Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Combination Therapy Versus Intensification of Statin Monotherapy: An Update.*

Draft review available for public comment from August 5, 2013 to September 3, 2013.

Research Review Citation: Monroe AK, Gudzune KA, Sharma R, Chelladurai Y, Ranasinghe PD, Ansari MT, Robinson KA. Combination Therapy Versus Intensification of Statin Monotherapy: An Update. Comparative Effectiveness Review No. 132. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2012-00007-I.) AHRQ Publication No. 14-EHC013-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator	Section	Comments	Response
Peer reviewer #1	Executive Summary	1A) ES2--lines 37 to 44 These KQ's are poorly designed. It was known that little new info was published since 2009 to answer KQ1 the way it was formulated. The whole effort falls apart from the design of KQ1 1B) KQ2 can be answered better by using the modeling approach I suggest above in my General Comments 1C) KQ3 is especially problematic. We all are taught not to over-interpret subgroups in clinical trials. In fact, subgroup analyses are considered hypothesis generating rather than clinically directive. To actually have AHRQ propose that subgroup analyses be used to drive clinical recommendations bumps up against one of the major tenets of interpretation of evidence. KQ3 should never had been proposed that way it was written.	Our review was an update of a prior EPC review. The KQs in our review are the KQs from 2009 review we were tasked with updating. When to conduct an update (what is sufficient number of new studies?) and when an update becomes a new review (i.e., when questions are modified) are open methods and policy issues. The rationale for KQ was to determine if the addition of an agent with a different mechanism of action from a statin would provide benefit above simply increasing statin, without increased adverse effects. This information may be useful for patients who do not tolerate higher dose statins. We have added discussion in the Introduction and Discussion to further outline this rationale and to discuss the other related evidence. We agree that new trials with statin mono vs. statin + "add on" combo agent (e.g., ACCORD, AIM HIGH) have clinical outcomes. They are important trials which answer the question of whether to add on a combination agent compared to same dose of statin. However, since the results of IMPROVE-IT trial (ezetimibe + statin) are not yet released a review with those additional questions (add on combination vs same dose statin) would be of limited value at this time; the report would need to be updated as soon as the IMPROVE-IT results are released It is true that subgroup analyses are hypothesis generating, however, the presentation of results by subpopulation is routinely considered. Modeling would not be appropriate given the inadequacy of the evidence.
Public reviewer #1 Richard Chapell	Executive Summary	ES2: "In addition, combination regimens may worsen clinical outcomes, such as the potential worsening of atherosclerosis reported with the combination of statin and ezetimibe." This is a very specific call-out to be included in the Background section. For reasons that will be discussed below, under "PG5", we believe this statement is not supported by the available evidence and recommend that it be removed. We also submit that such conclusions should be presented in the full context of the available evidence so as to minimize the risk of misinterpretation. ES6: According to the cited reference (Weng et al., J Clin Pharm Ther 2010; 35:139), rosuvastatin is a high potency statin at dosages above 5mg/day, not moderate as stated in Table 2. Please consider revising the analysis accordingly.	ES2: Simva vs. Simva/EZE: no benefit on CIMT mono v combo (Kastelein 2008). Statin/niacin vs statin/EZE: fewer adverse cardiac events with statin/niacin v statin/EZE (Taylor 2009), and another trial found that adding niacin to a statin did not improve outcomes (Boden 2011). Concern that possible explanation for these findings is that eze worsens outcomes, waiting for IMPROVE-IT for definitive answer. We have added text to the introduction section explaining that there is theoretical worsening based on above results. We also note that the IMPROVE-IT trial may be necessary for definitive answer. ES6: We agree and have revised this section and the analysis accordingly: rosuvastatin is evaluated as a high potency statin at dosages above 5mg/day, not moderate as previously stated ES11(a): Serious adverse events (SAE) were abstracted and assessed as reported and defined by the study investigators. None of the included reports provided a definition of SAE. It is likely that the FDA classification was used, but this is not stated explicitly. ES11(b)/ES16: We previously reported high SOE favoring monotherapy comparing SAEs between combination therapy and monotherapy. As shown in Table 10 of the report, the percentage of patients in each arm experiencing an SAE in each arm was low overall. There were no statistically significant

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		ES11(a): Table lists "Serious Adverse Events" as an outcome. We were unable to locate a definition of this term in the document. Therapeutic decision-making involves assessment of the trade-offs between potential risks and potential benefits of a given treatment. If the potential risks are not defined, then the decision-maker in not sufficiently well informed to make the best decision. We recommend that the authors define what is meant by "Serious Adverse Events". If different studies define the term differently, we suggest that the authors define the term for each study and assess whether it is appropriate to combine data from studies defining the term differently. ES11(b): High strength of evidence that dual therapy increases serious adverse events. As will be discussed below, we believe this conclusion is not supported by the available evidence. ES16: "We were unable to grade any strength of evidence as high, despite numerous trials within some comparisons." This statement is inconsistent with Table 3 of the executive summary, pages 37, 123 and 131 of the main document, and other places. While we do not believe that the strength of evidence can accurately be characterized as High in the one comparison and outcome for which that rating is applied, we also point this out to apprise the authors of potential inconsistencies in the document. We suggest that the document be reviewed to eliminate such inconsistencies.	differences between the arms. Two of these trials occurred within similar populations and with similar interventions; however, the third trial employed a potency escalating strategy over the course of the trial. As a result, only the initial period was eligible for inclusion in our study, yet SAE were reported over the course of the entire study. Therefore, we felt this study was sufficiently different from the other two, and therefore, not amenable to pooling with meta-analysis. We graded the SOE as insufficient, as we could only truly include two trials for this outcome and comparison. This has been reported consistently throughout the report.

Commentator	Section	Comments	Response
Public reviewer #2 AbbVie	Executive Summary	1. AHRQ's discussion of the anticipated ATP IV guidelines seems overly speculative and premature in the executive summary. This topic would be more appropriate to address in the "Discussion" section of the report. 2. While statin plus ezetimibe has not proven superior efficacy, this is not representative of all other statin combo therapies. AHRQ's statement to this effect seems to be an overly broad generalization.	1. We consider the discussion of the upcoming guidelines to be important in providing context for the report and findings. We have thus left this discussion in the ES 2. We stated several places the conclusions that combo statin/eze and statin/BAS lowered LDL better, mono lowered LDL better compared with statin/niacin or statin/fibrate; combo with all raised HDL better. We are unsure to what this comment refers.
Peer reviewer #2	Introduction	The Introduction is very well written and is very concise and is a good review of the issues and the topics. In fact, after reading the Introduction and all of the difficulties in evaluating these alternate drugs for lipid lowering, one might have stopped the report at that time and state that current studies are inadequate to evaluate alternative strategies for lowering LDL-C for those individuals who cannot substantially reduce their LDL-c on statin therapy without side effects.	Thank you. Our systematic review update provided the evidence base (or lack thereof) to support our conclusions even when those could be intuitively foretold.
TEP #1	Introduction	The introduction is appropriate.	Thank you.

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Commentator	Section	Comments	Response
TEP #2	Introduction	Table I has errors. Bile acid sequestrants raise triglycerides. Indeed, if triglycerides more than 300 mg/dl, they are contraindicated. Fibric acids and omega 3 fatty acids may raise LDL-C in those with mixed hyperlipidemia, but not in those with hypercholesterolemia alone You should mention that statins not only improve mortality and ASCVD outcomes, but the effect size increases at the 3rd year (CTT, Lancet 2010) Niacin comes in 3 forms- immediate release, intermediate release and sustained release. This is Important as toxicity may vary with these forms. Omega 3 fatty acids at a dose of 840 mg of EPA and DHA have been used primarily on the strength of the GISSI Prevenzione trial in Lancet almost 20 years ago. Unfortunately, more recent RCTs and metaanalyses don't support the contention that low dose omega 3 fatty acids protect against adverse CVD outcomes. They are used at higher dose in those with severe hypertriglyceridemia to prevent hyperlipidemic pancreatitis. There is no outcome data to support this unfortunately, but most lipid experts believe that once triglycerides exceed 2000 mg/dl, the likelihood of pancreatitis is increased. Since the receptors for triglyceride removal are saturated at 1000 mg/dl, there is a rationale for starting omega 3 fatty acids above this level.	We have added a footnote indicating that BAS are contraindicated in patients with TG > 300 mg/dL to Table 1. We have changed the effect of fibric acids and omega 3 on LDL to "variable" We have mentioned the effect size increase at the third year of therapy to the introduction section. We have added to the Introduction a section on the "Mechanism of Nicotinic Acid". Thank you. We have added discussion and references to "Mechanism of action of Omega-3 fatty acids" section. We consider this last point too specific to add to Introduction.

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TEP #3	Introduction	This is clear, well-written, and a balanced overview of the role of cholesterol in heart disease, and of the treatments used to address cholesterol. The key questions flow well from the introduction. The definition of high-risk seems tailored to address the disagreement between those that treat based on CV risk score and those that treat just based on LDL. There's no particular rationale given for the subgroup choices, other than to say that's what the previous review did	We have added discussion providing rationale for subgroups. For instance, the adverse effects may be different in elderly and in the ACCORD trial there was an increase in the risk for major adverse cardiac events in women receiving the combination therapy versus simvastatin alone
TEP #4	Introduction	pg 31 of 411, line 38: need to delete the parenthesis

pg 32 of 411, line 14, "a meta-analysis examining the association between triglycerides and CVD risk..." need to clarify a meta-analysis of what kind of trials?

Table 1 on pg 32 of 411: what is meant by "Limited" —is it a limited increase or decrease? For example, the omega-3 FA Lovaza increases LDL-C, while Vascepa does neither increase or decrease LDL-C. Maybe "variable" should be used instead of "limited". | We have clarified as a meta-analysis of population-based prospective studies and have added new reference (Hokanson, 1996).

We have changed the term to use "variable" per reviewer suggestion. |
| Peer reviewer #3 | Introduction | Well thought out, displays the problem well, | Thank you. |
| Public reviewer #1 Richard Chapell | Introduction | PG5: "Some concern exists that combination regimens may worsen clinical outcomes, such as the potential worsening of atherosclerosis reported with the combination of statin and ezetimibe". For a number of reasons, the available evidence does not support this statement. First, the cited study (Taylor et al., 2009; ARBITER 6) did not find a worsening of atherosclerosis associated with ezetimibe. Rather, mean carotid intimamedia thickness (cIMT, which is not a direct measure of atherosclerosis) was unchanged over the course of the study in the ezetimibe-treated group, a result also found in the ENHANCE trial | The following text was added to the Introduction section to address this reviewer's concerns:
"Despite the generally favorable effects of combination regimens on surrogate lipid markers in clinical trials, combination regimens have not consistently been shown to improve clinical outcomes. In the ACCORD trial, the addition of fenofibrate to simvastatin did not reduce the rates of cardiovascular deaths, MI or stroke more than same-dose simvastatin monotherapy among patients with diabetes. In addition, this combination therapy conferred benefit for men and possible harms for women. In the AIM-HIGH trial, patients with preexisting atherosclerotic CVD received niacin in addition to simvastatin or simvastatin monotherapy. While the patients taking combination therapy had greater increases in their HDL-c, there were no benefits on incidence of cardiovascular death, MI, stroke, or revascularization procedures. The ENHANCE compared the effect of ezetimibe in addition simvastatin to simvastatin alone on carotid |

Commentator	Section	Comments	Response
		using ezetimibe (Kastelein et al. New Engl J Med (2008) 358:1431), as well as in two large highdose atorvastatin monotherapy cIMT studies, RADIANCE 1 and CASHMERE (Kastelein et al. N Engl J Med (2007) 35: 1620; Simon et al, Fundam Clin Pharmacol. (2004) 18:131; Pfizer, Inc.; abstract. NCT #00163163. PhRMAWeb Synopsis. Protocol A2581051, 29 October 2007.). "Worsening of atherosclerosis" was not observed. As discussed further below, the validity of cIMT as a surrogate marker has become a subject of scientific controversy; however, even if one were to accept this marker as valid, it is noteworthy that in untreated patients, cIMT would be expected to increase rather than stay unchanged (Fleg et al. J Am Coll Cardiol (2008) 52:2198). For this reason, a beneficial treatment effect cannot be discounted based on these studies. In the longer SANDS cIMT trial where (in contrast to the above studies) a population with clearly high cIMT at baseline was studied, a beneficial effect of ezetimibe on cIMT reduction similar to that attributable to LDL-C reduction using statins was observed (Fleg et al, J Am Coll Cardiol. 2008; 52: 2198). Second, what was reported from ARBITER 6 (Taylor et al., 2009, ARBITER 6) was not a mean increase in cIMT, but a correlation between decreased LDL and increased cIMT in the ezetimibe group, observed in a post-hoc analysis of a subset of the originally randomized population after the study was prematurely stopped. This is an entirely different conclusion than showing a causal relationship between ezetimibe and increased cIMT. Moreover, in contrast to this ARBITER 6 observation, in the larger and full population of the ENHANCE trial, a statistically significant positive correlation between LDL-C change and cIMT change with ezetimibe was observe (Duivenvoorden et al, N Engl J Med (2010) 362: 1046). Third, increases in cIMT do	intima-media thickness (CIMT) in patients with hyperlipidemia. There was no difference in CIMT changes between the two groups despite significantly lower LDL-c levels in the combination therapy group. However, the subsequent ARBITER-6 HALTS study comparing statin+niacin with statin+ezetimibe revealed lower incidence of major cardiovascular events with statin+niacin than with statin+ezetimibe. Interestingly, the CVD benefits with combination therapy with niacin seen in ARBITER-6 HALTS was not replicated in AIM-HIGH, as the trial showed no reduction in CVD outcomes from adding niacin to a statin. Based on the combination of findings from these trials, investigators have suggested that ezetimibe either has no effect on or possibly worsens CVD outcomes as a possible theory to explain these discrepancies. The ongoing IMPROVE-IT trial will compare ezetimibe added to simvastatin to simvastatin monotherapy on cardiovascular death, MI, revascularization, or stroke (completion expected in September 2014) may help clarify the picture. Overall, these trials comparing statin monotherapy to combination therapy with the same statin dose plus another lipid lowering drug have demonstrated that this "add on" combination therapy can lead to superior lipid outcomes, but fails to reduce atherosclerosis or lead to decreased rates of cardiovascular death, MI, revascularization, or stroke.

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		not necessarily indicate progression of atherosclerosis. As pointed out in an editorial published in the same issue of NEJM as the ARBITER 6 study, use of this surrogate marker is controversial. It is now understood that cIMT changes induced by drug therapies do not consistently reflect effects on clinical outcomes. As noted above, in the RADIANCE 1 and CASHMERE trials of atorvastatin – a statin with robust clinical outcomes data –mean cIMT was unchanged. This is also the finding of a meta-analysis by Costanzo et al. (J. Am. Coll. Cardiol. 2010;56:2006). As an additional example of this inconsistency, although ARBITER 6 did show a decrease in cIMT among patients treated with niacin, this presumed benefit was not reflected in improved clinical outcomes among patients treated with niacin (Boden et al. N Engl J Med (2011) 365:2255; the AIM-HIGH study). Fourth, the results of two large placebo-controlled outcomes trials belie any adverse effect on ischemic cardiovascular clinical outcomes among patients treated with ezetimibe/simvastatin combination treatment. (Holme et al. Am J Cardiol (2010) 105:1802; Baigent et al.,Lancet (2011) 377:2181). If ezetimibe was truly causing worsening of atherosclerosis, clinical outcomes in these studies would be expected to have worsened as well. This occurred in neither trial. Thus, concerns that "that combination regimens may worsen clinical outcomes" are not supported by evidence. We note also that in March 2013, the independent, unblinded Data Safety Monitoring Committee for the >18,000 patient IMPROVE-IT cardiovascular outcomes study (comparing ezetimibe/simvastatin to simvastatin monotherapy) completed a planned review of study data an recommended that the study continue. In summary, a statement that atherosclerosis is worsened among patients receiving ezetimibe is inaccurate and	

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		unsupported, especially given the fact that the cited study is not further assessed in the draft review. We therefore recommend that the EPC remove this statement, both here and in the Executive Summary.	
Public reviewer #2AbbVie	Introduction	Table 1 shows the relative effect of different drug classes on LDL, HDL and TG. However, for KQ2 this report focused solely on LDL-c and HDL-c effects. The clinical relevance of modulating hyper TG levels is alluded to in several places in the document, but was not part of the KQ2 analysis. The heavy focus on LDL-c lowering effects rather than considering approaches to modulate a more complete high-risk lipid profile (notably TG) may provide a statin-bias to this report. The value of Table 1 could be enhanced by inclusion of the relative effect sizes or range for each drug.	We have added text to clarify that, per the ATP III recommendations; we captured TG for patients with diabetes. The effect on LDL of individual agents is provided in Table 1.
Peer reviewer #1	Methods	The methods used are technically fine but they are constrained by flawed KQ's and all efforts devolve from that challenging position.	Our review was an update of a prior EPC review. The KQs in our review are the KQs from 2009 review we were tasked with updating. The rationale for KQ was to determine if the addition of an agent with a different mechanism of action from a statin would provide benefit above simply increasing statin, without increased adverse effects. This information may be useful for patients who do not tolerate higher dose statins. We have added discussion in the Introduction and Discussion to further outline this rationale and to discuss the other related evidence.
Peer reviewer #2 [Lewis Kuller]	Methods	The statistical methods appear to be quite adequate. The amount of detail presented in this report is extraordinary. It is hard to understand why such detail would be required since the bottom line is that there is little evidence of any benefit or, for that matter, harm. In some ways there is more harm in adding these drugs as compared to raising the dose of the statins	Thank you for your comment. We have tried to revise the final report to be clearer and easier to read, yet also keeping within AHRQ current guidance regarding the level of detail presented in the Methods.

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TEP #1	Methods	The criteria are not justifiable because only titration studies are included, which excludes a number of important larger studies. Well known adverse events, for example with niacin and flushing, are not reported in the smaller studies that met the criteria.	Flushing was not considered an SAE. If the investigators included flushing as an AE, it would be captured under "1 or more AE." If flushing was so severe as to cause withdrawal, it would be captured under "withdrawal due to AE"
TEP #2	Methods	I have no criticisms in this area. The authors did a good job.	Thank you.
TEP #3	Methods	I agree with the changes in method from the prior report. Inclusion and exclusion criteria were clear and reasonable. Search strategy is reasonable generally, with the exception of some lack of clarity about the reason for excluding non-English literature. Risk of bias was assessed appropriately with accepted methods—Jadad doesn't differ terribly from the Cochrane ROB method, so I'm ok with having both. Agree with the plans for meta-analysis and the adjustments made to deal with the heterogeneous and sparse data	Thank you for these considerations of our methodology
TEP #4	Methods	I like Figure 1 on pg. 13. because it adds details to the general framework. Table 2, pg. 16 of 411--this table is useful. Table 3, pg. 21/411. Add the word "combination" to each row for clarity. For example, for bile acid sequestrant, "low potency vs. high potency monotherapy" change to "low potency combination vs. high potency monotherapy" pg 174 of 411, add "KQ"-Key Question and "SIP"-Scientific Information Packet to the Abbreviations list The search strategies were well described and logical. The outcomes definitions were appropriate. The statistical methods were appropriate.	Thank you. Thank you. We have made changes to tables 3 and per suggestion. We have added these terms to Appendix A – abbreviations list. Thank you.

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Peer reviewer #3	Methods	Inclusion criteria are good, statistical models are fine. I think it is mistake to not include low- risk CAD patients as again for the average clinician these are the true clinical question.	Low-risk CAD patients are unlikely to need intensive combination therapy and/or could attain goal with statin alone. We therefore chose to focus on moderate and high -risk CAD patients.
Public reviewer #1 Richard Chapell	Methods	PG10: Adherence is listed as an outcome of interest. In the types of randomized controlled trials identified in this analysis, adherence is optimized to the best ability of the researchers. Stated differently, adherence in this context is a measure of study quality, not an outcome measure. No useful conclusions can be drawn regarding real-world adherence based on adherence measures reported in such trials. We recommend that this RCT data not be utilized when assessing adherence. PG10: "Serious Adverse Events" are listed as an outcome without definition. For reasons discussed above, we recommend that the authors define this term. If different studies define it differently, we suggest that it be defined wherever it appears. If any studies fail to define it, we suggest that the omission be reported. PG11: Typo: "which increased out number of studies" PG12: According to the cited reference (Weng et al., J Clin Pharm Ther 2010; 35:139), rosuvastatin is a high potency statin at dosages above 5mg/day, not moderate as stated in Table 4. We suggest that the authors consider revising the analysis accordingly.	We agree that other measures of adherence would be useful, however, the adherence to treatment in a study is an important outcome to capture and consider in providing the results of a trial. Serious adverse events (SAE) were abstracted and assessed as reported and defined by the study investigators. None of the included reports provided a definition of SAE. It is likely that the FDA classification was used, but this is not stated explicitly. We agree and have revised this section and the analysis accordingly: rosuvastatin is evaluated as a high potency statin at dosages above 5mg/day, not moderate as previously stated

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Public reviewer #2 AbbVie	Methods	1. This report is based on relative comparisons of statin monotherapy as a class with various combinations of other add-on lipid modifying drugs. The relative efficacy and dose ranges for individual statin drugs is shown in Table 4 of the report and is based on a meta-analysis published in 2010 (Weng TC et al., 2010 J Clin Pharm Ther). While the data in Table 2 of the Weng paper and the data shown in Table 4 of the report are similar, they are not identical. Further, while relative efficacy to reduce high LDL-c levels may be similar across different statin drugs, these effects occur at different doses of the individual statins. The report does not clearly differentiate between pharmacodynamic efficacy and potency. Further, the comparison of statin monotherapy versus statin—fibrate or niacin combinations was not always made against the same statin as monotherapy.

2. Related to item 1 above, the general therapeutic comparison strategy is the evaluation of high efficacy statin therapy versus mid or low efficacy statin in combination with fibrate or niacin, and as noted above, these comparisons are not always generated with the same statin in the same study (see table 18 as an example). The clinical rationale for these comparisons may be clear, but they necessarily obscure any assessment of the relative pharmacological additivity associated with a specific statin combo therapy. | We have noted and addressed the discrepancy in rosuvastatin potency.

We have clarified that the decision to compare potency rather than individual agents and their doses was made a priori. |

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Peer reviewer #1	Results	Far too much detail of a repetitive nature is presented. This whole document was prepared through the narrow lens of a methodological response to the wrong questions. A much shorter report could have been generated in that regard. More emphasis on creative modeling would have been helpful and potential informative clinically. That was not done.	Reviewer suggests modeling expected clinical effects of LDL reduction achieved by statin monotherapy and combo therapy regimens. In our view, LDL lowering does not seem to lead to decreased clinical risk – would be extrapolating data too far. We have attempted to provide in the Executive Summary the concise version that the reviewer would like to see.
Peer reviewer #2	Results	The results are extensive and clearly required considerable effort. Unfortunately, much of the results are equivocal because of poor study designs, very short term studies, no hard outcomes	We agree. We provide discussion of the limitations of the primary research.
TEP #1	Results	The report does not include important larger trials, such as ENHANCE with ezetimibe, or the AIM-HIGH and HPS2-THRIVE studies with niacin, because they weren't designed as titration studies. The smaller studies that were included tend to be company supported, commercially driven and potentially more biased towards the combination agent.	The trials noted do not address our KQs and were thus not eligible for inclusion in the review. We have added further discussion in the Introduction and Discussion about the existing related evidence, such as reflected by the trials noted by the reviewer.

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TEP #2	Results	I think that if you use studies whose duration is 12 months or less you should consider them dose response studies and not query them for efficacy. It's simply too short an exposure to the lipid agent for this to occur. As noted above, statin trials show increasing benefit at the 3 year mark as compared to the one year mark. Moreover, safety issues may not be apparent early, especially because subjects are usually screened for clinical trials. I think efficacy and safety trials need to be segregated and should be looked at primarily in trials that last more than 12 months. The only exception would be studies in those with acute coronary syndrome where event rates are high early and a change in some of the efficacy endpoints (like readmission for recurrent ischemia) can be seen early. Unfortunately, there is little combination therapy in this group Although the short-term (12 months or less) trials give us an idea of what we can achieve with initial dosing of a statin versus combination Rx, longer-term trials are more realistic ("real-world") as they incorporate drop-outs. Problems with adherence must be considered both a safety and efficacy issue in my view. If high drop-out rates due to the drug, efficacy will by necessity by more limited.	We have discussed the duration of protocol in limitations section of the Discussion.

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TEP #2	Results	The results section is massive, but after getting a hang of how the results are presented, it's very easy to navigate and understand. To make it even better, could there be an overview page or something like that that would give the reader a heads up about each large section (combination) and what data is presented where? The TOC does this OK, but some heads up about the tables would be nice also. I agree with the overall structure being by combination regimen, as that is how I would like to access this data on the first pass. The tables overall are done very well—I appreciate the different ways of looking at the data—and all make sense to me clinically. Pg 69, table 9—"proportion" noted, but appears to be percentages - clarify and note percentages where applicable. pg 66, line 14—how was crossover data handled? (ezetimibe int)—The usual Cochrane recommendation is to limit data extraction to the first leg of the crossover study and only if there was random allocation—it looks like this was done in the results, but not sure if there needs to be a statement in the methods.	We have added a section to orient reader at beginning of results section. Thank you We changed "proportion" to "percentage". We added text to the methods to clarify how cross-over trials were considered: "We considered randomized cross-over trials and attempted to incorporate these per guidance from the Cochrane Handbook. For instance, where possible paired analysis would be chosen. As needed, a conservative analysis was conducted by incorporating cross-over trials by taking all measurements from combination regimen intervention periods and all measurements from monotherapy regimen intervention periods and analyzing them as if the trial were a parallel group trial." The reported analysis in the one eligible cross-over trial we identified necessitated the use of aggregate data (i.e., the second option above).

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TEP #4	Results	Section "Combination Therapy with Bile Acid Sequestrant and Statin versus Intensification of Statin Monotherapy" (pg 24 of 411)—please comment explicitly on findings regarding cardiovascular outcomes. Pg. 85 of 411, Table 10: The abbreviations for the potency comparison column was too brief. Instead of "H v M" why not "HPMono v MPCombo" Adding more letters to the abbreviation means less time looking at the legend as the abbreviation is more intuitive. The amount of detail presented was overwhelming, but necessary. The addition of forest plots and tables were helpful summaries of the text. Pg 102 of 411, line 24: unfinished sentence. Pg 148 of 411, Figure 23 is not centered.	We have added this to the text. This is the summary of evidence for subgroups in ezetimibe—columns and was relabeled. Corrected. Corrected.
Peer reviewer #3	Results	Looks ok.	Thank you.
Public reviewer #1 Richard Chapell	Results	PG15: "Four companies provided SIPs and the references provided by these four companies were carefully crosschecked against our existing database, yielding four new references, none of which were applicable to this review (Appendix E)." Our data submission included methodology and results from an as-yet unpublished study which we believe meets the inclusion criteria for the current review. This study has now been accepted by the American Journal of Cardiology, and should be available online by early September. It was not included in the review despite our efforts to conform to AHRQ guidelines for submission of unpublished data. Since Appendix E was not posted for comment, we are unable to determine whether any reasons were given for this exclusion. We do not have an appreciation for why AHRQ	AHRQ has no record of receiving any SIPs from the author or from Merck on this topic. Serious adverse events (SAE) were abstracted and assessed as reported and defined by the study investigators. None of the included reports provided a definition of SAE. It is likely that the FDA classification was used, but this is not stated explicitly. We previously reported high SOE favoring monotherapy when comparing SAEs between combination therapy and monotherapy; however, this reviewer's comment led us to reconsider the evidence and studies included in this comparison for this outcome. As shown in Table 10 of the report, the percentage of patients in each arm experiencing an SAE in each arm was low overall. There were no statistically significant differences between the arms. Two of these trials occurred within similar populations and with similar interventions; however, the third trial employed a potency escalating strategy over the course of the trial (Stein, 2004). As a result, only the initial period was eligible for inclusion in our study, yet SAE were reported over the course of the entire study. Therefore, we

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		solicits unpublished data if it is not going to be utilized by the EPC, and respectfully suggest that additional guidance be provided in the future. PG37: Again, "Serious Adverse Events" is undefined. PG40: "Mid potency statin combination therapy and high potency statin monotherapy: Three studies reported serious adverse events.97 103,105 ,110 Two studies favored monotherapy, although the absolute difference between arms was small (range 1 percent to 2 percent difference favoring monotherapy). One study showed no difference between monotherapy and combination therapy.103 ,110 We graded the strength of evidence as high." We respectfully submit that as to this comparison of serious adverse events, both the draft review's conclusion and the strength of evidence characterization warrant reconsideration. In the study by Stein et al., serious adverse events were reported in 12 out of 305 patients in the combination group, as compared to 9 out of 316 in the monotherapy group. While Stein et al did not report whether this difference is statistically significant, our own chi-squared test finds the difference between groups to be nonsignificant (p=0.45). This statistic does not support the conclusion that monotherapy is favored. The study by Foody et al. had multiple treatment arms, but only one mid-strength statin combination arm and one high strength statin monotherapy arm. The combination arm reported 8 patients out of 256 experienced a serious adverse event, while the monotherapy arm reported 3 patients out of 258.	felt this study was sufficiently different from the other two, and therefore, not amenable to pooling with meta-analysis. We graded the SOE as insufficient, as we could only truly include two trials for this outcome and comparison. This has been reported consistently throughout the report.
Public reviewer #2 Richard Chapell - continued	Results	Again, statistical significance was not reported, but our chi-squared test finds no significant difference between the two groups (p=.12). The third study, reported in two publications, found that the incidence of SAEs was the same (3%) in both groups. Again, this finding does not	We previously reported high SOE favoring monotherapy when comparing SAEs between combination therapy and monotherapy; however, this reviewer's comment led us to reconsider the evidence and studies included in this comparison for this outcome. As shown in Table 10 of the report, the percentage of patients in each arm experiencing an SAE in each arm was low overall. There were no statistically significant differences between the arms. Two of these trials

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		support the conclusion that monotherapy is favored. None of the studies, despite being fairly large, found a statistically significant effect. Drawing a conclusion based on such very small numerical trends in the data is contrary to sound methodology, particularly in the absence of a well-designed, properly conducted supportive meta-analysis. This concern is further compounded by the draft review's characterization that the strength of the evidence supporting a difference is "high" (or even "moderate," as the draft review inconsistently states on page 130). Strength of evidence is measured in six domains, including Precision, Consistency and Magnitude of effect. As acknowledged in the text, but not in Table 12, the magnitude of effect is small, ranging from zero to 1.9%. It is questionable whether the small, nonsignificant effects observed here meet the standard o "Minimum Important Difference" suggested by the AHRQ methods guide cited by the EPC as their method for assessing strength of evidence. The publication by Stein et al. specifically states that "There were no clinically meaningful differences in the treatment groups for the incidence of adverse events or in the number of discontinuations due to adverse events." Additionally, the data are not consistent. The AHRQ methods guide states that "If effect sizes indicate the same direction of effect and if the range of effect sizes is narrow, an evidence base can be judged to be consistent. " This condition does not apply to the three studies. Two studies are said to have "favored monotherapy" while the third found no difference. Moreover, it is questionable whether the direction of effect is meaningful when the standard of minimal important difference has not been met. It would be more accurate to state that the studies consistently found no clinically meaningful difference. We are unable to assess the conclusion that the evidence is	occurred within similar populations and with similar interventions; however, the third trial employed a potency escalating strategy over the course of the trial (Stein, 2004). As a result, only the initial period was eligible for inclusion in our study, yet SAE were reported over the course of the entire study. Therefore, we felt this study was sufficiently different from the other two, and therefore, not amenable to pooling with meta-analysis. We graded the SOE as insufficient, as we could only truly include two trials for this outcome and comparison. This has been reported consistently throughout the report.

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		"Precise" because the method by which precision was assessed is not cited. However, assuming that the data are precise, we point out that the effect sizes in all three studies precisely overlap with zero. The AHRQ methods guide states that "A precise estimate should enable decisionmakers to draw conclusions about whether one treatment is, clinically speaking, inferior, equivalent (neither inferior nor superior), or superior to another." As to this comparison of serious adverse events using the data described, we submit that the correct conclusion when applying these criteria is "equivalent". Finally, we point to the abundance of evidence not included in the current review, none of which points to an increased incidence of SAEs among patients treated with ezetimibe. While we realize that an evidence review must review only the evidence meeting pre-established inclusion criteria, it is also true that the current review is an update of an earlier review, which provides context for the current work. The 2009 AHRQ review found no difference in SAEs between patients treated with statins and those treated with a combination of statins and ezetimibe. In the absence of even a single result showing a statistically significant difference in serious adverse events, or a meta-analysis finding a significant combined effect, we submit that a conclusion favoring monotherapy over combination therapy is not supported. To the contrary, our application of AHRQ methodology to the data described finds moderate strength of evidence supporting the conclusion that there is no such difference. Given the absence of any evidence supporting the conclusion that serious adverse events are observed more frequently in the combination groups, we recommend that this conclusion be removed.	

Commentator	Section	Comments	Response
Public reviewer #2 AbbVie	Results	1. Under the combo statin + fibrate section, the references under the section "Acute Kidney Injury" (p. 92-93) are inaccurate. Neither of these manuscripts describes "Acute Kidney Injury" but rather increases in creatinine. These changes were completely reversible and not associated with clinical "Acute Kidney Injury", so the implication is misleading, especially given the long-term renal safety data with FIELD and ACCORD. "Renal-related Adverse Events" is a more appropriate section header. 2. There appears to be a typo in the second bullet on page 101. We believe it should read as follows, "A mid potency statin combined with niacin is more effective than high potency statin monotherapy for raising HDL-c (SOE: low).	We disagree with the reviewer. Increase in creatinine defines acute kidney injury, independent of the eventual outcome. We have not revised the text. Thank you, we have corrected this typographical error
TEP # 5	Results	Page 5: "All evidence for clinical outcomes (mortality, acute coronary events, and revasculartization procedures) were graded as insufficient across all potency comparisons" What does POTENCY COMPARISONS mean. Probably deserves at least brief definition in abstract Page 5: What about low potency statin + exetimibe? Page 11: "Atherosclerosis plays a major role in the development of atherosclerotic CVD" By definition Atherosclerosis is the sine qua non of atherosclerotic CVD Page 11: "…therapeutic strategies to decrease risk have focused on LDL-c reduction as the primary goal." LDL-c reduction is A primary goal (but not the only primary goal) Page 11: "in contrast to LDL-c, HDL-c has a protective role…" HDL-c levels have been associated with	Page 5: This has been revised as follows, "All evidence for clinical outcomes (mortality, acute coronary events, and revasculartization procedures) were graded as insufficient when comparing lower-potency combination therapy with higher-potency statin monotherapy." Page 5: In the abstract, only mid-potency combination therapy vs high-potency statin monotherapy is mentioned due to space considerations Page 11: Revised to read "Atherosclerosis (hardening of arteries caused by plaque deposition) causes coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease." Page 11: Revised to read "Due to the consistent and robust association of higher LDL-c levels with atherosclerotic CVD across experimental and epidemiologic studies, therapeutic strategies to decrease risk have focused on LDL-c reduction as a primary goal." Page 11: Revised to read," In contrast to LDL-c, high-density lipoprotein (HDL-c) has been associated with reduced risk of atherosclerotic CVD." Page 11: Revised to read "The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statins") are the most widely prescribed lipid-lowering agents and are often used as monotherapy. However some patients do not reach their treatment goals on statin monotherapy or are troubled by side

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		reduced risk (it is not correct to say that HDL-c has a protective role ; in fact recent clinical trials which have greatly increased HDL-c levels have not decreased risk)

Page 11: "While 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or "statins" are the most widely prescribed lipid-lowering agents and are often used as monotherapy; alternatively, statins can be combined with another medication such as bile acid sequestrants, cholesterol absorption inhibitor, fibric acids, nicotinic acid, and omega-3 fatty acids." This is a poorly constructed sentence and difficult to follow.

Page 12, line 4:" but fails reduce measure of" TO is missing in this sentence

Page 16, line 10: "Data Synthesis We compared lower potency statins in combination therapy to higher potency statin monotherapy,"The abstract only mentions mid and high potency statins, not low potency statins | effects, prompting interest in combination therapy as a way to improve lipid levels or reduce side effects without having to increase statin dosage. Statins can be combined with an additional lipid-modifying medication such as bile acid sequestrants, cholesterol absorption inhibitor, fibric acids, nicotinic acid, and omega-3 fatty acids. "

Page 12: Revised to read, "Overall, these trials comparing statin monotherapy to combination therapy with the same statin dose plus another lipid lowering drug have demonstrated that this "add on" combination therapy can lead to superior lipid outcomes, but fails to reduce atherosclerosis or lead to decreased rates of cardiovascular death, MI, revascularization, or stroke.58

Page 16: In the abstract, only mid-potency combination therapy vs high-potency statin monotherapy is mentioned due to space considerations |

Commentator	Section	Comments	Response
TEP # 5	Results	Page 17, line 44: "future investigators need to make these endpoints the primary outcomes of their trials and ensure that trials are of sufficient duration to actually capture these events" This recommendation is spot on. It is really the crux of the matter and very nicely highlighted by the data presented. Would make this point as loud and as often as you can. Page 28, line 9: "as the ACCORD trial showed benefit of combination therapy with fibrate in men and potential **harms with this combination therapy in women**" This is a very important point that is not given enough attention in the executive summary. Page 31, lines 7-27: COMMENT: While this information is interesting, it really has nothing to do with the current topic Table I on page 32: COMMENT: Fibrates can lead to a marked increase in Triglycerides, yet the table says "limited" Page 33, line 44: "which is the rate limiting step for cholesterol synthesis in the liver." HMG-CoA reductase is the rate limiting step for cholesterol synthesis THROUGHOUT the body Page 34, line 10: "The NCEP ATP III report established three CHD risk Strata" The ATP III update (2004) established 4 strata: low, intermediate, high, very high Page 36, line 26: "the combination conferred benefit for men and possible harms for women" This combination conferred POSSIBLE benefit for men and possible harms for women	Page 17: Thank you. Page 28: We mentioned the difference between men and women both in the Future Research Needs section of both the ES and Full Report and have included women as a subgroup of interest Page 31: requested text removed Page 32: We have removed the effect of all lipid-modifying agents on TG because this is not a main focus of the report Page 33: Revised to read: "… which is the catalyst for the rate-limiting step in cholesterol synthesis throughout the body." Page 34: This sentence was completely removed now that ATP III has been replaced by new cholesterol treatment guidelines Page 36: Revised to read: "In addition, this combination therapy conferred possible benefit for men and possible harms for women."

Commentator	Section	Comments	Response
TEP # 5	Results	Page 36COMMENT: the lack of mention of HPS2-Thrive is curious	HPS2-Thrive has been added to Table 29 and to text in the ES and discussion discussing large trials of combination therapy.
Peer reviewer # 4	Results	The authors categorized 40mg Simvastatin as "high-dose". In other literature, 40 mg is considered moderate dose and 80mg high dose. This is a very important distinction and the authors do not clarify the basis for their decision. In the comparison tables (e.g., Table 4), it would be useful to also list the number of patients enrolled. That information is given in other tables but it would also be useful to see in the table of relative effect size. In addition, to absolute reduction in LDL-c, it appears that %age reduction may be important. It is difficult to discern from the data report, the mean %age reduction of LDL-c with various regimens or the proportion of subjects who obtained a reasonable reduction, e.g., 15%. Overall the authors appropriately frame their analysis with the information that none of the studies or meta-analytic results permit any comment clinical outcomes. This is key and every effort should be made to emphasize this critically important point. They could also be more explicit in stating that the most potent drug in terms of LDL-c lowering, i.e., ezetimibe, still lacks any data in demonstrating efficacy in reduction of CV events and perhaps, the IMPROVE-IT may furnish some.	We have clarified in text that this was based on expected LDL-c reduction > 40%. We have revised the table as requested. We have added this summary information regarding effect on LDL to the SOE tables for each drug. We did not abstract data on the proportion of patients who achieved a reasonable LDL-c reduction. We have mentioned the pending results from IMPROVE-IT in the ES, Introduction, and Discussion sections.

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Commentator	Section	Comments	Response
Peer reviewer #1	Discussion	Please see my comments on the future research section. While it gives a list of the types of studies needed, that statement is made in a vacuum without regards to the very real impractical nature of the suggestions. This may satisfy a perceived methodological need to answer the KQs but is not helpful in getting to answers to the clinical questions. Proposing models or using comparative effectiveness approaches (? using the new era with EMRs) are examples of more creative approaches.	We have added text : "Alternative study designs such as observational studies using registry data from electronic medical records may also provide useful data on clinical outcomes" to Future Research section in ES and main report

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Commentator	Section	Comments	Response
Peer reviewer #2	Discussion	The implications are clearly stated, that we just do not know the answer to the question of how to further decrease LDL-C in those who are on moderate doses of statins and still have elevated LDL-C or ApoB or LDL particles. It perhaps would be better at this time to discuss, as mentioned, the <u>importance of evaluating compliance</u> with the statin therapy; second, <u>potential genotypic differences</u> which decrease the efficacy of the statins; and third, the potential for <u>very aggressive nonpharmacological, i.e. dietary intervention</u>, which would have to be individualized well-trained nutritionists and dieticians; and fourth, the <u>availability of the PCSK-9 therapies</u>. The obvious new research at the present time is whether PCSK-9 related drugs that substantially reduce LDL-C have the same benefit in reducing CHD as the statins. As mentioned in the introduction, do all individuals have to reach a certain goal, i.e. LDL <70 or ApoB <60-70? The availability of new technologies now to measure the extent of atherosclerosis, i.e. fast CT, provides an excellent opportunity to individualize the aggressiveness of therapy, especially in primary prevention and similarly, as has been reported, there are approaches to identification of the highest risk individuals even in secondary prevention. Although some discussion is given to the adverse effects of these alternative drugs, their tolerability and cost are not discussed. Probably at the present time ezetimibe is the only remaining drug which can be used in combination with a statin to further lower LDL-C or in those individuals who are intolerant to statin therapy and do not want injections with PCSK-9 inhibitor. There was no trial that suggests that the drug alone will reduce the risk	The reviewer highlights the following issues: Adherence – Added to "Implications for Clinical and Policy-Decision Making" Another issue facing clinicians is whether lack of response to lipid-lowering agents stems from non-adherence to therapy, which is common. {Caspard H, Chan AK, Walker AM. Compliance with a statin treatment in a usual-care setting: retrospective database analysis over 3 years after treatment initiation in health maintenance organization enrollees with dyslipidemia. Clin Ther 2005; 27: 1639–46}. We had insufficient data to assess whether adherence differed between lower-potency combination therapy and higher-dose statin monotherapy, however, this issue is irrelevant if the reason for suboptimal LDL-c response due to poor adherence to initial statin monotherapy. Genotypic differences and Aggressive non-pharmaceutical interventions Added to Limitations section (ES and main report), "Given several previous reviews on dietary modification and reduction of lipids and CVD risk, we did not include these therapies in this review. Further, we did not examine differences in statin response based on genetic variations PSCK-9 therapies: PCSK-9 is not FDA approved and was thus not considered within scope of our review. It is not available to clinicians in the US and thus would not help inform their decisions at this time, but should a new product be available then it would be appropriate to update the report. We agree with the reviewer in identifying the highest–risk patients and treating them aggressively. We have discussed the new (Nov 2013) cholesterol lowering guidelines in the report. We do not mention imaging modalities in the context of risk stratification because it is not mentioned in the new lipid-lowering guidelines. Added regarding tolerability/cost: "Clinicians would also have to consider tolerability and cost issues with their patients. We did not compare tolerability of the individual add-on agents against each other. Adherence data would potentially serve as a proxy measure of tolerability, however, was not consistently reported. Clinicians would also have to consider the cost of the add-on agents with their patients based on drug formularies, as the cost of these agents vary widely." We think that it would be over-reaching to make any statements about long-term benefits of ezetimibe without any clinical outcomes data to support that statement, therefore , we did not add additional statements about ezetimibe.

Commentator	Section	Comments	Response
		of coronary disease but there is enough evidence in the literature that lowering LDL-C almost any way will reduce coronary disease. Ezetimibe may be the only alternative that is tolerable in the long term for the majority of people. I believe that the HDL-C discussion is probably of limited value at the present time given the fact that none of the drug therapies for raising HDL-C except in people with very high triglycerides and low HDL, i.e. the VA-HIT study, have shown any real substantial benefit in reducing CHD or decreasing total mortality	

Commentator	Section	Comments	Response
TEP # 1	Discussion	The only conclusion with high SOE was that high-potency statin monotherapy produces fewer serious adverse events than combination of mid-potency statin with ezetimibe (p. ES- 14, lines 36-37). On page 40, lines 7-12, I do not see how the strength of evidence was rated as high after reviewing the articles cited in this section. The Foody article showed similar AEs between study arms. The Zieve article reported similar AE incidence, but numerically greater liver enzyme elevations and 1 case of elevated CK with statin monotherapy. The Ben-Yehuda article reported similar AE incidence, but higher discontinuations due to adverse events and numerically higher gastrointestinal AEs with combination therapy. There were 2 cases of elevated liver enzymes with combination therapy vs 1 with statin monotherapy. And in the Stein article, serious AEs occurred in 12 subjects (4%) with combination therapy and 9 (3%) with monotherapy. 3 of the 21 events were considered possibly related to study treatment (rash with monotherapy, and myalgia and elevated liver enzymes with combination therapy). I do not see how this translates into a strong conclusion that the statin/ezetimibe combination produces more serious AEs than high-dose statin. Also, on page 101-103, no serious adverse events or short-term side effects are reported with the combination of statin and niacin. Niacin has side effects, such as flushing that are well established in the literature. The report misses things that anyone who's ever used niacin has observed clinically and that have been shown in large trials. These are not the right conclusions and should not be used to inform policy and/or practice decisions. The limitations of this study, as noted in my comments, are not adequately described.	Serious adverse events (SAE) were abstracted and assessed as reported and defined by the study investigators. None of the included reports provided a definition of SAE. It is likely that the FDA classification was used, but this is not stated explicitly. We previously reported high SOE favoring monotherapy when comparing SAEs between combination therapy and monotherapy; however, this reviewer's comment led us to reconsider the evidence and studies included in this comparison for this outcome. As shown in Table 10 of the report, the percentage of patients in each arm experiencing an SAE in each arm was low overall. There were no statistically significant differences between the arms. Two of these trials occurred within similar populations and with similar interventions; however, the third trial employed a potency escalating strategy over the course of the trial (Stein, 2004). As a result, only the initial period was eligible for inclusion in our study, yet SAE were reported over the course of the entire study. Therefore, we felt this study was sufficiently different from the other two, and therefore, not amenable to pooling with meta-analysis. We graded the SOE as insufficient, as we could only truly include two trials for this outcome and comparison. This has been reported consistently throughout the report. Flushing was not considered an SAE. If the investigators included flushing as an AE, it would be captured under "1 or more AE." Of if flushing was so severe to cause withdrawal, it would be captured under "withdrawal due to AE"

Commentator	Section	Comments	Response
TEP # 2	Discussion	The authors have done an incredible amount of work on this project. They state their findings clearly. I don't think there is clinical relevance to equating HDL-C raising effects of combination therapy in this report. Whereas there is consistent RCT data supporting use of statins to lower LDL-C, there isn't good data at all to support pharmacologic raising of HDL-C. This needs to be clearly stated. Also, we need outcomes studies to see if adding a bile acid sequestrant or ezetemibe to a statin provides incremental benefit. This is difficult to do because a maximally tolerated statin still has the best level of evidence in RCTs and so should be initiated first.) Combination therapy trials have focused on getting LDL-C even lower. I think the research focus should be on achieving LDL-C reductions consistent with potent statins (50-60%) in those who can't tolerate full dose statin therapy. When LDL-C is lowered 50% with a statin and a bile acid sequestrate, is it as efficacious as a statin and ezetimibe and are both arms as efficacious as a potent statin that lowered LDL-C at least 50%.	Added to introduction section: However, only the VA-HIT study showed clinical benefit of raising HDL-c, and the study enrolled men with low baseline HDL-c We have added to the Key Findings portion of the discussion that the lack of data to support pharmacologic raising of HDL-c. Additionally, it would be useful to examine whether it is possible to achieve LDL-c reductions consistent with potent statins (50-60%) in patients who are unable to tolerate full dose statin therapy and what the clinical effects of these reductions would be. Furthermore, it would be useful to deteremine if LDL-c lowering of 50% achieved with a statin and a bile acid sequestrant is as efficacious as a statin and ezetimibe, and whether both are as efficacious as a potent statin alone. Finally, alternative study designs such as observational studies using registry data from electronic medical records may also provide useful data on clinical outcomes

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TEP # 3	Discussion	The implications are clear—I think the authors appropriately note their hesitation to make any strong conclusions given the lack of evidence, but they do provide some overall directions based on what limited, disease-oriented evidence is available. The limitations of the review, including decisions made to limit the scope of the review are clearly discussed and logical. The future research section clearly lays out what is needed to help answer the Key Questions with more useful data. The types of studies, the outcomes to be measured, the length of studies and the useful types of comparisons are all discussed. pg 163, line 39—this is an awkward initial statement. I expected something good after the "while...," clause. The actual conclusion is reasonable, but the wording is awkward. pg 195, line 4—"Drug is not" what? pg 209, line 1—table is generally OK, but heading of pharmaceutical support does not seem to match with data. I infer that the second heading statement should be "COI disclosure" or something like that	Thank you. Revised to read, "The current head-to-head comparisons of a combination regimen to intensification of statin therapy cannot help clinicians decide between different combination therapy options" pg 195, line 4—Drug is not approved pg 209, line 1—"Conflict of interest disclosure by author" added

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TEP # 4	Discussion	Yes, the key findings and their implications (or lack thereof) are clearly stated. Consideration may be given to adding a figure for LDL-C lowering such as: combination therapy with BAS and combination therapy with EZ >> statin monotherapy >> combination therapy with fibrates and combination therapy with niacin The limitations of the comparative effectiveness process are adequately stated. The limitations of the evidence base is adequately stated. Future research needs well stated. However, pg. 163 of 411, line 38—this sentence does not make sense to me. Note there are two periods on pg 162 of 411, line 16	Thank you. We did not add a figure for LDL-c lowering comparing the different combination regimens because we did not directly compare them. Corrections made as suggested.
Peer reviewer # 3	Discussion	I'm not sure this is clearly laid out. Begs the question, is it possible to do a larger data base rather than a RPCT.	We added text on the possibility of using registry/electronic medical record data to future research section.
Public reviewer #1 Richard Chapell	Discussion	PG130: "There is moderate strength evidence favoring high potency statin monotherapy in terms of lower rates of serious adverse effects as compared to mid potency statin in combination with ezetimibe." This statement (with which we disagree, see above) is contradicted elsewhere in the document. We suggest that the document be reviewed to eliminate such inconsistencies. PG132: Typo: "If these measure do"	This has been corrected and there are no longer inconsistencies.
Public reviewer #2 AbbVie	Discussion	1. In the "Future Research Needs" section, there is reference to the need for future studies in "high-risk" patients (and racial groups and gender is mentioned), but there is not a specific mention/emphasis of the need to evaluate patients with significantly abnormal HDL-C and TG in a comparison of statin vs. combo with fibrates. We believe the focus on "…multiple	1. We added additional description of high-risk groups 2. Our review was an update of a prior EPC review. The KQs in our review are the KQs from 2009 review we were tasked with updating. When to conduct an update (what is sufficient number of new studies?) and when an update becomes a new review (i.e., when questions are modified) are open methods and policy issues. The rationale for KQ was to determine if the addition of an agent with a different

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		combination regimens against each other as well as intensification of statin monotherapy…" is misplaced. Rather, appropriate patient selection based on baseline lipids would be a more important focus area. 2. We believe the posed research question was flawed. All studies that have looked at combo vs. mono therapy have been with a controlled LDL goal as the baseline target from which to go forward and randomize treatments. Few, if any studies, were designed with mono vs. combo therapy as the final target. Therefore, the answers may be limited by the specific question posed. We recommend AHRQ address this flaw in future research on this topic. 3. Studies that measured Non-HDL, as the newer guidelines (including the NCEP and International Atherosclerosis Society Guidelines) recommend, have shown better attainment of these goals, although the benefits have not been robustly demonstrated. Statins do not address these secondary goals, and combination therapies have been shown to be useful for this purpose. 4. The modern studies looking at low LDL with added combo therapy have not shown "hard" endpoint benefit, but have been seen as effective for secondary endpoints (Carotid Intimal Thickness, HDL and Non-HDL cholesterol goals), with acceptable risk profiles in treated patients	mechanism of action from a statin would provide benefit above simply increasing statin, without increased adverse effects. This information may be useful for patients who do not tolerate higher dose statins. We have added discussion in the Introduction and Discussion to further outline this rationale and to discuss the other related evidence. 3. We examined non-HDL in patients with DM (consistent with prior report and guideline recommendations). 4. No comment

Commentator	Section	Comments	Response
Peer reviewer #1	Clarity and Usability	The report follows the formulaic approach laid out the KQs. In that regard it is easy to understand the layout and locate desired information. The main points are not clearly presented since they are obscured by the density of the repetitive data presentations. There is little if anything that helps inform practice decisions. I am not convinced that it really informs policy because of the impractical nature of the recommendations.	We added a section to the beginning of results to help navigate this section.
TEP #1	Clarity and Usability	I do not feel that the conclusions can be used to support practice and policy decisions. The one point with strong SOE (fewer AEs with high-dose statins than mid-potency statin/ezetimibe) is not supported by the studies referred to. Well-known adverse events such as flushing with niacin (as well as other toxic effects) fall below the radar screen due to the selection criteria, which limits the included studies to ones that include statin titration. Any large niacin study (i.e., HPS2-THRIVE) shows a substantial patient withdrawal due to adverse events, primarily flushing. Adverse events with bile acid sequestrants are also well documented in the literature, although this evidence is not included in the report. I feel that the approach is basically flawed since the report ends up with small studies that because of size don't detect side effects.	We previously reported high SOE favoring monotherapy when comparing SAEs between combination therapy and monotherapy; however, this reviewer's comment led us to reconsider the evidence and studies included in this comparison for this outcome. As shown in Table 10 of the report, the percentage of patients in each arm experiencing an SAE in each arm was low overall. There were no statistically significant differences between the arms. Two of these trials occurred within similar populations and with similar interventions; however, the third trial employed a potency escalating strategy over the course of the trial (Stein, 2004). As a result, only the initial period was eligible for inclusion in our study, yet SAE were reported over the course of the entire study. Therefore, we felt this study was sufficiently different from the other two, and therefore, not amenable to pooling with meta-analysis. We graded the SOE as insufficient, as we could only truly include two trials for this outcome and comparison. This has been reported consistently throughout the report. Flushing was not considered an SAE. If the investigators included flushing as an AE, it would be captured under "1 or more AE." Of if flushing was so severe to cause withdrawal, it would be captured under "withdrawal due to AE"

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TEP #2	Clarity and Usability	The problem is that the paucity of outcome data makes any conclusions difficult to apply to clinical practice. Clinicians want to know what to do if a patient can't tolerate a statin. Specifically, they need to know whether addition of another lipid drug would provide incremental benefit. ACCORD and AIM HIGH didn't show benefits of adding a fibrate and niacin respectively to high risk populations already with optimal levels of LDL-C on a statin. I do think being able to show that certain statin combinations are more likely to lower LDL-C (bile acid sequestrates and ezetimibe are favored over niacin and fibrates) is of value. Indeed, bile acid sequestrants may lower A1c in those with diabetes and this could be a real advantage as compared to ezetimibe. On the other hand, telling us what combinations improve HDL-C is not useful as we have trials where HDL-C raising hasn't translated into incremental clinical benefit over statins. I would note that in the PROVE-IT trial, pravastatin 40 mg/dl did a better job of raising HDL-C than atorvastatin 80 mg/dl. It was atorvastatin's superior lowering of LDL-C that correlated with its superior efficacy as compared to pravastatin.	The Discussion includes a discussion of the related evidence, including the trials noted. We have mentioned in the introduction that only VA-HIT showed reduction in clinical events with HDL-c raising among men with baseline low HDL-c.
TEP # 3	Clarity and Usability	The report is very well-structured and organized—easy to read and find data. The main points are presented in several ways and are consistent and straightforward. The conclusions COULD be used to inform policy, but, as the authors note, the evidence behind them is so weak—it is not recommended to make policy from them. If the adequacy of the science improves, this report will provide decent structure for informing policy.	Thank you.

Commentator	Section	Comments	Response
TEP # 4	Clarity and Usability	Yes, the conclusions from this report can be useful to the clinician in making individualized decisions for the patient. The report is also helpful to the clinical trial investigator to point out areas where there is need for future research. This is a well written, detail-oriented review. Tables and figures are helpful to the reader in summarizing the information	Thank you.
Peer reviewer #3	Clarity and Usability	Main points are clear, but I don't believe policy can change without harder clinical outcomes.	Thank you.
Peer reviewer #2	General	This is a poorly conceived report that stems from a fundamental flaw in the research question. Consider the following logic path—elevated cholesterol (in particular LDL) is considered a risk factor for the development of CAD; trials of statins and meta-analyses of them (see CTT reports in Lancet) show a reduction in events associated with a reduction in LDL (log-linear relationship) It is well established that cholesterol lowering treatments other than statins can effectively lower LDL and when combined with a stain will add to the LDL lowering effect. That was the basis for approval for many of the agents by the FDA. Yes—it is an important question to know whether it is better to increase a dose of a statin or to add a second agent but KQ1 is set up to fail—there are no trials to adequately answer the question about long term benefits and risks. This was all knowable before AHRQ spent the money on this evidence review that fundamentally confirms that the the findings are "inconclusive". Such a statement is of little help to clinicians. To end up recommending (p 133) that "future studies conduct head-to head comparisons of	Our review was an update of a prior EPC review. The KQs in our review are the KQs from 2009 review we were tasked with updating. When to conduct an update (what is sufficient number of new studies?) and when an update becomes a new review (i.e., when questions are modified) are open methods and policy issues. The rationale for KQ was to determine if the addition of an agent with a different mechanism of action from a statin would provide benefit above simply increasing statin, without increased adverse effects. This information may be useful for patients who do not tolerate higher dose statins. We have added discussion in the Introduction and Discussion to further outline this rationale and to discuss the other related evidence. We agree that new trials with statin mono vs. statin + combo agent (ACCORD, AIM HIGH) have clinical outcomes and that they are important trials which answer the question of whether to add on a combination agent compared to same dose of statin. However, since the results of IMPROVE-IT trial are not yet released a review with those additional questions (combination vs same dose) would be of limited value. As mentioned before, we think even before simulated modeling studies are undertaken, direct observational evidence may be sought, and synthesized, in a subsequent systematic review. This would be a natural follow up sequel. In our understanding, the clinical questions are very relevant and need a sequence of systematic review process to answer. Look for robust trial evidence, when lacking, direct observational evidence, when still lacking indirect network meta-analyses, and lastly decision modeling. Our review update serves to highlight the gaps in the extant literature and forms the basis a subsequent step. In the EBM world, the process is iterative and methodical.

Commentator	Section	Comments	Response
		multiple combination regimens" is totally impractical. Who will fund such studies? What about the anticipated cost to the health care system to conduct such multiple comparisons (and dose comparisons)—there are probably at least 6 or 8 factorial combinations that can be considered at first blush. A much more clinically useful approach would have been to take the known relationship between LDL and events and attempt to map onto that relationship the anticipated impact of various maneuvers to increase the intensity of LDL lowering.	
Peer reviewer #2	General	I have serious doubts about whether this report is very clinically meaningful at the present time. First, the most important reason why statin therapy is not as effective in lowering LDL or ApoB is lack of adherence to the therapy. One would be very concerned that physicians increase or add drugs when patients are not adhering to therapy. This should be discussed in the document. No mention is made of a potential benefit of intensive nonpharmacological, i.e. dietary, intervention, to add it to statins for those individuals whose lipid levels have not reached their goal rather than adding some of the other drugs. Most of the dietary intervention trials have been inadequate in the intensity of the dietary intervention. The National Diet-Heart Study clearly documented that a high polyunsaturated fat intake of up to 12% or even higher and very low saturated fat have a fairly substantial impact on LDL-C. It may well be that individuals whose cholesterol levels have not decreased on statins may be hyperabsorbers of cholesterol, etc. Also, no mention is made of the genetic variations in response to statins and that perhaps one should look at the genotype of the	Added to "Implications for Clinical and Policy-Decision Making" Another issue facing clinicians is whether lack of response to lipid-lowering agents stems from non-adherence to therapy, which is common. {Caspard H, Chan AK, Walker AM. Compliance with a statin treatment in a usual-care setting: retrospective database analysis over 3 years after treatment initiation in health maintenance organization enrollees with dyslipidemia. Clin Ther 2005; 27: 1639–46}. We had insufficient data to assess whether adherence differed between lower-potency combination therapy and higher-dose statin monotherapy, however, this issue is irrelevant if the reason for suboptimal LDL-c response due to poor adherence to initial statin monotherapy. Other therapies, such as dietary interventions, were not within the scope of this review, as are extrapolations about genetic variations in response to statins. Added to Limitations section (ES and main report), "Given several previous reviews on dietary modification and reduction of lipids and CVD risk, we did not include these therapies in this review. Further, we did not examine differences in statin response based on genetic variations PCSK-9 is not FDA approved and was thus not considered within scope of our review. It is not available to clinicians in the US and thus would not help inform their decisions at this time, but should a new product be available then it would be appropriate to update the report.

Commentator	Section	Comments	Response
		individual before of prescribing an alternative drug. Similarly, and perhaps most important, the new PCSK-9 inhibiting drugs have profound effects on lipid levels and will become the first line or the alternative drugs for individuals who cannot reduce their cholesterol and thus, much of the information provided in this report will be out-of-date by the time it is widely distributed because of the evolving development of PCSK-9 drugs. These drugs have effects on LDL-C, which are almost as great or greater than those of the statins although at the present, they all must be taken subcutaneous or intramuscular rather than orally. Finally, as the report notes there is little to no evidence that adding these alternative drugs to statin therapy has any effect on outcome except in high triglycerides, low HDL, obese men (VA-HIT study). The data is quite clear at the present time that these drugs that change HDL-C have little effect on cardiovascular outcomes perhaps because changes in HDL particles or apolipoproteins may be more important than actually changing the HDL-C. Most of these drugs that have effects on HDL-C but little effects on HDL particles or apolipoproteins	
TEP #1	General	Some of the report's recommendations are clinically meaningful, and others are not. Most key questions cannot be answered because they only have a low level of evidence.	We agree that there is a lack of evidence, reflected in the SOE and in our discussions of the limitations in the evidence.

Commentator	Section	Comments	Response
TEP # 2	General	I am concerned about this report because although it is carried out with excellent attention to rating the quality of evidence: 1) It is focused on small, short-term (under 12 months) that change Low Density Lipoprotein Cholesterol (LDL-C) and High Density Lipoprotein Cholesterol (HDL-C) when these studies can't possibly provide meaningful information on outcomes; important to remember that estrogens and torcetrapib are two interventions that lower LDL-C, raise HDL-C and yet cause outcomes indicating harm, not good 2) Given the negative results of ACCORD and AIM-HIGH, as well as trials of CETP inhibitors, the value of raising HDL-C by pharmacologic means is suspect; I don't think it should receive equal footing with those trials that lower LDL-C. In other words, "reverse epidemiology" that posits if a low HDL-C is associated with bad outcomes, then raising HDL-C by medication must improve CVD outcomes is simply not true. This needs clear emphasis in the start of the paper 3) Ezetimibe is a problem for this analysis. Unfortunately, we don't have data showing that it provides incremental benefit to statin therapy in terms of atherosclerotic cardiovascular disease (ASCVD) outcomes. Mindful that some non-statin interventions (estrogen, torcetrapib) lowered LDL-C without benefit, but some non-statin interventions did (e.g partial ileal bypass), how do we use this evidence review to guide the clinician? I think we have to wait for further trials such as IMPROVE-IT.	We agree that the available evidence is limited and discuss these limitations in the Key Findings and Implications section: "The evidence suggests that some combination therapy regimens may confer benefits with respect to lowering LDL-c including bile acid sequestrants (up to 14 percent greater LDL-c reduction) and ezetimibe (up to 21 percent greater LDL-c reduction). LDL-c is an important factor in the development of atherosclerotic cardiovascular disease and higher levels of LDL-c have been associated with greater risk of this disease.[7,8] We also found that some combination therapy regimens may confer benefits with respect to raising HDL-c including ezetimibe and niacin (up to 6 percent and up to 27 percent, respectively). However, there is insufficient evidence to address whether these LDL-c lowering benefits achieved with these medications translate into decreased rates of atherosclerotic cardiovascular disease. We also address this issue in the Important Unanswered Questions section: "We found very limited evidence regarding these long-term benefits and serious harms among other combination therapy comparisons (bile acid sequestrants, fibrates, niacin, and omega-3 fatty acids). Overall, we are unable to conclude whether there are any long-term advantages or serious disadvantages to combination therapy with any agent as compared to intensification of statin monotherapy." With regards to HDL-c, we have added the following information, "… several large trials comparing statin monotherapy to combination therapy with the same statin dose plus another lipid lowering drug, such as ENHANCE, AIM-HIGH, and ACCORD-lipid. These trials have demonstrated that this "add on" combination therapy can lead to superior lipid outcomes, but fails to reduce atherosclerosis or lead to decreased rates of cardiovascular death, MI, revascularization, or stroke.[15] This evidence calls into question previous assumptions that lowering LDL-c or raising HDL-c are always reliable predictors of improved clinical outcomes, as well as increasing the importance of patient-centered clinical outcomes for evaluation the effectiveness of lipid modifying therapies.[7,16] We also added the following statement, "Low HDL-c levels are independent predictors of CHD[9,10] and have been associated with increased CVD risk among patients without vascular disease at baseline.[11] However, only the VA-HIT study showed clinical benefit of raising HDL-c among men with low baseline HDL-c.[12] We have added discussion of the potential impact of IMPROVE-IT.

Commentator	Section	Comments	Response
TEP #3	General	The key questions are well-stated and relevant. The target population of patients (and relevant subgroups) are clearly identified. The target audience is clear from the scope of the review, as primary care physicians are the most likely to use this date. I believe it's most useful to limit this review to the moderate and high-risk patients rather than all-comers, given that most of the data on combination will be in those with elevated risk. Grouping statins by their potency to reduce LDL is a necessary and logically reasonable way to categorize	Thank you for your consideration of our KQs and method decisions.
TEP #4	General	Line number 16-"among patients at moderate and high CHD risk, defined as a 10-year CHD risk greater than 10 percent or LDL greater than 160 mg/dL"... Change to: "among patients at high and moderate CHD risk, defined as a 10-year CHD risk greater than 10 percent or LDL greater than 160 mg/dL"...	Thank you, we have corrected this text.

Commentator	Section	Comments	Response
Peer reviewer #3	General	The report is clinically meaningful, however much of this data is relatively well known. As a practicing cardiologist, I find most of my primary care colleagues are aware of ways to combine medications and attempt to lower LDL or raise HDL. However, what is clinically missing and perhaps the most relevant is the long-term "hard" or clinical outcomes. At this point most practicing docs want to know more than LDL outcomes, how patient outcomes will be impacted. This is missing	Unfortunately, the available evidence does not address clinical outcomes. The following paragraph is in the Key Findings and Implications section: "The evidence suggests that some combination therapy regimens may confer benefits with respect to lowering LDL-c including bile acid sequestrants (up to 14 percent greater LDL-c reduction) and ezetimibe (up to 21 percent greater LDL-c reduction). LDL-c is an important factor in the development of atherosclerotic cardiovascular disease and higher levels of LDL-c have been associated with greater risk of this disease. We also found that some combination therapy regimens may confer benefits with respect to raising HDL-c including ezetimibe and niacin (up to 6 percent and up to 27 percent, respectively). However, there is insufficient evidence to address whether these LDL-c lowering benefits achieved with these medications translate into decreased rates of atherosclerotic cardiovascular disease. Prior trials comparing combination regimens to statin monotherapy such as ENHANCE, AIM-HIGH, and ACCORD-lipid have demonstrated that combination therapy can lead to superior lipid outcomes, but fail to reduce clinical outcomes such as cardiovascular death, MI, revascularization, or stroke. The following sentences are included in the Important Unanaswered Questions section: "We found very limited evidence regarding these long-term benefits and serious harms among other combination therapy comparisons (bile acid sequestrants, fibrates, niacin, and omega-3 fatty acids). Overall, we are unable to conclude whether there are any long-term advantages or serious disadvantages to combination therapy with any agent as compared to intensification of statin monotherapy."
Public reviewer #1 Richard Chapell	General	We are unable to comment on the quality of the appendices, which were not posted for public review and comment. Because there are several items we would have liked to have been able to look up in the appendices, we regret this omission.	AHRQ is looking into why the reviewer was not able to access the appendices.

Commentator	Section	Comments	Response
TEP # 5	General	This report is very well written and expansive. The report, deals well with the potential benefits but seems to skirt over harms. What about harms associated with intensive statin therapy such as diabetes or rhabdomyolysis What about the stroke signal seen in AIM-High?	Added to "***Mechanism of Action of HMG-CoA Reductase Inhibitors"*** There have been concerns regarding adverse effects of intensive statin therapy. For example, intensive statin therapy has been associated with an increased risk of diabetes compared to moderate statin therapy (Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis.JAMA. 2011;305(24):2556-2564). Rhabdomyolysis is a rare but dangerous complication of statin therapy (Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA. 2004 Dec 1;292(21):2585-90.) with higher risk at higher statin doses (http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm). We did not add information about stroke signal in AIM-HIGH, because our understanding is that the final results of AIM-HIGH appear to suggest that the signal of increased ischemic stroke with **niacin**, which was one of the reasons the study was stopped early, could have been the play of chance, with the final p value for ischemic stroke coming in at a nonsignificant 0.11.
Peer reviewer # 4	General	Overall, this is an exhaustive and valuable contribution to the literature. (One of the reasons it took so long was that the document is so long.) The question addressed is one of high interest to the clinician—whether addition of another lipid-lowering agent to a statin is useful and, specifically whether a lower dose of a statin in combination with another agent is as effective as a moderate dose statin alone. This would make sense if there were a lower risk of adverse effects with the former regimen and equal efficacy. Because there are no outcome data, however, this question is really not terribly relevant except perhaps in the case of patients who do not tolerate moderate dose statins (although such patients were not presumably enrolled into most trials). The review does not address the question with which clinicians more often struggle, is there additional benefit to adding a 2nd agent for a patient who is already on high dose statins? This is typically done when a patient fails to reach a given LDL-c target. Recent events, however, however, may	Thank you for your comments. Given the release of new cholesterol treatment guidelines in Nov 2013, we have rewritten all sections of the document discussing ATPIII and added pertinent information regarding the new treatment guidelines.

Commentator	Section	Comments	Response
		overtake the applicability and relevance of this review. As you likely know, after 4 years of sponsoring development of ATP IV, NHLBI withdrew its sponsorship a few weeks ago. The good news is that the guideline that had been under development is likely to be published under the auspices of AHA/ACCF within the next few weeks. Although the document is embargoed, it is very likely that the recommendations will be quite different from ATP III and more consistent with the recent AHA/ACCF/ACP guideline for management of stable ischemic heart disease which gave a class I recommendation to treatment with a moderate dose statin. There was no recommendation to treat to a target LDL-c. The relevant recommendations for the SIHD guideline are: 4.4.1.1. LIPID MANAGEMENT CLASS I 3. In addition to therapeutic lifestyle changes, a moderate or high dose of a statin therapy should be prescribed, in the absence of contraindications or documented adverse effects. *(Level of Evidence A)* CLASS IIa 1. For patients who do not tolerate statins, LDL cholesterol–lowering therapy with bile acid sequestrants,* niacin, or both is reasonable. (Level of Evidence: B) If the "ATP IV" guideline is anywhere similar to this, then the whole notion of adding a drug other than a statin in patients who tolerate a moderate or high-dose statin is now called into question. At the very least the introduction and discussion in the meta-analysis should anticipate these potential changes.	

Commentator	Section	Comments	Response
Peer reviewer #4	General	The review could also address some persisting, thorny questions about statins. Would it be possible to combine data about the incidence of myopathy and muscular symptoms among patients taking moderate or high dose statins?	These outcomes were abstracted individually across studies, however, the event rates reported were typically low. We did not attempt to pool these outcomes.