Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Comparative Effectiveness of Lipid-Modifying Agents*

Research Review Citation: Sharma M, Ansari MT, Soares-Weiser K, Abou-setta AM, Ooi TC, Sears M, Yazdi F, Tsertsvadze A, Moher D. Comparative Effectiveness of Lipid-Modifying Agents. Comparative Effectiveness Review No. 16. (Prepared by the University of Ottawa Evidence-based Practice Center under contract No. 290-02-0021.) Rockville, MD: Agency for Healthcare Research and Quality. September 2009. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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Comments on draft reviews and the authors' responses to the comments will be posted publicly on the Effective Health Care Web site within three months after the final review is published. Comments are not edited for spelling, grammar, or other content errors. The table below includes the response by the authors of the review to each comment submitted for the draft review.

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Executive Summary	If the evidence is low or very low, there does not seem to be support for the statement: "In summary, the evidence does not support routine use of any studied combination over higher dose statin therapy." Don't you mean "evidence is inconclusive about the benefits of routine use of any studied combination over higher dose statin therapy."	Addressed in the revision of the Executive Summary
Executive Summary	We disagree with thExecutive Summary statement "the evidence does not support routine use of any studied combination over higher dose statin therapy." for several reasons. Most importantly, we believe that the sum of evidence does support use of combination therapies……….. A way of phrasing an evidence-based conclusion might be "In summary, the available evidence supporting the hypothesis that the use of combination therapies leads to more favorable results than use of higher dose statin therapy is insufficient to enable one to reach firm conclusions." However, the additional evidence we provide should be sufficient to enable the EPC to reach a firm conclusion about combination therapies using ezetimibe.	Addressed in the revision of the Executive Summary Our conclusions are based on the focused key questions and results specifically related to them
Executive Summary	Based on the manner in which the Key Questions have been re-framed by the EPC, however, the review is actually significantly narrower in its focus. It is essentially focused on a very narrow assessment of high dose statin therapy versus combination therapy involving low dose statins. Given the significant potential for confusion, we believe that it is critical that this limited focus be consistently and clearly described throughout the report, including in the ExecutivExecutive Summary and Key Points. We also think that the conclusions that are described in the report should be very carefully written to reflect this narrow focus and the resulting limitations of the review.	The focus of the review has been clearly stated in the introduction and key questions
Executive Summary	Finally, we request that the EPC reconsider its criteria for including statements in Table A. These statements appear to be derived from the "Key Points" preceding the discussion of various study end points throughout the document. However, not all Key Points made it into Table A. For example, we believe that the Key Point "A single trial in a population requiring intensive lipid lowering (diabetic patients) demonstrated a significantly greater percentage mean change for combination therapy (simvastatin + ezetimibe) compared with higher dose simvastatin." is an important observation deserving of inclusion in Table A. If a conclusion is important enough to be a Key Point, it is probably important enough to be placed in Table A. We request that the EPC re-examine which analytic results should become Key Points, and which Key Points should become Table A conclusions, with the goal of achieving consistency.	Table A was a summary of conclusions based on a (apriori) select number of important outcomes for which strength of evidence was graded. Not all outcomes associated key points can be brought into this table

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Executive Summary	Minor issues: Typo - Ezetimibe trials are 'short' duration instead of 'sort' in Table A Beginning page 3: The term 'aggressive' is used here and 'intensive' used later. Please use a consistent term, or, if the difference is intentional, define both so that the distinction is clear.	Revised accordingly
Executive Summary	While Abbott recognizes the validity of the AHRQ CER?s methodology and understands how the CER reached its conclusions for the three specific questions posed, we respectfully submit that the current level of evidence reviewed is insufficient and that both the level and type of evidence merit reconsideration…………. We appreciate your consideration of our comments.	We look forward to respond to specific comments below
Executive Summary	We agree with the overall conclusions regarding combination therapy versus high dose statin monotherapy, based on the currently available evidence. However, we would like to note that there are patient populations in which combination therapy may be appropriate, such as patients with elevated triglycerides who need to achieve secondary goals (e.g. NCEP ATP III non-HDL goals).	In this revision and update, we additionally considered the outcomes of non-HDL-c and triglycerides for the subgroup with diabetes mellitus
Introduction	Page 23. Each class of drugs is given own paragraph except statins and fibrates are combined. Not a huge deal, but it strikes me as strange	Revised accordingly
Introduction	Under PK column: Delete food statement – add "food did not affect AUC of rosuvastatin" (from PI) Under PK column: add "minimally" to "metabolized by CYP 450-2C9" Under Labeled Indications column – add indicated to "slow progression of atherosclerosis in adult patients as part of a treatment strategy to lower TC and LDL-C to target levels" Under Labeled Indications column - Delete "HOFS" and add "HoFH" Under Dosing column – delete "HeFH, nFH, mixed dyslipidemia 5-40 od; initially 5 –10 and titrated as appropriate based on monitoring" and "40 mg dose reserved for inadequate response at lower doses" Replace with: Dose range is 5 – 40 mg once daily. Use 40 mg dose only for patients not reaching LDL-C goal with 20 mg. Hyperlipidemia, mixed dyslipidemia, hypertriglyceridemia, and atherosclerosis: starting dose 10 mg. Consider 20 mg starting dose for LDL-C > 190 mg/dL and aggressive lipid targets HoFH: starting dose 20 mg Under Dosing column – delete ↑ risk of myopathy and/or rhabdomyelitis,	Food comment was deleted, but comment that food did not affect AUC was not added because similar comments are not in other sections. - "minimally" added - "slow progression … " added; rest not added because it is common to the class - done dosing amendments made in manner consistent with table formatting

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	acute renal failure with higher dose, concurrent lipid lowering therapy, cyclosporine, lopinavir/ritonavir. This is covered in the Dose Adjustment column Under Dose Adjustments column – • Delete Elderly section – not in PI • Edit "Concomitant lipid lowering therapy" as follows: Concomitant lipid lowering therapy: use with caution due to enhanced risk of skeletal muscle effects and consider dose reduction; limit to 10 mg once daily when used in combination with gemfibrozil • Renal insufficiency statement: Rosuvastatin exposure is not influenced by mild to moderate renal impairment; however, exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment not on hemodialysis (Crestor Prescribing Information). Please edit to reflect dosage adjustment is in patients with severe renal impairment. • Add "Cyclosporine: limit to 5 mg once daily" • Add "Lopinavir/Ritonavir: Limit to 10 mg once daily" • Add "Coumarin Anti-coagulants: Combination prolongs INR. Monitor INRfrequently"	left in dosing column to be consistent with other meds; ensured that it is not duplicated in other columns From the new label: Elderly patients are at higher risk of myopathy and CRESTOR should be prescribed with caution in the elderly. [*see Warnings and Precautions,* (5.1) *and Clinical Pharmacology,* (12.3)] Rest revised accordingly
Introduction	In the pharmacokinetics column, consider adding the percentage by which fluvastatin is metabolized by each isozyme: 2C9 (75%), 2C8 (~5%), 3A4 (~20%) - Under labeled indications, add the pediatric indication Lescol and Lescol XL are indicated as an adjunct to diet to reduce Total-C, LDL-C, and Apo B levels in adolescent boys and girls who are at least one year post-menarche, 10-16 years of age, with heterozygous familial hypercholesterolemia whose response to dietary restriction has not been adequate and the following findings are present: 1. LDL-C remains ? 190 mg/dL or 2. LDL-C remains ? 160 mg/dL and ? There is a positive family history of premature cardiovascular disease or ? Two or more other cardiovascular disease risk factors are present In the dosing section, 20 mg is listed as the initial dose. However the following language should be included: For patients requiring LDL-C reduction to a goal of ?25%, the recommended starting dose is 40 mg as one capsule in the evening, 80 mg as one Lescol XL tablet administered as a single dose at any time of the day or 80 mg in divided doses of the 40 mg capsule given twice daily In the dosing section, several corrections should be made under interactions: ? Decrease Fluv Cmax and AUC, Increase plasma clearance with Rifampicin	Done pediatric label information not added because the detail is beyond this table, and this report pertains to adults dosing details are beyond the information included in this table

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	? Increase Fluv Cmax and AUC, and Decrease plasma clearance with Cimetidine, Ranitidine, Omeprazole	pharmacokinetic information included
Introduction	On page 201 of the review, the EPC acknowledges the limitation that the review does not examine the issue of maximal statin therapy. We request that this limitation be discussed in the Introduction as well. For patients who are receiving the maximum recommended or tolerated dose of a statin who are not at goal, initiating combination therapy may be the best option.	The section on the scope of the key questions addresses this concern
Introduction	Page seven ? Third paragraph, ecologic study?	Statement revised
Methods	Page 40. "Increasing statin dose or potency could potentially increase frequency of important adverse events such as rhabdomyolysis and liver damage. Combining statin therapy with another lipid-modifying agent could be an alternative provided short and long-term safety and efficacy are established with evidence." This is the worse example I found in the document… a) "could potentially" is redundant ("could increase the frequency" or "potentially increases the frequency." b) "…safety and efficacy are established with evidence." I don't think so… "supported" with evidence, perhaps, but the options are either safe and effective or they are not, "evidence" does not change that. Our knowledge of facts (evidence) might change our approach. Again, neither of these are huge, but it is a looseness of writing that appears in a few spots.	Revised accordingly
Methods	Throughout the report and appendix, statistical analyses (e.g., odds ratios, confidence intervals, etc.) were presented that were created / derived by the authors of the AHRQ review and therefore were not part of the original publications. It would be useful for AHRQ to provide an explanation of the data used to conduct or derive these analyses to better facilitate understanding and assessment of the results. Regarding overall methods, person-time (i.e., duration of therapy) does not appear to be considered in the analyses. This could have significant impact on results.	In systematic reviews statistical analyses are conducted by systematic review methodologists. Only raw/summary data available from reports of studies was used in this report. Both the types of studies included and data extracted were prespecified in order to limit potential biases and are detailed in the methods section. Our sensitivity analysis included long-term studies (> 6 months). However, count data or time to event data were not a common enough reported outcome to be considered for extraction and analysis
Methods	As an initial matter, we note that the Key Questions listed in the draft report have been modified from those that were published in final form back in 2006. The Key Questions that were originally reported as final compared combination therapy versus "high dose" statins. The Key Questions that are included within the draft report, however, compare combination therapy versus "higher dose" statins. While the EPC may	The key questions addressed in this report were worded in a manner which enabled extraction of relevant data. Thre is no published, agreed definition for what constitutes a high dose of statins whereas what is meant by a higher dose is transparent to the reader of the review. Further it is of relevance to the clinical setting in which, for individuals requiring intensive lipid lowering, there is a choice

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	view this change in wording as simply a clarifying change, we think that one might reasonably argue that this change actually represents a substantial change in the focus of the review. We request that, in the spirit of transparency, the EPC acknowledge this change in the report, as well as explain the underlying rationale for the change.	between increasing the statin dose or adding another agent.
Methods	Furthermore, although the revised Key Questions discuss comparisons between combination therapy versus? higher? dose statins, it is important to acknowledge that the EPC has, in fact, framed the key questions much more narrowly: Co-administration of ?lower-dose? statins with different lipid-modifying drugs are compared with ?higher-dose? statins. Lower and higher doses of statin are defined a priori by EPC on page 38. While these cut-offs may ease the burden on the reviewer to systematically abstract data from the literature, they ignore the richness in the potential benefits of other permutations of co-administering other lipid-modifying drugs in combination with low, lower doses of statins vs higher and highest doses of statins. The consequence of this is that, for example, evidence supporting a combination of other lipid-lowering therapy with simvastatin 40 mg relative to simvastatin 80 mg as monotherapy is omitted.	As noted by the reviewer the doses and Key questions addressed in this report are clearly outlined and were established a priori. There are other permutations of dosing which may be of interest and can be explored in other reviews specifically targeted to these areas.
Methods	It also does not take into account that the maximally tolerated dose of a statin can vary from individual to individual. Finally, it does not take into account that patients who are already at the highest tolerable dose of statin but do not meet treatment targets could benefit greatly from the co-administration of other lipid-modifying drugs to lower LDL-C. This is particularly true for the patient population that is the subject of this report (those needing ?aggressive lipid modifying therapy?). Each of these limitations is significant in that they relate to treatment decisions that physicians and patients confront in the real world on a daily basis.	In patients who are already at the highest tolerable dose of statin but do not meet treatment targets, the equipoise is whether to add another non-statin drug vs. to change to a more potent statin … this equipoise is clearly different than the one questioned and explored in this evidence report. In order to address this issue wording has been specifically added to remind the reader that the issue of individuals at maximal statin doses was not the focus of this review.
Methods	We have significant concerns regarding how this report is likely to be interpreted should the inclusion criteria remain in their current form. In order to minimize the potential for misinterpretation, we think it is important than this narrow focus be consistently and clearly described throughout the report. We also think that the report needs to clearly explain the limitations of any conclusions that should be drawn as a result of this narrow focus.	We feel the scope of the review and its purpose is adequately stated and appears in the relevant sections of the report.
Methods	We find it unfortunate that the literature searches ended over a year ago. Considerable literature has been published in the past year that is directly relevant to the subject of this report. A systematic review that fails to include information that is as much as a year old is not a useful examination of the best available evidence. We therefore request that the	We have updated the search to Aug 2008.Our reporting of results is systematic, planned apriori, and not guided by post-hoc considerations of the strength of evidence. A low event rate was not an apriori criterion of withholding the meta-analysis or reporting only CIs and not point estimates

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	literature searches be updated, and the latest information be included. We appreciate the EPC's reluctance to draw conclusions based on weak evidence. We would go so far as to argue that there are times when evidence is too weak even to be presented. For example, an odds ratio calculated for very rare events is not useful and is potentially misleading. In such instances it is often advisable to report the 95% confidence interval, but not the point estimate.	
Methods	Comment: CER focus on LDL-C does not adequately address role of combination therapy to treat mixed dyslipidemia and remaining CVD risk One key issue problematic to the CER's evaluation of combination therapy is its nearly exclusive focus on LDL-C control as a surrogate marker…………	We have revised and included non-HDL-c and TG synthesis for the relevant subgroup of participants with diabetes mellitus.
Methods	Page thirty - How about use of Vytorin?	Vytorin is the trade name for a combination of simvastatin and ezetimibe. Trials involving this combination which met inclusion criteria were included in the review. There may be advantages to combination medications with respect to adherence. These are addressed in the discussion
Methods	Even if the baseline measures are supposed to be comparable in randomized control trials, this is not always achieved, esp for the smaller studies. Change from baseline, or percentage change from baseline should be preferred whenever they are reported or could be calculated, over a post-treatment score.	Because most relevant trials reported continuous outcome data as percentage change from baseline, when available, the synthesis has been restricted to percentage change data only. Otherwise, we synthesized change score data (without combining it with post-treatment mean) when % change was not available for synthesis. In other words, we dropped the pos-treatment mean data from this review
Methods	Is indirect comparison useful in answering the research question in the first place? Would indirect comparison be helpful when head to head trials were not enough in this report? I did not see in the report any plan to compare across statins or the added medication. Indirect comparison could add to the review when used appropriately and assumptions of internal validity and similarity of the included studies are necessary for a regular meta-analysis, too. It is not about the method, but about how to use the method. The reasons listed in line 1133-1135 are NOT reasons not to use indirect comparison -- it is more about whether the includes studies are suitable for indirect comparison or you need an indirect comparison at all for this report.	This issue has been discussed with SRC. We did not consider indirect comparison as we anticipated a high probability of substantial differences in included population in statin monotherapy studies when compared with studies of statin in combination with another lipid modifying drug. Study population in combination studies would likely include more participants with: • severe dyslipidemia • combined dyslipidemia • inadequate response to prior statin treatment, or previously intolerant to maximal statin doses. This justification has been added to the methods section
Methods	Line 1147 - 1149: the logic of the sentence is not clear: what is the relationship between underpowered with 24 weeks or longer?	Revised as follows: *For clinical outcomes and serious adverse events, we anticipated that the available RCT data would be of an inadequate follow-up duration to capture these rare events and decided a priori to include evidence*

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		from eligible NRS that were 24 weeks or longer in follow-up
Methods	For cross-over designs -- page 33, the exclusion criteria is studies without paried observations or within-person difference. Then on page 34, "if relevant cross-over data were not available, only pre-crossover data was extracted and synthesized" -- the two statements were contradictary.	Table is corrected Revise Table 2, I/E criteria (under study design, exclude): *Crossover studies without paired observations or within-person differences or pre-crossover data*
Methods	line 1190: report what effect measures based on paired observations from the same individual.	Unclear comment
Methods	Line 1212-1213: discuss in your results whether this is a source of heterogeneity.	In the methods section, we have now justified and clarified why we do not consider this as an important issue of heterogeneity. *Since it was ensured that extracted indirect LDL-c data pertained to adequately fasted blood samples, indirect LDL-c data were considered valid estimation of true LDL-c (adequate fasting). We, therefore, did not distinguish between direct and indirect LDL-c measurements in quantitative or qualitative syntheses and heterogeneity assessments.*
Methods	Line 1216-1217: The first sentence is not clear --rephrase.	Revised and rephrased: *When reports did not explicitly state or allow clear inference of a dichotomous outcome, data were not assumed. For example, if all-cause mortality was not reported but it was stated that there were no serious adverse events, all-cause mortality was extracted as zero. When both were not reported and it was not clear that all participants completed the trial, all-cause mortality was not inferred*
Methods	Line 1236 - 1242: the grammar does not seem correct.	Revised: *The United States Food and Drug Administration defines SAE as any untoward medical occurrence that at any dose:* • *results in death* • *is life threatening* • *requires inpatient hospitalization or prolongation of existing hospitalization* • *results in persistent or significant disability/incapacity, or* *is a congenital anomaly or birth defect*
Methods	Data extraction section is quite fragmented -- need to increase the flow of the different elements and some sub-headings may be helpful.	Revised accordingly
Methods	Line 1254-1255: Unclear sentence.	Revised *A trial was considered to have employed intention-to-treat analysis when data were reported for all randomized participants. If the number of participants to whom the data belong were not clear, then*

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		authors' statement that ITTA was employed was considered as evidence of ITTA instead.
Methods	It is not clear how information in Table 3 would lead to pre-planned 7440 meta-analysis. However, 7440 would be a number that is way beyond being practical and possible for one review. Decision on combining studies (or not) need evaluation on clinical/methodological diversity and statistical heterogeneity -- it is impractical to consider all these for 7440 meta-analyses.	Clarification provided at the very end below the table for the peer reviewer, but not presented in the report. Further, in the revision we have removed the quantification of planned analyses from the methods section – although Table 3, after revision remains in the report but is now moved to the appendix section.
Methods	In the text, it should be long-term instead of longer term?	Changed accordingly
Methods	Any reference to support the definition of low/high dose for each Statin in page 38.	There is no consensus definition of low and high dose of statins. The distinction was operational, and was derived by consensus
Methods	Provide more clarification of balanced vs. unbalanced design for this report. Usually an unbalanced design means something different. What does it mean that "Both depending upon the comparison being explored"	Revised *Trials investigating several different doses of statin had multiple statin arms. When there were equal number of combination and monotherapy arms, trials were considered to have balanced arms and unbalanced otherwise. Such trials reported data that were only pooled (i.e. across different treatment doses or arms) or belonged to individual treatment arms, or both.*
Methods	Line 1371-1376: What is the point of these statements? Is it that two arms would be included in each analysis? Line 1377-1384: What is the criterion to decide between-group heterogeneity to be high? If it is too high, do you still pool? If not, how do use data in synthesis for such studies? What is the usual situation to have potential poolable treatment arms? Multiple doses? Line 1387-1390: So what are the standard operating procedures to minimize between trial heterogeneity? If you only include selected data, does that introduce bias into the analysis? On the other hand, if you decide a prior to use low vs. high doses, by collapsing several doses for each of the two groups, what is the point of testing heterogeneity among multiple treatment arms (assuming multiple doses) within each study, given you have already decided that it is all right to collapse them?	We understand these comments stem from the confusion created by the order of paragraphs in the draft report, and possibly lack of clarity. Paragraphs have been re-arranged and clarified, and hopefully it will be clear that we have not "already decided to collapse arms". Revision pertains to lines 1367-94. Please note that the SOP to minimize between trial heterogeneity is now stated as is also the criteria of it. Given unbalanced intervention and comparator treatment arms, simply incorporating all arm data introduces a unit of analysis error – double counting of at least one arm. This was overcome by first pooling of individual treatment arm data within appropriate intervention or comparator groups. We attempted within trial, within intervention group pooling of arms, but did not move forward with it if I-squared was substantial (implying dose response effect in this review). When faced with this heterogeneity, we used individual arm data but had to leave out one intervention or control arm (data) from synthesis because there was no corresponding comparator or intervention arm, respectively. So as not to leave the selection of

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		which treatment arm data will be incorporated in quantitative synthesis of evidence to the whims of reviewers, we had an a priori procedure: that the arm with statin doses that are closer/equal to the statin (i.e. statin) in the other arm will be used for dose-non specific synthesis; and closer (but meeting our prior definition of lower or higher statin dose) to the same drug in the other arm for lower vs. higher dose analyses. This procedure dose not introduces bias, but, in fact, is employed specifically to prevent reviewers' selection bias of data.
Methods	If you decide to use a broad category, then you could expect to have much heterogeneity and your data should reflect such heterogeneity. If you think such heterogeneity is too much, then you should not use a broad category in the first place. Using selected data from the study would not solve the problem of heterogeneity and I think, would introduce bias to the analysis.	We believe analytic plans are not guided by post hoc evidence of heterogeneity, but by a priori clinical equipoise (the equipoise determines the question asked and the analysis planned to answer it). A broad category is legitimate if an over all class effect in the general population is under investigation. So the rationale behind the attempt to undertake a meta-analysis is equipoise that the question requests to investigate – that is, despite diversity, is there a common drug effect? But when we actually see that there is no common drug effect because there is substantial between study heterogeneity in estimates, then we do not pool those estimates. In other words, the assumption of a common drug effect was wrong. On a side note, reviewer's comments related to pooling of data do not clearly distinguish between pooling within trials and pooling between trials. To clarify once again, pooling of data within trials was imperative to avoid unit of analysis error when treatment arms within a study were unbalanced – however, if pooling within study arms was deemed not appropriate because of pre-stated heterogeneity cut-off, there remained no option but to select individual treatment arms based on pre-stated transparent criteria to prevent reviewer's selection bias.
Methods	Line 1401-1402: unclear statement and needs clarification. How do you obtain a dispersion measure for this case?	Unclear question, which "case" is the reviewer asking about?
Methods	Line 1408-1409: What about the pre-crossover data mentioned earlier? Based on the current method manual, it is accetable to use pre-crossover data.	Revised *Data from crossover trials were combined with parallel non-crossover trials only if appropriate paired or pre-crossover data were available*
Methods	Based on current method manual, both test of heterogeneity and I^2 statistic should be used. It it not appropriate to use I^2 > 50% as a criterion to decide whether or not to pool. It is too simplistic and not considering the research question, clinical and methodological diversity. In practice, there are many cases that a meaningful combined estimate could be obtained with I^2 > 50%. Actually, for the current method	This issue has been discussed in a teleconference with AHRQ and SRC. We reproduce below our perspective that we shared with SRC. In the meeting it was decided that we do not need to justify why we do not pool. However, one might need to justify why pooling was undertaken. Below we explain our modus operandi. We want to emphasize the distinction between the decision to

| | manual, it specifically avoids to make recommendations on the decision to combine (or not) based on a test or test statistics. In the original paper, I^2 > 50% is defined as substantial heterogeneity but it is not tied to the decision of combining data. Instead, similar to the method's manual, it says that "Quantification of heterogeneity is only one component of a wider investigation of variability across studies, the most important being diversity in clinical and methodological aspects. Meta-analysts must also consider the clinical implications of the observed degree of inconsistency across studies." | synthesize evidence (which can be qualitative) with the decision to statistically pool or meta-analyze it to obtain a mathematical overall effect.
As stated above, synthesis of evidence is a dictate of the question posed for a systematic review. When the question enquires effect of an intervention in clinically diverse population, then of course it is investigating a general or common drug effect irrespective of clinical diversity. Synthesis of evidence must be undertaken to answer this question regardless of preconceptions of heterogeneity. Whether the synthesis will be qualitative or quantitative is a determinant of substantial statistical heterogeneity. What we pre-stated was that pooling (number crunching) will not be undertaken given substantial statistical heterogeneity. We as a group are uncomfortable to average numbers given high I-sqaured (regardless of presence or absence of obvious clinical or methodological diversity) because we feel that unmeasured or unreported diversity could be the underlying explanation. Thus to strive for a summary measure is nothing more than an obsession to homogenize heterogeneity. However, that we do not undertake statistical pooling in the face of substantial statistical heterogeneity should not be construed to mean that we shall not attempt to synthesize evidence.
Our strategy is one of the several currently recommended approaches (see section 9.5.3, Cochrane handbook version 5.0 updated February 2008). Chi square statistic is a less accurate measure of statistical heterogeneity compared with I-sqaured, especially when trials are small in size or many in number, -- -- Higgins and Thompson, 2002). Statistical heterogeneity could be due to clinical differences between trials or methodological differences (publication bias, methodological quality, trial duration), or even related to unknown or unrecorded trial characteristics (Thompson SG, 1994). In other words, substantial heterogeneity needs explanation, but lack of explanation should not diminish its impact when considering pooling of results. Being cautious of these differences (regardless of our ability to explain them) we chose to qualitatively synthesize results and explore heterogeneity given I-squared greater than 50%, as one of the currently practiced approaches. A summary measure in face of substantial heterogeneity leaves one with an open question -- to what clinical and methodological scenario does it apply, and is it the true middle ground?
On the other hand, when an hypothesis explores a common drug |

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		effect across diverse populations, then it is not unreasonable to consider meta-analysis when statistical heterogeneity is low, and to consider qualitative synthesis when heterogeneity is high.
Methods	As stated in P37, the general approach in evidence synthesis, the first layer is to "synthesize evidence regardless of statin type and dose, and trial population (does addition of another drug to statin therapy offer incremental benefit?)" -- therefore this is a very broad question with much explected heterogeneity and it is reasonable to assume the effect measure to have a distribution, if the research question itself is meaningful. Then "I^2 > 50%" is not appropriately used here for another reason as it is calculated based on the assumption that "all studies had one single treatment effect size".	We respectfully disagree. The underlying assumption of the reviewer is that given clinical diversity, there will be an effect that will be widely and variably distributed – this is one hypothesis. However, in a broad question there are two other possibilities – that there is no difference between treatments across all populations (the null effect) as well as that there is a common intervention effect across different populations. Give the two other possibilities, *attempt* to meta-analyses is not unreasonable – especially if the question posed investigates a common drug effect. Given the situation in which the data brings to light (post-hoc) substantial heterogeneity in treatment effects, a pooling of numbers implies averaging not the same drug effect but different ones.
Methods	Dermonian and Laird method is not good for rare events of binary outcomes, even if in the presence of heterogeneity. Use a fixed effects model instead, based on current research and the methods manual. For example, the results in Figures 3-5 are too rare for D & L method. Please make correction for other such analyses in the report.	Methods section is modified to reflect this and analyses are rerun with Peto odds method where appropriate (i.e. event rate <1%)
Methods	Is there a reference for 10 studies of Egger's regression test?	No. This is how we chose to operationalize just so the power of the test is not substantially compromised by a much lower number of studies
Methods	Qualitatively, or quantatitively, provide description on how you could address/explore heterogeneity among studies.	Revised. Qualitative exploration of heterogeneity is now added to the review methodology to be presented under each applicable analysis. The explored covariates are pre-stated. However, we would like to draw the attention of the reviewer to the table of planned analyses (Table 3 draft submission). Additional analyses looked into trial duration, allocation concealment, drug type and dosage, and clinical subgroups. These separate analyses were nothing but exploration of heterogeneity of the more general analyses! The only subtlety was they did not all come under one subheading.
Methods	I had a hard time to follow the data synthesis section in terms that again, it is quite fragmented and lacks structure. Provide a better organization of the section, corresponding to KQs, if possible, and put common stuff applying to all KQs together. Use sub-heading when necessary.	As stated above, revised and reorganized
Results	"harms and adherence" could include changes in mentation (depression, fuzzy thinking, etc. See Golomb et al.	Harms could include many other outcomes, but the scope of the review required that a select few important harms be considered for confirmatory analyses undertaken in answering the posed questions

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Results	I don't believe a low-risk person with an LDL of 191 is in need of "intensive lipid lowering." I am not certain where this thought comes from. The person could achieve goal (160) with diet alone….. ?????	The ATP III report defines LDL-c > 190 mg/dl as a severe elevation after therapeutic lifestyle changes. Many elevations of this degree have a strong genetic component, and as such this population is likely to contain a number of individuals who require intensive lipid lowering. In a low risk person, to decrease LDL-c to 160 (the recommended target by the ATP III panel), the recommended starting dose for the most potent statin is 20 mg, our defined"higher" statin dose by definition for rosuvastatin (Crestor package insert). Doubling of the dose will decrease LDL-c by an additional 6% at the most {Miller M. Optimal treatment of dyslipidemia in high-risk patients: intensive statin treatment or combination therapy? Prev Cardiol. 2007;10(1):31-5}. Thus based on the definitions in this report this group was prespecified as a population of interest with regard to the Key questions.
Results	The "outcomes without evidence" sections seem to vary. By this I mean if you look at the surrogate outcomes with evidence and the outcomes without evidence for any one questions across all drug families, you don't have a perfect overlap of outcomes. I think a table should be created for each of the three questions. Then in the table it would be noted if the outcome has evidence or it doesn't. If it has evidence, it is then presented. The way it is now, some outcomes are not reported for some drugs. (I am pretty sure this is right, but it was confusing. A Table would get rid of the confusion. Throughout the report the headings have the format of (for example): "Participants reach LDL < ATPIII targets: fibrate-statin combination versus statin monotherapy." Another small point, but I think it helps in the reading. It is the Fibrate section, not the reach LDL target section, so I suggest flipping all of these headers, e.g., "Fibrate-statin combination versus statin monotherapy: participants reach LDL < ATPIII targets" The organization was hard to follow. Could have more liberal use of "Key Point," as this was great. The Table I mentioned above would help.	Revised accordingly
Results	On page 44 of the draft review, the EPC lists publications for which additional data was requested, but not received. Because the EPC contacted the study authors, rather than the study sponsors, response was slow and fragmented. Our involvement with requests for data for the review began in May 2008 when lead authors of some manuscripts reporting the results of sponsored studies started to forward requests from Dr. Moher of the Chalmers institute. After determining the who and how of acquiring the	Comment addressed in extensive discussions with SRC. Additional data that conformed to guidelines passed on to the Industry by the SRC have been included

Section	Comment	Response
	requested information, acquisition of the data began. A point person was established and this was communicated to Chalmers with the request to notify us of any outstanding issues for related studies. We were informed on July 15 that the data base was closed and that any data submitted would not be used. We were surprised by this development, as none of the letters mentioned a submission deadline. Timelines: Letters from Chalmers to lead authors: April 16 to May 2, 2008 Forwarded to Merck by lead author: May 5 to May 23, 2008 Contact with Chalmers: May 23 and June 2, 2008 Closed study July 15, 2008 We request that mechanisms be put in place for improved communication between the EPCs and sponsors of clinical research to avoid such issues in the future.	
Results	Paragraph 3 Ballantyne et al (EXPLORER trial) reference is listed as "while funding was not reported or unclear"	The funding was not reported in the study publication.
Results	Under study design and population characteristics, consider adding?a history of muscle-related side effects with a statin (other than fluvastatin) [reference 104]? to the following sentence: Across trials, participants were of diverse clinical characteristics, including those with familial hypercholesterolemia and LDL-C above 190 mg/dL, diabetes mellitus, established vascular disease and/or CHD risk equivalent, and impaired renal function, ethnicity of African descent, and no prior statin exposure	The referenced study did not report pre-specified outcomes considered for Key question 1 – so this qualification is not to be reported under this ection of the report.
Results	Last sentence of last paragraph, add verbiage from publication: but was not considered to be related to study treatment. (pg. 676 in pub)	We are not clear exactly which study is being referred to here
Results	Under Serious Adverse Events in Table 15, the Derosa study (reference 118) should be included. The study reported no SAEs.	Thank You. The study was added to the Table and numbers updated accordingly.
Results	(page 115) Global change: for reference #121 (Durrington), fenofibrate dosing was 67 mg TID, not 67 mg/day. Requesting to make this correction of the following pages: Pg. 115, 118, 119, 120, 121, 122, 211, throughout appendix (Pg. 115) In paragraph 2 (reference #121), description of trials methodology unclear. Consider editing methodology on pg. 188 and 121 as well. Methods from publication described below: "In this study, following a 6-week double-blind phase in which patients received rosuvastatin 5 mg, rosuvastatin 10 mg, or placebo, patients were force-titrated at 6-week intervals in an 18-week, open-label phase in	Report and appendices revised accordingly for the study by Durrington et al. Thank You. The assessment for study quality requires certain information. We extracted specific elements of study design (randomization, double-blind, ITT, etc) and this information is not available in the report.

Section	Comment	Response
	which patients from one of the placebo groups received rosuvastatin 10, 20, and then 40 mg; patients from the other placebo group received fenofibrate 67 mg QD, BID, and then TID; and the rosuvastatin 5 and 10 mg groups continued receiving rosuvastatin at the same dose in addition to force-titrated fenofibrate 67 mg QD, BID, and TID. Dose titration was not done in patients with LDL-C ≤50 mg/dL."	
Results	………. These studies discussed heretofore underscore the clinical efficacy of combination therapy and urgent need to expand beyond LDL-C treatment alone to treat multiple lipid abnormalities and reduce residual CVD risk	Non-HDLc and TG are now investigated in relevant subgroup
Results	Paragraph 5 States for ref 122, between-treatment differences in mean percentage changed of less then 5%. Looking at publication, TC: HDL-C ratio: ATV/ERN-50%, RSV/ERN –84%, SMV/EZE –47%, RSV –43%	This portion is the ezetimibe statin combination section. Between treatment difference here would be -47 – (-43) = - 4%
Results	We will provide under separate cover data from nine studies, all of which compare a combination of ezetimibe and statin to a higher dose of the statin. ………………………	Issue addressed in discussions with SRC and additional data from authors has been incorporated in the report
Results	Finally, we note that the EPC appears to have misinterpreted the study by Stein et al. 2004 (Reference 140 in the Draft Report). The study compares statin/ezetimibe combination therapy to a higher dose of atorvastatin monotherapy. This is noted in the evidence tables of Appendix D, but not in the text of the review. Instead, data from Stein 2004 is combined with data from trials in which statin monotherapy is compared to the same dose of statin plus ezetimibe. The study design, as correctly recorded in Appendix D is the design most directly relevant to the Key Questions as designated by the EPC. We request that this study be considered in combination with others that share this design (i.e., Feldman et al 2004, Gaudiani et al., 2005 and others as presented in these comments). The study was penalized in the GRADE tables because of possibly inadequate concealment of allocation. As is the case for all Merck/Schering-Plough-sponsored studies, allocation was performed at a central location by personnel who were unaware of the identity of the patients being allocated. Clinicians at the individual study centers were unaware of the treatments to which patients were assigned. We request that the GRADE score of the study be modified accordingly.	Stein et al. 2004 (Reference 140 in the Draft Report) compared atorvastatin 10-40 + ezetimibe vs. atorvastatin 20-80 as monotherapy for the longest follow up of 14 weeks. As per our pre-specified definitions of lower vs. higher dose of atorvastatin (see methods section), this treatment comparison was not eligible for lower statin in combination vs. higher dose statin monotherapy analysis.

To rate allocation concealment, we used Shulz criteria. We can verify that there is no reported information in the paper meeting Shulz criteria demonstrating adequate allocation concealment |
| Results | Under study design and population characteristics, consider the same addition as above, a history of muscle-related side effects with a statin (other than fluvastatin) [reference 104]? Under the surrogate efficacy measures, add the LDL-C lowering results from Stein (reference 104). Also add LDL-C results to the Table on page | The trial population is better described under CPK results write-up. The trial was not included in LDL-c continuous outcome synthesis because we could not obtain numerical data of dispersion from the report (dispersion data was reported in figures only) – note that we specifically did not impute SE or SDs or estimate them from figures |

Section	Comment	Response
	75	
Results	The results from Stein (reference 104) should also be added to the myalgia section in the text and table. In this study, muscle-related side effects (MRSE) included myalgia (defined as muscle ache, pain, or discomfort), muscle cramps, lack of strength during effort, heaviness, and/or weakness without creatine kinase (CK) increases of greater than 3 times the upper limit of normal (ULN)………………..	MRSE is by trial's definition not synonymous with myalgia hence was not included in this category
Results	In both the CPK and rhabdomyolysis sections, a sentence describing the Stein study (reference 104) states that patients previously had statin associated ?myopathy?. Myopathy should be replaced with ?muscle-related side effects,? which is defined above. History or evidence of myopathy (muscle pain with creatine kinase increase >10 times upper limit of normal) was actually an exclusion criterion of the study. The Stein data can also be added to the section "Participants with at least one adverse event" in the text and table. 107 patients (54%) reported an AE (39 patients on ezetimibe, 34 patients on fluvastatin XL, and 34 patients on fluvastatin XL/ezetimibe)	There is a potential to confound the term myopathy with myosistis. Myopathy (muscle disorder) includes any one or more of myalgia, myosistis, muscle discomfort and weakness – however, just so there is no further confusion, we have revised the term as suggested The paper stated "Overall, 107 patients (54%) reported an adverse event……." This implied that we are dealing with patient reported AE and not all (i.e. laboratory) AE
Results	One key issue problematic to the CER?s evaluation of combination therapy is its nearly exclusive focus on LDL-C control as a surrogate marker. Emphasis on LDL-C reduction alone would be appropriate if the goal of combination therapy was solely to decrease LDL-C. However, as identified by the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)1, treatment for dyslipidemia is not only directed to attainment of LDL-C goals alone. …………… The CER's lack of recognition of non-HDL-C as a therapeutic target is surprising given its prominence in NCEP Guidelines and the increasing significance of non-HDL-C in emerging clinical studies 1-2 Furthermore, Abbott maintains that emerging clinical data supports the position that significant cardiovascular risk remains in numerous patients, even after LDL-C has been optimally treated with statin therapy. Part of the modifiable residual risk is attributable to elevated levels of triglycerides, elevated non-HDL-C and ApoB as well as lower than optimal HDL-C.	Non-HDL-c and TG are now investigated in the relevant subgroup for this review – i.e. those with Diabetes Mellitus
Results	Data from Derosa (reference 118) can be included in the AST/ALT section and the CPK section.	Information on adverse events was only collected if dichotomous data were available (number of people developing a certain AE in each arm – see methods section of the report). Table III of the current study only reports the mean difference from baseline of CPK,

Section	Comment	Response
		AST/ALT
Results	(page 117) Under Surrogate Outcomes – Please note the Durrington study evaluated ADA LDL-C goal, while heading of section states ATP III targets. (same comment on pages 122 and 127) (page 121) Under Participants with myalgia: - In the sentence starting with "One trial compared conditionally dose rosuvastatin…." Switch the word "conditionally" to "fixed" and the words "fixed higher" to "conditionally"	All patients in this trial had diabetes mellitus – i.e. were a high-risk group. According to table 5, LDL-c goal of < 100 mg/dL as per ADA also happens to be the same at ATP III LDL-c goal. Therefore, ATP III LDL-c goal is applicable to this study. The comment on fixed dose addressed accordingly in the report
Results	(page 142, para 5) Suggest editing line 5 as follows to increase clarity: Combination therapy increased the percent change significantly for HDL-C compared to monotherapy whereas higher dose monotherapy decreased the percent change significantly for LDL-C compared to combination therapy.	We would like to thank the reviewer for the suggestion. The problem is that in the latter part of the suggested revision, the intervention and control are now reversed and so the analysis would need to be negative instead of positive, which is against the standard norm that we have attempted to maintain throughout the manuscript
Results	It is interesting to note within the conceptual framework schematic in figure 1 on page 27 that the EPC had interest in studying the elderly as a special population subgroup. It appears that it established a cut point of >80 years of age, which represents the very aged, not the elderly. The traditional medical regulatory age for defining the elderly is >65. With extended longevity in recent decades one might consider extending that definition an additional ten years to 75 years of age. It seems that the EPC on behalf of the AHRQ might reconsider these methods because of the increasing population of older persons………………………………..	A decline in cellular and physiologic system increases vulnerability to adverse events of treatment. Subjects who are more likely to experience adverse events associated with higher dose statins or combination therapies are often excluded from clinical trials – generalisability underestimates the true adverse event rate (Davidson MH, Robinson JG. Safety of aggressive lipid management. J Am Coll Cardiol, 2007; 49(17):1753-62). Such patients are frail elderly, with small body size, and diminished renal and hepatic function. Although there is no universally accepted definition of frailty, it is adult population with reduced stress tolerance which is likely to experience different (degree, intensity and variety) drug associated efficacy and harms than the general adult population. Frailty affected 7% of adults over 65 years of age compared with 25-40% of octogenarians and older (Strandberg TE, Pitkälä KH. Lancet. 2007 Apr 21;369(9570):1328-9). Our apriori subgroup was therefore those > 80 years of age. In the discussion section we refer to the evidence the reviewer has cited
Results	Any implication on your results when you detect lateral asymmetry? Why one-tail P-value? (page 62). You are doing a lot of tests here and need caution against multiple tests.	Revised to 2 tailed p value. Implications will be dealt with in the discussion
Results	[As a result of a very broad question and a strict criterion of I^2 < 50% for combining, generally only non-significant results were combined (other than some cases that 2 or 3 studies showed similar significant effects, or only smaller studies were included so within study heterogeneity is high) while significant results usually showed a range across studies with I^2 >	Unclear comment -- sounds like this is a repetition of previous comments

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	50, even if similar set of studies were included in both situations with similar clinical/methodological diversity.	

Results	Improve the quality of included figures
	    1. The plots used different size of fonts -- for some figures, for example, figure 7 and other similar ones, the font size is too small, and also, it is more readable to have a line through the null point (in Figure 7, it is 1).
	    2. The squares are too big to see the confidence interval, for example, in Figure 8, 11, and others and to evaluate the heterogeneity among studies. The current plots give an impression of quite homogeneity. Also the scale in x-axis needs to be adjusted to show heterogeneity appropriately. This applies to many other plots, too, such as Figures 9, or 14, and others.
	        3. Figure 13, ORs and CIs are not shown properly. Similarly Figure 29?
	    4: "Favors monotheraphy" is on the left side of axis in some plots and right side in others -- make it consistent across plot if possible.
		Revised accordingly

Discussion	Importantly, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III Guidelines specifically recognize the need to treat beyond LDL-C by establishing non-HDL-C as a secondary target of therapy when triglycerides are ³ 200 mg/dL. The CER?s lack of recognition of non-HDL-C as a therapeutic target is surprising given its prominence in NCEP Guidelines and the increasing significance of non-HDL-C in emerging clinical studies 1-2……………………… Part of the modifiable residual risk is attributable to elevated levels of triglycerides, elevated non-HDL-C and ApoB as well as lower than optimal HDL-C. While additional studies are required to fully characterize the benefit of treating these factors, current Abbott-sponsored studies support the value of niacin+statin and fenofibric acid+statin combination therapies to comprehensively treat multiple abnormal lipid parameters and improve CVD outcomes.	Non-HDL-c and TG outcome measures have now been considered for the relevant subgroup population of those with diabetes mellitus
Conclusion	We agree with the overall conclusions regarding combination therapy versus high dose statin monotherapy, based on the currently available evidence. However, we would like to note that there are patient populations in which combination therapy may be appropriate, such as patients with elevated triglycerides who need to achieve secondary goals (e.g. NCEP ATP III non-HDL goals).	Non-HDL-c and TG outcome measures have now been considered for the relevant subgroup population of those with diabetes mellitus. The report has been modified.

Section	Comment	Response
Future Research	Fenofibrate and statin combination therapy Two major clinical trials are now in process….. …..	The SEACOAST studies are included, OCEANS was excluded during screening
Tables	Minor issues: Total trial sums at bottom of Table 4 seem incorrect (e.g., 13 trials for ezetimibe). Total for ezetimibe should be 37. This may be a cut-and-paste error. The study totals for niacin indicate there are 37 trials. Correct total is 13.	Revised
Tables	Table 22, first two rows of the results were same but different number of studies included? Table 35: the first four rows of the results were same but different number of studies included?`	The numbers are correct. The reason that they are the same is because events (e.g. All-cause mortality) was reported to have occurred in only two studies (Refid 421, 16392) while the other two studies provided data that was not analyzable (e.g. no cases of mortality in either arm). The numbers are correct. The reason that they are the same is because events (e.g. all-cause mortality) was reported to have occurred in only one study (Refid 6078) while the other two studies provided data that was not analyzable (e.g. no cases of mortality in either arm)
Figures	In some cases, for example, Figures 54 and 55, or 61, the heterogeneity could be due to one or two outlier studies. Exploration of heterogeneity should look at such studies and sensitivity analysis could be done by excluding such studies.	In general it is unwise to exclude studies from a meta-analysis on the basis of their results. However, only for a very obvious identified reason would we exclude outliers and rerun a particular analysis. Analysis in Figure 55 was re-run without the outliers and reported in the results section. Figure 54 and 61 are no longer being run in the update because they are post-treatment means/ change scores – see revised methods section
References	No comments submitted.	
Appendix C	C-1, C-2, C-3, C-4, C-7, C-8, Durrington (2004) should be as follows: Rosuvastatin 40, NONE 51 Rosuvastatin 10, Fenofibrate 67 titrated to TID 53 Rosuvastatin 5, Fenofibrate 67 titrated to TID 60 Rosuvastatin 5-10, Fenofibrate 67 titrated to TID 113 C-3 Achieving ATP III targets - participants with diabetes mellitus Durrington (2004) should be as follows: Rosuvastatin 40, NONE 50 Rosuvastatin 10, Fenofibrate 67 titrated to TID 53	Revised accordingly (maximum dose of 200 mg/day)

Section	Comment	Response
	Rosuvastatin 5, Fenofibrate 67 titrated to TID 60 Rosuvastatin 5-10, Fenofibrate 67 titrated to TID 113	
Appendix C	C-5 McKenney (2007-2): "Atorvastatin 20 Niacin (ER) 1000 65"; Replace Atorvastatin with Rosuvastatin Capuzzi (2003) - Total adverse events: Suggest changing to: Rosuvastatin 40, NONE 46 Rosuvastatin 10, Niacin (ER) 2000 80 Rosuvastatin 40, Niacin (ER) 1000 72 Rosuvastatin 10-40, Niacin (ER) 1000-2000 152	Revised accordingly for both trials
Appendix D	D4 Ballantyne 2007 (global change needed throughout Appendix D): • Change Trial baseline LDL-C: mean 191 mg/dL monotherapy and mean 189 mg/dL in combo therapy D19, D82 Catapano 2006 • Column 3 Combo Statin dose: change rosuvastatin to simvastatin • Column 4 change N to 1427; Column 6 change N to 1428 D36, D45, D51, D55 Kosoglou 2004_a (global change needed throughout appendix) • Change columns 4 and 6 to N=12 D53 Stein 2004 • Add to column 2: documented CHD • Delete rosuvastatin from column 3 and change to atorvastatin	Corrected D 19 Catapano corrected, D 82 does not need to be corrected – see table 3 in the paper For Kosoglou 2004_a, the suggested global change was made to column 4 only. Column 6 was correct, see Table 2 of the paper To Stein 2004, correction was made in column 3. However, we disagree that column 2 (population) should be corrected to state documented CHD since only 30% of participants had documented CHD
Appendix D	D118, D120, D125, D128 McKenney 2007 • Participant column is empty D127-D136 Capuzzi 2003 • Column 4: delete 2000; various doses were used depending on arm D125-D136 McKenney 2007 1 • Column 4: delete 2000; both 1000 mg and 2000 mg were used depending on arm	Revised accordingly for the suggested studies

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Appendix D	Comment: - For all rows including Stein (2008) replace ?myopathy? in the population description with ?muscle-related side effects.? - On page D-68, participants experiencing an adverse event, and page D-85, participants experiencing myalgia, include the data from Stein (2008). - On page D-75, the number of withdrawals due to an AE with monotherapy should be 5 not 6 in the Stein (2008) column.	Muscle related side effects replaced the term "myopathy" These two comments have been made earlier in this section and are addressed above. One patient the reviewer has not counted is the one who withdrew due to abnormal labs – abnormal labs would also count as adverse event. Therefore, the number remains 6
Appendix D	- Add data from Derosa (2004) to page D-107, participants experiencing elevated serum AST and/or ALT, and to page D-108, participants experiencing CPK greater than 10 times ULN.	Information on adverse events were only collected if dichotomous data were available (number of people developing a certain AE in each arm). Table III of the current study (Table III) only reported the mean difference from baseline of CPK, AST/ALT
Appendix D	- On page D-149, the number of participants withdrawing due to an AE, should be 1 with combination therapy and 4 with fluvastatin therapy in the Sprecher (1994) trial.	Revised accordingly
Appendix E	E-10 All cause mortality, participants with events - statin monotherapy: 1/53 should be 1/51 (placebo/fenofibrate group vs. placebo/rosuvastatin group). E-10 Participants reaching ATPIII LDL-c goals (follow-up 18 weeks), Participants with events – combination therapy: 83/110 should be 85/113 (75%)	All cause mortality: changes made on GRADE table Appendix E, fibrate all-cause mortality in intensive lipid lowering treatment i.e. ref id 595, Durrington (2004) Changes were made for ATPIII LDL-c goals accordingly
Appendix E	Derosa (reference 118) can be added to Table 52 as the study included diabetic patients and reported no SAEs.	Derosa did measure SAE – zero rates in both arms. Table 15 was updated Derosa 2004, and Table 52 GRADE was also updated stating that this study had NO SERIOUS ADVERSE EVENTS
Appendix E	Comment: The conclusions of the review are justifiably weak, because they are supported by evidence described as low quality. However, because of limitations of space, papers seldom describe full study methods. Here, we provide additional data on five key studies, and request that the GRADE tables be revised accordingly. While we recognize that many low-quality studies are published each year, such studies are uninformative, and uninformative studies do not meet our needs. For this reason, we have standard procedures to ensure that double blinding is maintained, allocation is properly concealed and proper intent-to-treat (ITT) methods are followed. Our study centers are under constant scrutiny, by our own inspectors and those of the FDA, to ensure that these procedures are followed. Feldman et al. (Ref 38 in the draft review)	We considered ITT analysis based on the definition employed in the Cochrane handbook and the paper of Montori and Guyatt CMAJ; 165 (10): 2001: 1339-41.

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	Feldman was penalized because no ITT analysis was described. We find this surprising, because the publication states that "Efficacy analyses were based on a modified intention-to-treat population that included all patients with a baseline measurement and ?1 measurement after baseline?For the primary time point (last measurement in the first treatment period before possible simvastatin titration) and the secondary time point (last measurement in entire study), data were carried forward."	Feldman et al.'s and Gaudiani et al.'s studies did not qualify ITT because analyses were modifications of what is considered an intention to treat. By definition ITTA would include all patients randomized. Events post randomization affecting analysis may lead to post randomization imbalance
	If this description is insufficient, we request that the EPC explain what additional information is required.	
	Gaudiani et al. (Ref 116)	
	Gaudiani was penalized for lack of an ITT analysis, despite the description in the publication: "All analyses were based on a modified intention-to-treat population, which included all patients with a baseline and at least one post-treatment measurement." If this description is insufficient, the study protocol (on file with the FDA) states "For the efficacy analysis, the primary analysis will be an intention-to-treat approach after 12 weeks of treatment. When a patient has multiple measurements within a relative day range, the valid measurement from the last visit will be used in the primary analysis. Dropouts for various reasons are not unexpected, and they will be included in the analysis via an endpoint approach. Every patient?s last observed value will be used in the primary analysis."	
	The table further states that there were "2 trials, one with adequate allocation concealment and double-blind procedure,38" implying that Feldman et al. (Reference 38) had adequate concealment and double-blind procedure while Gaudiani did not. Again, this is surprising, since the Gaudiani publication describes that study as double-blind, while the Feldman publication never uses the term "double-blind." Both studies utilized appropriate blinding procedures. Neither the patients, clinicians or laboratory personnel were aware of the patients' group assignments. After randomization, both the patients and clinicians were blinded to the results of the interim lipid analyses……….For both studies, allocation occurred at a central location by personnel blinded to the identity of the patients……….	Appropriately corrected. However, we choose not to consider additional info in quality assessment of these studies because the information did not come to the EPC through one of the authors.
	Quotes from Protocol 023 (The Feldman study)………….	
	Quotes from Protocol 21 (The Gaudiani study)…………….	
	Kastelein et al. (Ref 33)	
	Kastelein was penalized because "Double-blind, and intention-to-treat	

Section	Comment	Response
	analysis procedures were not reported." despite the fact that the study was described in the publication as "double-blind" and Jadad et al., 1996 explicitly states that "A study must be regarded as double-blind if the word "double blind" is used." Davidson et al. (Ref 35) Davidson was penalized because "no intention-to-treat analysis was described". Here is a description of the ITT analysis, taken from the Clinical Study Report, on file with the FDA. "For the endpoint analysis, any dropout before Week 12 would be included in the analysis as long as the subject had a valid postbaseline lipid value. That is, for the endpoint analysis, data would be carried forward to endpoint in the Intent-to-Treat analysis." Stein et al. (Ref 140) Stein was penalized because of possibly inadequate concealment of allocation. Allocation was performed at a central location by personnel who were unacquainted with the patients………..	Kastelein's paper was considered double blind, however, an additional score was not given for appropriateness of the method of double blinding. Again, we considered ITT based on the definition employed in the Cochrane handbook and the paper of Montori and Guyatt CMAJ; 165 (10): 2001: 1339-41. Since number analyzed is not equal to number randomized, we did not consider it as an ITTA. The appropriate reference is 135 not 35. We considered ITTA based on the definition employed in the Cochrane handbook and the paper of Montori and Guyatt CMAJ; 165 (10): 2001: 1339-41. This definition does not qualify as an ITTA – because not all randomized subjects may have a valid post-baseline measurement. Additionally, the footnote to Table 2 in the paper suggests that number analyzed was not the intention-to-treat population (i.e. not all randomized participants were included in analysis) We have verified that our quality assessment was appropriate and no change has been made because additional information cited here was not sent to us from one of the authors/investigators.