drugs on adverse events. **Omega-3 fatty acids + statins versus statins alone**: meta-analyses yielded nonsignificant estimates for serious adverse events, withdrawal due to adverse events, elevated aspartate aminotransferase and alanine aminotransferase, total adverse events, dyspepsia, headache, constipation, upper respiratory infection, and elevated creatine kinase /creatine phosphokinase. However, one RCT reported significantly elevated fasting blood glucose in the omega-3 fatty acids plus statin group. For omega-3 fatty acids in combination with other cardiovascular drugs (statins, aspirin, aspirin and clopidogrel, aspirin plus dipyridamole and calcium channel blockers, warfarin, ramipril and/or irbesartan, or fenofibrate), no significant differences were found in harms outcomes.	One study of Lovaza found no increase in major or minor bleeding with the product.[6] A study of Omacor found side effects that included belching, heartburn or reflux, nausea and vomiting, loose stool, epistaxis, and inability to ingest the product; these effects were reported by both study arms.[5] A study of fish oil capsule administration found an increase in SOD and MDA.[4]	No further information found	4 reviewers stated that the conclusions are still supported by the evidence. 1 said that the release of prescription grade omega 3s might change this conclusion. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Vitamin E Ten RCTs examined vitamin E plus aspirin, nifedipine, furosemide, or statins. No statistically significant differences were observed for total adverse events, incidence of headache, gastrointestinal discomfort, incidence of cancer, abnormalities in fasting blood glucose, glycosylated hemoglobin, leukopenia, or	No new studies were identified	No information found	5 reviewers stated that the conclusions are still supported by the evidence. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
anemia.				
Vitamin K Vitamin K plus warfarin versus warfarin alone: no significant differences were found for bleeding or withdrawal due to adverse events.	No new studies were identified	No information found	5 reviewers stated that the conclusions are still supported by the evidence. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
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.	1 study of resveratrol supplementation reported no adverse effects and no significant change in hepatic, thyroid, renal, or hematologic function.[8]	No information found	3 reviewers stated that the conclusions are still supported by the evidence. 4 said they did not know. 1 did not respond.	Original conclusion is still valid and this portion of the original report does not need updating
Key Question 3a. Do the effect estimates of clinical or intermediate harms vary by age, ethnicity, gender, or health status?				
Evidence was inadequate to address this question.	No new studies were identified	No information found	5 reviewers stated that the conclusions are still supported by the evidence. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Key Question 3b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for harms outcomes?				
For vitamin E + aspirin vs. aspirin alone, one RCT found no significant difference in the rates of adverse events (headache, gastrointestinal discomfort, and withdrawal due to adverse events).	No new studies were identified	No information found	5 reviewers stated that the conclusions are still supported by the evidence. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Key Question 4. Pharmacokinetic outcomes with cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement				
Twelve randomized controlled trials contributed evidence on pharmacokinetic outcomes. The clinical significance of the				

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
interaction was evaluated using the FDA guidance. According to this guidance, the statistical significance of interactions alone cannot determine the clinical significance of interactions.				
Echinacea *Echinacea* angustifolia root (600 mg) plus *E. purpurea* root (675 mg) qid, 2 weeks and a single dose of 25 mg warfarin: no clinically significant interactions.	No new studies were identified	No information found	3 reviewers stated that the conclusions are still supported by the evidence. 5 said they didi not know.	Original conclusion is still valid and this portion of the original report does not need updating
Garlic **Garlic + warfarin**: Allicin pretreatment (7.4 mg/day) for 2 weeks with a single dose of 25 mg warfarin: interaction Unclear; no clinically relevant interactions for some pharmacokinetic outcomes, with insufficient evidence for other important outcomes. **Garlic + statins:** 3,600 µg bid) plus 20 mg single doses of both simvastatin and pravastatin showed insufficient evidence for pharmacokinetic interactions.	No new studies were identified	No information found	4 reviewers stated that the conclusions are still supported by the evidence. 4 said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Ginger Ginger + warfarin: No clinically significant interactions between 7-day pretreatment with ginger and a single 25 mg dose of warfarin.	No new studies were identified	No information found	4 reviewers stated that the conclusions are still supported by the evidence. 4 said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Ginkgo biloba Ginkgo + warfarin: no clinically significant interactions between 7-day pretreatment with *G. biloba* and a single 25 mg dose of warfarin.	No new studies were identified	No information found	4 reviewers stated that the conclusions are still supported by the evidence. 4 said they didnot know.	Original conclusion is still valid and this portion of the original report does not need

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
G. biloba and ticlopidine: no clinically significant interactions. *G. biloba* and single doses of digoxin: Insufficient evidence addressed interactions.				updating
Ginseng *Panax ginseng* (Korean ginseng) + warfarin: no clinically significant interactions. American ginseng (*P. quinquefolius* 2 g/day from weeks 2 to 4) + warfarin: interactions unclear. Low-strength evidence suggested no clinically relevant interactions for some pharmacokinetic outcomes, with insufficient evidence for other important outcomes.	No new studies were identified	No information found	3 reviewers stated that the conclusions are still supported by the evidence. 5 said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Hawthorn Hawthorne (84.3 mg/day of oligomeric procyanidines) + digoxin (21 days) versus digoxin alone (10 days): no significant differences in pharmacokinetic outcomes.	No new studies were identified	No information found	4 reviewers stated that the conclusions are still supported by the evidence. 4 said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Omega-3 Fatty Acids Omega-3s + statins: Three small open-label randomized crossover studies investigated interactions between omega-3 fatty acids (4 g/day) and various statins over a 14-day period. Simvastatin: Insufficient evidence for interactions Rosuvastatin and atorvastatin: evidence for interactions unclear or insufficient	No new studies were identified	No information found	4 reviewers stated that the conclusions are still supported by the evidence. 1 cited studies on new prescription grade omega-3s. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
Other Supplements No studies were found examining pharmacokinetic interactions between a	No new studies were identified	No information found	4 reviewers stated that the conclusions are still supported by the evidence.	Original conclusion is still valid and this

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
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.			1did not respond. 3 reviewers said they did not know.	portion of the original report does not need updating
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 pre-identified subgroups such as age and gender.	No new studies were identified	No information found	4 reviewers stated that the conclusions are still supported by the evidence. 1 did not respond. 3 reviewers said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating
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.	No new studies were identified	No information found	4 reviewers stated that the conclusions are still supported by the evidence. 4 said they did not know.	Original conclusion is still valid and this portion of the original report does not need updating

Legend: ACE angiotensin converting enzyme; Apo apolipoprotein; ARB angiotensin receptor blocker; AUC area under the curve; CHD coronary heart disease; CVD cardiovascular disease; HDL high density lipoprotein; INR international normalized ratio; LDL low density lipoprotein; PTT partial thromboplastin time; RCT randomized controlled trial; SCEPC: Southern California Evidence-based Practice Center; TG triglyceride; VLDL very low density lipoprotein

References

1. Seely D, Kanji S, Yazdi F, et al. Dietary Supplements in Adults Taking Cardiovascular Drugs. Comparative Effectiveness Review No. 51. (Prepared by the University of Ottawa Evidence-based Practice Center under Contract No. HHSA 290-2007-10059-I.) AHRQ Publication No. 12-EHC021-EF Agency for Healthcare Research and Quality. Rockville, MD: Apr April 2012. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22696775.

2. Shekelle PG, Newberry SJ, Maglione M, et al. Assessment of the Need to Update Comparative Effectiveness Reviews: Report of an Initial Rapid Program Assessment (2005-2009) (Prepared by the Southern California Evidence-based Practice Center). Rockville, MD: Agency for Healthcare Research and Quality; October 2009.

3. Shojania KG, Sampson M, Ansari MT, et al. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med. 2007 Aug 21;147(4):224-33. PMID 17638714.

4. Carrepeiro MM, Rogero MM, Bertolami MC, et al. Effect of n-3 fatty acids and statins on oxidative stress in statin-treated hypercholestorelemic and normocholesterolemic women. Atherosclerosis. 2011 Jul;217(1):171-8. PMID 21561620.

5. Mackay I, Ford I, Thies F, et al. Effect of Omega-3 fatty acid supplementation on markers of platelet and endothelial function in patients with peripheral arterial disease. Atherosclerosis. 2012 Apr;221(2):514-20. PMID 22296885.

6. Cohen MG, Rossi JS, Garbarino J, e Insights into the inhibition of platelet activation by omega-3 polyunsaturated acids: beyond aspirin and clopidogrel. Thrombosis Research. 2011 Oct;128(4) 40. PMID 21621252.

7. Miller ER, 3rd, Juraschek SP, Ande CA, et al. The Effects of n-3 Long-Cha Polyunsaturated Fatty Acid Supplemen on Biomarkers of Kidney Injury in Adu With Diabetes: Results of the GO-FISH trial. Diabetes Care. 2012 Dec 28PMID 23275364.

8. Tome-Carneiro J, Gonzalvez M, Lar M, et al. Consumption of a grape extrac supplement containing resveratrol decre oxidized LDL and ApoB in patients undergoing primary prevention of cardiovascular disease: a triple-blind, 6 month follow-up, placebo-controlled, randomized trial. Mol Nutr Food Res. 2 May;56(5):810-21. PMID 22648627.

9. Ballantyne CM, Bays HE, Kastelein al. Efficacy and safety of eicosapentaen acid ethyl ester (AMR101) therapy in st treated patients with persistent high triglycerides (from the ANCHOR study Am J Cardiol. 2012 Oct 1;110(7):984-9 PMID 22819432.

10. Bays HE, Braeckman RA, Ballanty CM, et al. Icosapent ethyl, a pure EPA omega-3 fatty acid: effects on lipoprote particle concentration and size in patien with very high triglyceride levels (the MARINE study). J Clin Lipidol. 2012 Nov;6(6):565-72. PMID 23312052.

Appendices

Appendix A: Search Methodology

Appendix B: Evidence Table

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

DATABASE SEARCHED & TIME PERIOD COVERED:
MEDLINE ON OVID – January 2011-11/29/2012

LANGUAGE:
English

SEARCH STRATEGY:
exp Cardiovascular diseases/dt or exp Adrenergic beta-Antagonists/ or (Adrenergic adj2 Antagonist*).ti,ab. or ((beta adj1 Adrenergic adj2 block*) or beta block*).ti,ab. or exp Acebutolol/ or (acebutolol or acebutalol or Apo-Acebutolol or Apo-Acebulalol or Sectral or Prent).ti,ab. OR exp Betaxolol/ or (betaxolol or Kerlon or Kerlone).ti,ab. or exp Bisoprolol/ or (bisoprolol or Concor or Concore or Zebeta or Monocor).ti,ab. or (carvedilol or Apo-carvedilol or Coreg or Dilatrend or Eucardic or Kredex).ti,ab. or exp Labetalol/ or (labetalol or Labetolol or Normodyne or Trandate).ti,ab. or exp Metoprolol/ or (metoprolol or Betaloc or Betalok or Lopressor or Seloken).ti,ab. OR exp Nadolol/ or (nadolol or Corgard or Solgol).ti,ab. or (nebivolol or Nebilet or Silostar).ti,ab. or exp Pindolol/ or (pindolol or Visken).ti,ab. or exp Propranolol/ or (propranolol or Avlocardyl or Deralin or Dociton or Inderal or Obsidan).ti,ab. or exp Sotalol/ or (sotalol or Darob).ti,ab. or exp Timolol/ or (timolol or Blocadren).ti,ab. OR exp Calcium Channel Blockers/ or ((calcium block* adj2 exogenous) or (calcium antagonist* adj2 exogenous) or (calcium inhibitor* adj2 exogenous) or calcium channel block*).ti,ab. or (Dihydropyridine or Lemildipine).ti,ab. or exp Amlodipine/ or (amlodipine or Norvasc or Istin).ti,ab. or exp Felodipine/ or (felodipine or Plendil or Renedil).ti,ab. or exp Isradipine/ or (isradipine or DynaCirc or Lomir or Prescal).ti,ab. OR exp Nicardipine/ or (nicardipine or Cardene).ti,ab. or exp Nifedipine/ or (nifedipine or Adalat or Cordipin or Nifediac or Nifedical or Procardia).ti,ab. or exp Nimodipine/ or (nimodipine or Nimotop).ti,ab. or exp Nisoldipine/ or (nisoldipine or Sular).ti,ab. or exp Diltiazem/ or (diltiazem or Cardizem or Dilacor or Dilzem or Tiazac).ti,ab. OR exp Verapamil/ or (verapamil or Bosoptin or Calan or Cordilox or Covera-HS or Isoptin or Iproveratril or Verelan).ti,ab. or exp Angiotensin-Converting Enzyme Inhibitors/ or ((Angiotensin-Converting Enzyme adj1 Inhibitor*) or ACE inhibitor* or (Angiotensin-Converting Enzyme adj1 antagonist*)).ti,ab. or (dipeptidyl carboxypeptidase inhibitor* or (Kininase II adj2 inhibitor*) or (Kininase II adj2 antagonist*)).ti,ab. or (benazepril or Cibacen or Lotensin).ti,ab. OR 13 exp Captopril/ or (captopril or Capoten or Lopirin).ti,ab. or exp Enalapril/ or (enalapril or Renitec or Renitek or Vasotec).ti,ab. or exp Fosinopril/ or (fosinopril or Dynacil or Fozitec or Monopril or Staril or Tensocardil).ti,ab. or exp Lisinopril/ or (lisinopril or Lysinopril or Prinivil or Zestril).ti,ab. or (moexipril or Perdix or Univasc).ti,ab. or exp Perindopril/ or (perindopril or Aceon or Coversyl or Prestarium).ti,ab. OR (Quinapril or Accupril).ti,ab. or exp Ramipril/ or (Ramipril or Acovil or Altace or Triatec or Tritace or Vesdil).ti,ab. or (Trandolapril or Gopten or Mavik or Odrik).ti,ab. or (Candesartan or Atacand).ti,ab. or (eprosartan or Teveten).ti,ab. or (irbesartan or Aprovel or Avapro or Karvea).ti,ab. or exp Losartan/ or (losartan or Cozaar).ti,ab. or (olmesartan or Benicar).ti,ab. or (telmisartan or Micardis or Pritor).ti,ab. or (valsartan or Diovan).ti,ab. or ((Renin adj1 Inhibit*) or Renin antagonist*).ti,ab. or (Aliskiren or Tekturna).ti,ab. OR (aldosterone receptor antagonist$1 or (Eplerenone or Inspra)).ti,ab. or exp Spironolactone/ or (Spironolactone or

Aldactone or Verospirone).ti,ab. or exp Vasodilator Agents/ or Vasodilator$1.ti,ab. or exp Clonidine/ or (clonidine or Apo-Clonidine or Catapres or Duraclon).ti,ab. or exp Guanabenz/ or (guanabenz or Wytensin).ti,ab. or exp Guanfacine/ or (guanfacine or Intuniv or Tenex).ti,ab. or exp Methyldopa/ or (Methyldopa or Apo-Methyldopa or Aldoril or Aldomet or Dopamet or Dopegyt).ti,ab. or exp Diazoxide/ or (Diazoxide or Hyperstat or Proglycem).ti,ab. or exp Hydralazine/ or (Hydralazine or Apo-Hydralazine or Apresoline or Dralzine).ti,ab. or exp Minoxidil/ or (minoxidil or Loniten).ti,ab. OR exp Isosorbide Dinitrate/ or (Isosorbide Dinitrate or Dilatrate or Cedocard or Isoket or Isotrate or Isordil or Sorbitrate).ti,ab. or exp Nitroglycerin/ or (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. or exp Phosphodiesterase inhibitors/ or ((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. or (sildenafil or Revatio or tadalafil or vardenafil).ti,ab. or (Cilostazol or Pletal).ti,ab. or exp Alprostadil/ or Alprostadil.ti,ab. OR exp Epoprostenol/ or (Epoprostenol or Flolan).ti,ab. or exp iloprost/ or (iloprost or Ciloprost or Ventavis).ti,ab. or (Endothelin antagonist$1 or (Endothelin adj1 inhibit*)).ti,ab. or (treprostinil or Remodulin or bosentan or Tracleer or ambrisentan or Letairis).ti,ab. or exp Papaverine/ or papaverine.ti,ab. or exp Isoxsuprine/ or (isoxsuprine or Duvadilan).ti,ab. OR exp Adrenergic alpha-Antagonists/ or ((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. OR exp Doxazosin/ or (doxazosin or Cardura or Carduran or Diblocin or Doxazomerck or Doxazosin or Progandol).ti,ab. or exp Prazosin/ or (prazosin or Minipress or Furazosin or Pratsiol).ti,ab. OR (terazosin or Adecur or Apo-Terazosin or Deflox or Dysalfa or Flotrin or Heitrin or Hytrin or Hytrine or Magnurol).ti,ab. or exp Anti-Arrhythmia Agents/ or ((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. OR exp Disopyramide/ or (disopyramide or Norpace or Rhythmodan).ti,ab. or exp Procainamide/ or (procainamide or Apo-Procainamide or Biocoryl or Novocainamide or Novocamid or Procamide or Pronestyl or Procan or Procanbid).ti,ab. OR exp Quinidine/ or (quinidine or Apo-Quinidine or Chinidin or Quinidex or Quinora).ti,ab. or exp Mexiletine/ or Mexiletine.ti,ab. or exp Encainide/ or (encainide or Enkaid).ti,ab. or exp Flecainide/ or (Flecainide or Tambocor).ti,ab. OR exp Propafenone/ or (propafenone or Apo-Propafenone or Arythmol or Baxarytmon or Fenoprain or Rythmol or Rytmonorm).ti,ab. or exp Amiodarone/ or (amiodarone or Amiodarona or Cordarone or Cordarex or Pacerone or Trangorex).ti,ab. or (dofetilide or Tikosyn).ti,ab. or (dronedarone or Multaq).ti,ab. or exp Cardiotonic Agents/ or ((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. or (cardiotonics or cardio-tonics or cardiac stimulant* or myocardial stimulant* or inotropic agent*).ti,ab. OR exp Digoxin/ or (digoxin or Digacin or Digitek or Dilanacin or Lanacordin or Lanicor or Lanoxicaps or Lanoxin or Lenoxin).ti,ab. or exp Antilipemic Agents/ or (Antilipemic$1 or anti-lipemic$1 or hypolipidemic$1 or hypo-lipidemic$1).ti,ab. or ((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. OR (antihyperlipemics or anti-hyperlipemics or antihyperlipidemics or anti-hyperlipidemics).ti,ab. OR exp Cholestyramine Resin/ or (cholestyramin$1 or colestyramin$1 or Cuemid or Quantalan or Questran).ti,ab. OR

exp Colestipol/ or (colestipol or Colestid).ti,ab. or (colesevelam or CholestaGel or Welchol).ti,ab. OR (Bile acid sequestrant$1 or bile acid-binding drug$1 or bile acid-binding agent$1 or (Anticholesteremic$1 or Hypocholesteremic$1 or (cholesterol adj2 inhibitor$1) or cholesterol-lowering drug$1 or cholesterol-lowering agent$1 or cholesterol-lowering medication$1)).ti,ab. OR (ezetimibe or Zetia or (fenofibrate or Antara or Fenoglide or Fibricor or Lipofen or Lofibra or TriCor or Triglide or Trilipix)).ti,ab. or exp Gemfibrozil/ or (Gemfibrozil or Apo-Gemfibrozil or Lopid or Trialmin).ti,ab. or ((Hydroxymethylglutaryl-CoA Reductase adj1 inhibit*) or (HMG-CoA Reductase adj1 inhibit*) or (Hydroxymethylglutaryl-CoA adj1 inhibit$) or (Hydroxymethylglutaryl-Coenzyme A adj1 inhibit$)).ti,ab. OR (atorvastatin or Liptor or (fluvastatin or Lescol)).ti,ab. or exp Lovastatin/ or (lovastatin or Altocor or Altoprev or Mevacor).ti,ab. or exp Pravastatin/ or (pravastatin or Apo-Pravastatin or Lipostat or Pravasin$1 or Pravachol or Selektine).ti,ab. or (rosuvastatin or Crestor).ti,ab. OR exp Simvastatin/ or (simvastatin or Synvinolin or Zocor).ti,ab. or exp Anticoagulants/ or (Anticoagulant$1 or anti-coagulant$1 or bloodthinn* or blood-thinn*).ti,ab. or exp Warfarin/ or (warfarin or Apo-Warfarin or Coumadin$1).ti,ab. or exp Dalteparin/ or (dalteparin or Fragmin$1).ti,ab. OR exp Heparin/ or heparin.ti,ab. or (tinzaparin or Innohep).ti,ab. or exp Platelet Aggregation Inhibitors/ or (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. OR exp Aspirin/ 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. or exp Ticlopidine/ or (ticlopidine or Ticlid).ti,ab. or (clopidogrel or Plavix).ti,ab. OR exp Diuretics/ or (diuretic$1 or water pill$1).ti,ab. or exp Bumetanide/ or (Bumetanide or bumex).ti,ab. or exp Ethacrynic Acid/ or (etacrynic acid or ethacrynic acid or Edecrin).ti,ab. or exp Furosemide/ or (furosemide or Errolon or Fursemide or Fusid or Lasix).ti,ab. or (torsemide or Demadex or torasemide).ti,ab. OR (k-sparing or potassium-sparing).ti,ab. or exp Amiloride/ or (Amiloride or Amidal or Amiduret or Kaluril or Midamor or Midoride or Modamide).ti,ab. or exp Triamterene/ or (triamterene or Dyrenium).ti,ab. or thiazide diuretic$1.ti,ab. or exp Bendroflumethiazide/ OR (Bendroflumethiazide or Bendrofluazide).ti,ab. or exp Chlorothiazide/ or (chlorothiazide or Chlotride or Diuril).ti,ab. or exp Hydrochlorothiazide/ or (hydrochlorothiazide or Apo-Hydro or Dichlotride or Esidrex or HydroDIURIL or Microzide or Oretic).ti,ab. or exp Methyclothiazide/ or (methyclothiazide or Aquatensen or Enduron).ti,ab. OR exp Polythiazide/ or (polythiazide or Renese).ti,ab. or exp Chlorthalidone/ or (chlorthalidone or Apo-Chlorthalidone or Hygroton or Thalitone).ti,ab. or exp Indapamide/ or (indapamide or Lozol or Metindamide).ti,ab. or exp Metolazone/ or (metolazone or Mykrox or Zaroxolyn or Zytanix).ti,ab.

AND
((diet or diets or dietary or supplement*).ti,ab. or (dt or tu).fs.) AND (exp Vitamins/ or vitamin$1.ti,ab. or exp Magnesium/ or magnesium.ti,ab.))) OR exp Dietary Supplements/ or (Neutraceutical* or Nutraceutical* or (diet* adj1 supplement*) or (nutrition* adj1 supplement*) or (food$1 adj1 supplement*) or (botanic* adj1 supplement*)).ti,ab. OR exp Phytotherapy/ or exp Plant Preparations/ or exp Plant Extracts/ or exp Drugs, Chinese Herbal/ or exp Plants, Medicinal/ OR ((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. OR 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. or exp Garlic/ or (garlic or allium or (nectar adj2 god$1) or pa-se-waa or poor man's treacle or stinking rose$1).ti,ab. or exp Ginkgo biloba/ or (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. or exp Panax/ or (Panax or Ginseng or Jen Shen or Ninjin or Renshen or Schinseng or Shinseng).ti,ab. OR 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. or (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. OR ("Coenzyme Q10" or "CoQ 10" or CoQ10 or idebenone or ubiquinone or ubidecarenone or ubisemiquinone or "vitamin q10").ti,ab. or exp Fish Oils/ or (fish adj2 oil$1).ti,ab. or exp Fatty Acids, Omega-3/ 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. or (Eicosapentanoic acid$1 or decosahexanoic acid$1 or alpha linoleic acid$1).ti,ab. OR exp Withania/ or (Withania or Ashwaganda or Indian ginseng or winter cherry or winter cherries or wintercherry or wintercherries or Ayurvedic ginseng).ti,ab. or exp Ginger/ or (ginger or Zingiber officinale or Gamma oryzanol).ti,ab. OR exp Functional Food/ or (functional food$1 or (therapeutic* adj2 food$1)).ti,ab. OR Citrus paradisi/ or Vaccinium macrocarpon/ or Viburnum/ or Blueberry Plant/ or Punicaceae/ or ((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. AND (exp beverages/ or (beverage* or drink* or juice* or tea or teas).ti,ab.) OR ((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. or exp Plant oils/ or exp Olea/ or Linaceae/ or Flax/ or (Linaceae or flax or flaxseed* or Linum or linseed*).ti,ab. or 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. or exp Caffeine/ or caffein*.ti,ab. OR exp Niacin/ or (niacin or Niacor or Niaspan or Nicobid or Nicolar or Nicotinex or Slo-Niacin).ti,ab.
NUMBER OF RESULTS AFTER REMOVAL OF INTERNAL DUPLICATES: 4998
MANUAL FILTERING IN ENDNOTE:
KEYWORD: Animals NOT human OR TITLE: Mouse/Mice/Murine/Animal/Rat/Rats

NEW TOTAL: 3146
FILTERING IN ENDNOTE FOR THE FOLLOWING CORE JOURNALS:
ANNALS OF INTERNAL MEDICINE
BMJ
JAMA

LANCET
NEW ENGLAND JOURNAL OF MEDICINE

FILTERING IN ENDNOTE FOR THE FOLLOWING SPECIALTY JOURNALS:
AMERICAN JOURNAL OF CARDIOLOGY
AMERICAN JOURNAL OF CLINICAL NUTRITION
ATHEROSCLEROSIS
BRITISH JOURNAL OF CLINICAL PHARMACOLOGY
CIRCULATION: CARDIOVASCULAR QUALITY AND OUTCOMES
JOURNAL OF CLINICAL PHARMACOLOGY
THROMBOSIS RESEARCH

NUMBER OF RESULTS AFTER JOURNAL FILTERING: 132

Appendix B: Evidence Table

Author Year Study Design and Aim	Population (n screened, n included, age, % female, ethnicity, comorbidities, inclusion/exclusion criteria)	CVD Drug	Dietary Supplement	Control(s)	Outcome Measures	Conclusions
Omega-3 Fatty acids						
Miller 2013[7] 12-week single center randomized crossover trial of n-3s	31 participants (mean age 67.4; mean BMI 31.6; 55% male; 35% white/61% black;)	65% on statins, 68% on ACEs/ ARBs, 39% on diuretics, 81% on meds for Type II DM	Mixture of omega-3 FA 3g/d	Corn oil	Markers of kidney injury and function: KIM-1, NGAL, LFABP, NAG, microalbuminuria	Omega-3s had no significant effects on urine albumin excretion overall ; but in subgroup analysis,omega-3s decreased albumin excretion in participants on ACEs or ARBs (drugs that affect the renin-angiotensin-aldosterone system), which was 70% of the study population
Ballantyne 2012[9] 12-week multi-center randomized controlled double blinded trial of Vascepa (AMR101) + statins (ANCHOR)	702 high-risk statin-treated patients (mean age 61, report stratified by treatment), 61% male, 97% white, all with TG<500 and ≥200)	Atorvastatin (19%), simvastatin (58%), Rosuvastatin (24%)	Vascepa 2 or 4gm/d	Placebo	TG, LDL-C, non-HDL, VLDL, LpPLA2, ApoB, TC, HDL, VLDL-TG, HsCRP	Vascepa showed dose-dependent lowering effect on non-HDL, LPL, ApoB, LDL, CRP; 4g/d and 2g/d decreased TG by 21.5% and 10.1%, respectively. Vascepa had greater TG-lowering effects on those with higher-efficacy statin regimens and/or higher baseline TG.
Bays 2012[10] 12-week multi-center randomized controlled double blinded trial of Icosapent ethyl(MARINE)	229 patients with hypertriglyceridemia (TG ≥500mg/dL) mean age 52.1-53.9; approx.. 93% ≤65; 75% male~90% Caucasian; mean BMI~31; % Type 2 DM 30%; at high risk for CVD 53-60%)	statins	Icosapent ethyl (pure EPA)2g or 4g/d	placebo	VLDL, LDL, small LDL, HDL concentrations and particle size	IPE 4g/d decreased median concentrations of large VLDL, total LDL, small LDL, and total HDL particles and decreased VLDL particle size. IPE 2g/d did not have significant effects. LDL particle concentration declined numerically more in statin-treated patients than among those not receiving statins, but the number receiving statins was small.
Cohen 2011[6]	30 US adults divided into 3	Group B:	Lovaza	None	Platelet activation:	Mean bleeding time increased in a

Author Year Study Design and Aim	Population (n screened, n included, age, % female, ethnicity, comorbidities, inclusion/exclusion criteria)	CVD Drug	Dietary Supplement	Control(s)	Outcome Measures	Conclusions
24-week Pilot non-controlled trial to assess effects of Lovaza alone, Lovaza+aspirin or Aspirin+clopidogrel	groups of 10: A. healthy adults (mean age 43; 30% female; 100% Caucasian); B. adults with a stable cardiovascular condition requiring daily aspirin (mean age 51; 40% female; 20% black); adults requiring daily aspirin +clopidogrel(mean age 54; 50% female; 20% black; 100% had CVD; 30% had diabetes) Exclusion criteria: chronic liver disease, liver transaminase levels greater than normal; renal insufficiency (serum creatinine>2, or clearance <60ml/min), recent bleeding episodes; thrombocytosis, thrombocytopenia, history of anemia, baseline hemoglobin<11, gastric bleeding diathesis, stroke in the past 12 months GI or genitourinary bleeding within the previous 3 months, INR>1.3 and previous treatment with an IV platelet inhibitor; Patients taking fish or flaxseed oil had to go through a 2-week	aspirin (<325mg qd) Group C: clopidogrel (75 mg qd(+aspirin (<325mg)	EPC+DHA, escalating doses (1, 2, 4, and 8 gm, qd) in consecutive 6-week periods		electrophoretic quasielastic light scattering (EQELS); Platelet aggregation: light transmission aggregometry (LTA); Bleeding time	dose-dependent manner with increasing omega-3-PUFA doses. LTA did not detect additional antiplatelet effects of omega-3s beyond those of aspirin and clopidogrel. EQELS showed a significant increase in negative resting platelet charge cf. baseline and an attenuated response to arachidonic acid mediated platelet activation. Omega-3 PUFA increase total platelet surface charge and therefore attenuate platelet activation. No evidence of major or minor bleeding was seen with omega-3s.

Author Year Study Design and Aim	Population (n screened, n included, age, % female, ethnicity, comorbidities, inclusion/exclusion criteria)	CVD Drug	Dietary Supplement	Control(s)	Outcome Measures	Conclusions
	washout					
Carrepeiro 2011[4] Crossover double blind placebo-controlled study to assess whether n-3 FA increase oxidative stress in normo- and hypercholesterolemic women and how n-3s and statins interact Treatment periods were 6 weeks with a 90-day washout period between them	43 female participants in Spain (960 screened); Inclusion criteria: 40-80 yrs of age; controlled or absent cholesterolemia and hypertension; no hx of diabetes, CVD, intervention, or renal failure; no hormone replacement; absent or moderate alcohol consumption; no use of dietary supplements for 6 months	Statin treatment for > 6mos. (atorvastatin 33%, simvastatin 57%, Rosuvastatin and pravastatin 5% each), statin doses ranged from 9 to 40mg with most on 10 or 20	Ocean Nutrition Canada Limited omega 3 fish oil capsules containing 90-1100 mg oil and 2 mg tocopherol per gm oil	Soy and corn oil containing capsules	Total cholesterol, HDL, LDL, serum and plasma glucose, malondialdehyde (MDA) concentration as marker of oxidative stress, tocopherol concentration, antioxidant enzyme activity (catalase, glutathione peroxidase, superoxide dismutase	BMI, w/h ratio, glucose, total cholesterol, HDL, and LDL remained constant throughout the trial. Triglycerides decreased in n-3 supplemented groups. n-3 also increased MDA and SOD activity but reduced catalase expression. Statins reduced LDL and increased SOD. The combination of statins and n-3s showed a trend in reducing tryglycerides (beyond that of n-3s alone) but no other significant effects; n-3s reduced some of the effects of statis on LDL (but not significantly); in addition, n-3 fa increased oxidative stress and this effect was not counterbalanced by statins
Mackay 2012[5] Randomized cross-over double-blind study of the effects of omega 3s on markers of platelet and endothelial function in patients with intermittent claudication (IC) and peripheral vascular disease (PVD) Treatment periods were 6 weeks with	150 consecutive patients with hx of stable IC and PVD at a UK academic medical center (1044 screened; 408 refused; 485 failed to meet inclusion criteria)(mean age 68.55 (9.35)33% female, 67% w/ no hx of angina; 87% with no hx of MI; 40% not on antihypertensives; 77% not on beta blockers; 31% with no hx of htn/38% controlled/31% not	Statins and aspirin. Other agents differed by patient but included antihypertensives, beta blockers	Omacor® (850-882 mg EPA and DHA)	80:20 palm: soybean oil	Platelet and endothelial assays (platelet aggregation, P-selectin expression, fibrinogen), von Willebrand factor (primary outcome), high sensitivity c reactive protein, IL-6 inter-cellular adhesion molecule 1, phospholipid FA composition	Group A received omacor 1st, Group B received placebo 1st 33 pts were lost to followup Omega 3s had no effect on vWF or on any other outcomes. Compliance as measured by plasma PL fatty acid composition was 76%. Side effects: majority occurred during 1st treatment phase and included belching, heartburn or reflux, nausea and vomiting, loose

Author Year Study Design and Aim	Population (n screened, n included, age, % female, ethnicity, comorbidities, inclusion/exclusion criteria)	CVD Drug	Dietary Supplement	Control(s)	Outcome Measures	Conclusions
84-day washout	controlled **Inclusion criteria**: ABPI<0.8 and receiving statins and aspirin **Exclusion criteria**: inability to give informed consent, consumption of more than 2 portions of oily fish weekly or use of fish oil supplements; pain at rest; ulceration; liver impairment or abnormal platelet count or diabetes; use of clopidogrel, warfarin, or NSAIDS					stool, epistaxis and an inability to ingest the omega-2 or placebo tablets. In the 1st phase, of 18 people who reported side effects, 12 were receiving omega-3s and 6 were receiving placebo. In the 2nd phase, 4 patients reported side effects, 2 from each arm. Six patients withdrew due to side effects: 4 in the omega-3s group and 2 in the placebo group.
Resveratrol						
Tomé-Carneiro 2012[8] Triple-blind RCT to assess effects of resveratrol on intermediary endpoints in patients undergoing primary CVD prevention	Patients undergoing primary CVD prevention care recruited from an academic medical center cardiology service in Madrid. Inclusion criteria: diabetes or hypercholesterolemia under statin treatment, and at least 1 of the following risk factors: smoking, arterial hypertension, and/or overweight obesity (BMI>30). Exclusion criteria: age< 18, >80, pregnancy, known grape allergy, use of food complements; documented CVD, other known chronic	Statins	Stilvid® resveratrol-enriched grape extract and grape extract (GE) not enriched for resveratrol	Not described	Blood lipids, glucose, creatine, albumin, bilirubin, Tchol, HDL chol, LDL, alanine amino transferase, gamma glutamyl transferase, creatine phosphokinase. Urate; T4, TSH, bloodwork (RBC, sedimentation rate, Hb concentration, Hba1c, hematocrit, MCV, MCH, platelets, mean platelet volume, leukocytes, neutrophils,	No changes were seen after 6 months in the placebo group. In the GE group, only LDL decreased 2.9%. In the Stilvid group, LDL, ApoB, LDLox, and LDLox/ApoB decreased and nonHDL/ApoB increased. No changes were seen in liver, thyroid, or kidney function. No AEs reported. Thus resveratrol might exert additional cardioprotection beyond statins. Adverse effects: No significant change in hepatic, thyroid, renal, or hematologic function.

Author Year Study Design and Aim	Population (n screened, n included, age, % female, ethnicity, comorbidities, inclusion/exclusion criteria)	CVD Drug	Dietary Supplement	Control(s)	Outcome Measures	Conclusions
	pathology				lymphocytes, monocytes, eosinophils, basophils, ApoB, LDLox	

Legend: ACE angiotensin converting enzyme; Apo apolipoprotein; ARB angiotensin receptor blocker; AUC area under the curve; BMI body mass index; CHD coronary heart disease; CVD cardiovascular disease; EQELS electrophoretic quasielastic light scattering; Hbalc hemoglobin a1c; HDL high density lipoprotein; hsCRP high-sensitivity C-reactive Protein; HTN hypertension; hx history; INR international normalized ratio; KIM-1 Kidney Injury Molecule-1; LDL low density lipoprotein; LFABP liver-type fatty acid binding protein; LTA light transmission aggregometry; MCV mean corpuscular volume; MDA malondialdehyde; NAG n-acetyl beta glucosaminidase; NGAL neutrophil gelatinase-associated lipocalin; PTT partial thromboplastin time; PUFA polyunsaturated fatty acid; RBC red blood cell; RCT randomized controlled trial; SCEPC: Southern California Evidence-based Practice Center; SOD superoxide dismutase; T4 thyroxine; TG triglyceride; TSH thyroid stimulating hormone; VLDL very low density lipoprotein;

Appendix C: Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

Title: Dietary Supplements in Adults Taking Cardiovascular Drugs

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 1. Clinical cardiovascular effectiveness/ efficacy outcomes (e.g., mortality and specific cardiovascular or cerebrovascular conditions such as myocardial infarction and stroke)?			
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.	☐	New Evidence:	☐
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.	☐	New Evidence:	☐
Magnesium In a crossover trial of oral magnesium aspartate or placebo administered daily for 8 weeks to 40 hypertensive patients with no comorbidities on therapeutic doses of beta-blockers, a single event of myocardial infarction was noted.		New Evidence:	

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
	☐		☐
Omega-3 Fatty Acids In three short-term efficacy trials of omega-3 fatty acid and statin coadministration, effects on mortality and arrhythmia were insignificant. Three studies combining omega-3 fatty acids with aspirin, warfarin, and fenofibrate had no significant effects on mortality or 10-year risk. 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 provided insufficient evidence on the outcome of acute myocardial infarction.	☐	New Evidence:	☐
Vitamin E An efficacy trial of vitamin E plus aspirin versus aspirin alone in patients with previous neurologic deficit provided insufficient evidence with sparse events of stroke and transient ischemic attack.	☐	New Evidence:	☐
Vitamin K One 6-month efficacy trial in 70 selected groups of patients with unstable international normalized ratios (INRs) anticoagulated with warfarin with coadministered vitamin K resulted in no strokes and 1 death.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Other Supplement-Cardiovascular Drug Combinations and Outcomes Three notable trials reported outcomes that were not gradable. 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 Omega-3 fatty acids daily along with therapeutic doses of aspirin, dipyridamole, and calcium channel antagonists, resulted in significantly lower rates of restenosis compared with the cardiovascular drugs alone; however, the mean percentage reduction in luminal diameter was not significantly different between the two groups. No differences were noted in rates of restenosis in a similar but lower quality trial among men not taking dipyridamole. 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.	☐	New Evidence:	☐
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 or documentation of any dose-response effect.	☐	New Evidence:	☐
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.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 2. Intermediate cardiovascular efficacy outcomes of cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement			
No studies reported outcomes evaluating incidence of metabolic syndrome, incidence of hypotension, carotid-intima media thickness, or change in 10-year Framingham risk profile.	☐	New Evidence:	☐
Coenzyme Q10 Among patients with mixed CVD risk, no significant differences were seen between the combination of coenzyme Q10 plus a cardiovascular drug and the 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)	☐	New Evidence:	☐
Echinacea In one small study of patients with low CHD risk, post-treatment levels of INR and platelet aggregation were not significantly different in the combination of *Echinacea* plus warfarin than with warfarin alone.	☐	New Evidence:	☐
Garlic Four studies examined the effects of garlic in combination with warfarin (48 participants with unclear CHD risk and 16 males with low CHD risk61), nitrates (60 participants with		New Evidence:	

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
high CHD risk), and statins plus aspirin (19 participants with high CHD risk). Garlic plus warfarin versus warfarin alone on post-treatment lipid profile, blood pressure, INR, platelet aggregability, and platelet count: no significant difference (insufficient) Garlic plus warfarin versus warfarin alone: significant improvement of HDL-C levels for garlic plus warfarin versus warfarin alone. Garlic plus nitrates significantly improved total cholesterol (MD, -28.20 mg/dL [95% CI, -48.30 to -8.10]) and HDL-C levels, but not triglyceride levels (MD, -10.30 mg/dL [95% CI, 27.60 to 7.00]) in patients with high CVD risk. Garlic plus statins plus aspirin had no different effect on lipid profile, C-reactive protein, platelet count, and Agatston calcium score than statins plus aspirin in participants with CAD.	☐		☐
Ginger Ginger plus warfarin vs. warfarin alone: no significant difference in post-treatment INR (inconclusive; grade: insufficient) or platelet aggregability.	☐	New Evidence:	☐
Ginkgo biloba Five RCTs investigated this supplement in combination with antiplatelet agents (acetylsalicylic acid, clopidogrel, or ticlopidine), an anticoagulant (warfarin), or a vasodilator (cilostazol). For *G. biloba* plus antiplatelet agents (104 participants in total, mixed CHD risk), 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).	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
G. biloba plus antiplatelet combination versus antiplatelet-only (2 trials, mixed- low risk): no significant differences in platelet aggregation and bleeding time. *G. biloba* plus warfarin versus warfarin: no significant difference in post-treatment levels of platelet aggregability or INR (result for INR inconclusive). *G. biloba* plus cilostazol combination group improved platelet aggregability (MD, 18.00 percent [95% CI, 1.92 to 34.08]) and bleeding time (MD, 1.02 minutes [95% CI, 0.10 to 1.94]) versus cilostazol only.			
Ginseng Ginseng plus warfarin vs. warfarin alone: conflicting results for INR (3 studies) no significant differences for PT time, platelet count, or platelet aggregability.	☐	New Evidence:	☐
Hawthorn Hawthorn plus digoxin vs. digoxin alone: no significant difference in an ECG measure (PR interval) in 1 small trial of low-risk patients.	☐	New Evidence:	☐
Magnesium Oral magnesium plus hydrochlorothiazide vs. hydrochlorthiazide alone: no significant difference in SBP and DBP in small studies of patients with unclear or participants with low/moderate CHD risk. No difference in post-treatment total cholesterol and triglyceride levels. Oral magnesium plus beta-adrenergic antagonists vs. beta-adrenergic antagonists alone: no significant difference in SBP or DBP.	☐	New Evidence:	☐
Niacin (no more than 250 mg/day) Niacin plus propranolol vs. propranolol alone: no significant difference in post-treatment levels of triglycerides and total cholesterol 1 small trial of patients with hyperlipoproteinemia		New Evidence:	

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
(unclear CHD risk).	☐		☐
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. **Omega-3s plus statins vs. statins alone**: The effect on post-treatment triglyceride (TG) levels of adding the supplement to statins differed by baseline triglyceride levels. For baseline TG >200 mg/dL, post-treatment TG levels were significantly lower in the combination arm (two trials) than in the statin arm. However, a meta-analysis of four studies with participants with lower baseline levels of TG (< 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 (PTT, activated partial thromboplastin time [aPTT], platelet aggregation), there were no significant differences between combination and control groups. Conflicting findings in trials of elderly males undergoing angioplasty for post-treatment levels of non-HDL-C, total	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
cholesterol/HDL-C ratio, and platelet count **Omega-3 fatty acids+ACE inhibitors**: no changes in blood pressure compared with ACE inhibitors alone, but significantly more participants experienced at least 50 percent reduction in proteinuria in favor of the combination treatment. **Omega-3 fatty acids+fenofibrate**: Incidence of hypertension among participants with high triglyceride levels was not significantly different in the combination versus control group. **Omega-3 fatty acids+calcium channel blockers:** 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. These trials were not pooled because dipyridamole was an additional drug in one trial and not in another. **Omega-3 fatty acids+niacin and aspirin versus niacin and aspirin alone**: one underpowered trial (14 participants with atherogenic dyslipidemia, unclear CHD risk) showed no difference in post-treatment lipid profile. **Omega-3 fatty acids+warfarin vs. warfarin**: no significant difference in post-treatment INR values between groups.			
Vitamin E Ten RCTs and one controlled clinical trial examined the use of vitamin E with antiplatelet agents (aspirin or ticlopidine), diuretics (furosemide), fibrates (gemfibrozil), Ca-channel blockers (nifedipine), or statins. Vitamin E+antiplatelet agent (aspirin or ticlopidine) versus aspirin or ticlopidine alone: no difference in post-treatment total cholesterol and triglyceride levels in pts with	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
atherosclerosis, but platelet aggregation was significantly decreased. Vitamin E+furosemide: no significant effect on BP in pts. with essential hypertension Vitamin E+nifedipine significant decrease in total cholesterol, LDL-C, and triglycerides, but not HDL-C or SBP in elderly pts at high risk for CHD. Vitamin E+gemfibrozil or vitamin E+statins: no significant difference in lipid profile. No significant difference in BP for vitamin E+gemfibrozil, and no significant difference in C-reactive protein, PT time, and platelet count for vitamin E+statins compared with drugs alone.			
Vitamin K Vitamin K+coumarin derivative (warfarin): increase in percent of time INR was in therapeutic range and in percent of patients achieving stable INR compared with warfarin alone (1 trial). Vitamin K may improve the stability of anticoagulant therapy.	☐	New Evidence:	☐
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.	☐	New Evidence:	☐
Key Question 2a. Do the effect estimates of intermediate cardiovascular outcomes vary by age, ethnicity, gender, or health status?			
Insufficient evidence was found to assess subgroup differences.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
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. One study that assessed statistical interaction using general linear modeling found no significant interactions 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. Another trial 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.	☐	New Evidence:	☐
Key Question 3. Clinical or intermediate harms with cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement			
A total of 58 studies assessed harms. 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. **Coenzyme Q + statins, fenofibrate, ACE inhibitors, or statins**: No statistically significant differences were observed for total adverse events, abnormalities in fasting blood glucose, myoglobin, creatine phosphokinase (CPK), electrocardiogram (ECG), or retinopathy.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
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.	☐	New Evidence:	☐
Garlic Four small short-term RCTs examined garlic in combination with warfarin, nitrates, or statins plus aspirin in healthy males or those with cardiovascular conditions. No significant between-group differences were observed across outcomes such as fasting blood glucose, anemia, and leukopenia. Wide confidence intervals for differences in bleeding and fasting blood glucose precluded drawing any meaningful conclusions.	☐	New Evidence:	☐
Ginkgo biloba Seven small RCTs examined *G. biloba* plus warfarin, digoxin, aspirin, aspirin and/or pentoxiphylline, nitrates, cilostazol or clopidogrel, or ticlopidine. Across all cardiovascular medications, nonsignificant results were observed for 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, upset stomach, anemia, abnormal white blood cell count, gastrointestinal events, diarrhea, constipation, hypoglycemia, hyperglycemia, leukopenia, thrombocytopenia, and abnormal ECG.	☐	New Evidence:	☐
Ginseng Three RCTs examined the effects of *Panax ginseng*, American ginseng, and Korean ginseng plus warfarin versus warfarin alone. No statistically significant effects were observed in withdrawal due to adverse events, bleeding, renal dysfunction, hepatotoxicity, PT time, total adverse events,	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
headache, dizziness, indigestion, INR above 3.5, diarrhea, constipation, hematocrit, and anemia.			
Hawthorn Hawthorn + digoxin versus digoxin alone: no statistically significant differences in incidence of flatulence, nausea, insomnia, headache, and dizziness (8 healthy participants).	☐	New Evidence:	☐
Magnesium Magnesium + hydrochlorothiazide or beta-adrenergic antagonists.: no statistically significant differences in withdrawal due to adverse events, renal dysfunction, serious adverse events, diarrhea, vomiting, nausea, adverse events, hypercalcemia, abnormal fasting blood glucose, or abnormal ECG.	☐	New Evidence:	☐
Niacin (not more than 250 mg/day) Niacin plus propranolol versus propranolol alone (in patients with hyper lipoproteinemia): No statistically significant differences in nausea, flushing or hypotension.	☐	New Evidence:	☐
Omega-3 Fatty Acids Twenty-two studies (21 RCTs and 1 retrospective cohort study) examined the effect of combining omega-3 fatty acids plus CVD drugs on adverse events. **Omega-3 fatty acids + statins versus statins alone**: meta-analyses yielded nonsignificant estimates for serious adverse events, withdrawal due to adverse events, elevated aspartate aminotransferase and alanine aminotransferase, total adverse events, dyspepsia, headache, constipation, upper respiratory infection, and elevated creatine kinase /creatine phosphokinase. However, one RCT reported significantly elevated fasting blood glucose in the omega-3 fatty acids plus statin group.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
For omega-3 fatty acids in combination with other cardiovascular drugs (statins, aspirin, aspirin and clopidogrel, aspirin plus dipyridamole and calcium channel blockers, warfarin, ramipril and/or irbesartan, or fenofibrate), no significant differences were found in harms outcomes.			
Vitamin E Ten RCTs examined vitamin E plus aspirin, nifedipine, furosemide, or statins. No statistically significant differences were observed for total adverse events, incidence of headache, gastrointestinal discomfort, incidence of cancer, abnormalities in fasting blood glucose, glycosylated hemoglobin, leukopenia, or anemia.	☐	New Evidence:	☐
Vitamin K Vitamin K plus warfarin versus warfarin alone: no significant differences were found for bleeding or withdrawal due to adverse events.	☐	New Evidence:	☐
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.	☐	New Evidence:	☐
Key Question 3a. Do the effect estimates of clinical or intermediate harms vary by age, ethnicity, gender, or health status?			
Evidence was inadequate to address this question.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 3b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for harms outcomes?			
For vitamin E + aspirin vs. aspirin alone, one RCT found no significant difference in the rates of adverse events (headache, gastrointestinal discomfort, and withdrawal due to adverse events).	☐	New Evidence:	☐
Key Question 4. Pharmacokinetic outcomes with cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement			
Twelve randomized controlled trials contributed evidence on pharmacokinetic outcomes. The clinical significance of the interaction was evaluated using the FDA guidance. According to this guidance, the statistical significance of interactions alone cannot determine the clinical significance of interactions.			
Echinacea *Echinacea* angustifolia root (600 mg) plus *E. purpurea* root (675 mg) qid, 2 weeks and a single dose of 25 mg warfarin: no clinically significant interactions.	☐	New Evidence:	☐
Garlic **Garlic + warfarin**: Allicin pretreatment (7.4 mg/day) for 2 weeks with a single dose of 25 mg warfarin: interaction Unclear; no clinically relevant interactions for some pharmacokinetic outcomes, with insufficient evidence for other important outcomes. **Garlic + statins:** 3,600 µg bid) plus 20 mg single doses of both simvastatin and pravastatin showed insufficient evidence for pharmacokinetic interactions.	☐	New Evidence:	☐
Ginger Ginger + warfarin: No clinically significant interactions between 7-day pretreatment with ginger and a single 25 mg dose of warfarin.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Ginkgo biloba Ginkgo + warfarin: no clinically significant interactions between 7-day pretreatment with *G. biloba* and a single 25 mg dose of warfarin. *G. biloba* and ticlopidine: no clinically significant interactions. *G. biloba* and single doses of digoxin: Insufficient evidence addressed interactions.	☐	New Evidence:	☐
Ginseng *Panax ginseng* (Korean ginseng) + warfarin: no clinically significant interactions. American ginseng (*P. quinquefolius* 2 g/day from weeks 2 to 4) + warfarin: interactions unclear. Low-strength evidence suggested no clinically relevant interactions for some pharmacokinetic outcomes, with insufficient evidence for other important outcomes.	☐	New Evidence:	☐
Hawthorn Hawthorne (84.3 mg/day of oligomeric procyanidines) + digoxin (21 days) versus digoxin alone (10 days): no significant differences in pharmacokinetic outcomes.	☐	New Evidence:	☐
Omega-3 Fatty Acids Omega-3s + statins: Three small open-label randomized crossover studies investigated interactions between omega-3 fatty acids (4 g/day) and various statins over a 14-day period. Simvastatin: Insufficient evidence for interactions Rosuvastatin and atorvastatin: evidence for interactions unclear or insufficient	☐	New Evidence:	☐
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	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
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 pre-identified subgroups such as age and gender.	☐	New Evidence:	☐
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.	☐	New Evidence:	☐
Are there new data that could inform the key questions that might not be addressed in the conclusions?			