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Systematic Review and Network Meta-Analysis on the Efficacy of Evolocumab and Other Therapies for the Management of Lipid Levels in Hyperlipidemia

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***Background*—**The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors evolocumab and alirocumab substantially reduce low-density lipoprotein cholesterol (LDL-C) when added to statin therapy in patients who need additional LDL-C reduction.

***Methods and Results*—**We conducted a systematic review and network meta-analysis of randomized trials of lipid-lowering therapies from database inception through August 2016 (45 058 records retrieved). We found 69 trials of lipid-lowering therapies that enrolled patients requiring further LDL-C reduction while on maximally tolerated medium- or high-intensity statin, of which 15 could be relevant for inclusion in LDL-C reduction networks with evolocumab, alirocumab, ezetimibe, and placebo as treatment arms. PCSK9 inhibitors significantly reduced LDL-C by 54% to 74% versus placebo and 26% to 46% versus ezetimibe. There were significant treatment differences for evolocumab 140 mg every 2 weeks at the mean of weeks 10 and 12 versus placebo (−74.1%; 95% credible interval −79.81% to −68.58%), alirocumab 75 mg (−20.03%; 95% credible interval −27.32% to −12.96%), and alirocumab 150 mg (−13.63%; 95% credible interval −22.43% to −5.33%) at ≥12 weeks. Treatment differences were similar in direction and magnitude for PCSK9 inhibitor monthly dosing. Adverse events were similar between PCSK9 inhibitors and control. Rates of adverse events were similar between PCSK9 inhibitors versus placebo or ezetimibe.

***Conclusions*—**PCSK9 inhibitors added to medium- to high-intensity statin therapy significantly reduce LDL-C in patients requiring further LDL-C reduction. The network meta-analysis showed a significant treatment difference in LDL-C reduction for evolocumab versus alirocumab. **(*J Am Heart Assoc*. 2017;6:e005367. DOI: 10.1161/JAHA.116.005367.)**

Key Words: alirocumab • evidence-based medicine • evolocumab • ezetimibe • lipids • low-density lipoprotein cholesterol • meta-analysis • proprotein convertase subtilisin/kexin type 9 inhibitor • statin therapy

Lowering low-density lipoprotein cholesterol (LDL-C) levels with statins reduces the risk of atherosclerotic cardiovascular disease (CVD).[1-6] The IMPROVE-IT trial[7] substantiates that LDL-C reduction with nonstatin therapy further reduces risk of CVD, although the absolute reduction in cardiovascular events was small because of modest LDL-C lowering with ezetimibe on top of a statin.[8] There remains, however, a population of high-risk patients who have elevated LDL-C despite statin therapy and who have residual risk of cardiovascular events and mortality.[9] As a result, there is an unmet need for new therapies to provide this high-risk population with incremental LDL-C reduction beyond that

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Accompanying Data S1, S2, Tables S1, S2, and Figures S1 through S7 are available at http://jaha.ahajournals.org/content/6/10/e005367/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Patients who need additional lowering of low-density lipoprotein-cholesterol (LDL-C) despite statin therapy may benefit from additional lipid-lowering therapy such as evolocumab or alirocumab (proprotein convertase subtilisin/kexin type 9 inhibitors [PCSK9]).
- A systematic literature review found 74 total studies that explored LDL-C lowering in patients receiving statin background therapy; of these, 15 were used to conduct a network meta-analysis of evolocumab, alirocumab, and ezetimibe.
- A network meta-analysis found that evolocumab 140 mg every 2 weeks reduced LDL-C by 74% versus placebo and 46% versus ezetimibe; alirocumab 75 mg every 2 weeks, 54% and 26%; alirocumab 150 mg every 2 weeks, 60% and 32%; evolocumab 420 mg every month, 72% and 48%; and alirocumab 300 mg every month, 52% and 28%.

What Are the Clinical Implications?

- Studies of PCSK9 inhibitors in a range of populations and risk profiles have consistently showed a substantial relative reduction in LDL-C additional to that provided by statins—often more than 60%, as shown in the present analysis.
- Such incremental LDL-C reduction can allow patients with high unmet need (eg, those at very high cardiovascular risk) to achieve LDL-C levels below target, which is expected to reduce their residual risk of cardiovascular events.

which can be achieved by statins and other oral lipid-lowering therapies. Moreover, there is evidence that the lower LDL-C achieved provides further risk reduction.[10,11]

Produced mostly in the liver, proprotein convertase subtilisin/kexin type 9 (PCSK9) in plasma binds to hepatic LDL receptors on the cell surface and targets them for degradation, thereby decreasing the number of LDL receptors and increasing LDL-C levels. PCSK9 was identified as a target when people with variants that upregulated or downregulated this protein led to, respectively, greater and lesser risk of cardiovascular events.[6] The PCSK9 inhibitors evolocumab and alirocumab were recently approved for LDL-C reduction when added to maximally tolerated statin therapy.

To date there are no head-to-head studies comparing the LDL-C–lowering capacity of PCSK9 inhibitors to each other. In the absence of such trials indirect treatment comparisons and network meta-analyses based on a robust systematic literature review can inform evidence-based healthcare decision making.[12] Within network meta-analyses, indirect treatment comparison allows the comparison of 2 therapies that share a common comparator,[13] whereas mixed treatment comparison allows a combination of direct and indirect evidence.[14,15]

Systematic reviews with subsequent meta-analyses have been conducted using clinical studies of PCSK9 inhibitors.[16–20] However, such studies have either pooled PCSK9 inhibitors together as a class[16–19] or provided pooled efficacy estimates for evolocumab versus control and alirocumab versus control without making any formal indirect comparisons.[20] Finally, none of the meta-analyses specifically focused on patients whose hypercholesterolemia was not controlled with statin therapy alone, the primary populations for which evolocumab and alirocumab are indicated.[21–24]

We therefore conducted a systematic review and network meta-analysis to compare LDL-C reduction with evolocumab to other lipid-lowering therapies (including alirocumab) in patients receiving statin background therapy.

Methods

Objectives, Study Selection, Quality Assessment, and Data Abstraction

We conducted this systematic review and network meta-analysis with a target population of patients with hypercholesterolemia whose condition is not adequately controlled according to European lipid goals[25] with moderate- to high-intensity statin background therapy and who remain at risk of cardiovascular events. The therapies (ie, interventions) we assessed were evolocumab and other pharmacologic agents for the management of hypercholesterolemia. The control for each therapy was placebo (ie, background statin therapy alone) and all other therapies that share a common comparator. The efficacy outcomes of interest were percentage change from baseline in LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, apolipoprotein B (ApoB), and lipoprotein (a) [Lp(a)] and cardiovascular events (not the focus of this article owing to a lack of available data for analysis). The safety outcomes of interest were any adverse event (AE), treatment-related AE, and serious AE.

The systematic review adhered to methods published by the Centre for Reviews and Dissemination[26] and the Cochrane Collaboration.[27] Randomized studies were included if they enrolled adults (≥18 years) with primary familial or nonfamilial hypercholesterolemia who were candidates for evolocumab or other pharmacological lipid-lowering therapies added to statins. Only studies with ≥12 weeks of follow-up and ≥10 patients per group were included. Studies were excluded if they included patients with organ transplantations, infectious diseases such as HIV/AIDS, New York Heart Association grade III-IV heart failure, or stage 4 or 5 renal dysfunction. Studies were excluded if patients were only receiving a low-intensity statin as background, as were those that solely studied statin therapy. Only doses and frequencies that are

marketed in the United States or European Union or investigated in phase 3 studies were included.

We searched MEDLINE, Embase, the Cochrane Databases of Systematic Reviews and Controlled Trials CENTRAL, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database from inception to August 2016. The search strategy was limited where possible to randomized studies and those in humans but was not limited by date or language. We searched clinical trial registries and conference abstracts, presentations or posters, in order to identify unpublished studies. For studies sponsored by Amgen, the sponsor of the evolocumab clinical trial program, we used both publications and clinical study reports. Keywords for the searches included the hypercholesterolemia disease state and all therapies used to modify atherogenic lipids (see Data S1). For quality assurance, the Embase search strategy was peer-reviewed by a second information specialist using the Canadian Agency for Drugs and Technologies in Health peer review checklist.[28]

Two independent reviewers screened titles and abstracts to exclude records that obviously did not meet inclusion criteria; 2 reviewers then obtained and independently screened full texts for inclusion in the systematic review.

Data were extracted by 1 reviewer and independently checked for errors by another reviewer. The same process was used to assess the methodological quality of all included studies using the Cochrane Collaboration Risk of Bias Assessment Tool.[27] Throughout the screening and data extraction process, discrepancies between reviewers were resolved through discussion or by consulting a third reviewer.

Data Synthesis and Analysis

Networks were created including studies that provided sufficient data for synthesis and with the aim of ensuring as much homogeneity as possible (eg, based on study design and clinical characteristics). All available data from the included studies were incorporated except data from patients in evolocumab studies with no statin use before enrollment (30% of LDL-C Assessment w/PCSK9 MonoclonaL Antibody Inhibition Combined with Statin ThErapy – 2 (LAPLACE-2))[29] and patients assigned to diet alone based on their cardiovascular risk (12% of Durable Effect of PCSK9 antibody CompARed wiTh placEbo Study (DESCARTES)).[30]

We conducted meta-analyses only if the underlying studies were considered to be statistically and clinically homogenous. We assessed statistical heterogeneity with the chi-squared test ($P<0.10$ was considered significant for heterogeneity) and the I^2 value and by visual inspection of the forest plots. We could not assess publication bias because there were not enough studies in each direct meta-analysis to generate a funnel plot. Stata (StataCorp; College Station, TX) version 13.1 was used to conduct direct meta-analyses using random effects models. To explore the robustness of results, sensitivity analyses were performed by excluding specific studies (eg, if they were associated with heterogeneity in direct meta-analyses, or unique populations such those enrolled in studies conducted in Japan) or by relaxing inclusion criteria and including additional studies.

The network meta-analysis was conducted using Bayesian models[31] in WinBUGS (MRC Biostatistics Unit; Cambridge, UK) version 1.4.3. We estimated the mean treatment difference or risk ratio for each comparison after an initial burn-in of 40 000 Markov chain Monte Carlo simulations, followed by a further 40 000 simulations. Two chains were used. We used noninformative normal priors (mean 0, variance 10 000) for treatment effects and a noninformative uniform prior (interval 0, 5) to estimate the between-study standard deviation. We assessed convergence and autocorrelation by monitoring the trace and autocorrelation plots in WinBUGS. None of the models showed any problems with convergence. We obtained the median estimate of the mean difference or risk ratio from the posterior distribution and reported it with the 2.5% and 97.5% estimates of the distribution (the 95% credible interval [CrI]). We assessed model fit using residual deviance and the deviance information criterion. All analyses used random-effects models and the treatment effect from each study (ie, mean difference, rather than the mean and standard error for each group).

Within the network meta-analysis, we reviewed assumptions of homogeneity based on the I^2 statistic from the direct meta-analyses, similarity using the baseline characteristics and designs of the included studies, and consistency using the IFPLOT command in Stata in comparisons with both direct and indirect comparisons. We conducted sensitivity analyses to explore any heterogeneity by excluding individual studies or those in different populations. We also conducted sensitivity analyses combining both evolocumab dosing groups and including studies with all background therapies.

We excluded on a post hoc basis nodes in the networks that included fenofibrate or anacetrapib from this article. The anacetrapib arm was excluded because this cholesterylester transfer protein inhibitor's cardiovascular outcomes trial is ongoing, and all of the prior trials in this drug class have been neutral or negative in risk reduction.[32] Moreover, a recent meta-analysis of lipid-lowering therapy found that therapies that upregulated LDL receptor function were linearly associated with reductions in cardiovascular events per 1 mmol/L reduction in LDL-C. This relationship was less consistent with fibrates and cholesterylester transfer protein inhibitors, and statin-era trials in particular were negative or neutral in reducing cardiovascular events.[5] We also excluded bococizumab after Pfizer announced they were halting clinical and commercial development of this PCSK9 inhibitor.[33] Pfizer

noted in its press release that studies of bococizumab showed reduced efficacy over time and more injection-site reactions than evolocumab and alirocumab.[33]

Evolocumab can be administered as 140 mg every 2 weeks (Q2W) or 420 mg monthly (QM), and we generated separate networks for each dosing option. The co–primary end points for most evolocumab studies were the percentage change in LDL-C from baseline to the mean of 10 and 12 weeks and to week 12. The co–primary end point of 10 and 12 weeks allows a better representation of the efficacy of evolocumab across the dosing period, particularly for monthly administration, and is included in international prescribing information. To be concise, this analysis for evolocumab (140 mg Q2W) is the focus of the main text and sensitivity analysis. Key results for week 12 are reported in Figure S1. Because data from some comparator studies were available only for follow-up of longer than 12 weeks (eg, up to 78 weeks), we analyzed values using evolocumab at the mean of 10 and 12 weeks or at week 12 versus comparators at ≥12 weeks. In practice, week-12 data were available for percentage reduction in LDL-C but less consistently for other lipid end points.

If the outcome was not available at week 12, we used the nearest time point after week 12. For alirocumab studies, in which dose titration is often employed, we specifically aimed to analyze patients who were taking only 75 mg Q2W, only 150 mg Q2W, or only 300 mg QM.

Results

Figure 1 displays the systematic review flow diagram. The systematic review found 45 058 unique records, of which 44 318 were excluded based on the title and abstract. The full papers of the 740 remaining records were assessed for eligibility, and 502 were excluded with reasons, leaving 238 records reporting 74 studies (studies and records included and excluded are displayed in Data S2). These 74 studies had study data available, and 69 of them focused on a population requiring further LDL-C reduction while on maximally tolerated statin therapy. The remaining 5 studies were in statin-intolerant patients. Table S1 displays population characteristics of the studies.

A total of 54 studies were excluded from all LDL-C networks (Table S2), and 15 in which patients predominantly received moderate- or high-intensity statin background therapy were included in the primary networks (ie, those most closely aligned with the research question) (Table 1, Figure 2).[29,30,34-45] We created separate networks for comparing evolocumab to other lipid-lowering therapies by dosing regimen: 140 mg Q2W or 420 mg QM (Figure 2). Both networks included placebo and ezetimibe (10 mg daily). The evolocumab 140 mg Q2W network also included alirocumab 75 mg and 150 mg Q2W; the evolocumab 420 mg QM network included alirocumab 300 mg QM.

There were 4 studies of evolocumab[29,34-36] LDL-C Assessment w/PCSK9 MonoclonaL Antibody Inhibition Combined with Statin ThErapy – Thrombolysis In Myocardial Infarction – 57 (LAPLACE-TIMI-57), LAPLACE-2, Stud**Y** of LDL-Cholesterol Reduction Using a Monoclonal PCS**K**9 **A**ntibody in Japanese Patients **W**ith **A**dvanced Cardiovascular Risk – 1 (YUKAWA-1), and YUKAWA-2) in both networks, all of which were 12 weeks in duration. There was 1 additional study of evolocumab (DESCARTES[30]) in the 420 mg QM network that was 52 weeks in duration. All studies compared evolocumab to placebo, and 1 study[29] (LAPLACE-2) also included a comparison with ezetimibe.

In total, there were 9 studies of alirocumab[37,38,40,41,45-48] in the Q2W network (McKenney 2012 and ODYSSEY COMBO I and II, OPTIONS I and II, CHOICE I, JAPAN, HIGH FH, and LONG-TERM), of which 2 (McKenney 2012 and CHOICE I) were included in the QM network.[37,41,48] Alirocumab studies were 12 to 104 weeks in duration. All studies reported 12- and 24-week data except 1 that reported 24-week data only (in the network meta-analyses, the 12-week data were used except for the study in which it was not available). The alirocumab 75- and 150-mg Q2W doses were included as separate therapies in the Q2W network, and the 300-mg QM dose was included in the QM network. Six studies compared alirocumab to placebo, and 3 studies[38,47] (ODYSSEY COMBO II and ODYSSEY OPTIONS I and II) compared alirocumab 75 mg Q2W to ezetimibe.

Finally, there was 1 eligible study[44] comparing ezetimibe to placebo (Masana 2005).

Risk of bias was assessed by judging how well all included studies reported across 8 domains of the Cochrane Risk of Bias Assessment Tool (Figure S2). In this article we focus on those studies that were included in the primary analysis LDL-C networks. All evolocumab studies[29,30,34-36] had low risk of bias across all criteria. The risk of bias in 5 alirocumab studies[37,38,40,41,46-49] was unclear in at least 1 area. The most common reason for an unclear risk of bias was insufficient reporting of allocation of concealment and randomization methods.

Lipid-Lowering Efficacy of Evolocumab Compared to Other Therapies

Direct head-to-head comparisons are displayed in Figure S3.

Treatment differences between lipid-lowering therapies for the percentage reduction in LDL-C from baseline are displayed in Figure 3 for evolocumab at the mean of weeks 10 and 12 versus comparators at ≥12 weeks and in Figure S3 for evolocumab at week 12 versus comparators at ≥12 weeks. All treatment differences between evolocumab

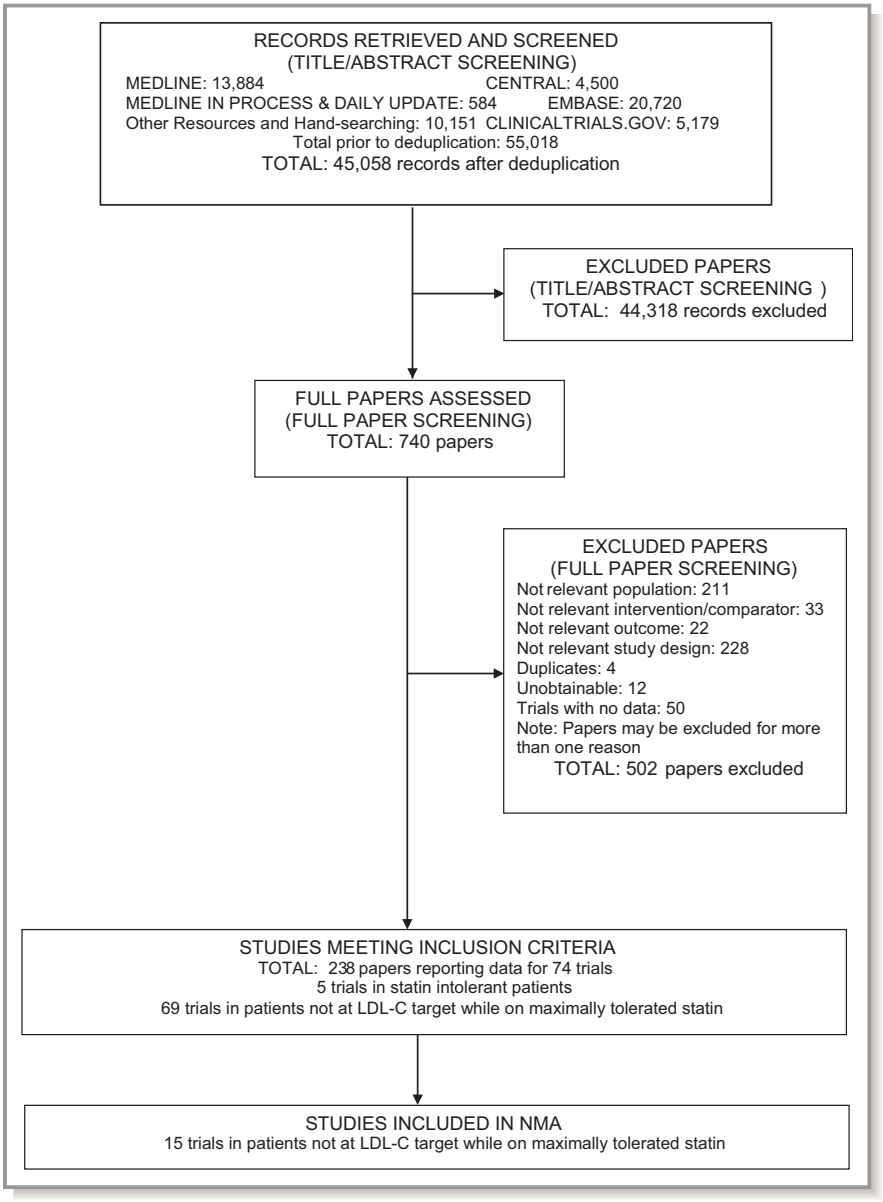

Figure 1. Study flow diagram of the systematic review. Articles in the "Excluded Papers" stage could be excluded for ≥1 reason. The network meta-analysis of statin-intolerant patients yielded a small sample size and did not include pending results of a phase 3 study of evolocumab in this population. LDL - C indicates low-density lipoprotein cholesterol; NMA, network meta-analysis.

140 mg, alirocumab 75 mg, alirocumab 150 mg, or ezetimibe and placebo were statistically significant.

Among PCSK9 inhibitors, evolocumab had a greater LDL-C reduction than alirocumab. For evolocumab 140 mg Q2W at the mean of weeks 10 and 12 versus comparators at ≥12 weeks, the treatment difference versus alirocumab 75 mg was −20.03% (95% CrI −27.32% to −12.96%) and −13.63% (95% CrI −22.43% to −5.33%) compared with alirocumab 150 mg. The treatment difference between evolocumab 420 mg QM and alirocumab 300 mg QM was −19.21% (95% CrI −28.52% to −10.35%) for evolocumab at the mean of weeks 10 and 12 and comparators at ≥12 weeks. Treatment differences were similar for evolocumab at week 12 versus comparators at ≥12 weeks (Figure S1).

We also conducted a post hoc analysis of evolocumab 140 mg Q2W and 420 mg QM combined as 1 treatment arm at the mean of weeks 10 and 12 versus alirocumab 75 mg (−18.32%, 95% CrI −24.30% to −12.40%) or 150 mg (−11.06%, 95% CrI −18.72% to −3.73%) Q2W at ≥12 weeks (Figures S4A and S5A). Another post hoc analysis included all

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Table 1. Specific Details About Studies Included in Main Q2W or QM Network

Study Name	Follow-Up, Weeks	Age, y*	Investigational Drug and Dose	Control	Type HC	CVD Risk Status	FH Status	Type 2 Diabetes Mellitus Status	Obesity Status	Background Therapy
DESCARTES[30]	52	55.9 (10.8)†	EvoMab 420 mg QM	Placebo	Primary or secondary HC	With or without CVD or equivalent	NR/unclear	With and without	All	Diet through 80 mg atorvastatin+ezetimibe
LAPLACE-TIMI 57[34]	12	62.0 (55.0-67.0)	EvoMab 70, 105, or 140 mg Q2W; 280, 350, or 420 mg QM	Placebo	Primary HC	Without prior CVD	NR/unclear	With and without	Overweight	Statin±ezetimibe at physician discretion
LAPLACE-2[29]	12	59.6 (9.9)†	EvoMab 140 mg Q2W; 420 mg QM	Placebo	Mixed dyslipidemia	NR/unclear	NR/unclear	With and without	Overweight	Moderate to high dose atorvastatin or rosuvastatin, moderate dose simvastatin
YUKAWA-1[35]	12	61.5 (9.7)	EvoMab 70 or 140 mg Q2W; 280 or 420 mg QM	Placebo	Primary or secondary HC	With or without CVD or equivalent	NR/unclear	With and without	Overweight	Statin as prescribed by physician
YUKAWA-2[36]	12	62 (11)†	EvoMab 140 mg Q2W; 420 mg QM	Placebo	Primary or secondary HC	With or without CVD or equivalent	HoFH and HeFH eligible	With and without	NR/unclear	20 mg atorvastatin (intensive dose for Japanese population)
McKenney 2012[37]	12	56.7 (10.0)	AliMab 50, 100, 150, or 200 mg Q2W; 300 mg QM	Placebo	Primary HC	NR/unclear	NR/unclear	With and without	Overweight	10, 20, 40 mg atorvastatin
ODYSSEY CHOICE I[41]	56	60.7 (9.1)‡	AliMab 75 mg Q2W or 300 mg QM	Placebo	Primary HC	Moderate- to very-high-risk, no CVD	HoFH excluded	With and without	Normal, overweight, and obese	Maximally-tolerated atorvastatin, rosuvastatin, or simvastatin
ODYSSEY COMBO I[40]	52	63.0 (9.5)§	AliMab 75 mg Q2W	Placebo	Primary or secondary HC	With or without CVD or equivalent	No FH patients	With and without	NR/unclear	Maximally tolerated statin with/without other lipid-lowering therapy
ODYSSEY COMBO II[38]	104	61.7 (9.4)§	AliMab 75 mg Q2W	Ezetimibe	Primary or secondary HC	With or without CVD or equivalent	NR/unclear	NR/unclear	NR/unclear	Stable maximally tolerated statin therapy
ODYSSEY HIGH FH[39]	78	49.8 (14.2)§	AliMab 150 mg Q2W	Placebo	HeFH only	NR/unclear	HeFH only	NR/unclear	NR/unclear	Maximally tolerated statin with/without other lipid-lowering therapy
ODYSSEY JAPAN[45]	24	60.3 (9.7)§	AliMab 75 mg Q2W	Placebo	NR/unclear	With or without CVD	NR/unclear	NR/unclear	NR/unclear	Stable lipid lowering therapy

Continued

Table 1. Continued

Study Name	Follow-Up, Weeks	Age, y*	Investigational Drug and Dose	Control	Type HC	CVD Risk Status	FH Status	Type 2 Diabetes Mellitus Status	Obesity Status	Background Therapy
ODYSSEY LONG TERM[46]	78	60.4 (10.4)	AliMab 150 mg Q2W	Placebo	Primary HC	With or without CVD or equivalent	HeFH included	NR/unclear	NR/unclear	Maximally tolerated statin with/without other lipid-lowering therapy
ODYSSEY OPTIONS I[42]	24	64.2 (10.4)‖	AliMab 75 mg Q2W	Placebo, ezetimibe	Primary or secondary HC	CVD or equivalent	Non-FH or HeFH	With and without	NR/unclear	Statins according to study group assignment
ODYSSEY OPTIONS II[43]	24	57.9 (8.9)¶	AliMab 75 mg Q2W	Placebo, ezetimibe	Primary or secondary HC	CVD or equivalent	Non-FH or HeFH	NR/unclear	NR/unclear	Statins according to study group assignment
Masana 2005[44]	48	61 (28-83)#	Ezetimibe	Placebo	Primary or secondary HC	With or without CVD or equivalent	NR/unclear	With and without	Overweight	Up to 80 mg simvastatin

CVD indicates cardiovascular disease; EvoMab, evolocumab; FH, familial hypercholesterolemia; HC, hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; NR, not reported; Q2W, every 2 weeks; QM, monthly.

*Values are mean (standard deviation) or median (interquartile range). Mean age for all patients given unless unavailable, in which case the intervention group was used (marked with footnote). There was no indication in the references that ages were statistically different between groups.

†All evolocumab patients.

‡Alirocumab 75 mg Q2W taking statins.

§All alirocumab patients.

‖Alirocumab 75/150 mg Q2W+atorvastatin 40 mg.

¶Alirocumab 75/150 mg Q2W+rosuvastatin 20 mg.

#All ezetimibe patients. Values in parentheses represent the range of ages observed.

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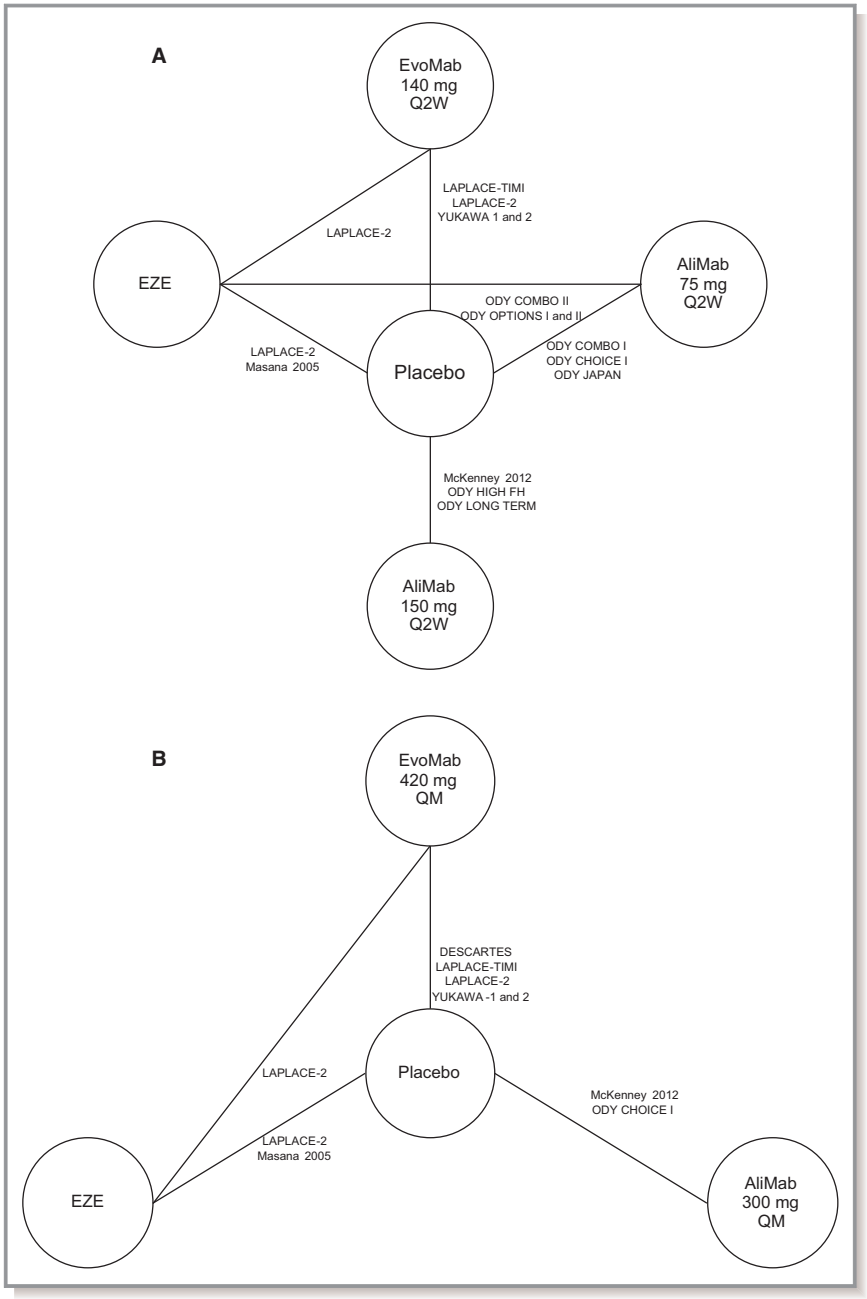

Figure 2. Network of available connections for comparing change in LDL-C. A, Evolocumab 140 mg Q2W (every 2 weeks). B, Evolocumab 420 mg QM (every month). Lines between boxes denote direct comparisons. AliMab indicates alirocumab; EvoMab, evolocumab; EZE, ezetimibe; LDL-C, low-density lipoprotein cholesterol; ODY, ODYSSEY.

studies that met inclusion criteria, regardless of the background therapy (eg, ezetimibe, other lipid-lowering therapies, low-intensity/no statin) (Figures S4B and S5B): evolocumab 140 mg Q2W at the mean of weeks 10 and 12 versus alirocumab at weeks ≥12 was −16.76% (95% CrI, −22.54% to −11.02%) for 75 mg Q2W and −9.88% (95% CrI, −17.60% to −2.29%) for 150 mg Q2W.

Direct meta-analyses suggested that high statistical heterogeneity ($I^2 \geq 70\%$) was observed for some comparisons. This was investigated using sensitivity analyses (excluding studies conducted in Japan[35,36,45] [YUKAWA-1, YUKAWA-2, and ODYSSEY-JAPAN], and also ODYSSEY HIGH FH[39]). Sensitivity analyses of direct head-to-head comparisons did not substantially change the results but did reduce the statistical heterogeneity (Figure S3). In the network meta-analysis, moreover, we performed several sensitivity analyses excluding studies conducted in Japan[35,36,45] or ODYSSEY HIGH FH,[39] all of which drove heterogeneity (Figure S6). In

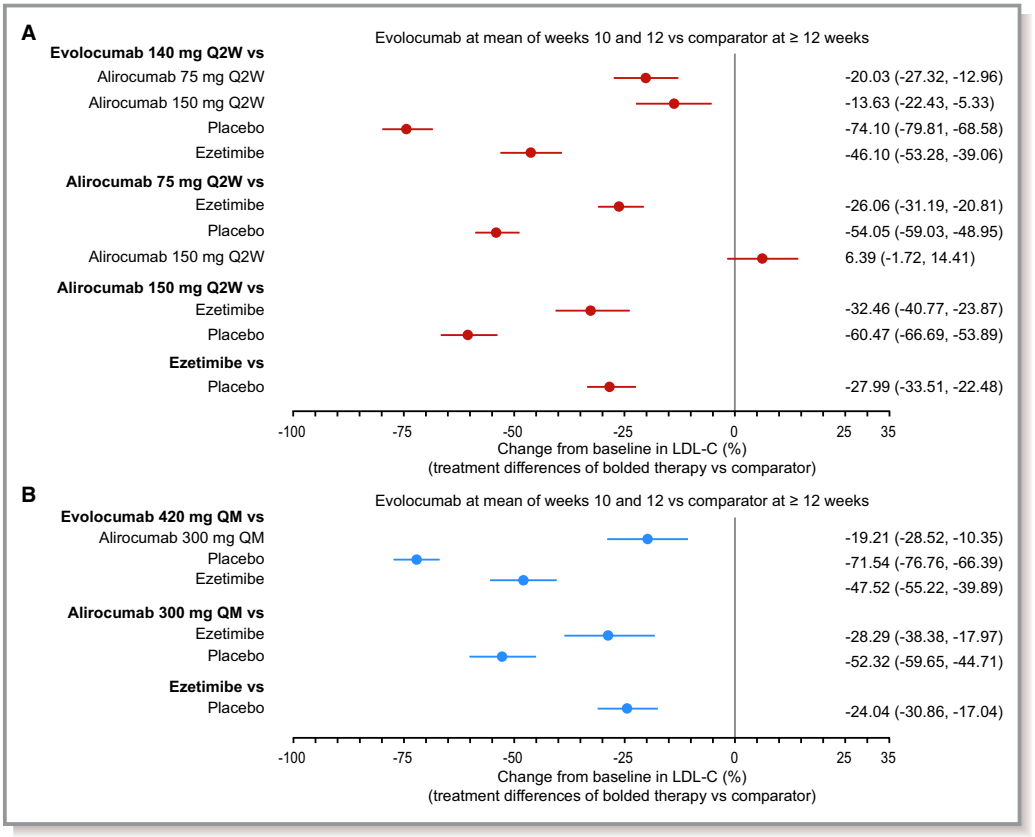

Figure 3. Treatment difference in percentage LDL-C change (95% credible interval) in response to evolocumab 140 mg Q2W network (A) or evolocumab 420 mg QM network (B): evolocumab at the mean of weeks 10 and 12 vs comparator at ≥12 weeks. LDL-C indicates low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, every month.

general, the conclusions of these sensitivity analyses with regard to percentage LDL-C reduction were consistent in direction and statistical significance with the main analyses, although the magnitudes changed slightly.

Networks were developed for other lipid end points (Figures S4C through S4E). Network meta-analysis of HDL-C results demonstrated a moderate increase from baseline associated with evolocumab and alirocumab compared with placebo or ezetimibe. Network meta-analysis results for non-HDL-C were similar in direction and magnitude to LDL-C results; the same was true of the results for ApoB and Lp(a), although the networks were smaller for these comparisons (Figure S7).

Safety

There were no statistically significant differences in the risk of any, treatment-related, or serious AEs between

Table 2. Risk Ratio (95% CI) for Occurrence of Any AE, Treatment-Related AE, and Serious AE

Comparison	Any AE	Treatment-Related AE	Serious AE
Evolocumab 140 mg Q2W vs placebo	1.10 (0.93-1.29)	1.10 (0.42-2.85)	0.96 (0.44-2.09)
Evolocumab 420 mg QM vs placebo	1.03 (0.91-1.18)	1.47 (1.03-2.09)	0.91 (0.38-2.16)
Alirocumab 75 mg Q2W vs placebo	1.06 (0.92-1.22)	1.25 (0.87-1.81)	1.00 (0.74-1.34)
Alirocumab 150 mg Q2W vs placebo	1.25 (0.76-2.08)	NR	1.05 (0.40-2.75)
Alirocumab 300 mg QM vs placebo	1.26 (0.89-1.79)	1.17 (1.01-1.35)	1.03 (0.07-15.78)
Ezetimibe vs placebo	1.04 (0.89-1.21)	1.17 (0.68-2.00)	0.77 (0.44-1.36)

AE indicates adverse event; CI, confidence interval; NR, not reported; Q2W, every 2 weeks; QM, monthly.

evolocumab, alirocumab, or ezetimibe and placebo except for the QM doses of evolocumab and alirocumab (Table 2). Evolocumab 420 mg and alirocumab 300 mg QM resulted in risk ratios of treatment-related AEs of 1.47 (95% confidence interval 1.03–2.09) and 1.17 (95% confidence interval 1.01–1.35) compared with placebo. There were, however, very few treatment-related AEs, and none was considered serious.

Discussion

Our systematic review of lipid-lowering therapies added to medium- to high-intensity statin therapy and subsequent network meta-analysis confirms the substantial LDL-C reductions of PCSK9 inhibitors versus placebo or ezetimibe in individual trials. Among the PCSK9 inhibitors, evolocumab appeared to have a greater reduction than alirocumab (75 mg Q2W, ≈20%; 150 mg Q2W, ≈10%; 300 mg QM, ≈20%). These treatment differences were directionally consistent in the various analyses we conducted (ie, exclusion of studies leading to heterogeneity, variation of dosing amount and interval, broader background therapy spectrum). There was also some evidence of proportional treatment differences between evolocumab and other therapies in HDL-C, non-HDL-C, ApoB, and Lp(a). The incidence of AEs was similar between individual therapies and placebo except for significantly higher treatment-related AEs for evolocumab and alirocumab QM versus placebo.

Our work provides information on PCSK9 inhibitors and ezetimibe added to statin therapy in those requiring further LDL-C reduction. The trials generally evaluated patients either with CVD or at high risk of a CVD event, which is the expected target population for PCSK9 inhibitors both now and after cardiovascular outcomes trials for these medications are completed.[50,51] We also characterized the reductions observed for PCSK9 inhibitors in other parameters including non-HDL-C and Lp(a). Non-HDL-C is emerging as a meaningful measure of CVD event risk,[52] and Lp(a) is associated with CVD event risk but is not reduced by statins.[53,54]

Finally, we analyzed dose-specific LDL-C reductions between PCSK9 inhibitors, which have not been a focus of published meta-analyses.[16-18] The classwide reduction of LDL-C with PCSK9 inhibitors observed in these meta-analyses[16-18] is consistent with what we observed in the comparison of individual PCSK9 inhibitors versus placebo or ezetimibe.

In our network meta-analysis we found evidence of a significantly greater reduction of evolocumab versus alirocumab. The treatment difference of evolocumab 140 mg Q2W versus alirocumab 75 mg was larger than the comparison to alirocumab 150 mg. The treatment difference between evolocumab 420 mg QM versus alirocumab 300 mg QM reflected the fact that more of the study drug was administered to patients treated with evolocumab than to those treated with alirocumab. The treatment difference between evolocumab and alirocumab was directionally consistent in the various analyses we conducted. Our approach differed from that of other meta-analyses by analyzing evolocumab and alirocumab separately. Lipinski and colleagues[17] and Li and colleagues[16] analyzed PCSK9 inhibitors as a class. Navarese and colleagues' meta-analysis[18] likewise considered the class in the primary analysis but suggests, in a secondary analysis, that there was a significantly greater reduction in LDL-C with evolocumab versus placebo than alirocumab versus placebo.

We studied other atherogenic lipids when the data were available, and the direction and magnitude of treatment differences between the lipid-lowering therapies were in line with those for LDL-C. HDL-C was increased modestly with evolocumab compared with other therapies, but the difference was not always significant. Non-HDL-C and ApoB were reduced, as expected, in line with LDL-C. Lp(a) was reduced by ≈38% with evolocumab versus placebo, and there was a modest treatment difference favoring evolocumab versus alirocumab. This estimated modest ≈9% to 14% difference in Lp(a) is of uncertain clinical significance. Other meta-analyses found similar results in the PCSK9 class as a whole.[16-18]

There are limitations to this review. In terms of comparing the LDL-C–lowering capacity of PCSK9 inhibitors to each other, to date there have been no such head-to-head studies that would be the best way to remove any potential residual confounders. Thus, this review is limited by the quantity and quality of the data available from the included clinical trials. Additionally, because 75 and 150 mg Q2W were not studied in a parallel-group trial, FDA review[55] concluded that there is lack of availability of a well-characterized estimate of the treatment effect for each dose. Another limitation of our analysis is that most of the studies included in the networks were relatively short-term (mostly 12 and 24 weeks). Longer-term follow-up studies of evolocumab and alirocumab have not shown evidence of loss of efficacy or increased rates of AEs.[30,46,50,56]

Conclusions

Based on network meta-analyses, the PCSK9 inhibitors evolocumab and alirocumab were associated with reductions in LDL-C of 54% to 74% versus placebo and 26% to 46% versus ezetimibe in patients not adequately controlled by statins alone. Recognizing the limitations of indirect comparison, our synthesis of the available data shows a greater reduction with evolocumab in LDL-C versus alirocumab 75 mg Q2W with evidence also suggesting more intense LDL-C reduction

versus alirocumab 150 mg Q2W. There was some evidence to suggest that evolocumab may also significantly increase HDL-C and decrease non-HDL-C, ApoB, and Lp(a) levels in comparison to alirocumab and other treatments. Further research is needed into the effects of evolocumab and alirocumab on the risk of cardiovascular events.

Author Contributions

All authors contributed to the scope and content of the article before the outline was composed, and all authors approved the final draft for submission.

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Disclosures

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Supplemental Materials

A Systematic Review and Network Meta-analysis on the Efficacy of Evolocumab and Other Therapies for the Management of Lipid Levels in Hyperlipidemia

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Contents

Data S1. Full Search Strategy

MEDLINE only, others available upon request
Medline (Ovid): 1946 to July Week 3 2016
Searched: January 8, 2016

1 exp hyperlipidemias/ (60308)
2 (hypercholesterol?emi$ or hypercholesterin?emi$ or cholester?emi$ or cholesterin?emi$ or hyperlipid?emi$ or hyperlipoprotein?emia$ or lip?emia$ or lipid?emi$ or hyperlip?emi$ or hefh or hofh or fh or hypertriglycerid?emia$ or mckusick 14575 or triglycerid?emia$ or (triglyceride adj1 storage adj1 disease$)).ti,ab,ot,hw. (91009)
3 ((cholesterol$ or lipid$ or LDL) adj3 (elevat$ or ascend$ or increas$ or high or rais$)).ti,ab,ot,hw. (74673)
4 or/1-3 (150149)
5 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (33177)
6 (statin$ or hydroxymethylglutaryl coenzyme A reductase inhibit$ or HMG CoA reductase inhibit$ or HMGCoA reductase inhibit$).ti,ab,ot,hw. (30946)
7 (atorvastatin or Lipitor or torvast or atorlip or atovarol or ci 981 or ci981 or glustar or lipibec or lowlipen or sortis or storvas or tahor or ym 548 or ym548 or zarator or 134523-00-5 or 134523-03-8).ti,ab,ot,hw,rn. (6950)
8 (Bervastatin or ls 2904 or ls2904 or 132017-01-7).ti,ab,ot,hw,rn. (0)
9 (crilvastatin or pmd 387 or pmd387 or 120551-59-9).ti,ab,ot,hw,rn. (5)
10 (dalvastatin or rg 12561 or 132100-55-1 or 135910-20-2).ti,ab,ot,hw,rn. (4)
11 (fluindostatin or Canef or cranoc or fluindostatin sodium or fluvastatin or fluvastatin sodium or fractal lp or lescol or lescol or leucol or lochol or locol or sri 62320 or sri62320 or vastin or xu 62320 or xu62320 or 93957-54-1).ti,ab,ot,hw,rn. (1761)
12 (glenvastatin or hr 780 or hr780).ti,ab,ot,hw,rn. (12)
13 (mevinolin or altocor or altoprev or artein or belvas or Birotin or cholestra or cysin or ellanco or elstatin or l 654969 or lipdip or lipivas or lofacol or lomar or lostatin or lovacel or lovacol or lovalip or lovalord or lovastan or lovastatin or lovasterol or lovastin or lovatadin or lowachol or lozutin or medostatin or mevacor or meverstin or mevinacor or "mk 0803" or mk 803 or mk0803 or mk803 or monacolin K or monakolin k or msd 803 or neolipid or nergadan or ovasta or rodatin rovacor or taucor or 75330-75-5).ti,ab,ot,hw,rn. (5443)
14 (mevinolinic acid or mevinolinate or 75225-51-3).ti,ab,ot,hw,rn. (21)
15 (Monacolin or 76343-78-7 or 79394-47-1).ti,ab,ot,hw,rn. (137)
16 (pitavastatin or alipza or itavastatin or livalo or livazo or nivastatin or nk 104 or nk104 or nks 104 or nks104 or pitava or ribar or vezepra or 147526-32-7).ti,ab,ot,hw,rn. (632)
17 (Pravastatin or astin or bristacol or cholespar or cs 514 or cs514 or elisor or epatostantin or eptastatin or eptastatin sodium or eptastatine or kenstatin or lipemol or lipidal or liplat or lipostat or liprevil or mevalotin or novales or prareduct or prascolend or prastan or prava or pravachol or pravacol or pravaselect or pravasin or pravasine or pravator or pravyl or sanaprav or selektine or selipran or sq 31000 or sq31000 or stanidine or vasopran or vasten or xipral or 81093-37-0 or 81131-70-6).ti,ab,ot,hw,rn. (4390)

18 (Simvastatin or Avastinee or cholestat or clinfar or colastatina or colestricon or covastin or denan or epistatin or esvat or ethical or eucor or ifistatin or kavelor or klonastin or kolestevan or l 644128 or l644128 or lipecor or lipex or lipinorm or liponorm or lipovas or lodales or medipo or mersivas or mk 733 or mk733 or nor-vastina or normofat or orovas or rechol or simbado or simcard or simchol or simovil or simtin or simvacor or simvahex or simvalord or simvastar or simvata or simvatin or simvor or simvotin or sinvacor or simvastatin or sinvinolin or sivastin or starzoco or synvinolin or torio or valemia or vasilip or vasotenal or vazim or vidastat or zimmex or Zocor or zocor forte or zocord or zovast or 79902-63-9).ti,ab,ot,hw,rn. (66137)
19 (Rosuvastatin or crestor or rosuvas or s 4522 or s4522 or zd 4522 or zd4522 or 147098-18 or 147098-20-2).ti,ab,ot,hw,rn. (2479)
20 tenivastatin.ti,ab,ot,hw,rn. (0)
21 or/5-20 (104468)
22 (evolocumab or repatha or 1256937-27-5 or AMG-145 or amg145).af. (117)
23 (ezetimibe or zetia or ezetrol or ezetib or sch 582235 or sch58235 or 163222-33-1).af. (2149)
24 (Alirocumab or praluent or regn 727 or regn727 or sar 236553 or sar236553 or 1245916-14-6).af. (105)
25 (bococizumab or "pf 04950615" or pf04950615 or rn 316 or rn 316 or 1407495-02-6).af. (11)
26 (((PCSK-9 or PCSK9 or PCSK 9) adj2 inhibit$) or (anti-PCSK-9 or anti PCSK-9)).ti,ab,ot,hw. (245)
27 or/22-26 (2430)
28 nicotinic acids/ or niacin/ (16586)
29 (acipimox or acipemox or olbetam or albermox or 51037-30-0).ti,ab,ot,hw,rn. (299)
30 (vitamin B3 or vitamin PP or 54-86-4 or 59-67-6 or acido nicotinico or acidum nicotinicum or akotin or apelagrin or apo-nicotinic acid or beta pyridine carboxylic acid or bionic or davitamon pp or direktan or direktane or efacin or efasin or endur acin or enduracin or naotin or natinate or niac or niacin$ or niacor or Niaspan or nicacid or nicangin or nico or nicobid or nicocap or nicocidin or nicocrisina or nicodan or nicodane or nicolar or niconacid or niconacide or nicoseptin wirkstoff or nicosode or nicospan or nicosyl or nicotabs or nicotamin or nicotine or nicotin acid or nicotinat or nicotinate or nicotinese or nicotinipca or nicotyl or nicovasen or nicyl or nikacid or nipellan or novoniacin or nyacine or nyclin or pellagramin or pellagramine or pellagrin$ or pelonin or pelonine or pepevit or peviton or pp factor or "pyridine 3 carbonic acid" or pyridine beta carboxylic acid or "s 115" or slo niacin or sodium nicotinate or vasotherm or vitaplex n or wampocap or wampopap).ti,ab,ot,hw,rn. (59318)
31 or/28-30 (64551)
32 Cholestyramine Resin/ (2587)
33 (((bile adj2 acid) or anion exchange) adj2 (sequestrant$ or resin$)).ti,ab,hw,ot. (2797)
34 (chol-less or choles or cholesthexal or cholestyramin$ or cholybar or cholytar or colestepril or colestiramina or colestran or colestrol or colestyramin or cuemid or lipocol-merz or lismol or locholest or prevalite or quantalan or questran or resincoles$ or vasosan or 11041-12-6 or 58391-37-0).ti,ab,ot,hw,rn. (3358)

35 (colestipol or cholestabyl or cholestipol or colestid or lestid or u 26597a or "u 26797 a" or 25085-17-0 or 37296-80-3 or 50925-79-6).ti,ab,ot,hw,rn. (525)
36 (Colesevelam or cholestagel or gt 31 104 or gt 31 104hb or gt 31-104 or gt 31-104hb or gt31 104 or gt31 104hb or gt31-104 or gt31-104hb or welchol or 182815-43-6 or 182815-44-7).ti,ab,ot,hw,rn. (234)
37 or/32-36 (6173)
38 fibric acids/ or bezafibrate/ or fenofibrate/ or gemfibrozil/ (4897)
39 (fibrate$ or fibric acid$ or arhalofenate or atromid or beclobrate or beclobrinic acid or bezafibrate or biclofibrate or binifibrate or choline fenofibrate or ciprofibrate or clinofibrate or clofibrate or clofibrate aluminium or clofibric acid or clofibride or dulofibrate or eniclobrate or etofibrate or etofylline clofibrate or fenirofibrat or fenofibric acid or halofenate or lifibrate or methylclofenapate or nicofibrate or picafibrate or pirifibrate or ponfibrate or ronifibrate or salafibrate or serfibrate or simfibrate or sitofibrate or tazasubrate or tiadenol diclofibrate or timofibrate or tocofibrate or urefibrate or xantifibrate).ti,ab,ot,hw,rn. (9516)
40 (Bezafibrate$ or befizal or benzafibrate or benzofibrate or bezafibrate retard or bezalip or bezatol or bezifal or bezofibrate or bf 759 or bf759 or bm 15075 or bm15075 or cedur or lo 44 or lo44 or norlip or 41859-67-0).ti,ab,ot,hw,rn. (1552)
41 (Ciprofibrate$ or lipanor or modalim or win 35833 or 52214-84-3).ti,ab,ot,hw,rn. (527)
42 (Fenofibrate$ or Antara or apo-feno-micro or aterolis or bisterol$ or climage or controlip or durafenat or evothyl or fegenor or felosma or fenobrate or fenofanton or fenogal or fenoglide or fenox or fibrafen or "grs 001" or hyperchol or katalip or lexemin or lipanthyl or lipantil or lipantyl or liparison or lipidax or lipidil or lipilo or lipirex or lipoclar or lipofen or lipolin or liposit or lipsin or livesan ge or lofibra or nopid 200 or normalip or nubrex or procetofen or procetofenate or procetofene or proketofen or qualipantyl or rapidil or redose 200 or rorit or secalip or sigurtil or trichol or tricor or triglide or trolip or zerlubron or zumafib or 49562-28-9).ti,ab,ot,hw,rn. (2966)
43 (gemfibrozil or ausgem or bolutol or brozil or chlorestrol or cholespid or ci 719 or ci719 or clearol or decrelip or detrichol or elmogan or fetinor or fibralip or fibrocit or gedum or gemfi$ or gemizol or gemlipidor gemnpid or gemzil or genfibrozil or gevilon$ or gozid or grifogemzilo or hidil or hipolixan or ipolipid or jezil or lanaterom or lifibron or lipazil or lipidys or lipigem or lipira or lipison or lipistorol or lipizyl or lipofor or lipolo or lipostorol or lipozid or lipozil or lipur or lopid$ or low-lip or lowin or manobrozil or mariston or mersikol or normolipor panazil or polyxit or progemzal or recozil or reducelor regulip or synbrozilor triglizil or uragem or zilop or 25812-30-0).ti,ab,ot,hw,rn,tn. (2012)
44 or/38-43 (12790)
45 (lomitapide or lojuxta or Juxtapid or 182431-12-5 or 202833-31-6 or 202914-84-9 or 210823-48-6 or aegr 733 or aegr733 or bms 201038$).af. (91)
46 exp Blood Component Removal/ or apheresis.ti,ab,hw,ot. (19364)
47 (anacetrapib or "mk 0859" or mk 859 or mk0859 or mk859 or 875446-37-0).af. (153)
48 (mipomersen or isis 301012 or isis301012 or kynamro or 629167-92-6).af. (153)
49 21 or 27 or 31 or 37 or 44 or 45 or 46 or 47 or 48 (201944)
50 4 and 49 (20612)
51 randomized controlled trial.pt. or "randomized controlled trials as topic"/ (527845)

52 controlled clinical trial.pt. (91264)
53 random$.ti,ot. (131969)
54 placebo.ab. (162592)
55 drug therapy.fs. (1887319)
56 random$.ab. (739171)
57 trial.ab. (334669)
58 groups.ab. (1422792)
59 or/51-58 (3755812)
60 animals/ not (animals/ and humans/) (4248029)
61 59 not 60 (3205214)
62 50 and 61 (13884)

Based on Trials filter: Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Data S2. Trials Included/Excluded, Full Paper Selection Stage

A. List of included trials (74 trials)

Abbott/NCT00300430	Abbott. Study to evaluate the long-term safety and efficacy of ABT-335, in combination with three different statins in subjects with mixed dyslipidemia. NCT00300430. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2009 [accessed June 25, 2014]. Available from: http://ClinicalTrials.gov/show/NCT00300430
Abbott/NCT01674712/EUCTR2011-005924-16-CZ	Abbott. A 12-week study to compare the efficacy and safety of fixed combinations of fenofibrate/simvastatin 145/20mg and fenofibrate/simvastatin 145/40mg tablets versus fenofibrate or simvastatin monotherapies in subjects with abnormal blood levels of fats (lipids) and at high risk of cardiovascular disease. NCT01674712. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed July 15, 2015]; Available from: http://ClinicalTrials.gov/show/NCT01674712. Abbott Laboratories Ireland Limited. A 12-week study to compare the efficacy and safety of fixed combinations of fenofibrate simvastatin 145/20mg and fenofibrate simvastatin 145/40mg tablets versus fenofibrate or simvastatin monotherapies in subjects with abnormal levels of fats (lipids) in the blood and at high risk of cardiovascular disease. EUCTR2011-005924-16-CZ. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2012 [accessed June 4, 2014]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-005924-16. Foucher C, Aubonnet P, Reichert P, Berli M, Schaeffer A, Calvo Vargas CG, et al. New fixed-dose combinations of fenofibrate/simvastatin therapy significantly improve the lipid profile of high-risk patients with mixed dyslipidemia versus monotherapies. *Cardiovasc Ther.* 2015;33:329-337.
ACCORD Lipid Trial	Accord Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR, 3rd, Leiter LA, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1563-1574. [Erratum, *N Engl J Med.* 2010;362:1748].
ARBITER 2	Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation.* 2004;110:3512-3517 [Errata, *Circulation.* 2004;110:3615 and *Circulation.* 2004;110:3512-3517.

ARBITER 6-HALTS/NCT00397657	Villines TC, Stanek EJ, Devine PJ, Turco M, Miller M, Weissman NJ, et al. The ARBITER 6-HALTS Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis): Final results and the impact of medication adherence, dose, and treatment duration. *J Am Coll Cardiol.* 2010;55:2721-2726. Walter Reed Army Medical Center, Abbott. Comparative study of the effect of ezetimibe versus extended-release niacin on atherosclerosis. NCT00397657. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2009 [accessed March 7, 2014]. Available from: http://ClinicalTrials.gov/show/NCT00397657. Devine PJ, Turco MA, Taylor AJ. Design and rationale of the ARBITER 6 trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol)-6-HDL and LDL Treatment Strategies in atherosclerosis (HALTS). *Cardiovasc Drugs Ther.* 2007;21:221-225. Taylor AJ, Villines TC, Stanek EJ, Devine PJ, Griffen L, Miller M, et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med.* 2009;361:2113-2122.
Chen 2013	Chen YP, Chang KC, Tseng WK, Yin WH, Chen JW, Lee YT, et al. Increased rosuvastatin dose versus concomitant fenofibrate and rosuvastatin therapy to achieve lipid goal in patients with diabetes or atherosclerosis with metabolic syndrome. *Acta Cardiol Sin.* 2013;29:421-428.

DEFINE/NCT00685776	Gotto AM, Cannon CP, Shah S, Liu S, Li S, Stepanavage M, et al. Effects on lipids and safety following cessation of treatment with cholesteryl ester transfer protein inhibitor anacetrapib in patients with or at high risk for coronary heart disease. Presented at American Heart Association Scientific Sessions; November 12-16, 2011; Orlando, FL, USA. *Circulation.* 2011;124(21 suppl 1). Merck Sharp Dohme Corp. Study to assess the tolerability and efficacy of anacetrapib in patients with coronary heart disease (CHD) or CHD risk-equivalent disease (MK-0859-019). NCT00685776. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed July 9, 2014]. Available from: http://ClinicalTrials.gov/show/NCT00685776 Cannon CP, Dansky HM, Davidson M, Gotto Jr AM, Brinton EA, Gould AL, et al. Design of the DEFINE trial: Determining the EFficacy and Tolerability of CETP INhibition with AnacEtrapib. *Am Heart J.* 2009;158:513-519.e3. Merck Sharp Dohme Corp. A 76-week, worldwide, multicenter, double-blind, randomized, placebo-controlled study to assess the tolerability and efficacy of anacetrapib when added to ongoing therapy with a statin in patients with hypercholesterolemia or mixed hyperlipidemia. EUCTR2007-005839-28-ES. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2008 [accessed July 2, 2014]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-005839-28 Cannon CP, Shah S, Dansky HM, Davidson M, Brinton EA, Gotto AM, et al. Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med.* 2010;363:2406-2415. Brinton EA, Kher U, Shah S, Cannon CP, Davidson M, Gotto AM, et al. Effects of anacetrapib on plasma lipids in specific patient subgroups in the DEFINE (Determining the Efficacy and Tolerability of CETP INhibition with AnacEtrapib) trial. *J Clin Lipidol.* 2015;9:65-71. Gotto AM, Jr., Kher U, Chatterjee MS, Liu Y, Li XS, Vaidya S, et al. Lipids, safety parameters, and drug concentrations after an additional 2 years of treatment with anacetrapib in the DEFINE study. *J Cardiovasc Pharmacol Ther.* 2014;19:543-549.

DESCARTES/Amgen 20110109	Amgen Inc. Durable effect of PCSK9 antibody compared with placebo study. NCT01516879. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed May 29, 2014]. Available from: http://ClinicalTrials.gov/show/NCT01516879 Amgen Inc. A double-blind, randomized, placebo-controlled, multicenter study to evaluate long-term tolerability and durable efficacy of AMG 145 on LDL-C in hyperlipidemic subjects - DESCARTES, durable effect of PCSK9 antibody Compared with placebo study. EUCTR2011-003827-37-CZ. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2011 [accessed June 2, 2014]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-003827-37 Blom DJ, Hala T, Bolognese M, Lillestol MJ, Toth PD, Burgess L, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med.* 2014;370:1809-1819. Amgen Inc. A double-blind, randomized, placebo-controlled, multicenter study to evaluate long-term tolerability and durable efficacy of AMG 145 on LDL-C in hyperlipidemic subjects - DESCARTES, durable effect of PCSK9 antibody Compared with placebo study [data supplied by Amgen]. 2014. Amgen Inc. Clinical Study Report 20110109: a double-blind, randomized, placebo-controlled, multicenter study to evaluate long-term tolerability and durable efficacy of AMG 145 on LDL-C in hyperlipidemic subjects. Thousand Oaks: 2014. Blom D, Hala T, Bolognese M, Lillestol MJ, Toth PD, Burgess L, et al. The double-blind durable effect of pcsk9 antibody compared with placebo study (descartes): A 52-week, phase 3, double-blind, randomized, placebo-controlled trial of evolocumab (AMG 145) in hyperlipidemic patients. *Endocr Pract.* 2015;21:28A. Toth PP, Banach M, Djedjos C, Yang X, Elliott M, Davis M, et al. Effect of evolocumab on low-density lipoprotein particles. *J Am Coll Cardiol.* 2016;67(13 Suppl 1):1909. Blom D, Djedjos CS, Tsirtsonis K, Wasserman SM, Scott R, Roth E. Effects of evolocumab (AMG 145) on vitamin-and serum adrenal and gonadal hormone levels; results from the 52-week, phase 3, double-blind, randomized, placebo controlled descartes study. *Atherosclerosis.* 2015;241:e67.
EASEGO/NCT00166530	Merck Sharp Dohme Corp. EASEGO study: doubling of atorvastatin/simvastatin or INEGY in patients with hypercholesterolemia and coronary artery disease (CAD). NCT00166530. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2008 [accessed May 29, 2014]. Available from: http://ClinicalTrials.gov/show/NCT00166530 Roeters van Lennep HWO, Liem AH, Dunselman PHJM, Dallinga-Thie GM, Zwinderman AH, Jukema JW. The efficacy of statin monotherapy uptitration versus switching to ezetimibe/simvastatin: results of the EASEGO study. *Curr Med Res Opin*. 2008;24:685-694.
ENHANCE	Kastelein JJP, Akdim F, Stroes ESG, Zwinderman AH, Bots ML, Stalenhoef AFH, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med.* 2008;358:1431-1443. NCT00552097. Effect of Ezetimibe Plus Simvastatin Versus Simvastatin Alone on Atherosclerosis in the Carotid Artery (ENHANCE) (P02578). 2007.

ESSENTIAL	Matsue Y, Matsumura A, Suzuki M, Hashimoto Y, Yoshida M. Differences in action of atorvastatin and ezetimibe in lowering low-density lipoprotein cholesterol and effect on endothelial function: randomized controlled trial. *Circ J.* 2013;77:1791-1798.
Ezetimibe Study Group	Stein E, Stender S, Mata P, Sager P, Ponsonnet D, Melani L, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. *Am Heart J.* 2004;148:447-455.
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TESLA/Amgen 20110233	Amgen Inc. Trial evaluating PCSK9 antibody in subjects with LDL receptor abnormalities (TESLA). NCT01588496. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 [accessed July 15, 2014]. Available from: http://clinicaltrials.gov/ct2/show/NCT01588496. Amgen Inc. A clinical study to assess the safety, tolerability and efficacy of AMG 145 in subjects with homozygous familial hypercholesterolemia. EUCTR2011-005399-40-BE. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2012 [accessed July 15, 2014]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-005399-40. Amgen Inc. A 2-part, phase 2/3 study to assess the safety, tolerability and efficacy of AMG 145 in subjects with homozygous familial hypercholesterolemia. Part B: double-blind, randomized, placebo-controlled, multicenter study to evaluate safety, tolerability and efficacy of AMG 145 in subjects with homozygous familial hypercholesterolemia [Protocol supplied by Amgen], 2013. Amgen Inc. A 2-part, phase 2/3 study to assess the safety, tolerability and efficacy of AMG 145 in subjects with homozygous familial hypercholesterolemia [protocol supplied by Amgen]. Thousand Oaks, 2013. 87p. Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2015;385:341-350. Raal F, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R, et al. Trial evaluating evolocumab, a PCSK9 antibody, in patients with homozygous FH (TESLA): Results of the randomized, double-blind, placebo-controlled trial. *Atheroscler.* 2014;235:e12.
Torimoto 2013	Torimoto K, Okada Y, Mori H, Hajime M, Tanaka K, Kurozumi A, et al. Efficacy of combination of Ezetimibe 10 mg and rosuvastatin 2.5 mg versus rosuvastatin 5 mg monotherapy for hypercholesterolemia in patients with type 2 diabetes. *Lipids Health Dis.* 2013;12:137. University of Occupational and Environmental Health (School of Medicine). Ezetimibe 10 mg + rosuvastatin 2.5 mg versus rosuvastatin 5 mg for hypercholesterolemia in patients with type 2 diabetes. JPRN-UMIN000011005. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2013 [accessed July 16, 2014]. Available from: https://upload.umin.ac.jp/cgi-open bin/ctr/ctr.cgi?function=brows&action=brows& type=summary&recptno=R000012861&language=E.

TREAC/NCT00203476	Tuscaloosa Research Education Advancement Corporation, American Society of Health-System Pharmacists Research and Education Foundation. A prospective, open label comparison of ezetimibe, niacin, and colestipol as adjunct therapy in lipid reduction. NCT00203476. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2007 [accessed June 27, 2014]. Available from: http://ClinicalTrials.gov/show/NCT00203476.
TRIPLE	Trip M, Huijgen R, Bruckert E, Abbink E, Stalenhoef A, Imholz B, et al. Colesevelam added to stable combination of statin and ezetimibe in patients with familial hypercholesterolemia: the triple trial. Presented at 15th International Symposium on Atherosclerosis; June 14-18, 2009; Boston, MA: USA. *Atheroscler Suppl.* 2009;10(2). Huijgen R, Trip MD, Bruckert E, Stalenhoef AFH, Imholz BPM, Durrington PN, et al. Colesevelam added to a stable combination of a maximally tolerated statin and ezetimibe in patients with heterozygous familial hypercholesterolemia; the TRIPLE trial. Presented at European Society of Cardiology, ESC Congress; August 29 - September 2, 2009; Barcelona, Spain. *Eur Heart J.* 2009;30:367. Huijgen R, Abbink EJ, Bruckert E, Stalenhoef AFH, Imholz BPM, Durrington PN, et al. Colesevelam added to combination therapy with a statin and ezetimibe in patients with familial hypercholesterolemia: a 12-week, multicenter, randomized, double-blind, controlled trial. *Clin Ther.* 2010;32:615-625. Sanofi, Genzyme. A study of the safety and efficacy of patients with familial hypercholesterolaemia taking colesevelam as add-on therapy to their existing medication. NCT00655265. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed July 3, 2014]. Available from: http://ClinicalTrials.gov/show/NCT00655265.
Bando 2016	Bando Y, Toyama H, Kanehara H, Hisada A, Okafuji K, Toya D, et al. Switching from atorvastatin to rosuvastatin lowers small, dense low-density lipoprotein cholesterol levels in Japanese hypercholesterolemic patients with type 2 diabetes mellitus. *Diabetes Res Clin Prac.* 2016;111:66-73.
Wink 2002	Wink J, Giacoppe G, King J. Effect of very-low-dose niacin on high-density lipoprotein in patients undergoing long-term statin therapy. *Am Heart J.* 2002;143:514-518.
Yamagishi 2010	Yamagishi T. Efficacy and safety of ezetimibe added on to rosuvastatin (2.5 mg) compared with uptitration of rosuvastatin (5 mg) in hyperlipidemic patients. *Jpn Pharmacol Ther.* 2010;38:305-311.
Yamazaki 2013	Yamazaki D, Ishida M, Watanabe H, Nobori K, Oguma Y, Terata Y, et al. Comparison of anti-inflammatory effects and high-density lipoprotein cholesterol levels between therapy with quadruple-dose rosuvastatin and rosuvastatin combined with ezetimibe. *Lipids Health Dis.* 2013;12(1).
YUKAWA-1/Amgen 20110231	Amgen. A double-blind, randomized, placebo-controlled, multicenter study to evaluate tolerability and efficacy of evolocumab (AMG 145) in Japanese subjects. NCT01652703. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed July 14, 2014]. Available from: http://ClinicalTrials.gov/show/NCT01652703. Hirayama A, Honarpour N, Yoshida M, Yamashita S, Huang F, Wasserman SM, et al. Effects of evolocumab (AMG 145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk--primary results from the phase 2 YUKAWA study. *Circ J.* 2014;78:1073-1082. Amgen Inc. Effects of evolocumab (AMG 145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk--primary results from the phase 2 YUKAWA study [data supplied by Amgen]. 2014.

	Amgen Inc. Study of LDL-cholesterol reduction using evolocumab (AMG145) in Japanese patients with advanced cardiovascular risk. NCT01953328. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed July 14, 2014]. Available from: http://ClinicalTrials.gov/show/NCT01953328.
	Amgen Inc. A double-blind, randomized, placebo-controlled, multicenter study to evaluate safety, tolerability and efficacy of evolocumab (AMG 145) on LDL-C in combination with statin therapy in Japanese subjects with high cardiovascular risk and with hyperlipidemia or mixed dyslipidemia. YUKAWA 2 protocol. Thousand Oaks, 2014.
YUKAWA-2/Amgen 20120122	Amgen Inc. A double-blind, randomized, placebo-controlled, multicenter study to evaluate safety, tolerability and efficacy of evolocumab (AMG 145) on LDL-C in combination with statin therapy in Japanese subjects with high cardiovascular risk and with hyperlipidemia or mixed dyslipidemia. YUKAWA 2 [data supplied by Amgen]. 2014.
	Kiyosue A, Honarpour N, Xue A, Wasserman S, Hirayama A. Effects of Evolocumab (AMG 145) in hypercholesterolemic, statin-treated, japanese patients at high cardiovascular risk: results from the phase III YUKAWA 2 study (1107-104). Abstract presented at American College of Cardiology (ACC); 14-16 March 2015; San Diego, US. [Internet]. 2015 [accessed April 30, 2015]; Available from: http://www.abstractsonline.com/pp8/#!/3658/presentation/33656.
	Kiyosue A, Honarpour N, Kurtz C, Xue A, Wasserman SM, Hirayama A. A Phase 3 Study of Evolocumab (AMG 145) in Statin-Treated Japanese Patients at High Cardiovascular Risk. *Am J Cardiol.* 2016;117:40-47.

	Constance C, Ben-Yehuda O, Wenger NK, Zieve F, Lin J, Shah A, et al. Effects of ezetimibe added to atorvastatin versus atorvastatin up-itration on attainment of single and dual levels for low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol, apolipoprotein B, or high-sensitivity C-reactive protein in older adults with high coronary heart disease risk. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; May 13-16, 2010; Chicago, IL, USA. *J Clin Lipidol.* 2010;4:224-225. Zieve F, Ben-Yehuda O, Constance C, Wenger N, Bird S, Lee R, et al. Efficacy of ezetimibe added to atorvastatin vs uptitration of atorvastatin in the elderly. Presented at 15th International Symposium on Atherosclerosis; June 14-18, 2009; Boston, MA, USA. *Atheroscler Suppl.* 2009;10(2). Constance C, Ben-Yehuda O, Wenger NK, Zieve F, Lin J, Hanson ME, et al. Atorvastatin 10 mg plus ezetimibe versus titration to atorvastatin 40 mg: attainment of European and Canadian guideline lipid targets in high-risk subjects >65 years. *Lipids Health Dis.* 2014;13:13.
ZETELD	Zieve F, Wenger NK, Ben-Yehuda O, Constance C, Bird S, Lee R, et al. Safety and efficacy of ezetimibe added to atorvastatin versus up titration of atorvastatin to 40 mg in Patients > or = 65 years of age (from the ZETia in the ELDerly [ZETELD] study). *Am J Cardiol.* 2010;105:656-663. Ben-Yehuda O, Wenger NK, Constance C, Zieve F, Hanson ME, Lin JX, et al. The comparative efficacy of ezetimibe added to atorvastatin 10 mg versus uptitration to atorvastatin 40 mg in subgroups of patients aged 65 to 74 years or greater than or equal to 75 years. *J Ger Cardiol.* 2011;8:1-11. Merck Sharp Dohme Corp. Ezetimibe and atorvastatin vs. atorvastatin in patients age 65 and older at high risk for coronary heart disease (CHD)(0653-112). NCT00418834. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed July 3, 2014]. Available from: http://ClinicalTrials.gov/show/NCT00418834. Zieve FJ, Foody JM, Brown WV, Adewale AJ, Flaim D, Lowe RS, et al. Safety and efficacy of ezetimibe/simvastatin combination versus atorvastatin in patients 65 years of age and older. *J Clin Lipidol.* 2010;4:225.

B. List of excluded trials and reason for exclusion (440 trials)

Publication citation	Reason(s) for exclusion
Abbott Laboratories Ireland Limited. A 12-week, double-blind, randomized study to compare the efficacy and safety of fixed combinations of fenofibrate /simvastatin 145/20mg and fenofibrate/simvastatin 145/40mg tablets vs. matching monotherapies in dyslipidemic subjects at high risk of cardiovascular disease. EUCTR2011-005924-16. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2012 [accessed 15.7.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-005924-16	Duplicate
Adams SP, Sekhon SS, Wright JM. Lipid-lowering efficacy of rosuvastatin. Cochrane Database Syst Rev. 2014.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
Adams SP, Tsang M, Wright JM. Lipid-lowering efficacy of atorvastatin. Cochrane Database Syst Rev. 2015.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
Aegerion Pharmaceuticals Inc. A safety and efficacy study of AEGR-733 to treat homozygous familial hypercholesterolemia (FH). NCT00730236. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2008 [accessed 17.7.14]. Available from: http://clinicaltrials.gov/show/NCT00730236	Not relevant trial design (not RCT)
Aegerion Pharmaceuticals. A phase III study of microsomal triglyceride transfer protein (MTP) inhibitor AEGR-733 in patients with homozygous familial hypercholesterolemia on current lipid-lowering therapy. EUCTR2008-007058-36. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2009 [accessed 2.6.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-007058-36	Not relevant trial design (not RCT)
Aegerion Pharmaceuticals. A phase III, long term, open label, follow on study of microsomal triglyceride transfer protein (MTP) inhibitor 'lomitapide' (AEGR-733) in patients with homozygous familial hypercholesterolemia. EUCTR2010-023742-79. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2011 [accessed 30.5.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-023742-79	Not relevant trial design (not RCT)
Aggarwal RK, Showkathali R. Rosuvastatin calcium in acute coronary syndromes. Expert Opin Pharmacother 2013;14(9):1215-1227.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Agouridis AP, Kostapanos MS, Tsimihodimos V, Kostara C, Mikhailidis DP, Bairaktari ET, et al. Effect of rosuvastatin monotherapy or in combination with fenofibrate or ω-3 fatty acids on lipoprotein subfraction profile in patients with mixed dyslipidaemia and metabolic syndrome. Int J Clin Pract 2012;66(9):843-53.	Not relevant population (statin status unclear)
Aguilar-Salinas CA, Gomez-Perez FJ, Posadas-Romero C, Vazquez-Chavez C, Meaney E, Gulias-Herrero A, et al. Efficacy and safety of atorvastatin in hyperlipidemic, type 2 diabetic patients. A 34-week, multicenter, open-label study. Atherosclerosis 2000;152(2):489-96.	Not relevant population; compares different doses of statin
Al Badarin F, O'Keefe J. Fibrates lower the risk of myocardial infarction but not stroke or mortality in patients with cardiovascular disease: a meta-analysis and systematic review. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 13-16 May 2010; Chicago, IL: United States. J Clin Lipidol 2010;4(3):222-223.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Amarenco P, Labreuche J, Bruckert E. Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis. Presented at 19th European Stroke Conference; 25-28 May 2010; Barcelona: Spain. Cerebrovasc Dis 2010;29:166.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking

Publication citation	Reason(s) for exclusion
Ambegaonkar BM, Tipping D, Polis AB, Tomassini JE, Tershakovec AM. Achieving goal lipid levels with ezetimibe plus statin add-on or switch therapy compared with doubling the statin dose. A pooled analysis. Atherosclerosis. [Journal Article Research Support, Non-U.S. Gov't]. 2014 Dec;237(2):829-37.	Not relevant study design (Meta-analysis)
Amgen Inc. A multicenter, open-label extension (OLE) study to assess the long-term safety and efficacy of evolocumab. EUCTR2014-001524-30. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2014 [accessed 19.3.15]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-001524-30.	Not relevant study design (not RCT, open label extension)
Amgen Inc. Study designed to evaluate the safety and efficacy of AMG 145, in people with elevated LDL-C and not treated with any other lipid-lowering medications.To do this, AMG 145 will be compared with placebo and with ezetimibe. EUCTR2012-001362-15-BE. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2012 [accessed 27.10.14].	Not relevant population (not intolerant or resistant to statin treatment)
Amgen Inc. Study to assess the long term safety and efficacy of AMG 145 in patients with high concentrations of lipids in the blood. EUCTR2012-004357-83-IT. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2013 [accessed 3.6.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-004357-83	Not relevant population; mixed refractory and naive population with no separate results or indication of numbers in each category at baseline
Amgen. Ascending multiple dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of AMG 145 in subjects with hyperlipidemia on stable doses of a statin. NCT01133522. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 [accessed 14.7.14]. Available from: http://ClinicalTrials.gov/show/NCT01133522	Not relevant trial design (<12 wks)
Amgen. Global assessment of plaque regression with a PCSK9 antibody as measured by intravascular ultrasound. NCT01813422. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT01813422	Not relevant outcomes
Amgen. Open label study of long term evaluation against LDL-C trial. NCT01439880. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT01439880	Not relevant population; mixed refractory and naive population with no separate results or indication of numbers in each category at baseline
Amgen. Trial assessing long term use of PCSK9 inhibition in subjects with genetic LDL disorders. NCT01624142. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 15.7.14]. Available from: http://ClinicalTrials.gov/show/NCT01624142	Not relevant trial design (Not RCT)
Amgen. Trial assessing long term use of PCSK9 inhibition in subjects with genetic LDL disorders (TAUSSIG). NCT01624142. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 [accessed 15.7.14]. Available from: http://clinicaltrials.gov/show/NCT01624142	Not relevant trial design (not RCT)
Amgen. Trial evaluating PCSK9 antibody in subjects with LDL receptor abnormalities. NCT01588496. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT01588496	Duplicate of
Ansquer J-C, Corda C, Le Malicot K, Jessent V. Effects of atorvastatin 10 mg and fenofibrate 200 mg on the low-density lipoprotein profile in dyslipidemic patients: a 12-week, multicenter, randomized, open-label, parallel-group study. Current Therapeutic Research, Clinical & Experimental 2009;70(2):71-93.	Not relevant population (mixed dyslipidemic and mixed statin history, numbers and separate data NR)
Armitage J. HPS2-THRIVE: treatment of HDL to reduce the incidence of vascular events: a randomised trial of the long term clinical effects of raising HDL cholesterol with extended release niacin/laropiprant [Internet]. 2010 [accessed 27.10.14].	Not relevant population (around 38% of patients were at lipid target at baseline)
Arntz HR, Bonner G, Kikis D, Kirch W, Klor HU, Lederle RM, et al. [Effectiveness of pravastatin and bezafibrate in primary hypercholesterolemia]. Dtsch Med Wochenschr 1991;116(1):7-12.	Not relevant population

Publication citation	Reason(s) for exclusion
Arshad AR. Comparison of low-dose rosuvastatin with atorvastatin in lipid-lowering efficacy and safety in a high-risk pakistani cohort: an open-label randomized trial. Journal of Lipids 2014;2014:875907.	Not relevant population (mixed statin history; separate data and numbers of participants NR)
Assmann G, Huwel D, Schussman KM, Smilde JG, Kosling M, Withagen AJAM, et al. Efficacy and safety of atorvastatin and pravastatin in patients with hypercholesterolemia. Eur J Intern Med 1999;10(1):33-39.	Not relevant population (mixed)
AstraZeneca A. B. A study to evluate the safety of rosuvastatin in children and adolescents with homozygous familial hypercholesterolemia. EUCTR2014-004746-99-BE. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2014 [accessed 19.3.15] [updated 23/02/2015]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-004746-99.	Not relevant population (statin status unclear)
AstraZeneca AB. A 12-week open-label, randomised, parallel-group, multicentre, phase IIIb study to compare the efficacy and safety of rosuvastatin (CRESTOR) 10 mg and 20 mg in combination with ezetimibe 10 mg and sivastatin 40 mg and 80 mg in combination with ezetimibe 10 mg (fixed dose combination) in patients with hypercholesterolaemia and coronary heart disease (CHD) or a CHD risk equivalent, atherosclerosis or a 10-year CHD Risk of >20% (GRAVITY). EUCTR2007-002810-20. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2007 [accessed 30.5.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-002810-20	Not relevant population (numbers of refractory pts unclear); not relevant trial design (treatment periods only 6wks)
AstraZeneca AB. A randomized, double blind, placebo controlled, multi center, cross over study of rosuvastatin in children and adolescents (aged 6 to <18 years) with homozygous familial hypercholesterolemia (HoFH). EUCTR2014-000972-24. In: PharmNet.Bund [Internet]. Cologne: German Institute of Medical Documentation and Information (DIMDI). 2014 [accessed 19.3.15]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-000972-24/DE.	Not relevant population (statin status unclear)
AstraZeneca. An open-label randomised, multicentre, phase-IIIb, parallel-group switching study to compare the efficacy and safety of lipid-lowering agents atorvastatin, pravastatin, simvastatin and rosuvastatin in subjects with Type IIa and IIb hypercholesterolaemia (MERCURY I) [Internet]. 2002 [accessed 6.6.14]. Available from: http://www.astrazenecaclinicaltrials.com/_mshost800325/content/clinical-trials/resources/pdf/8610186	Not relevant population (statin status unclear); not relevant trial design (8wk treatment period)
AstraZeneca. Compare the efficacy of rosuvastatin to atorvastatin in high risk patients with hypercholesterolemia. NCT00683618. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00683618	Not relevant population (unclear population); not relevant trial design (6wks treatment period)
AstraZeneca. Evaluation of the efficacy and safety of rosuvastatin 5 mg versus pravastatin 40 mg and atorvastatin 10 mg in type IIa and IIb hypercholesterolaemic patients. NCT00631189. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00631189	Not relevant trial design
AstraZeneca. Rosuvastatin ORBITAL Germany. NCT00379249. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2009 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00379249	Not relevant intervention/ comparator
NCT02226198. A Study to Evaluate the Efficacy and Safety of Rosuvastatin in Children and Adolescents With Homozygous Familial Hypercholesterolemia. 2014.	Not relevant trial design (crossover with only 6wks treatment period)
Athyros VG, Kakafika AI, Papageorgiou AA, Paraskevas KI, Tziomalos K, Anagnostis P, et al. Effects of statin treatment in men and women with stable coronary heart disease: a subgroup analysis of the GREACE Study. Curr Med Res Opin 2008;24(6):1593-9.	Not relevant population; not relevant trial design
Athyros VG, Kakafika AI, Papageorgiou AA, Tziomalos K, Skaperdas A, Pagourelias E, et al. Atorvastatin decreases triacylglycerol-associated risk of vascular events in coronary heart disease patients. Lipids 2007;42(11):999-1009.	Not relevant population

Publication citation	Reason(s) for exclusion
Athyros VG, Papageorgiou AA, Hatzikonstandinou HA, Didangelos TP, Carina MV, Kranitsas DF, et al. Safety and efficacy of long-term statin-fibrate combinations in patients with refractory familial combined hyperlipidemia. Am J Cardiol 1997;80(5):608-13.	Not relevant population (statin status unclear)
Bach LA, Wirth A, O'Brien RC, Jerums G, Cooper ME. Cholesterol lowering effects of simvastatin in patients with non-insulin dependent diabetes mellitus. Diabetes, Nutrition and Metabolism - Clinical and Experimental 1991;4(2):123-128.	Not relevant population; not relevant trial design (dose doubled for non-responders but outcomes only for 6wks)
Bach RG, Cannon C, Giugliano R, White J, Lokhnygina Y, Tershakovec A, et al. Increasing Age and the Benefit From Higher-intensity Lipid Lowering With Ezetimibe/Simvastatin vs. Simvastatin Alone: Results From the IMPROVE-IT Trial. Circulation. 2015 November 10, 2015;132(Suppl 3):A16708.	Not relevant population (statin status mixed)
Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins.[Erratum appears in Lancet. 2005 Oct 15-21;366(9494):1358], [Erratum appears in Lancet. 2008 Jun 21;371(9630):2084]. Lancet 2005;366(9493):1267-78.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Ballantyne CM, Bays HE, Shah AK, Sisk C, Dong Q, Maccubbin D. Extended release niacin/laropiprant lowers atherogenic lipids across patient subgroups. Presented at 79th European Atherosclerosis Society Congress, EAS; 26-29 Jun 2011; Gothenburg: Sweden. Atheroscler Suppl 2011;12(1):25.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Ballantyne CM, Blazing MA, King TR, Brady WE, Palmisano J. Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia. Am J Cardiol 2004;93(12):1487-94.	Not relevant population (mixed)
Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: A prospective, randomized, double-blind trial. Circulation 2003;107(19):2409-2415.	Not relevant population (mixed)
Ballantyne CM, Lipka LJ, Sager PT, Strony J, Alizadeh J, Suresh R, et al. Long-term safety and tolerability profile of ezetimibe and atorvastatin coadministration therapy in patients with primary hypercholesterolaemia. Int J Clin Pract 2004;58(7):653-8.	Not relevant population (mixed)
Ballantyne CM, Miller M, Niesor EJ, Burgess T, Kallend D, Stein EA. Effect of dalcetrapib plus pravastatin on lipoprotein metabolism in dyslipidemic patients: results of a phase 2B dose-ranging study. Presented at American College of Cardiology's 59th Annual Scientific Session and i2 Summit: Innovation in Intervention; 14-16 Mar 2010; Atlanta, GA: United States. J Am Coll Cardiol 2010;55(10 suppl 1):A47.E444.	Not relevant comparator (different doses of Dalceptrapib plus pravastatin vs. placebo); not relevant outcomes (lipid size)
Ballantyne CM, Schiebinger R, Cain V. Randomized comparison of rosuvastatin plus ezetimibe versus simvastatin plus ezetimibe: results of the gravity study. Presented at American College of Cardiology's 59th Annual Scientific Session and i2 Summit: Innovation in Intervention; 14-16 Mar 2010; Atlanta, GA: United States. J Am Coll Cardiol 2010;55(10 suppl 1):A49.E463.	Not relevant population (numbers of refractory pts unclear); not relevant trial design (treatment periods only 6wks)
Ballantyne CM, McKenney JM, MacDougall DE, Margulies JR, Robinson PL, Hanselman JC, et al. Effect of ETC-1002 on Serum Low-Density Lipoprotein Cholesterol in Hypercholesterolemic Patients Receiving Statin Therapy. Am J Cardiol. 2016 Jun 15;117(12):1928-33.	Not relevant intervention/ comparator - ETC-1002, new potential lipid lowering therapy but unlicensed and still in development
Ballantyne CM, MacDougall DE, Margulies JR, Robinson PL, Hanselman JC, Lalwani ND. ETC-1002 Incrementally Lowers Low Density Lipoprotein-cholesterol in Patients With Hypercholesterolemia Receiving Stable Statin Therapy. Circulation. 2015 November 10, 2015;132(Suppl 3):A17499.	Not relevant intervention/ comparator - ETC-1002, new potential lipid lowering therapy but unlicensed and still in development

Publication citation	Reason(s) for exclusion
Banga JD, Jacotot B, Pfister P, Mehra M. Long-term treatment of hypercholesterolemia with fluvastatin: a 52-week multicenter safety and efficacy study. Am J Med 1994;96(6A):6A87S-6A93S.	Not relevant population
Bardini G, Giorda CB, Pontiroli AE, Le Grazie C, Rotella CM. Ezetimibe + simvastatin versus doubling the dose of simvastatin in high cardiovascular risk diabetics: a multicenter, randomized trial (the LEAD study). Cardiovasc Diabetol 2010;9(20).	Not relevant trial design (6wk treatment period)
Barrett PHR, Pang J, Chan DC, Hamilton SJ, Tenneti VS, Watts GF. Effect of niacin on triglyceride-rich lipoprotein apolipoprotein b-48 kinetics in type 2 diabetic subjects on a statin. Atherosclerosis. 2014;235(2):e167-e8.	Not relevant study design (less than 10 participants per arm)
Barrios V, Amabile N, Paganelli F, Chen JW, Allen C, Johnson-Levonas AO, et al. Lipid-altering efficacy of switching from atorvastatin 10 mg/day to ezetimibe/simvastatin 10/20 mg/day compared to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease. Int J Clin Pract 2005;59(12):1377-86.	Not relevant trial design (<12 wks)
Barter PJ, O'Brien RC. Achievement of target plasma cholesterol levels in hypercholesterolaemic patients being treated in general practice. Atherosclerosis 2000;149(1):199-205.	Not relevant population; mixed refractory and naive population with no separate results or indication of numbers in each category at baseline
Bays HE, Averna M, Majul C, Muller-Wieland D, De Pellegrin A, Giezek H, et al. Ezetimibe & atorvastatin coadministration vs atorvastatin uptitration or switching to rosuvastatin in primary hypercholesterolemic patients at high cardiovascular risk. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 30 May - 2 Jun 2013; Las Vegas, NV: United States. J Clin Lipidol 2013;7(3):280.	Not relevant trial design (<12 wks)
Bays HE, Averna M, Majul C, Muller-Wieland D, Pellegrin A, Giezek H, et al. Efficacy and safety of ezetimibe added to atorvastatin versus atorvastatin uptitration or switching to rosuvastatin in patients with primary hypercholesterolemia. Am J Cardiol 2013;112(12):1885-1895.	Not relevant trial design (6wk treatment period)
Bays HE, Ballantyne C, Shah A, Sisk CM, Dong Q, Maccubbin D. Extended release niacin/laropiprant lowers atherogenic lipids across patient subgroups. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 19-22 May 2011; New York, NY: United States. J Clin Lipidol 2011;5(3):239.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Bays HE, Brinton EA, Triscari J, Chen E, Maccubbin D, MacLean A, et al. Extended-release niacin/laropiprant significantly improves lipid levels in type 2 diabetes patients irrespective of baseline glycemic control. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 31 May - 3 Jun 2012; Scottsdale, AZ: United States. J Clin Lipidol 2012;6(3):270-271.	Not relevant comparator (niacin/laropiprant)
Bays HE, Jones PH, Mohiuddin SM, Kelly MT, Sun H, Setze CM, et al. Long-term safety and efficacy of fenofibric acid in combination with statin therapy for the treatment of patients with mixed dyslipidemia. J Clin Lipidol 2008;2(6):426-435.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Bays HE, Ose L, Fraser N, Tribble DL, Quinto K, Reyes R, et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clin Ther 2004;26(11):1758-73.	Not relevant population (mixed)
Bays HE, Shah A, Lin J, McCrary Sisk C, Paolini JF, Maccubbin D. Efficacy and tolerability of extended-release niacin/laropiprant in dyslipidemic patients with metabolic syndrome. J Clin Lipidol 2010;4(6):515-21.	Not relevant population; not relevant intervention/comparator
Bays HE, Shah A, Macdonell G, Taggart WV, Gumbiner B. Effects of coadministered ezetimibe plus fenofibrate in mixed dyslipidemic patients with metabolic syndrome. Metab Syndr Relat D 2011;9(2):135-42.	Not relevant population
Bays H. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol 2014;63(23):2531-2540.	Not relevant population (not previously received statins)

Publication citation	Reason(s) for exclusion
Behounek BD, McGovern ME, Kassler-Taub KB, Markowitz JS, Bergman M, Colman P, et al. Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. Am J Cardiol 1993;72(14):1031-1037.	Not relevant outcome data (some patients received increased dose of statin if did not respond but data are not reported separately)
Behounek BD, McGovern ME, Kassler-Taub KB, Markowitz JS, Bergman M. A multinational study of the effects of low-dose pravastatin in patients with non-insulin-dependent diabetes mellitus and hypercholesterolemia. Pravastatin Multinational Study Group for Diabetes. Clin Cardiol 1994;17(10):558-62.	Not relevant population
Berberoglu Z, Guvener N, Asik M, Yazici AC, Bayraktar N. Effects of achieving LDL-cholesterol levels <70 mg/dL with simvastatin or atorvastatin on steroidogenesis in high-risk diabetic patients. Endocrinologist 2009;19(3):102-107.	Not relevant population
Bertolini S, Bon GB, Campbell LM, Farnier M, Langan J, Mahla G, et al. Efficacy and safety of atorvastatin compared to pravastatin in patients with hypercholesterolemia. Atherosclerosis 1997;130(1-2):191-7.	Not relevant population; mixed refractory and naive population with no separate results or indication of numbers in each category at baseline
Betteridge J, Guyton JR, Farnier M, Leiter LA, Lin J, Shah A, et al. Greater dissociation of apolipoprotein B and LDL cholesterol targets in diabetes versus non-diabetes patients receiving lipid-lowering therapy. Presented at 47th Annual Meeting of the European Association for the Study of Diabetes, EASD; 12-16 Sept 2011; Lisbon: Portugal. Diabetologia 2011;54:S278.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Binbrek AS, Elis A, Al-Zaibag M, Eha J, Keber I, Cuevas AM, et al. Rosuvastatin versus atorvastatin in achieving lipid goals in patients at high risk for cardiovascular disease in clinical practice: a randomized, open-label, parallel-group, multicenter study (DISCOVERY Alpha study). Curr Ther Res Clin Exp 2006;67(1):21-43.	Not relevant population (mixed statin naïve and statin treated but only around 30% were statin treated and data not reported separately)
Binbrek AS, Elis A, Al-Zaibag M, Eha J, Keber I, Cuevas AM, Mukherjee S, Miller TR, Discovery Alpha Study G. Rosuvastatin versus atorvastatin in achieving lipid goals in patients at high risk for cardiovascular disease in clinical practice: A randomized, open-label, parallel-group, multicenter study (DISCOVERY Alpha study). Current Therapeutic Research, Clinical & Experimental 2006;67(1):21-43.	Not relevant population (mixed statin history; separate data NR; only 40% had previously been treated with statin)
Blazing MA, Giugliano RP, DeLemos J, Cannon CP, Musliner T, Tershakovec AM, et al. On-treatment analysis of the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). Circulation. 2014 December 2, 2014;130(23):2112.	Not relevant population (mixed statin history, numbers and separate data NR)
Blom D, Monsalvo ML, Tsirtsonis K, Wasserman S, Roth E. Effects of evolocumab (AMG 145) treatment on vitamin e levels: results from the 52-Week phase 3 double-blind, randomized, placebo-controlled DESCARTES study (1107-102). Abstract presented at American College of Cardiology (ACC); 14-16 March 2015; San Diego, US. [Internet]2015 [accessed 30.4.15].	Not relevant outcomes (DESCARTES; Sub group analysis of patients having vitamin E)
Boekholdt SM, Arsenault BJ, Hovingh GK, Mora S, Pedersen TR, Larosa JC, et al. Levels and changes of HDL cholesterol and apolipoprotein A-I in relation to risk of cardiovascular events among statin-treated patients: a meta-analysis. Circulation 2013;128(14):1504-12.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis.[Erratum appears in JAMA. 2012 Apr 25;307(16):1694], [Erratum appears in JAMA. 2012 May 9;307(18):1915]. JAMA 2012;307(12):1302-9.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarenco P, Pedersen TR, LaRosa JC, Waters DD, DeMicco DA, Simes RJ, Keech AC, Colquhoun D, Hitman GA, Betteridge DJ, Clearfield MB, Downs JR, Colhoun HM, Gotto AM, Jr., Ridker PM, Grundy SM, Kastelein JJP. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. J Am Coll Cardiol 2014;64(5):485-94.	Not relevant study design (meta-analysis; used for reference checking)

Publication citation	Reason(s) for exclusion
Boh M, Opolski G, Poredos P, Ceska R, Jezovnik M. Therapeutic equivalence of the generic and the reference atorvastatin in patients with increased coronary risk. Int Angiol 2011;30(4):366-74.	Not relevant population
Briasoulis A, Agarwal V, Valachis A, Messerli FH. Antihypertensive effects of statins: a meta-analysis of prospective controlled studies. J Clin Hypertens 2013;15(5):310-320.	Not relevant trial design
Bronx V. A. Medical Center. Tolerability and lipid lowering effect of weekly/biweekly crestor in statin intolerant patients treated with Zetia. NCT00972829. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2009 [accessed 27.6.14]. Available from: http://ClinicalTrials.gov/show/NCT00972829	Not relevant outcome (early termination)
Brown WV, Bays HE, Hassman DR, McKenney J, Chitra R, Hutchinson H, et al. Efficacy and safety of rosuvastatin compared with pravastatin and simvastatin in patients with hypercholesterolemia: a randomized, double-blind, 52-week trial. Am Heart J 2002;144(6):1036-1043.	Not relevant population (Mixed statin naïve and statin treated)
Bruckert E, De Gennes JL, Malbecq W, Baigts F. Comparison of the efficacy of simvastatin and standard fibrate therapy in the treatment of primary hypercholesterolemia and combined hyperlipidemia. Clin Cardiol 1995;18(11):621-9.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Bruckert E, Labreuche J, Amarenco P. Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis. Atherosclerosis 2010;210(2):353-61.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Brudi P, Guyton JR, Betteridge J, Farnier M, Leiter LA, Lin J, et al. Meta-analysis evaluating the proportions of patients with and without diabetes achieving lipid/lipoprotein goals with ezetimibe/statin combination therapy versus statin alone. Presented at 46th Annual Meeting of the European Association for the Study of Diabetes, EASD; 20-24 Sept 2010; Stockholm: Sweden. Diabetologia 2010;53:S512.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Brudi PDP, Betteridge J, Guyton J, Farnier M, Leiter L, Lin J, et al. Greater dissociation of apolipoprotein B and LDL cholesterol targets in diabetes versus nondiabetes patients receiving lipid-lowering therapy. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 19-22 May 2011; New York, NY: United States. J Clin Lipidol 2011;5(3):198-199.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Brunetti L, Hermes-Desantis ER. The role of colesevelam hydrochloride in hypercholesterolemia and type 2 diabetes mellitus. Ann Pharmacother 2010;44(7-8):1196-206.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Byington RP, Jukema JW, Salonen JT, Pitt B, Bruschke AV, Hoen H, et al. Reduction in cardiovascular events during pravastatin therapy. Pooled analysis of clinical events of the Pravastatin Atherosclerosis Intervention Program. Circulation 1995;92(9):2419-25.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Cannon CP. IMPROVE-IT trial: a comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes after acute coronary syndromes. Circulation. 2014 December 2, 2014;130(23):2109.	Not relevant population (mixed statin history, numbers and separate data NR)
Cannon CP. IMPROVE-IT: where is the ground in aggressive LDL lowering after ACS? Presented at ESC Congress 2015; 29 Aug-2 Sep 2015; London: United Kingdom. 2015.	Not relevant population (mixed statin naïve and statin treated)
Carr-Lopez S, Exstrum T, Morse T, Shepherd M, Bush AC. Efficacy of three statins at lower maintenance doses. Clin Ther 1999;21(2):331-339.	Not relevant population
Carter NJ. Rosuvastatin: a review of its use in the prevention of cardiovascular disease in apparently healthy women or men with normal LDL-C levels and elevated hsCRP levels. Am J Cardiovasc Drugs 2010;10(6):383-400.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Catapano AL, Reiner T, De Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS Guidelines for the management of dyslipidaemias. The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis 2011;217(1):3-46.	Not relevant trial design (guidelines/guidance)

Publication citation	Reason(s) for exclusion
Catapano AL, Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS Guidelines for the management of dyslipidaemias. The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis 2011;217(SUPPL. 1):S1-S44.	Not relevant trial design (guidelines/guidance)
Chan DC, Hamilton SJ, Rye KA, Chew GT, Jenkins AJ, Lambert G, et al. Fenofibrate concomitantly decreases serum proprotein convertase subtilisin/kexin type 9 and very-low-density lipoprotein particle concentrations in statin-treated type 2 diabetic patients. Diabetes, Obesity & Metabolism 2010;12(9):752-6.	Not relevant trial design (too few pts)
Choi HD, Shin WG. Safety and efficacy of statin treatment alone and in combination with fibrates in patients with dyslipidemia: a meta-analysis. Curr Med Res Opin 2014;30(1):1-10.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Clement Atlee W, Vasudevan M. Comparing the effect of monotherapies of hyperlipidemia over placebo treatment. Int J Drug Dev Res. 2014;6(3):68-76.	Not relevant population (statin status unclear)
Cromwell WC, Thomas GS, Boltje I, Chin W, Davidson M. Safety and efficacy of mipomersen administered as add-on therapy in patients with hypercholesterolemia and high cardiovascular risk. Presented at 60th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC; 2-5 April 2011; New Orleans, LA: United States. J Am Coll Cardiol 2011;57(14 suppl 1):E504.	Not relevant population - mipomersen trial not in HoFH
Cromwell WC, Thomas GS, Boltje I, Chin W, Davidson M. Safety and efficacy of mipomersen administered as addon therapy in patients with hypercholesterolemia and high cardiovascular risk. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 31 May - 3 Jun 2012; Scottsdale, AZ: United States. J Clin Lipidol 2012;6(3):291-292.	Not relevant population - mipomersen trial not in HoFH
CymaBay Therapeutics I. A 12-week, open-label, dose-escalating, phase 2 study to evaluate the effects of MBX-8025 in patients with Homozygous Familial Hypercholesterolemia (HoFH). 2015. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-004856-68	Not relevant intervention
Daiichi Sankyo Inc. A study to determine the effect of WelChol tablets on cholesterol in patients who have been taking simvastatin for at least 4 weeks. NCT00753779. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2008 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00753779	Not relevant trial design (6wk treatment period)
Daniel AS, Merck Sharp Dohme Corp, Hospital Italiano de Buenos Aires. Lipid efficacy of the extended release niacin/laropiprant combination in patients with cardiovascular disease. NCT01308203. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 27.10.14]. Available from: http://ClinicalTrials.gov/show/NCT01308203	Not relevant outcome (early termination)
Dargush A, Shah S, O'Dell K, Bhattacharyya M. Magnitude of benefit when ezetimibe is added to statin therapy: a meta-analysis. Presented at Joint Forces Pharmacy Seminar, JFPS; 28 Oct - 1 Nov 2012; San Diego, CA: United States. J Am Pharm Assoc 2012;52(5):679.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Davidson M, McKenney J, Stein E, Schrott H, Bakker-Arkema R, Fayyad R, et al. Comparison of one-year efficacy and safety of atorvastatin versus lovastatin in primary hypercholesterolemia. Atorvastatin Study Group I. Am J Cardiol 1997;79(11):1475-81.	Not relevant population; mixed refractory and naive population with no separate results or indication of numbers in each category at baseline
Davidson M. The efficacy of colesevelam HCL in the treatment of heterozygous familial hypercholesterolemia in pediatric and adult patients. Clin Ther 2013;35(8):1247-1252.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol 2002;40(12):2125-34.	Not relevant population (mixed)

Publication citation	Reason(s) for exclusion
Davidson MH, Rooney M, Pollock E, Drucker J, Choy Y. Effect of colesevelam and niacin on low-density lipoprotein cholesterol and glycemic control in subjects with dyslipidemia and impaired fasting glucose. J Clin Lipidol. 2013 Sep-Oct;7(5):423-32.	Not relevant population (mixed statin history, numbers and separate data NR)
Davidson MH, Rooney MW, Drucker J, Eugene Griffin H, Oosman S, Beckert M. Efficacy and tolerability of atorvastatin/fenofibrate fixed-dose combination tablet compared with atorvastatin and fenofibrate monotherapies in patients with dyslipidemia: a 12-week, multicenter, double-blind, randomized, parallel-group study. Clin Ther 2009;31(12):2824-2838.	Not relevant population
De Caterina R, Scarano M, Marfisi R, Lucisano G, Palma F, Tatasciore A, et al. Cholesterol-lowering interventions and stroke: insights from a meta-analysis of randomized controlled trials. J Am Coll Cardiol 2010;55(3):198-211.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Dias C, Shaywitz A, Cooke B, Uy S, Emery M, Gibbs J, et al. Effects of amg 145, a fully human monoclonal antibody against pcsk9, on low-density lipoprotein cholesterol in subjects taking statins: a phase 1, randomized, doubleblind, placebo-controlled, ascending multiple-dose study. Presented at 61st Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC; 24-27 Mar 2012; Chicago, IL: United States. J Am Coll Cardiol 2012;59(13 Suppl 1):E1379.	Not relevant trial design (<12 wks)
Dias C, Shaywitz A, Smith B, Gao B, Gibbs J, Emery M, et al. AMG 145 a fully human monoclonal antibody against PCSK9, reduces LDL-C in healthy volunteers and patients on stable doses of statins. Presented at 65th Annual Meeting of the Canadian Cardiovascular Society; 27-31 Oct 2012; Toronto, ON: Canada. Can J Cardiol 2012;28(5 suppl 1):S148.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Dias C, Shaywitz A, Smith B, Gao B, Gibbs J, Emery M, et al. AMG 145-a fully human monoclonal antibody against PCSK9, REDUCES LDL-C in healthy volunteers and patients on stable doses of statins. Can J Cardiol. 2012;28(5 SUPPL. 1):S148.	Not relevant study design (pooled analysis)
Dias CS, Shaywitz AJ, Wasserman SM, Smith BP, Gao B, Stolman DS, et al. Effects of AMG 145 on low-density lipoprotein cholesterol levels: results from 2 randomized, double-blind, placebo-controlled, ascending-dose phase 1 studies in healthy volunteers and hypercholesterolemic subjects on statins. J Am Coll Cardiol 2012;60(19):1888-98.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Ditschuneit HH, Dreyer M, Dammann HG, Ditschuneit H. [Pravastatin, cholestyramine and gemfibrozil in long-term therapy of primary hypercholesterolemia. An open randomized comparative study]. Med Klin 1991;86(3):142-8.	Not relevant population
Ducobu J, Van Haelst L, Salomon H. Efficacy of micronised fenofibrate in patients with primary hyperlipidaemia: a comparison with pravastatin. Br J Cardiol 2002;9(6):343-350.	Not relevant population (mixed); Not relevant trial design
Duell PB, Santos RD, East C, Guyton JR, Moriarty PM, Donovan JM, et al. Long-term safety and efficacy of mipomersen in patients with familial hypercholesterolemia uncontrolled by maximally tolerated lipid lowering therapy. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 31 May - 3 Jun 2012; Scottsdale, AZ: United States. J Clin Lipidol 2012;6(3):291.	Not relevant population (mipomersen trial in FH); not relevant trial design
Dufour R, Moriarty PM, Genestin E, Sasiela WJ, Du Y, Ferrand AC, et al. Effect of REGN727/SAR236553 anti-proprotein convertase subtilisin/kexin type 9 fully human monoclonal antibody in patients with elevated triglycerides/low high-density lipoprotein cholesterol: data from three phase 2 studies (NCT:01266876; 01288469; 01288443). Presented at American Heart Association 2012 Scientific Sessions and Resuscitation Science Symposium; 3-6 Nov 2012; Los Angeles, CA: United States. Circulation 2012;126(21 suppl 1).	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Dujovne CA, Ettinger MP, McNeer JF, Lipka LJ, LeBeaut AP, Suresh R, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. [Erratum appears in Am J Cardiol. 2003 Jun 1;91(11):1399]. Am J Cardiol 2002;90(10):1092-7.	Not relevant population (mixed)
Dujovne CA, Le Beaut A, Lipka LJ, Suresh R, Veltri EP, Alderman J, et al. Evaluation of the efficacy, safety, and tolerability of ezetimibe in primary hypercholesterolaemia: a pooled analysis from two controlled phase III clinical studies. Int J Clin Pract 2003;57(5):363-368.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking

Publication citation	Reason(s) for exclusion
Eli Lilly and Company. A phase 2 efficacy and safety study of LY2484595 alone and in combination with atorvastatin, simvastatin, and rosuvastatin in patients with hypercholesterolemia or low HDL-C. EUCTR2009-017479-29-DE. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2010 [accessed 27.10.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-017479-29	Not relevant population (mixed statin history; separate data and numbers of participants NR)
Eriksson M, Budinski D, Hounslow N. Comparative efficacy of pitavastatin and simvastatin in high-risk patients: a randomized controlled trial. Adv Ther 2011;28(9):811-23.	Not relevant population (statin naive)
Eriksson M, Budinski D, Hounslow N. Long-term efficacy of pitavastatin versus simvastatin. Adv Ther 2011;28(9):799-810.	Not relevant population (statin naive)
Esperion Therapeutics I. A randomized, double-blind, placebo-controlled, multi-center long-term safety and tolerability study of etc-1002 in patients with hyperlipidemia at high cardiovascular risk who are not adequately. 2016; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-004136-36.	Not relevant intervention/ comparator - ETC-1002, new potential lipid lowering therapy but unlicensed and still in development
Farnier M, Chen E, Johnson-Levonas AO, McCrary Sisk C, Mitchel YB. Effects of extended-release niacin/laropiprant, simvastatin, and the combination on correlations between apolipoprotein B, LDL cholesterol, and non-HDL cholesterol in patients with dyslipidemia. Vasc Health Risk Manag 2014;10:279-90.	Not relevant population (mixed dyslipidemic, separate data for subgroups but based on TG levels and not LDL-C)
Farnier M, Guyton JR, Jensen E, Polis A, Johnson- Levonas AO, Brudi P. Effects of ezetimibe, simvastatin and ezetimibe/simvastatin on correlations between apolipoprotein B, LDL cholesterol and non-HDL cholesterol in patients with primary hypercholesterolemia. Presented at ESC Congress; 25-29 Aug 2012; Munich: Germany. Eur Heart J 2012;33:281-282.	Not relevant population; not relevant trial design
Farnier M, Taggart W, Dong Q, Shah A, Brudi P. Influence of fenofibrate, simvastatin and/or ezetimibe on correlation of LDL and non-HDL cholesterol with apolipoprotein B in mixed dyslipidemic patients. Presented at 78th EAS Congress; 20-23 Jun 2010; Hamburg: Germany. Atheroscler Suppl 2010;11(2):68.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Farnier M. Cerivastatin in the treatment of mixed hyperlipidemia: the RIGHT study. Am J Cardiol 1998;82(4B):47J-51J.	Not relevant intervention
Fazio S, Guyton JR, Lin J, Tomassini JE, Shah A, Tershakovec AM. Long-term efficacy and safety of ezetimibe/simvastatin coadministered with extended-release niacin in hyperlipidaemic patients with diabetes or metabolic syndrome. Diabetes, Obesity & Metabolism 2010;12(11):983-93.	Not relevant population
Feldman T, Ose L, Shah A, Zakson M, Meehan A, Johnson-Levonas AO, et al. Efficacy and safety of ezetimibe/simvastatin versus simvastatin monotherapy in hypercholesterolemic patients with metabolic syndrome. Metab Syndr Relat D 2007;5(1):13-21.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Ferdinand KC, Davidson MH, Kelly MT, Setze CM. One-year efficacy and safety of rosuvastatin + fenofibric acid combination therapy in patients with mixed dyslipidemia: evaluation of dose response. Am J Cardiovasc Drugs 2012;12(2):117-25.	Not relevant trial design; not relevant populaton
Ferrari P, Weidmann P, Riesen WF, Martius F, Luban S, Pasotti E, et al. [Pravastatin in the treatment of primary hypercholesterolemia: a Swiss multicenter study]. Schweiz Med Wochenschr 1993;123(37):1736-41.	Not relevant population; not relevant trial design
Fichtenbaum CJ, Yeh TM, Evans SR, Aberg JA. Treatment with pravastatin and fenofibrate improves atherogenic lipid profiles but not inflammatory markers in ACTG 5087. J Clin Lipidol 2010;4(4):279-287.	Not relevant population (HIV infected individuals)
Furiex Pharmaceuticals Inc. Study of the safety and tolerability associated with PPD10558 versus atorvastatin in patients previously intolerant to statins due to statin-associated myalgia (SAM). NCT01279590. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2011 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT01279590	Not relevant comparator (PPD10558 versus atorvastatin)
Gagné C, Bays HE, Weiss SR, Mata P, Quinto K, Melino M, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol 2002;90(10):1084-91.	Not relevant trial design (only 8wk treatment period)
Gagne C, Gaudet D, Bruckert E. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation 2002;105(21):2469-2475.	Not relevant trial design (only 8wk treatment period)

Publication citation	Reason(s) for exclusion
Garvey WT, Goldberg RB, Handelsman Y, Fonseca VA, Hernandez-Triana E, Jones MR, et al. Colesevelam significantly reduces low-density lipoprotein particle concentration in patients with prediabetes and hypercholesterolemia. Presented at 8th Annual World Congress on Insulin Resistance Diabetes and Cardiovascular Disease, WCIRDC; 4-6 Nov 2011; Los Angeles, CA: United States. Diab Vasc Dis Res 2011;8(1):85-86.	Not relevant population
Gaudet D, Kereiakes D, McKenney J, Roth E, Hanotin C, Gipe D, et al. Alirocumab, a fully human monoclonal antibody to pcsk9, reduces high plasma lp(a) concentration: pooled analysis of 352 patients from phase 2. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 30 May - 2 Jun 2013; Las Vegas, NV: United States. J Clin Lipidol 2013;7(3):283-284.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Gaudet D, Kereiakes D, McKenney J, Roth E, Hanotin C, Gipe D, et al. Effect of SAR236553/REGN727 fully human monoclonal anti-proprotein convertase subtilisin/kexin type 9 antibody on plasma lipoprotein(a) concentrations: pooled analysis from three phase 2 studies (NCT:01266876; 01288469; 01288443). Presented at American Heart Association 2012 Scientific Sessions and Resuscitation Science Symposium; 3-6 Nov 2012; Los Angeles, CA: United States. Circulation 2012;126(21 Suppl 1).	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Gaudet D, Kereiakes DJ, McKenney JM, Roth EM, Hanotin C, Gipe D, Du Y, Ferrand A-C, Ginsberg HN, Stein EA. Effect of alirocumab, a monoclonal proprotein convertase subtilisin/kexin 9 antibody, on lipoprotein(a) concentrations (a pooled analysis of 150 mg every two weeks dosing from phase 2 trials). Am J Cardiol 2014;114(5):711-5.	Not relevant study design (pooled analysis of three trials; two have been reported as individual studies and one is not relevant as only 8wks duration)
Gaudet D, Watts GF, Robinson J, Thompson D, Sasiela W, Edelberg J, et al. Sustained treatment effect of alirocumab on Lp(a): pooled analyses from 4,915 patients in ten phase 3 trials in the ODYSSEY program. Presented at ESC Congress 2015; 29 Aug-2 Sep 2015; London: United Kingdom. 2015.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Gavin IJR, Jones MR, Ford DM, Truitt KE. Safety and efficacy of colesevelam HCl in the treatment of elderly patients. Drugs Aging 2014;31(6):461-470.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
Geiss HC, Otto C, Hund-Wissner E, Parhofer KG. Effects of ezetimibe on plasma lipoproteins in severely hypercholesterolemic patients treated with regular LDL-apheresis and statins. Atherosclerosis 2005;180(1):107-12.	Not relevant trial design (<12 wks)
Geng Q, Ren J, Chen H, Lee C, Liang W. Adverse events of statin-fenofibric acid versus statin monotherapy: a meta-analysis of randomized controlled trials. Curr Med Res Opin 2013;29(3):181-188.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Genzyme Europe B.V. A prospective randomized, double-blind, placebo-controlled study to assess the safety and efficacy of mipomersen in patients with severe hypercholesterolemia on a maximally tolerated lipid-lowering regimen and who are not on apheresis. EUCTR2008-006020-53. In: PharmNet.Bund [Internet]. Cologne: German Institute of Medical Documentation and Information (DIMDI). 2008 [accessed 30.5.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-006020-53	Not relevant population (HeFH and HoFH population for mipomersen. No evidence for HoFH only)
Genzyme, Isis Pharmaceuticals, Sanofi. Open label extension of ISIS 301012 (Mipomersen) to treat familial hypercholesterolemia. NCT00477594. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 27.10.14]. Available from: http://ClinicalTrials.gov/show/NCT00477594	Not relevant population (mipomersen trial not solely in HoFH patients)
Genzyme, Isis Pharmaceuticals. Dose-escalating safety study of ISIS 301012 in homozygous familial hypercholesterolemia subjects on lipid lowering therapy. NCT00280995. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 14.7.14]. Available from: http://ClinicalTrials.gov/show/NCT00280995	Not relevant trial design (<12 wks)
Genzyme, Isis Pharmaceuticals. Safety and efficacy of mipomersen (ISIS 301012) as add-on therapy in high risk hypercholesterolemic patients. NCT00770146. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00770146	Not relevant population - mipomersen trial not in HoFH

Publication citation	Reason(s) for exclusion
Genzyme, Isis Pharmaceuticals. Safety and efficacy of mipomersen in patients with severe hypercholesterolemia on a maximally tolerated lipid-lowering regimen and who are not on apheresis. NCT00794664. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00794664	Not relevant population
Genzyme, Isis Pharmaceuticals. Safety and efficacy study of ISIS 301012 (mipomersen) administration in high risk statin intolerant subjects. NCT00707746. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 30.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00707746	Not relevant population - mipomersen trial not in HoFH
Genzyme, Sanofi. A study of the safety and efficacy of two different regimens of mipomersen in patients with familial hypercholesterolemia and inadequately controlled low-density lipoprotein cholesterol. NCT01475825. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 27.10.14]. Available from: http://ClinicalTrials.gov/show/NCT01475825	Not relevant population (mipomersen trial in HeFH)
Giannini SD. [Comparison of lipid-lowering effects of lovastatin and bezafibrate in patients with primary hypercholesterolemia. The Brazilian multicenter study]. Rev Bras Med 1990;47(5):177-184.	Not relevant population
Giugliano RP, Wiviott SD, Blazing MA, Murphy SA, Zhou J, White JA, et al. Safety and efficacy of long-term very low achieved LDL-C in the IMPROVE IT trial. Presented at ESC Congress 2015; 29 Aug-2 Sep 2015; London: United Kingdom. 2015.	Not relevant population (mixed statin status)
Giugliano RP. Achievement of dual LDL-C (<70 mg/dL) and hs-CRP (<2 mg/L) goals more frequent with addition of ezetimibe and associated with better outcomes in IMPROVE-IT. Presented at ESC Congress 2015; 29 Aug-2 Sep 2015; London: United Kingdom. 2015.	Not relevant population (mixed statin status)
Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB, Ezetimibe Study G. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc 2004;79(5):620-9.	Not relevant population
Gray J, Edwards SJ, Lip GYH. Comparison of sequential rosuvastatin doses in hypercholesterolaemia: a meta-analysis of randomised controlled trials. Curr Med Res Opin 2010;26(3):537-47.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Grundy SM, Vega GL, McGovern ME, Tulloch BR, Kendall DM, Fitz-Patrick D, et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. Arch Intern Med 2002;162(14):1568-76.	Not relevant population (mixed)
Gudzune KA, Monroe AK, Sharma R, Ranasinghe PD, Chelladurai Y, Robinson KA. Effectiveness of combination therapy with statin and another lipid-modifying agent compared with intensified statin monotherapy: a systematic review. Ann Intern Med 2014;160(7):468-76.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
Gumbiner B, Joh T, Udata C, Forgues P, Baum CM, Garzone PD. Effects of 12 weeks of treatment with RN316 (PF-04950615), a humanized IgG2a monoclonal antibody binding proprotein convertase subtilisin kexin type 9, in hypercholesterolemic subjects on high and maximal dose statins. Presented at American Heart Association 2012 Scientific Sessions and Resuscitation Science Symposium; 3-6 Nov 2012; Los Angeles, CA: United States. Circulation 2012;126(23):2782.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Gumbiner B, Udata C, Joh T, Liang H, Wan H, Shelton D, et al. The effects of single dose administration of RN316 (PF-04950615), a humanized IGG2A monoclonal antibody binding proprotein convertase subtilisin kexin type 9, in hypercholesterolemic subjects treated with and without atorvastatin. Presented at American Heart Association 2012 Scientific Sessions and Resuscitation Science Symposium; 3-6 Nov 2012; Los Angeles, CA: Unites States. Circulation 2012;126(21 suppl 1).	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Gumprecht J, Gosho M, Budinski D, Hounslow N. Comparative long-term efficacy and tolerability of pitavastatin 4 mg and atorvastatin 20-40 mg in patients with type 2 diabetes mellitus and combined (mixed) dyslipidaemia. Diabetes, Obesity & Metabolism 2011;13(11):1047-55.	Not relevant population (statin status unclear)
Guo J, Meng F, Ma N, Li C, Ding Z, Wang H, et al. Meta-analysis of safety of the coadministration of statin with fenofibrate in patients with combined hyperlipidemia. Am J Cardiol 2012;110(9):1296-301.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking

Publication citation	Reason(s) for exclusion
Guyton JR, Betteridge DJ, Farnier M, Leiter LA, Lin J, Shah A, et al. Achievement of recommended lipid and lipoprotein levels with combined ezetimibe/statin therapy versus statin alone in patients with and without diabetes. Diab Vasc Dis Res 2011;8(2):160-72.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Guyton JR, Farnier M, Jensen EH, Polis AB, Johnson-Levonas AO, Brudi P. Effects of ezetimibe, simvastatin, and ezetimibe/ simvastatin on apolipoprotein B, low-density lipoprotein cholesterol, and non-high-density lipoprotein cholesterol targets in patients with primary hypercholesterolemia. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 31 May - 3 Jun 2012; Scottsdale, AZ: United States. J Clin Lipidol 2012;6(3):289-290.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Habib G, Paillard F, Charpentier G, Angellier JF, Roux T, Portal JJ, et al. A multicenter, open-label, randomized study comparing the efficacy of atorvastatin versus usual care in reducing refractory hypercholesterolemia in high-risk patients to target levels. Curr Ther Res Clin Exp 2000;61(4):175-190.	Not relevant population (statin status unclear)
Hamilton SJ, Chew GT, Davis TME, Watts GF. Fenofibrate improves endothelial function in the brachial artery and forearm resistance arterioles of statin-treated Type 2 diabetic patients. Clin Sci 2010;118(10):607-15.	Not relevant trial design (too few pts)
Handelsman Y, Goldberg RB, Rosenstock J, Garvey WT, Fonseca VA, Hernandez-Triana E, et al. Colesevelam for hispanic patients with hypercholesterolemia and prediabetes. Pharmacotherapy. 2010;30(10):390e-1e.	Not relevant population (statin status unclear)
Hao Y, Zhang H, Yang X, Wang L, Gu D. Effects of fibrates on C-reactive protein concentrations: a meta-analysis of randomized controlled trials. Clin Chem Lab Med 2012;50(2):391-7.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Harivenkatesh N, David DC, Haribalaji N, Sudhakar MK. Efficacy and safety of alternate day therapy with atorvastatin and fenofibrate combination in mixed dyslipidemia: a randomized controlled trial. J Cardiovasc Pharmacol Ther 2014;19(3):296-303.	Not relevant population (mixed dyslipidemic and mixed statin history, numbers and separate data NR)
Hoogerbrugge N, Jansen H, De Heide L, Zillikens MC, Deckers JW, Birkenhager JC. The additional effects of acipimox to simvastatin in the treatment of combined hyperlipidaemia.[Republished from J Intern Med. 1997 Feb;241(2):151-5; PMID: 9077372]. J Intern Med 1998;243(5):151-6.	Not relevant trial design
Hopkins PN, Swergold GD, Mellis S, Bruckert E, Luc G, Mendoza J, et al. A randomized placebo-phase clinical trial with the monoclonal antibody alirocumab demonstrates reductions in low-density lipoprotein cholesterol in patients with proprotein convertase subtilisin/kexin type 9 gain-of-function mutations. Presented at American Heart Association 2013 Scientific Sessions and Resuscitation Science Symposium; 16-20 Nov 2013; Dallas, TX: United States. Circulation 2013;128(22 suppl 1).	Not relevant trial design; <10 pts per arm
Hospital of the University of Munich. Effect of mipomersen on LDL-cholesterol levels in patients with severe LDL-hypercholesterolemia and atherosclerosis treated by regular LDL-apheresis. EUCTR2011-002539-24. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2012 [accessed 27.10.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-002539-24	Not relevant population (statin history unclear)
Hounslow N, Budinski D, Eriksson M. Pitavastatin 4 mg shows comparable LDL-cholesterol and superior triglyceride reduction to simvastatin 40 mg in high-risk primary hypercholesterolemia or combined dyslipidemia. Presented at 78th EAS Congress; 20-23 Jun 2010; Hamburg: Germany. Atheroscler Suppl 2010;11(2):188.	Not relevant population; Not relevant trial design (not RCT)
Hounslow N. Pitavastatin LDL-C target attainment in elderly and CHD risk populations in a Phase 3 programme. Presented at European Society of Cardiology, ESC Congress; 28 Aug - 1 Sept 2010; Stockholm: Sweden. Eur Heart J 2010;31:256-257.	Not relevant trial design - summary of phase 3 trial programme
Hovingh GK, Kastelein JJ, van Deventer SJ, Round P, Ford J, Saleheen D, et al. Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet. 2015 Aug 1;386(9992):452-60.	Not relevant population (statin status unclear)

Publication citation	Reason(s) for exclusion
HPS Thrive Collaborative Group, Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, Wallendszus K, Craig M, Jiang L, Collins R, Armitage J. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med 2014;371(3):203-12.	Not relevant population (around 38% of patients were at lipid targets at baseline)
Hu M, Yang Y, Yamashita S, Masuda D, Tomlinson B. Effect of niacin on oxidized low-density lipoprotein levels in Chinese patients with dyslipidaemia. Atherosclerosis 2014;235(2):e256.	Not relevant population (statin history unclear); not relevant outcome (ox-LDL and correlation study)
Illingworth DR, Crouse JR, Hunninghake DB, Davidson MH, Escobar ID, Stalenhoef AFH, et al. A comparison of simvastatin and atorvastatin up to maximal recommended doses in a large multicenter randomized clinical trial. Curr Med Res Opin 2001;17(1):43-50.	Not relevant population (mixed)
Inazawa T, Sakamoto K, Kohro T, Iijima R, Kitazawa T, Hirano T, et al. RESEARCH (Recognized effect of Statin and ezetimibe therapy for achieving LDL-C Goal), a randomized, doctor-oriented, multicenter trial to compare the effects of higher-dose statin versus ezetimibe-plus-statin on the serum LDL-C concentration of Japanese type-2 diabetes patients design and rationale. Lipids Health Dis 2013;12:142.	Duplicate of
Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen. Ezetimibe for hypercholesterolaemia. Köln: IQWiG, 2011. 134p. Available from: https://www.iqwig.de/download/A10-02_Abschlussbericht_Ezetimib_bei_Hypercholesterinaemie.pdf	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Merck Sharp Dohme Corp. Efficacy of ezetimibe/simvastatin 10/20 mg and MK0524A (1-2 g/Day) in mixed hyperlipidemia and two or more risk factors. NCT00738985. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2011 [accessed 27.6.14]. Available from: http://ClinicalTrials.gov/show/NCT00738985	Not relevant outcome (early termination)
Insull Jr W, Toth PP, Superko HR, Thakkar RB, Krause S, Jiang P, et al. Combination of niacin extended-release and simvastatin results in a less atherogenic lipid profile than atorvastatin monotherapy. Vasc Health Risk Manag 2010;6(1):1065-1075.	Not relevant population (statin status unclear)
Isaacsohn J, Insull Jr W, Stein E, Kwiterovich P, Ma P, Brazg R, et al. Long-term efficacy and safety of cerivastatin 0.8 mg in patients with primary hypercholesterolemia. Clin Cardiol 2001;24(10 SUPPL.):IV1-IV9.	Not relevant population (mixed statin naïve and statin treated but numbers not reported and data not reported separately); not relevant comparator (different doses of cerivastatin vs. placebo)
Isis Pharmaceuticals Inc. A randomized, double-blind, placebo-controlled phase 3 study of ISIS 304801 administered subcutaneously to patients with hypertriglyceridemia. EUCTR2014-003434-93. In: PharmNet.Bund [Internet]. Cologne: German Institute of Medical Documentation and Information (DIMDI). 2014 [accessed 19.3.15]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2014-003434-93.	Not relevant population (mixed statin history; separate data and numbers of participants NR)
Ito MK. Dyslipidemia: management using optimal lipid-lowering therapy. Ann Pharmacother 2012;46(10):1368-81.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Itoh M, Kato T, Sawai Y, Inagaki K, Kanayama H, Katada N. Comparison of efficacy of pitavastatin and colestimide in Japanese patients with diabetes mellitus complicated by hyperlipidaemia and metabolic syndrome. Presented at 45th EASD Annual Meeting of the European Association for the Study of Diabetes; 30 Sept - 2 Oct 2009; Vienna: Austria. Diabetologia 2009;52(S1):S491-492.	Not relevant population
Izawa A, Kashima Y, Miura T, Ebisawa S, Kitabayashi H, Yamamoto H, et al. Assessment of lipophilic vs. hydrophilic statin therapy in acute myocardial infarction - ALPS-AMI study. Circ J. 2015;79(1):161-8.	Not relevant population (statin history unclear)
Jiang Z, Gong RR, Qiu L, Wang Q, Su M, Liu XJ, Hu MS, Lin J, Fang DZ. Efficacy and safety of pitavastatin versus simvastatin: a meta-analysis of randomized controlled trials. Clin Drug Investig 2014;34(9):599-608.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking

Publication citation	Reason(s) for exclusion
Jones PH, Bays H, Chaudhari U, Pordy R, Lorenzato C, Miller K, et al. Pooled safety and adverse events in nine randomized, placebo-controlled, phase 2 and 3 clinical trials of alirocumab (914-08). Abstract presented at American College of Cardiology (ACC); 14-16 March 2015; San Diego, US. [Internet]. 2015 [accessed 30.4.15]; Available from: http://www.abstractsonline.com/pp8/#!/3658/presentation/28389.	Not relevant study design (Pooled data)
Jones PH, Cusi K, Davidson MH, Kelly MT, Setze CM, Thakker K, et al. Efficacy and safety of fenofibric acid co-administered with low- or moderate-dose statin in patients with mixed dyslipidemia and type 2 diabetes mellitus: results of a pooled subgroup analysis from three randomized, controlled, double-blind trials. Am J Cardiovasc Drugs 2010;10(2):73-84.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Jones PH, Davidson MH, Goldberg AC, Pepine CJ, Kelly MT, Buttler SM, et al. Efficacy and safety of fenofibric acid in combination with a statin in patients with mixed dyslipidemia: pooled analysis of three phase 3, 12-week randomized, controlled studies. J Clin Lipidol 2009;3(2):125-137.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Jones PH, Hunninghake DB, Ferdinand KC, Stein EA, Gold A, Caplan RJ. Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin Study Group. Effects of rosuvastatin versus atorvastatin, simvastatin, and pravastatin on non-high-density lipoprotein cholesterol, apolipoproteins, and lipid ratios in patients with hypercholesterolemia: additional results from the STELLAR trial. Clin Ther 2004;26(9):1388-99.	Not relevant population (mixed)
Jover E, Aranda JL, Nogués X, Palacio A, Rubiés-Prat J. [Multicenter comparative study on safety, tolerance, and effectiveness of lovastatin combined or not with cholestyramine, and gemfibrozil combined or not with cholestyramine in the treatment of primary hypercholesterolemia]. Med Clin 1996;106(20):776-9.	Not relevant population (mixed)
Jukema JW, Liem AH, Dunselman PHJM, Van Der Sloot JAP, Lok DJA, Zwinderman AH. LDL-C/HDL-C ratio in subjects with cardiovascular disease and a low HDL-C: results of the RADAR (Rosuvastatin and Atorvastatin in different Dosages and Reverse cholesterol transport) study. Curr Med Res Opin 2005;21(11):1865-1874.	Not relevant population
Kadikoylu G, Yukselen V, Yavasoglu I, Bolaman Z. Hemostatic effects of atorvastatin versus simvastatin. Ann Pharmacother 2003;37(4):478-84.	Not relevant population
Kang S, Liu Y, Liu XB. Effects of aggressive statin therapy on patients with coronary saphenous vein bypass grafts: a systematic review and meta-analysis of randomized, controlled trials. Clin Ther 2013;35(8):1125-1136.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Karalis I, Bergheanu SC, Van Tol A, Dallinga-Thie GM, Liem AH, Jukema JW. Effect of increasing doses of rosuvastatin and atorvastatin on apolipoproteins, enzymes involved in lipoprotein metabolism and inflammatory parameters. Presented at European Society of Cardiology, ESC Congress; 28 Aug - 1 Sept 2010; Stockholm: Sweden. Eur Heart J 2010;31:104-105.	Not relevant population
Karlson BW, Barter PJ, Lundman P, Palmer M, Nicholls SJ. Impact of increasing statin dose on the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio: results from VOYAGER. Presented at 15th Svenska Kardiovaskulara Varmotet; 17-19 Apr 2013; Goteborg: Sweden. Scand Cardiovasc J 2013;47:38.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Karlson BW, Palmer MK, Nicholls SJ, Lundman P, Barter PJ. Doses of rosuvastatin, atorvastatin and simvastatin inducing an equipotent effect on LDL-C: results from the voyager meta-analysis. Atherosclerosis 2014;235(2):e35.	Not relevant population (statin history unclear); not relevant study design (IPD from VOYAGER database)
Karlson BW, Palmer MK, Nicholls SJ, Lundman P, Barter PJ. Doses of rosuvastatin, atorvastatin and simvastatin inducing an equipotent effect on LDL-C: results from the voyager meta-analysis. Atherosclerosis. 2014;235(2):e35.	Not relevant study design (Meta-analysis of IPD data)
Karlson BW, Palmer MK, Nicholls SJ, Lundman P, Barter PJ. Impact of statin therapy on low-density lipoprotein cholesterol and triglyceride levels in patients with hypertriglyceridaemia: a VOYAGER meta-analysis. Eur Heart J. 2014;35:217.	Not relevant study design (Meta-analysis of IPD data)
Karlson BW, Toth PP, Palmer MK, Barter PJ, Nicholls SJ. Achievement of combined goals of low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol with three different statins: results from VOYAGER. IJC Metabolic and Endocrine. 2014;5:61-6.	Not relevant study design (Meta-analysis of IPD data)

Publication citation	Reason(s) for exclusion
Kastelein JJ, Kereiakes DJ, Cannon CP, Bays HE, Minini P, Lee LV, et al. Additional LDL-C Reduction Achieved With Alirocumab Dose Increase on Background Statin. Circulation. 2015 November 10, 2015;132(Suppl 3):A17099.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
Kastelein JJP. Efficacy and safety of the PCSK9 monoclonal antibody alirocumab vs placebo in 1254 patients with heterozygous familial hypercholesterolaemia (HeFH): analyses up to 78 weeks from four ODYSSEY trials. Presented at ESC Congress 2015; 29 Aug-2 Sep 2015; London: United Kingdom. 2015.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
Kato T, Inagaki K, Sawai Y, Kanayama H, Katada N, Itoh M. Comparison of efficacy of pitavastatin and colestimide in Japanese patients with diabetes mellitus complicated by hyperlipidemia and metabolic syndrome. Experimental & Clinical Endocrinology & Diabetes 2011;119(9):554-8.	Not relevant population; not relevant intervention/comparator
Keene D, Price C, Shun-Shin MJ, Francis DP. Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117,411 patients. Br Med J 2014;349:g4379.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
Khera AV, Patel PJ, Reilly MP, Rader DJ. The addition of niacin to statin therapy improves high-density lipoprotein cholesterol levels but not metrics of functionality. Presented at 62nd Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC; 9-11 Mar 2013; San Francisco: United States. J Am Coll Cardiol 2013;61(10 suppl 1):E1390.	Not relevant population
Kipnes MS, Roth EM, Rhyne JM, Setze CM, Lele A, Kelly MT, et al. Year two assessment of fenofibric acid and moderate-dose statin combination: a phase 3, open-label, extension study. Clin Drug Investig 2010;30(1):51-61.	Not relevant trial design; not relevant comparator
Knopp RH, Brown WV, Dujovne CA, Farquhar JW, Feldman EB, Goldberg AC, et al. Effects of fenofibrate on plasma lipoproteins in hypercholesterolemia and combined hyperlipidemia. Am J Med 1987;83(5B):50-9.	Not relevant population
Knopp RH, Gitter H, Truitt T, Bays H, Manion CV, Lipka LJ, et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. Eur Heart J 2003;24(8):729-741.	Not relevant population (mixed)
Koren M, Giugliano RP, Raal F, Sullivan D, Bolognese M, Langslet G, et al. Safety, tolerability, and efficacy of long-term administration of AMG 145: preliminary results from the OSLER study. Presented at European Society of Cardiology, ESC Congress; 31 Aug - 4 Sept 2013; Amsterdam: Netherlands. Eur Heart J 2013;34:767.	Not relevant population; mixed refractory and naive population with no separate results or indication of numbers in each category at baseline
Koren M, Rosenson R, Khan B, Honarpour N, Elliot M, Somaratne R, et al. LDL cholesterol reduction in elderly patients with the PCSK9 monoclonal antibody evolocumab (AMG 145): a pooled analysis of 1779 patients in phase 2, 3 and open label extension studies (1107-101). Abstract presented at American College of Cardiology (ACC); 14-16 March 2015; San Diego, US. [Internet]. 2015 [accessed 30.4.15]; Available from: http://www.abstractsonline.com/pp8/#!/3658/presentation/33653.	Not relevant study design (Pooled data)
Koren M, Stein E, Roth E, McKenney JM, Gipe D, Hanotin C, et al. Efficacy, safety and tolerability of 150 mg Q2W dose of the anti-PCSK9 mAb, REGN727/SAR236553: data from 3 phase 2 studies. Presented at ESC Congress; 25-29 Aug 2012; Munich: Germany. Eur Heart J 2012;33:37.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Koren M, Stein E, Roth E, McKenney JM, Gipe D, Hanotin C, et al. Efficacy, safety and tolerability of 150 mg Q2W dose of the anti-PCSK9 mAb, REGN727/SAR236553: data from 3 phase 2 studies. Eur Heart J. 2012;33:37.	Not relevant study design (pooled analysis)
Koren MJ, Giugliano RP, Raal F, Sullivan D, Bolognese M, Langslet G, et al. Safety, tolerability, and efficacy of long-term administration of AMG 145: preliminary results from the osler study. Presented at 66th Annual Meeting of the Canadian Cardiovascular Society; 17-20 Oct 2013; Montreal, QC: Canada. Can J Cardiol 2013;29(10 suppl 1):S332.	Not relevant population; mixed refractory and naive population with no separate results or indication of numbers in each category at baseline

Publication citation	Reason(s) for exclusion
Koren MJ, Giugliano RP, Raal F, Sullivan D, Bolognese M, Langslet G, et al. Randomized comparison of the safety, tolerability, and efficacy of long-term administration of AMG 145 versus standard of care in 1104 patients: 52-week results from the OSLER study. Presented at American Heart Association's Scientific Sessions; 16-20 Nov 2013; Dallas, TX: United States. Circulation 2013;128(24):2717-2718.	Not relevant population; mixed refractory and naive population with no separate results or indication of numbers in each category at baseline
Koren MJ, Giugliano RP, Raal FJ, Sullivan D, Bolognese M, Langslet G, et al. Efficacy and safety of longer-term administration of evolocumab (AMG 145) in patients with hypercholesterolemia: 52-week results from the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) randomized trial. Circulation 2014;129(2):234-43.	Not relevant population; mixed refractory and naive population with no separate results or indication of numbers in each category at baseline
Koren MJ, Giugliano RP, Raal FJ, Sullivan D, Bolognese M, Langslet G, et al. Efficacy and safety of longer-term administration of evolocumab (AMG 145) in patients with hypercholesterolemia: 52-week results from the open-label study of long-term evaluation against LDL-C (OSLER) randomized trial. Circulation. 2014 January 14, 2014;129(2):234-43.	Not relevant population (mixed populations from other Amgen trials)
Koren MJ, Guigliano R, Raal F, Sullivan D, Bolognese M, Langslet G, et al. Two year analysis of the safety and tolerability of evolocumab: the OSLER-1 Study (914-10). Abstract presented at American College of Cardiology (ACC); 14-16 March 2015; San Diego, US. [Internet]. 2015 [accessed 30.4.15]; Available from: http://www.abstractsonline.com/pp8/#!/3658/presentation/36653.	Not relevant population (mixed populations from other Amgen trials)
Koren MJ, Lundqvist P, Bolognese M, Neutel JM, Monsalvo ML, Yang J, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol. 2014;63(23):2531-40.	Not relevant population (not receiving statins)
Koren MJ, Scott R, Kim JB, Knusel B, Liu T, Lei L, et al. Efficacy and safety of a fully human monoclonal antibody against PCSK9 as monotherapy for hypercholesterolemia: results from the MENDEL study, a global phase 2 trial of AMG 145. Circulation. 2012;126(23):2791.	Not relevant population (not receiving statins)
Koren MJ, Stein E, Roth E, McKenney J, Gipe D, Hanotin C, et al. Efficacy, safety and tolerability of alirocumab 150 mg q2w, a fully human pcsk9 monoclonal antibody: a pooled analysis of 352 patients from phase 2. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 30 May - 2 Jun 2013; Las Vegas, NV: United States. J Clin Lipidol 2013;7(3):279-280.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Koren MJ, Doshi S, Castro R, Gibbs JP, Emery MG, Somaratne R, et al. Comparisons of Peak LDL-C Reduction and Duration of Effect With Lower or Higher Dosing Regimens of the PCSK9 Inhibitor Evolocumab. Circulation. 2015 November 10, 2015;132(Suppl 3):A12729.	No relevant outcomes
Koshelskaya O, Sushkova A, Suslova T, Karpov R. Lipid and pleotropic effects of atorvastatin therapy and its combination with ezetimibe in patients with coronary artery disease and diabetes. Atherosclerosis 2014;235(2):e257.	Not relevant population (statin history unclear)
Kowa Research Europe Ltd. Double-blind follow-on study of pitavastatin (4 mg) versus simvastatin (40 mg and 80 mg), with a single-blind extension of treatment, in patients with primary hypercholesterolemia or combined dyslipidemia and 2 or more risk factors for coronary heart disease. EUCTR2005-005981-35-GB. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2006 [accessed 2.6.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2005-005981-35	Not relevant trial design (extension of excluded study)
Kowa Research Europe Ltd. Open-label, long-term (=1 year) extension study of pitavastatin 2 mg and 4 mg qd in elderly patients with primary hypercholesterolemia or combined dyslipidemia. EUCTR2005-005980-27-GB. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2006 [accessed 2.6.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2005-005980-27	Not relevant population; not relevant trial design (follow-up to excluded trial)

Publication citation	Reason(s) for exclusion
Krempf M, Bergeron J, Elassal J, Minini P, Miller K, Kastelein JJP. Efficacy of alirocumab according to background statin intensity and other lipid-lowering therapy in heterozygous familial hypercholesterolemia or high cv risk populations: phase 3 sub-group analyses. Atherosclerosis 2015;241(1):e21.	Not relevant study design (subgroup analysis using data from six pooled alirocumab trials)
Kumamoto University. Comparison of pitavastatin with atorvastatin in increasing high density lipoprotein - cholesterol (HDL-C) and adiponectin in patients with dyslipidemia and coronary artery disease (CAD). NCT00861861. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2009 [accessed 16.4.15] [updated September 2008]; Available from: http://clinicaltrials.gov/show/NCT00861861.	Not relevant population (statin status unclear)
Kurogi K, Sugiyama S, Sakamoto K, Tayama S, Nakamura S, Biwa T, Matsui K, Ogawa H, Investigators C-C. Comparison of pitavastatin with atorvastatin in increasing HDL-cholesterol and adiponectin in patients with dyslipidemia and coronary artery disease: the COMPACT-CAD study. J Cardiol 2013;62(2):87-94.	Not relevant population (mixed population 62% had not previously received statin)
Laboratoires Merck Sharp & Dohme. A multicenter, randomized, double-blind, placebo-controlled, 12-week study to evaluate the efficacy and safety of extended release (ER) niacin/laropiprant when added to ongoing lipid-modifying therapy in dyslipidemic patients. EUCTR2008-000465-37-FR. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2008 [accessed 2.6.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-000465-37	Not relevant population; not relevant trial design (withdrawn prior to recruitment)
Lecerf JM, Luc G, Baigts F, Devulder B. [Comparison of the efficacy between simvastatin and gemfibrozil in primary hypercholesterolemia]. Rev Med Interne 1993;14(4):269-74.	Not relevant population (mixed)
Lee J-H, Kang H-J, Kim H-S, Sohn D-W, Oh B-H, Park Y-B. Effects of ezetimibe/simvastatin 10/20 mg vs. atorvastatin 20 mg on apolipoprotein B/apolipoprotein A1 in Korean patients with type 2 diabetes mellitus: results of a randomized controlled trial. Am J Cardiovasc Drugs 2013;13(5):343-51.	Not relevant population
Leiter LA, Bays H, Conard S, Lin J, Hanson ME, Shah A, et al. Attainment of Canadian and European guidelines' lipid targets with atorvastatin plus ezetimibe vs. doubling the dose of atorvastatin. Int J Clin Pract 2010;64(13):1765-72.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Leiter LA, Betteridge DJ, Farnier M, Guyton JR, Lin J, Shah A, et al. Lipid-altering efficacy and safety profile of combination therapy with ezetimibe/statin vs. statin monotherapy in patients with and without diabetes: an analysis of pooled data from 27 clinical trials. Diabetes, Obesity & Metabolism 2011;13(7):615-28.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Li C, Zhang W, Zhou F, Chen C, Zhou L, Li Y, et al. Cholesteryl ester transfer protein inhibitors in the treatment of dyslipidemia: a systematic review and meta-analysis. PLoS One 2013;8(10).	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Li C, Lin L, Zhang W, Zhou L, Wang H, Luo X, et al. Efficiency and safety of proprotein convertase subtilisin/kexin 9 monoclonal antibody on hypercholesterolemia: a meta-analysis of 20 randomized controlled trials. J Am Heart Assoc. 2015 Jun;4(6):e001937.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Li N, Li Q, Tian X-Q, Qian H-Y, Yang Y-J. Mipomersen is a promising therapy in the management of hypercholesterolemia: a meta-analysis of randomized controlled trials. Am J Cardiovasc Drugs 2014;14(5):367-76.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
Liang L, Qiqn JL, Xue HY, Lin P, Yang L. [Treatment with atorvastatin for unstable angina: a systematic review]. Chinese Pharmacological Bulletin 2012;28(11):1500-1507.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Lipinski MJ, Benedetto U, Escarcega RO, Biondi-Zoccai G, Lhermusier T, Baker NC, et al. The impact of proprotein convertase subtilisin-kexin type 9 serine protease inhibitors on lipid levels and outcomes in patients with primary hypercholesterolaemia: a network meta-analysis. Eur Heart J 2016 Feb 7;37(6):536-45.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking

Publication citation	Reason(s) for exclusion
Lipinski MJ, Escarcega RO, Lhermusier T, Baker NC, Torguson R, Brewer HB, et al. The Impact of PCSK9 Inhibitors on Lipid Levels and Outcomes in Patients With Primary Hypercholesterolemia: A Network Meta-analysis. Circulation. 2015 November 10, 2015;132(Suppl 3):A19342.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Loomba RS, Arora R. Prevention of cardiovascular disease utilizing fibrates: a pooled meta-analysis. Am J Ther 2010;17(6):e182-8.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Lundman P, Nicholls SJ, Brandrup-Wognsen G, Palmer M, Barter PJ. Does gender impact on statin dose response? results from the VOYAGER individual patient data meta-analysis. Presented at 78th EAS Congress; 20-23 Jun 2010; Hamburg: Germany. Atheroscler Suppl 2010;11(2):75.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Mamata Medical College. A comparison of two drugs used in patients with high cholesterol levels. CTRI/2014/11/005169. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2014 [accessed 16.4.15] [updated 15-01-2013]; Available from: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=5897.	Not relevant population (statin status unclear)
Martineau P, Gaw A, de Teresa E, Farsang C, Gensini GF, Leiter LA, et al. Effect of individualizing starting doses of a statin according to baseline LDL-cholesterol levels on achieving cholesterol targets: the achieve cholesterol targets fast with atorvastatin stratified titration (ACTFAST) study. Atherosclerosis 2007;191(1):135-46.	Not relevant trial design
Martinez-Abundis E, Barrera-Duran C, Gonzalez-Ortiz M, Hernandez-Salazar E. Effect of simvastatin plus inulin vs. Simvastatin plus ezetimibe in mixed dyslipidemia. Presented at 70th Scientific Sessions of the American Diabetes Association; 25-29 Jun 2010; Florida: United States. Diabetes 2010.	Not relevant population (mixed statin history and no separate results; dyslipidemic population)
Matalka MS, Ravnan MC, Deedwania PC. Is alternate daily dose of atorvastatin effective in treating patients with hyperlipidemia? The Alternate Day Versus Daily Dosing of Atorvastatin Study (ADDAS). Am Heart J 2002;144(4):674-7.	Not relevant population; compares daily vs. every other day treatment schedules
McCormack T, Harvey P, Gaunt R, Allgar V, Chipperfield R, Robinson P. Incremental cholesterol reduction with ezetimibe/simvastatin, atorvastatin and rosuvastatin in UK General Practice (IN-PRACTICE): randomised controlled trial of achievement of Joint British Societies (JBS-2) cholesterol targets. Int J Clin Pract 2010;64(8):1052-1061.	Not relevant trial design (6wk treatment period)
McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. J Pediatr 2003;143(1):74-80.	Not relevant population
McDonagh M, Peterson K, Holzhammer B, Fazio S. A Systematic Review of PCSK9 Inhibitors Alirocumab and Evolocumab. J Manag Care Spec Pharm 2016 Jun;22(6):641-53q.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
McGowan M, Parhofer K. Evaluation of mipomersen, an ApoB synthesis inhibitor, for potential to control LDL-C in patients with severe heterozygous familial hypercholesterolemia who may be eligible for apheresis. Presented at ESC Congress; 25-29 Aug 2012; Munich: Germany. Eur Heart J 2012;33:1076.	Not relevant population - mipomersen trial not in HoFH
McGowan MP, Tardif J-C, Ceska R, Burgess LJ, Soran H, Gouni-Berthold I, et al. Randomized, placebo-controlled trial of mipomersen in patients with severe hypercholesterolemia receiving maximally tolerated lipid-lowering therapy. PLoS One 2012;7(11):e49006.	Not relevant population - mipomersen trial not in HoFH
Mearns BM. Dyslipidaemia: 1-Year results from OSLER trial of anti-PCSK9 monoclonal antibody evolocumab. Nat Rev Cardiol 2014;11(2):63.	Not relevant population; mixed refractory and naive population with no separate results or indication of numbers in each category at baseline
Melani L, Mills R, Hassman D, Lipetz R, Lipka L, LeBeaut A, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: A prospective, randomized, double-blind trial. Eur Heart J 2003;24(8):717-728.	Not relevant population (mixed)

Publication citation	Reason(s) for exclusion
Merck & Co Inc. A multicenter, randomized, double-blind, parallel arm, 12-week trial to evaluate the efficacy and safety of ezetimibe/simvastatin combination tablet versus atorvastatin in elderly patients with hypercholesterolemia at moderately high risk and high risk for CHD. EUCTR2007-004448-60-LT. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2007 [accessed 2.6.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-004448-60	Not relevant population (therapy naïve)
Merck Sharp & Dohme Corp, P. T. Schering-Plough Tbk Indonesia. Adding ezetimibe tablet to ongoing treatment with atorvastatin in subjects with high cholesterol and multiple coronary heart disease risk factors (Study P04060)(completed). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). NCT00319449. . 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00319449	Not relevant trial design (6wk treatment period)
Merck Sharp & Dohme Corp. A 12 week study of MK0653A in patients who have been hospitalized for a possible heart problem (0653A-808)(completed). NCT00132717. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00132717	Not relevant comparator (mixed statin treatment history with no separate data)
Merck Sharp & Dohme Corp. A worldwide, multicenter, double-blind, randomized, placebo-controlled, 12-week study to assess the efficacy and tolerability of anacetrapib when added to ongoing lipid-lowering therapy in adult patients with homozygous familial hypercholesterolemia (HoFH). EUCTR2012-002434-37-GB. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2012 [accessed 11.7.14] [updated 23/05/2013]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-002434-37.	Not relevant outcome (early termination)
Merck Sharp Dohme Corp, Merck Shering-Plough, J. V. Study. A study to assess the cholesterol lowering effect of ezetimibe/simvastatin combination tablet compared to another cholesterol lowering drug in elderly patients with high cholesterol at high or moderately high risk for coronary heart disease (0653A-128). NCT00535405. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT00535405.	Not relevant population (statin status unclear)
Merck Sharp Dohme Corp, Schering Plough. Ezetimibe and simvastatin in primary hypercholesterolemia, diabetes mellitus Type 2, and coronary heart disease (completed). NCT00423488. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00423488	Not relevant trial design (6wk treatment period)
Merck Sharp Dohme Corp. A study comparing ezetimibe plus simvastatin versus simvastatin alone in patients at risk for heart disease (0653-023). NCT00551447. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2007 [accessed 16.4.15] [updated January 2002]; Available from: http://clinicaltrials.gov/show/NCT00551447.	Not relevant population (statin status unclear)
Merck Sharp Dohme Corp. A study of ezetimibe added on to rosuvastatin versus up titration of rosuvastatin in patients with hypercholesterolemia (MK0653-139). NCT00783263. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00783263	Not relevant trial design (6wk treatment period)
Merck Sharp Dohme Corp. A study of MK0653A (ezetimibe (+) simvastatin) in patients with hypercholesterolemia (0653A-038). NCT00092651. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2004 [accessed 16.4.15] [updated September 2002]; Available from: http://clinicaltrials.gov/show/NCT00092651.	Not relevant population (statin status unclear)
Merck Sharp Dohme Corp. A study of MK0653A (ezetimibe (+) simvastatin) in patients with hypercholesterolemia (0653A-038). NCT00092651. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT00092651.	Not relevant population (statin status unclear); Not relevant outcomes
Merck Sharp Dohme Corp. A study of MK0859 in patients with primary hypercholesterolemia or mixed hyperlipidemia. NCT00565292. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2007 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00565292	Not relevant population

Publication citation	Reason(s) for exclusion
Merck Sharp Dohme Corp. A study to assess the cholesterol lowering effect of an ezetimibe/simvastatin combination tablet compared to another cholesterol lowering drug in patients with high cholesterol and with high cardiovascular risk (0653A-809)(completed). NCT00479713. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00479713	Not relevant trial design (6wk treatment period)
Merck Sharp Dohme Corp. A study to evaluate an investigational drug in patients with mixed hyperlipidemia (0653A-071). NCT00093899. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2004 [accessed 19.3.15] [updated November 2004]; Available from: http://clinicaltrials.gov/show/NCT00093899.	Not relevant population (statin status unclear)
Merck Sharp Dohme Corp. A study to evaluate an investigational drug in patients with mixed hyperlipidemia (0653A-071). NCT00093899. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT00093899.	Not relevant population (statin status unclear); Not relevant outcomes
Merck Sharp Dohme Corp. A study to evaluate ezetimibe in Korean patients with primary hypercholesterolemia (0653-042). NCT00157911. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2005 [accessed 19.3.15] [updated December 2002]; Available from: http://clinicaltrials.gov/show/NCT00157911.	Not relevant population (statin status unclear)
Merck Sharp Dohme Corp. A study to evaluate ezetimibe in Korean patients with primary hypercholesterolemia (0653-042). NCT00157911. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT00157911.	Not relevant population (statin status unclear)
Merck Sharp Dohme Corp. A worldwide, multicenter, double-blind, randomized, parallel, placebo-controlled study to evaluate the long-term efficacy, safety and tolerability of extended-release (ER) niacin and laropiprant (ERN/LRPT) in patients with dyslipidemia. EUCTR2009-012772-27. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2009 [accessed 2.6.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-012772-27	Not relevant outcome (flushing AEs with statins)
Merck Sharp Dohme Corp. An extension study of an investigational drug in patients with hypercholesterolemia (0653A-038). NCT00092664. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2004 [accessed 16.4.15] [updated January 2003]; Available from: http://clinicaltrials.gov/show/NCT00092664.	Not relevant population (statin status unclear)
Merck Sharp Dohme Corp. An extension study of an investigational drug in patients with hypercholesterolemia (0653A-038). NCT00092664. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT00092664.	Not relevant population (statin status unclear)
Merck Sharp Dohme Corp. An investigational drug study in patients with elevated cholesterol and coronary heart disease (0653-804)(completed). NCT00092638. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00092638	Not relevant trial design (6wk treatment period)
Merck Sharp Dohme Corp. Co-administration study in patients with elevated cholesterol and coronary heart disease (0653-802)(completed). NCT00092612. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00092612	Not relevant trial design (6wk treatment period)
Merck Sharp Dohme Corp. Effectiveness of two approved drugs in lowering high cholesterol (0733-224). NCT00092157. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT00092157.	Not relevant population (statin status unclear)
Merck Sharp Dohme Corp. Efficacy and safety of extended release (ER) niacin/laropiprant when added to ongoing lipid-modifying therapy in patients with high cholesterol or abnormal lipid levels (MK-0524A-133). NCT01274559. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT01274559.	Not relevant outcome (early termination)

Publication citation	Reason(s) for exclusion
Merck Sharp Dohme Corp. Efficacy and tolerability of anacetrapib added to ongoing lipid-lowering therapy in adult participants with homozygous familial hypercholesterolemia (HoFH) (MK-0859-042). NCT01841684. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 11.7.14]; Available from: http://ClinicalTrials.gov/show/NCT01841684.	Not relevant outcome (early termination)
Merck Sharp Dohme Corp. Ezetimibe (+) simvastatin vs. atorvastatin comparative study in DM or metabolic syndrome patients. NCT00157924. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2008 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00157924	Not relevant trial design (6wk treatment period)
Merck Sharp Dohme Corp. Ezetimibe/simvastatin (MK-0653A) versus rosuvastatin versus doubling statin dose in participants with cardiovascular disease and diabetes mellitus (MK-0653A-133)(completed). NCT00862251. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00862251	Not relevant trial design (6wk treatment period)
Merck Sharp Dohme Corp. IMPROVE-IT: examining outcomes in subjects with acute coronary syndrome: vytorin (ezetimibe/simvastatin) vs simvastatin (P04103 AM5). NCT00202878. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 11.7.14]; Available from: http://ClinicalTrials.gov/show/NCT00202878.	Not relevant population (mixed statin history, numbers and separate data NR)
Merck Sharp Dohme Corp. Investigational drug study in patients with elevated cholesterol and coronary heart disease (0653-801)(completed). NCT00092599. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00092599	Not relevant trial design (6wk treatment period)
Merck Sharp Dohme Corp. Lipid efficacy and safety in patients with mixed hyperlipidemia (MK-0524B-024). NCT00289900. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT00289900.	Not relevant population (statin status unclear)
Merck Sharp Dohme Corp. MK0524B lipid study (0524B-063). NCT00479882. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00479882	Not relevant population (mixed)
Merck Sharp Dohme Corp. MK0859 dose-ranging study (0859-003). NCT00325455. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT00325455.	Not relevant population (statin status unclear)
Merck Sharp Dohme Corp. Randomized parallel group trial of the efficacy and safety of ezetimibe with a statin versus statin dose doubling in patients with persistent primary hypercholesterolemia. NCT00652847. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2008 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00652847	Not relevant trial design (6wk treatment period)
Merck Sharp Dohme Corp. Study of an approved drug with a statin (a medication that lowers cholesterol levels) as compared to statin therapy alone in patients with high cholesterol (0653-040)(completed). NCT00092586. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00092586	Not relevant trial design (6wk treatment period)
Merck Sharp Dohme Corp. Study of ezetimibe and fenofibrate in patients with mixed hyperlipidemia (0653-036). NCT00092573. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2004 [accessed 16.4.15] [updated April 2003]; Available from: http://clinicaltrials.gov/show/NCT00092573.	Not relevant study design (Not RCT); Not relevant population (statin status unclear); Not relevant outcomes
Merck Sharp Dohme Corp. Study of ezetimibe and fenofibrate in patients with mixed hyperlipidemia (0653-036). NCT00092573. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT00092573.	Not relevant population (statin status unclear); Not relevant outcomes
Merck Sharp Dohme Corp. To evaluate ezetimibe plus atorvastatin versus atorvastatin in patients with high cholesterol not controlled on atorvastatin 20 mg (0653-079)(completed). NCT00276458. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00276458	Not relevant trial design (6wk treatment period)

Publication citation	Reason(s) for exclusion
Merck Sharp Dohme Corp. To Evaluate Ezetimibe Plus Atorvastatin Versus Atorvastatin in Patients With High Cholesterol Not Controlled on Atorvastatin 40 mg (0653-090)(completed). NCT00276484. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00276484	Not relevant trial design (6wk treatment period)
Merck Sharp Dohme Corp. To evaluate ezetimibe/simvastatin and niacin (extended release tablet) in patients with Type IIa or Type IIb hyperlipidemia (0653A-091)(COMPLETED). NCT00271817. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [27.10.14]. Available from: http://ClinicalTrials.gov/show/NCT00271817	Not relevant population (statin history unclear)
Merck Sharp Dohme Corp. TWICE (ezetimibe together with any statin cholesterol enhancement) (0653-060). NCT00328523. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT00328523.	Not relevant intervention/comparator
Merck Sharp Dohme Corp. Two investigational drugs in patients with mixed hyperlipidemia (0653-036). NCT00092560. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2004 [accessed 16.4.15].	Not relevant study design (Not RCT); Not relevant population (statin status unclear)
Merck Sharp Dohme Corp. Vytorin (10/20 Or 10/40) compared to atorvastatin (10 mg or 20 mg) in patients with coronary artery disease (0653A-126)(completed). NCT00442897. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00442897	Not relevant trial design (6wk treatment period)
Merck S, Dohme C. A Clinical Trial to Assess the Efficacy and Safety of MK-0653C in Japanese Participants With Hypercholesterolemia (MK-0653C-383). 2016; Available from: https://ClinicalTrials.gov/show/NCT02550288.	Not relevant population (statin status unclear and stabilized on diet)
Mikhailidis DP, Lawson RW, McCormick AL, Sibbring GC, Tershakovec AM, Davies GM, et al. Comparative efficacy of the addition of ezetimibe to statin vs statin titration in patients with hypercholesterolaemia: systematic review and meta-analysis. Curr Med Res Opin 2011;27(6):1191-1210.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Mikhailidis DP, Wierzbicki AS. The Greek atorvastatin and coronary-heart-disease evaluation (GREACE) study. Curr Med Res Opin 2002;18(4):215-219.	Not relevant population; not relevant trial design
Miller PE, Martin SS, Joshi PH, Jones SR, Massaro JM, D'Agostino RB, et al. Pitavastatin 4 mg Provides Significantly Greater Reduction in Remnant Lipoprotein Cholesterol Compared With Pravastatin 40 mg: Results from the Short-term Phase IV PREVAIL US Trial in Patients With Primary Hyperlipidemia or Mixed Dyslipidemia. Clin Ther. [Journal Article Research Support, Non-U.S. Gov't]. 2016 Mar;38(3):603-9.	Not relevant population (statin status unclear)
Milionis H, Barkas F, Ntaios G, Papavasileiou V, Vemmos K, Michel P, et al. Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors to treat hypercholesterolemia: Effect on stroke risk. Eur J Intern Med 2016 Jun 28;28:28.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Mita T, Nakayama S, Abe H, Gosho M, Iida H, Hirose T, et al. Comparison of effects of pitavastatin and atorvastatin on glucose metabolism in type 2 diabetic patients with hypercholesterolemia. Journal of Diabetes Investigation 2013;4(3):297-303.	Not relevant trial design (quasi randomized)
Moon KT. No added benefit of fenofibrate for cardiovascular risk in diabetes mellitus. Am Fam Physician 2011;83(5):612.	Not relevant trial design (secondary publication for ACCORD trial)
Morales DCV, Parker B, Lorson L, White CM, Polk D, Thompson P. Greater reductions in total and low density lipoprotein cholesterol are associated with concomitant development of statin myopathy. Presented at 60th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC; 2-5 Apr 2011; New Orleans, LA: United States. J Am Coll Cardiol 2011;57(14 suppl 1):E574.	Not relevant population; not relevant comparator - assessing incidence of statin myopathy in statin intolerant (previous statin-associated muscle complaints) randomized to 20mg simvastatin vs. placebo

Publication citation	Reason(s) for exclusion
Moriarty P, Lecorps G, Hanotin C, Pordy R, Roth EM. Homogeneity of treatment effect of REGN727/SAR236553, a fully human monoclonal antibody against PCSK9, in lowering LDL-C: data from three phase 2 studies. European Society of Cardiology, ESC Congress; 31 Aug - 4 Sept 2013; Amsterdam: Netherlands. Eur Heart J 2013;34:18.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Morrone D, Weintraub W, Toth P, Hanson M, Lowe R, Lin J, et al. Efficacy of ezetimibe/statins and statin monotherapy and factors associated with treatment response: pooled analysis of >21,000 subjects from 27 trials. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 19-22 May 2011; New York, NY: United States. J Clin Lipidol 2011;5(3):236-237.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Naci H, Brugts JJ, Fleurence R, Ades AE. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. Eur J Prev Cardiolog 2013;20(4):658-670.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
National Heart Institute Mexico. Effect of fenofibrate on endothelial function and high-density lipoproteins (HDL) in patients with coronary heart disease. NCT00552747. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2011 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00552747	Not relevant outcomes; not relevant trial design (8wks treatment period)
National Institute for Health and Clinical Excellence. Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolemia [Internet]. London, 2007 [accessed 30.5.14] Available from: http://www.nice.org.uk/nicemedia/live/11886/38799/38799.pdf	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
NCT02293538. FID# 114657 in Contact Lens Wearers. 2014.	Not relevant population (statin status unclear); Not relevant outcomes; Not relevant intervention; Not relevant comparators
NCT02458287. Efficacy, Safety, Tolerability And Actual Use Study Of Bococizumab And An Autoinjector (Pre-Filled Pen) In Subjects With Hyperlipidemia Or Dyslipidemia. 2015.	Not relevant study design (10wk treatment period)
Newman TJ, Kassler-Taub KB, Gelarden RT, Korzin EG, DeVault AR, McGovern ME, et al. Safety of pravastatin in long-term clinical trials conducted in the United States. Journal of Drug Development, Supplement 1990;3(1):275-281.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Nicholls SJ, Lundman P, Brandrup-Wognsen G, Palmer M, Barter PJ. Effects of age and statin dose on lipid levels: results from the VOYAGER individual patient data meta-analysis. Presented at 78th EAS Congress; 20-23 Jun 2010; Hamburg: Germany. Atheroscler Suppl 2010;11(2):119-120.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Nicholls SJ, Ruotolo G, Brewer HB, Wang MD, Liu L, Willey MB, et al. Evacetrapib alone or in combination with statins lowers lipoprotein(a) and total and small LDL particle concentrations in mildly hypercholesterolemic patients. J Clin Lipidol. 2016 May-Jun;10(3):519-27.e4.	Not relevant population (statin status unclear and patients selected on low HDL as well as high LDL-C)
NIHR Horizon Scanning Centre. SAR236553/REGN727 for the reduction of elevated total cholesterol and low density lipoprotein cholesterol [Internet], 2012 [accessed 6.6.14] Available from: http://www.hsc.nihr.ac.uk/topics/sar236553-regn727-for-the-reduction-of-elevated-to/	Not relevant trial design
Nissen SE, Nicholls SJ, Wolski K, Howey DC, McErlean E, Wang MD, et al. Effects of a potent and selective PPAR-alpha agonist in patients with atherogenic dyslipidemia or hypercholesterolemia: two randomized controlled trials. JAMA 2007;297(12):1362-1373.	Not relevant trial design
Novartis Pharma Services A. G. A phase 2 12-week multi-center, randomized, double-blind, placebo-controlled, parallel-group adaptive design study to evaluate the safety and efficacy of LCQ908 for weight reduction and reduced LDL cholesterol in patients with obesity and mixed dyslipidemia. EUCTR2009-010198-19. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2009 [accessed 2.6.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-010198-19	Not relevant population (mixed); not relevant comparator (weight reduction)

Publication citation	Reason(s) for exclusion
O'Brien RC, Simons LA, Clifton P, Cooper ME, Jennings GL, Jerums G, et al. Comparison of simvastatin and cholestyramine in the treatment of primary hypercholesterolaemia.[Erratum appears in Med J Aust 1991 Feb 18;154(4):296]. Med J Aust 1990;152(9):480-3.	Not relevant population
Ogawa H, Matsui K, Saito Y, Sugiyama S, Jinnouchi H, Sugawara M, et al. Differences between rosuvastatin and atorvastatin in lipid-lowering action and effect on glucose metabolism in Japanese hypercholesterolemic patients with concurrent diabetes - lipid-lowering with highly potent statins in hyperlipidemia with type 2 diabetes patients (LISTEN) study. Circ J. 2014;78(10):2512-5.	Not relevant population (not receiving statins)
Oida K, Taniguchi N, Kono M, Kutsumi Y. Direct comparison of hypolipidemic effects of pitavastatin and atorvastatin. Ther Res 2007;28(4):733-9.	Not relevant trial design (no mention of randomization)
Oikawa S, Yamashita S, Nakaya N, Sasaki J, Kono S, Effect of F, et al. Efficacy and Safety of Long-term Coadministration of Fenofibrate and Ezetimibe in Patients with Combined Hyperlipidemia: Results of the EFECTL Study. Journal of Atherosclerosis & Thrombosis 2016; Jul 8;8:8.	Not relevant population (statin status unclear)
Olsson AG, Eriksson M, Johnson O, Kjellström T, Lanke J, Larsen ML, et al. A 52-week, multicenter, randomized, parallel-group, double-blind, double-dummy study to assess the efficacy of atorvastatin and simvastatin in reaching low-density lipoprotein cholesterol and triglyceride targets: the treat-to-target (3T) study. Clin Ther 2003;25(1):119-38.	Not relevant population (statin naive)
Paez Moreno JP, Gonzalez G. Comparative study of bezafibrate and probucol in hyperlipidaemia. Curr Med Res Opin 1989;11(8):523-32.	Not relevant population
Panta R, Dahal K. Efficacy and safety of mipomersen in treatment of dyslipidemia: A meta-analysis of randomized controlled trials. Endocr Rev. 2014.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
Pasternak RC, Brown LE, Stone PH, Silverman DI, Gibson CM, Sacks FM. Effect of combination therapy with lipid-reducing drugs in patients with coronary heart disease and "normal" cholesterol levels. A randomized, placebo-controlled trial. Harvard Atherosclerosis Reversibility Project (HARP) Study Group. Ann Intern Med 1996;125(7):529-40.	Not relevant population
Patel N, Hegele RA. Mipomersen as a potential adjunctive therapy for hypercholesterolemia. Expert Opin Pharmacother 2010;11(15):2569-72.	Not relevant trial design (not an original report of trial)
Patel P, Barkate H. Comparison of efficacy and safety of choline fenofibrate (fenofibric acid) to micronized fenofibrate in patients of mixed dyslipidemia: A randomized, open-label, multicenter clinical trial in Indian population. Indian J Endocrinol Metab 2016 Jan-Feb;20(1):67-71.	Not relevant population (statin status unclear and mixed dyslipidemia with patients selected on basis of TG 150 to 500 mg/dL)
Pearson TA, Denke M, McBride P, Battisti WP, Brady WE, Palmisano J. Effectiveness of the addition of ezetimibe to ongoing statin therapy in modifying lipid profiles and attaining low-density lipoprotein cholesterol goals in older and elderly patients: subanalyses of data from a randomized, double-blind, placebo-controlled trial. Am J Geriatr Pharmacother 2005;3(4):218-228.	Not relevant trial design (6wk treatment period)
Pedersen TR, Faergeman O, Kastelein JJP, Olsson AG, Tikkanen MJ, Holme I, et al. Design and baseline characteristics of the Incremental Decrease in End Points through Aggressive Lipid Lowering study. Am J Cardiol 2004;94(6):720-724.	Not relevant population
Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WMM, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur J Prev Cardiolog 2012;19(4):585-667.	Not relevant trial design (guidelines/guidance)
Philpott AC, Hubacek J, Sun YC, Hillard D, Anderson TJ. Niacin improves lipid profile but not endothelial function in patients with coronary artery disease on high dose statin therapy. Atherosclerosis 2013;226(2):453-458.	Not relevant population

Publication citation	Reason(s) for exclusion
Pordy R, Lecorps G, Bessac L, Sasiela WJ, Ginsberg H. Alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9: therapeutic dosing in phase 3 studies. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 30 May - 2 Jun 2013; Las Vegas, NV: United States. J Clin Lipidol 2013;7(3):279.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Positive Trial Group. Primary prevention of major adverse cardiac events (MACE) with standard and intensive statin treatment in patients with diabetes: survival and cardiovascular event assessments. NCT01173939. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2011 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT01173939	Not relevant population; not relevant comparator
Preiss D, Seshasai SRK, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA 2011;305(24):2556-2564.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Preiss D, Tikkanen MJ, Welsh P, Ford I, Lovato LC, Elam MB, et al. Lipid-modifying therapies and risk of pancreatitis: a meta-analysis. JAMA 2012;308(8):804-811.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Qamar A, Usman H, Reilly M, Dunbar R, Rader D. Niacin reverses increased plasma PCSK9 induced by statin and fibrate therapy: a novel mechanism for further LDL reduction. Presented at American Heart Association Scientific Sessions and Resuscitation Science Symposium; 3-6 Nov 2012; Los Angeles. Circulation 2012;126(21 suppl 1).	Not relevant trial design
Quaglini S, Stefanelli M, Boiocchi L, Campari F, Cavallini A, Micieli G. Cardiovascular risk calculators: understanding differences and realising economic implications. Int J Med Inf 2005;74(2-4):191-9.	Not relevant population
Raal FJ, Tuomilehto J, Lee LV, Louie M, Minini P, Ginsberg H. Efficacy and safety of alirocumab stratified by age in phase 3 trials. J Am Coll Cardiol. 2016;67(13, Supplement):2005.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
Reckless JPD, Henry P, Pomykaj T, Lim ST, Massaad R, Vandormael K, et al. Lipid-altering efficacy of ezetimibe/simvastatin 10/40 mg compared with doubling the statin dose in patients admitted to the hospital for a recent coronary event: the INFORCE study. Int J Clin Pract 2008;62(4):539-54.	Not relevant comparator (mixed statin treatment status)
Regeneron Pharmaceuticals. Study of REGN1500 in patients with homozygous familial hypercholesterolemia (HoFH). NCT02265952. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT02265952.	Not relevant population (statin status unclear); Not relevant study design (not RCT)
Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J 2011;32(14):1769-1818.	Not relevant trial design (guidelines/guidance)
Rensing UFE, Roskamm H, Betz P, Benesch L, Blumchen G, Wieland H, et al. [Lipid intervention and coronary artery disease (CAD) in men below 56 years of age. The coronary intervention study: CIS]. Z Kardiol 1999;88(4):270-282.	Not relevant population
Robinson J, Abrams B, Hanson M, Lin J, Sha A, Tershakovec A. Achievement of specified lipid and high-sensitivity C-reactive protein levels with statin-ezetimibe versus statin in male and female patients using combined data from 22,913 patients. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 13-16 May 2010; Chicago, IL: United States. J Clin Lipidol 2010;4(3):200-201.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Robinson JG, Ballantyne CM, Hsueh W, Rosen J, Lin J, Shah A, et al. Achievement of specified low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol apolipoprotein B, and high-sensitivity C-reactive protein levels with ezetimibe/simvastatin or atorvastatin in metabolic syndrome patients with and without atherosclerotic vascular disease (from the VYMET study). J Clin Lipidol 2011;5(6):474-82.	Not relevant population
Rodney RA, Sugimoto D, Wagman B, Zieve F, Kerzner B, Strony J, et al. Efficacy and safety of coadministration of ezetimibe and simvastatin in African-American patients with primary hypercholesterolemia. J Natl Med Assoc 2006;98(5):772-8.	Not relevant population (mixed)

Publication citation	Reason(s) for exclusion
Ros E, Olivan J, Mostaza JM, Vilardell M, Pinto X, Civeira F, et al. Atorvastin versus bezafibrate in mixed hyperlipidaemia: randomised clinical trial of efficacy and safety (the ATOMIX study). Clin Drug Investig 2003;23(3):153-65.	Not relevant population
Rosen JB, Jimenez JG, Pirags V, Vides H, Massaad R, Hanson ME, et al. Consistency of effect of ezetimibe/simvastatin compared with intensified lipid-lowering treatment strategies in obese and non-obese diabetic subjects. Lipids Health Dis 2013;12(1).	Not relevant population (mixed)
Rosenson RS, Jacobson TA, Priess D, Djedjos C, Dent R, Bridges I, et al. Efficacy and safety of the PCSK9 inhibitor evolocumab in patients with mixed hyperlipidemia. Can J Cardiol. 2015;Conference Publication:(var.pagings). 31 (10 SUPPL. 1):S294-S5.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
Roth EM, Jones P, Kelly MT, Setze CM, Lele A, Sleep DJ. Effect of ABT-335 (fenofibric acid) and rosuvastatin combination therapy on multiple lipid parameters in patients with hypercholesterolemia: subgroup analysis of a phase 3, 12-week, randomized, controlled study. Presented at Arteriosclerosis, Thrombosis, and Vascular Biology Annual Conference; 29 Apr - 1 May 2009; Washington, DC: United States. Arterioscler Thromb Vasc Biol 2010;29(7):e68-e69.	Not relevant trial design (<12 wks)
Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med 2012;367(20):1891-900.	Not relevant trial design (<12 wks)
Roth EM, Taskinen MR, Ginsberg H, Kastelein J, Colhoun HM, Merlet L, Pordy R, Baccara-Dinet MT. A 24-week study of alirocumab as monotherapy versus ezetimibe: the first phase 3 data of a proprotein convertase subtilisin/kexin type 9 inhibitor. Presented at 63rd Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention; 29-31 Mar 2014; Washington: United States. J Am Coll Cardiol 2014;63(12 SUPPL 1):A1370.	Not relevant population (not required to have been previously treated with statin and no separate data reported)
Roth EM, Taskinen MR, Ginsberg HN, Kastelein JJ, Colhoun HM, Robinson JG, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized Phase 3 trial. Int J Cardiol. 2014 Sep;176(1):55-61.	Not relevant population (not receiving statins)
Roth EM, Taskinen M-R, Ginsberg HN, Kastelein JJP, Colhoun HM, Robinson JG, Merlet L, Pordy R, Baccara-Dinet MT. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia : results of a 24 week, double-blind, randomized Phase 3 trial. Int J Cardiol 2014;176(1):55-61.	Not relevant population ("hypercholesterolemic patients at moderate cardiovascular risk not receiving statins or other lipid-lowering therapy")
Roth EM. Alirocumab for hyperlipidemia: ODYSSEY Phase III clinical trial results and US FDA approval indications. Future Cardiol 2016 Mar;12(2):115-28.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015 Mar 15;372(16):1500-9.	Not relevant population (mixed populations from other Amgen trials)
Saha SA, Arora RR. Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: a pooled meta-analysis of randomized placebo-controlled clinical trials. Int J Cardiol 2010;141(2):157-66.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Saha SA, Arora RR. Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus - a pooled meta-analysis of randomized placebo-controlled clinical trials. Int J Cardiol 2010;141(2):157-166.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Sanofi, Genzyme. A study of the safety and efficacy of two different regimens of mipomersen in patients with familial hypercholesterolemia and inadequately controlled low-density lipoprotein cholesterol. NCT01475825. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT01475825	Not relevant population - mipomersen trial not in HoFH

Publication citation	Reason(s) for exclusion
Sanofi, Regeneron Pharmaceuticals. Evaluation of alirocumab SAR236553 (REGN727) when co-administered with atorvastatin in patients with primary hypercholesterolemia and LDL-cholesterol ≥ 100 mg/dL. NCT01288469. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT01288469	Not relevant trial design (8wks treatment period)
Sanofi, Regeneron Pharmaceuticals. Open label study of long term safety evaluation of alirocumab. NCT01954394. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015 [accessed 19.3.15]; Available from: http://ClinicalTrials.gov/show/NCT01954394.	Not relevant study design (Not RCT); Not relevant comparator
Sanofi. Evaluation of efficacy and safety of AVE5530 co-administered with atorvastatin in primary hypercholesterolemia. NCT00741715. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2009 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00741715	Not relevant population (not receiving or willing and able to discontinue ongoing lipid-lowering therapy)
Sanofi. Evaluation of safety and efficacy of AVE5530 as add-on to ongoing high doses of statins in patients with primary severe hypercholesterolemia. NCT00766688. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2009 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00766688	Not relevant population (unclear population and trial was terminated)
Sanofi-Aventis Recherche & Développement. A multicenter, double-blind, randomized, 12-month, placebo-controlled study to evaluate the lipid-lowering effect, safety and tolerability of AVE5530 25 mg/day and 50mg/day when added to ongoing stable statin therapy (HMG-CoA reductase inhibitors) in patients with primary hypercholesterolemia. EUCTR2008-001550-41-FR. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2008 [accessed 2.6.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-001550-41	Not relevant intervention/comparator (AVE5530)
Sanofi-aventis Recherche & Développement. Efficacy and Safety of SAR236553 (REGN727) Versus Ezetimibe in Patients with Hypercholesterolemia. EUCTR2011-001424-38-BE. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2012 [accessed 27.10.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-001424-38	Not relevant population ("hypercholesterolemic patients at moderate cardiovascular risk not receiving statins or other lipid-lowering therapy")
Sanofi-Aventis Recherche & Développement. Phase III Study To Evaluate Alirocumab in Patients With Hypercholesterolemia Not Treated With a Statin (ODYSSEY CHOICE II). EUCTR2013-002659-14-BE. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2013 [accessed 27.10.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-002659-14	Not relevant population (statin naive)
Sanofi, Regeneron P. Efficacy and Safety of Alirocumab in Patients With Hypercholesterolemia Not Adequately Controlled With Non-statin Lipid Modifying Therapy or the Lowest Strength of Statin. 2016; Available from: https://ClinicalTrials.gov/show/NCT02584504.	Not relevant population (patients must have taken non-statin or low statin therapy only, not on maximally tolerated statin)
Sanofi-Aventis G. A Randomized, Open-Label, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab Versus Usual Care in Patients with Type 2 Diabetes and Mixed Dyslipidemia at High Cardiovascular Ris. 2016; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-001934-19.	Not relevant population (inclusion based on non-HDLC not adequately controlled with maximally tolerated statin therapy)
Santanu G, Suhrita P, Mookerjee S, Tania K, Mita S, Pramit G, et al. Lipid modifying action of atorvastatin in comparison to combination of atorvastatin and nicotinic acid in patients with ischaemic heart disease. Indian Heart J 2011;63(5):434-7.	Not relevant population
Sattar N, Preiss D, Robinson JG, Djedjos CS, Elliott M, Somaratne R, et al. Lipid-lowering efficacy of the PCSK9 inhibitor evolocumab (AMG 145) in patients with type 2 diabetes: a meta-analysis of individual patient data. Lancet Diabetes Endocrinol 2016 May;4(5):403-10.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking

Publication citation	Reason(s) for exclusion
Sahebkar A, Simental-Mendia LE, Guerrero-Romero F, Golledge J, Watts GF. Efficacy and Safety of Evacetrapib for Modifying Plasma Lipids: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Curr Pharm Des 2016;22(5):595-608.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
Schering Plough, Merck Sharp Dohme Corp. Comparison of co-administration of ezetimibe plus simvastatin versus simvastatin alone in primary hypercholesterolemia (P03476)(Study P03476)(completed). NCT00651274. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2008 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00651274	Not relevant trial design (6wk treatment period)
Schering Plough, Merck Sharp Dohme Corp. Comparison of ezetimibe added to ongoing statin therapy versus doubling the dose of statin in the treatment of hypercholesterolemia (P04355)(completed). NCT00652327. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2010 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00652327	Not relevant trial design (8wks treatment period)
Schering Plough, Merck Sharp Dohme Corp. Ezetimibe plus atorvastatin versus atorvastatin alone in subjects with primary hypercholesterolemia (Study P03406)(completed). NCT00651404. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2010 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00651404	Not relevant trial design (6wk treatment period)
Schering Plough. A multicenter, randomized, parallel-groups, double-blind placebo controlled study comparing the efficacy, safety, and tolerability of co-administration of ezetimibe 10 mg with ongoing treatment with simvastatin 20 mg versus doubling the dose of simvastatin in subjects with primary hypercholesterolemia diabetes mellitus type 2 and coronary heart disease. EUCTR2004-002236-26. In: EU Clinical Trials Register (EUCTR) [Internet]. London: European Medicines Agency (EMA). 2005 [accessed 14.7.14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2004-002236-26	Not relevant trial design (<12 wks)
Schering Plough. The effects of ezetimibe/simvastatin 10/20 mg versus simvastatin 40 mg in high cholesterol and coronary heart disease study (P04039AM2)(completed). NCT00423579. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2009 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00423579	Not relevant trial design (6wk treatment period)
Schulte KL, Beil S. Efficacy and tolerability of fluvastatin and simvastatin in hypercholesterolaemic patients: a double-blind, randomised, parallel-group comparison. Clin Drug Investig 1996;12(3):119-126.	Not relevant population; not relevant outcomes; not relevant trial design (<12wks treatment period)
Schwartzkopff W, Bimmermann A, Schleicher J. [Comparison of the effectiveness of the HMG-CoA-reductase inhibitors pravastatin versus colestyramine in hypercholesterolemia]. Arzneimittelforschung 1990;40(12):1322-7.	Not relevant population
Seehusen DA. Statins for primary cardiovascular prevention. Am Fam Physician 2011;84(7):767-769.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Shankar PK, Bhat R, Prabhu M, Reddy BP, Reddy MS, Reddy M. Efficacy and tolerability of fixed-dose combination of simvastatin plus ezetimibe in patients with primary hypercholesterolemia: Results of a multicentric trial from India. J Clin Lipidol. 2007 Aug;1(4):264-70.	Not relevant population (mixed statin history, numbers and separate data NR)
Shankar PK, Bhat R, Prabhu M, Reddy BPS, Reddy MS, Reddy M. Efficacy and tolerability of fixed-dose combination of simvastatin plus ezetimibe in patients with primary hypercholesterolemia: results of a multicentric trial from India. J Clin Lipidol 2007;1(4):264-270.	Not relevant population (statin naive)
Shaywitz AJ, Dias C, Smith B, Gao B, Gibbs J, Emery M, et al. AMG 145, a fully human monoclonal antibody against PCSK9, reduces LDL-C in healthy volunteers and patients on stable doses of statins. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 31 May - 3 Jun 2012; Scottsdale, AZ: United States. J Clin Lipidol 2012;6(3):286-287.	Not relevant trial design

Publication citation	Reason(s) for exclusion
Smith SC, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation 2011;124(22):2458-2473.	Not relevant trial design (guidelines/guidance)
Smulders YM, Burgers JS, Scheltens T, van Hout BA, Wiersma T, Simoons ML. Clinical practice guideline for cardiovascular risk management in the Netherlands. Neth J Med 2008;66(4):169-174.	Not relevant trial design (guidelines/guidance)
Soomro AY, Ediger M, Pandya B, Raza MR, Khan Z, Meghani M, et al. Efficacy and safety of proprotein convertase subtilisin/kexin type 9 inhibitors treatment in familial hypercholesterolemia: A comprehensive meta-analysis of all randomized clinical trials. J Am Coll Cardiol. 2016;67(13 SUPPL. 1):1984.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
Sponseller CA, Morgan RE, Kryzhanovski VA, Campbell SE, Davidson MH. Comparison of the lipid-lowering effects of pitavastatin 4 mg versus pravastatin 40 mg in adults with primary hyperlipidemia or mixed (combined) dyslipidemia: a phase IV, prospective, US, multicenter, randomized, double-blind, superiority trial. Clin Ther 2014;36(8):1211-22.	Not relevant population (mixed statin history, numbers and separate data NR)
Stein EA, Bergeron J, Gaudet D, Weiss R, Dufour R, Du Y, Yang F, Andisik M, Torri A, Pordy R, Gipe D. One year open-label treatment with alirocumab 150 mg every two weeks in heterozygous familial hypercholesterolemic patients. Presented at 63rd Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention; 29-31 Mar 2014; Washington: United States. J Am Coll Cardiol 2014;63((12 SUPPL 1)):A1371.	Not relevant comparator; not relevant study design (single arm extension study)
Stein EA, Dufour R, Gagne C, Gaudet D, East C, Tribble D, et al. A randomized, double-blind, placebo-controlled study to assess efficacy and safety of mipomersen as add-on therapy in heterozygous familial hypercholesterolemia patients with coronary artery disease. Presented at European Society of Cardiology, ESC Congress; 28 Aug - 1 Sept 2010; Stockholm: Sweden. Eur Heart J 2010;31:898.	Not relevant population - mipomersen trial not in HoFH
Stein EA, Giugliano RP, Koren MJ, Raal FJ, Roth EM, Weiss R, Sullivan D, Wasserman SM, Somaratne R, Kim JB, Yang J, Liu T, Albizem M, Scott R, Sabatine MS, Investigators P. Efficacy and safety of evolocumab (AMG 145), a fully human monoclonal antibody to PCSK9, in hyperlipidaemic patients on various background lipid therapies: pooled analysis of 1359 patients in four phase 2 trials. Eur Heart J 2014;35(33):2249-59.	Not relevant study design (pooled analysis of four trials, which have already been considered in the review as separate studies)
Stein EA, Koren M, Honarpour N, Kurtz C, Yang J, Wasserman S, et al. Clinical equivalence of Evolocumab 140 mg every two weeks and 420 mg monthly dosing regimens: a pooled analysis of 3146 patients in phase 3 studies (1107-103). Abstract presented at American College of Cardiology (ACC); 14-16 March 2015; San Diego, US. [Internet]. 2015 [accessed 30.4.15]; Available from: http://www.abstractsonline.com/pp8/#!/3658/presentation/33655.	Not relevant study design (Pooled data)
Stein EA, Ose L, Retterstol K, Tonstad S, Schleman M, Harris S, et al. Further reduction of low-density lipoprotein cholesterol and C-reactive protein with the addition of ezetimibe to maximum-dose rosuvastatin in patients with severe hypercholesterolemia. J Clin Lipidol 2007;1(4):280-286.	Not relevant population; not relevant trial design
Stein EA. Low-density lipoprotein cholesterol reduction by inhibition of PCSK9. Curr Opin Lipidol 2013;24(6):510-517.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Stein E. PCSK9 Inhibitors for Hyperlipidemia - Represented in NEJM by the OSLER and ODYSSEY trials. Presented at ESC Congress 2015; 29 Aug-2 Sep 2015; London: United Kingdom. 2015.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
Stender S, Budinski D, Hounslow N. Pitavastatin demonstrates long-term efficacy, safety and tolerability in elderly patients with primary hypercholesterolaemia or combined (mixed) dyslipidaemia. Eur J Prev Cardiolog 2013;20(1):29-39.	Not relevant population (statin status unclear) ; Not relevan trial design (not RCT)
Stender S, Hounslow N. Robust efficacy of pitavastatin and comparable safety to pravastatin. Presented at 15th International Symposium on Atherosclerosis; 14-18 Jun 2009; Boston, MA: United States. Atheroscler Suppl 2009;10(2).	Not relevant population

Publication citation	Reason(s) for exclusion
Strony J, Hoffman R, Hanson M, Veltri E. Tolerability and effects on lipids of ezetimibe coadministered with pravastatin or simvastatin for twelve months: results from two open-label extension studies in hypercholesterolemic patients. Clin Ther 2008;30(12):2280-97.	Not relevant trial design; not relevant comparator
Sturmer W, Kromer EP, Riegger AJ, Kochsiek K. [Lipid status and basal steroid hormone level following 16 weeks of lovastatin therapy in primary hypercholesterolemia]. Klin Wochenschr 1991;69(7):307-12.	Not relevant population; not relevant trial design
Sun Pharmaceutical Industries Ltd. A clinical trial to study the effects of rosuvastatin and fenofibrate in patients with primary hypercholesterolemia not adequately controlled with statin or fibrate monotherapy. CTRI/2009/091/001061. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2010 [accessed 2.6.14]. Available from: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=1191	Not relevant comparator; not relevant trial design
Superko HR, Krauss RM, DiRicco C. Effect of fluvastatin on low-density lipoprotein peak particle diameter. Am J Cardiol 1997;80(1):78-81.	Not relevant population (statin status unclear)
Swergold G, Smith W, Mellis S, Logan D, Webb C, Wu R, et al. Inhibition of proprotein convertase subtilisin/kexin type 9 with a monoclonal antibody REGN727/SAR236553, effectively reduces low-density-lipoprotein cholesterol, as mono or add-on therapy in heterozygous familial and non familial hypercholesterolemia. Presented at American Heart Association's Scientific Sessions; 12-16 Nov 2011; Orlando, FL: United States. Circulation 2011;124(21 suppl 1).	Not relevant population; Not relevan trial design (<12 wks)
Takagi H, Umemoto T. Atorvastatin decreases lipoprotein(a): a meta-analysis of randomized trials. Int J Cardiol 2012;154(2):183-6.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Takeda. Efficacy of lapaquistat acetate and simvastatin in subjects with primary dyslipidemia. NCT00256178. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00256178	Not relevant population; not relevant comparator
Taskinen M-R. Consistent reductions in atherogenic lipid parameters with the PCSK9 inhibitor alirocumab in patients not receiving background statin. Presented at ESC Congress 2015; 29 Aug-2 Sep 2015; London: United Kingdom. 2015.	Not relevant study design; review/meta-analysis/pooled analysis for reference checking
Taylor F, Huffman MD, Macedo AF, Moore THM, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2011, Issue 1. Art. No.: CD004816. DOI: DOI:10.1002/14651858.CD004816.pub4.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Taylor F, Ward K, Moore TH, Burke M, Davey Smith G, Casas JP, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013 [accessed 20.5.14], Issue 1. Art. No.: CD004816. DOI: DOI:10.1002/14651858.CD004816.pub5.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Teramoto T, Takeuchi M, Morisaki Y, Ruotolo G, Krueger KA. Efficacy, safety, tolerability, and pharmacokinetic profile of evacetrapib administered as monotherapy or in combination with atorvastatin in Japanese patients with dyslipidemia. Am J Cardiol 2014;113(12):2021-9.	Not relevant population (mixed statin history; separate data and numbers of participants NR)
Thomas GS, Cromwell WC, Ali S, Chin W, Flaim JD, Davidson M. Mipomersen, an apolipoprotein B synthesis inhibitor, reduces atherogenic lipoproteins in patients with severe hypercholesterolemia at high cardiovascular risk: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol 2013;62(23):2178-84.	Not relevant population (HeFH and HoFH population for mipomersen. No evidence for HoFH only)
Thompson PD, MacDougall DE, Newton RS, Margulies JR, Hanselman JC, Orloff DG, et al. Treatment with ETC-1002 alone and in combination with ezetimibe lowers LDL cholesterol in hypercholesterolemic patients with or without statin intolerance. J Clin Lipidol. 2016 May-Jun;10(3):556-67.	Not relevant intervention/ comparator - ETC-1002, new potential lipid lowering therapy but unlicensed and still in development
Tikkanen MJ, Helve E, Jäättelä A, Kaarsalo E, Lehtonen A, Malbecq W, et al. Comparison between lovastatin and gemfibrozil in the treatment of primary hypercholesterolemia: the Finnish Multicenter Study. Am J Cardiol 1988;62(15):35J-43J.	Not relevant population (mixed statin history)

Publication citation	Reason(s) for exclusion
Tomassini JE, Lin J, Polis AB, Shah A, Brudi P, Tershakovec A, et al. Variability of the ldl-c lowering response to ezetimibe and ezetimibe 1 statin therapy in hypercholesterolemic patients. Presented at nnual Scientific Sessions of the National Lipid Association, NLA; 30 May - 2 Jun 2013; Las Vegas, NV: United States. J Clin Lipidol 2013;7(3):281-282.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Toth P, Martin SS, Joshi P, Jones S, Massaro J, D'Agostino R, Sponseller C. Pitavastatin 4 mg provides significantly greater reduction in remnant lipoprotein cholesterol compared to pravastatin 40 mg: results from the prevail trial. Atherosclerosis 2014;235(2):e261-e262.	Not relevant population (mixed statin history, numbers and separate data NR)
Toth PP, Barter PJ, Palmer MK, Carlson BW. Achievement of atp iii combined ldl-c and non-hdl-c goals of ,100 and ,130 mg/dl or <70 and ,100 mg/ dl with 3 different statins: results from voyager. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 30 May - 2 Jun 2013; Las Vegas, NV: United States. J Clin Lipidol 2013;7(3):284-285.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Toth PP, Catapano A, Farnier M, Foody J, Tomassini J, Jensen E, et al. Effects of ezetimibe, ezetimibe coadministered with statins and statin therapies on fasting glucose changes in patients with hypercholesterolemia. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 30 May - 2 Jun 2013; Las Vegas, NV: United States. J Clin Lipidol 2013;7(3):277-278.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Toth PP, Hamon S, Jones SR, Joshi PH, Martin SS, Pordy R, et al. Alirocumab, a proprotein convertase subtilisin/kexin type 9 monoclonal antibody, reduces cholesterol concentrations of all serum low-density lipoprotein cholesterol fractions. Presented at American Heart Association Scientific Sessions and Resuscitation Science Symposium; 16-20 Nov 2013; Dallas, TX: United States. Circulation 2013;128(22 suppl 1).	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Toth PP, Morrone D, Weintraub W, Hanson M, Lowe R, Lin J, et al. Safety profile of statins alone or combined with ezetimibe: a pooled analysis of over 21,000 patients. Presented at Annual Scientific Sessions of the National Lipid Association, NLA: 19-22 May 2011; New York, NY: United States. J Clin Lipidol 2011;5(3):204.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Toth PP, Morrone D, Weintraub WS, Hanson ME, Lowe RS, Lin J, et al. Safety profile of statins alone or combined with ezetimibe: a pooled analysis of 27 studies including over 22,000 patients treated for 6-24 weeks. Int J Clin Pract 2012;66(8):800-812.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Triscari J, Chen E, Johnson-Levonas AO, Mitchel YB, Ruck RA, MacLean A, et al. Effects of extended-release niacin/laropiprant on apolipoprotein B, LDL-Cholesterol, and non-hdlcholesterol targets in patients with type 2 diabetes. Presented at Annual Scientific Sessions of the National Lipid Association, NLA; 31 May - 3 Jun 2012; Scottsdale, AZ: United States. J Clin Lipidol 2012;6(3):285.	Not relevant comparator (niacin/laropiprant)
Tsimikas S, Witztum J, Catapano A. Effect of mipomersen on lipoprotein(A) in patients with hypercholesterolemia across four phase iii studies. Presented at 61st Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC; 24-27 Mar 2010; Chicago, IL: United States. J Am Coll Cardiol 2012;59(13 suppl 1):E1494.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Tunceli K, Lawson RW, Sibbring GC, McCormick AL, Tershakovec AM, Davies GM, et al. Comparative efficacy of ezetimibe-statin combination therapy and statin monotherapy in patients with hypercholesterolemia: systematic review and metaanalysis of randomised controlled trials. Presented at ISPOR 13th Annual European Congress; 6-9 Nov 2010; Prague: Czech Republic. Value Health 2010;13(7):A342.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Ueda S. [Randomised controlled trial in Japanese patients with atherosclerotic disease]. Japanese Journal of Clinical Pharmacology and Therapeutics 2008;39(5):143-146.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Uemura Y, Watarai M, Ishii H, Koyasu M, Takemoto K, Yoshikawa D, et al. Atorvastatin 10 mg plus ezetimibe 10mg compared with atorvastatin 20 mg: impact on the lipid profile in Japanese patients with abnormal glucose tolerance and coronary artery disease. J Cardiol 2012;59(1):50-6.	Not relevant trial design (crossover without washout)

Publication citation	Reason(s) for exclusion
University Medical Centre Ljubljana. Niacin/laropiprant and endothelial function. NCT01126073. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2011 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT01126073	Not relevant population (already reached LDL-C at baseline)
University of California San Diego, Merck Sharp Dohme Corp. Ezetimibe in patients hypo-responsive to statins. NCT00965055. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 29.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00965055	Not relevant outcome (early termination)
University of Pennsylvania, Chestnut Hill Health System. Safety of red yeast rice for high cholesterol in individuals with statin intolerance. NCT00639223. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2009 [accessed 30.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00639223	Not relevant intervention/comparator (red yeast rice vs. placebo)
University of Roma La Sapienza. Cholesterol-lowering effects of nutraceuticaLs versus ezetimibe in statin-intolerant patients. NCT01807078. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 30.5.14]. Available from: http://clinicaltrials.gov/show/NCT01807078	Not relevant population; not relevant comparator (nutraceutical)
Uusitupa M, Ebeling T, Happonen P, Voutilainen E, Turtola H, Parviainen M, et al. Combination therapy with lovastatin and guar gum versus lovastatin and cholestyramine in treatment of hypercholesterolemia. J Cardiovasc Pharmacol 1991;18(4):496-503.	Not relevant comparator
Vallés F, Anguita M, Anglada J, Aguirre C, Fabiani F, Plaza L, et al. A multicenter double-blind study comparing lovastatin and gemfibrozil in the treatment of primary hypercholesterolemia. Atherosclerosis 1991;91 Suppl:S3-9.	Not relevant population
Van Dam MJ, Penn HJAM, Den Hartog FR, Kragten HA, Trip MD, Buirma RJA, et al. A comparison of the efficacy and tolerability of titrate-to-goal regimens of simvastatin and fluvastatin: a randomized, double-blind study in adult patients at moderate to high risk for cardiovascular disease. Clin Ther 2001;23(3):467-478.	Not relevant population (mixed)
van der Harst P, Asselbergs FW, Hillege HL, Bakker SJL, Voors AA, van Veldhuisen DJ, et al. Effect of withdrawal of pravastatin therapy on C-Reactive protein and low-density lipoprotein cholesterol. Am J Cardiol 2007;100(10):1548-1551.	Not relevant trial design (trial looking at effects of withdrawal after a RCT)
Vergani C, Stefanoni P. Efficacy and tolerability of gemfibrozil in hypercholesterolemic patients previously treated with simvastatin. Adv Ther 1993;10(4):189-196.	Not relevant population; not relevant trial design (<10pts per arm)
Villasis-Keever MA, Rendon-Masias ME, Pineda-Cruz R, Escamilla-Nunez A, Mould-Quevedo JF. A meta-analysis of efficacy of atorvastatin in comparison to pravastatin, simvastatin and rosuvastatin for the control of dyslipidemia and cardiovascular events prevention. Presented at 15th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR; 15-19 May 2010; Atlanta, GA: United States. Value Health 2010;13(3):A150.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Visser M, Akdim F, Basart D, Kastelein J, Nederveen A, Kwoh T, et al. Effect of mipomersen treatment on hepatic triglyceride content in subjects with familial hypercholesterolemia. Presented at 15th International Symposium on Atherosclerosis; 14-18 Jun 2009; Boston, MA: United States. Atheroscler Suppl 2009;10(2).	Not relevant population (no HoFH for mipomersen)
Visser M, Wagener G, Baker B, Geary R, Donovan J, Beuers U, et al. A randomized, double-blind, placebo-controlled trial to evaluate the effect of weekly subcutaneous injections of mipomersen, an apolipoprotein B-100 synthesis inhibitor, on low density lipoprotein cholesterol in high-risk statin-intolerant patients with hypercholesterolemia. Presented at American Heart Association's Scientific Sessions; 12-16 Nov 2011; Orlando, FL. Circulation 2011;124(21 suppl 1).	Not relevant population (no HoFH for mipomersen)
Visser ME, Kastelein JJP, Stroes ESG. Apolipoprotein B synthesis inhibition: results from clinical trials. Curr Opin Lipidol 2010;21(4):319-323.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Visser ME, Wagener G, Baker BF, Geary RS, Donovan JM, Beuers UHW, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, lowers low-density lipoprotein cholesterol in high-risk statin-intolerant patients: a randomized, double-blind, placebo-controlled trial. Eur Heart J 2012;33(9):1142-9.	Not relevant population - mipomersen trial not in HoFH

Publication citation	Reason(s) for exclusion
Wan H, Gumbiner B, Joh T, Udata C, Forgues P, Garzone PD. Effects of RN316 (pf-04950615), a humanized igg2a monoclonal antibody binding proprotein convertase subtilisin kexin type 9, on lipoprotein particles in hypercholesterolemic subjects. Presented at 62nd Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC; 9-11 Mar 2013; San Francisco, CA: United States. J Am Coll Cardiol 2013.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Watts G, Lambert G, Hamilton S, Chew G, Jenkins A, Chan D. Plasma proprotein convertase subtilising/KEXIN type 9 (PCSK9) concentrations are decreased by fenofibrate in statin-treated type 2 diabetic patients. Presented at 15th International Symposium on Atherosclerosis; 14-18 Jun 2009; Boston, MA: United States. Atheroscler Suppl 2009;10(2).	Not relevant trial design (crossover trial with only 12pts so <10pts per arm)
Weng TC, Yang YH, Lin SJ, Tai SH. A systematic review and meta-analysis on the therapeutic equivalence of statins. J Clin Pharm Ther 2010;35(2):139-151.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Weng TC, Yang YHK, Lin SJ, Tai SH. A systematic review and meta-analysis on the therapeutic equivalence of statins. J Clin Pharm Ther 2010;35(2):139-51.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Wensel TM, Waldrop BA, Wensel B. Pitavastatin: a new HMG-CoA reductase inhibitor. Ann Pharmacother 2010;44(3):507-14.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Willich SN, Englert H, Sonntag F, Völler H, Meyer-Sabellek W, Wegscheider K, et al. Impact of a compliance program on cholesterol control: results of the randomized ORBITAL study in 8108 patients treated with rosuvastatin. Eur J Prev Cardiolog 2009;16(2):180-7.	Not relevant intervention; not relevant comparator (compares with or without compliance intervention
Worthy G, Gandra SR, Bridges I, Worth G, Dent R, Forbes CA, et al. A systematic review and network meta-analysis on the efficacy of evolocumab and other lipid-lowering therapies for the management of lipid levels in hyperlipidemia. Value Health. 2016;19(3):A53.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Yamasaki T, Iwashima Y, Jesmin S, Ohta Y, Kusunoki H, Hayashi S, et al. Comparison of efficacy of intensive versus mild pitavastatin therapy on lipid and inflammation biomarkers in hypertensive patients with dyslipidemia. PLoS One. 2014;9(2):e89057.	Not relevant study design (Not RCT); Not relevant population (statin status unclear)
Yamagishi T. [Efficacy and safety of ezetimibe added on to rosuvastatin (2.5 mg) compared with uptitration of rosuvastatin (5 mg) in hyperlipidemic patients]. Jpn Pharmacol Ther 2010;38(3):305-311.	Duplicate of publication already assessed
Yan F, Tian L, Xiao Z, Li S, Fu M, Tian H. Comparison of the efficacy of fenofibrate and acipimox on plasma lipoprotein subclasses distribution in the Chinese population with Type 2 diabetes mellitus and hypertriglyceridemia. Clinical Lipidology 2014;9(2):171-177.	Not relevant population (statin history unclear and "None had taken lipid-lowering drugs….for at least 3mths")
Ye Y, Zhao X, Zhai G, Guo L, Tian Z, Zhang S. Effect of high-dose statin versus low-dose statin plus ezetimibe on endothelial function: a meta-analysis of randomized trials. J Cardiovasc Pharmacol Ther 2012;17(4):357-65.	Not relevant trial design; review/meta-analysis/pooled analysis for reference checking
Zema MJ. Add-on therapy for hypercholesterolemia: a pilot comparison of two gastrointestinally-acting agents in statin-treated patients. J Clin Lipidol 2009;3(2):119-124.	Not relevant trial design (crossover trial with only 12pts so <10pts per arm and treatment duration of only 6wks)
Zou X, Si QJ. Is combined lipid-regulating therapy safe and feasible for the very old patients with mixed dyslipidemia? J Geriatr Cardiol. 2013 Dec;10(4):349-54.	Not relevant study design (Not RCT)
Zubareva M, Tripoten M, Rozhkova T, Solovieva E, Balakhonova T, Rogoza A, et al. Effects of Ezetimibe, intial doses of statins, and its combination on lipids in high risk patients with hyperlipideamia. Presented at 78th EAS Congress; 20-23 Jun 2010; Hamburg: Germany. Atheroscler Suppl 2010;11(2):189.	Not relevant trial design (6wk treatment period)

C. List of unobtainable trials (12 trials)

Publication citation
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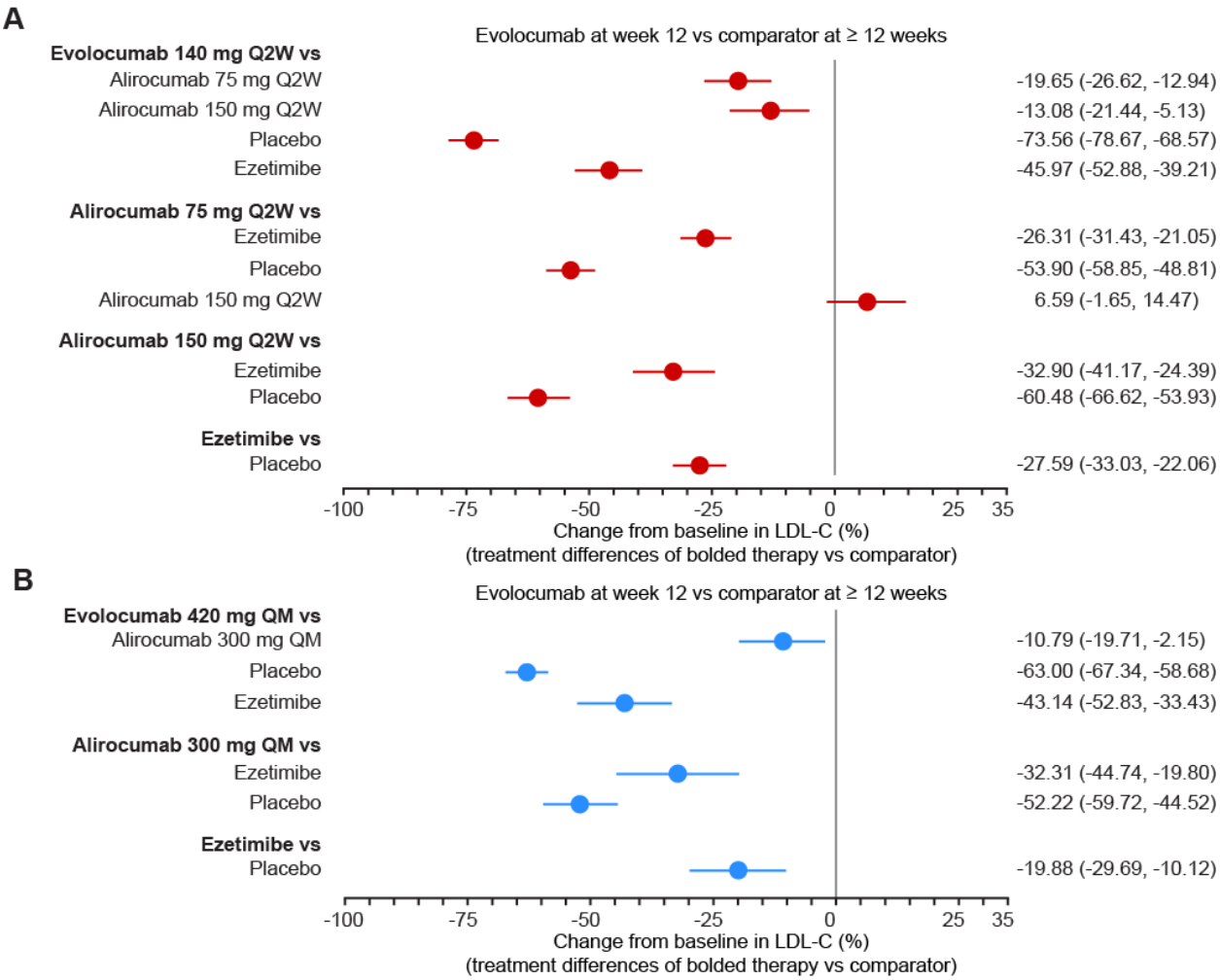
Supplemental Figures

Figure S1. Treatment Difference in Percent LDL-C (95% Credible Interval) Change from Baseline, Evolocumab 140 mg Q2W (Panel A) or Evolocumab 420 mg QM (Panel B) at Week 12 vs Comparator at Week 12



LDL-C indicates low-density liprotein cholesterol; Q2W, every 2 weeks; QM, every month.

Figure S2. Risk of Bias Assessed in 69 Trials

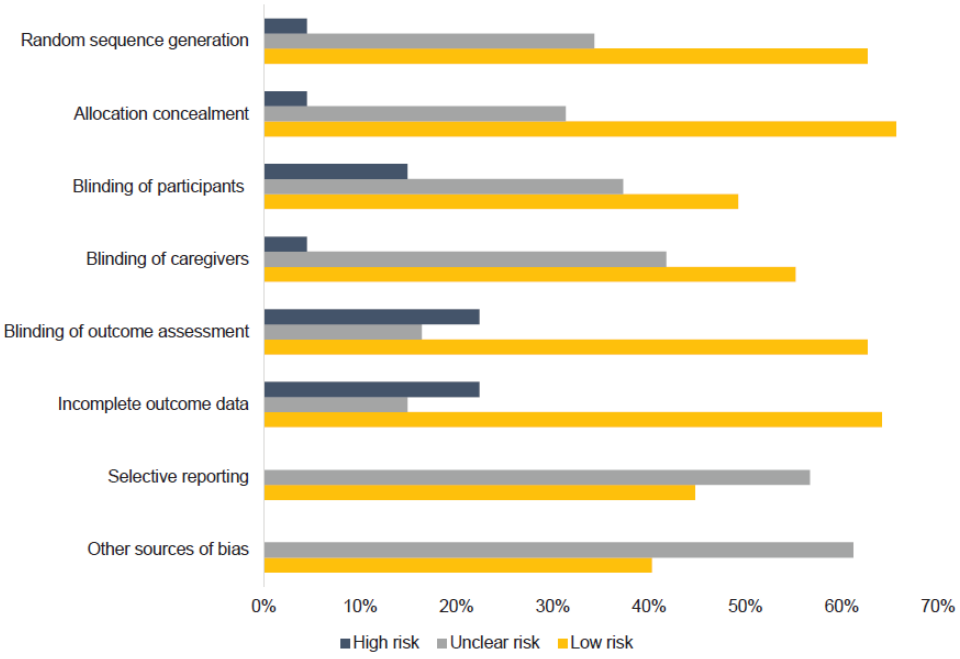
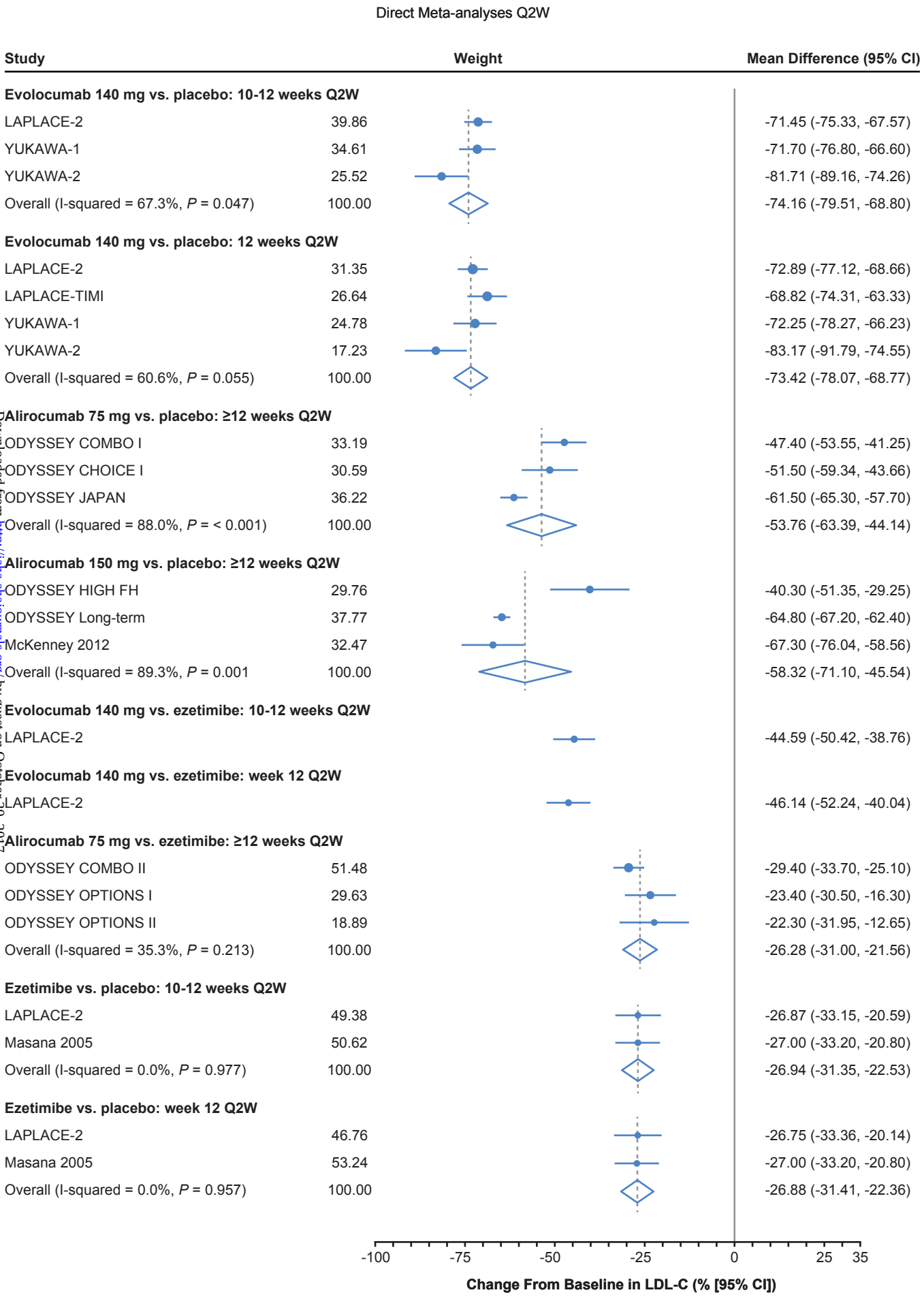


Figure S3. Direct Meta-analyses of LDL-C Reduction (Following 2 Pages).

Sensitivity analyses indicated via footnote. [a]Excluding YUKAWA studies[1, 2]: −71.45 (95% CI −75.33, −67.57); I^2: NA (only LAPLACE-2). [b]Excluding YUKAWA studies[1, 2]: −71.24 (−75.16, −67.33); I^2: 24.5%, *P*=0.25. [c]Alirocumab was titrated to 150 mg at week 12 for patients whose LDL-C did not reduce sufficiently.These results are for 12 weeks before titration for ODYSSEY COMBO I and ODYSSEY JAPAN and for 24 weeks for ODYSSEY CHOICE I. [d]Excluding ODYSSEY JAPAN[3]: −48.96 (−53.80 to −44.12); I^2: 0%, *P*=0.420. [e]Excluding YUKAWA studies[1, 2]: −68.13 (−72.03 to −64.23); I^2: NA (only LAPLACE-2). [f]Excluding YUKAWA studies[1, 2]: −60.21 (−64.86 to −55.55); I^2: 67.4%, *P*=0.047.

CI indicates confidence interval; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; Q2W, every 2 weeks; QM, every month. Study acronym definitions are available in the source references.



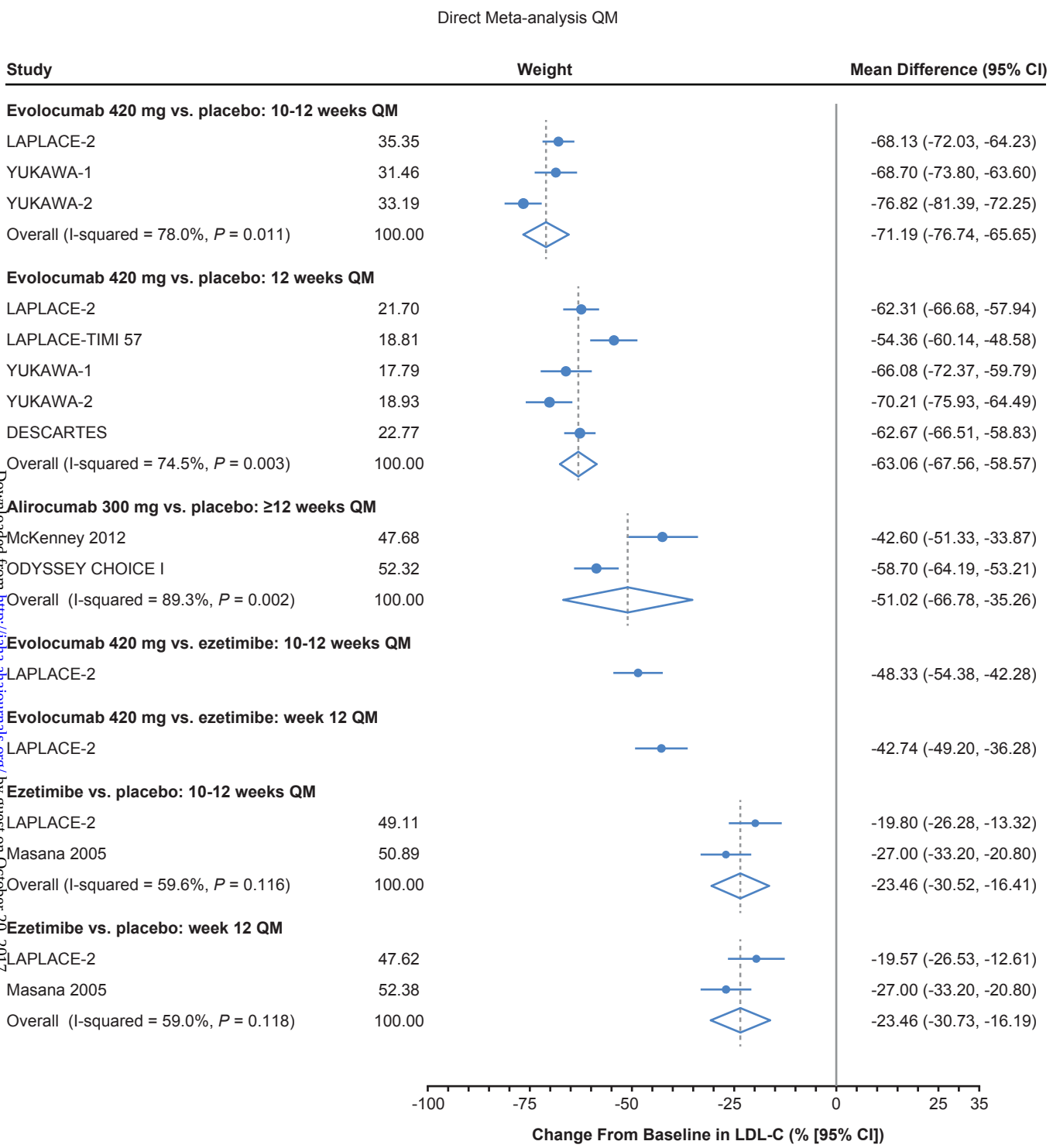
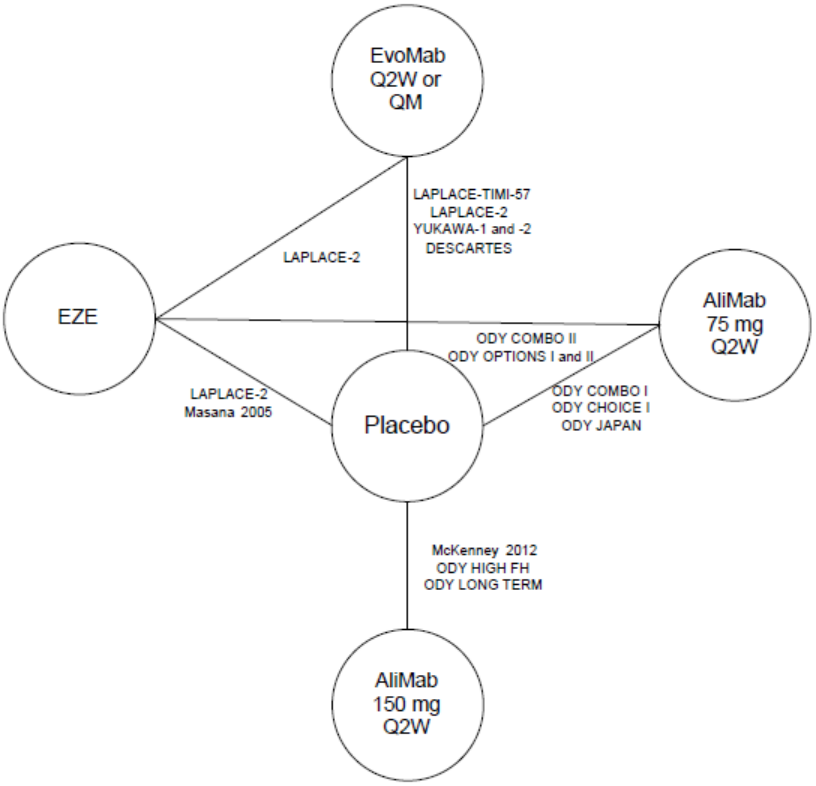
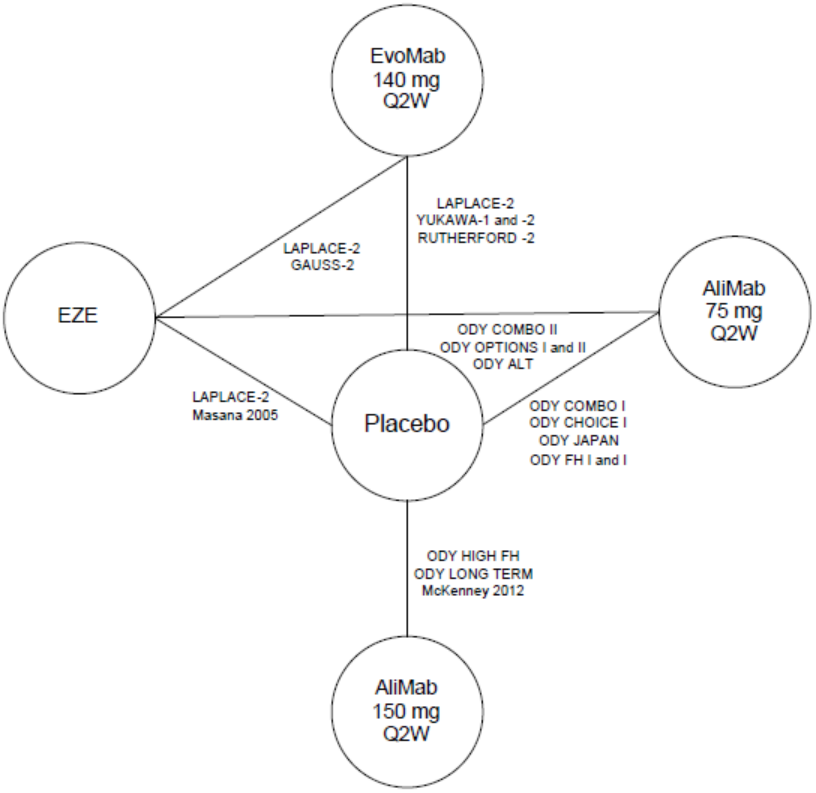


Figure S4. Network for Comparing Other Lipids With Evolocumab 140 mg Q2W vs Other Therapies. AliMab indicates alirocumab; ApoB, apolipoprotein B; EvoMab, evolocumab; EZE, ezetimibe; HDL-C, high-density lipoprotein-cholesterol; Lp(a), lipoprotein(a); non-HDL-C, non-high–density lipoprotein-cholesterol; Q2W, every 2 weeks; QM, every month. Study acronym definitions are available in the source references.

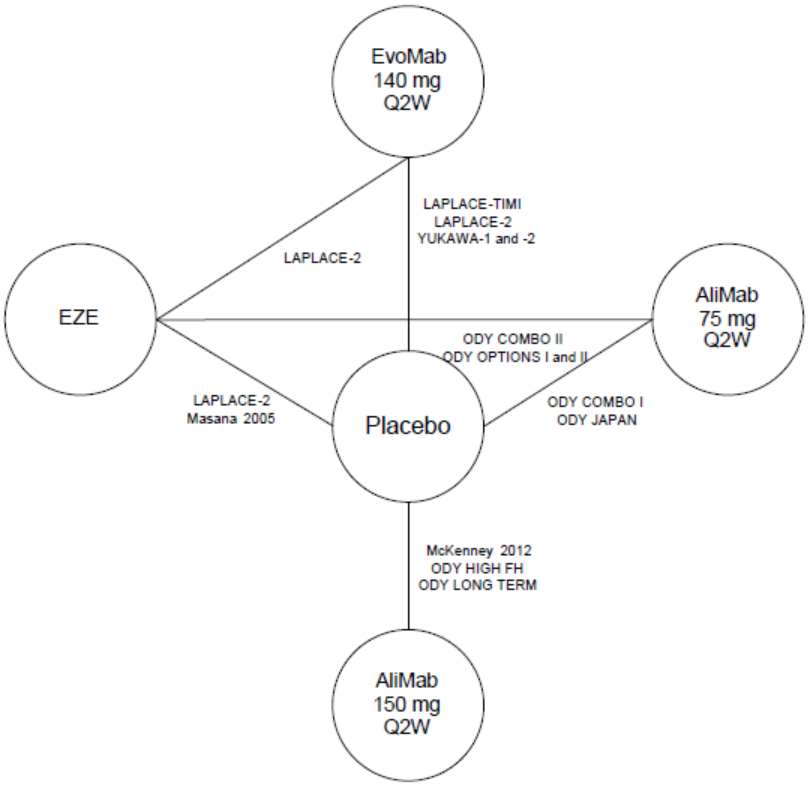
A. Sensitivity Analysis Combining Evolocumab Q2W and QM Dosing



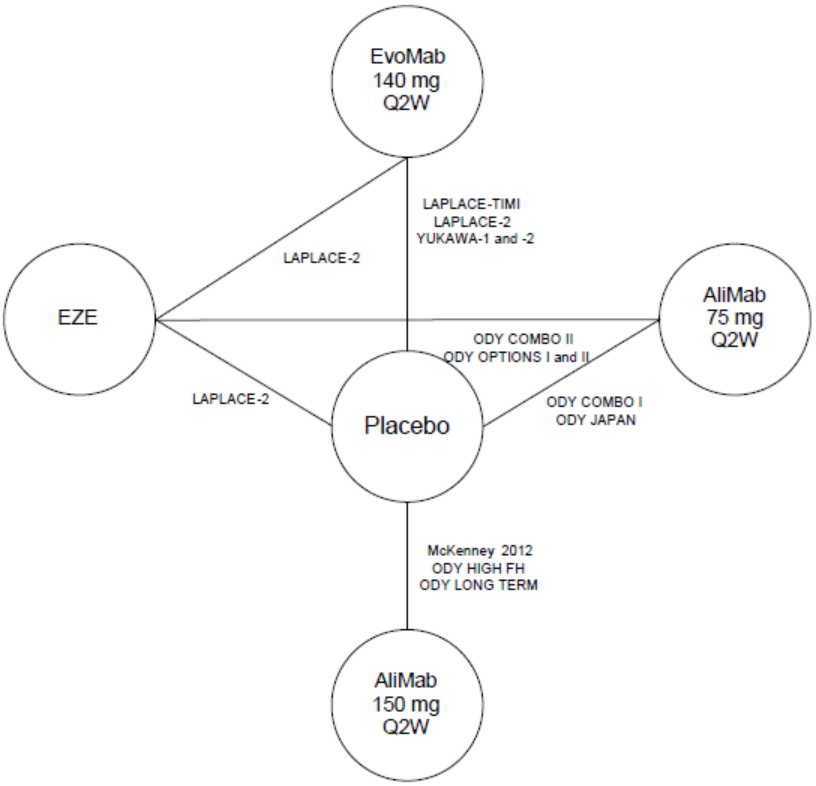
B. Evolocumab 140 mg Q2W With any Background Therapy



C. HDL-C and Non-HDL-C



D. ApoB



E. Lp(a)

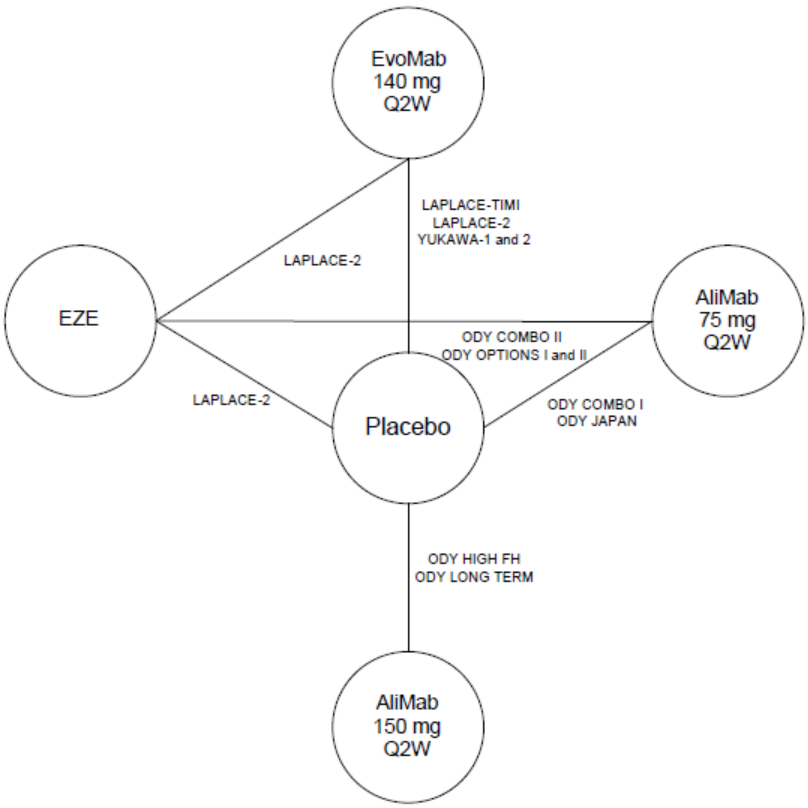
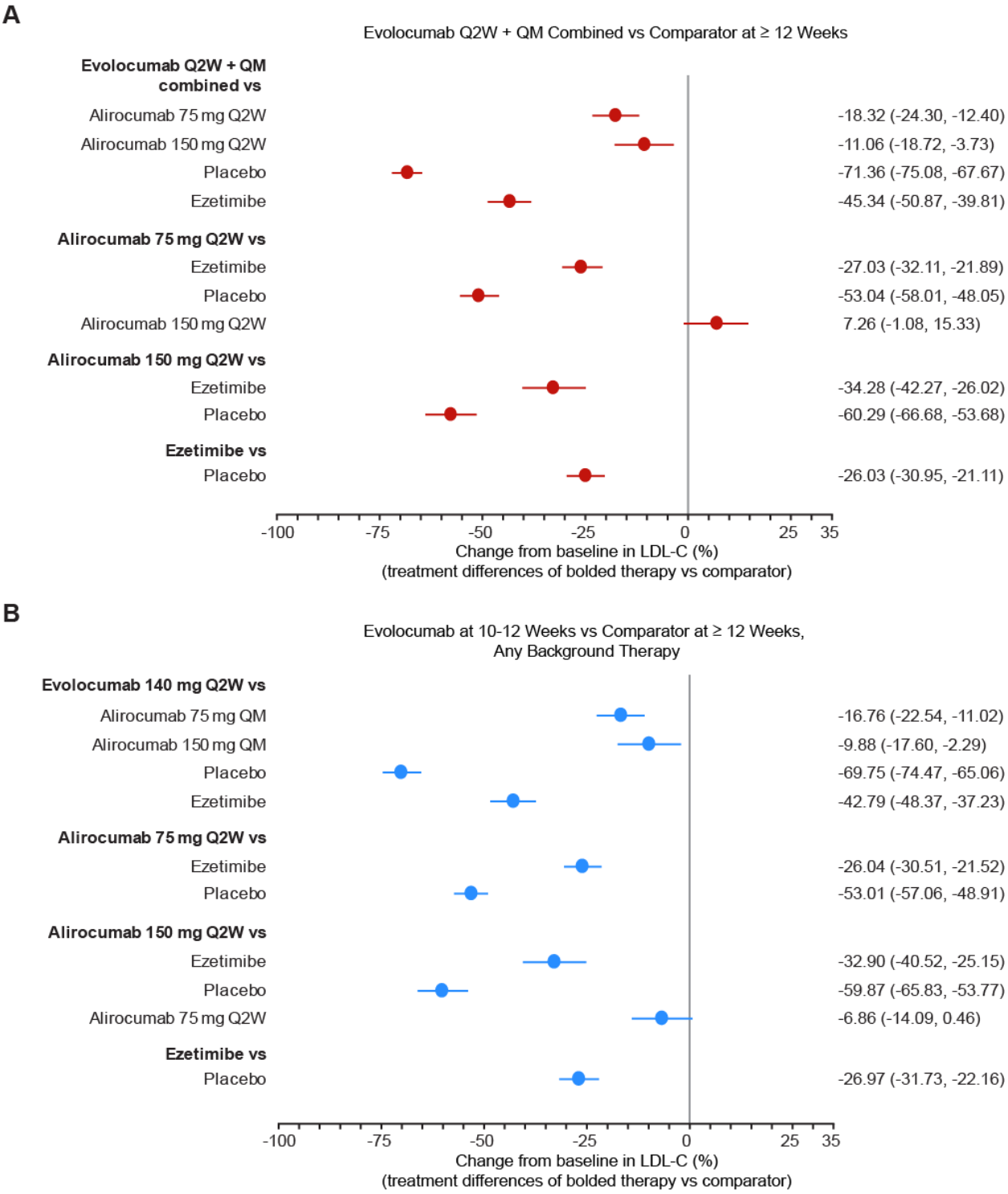
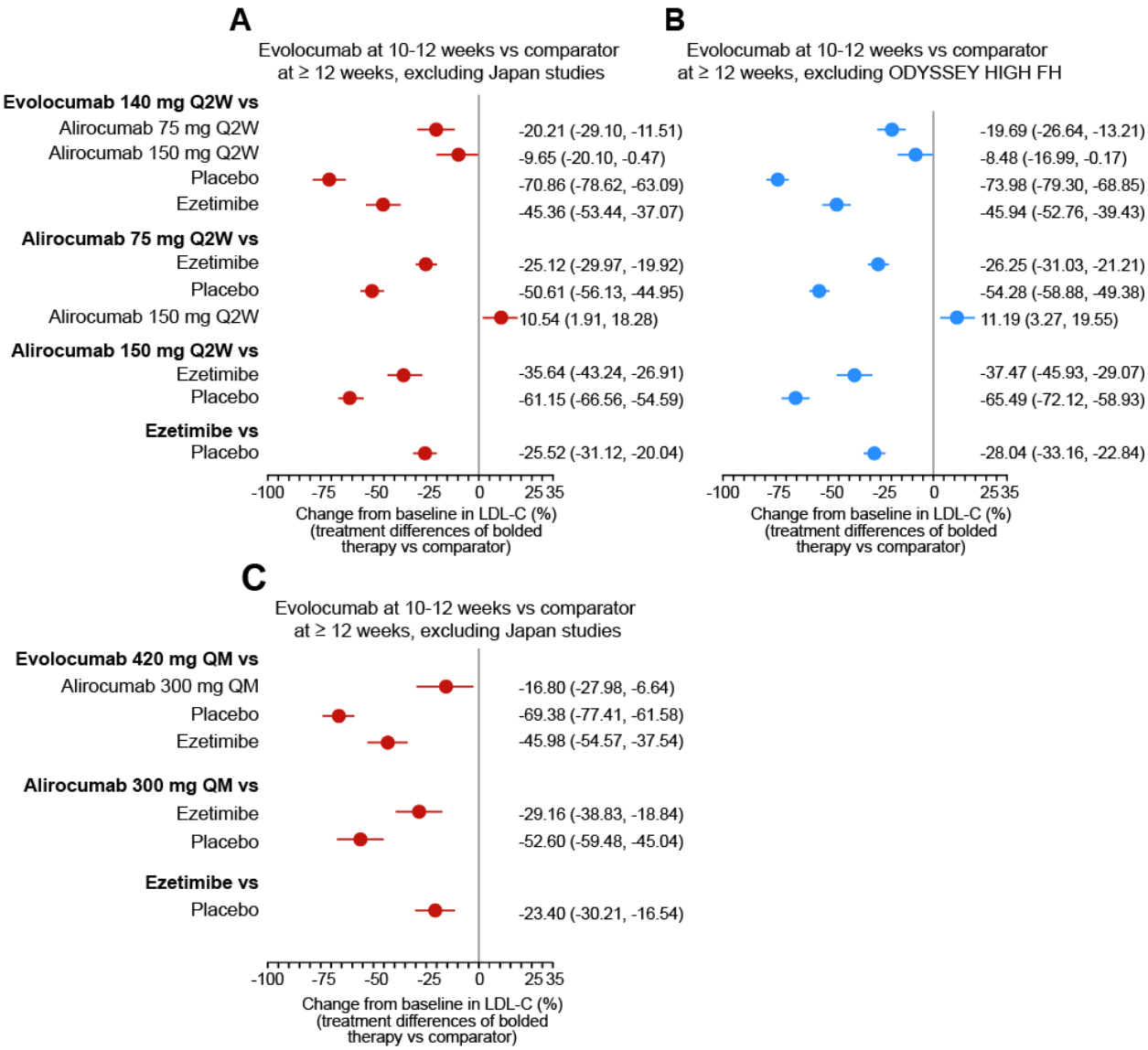


Figure S5. Treatment Difference in Percent LDL-C (95% Credible Interval) Change: Panel A, Evolocumab 140 mg Q2W and 420 mg Every Month Combined at the Mean of Weeks of 10 and 12 vs Comparator at ≥ 12 Weeks; Panel B, Evolocumab 140 mg Q2W at the Mean of Weeks of 10 and 12 vs Comparator at ≥ 12 Weeks With Any Background Therapy



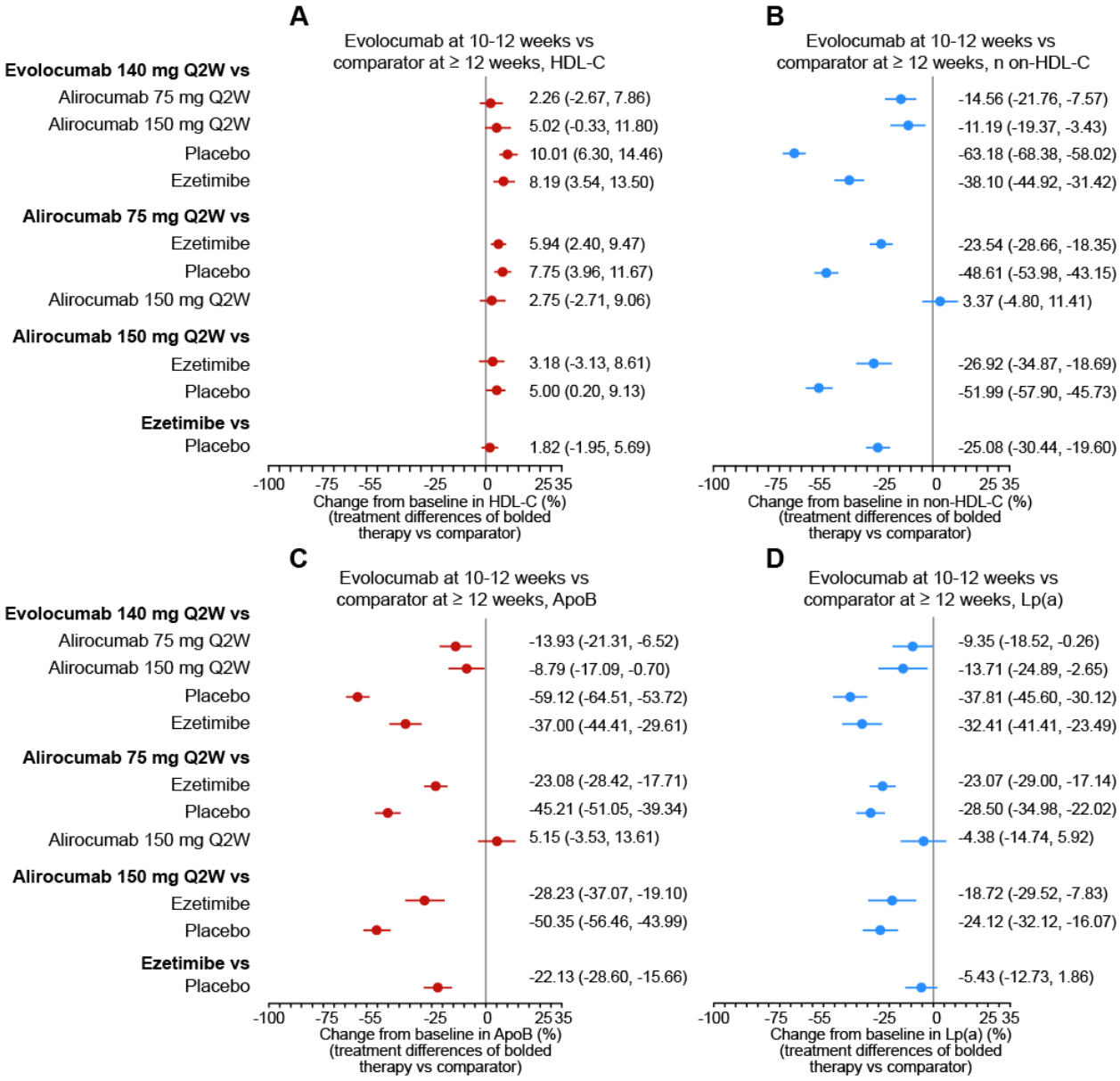
LDL-C indicates low-density liprotein cholesterol; Q2W, every 2 weeks; QM, every month.

Figure S6. Sensitivity Analysis: Treatment Difference in Percent LDL-C (95% Credible Interval) Change from Baseline, Evolocumab 140 mg Q2W at the Mean of Weeks 10 and 12 vs Comparator at ≥ 12 Weeks: Panel A, Excluding Japan Studies; Panel B, ODYSSEY HIGH FH. Evolocumab 420 mg Every 4 Weeks at Weeks 10 and 12 vs Comparator at ≥ 12 Weeks: Panel C, Excluding Studies Conducted in Japan.



[a]One study of alirocumab 75 mg Q2W did not report 12-week results for secondary lipid endpoints, so 24-week results were used. Therefore data labelled alirocumab 75 mg includes data from those who were titrated to alirocumab 150 mg from week 12. LDL-C indicates low-density liprotein cholesterol; Q2W, every 2 weeks; QM, every month.

Figure S7. Treatment Difference in Percent (95% Credible Interval) Change from Baseline, Evolocumab 140 mg Q2W at the Mean of Weeks of 10 and 12 vs Comparator at ≥ 12 Weeks: Panel A, HDL-C; Panel B, Non-HDL-C; Panel C, ApoB; Panel D, Lp(a).



LDL-C indicates low-density liprotein cholesterol; Q2W, every 2 weeks; QM, every month.

Supplemental Tables

Table S1. Methodology and Characteristics of Included Studies

Characteristic	No. of trials out of 69 (%)
Type of hyperlipidemia	
Primary	24 (34.8)
Secondary	19 (27.5)
Primary and secondary	23 (33.3)
NR/unclear	3 (4.4)
HeFH/HoFH status	
HoFH	2 (2.9)
HeFH	9 (13.0)
Mixed HoFH and HeFH	4 (5.8)
HoFH excluded	8 (11.6)
FH excluded	7 (10.2)
NR/unclear	39 (56.5)
Overall risk category of population	
Population with previous CVD events and/or at high risk	17 (24.6)
Population without previous CVD events	4 (5.8)
Mixed population with and without previous CVD events/high risk of CVD	29 (42.0)
NR/unclear	19 (27.5)
Type 2 diabetes status	
Type 2 diabetic population	7 (10.2)
Non-diabetic population	2 (2.9)
Mixed type 2 and non-diabetic population	35 (50.7)
NR/unclear	25 (36.2)
Ethnicity	
Predominantly (>90%) White	7 (10.2)
Japanese	12 (17.4)
South Asian Canadian	1 (1.5)
Mixed	22 (31.9)
NR/unclear	27 (39.1)
Smoking status	
Smokers and nonsmokers	17 (24.6)
Smokers, nonsmokers, and ex-smokers	7 (10.2)
Nonsmokers and ex-smokers	1 (1.5)
NR/unclear	44 (63.8)
Gender	
Mixed gender	66 (95.7)
Males only	1 (1.5)
NR/unclear	2 (2.9)
Obesity status	
Normal (BMI 18.50-24.99 kg/m^2)	3 (4.4)
Overweight (BMI ≥ 25.00 kg/m^2)	12 (17.4)
Obese (BMI ≥ 30.00 kg/m^2)	2 (2.9)
Mixed (normal, overweight and obese)	8 (11.6)
NR/unclear	44 (63.8)
Hypertension status	
Hypertensive patients included	36 (52.2)
NR/unclear	33 (47.8)

CVD indicates cardiovascular disease, HeFH, heterozygous familial hypercholesterolemia; HoFH, homozyqous familial hypercholesterolemia; NR, not reported.

Table S2. Studies Retrieved by the Systematic Review but Excluded From the Network Meta-Analysis

Study	Details	Reason
Abbott/NCT00300430	3 different statin + fenofibrate comparisons	No comparison of interest for NMA
Abbott/NCT01674712/ EUCTR2011-005924-16-CZ	Fenofibrate monotherapy or in combination with simvastatin	No comparison of interest for NMA
ACCORD Lipid Trial	Fenofibrate vs placebo	No comparison of interest for NMA
Arai 2016	Anacetrapib vs placebo	No comparison of interest for NMA
ARBITER 2	Required data not available	Data not available
ARBITER 6-HALTS/ NCT00397657	Required data not available	Data not available
Bando 2016	Statin vs statin (switching agent)	No comparison of interest for NMA
Chen 2013	Required data not available	Data not available
DEFINE	Anacetrapib vs placebo	No comparison of interest for NMA
EASEGO	No common switching of statin dose in placebo group (some moderate to moderate, some moderate to high) and some subjects in ezetimibe group switched from moderate to low dose statin	Unstable or low statin dose
ENHANCE	24-month outcomes and different run-in period	Ineligible study design
ESSENTIAL	Required data not available	Data not available
Ezetimibe Study Group	In placebo group atorvastatin went from moderate to high. Dose doubling / quadrupling was common in both arms	Unstable or low statin dose
Farnier 2010 (pravastatin trial)	Low-dose statin	Unstable or low statin dose
Farnier 2011 (simvastatin trial)	Statin dose not stable	Unstable or low statin dose
Farnier 2012	Statin dose not stable	Unstable or low statin dose
GAUSS/Amgen 20090159	Evolocumab vs ezetimibe in statin-intolerant patients	No background statin therapy/Ineligible patient population
GAUSS-2/Amgen 20110116	Evolocumab vs ezetimibe in statin-intolerant patients	No background statin therapy/Ineligible patient population
GAUSS-3/Amgen 20120332	Evolocumab vs ezetimibe in statin-intolerant patients	No background statin therapy/Ineligible patient population
Gelabert 2004	Required data not available	Data not available
Goshima 2010	Low-dose statin	Unstable or low statin dose
INFINITY	Statin subjects: 40% switched from moderate to high atorvastatin and 60% from high to high. Dose doubling was common in both arms post randomization	Unstable or low statin dose
Kastelein 2015	Required data not available (trial of LY3015014)	Data not available
Kei 2013	Low statin dose, no SD/SE	Unstable or low statin dose
Kersting 2000	Required data not available	Data not available
Kowa Research Europe/NCT00344370	Statin vs statin	No comparison of interest for NMA
Kush 2009	54% not on statin at baseline and no details of statin intensity (Asian population)	Ineligible population
McClean 2011	Some statin naïve subjects	Ineligible population
Nadaraia 2011	Unknown statin intensity	Data not available
Novartis/NCT01551173	Statin vs statin	No comparison of interest for NMA
ODYSSEY ALTERNATIVE	Alirocumab vs placebo in statin-intolerant patients	No background statin therapy
ODYSSEY FH I	Alirocumab vs placebo in FH only	Ineligible background therapy (prinicipally statin+ezetimibe)

Study	Details	Reason
ODYSSEY FH II	Alirocumab vs placebo in FH only	Ineligible background therapy (prinicipally statin+ezetimibe)
Okada 2011	Statin dose not stable, included some low dose	Unstable or low statin dose
PEAS	Low dose statin	Unstable or low statin dose
Pfizer/NCT01592240	Bococizumab vs placebo	No comparison of interest for NMA
RADICHOL 1	Mipomersen vs placebo in HoFH	Ineligible population
REALIZE/NCT01524289	Anacetrapib vs placebo	No comparison of interest for NMA
RESEARCH	Japanese diabetic patients, some on low dose statin	Unstable or low statin dose
RUTHERFORD/ Amgen 20090158	Evolocumab vs placebo in HeFH patients	Ineligible background therapy (prinicipally statin+ezetimibe)
RUTHERFORD-2/Amgen 20110117	Evolocumab vs placebo in HeFH patients	Ineligible background therapy (prinicipally statin+ezetimibe)
Sanofi NCT01812707	Low dose statin, no SD/SE	Unstable or low statin dose
Sawayama 2011	Required data not available	Data not available
Scott 2010	Fenofibrate vs placebo (simvastatin background)	No comparison of interest for NMA
SEACOAST II	Required data not available (median at 24 weeks)	Data not available
SEARCH/ISRCTN74348595	Required data not available (no change or % change in LDL-C)	Data not available
Simvastatin To Atorvastatin switch Trial (STAT)	Required data not available and comparison of moderate to high intensity statin	No comparison of interest for NMA
Six Cities Study	Patients were previously treated with statin but discontinued statin prior to the start of the trial consequent baseline lipid values were from a no statin baseline.	Ineligible population
Stein 2008/NCT00125125	Required data not available	Data not available
Study P06027	Included 2.5 mg rosuvastatin	Unstable or low statin dose
TESLA/Amgen 20110233	Evolocumab vs placebo in HoFH	Ineligible population
Torimoto 2013	Included 2.5 mg rosuvastatin	Unstable or low statin dose
TREAC/NCT00203476	Required data not available	Data not available
TRIPLE	Required data not available	Data not available
Wink 2002	Required data not available	Data not available
Yamagishi 2010	Low-dose rosuvastatin (2.5 mg)	Unstable or low statin dose
Yamazaki 2013	Required data not available	Data not available
ZETELD	Low-dose atorvastatin (10 mg)	Unstable or low statin dose

Shaded rows are included in a sensitivity analysis but not in the main analyses. SD indicates standard deviation; SE, standard error. Study acronym definitions are available in the source references.

Supplemental References

1. Hirayama A, Honarpour N, Yoshida M, Yamashita S, Huang F, Wasserman SM, Teramoto T. Effects of evolocumab (AMG 145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk--primary results from the phase 2 YUKAWA study. *Circ J*. 2014;78:1073-1082

2. Kiyosue A, Honarpour N, Kurtz C, Xue A, Wasserman SM, Hirayama A. A phase 3 study of evolocumab (AMG 145) in statin-treated Japanese patients at high cardiovascular risk. *Am J Cardiol*. 2016;117:40-47

3. Teramoto T, Kobayashi M, Tasaki H, Yagyu H, Higashikata T, Takagi Y, Uno K, Baccara-Dinet MT, Nohara A. Efficacy and safety of alirocumab in Japanese patients with heterozygous familial hypercholesterolemia or at high cardiovascular risk with hypercholesterolemia not adequately controlled with statins. ODYSSEY JAPAN randomized controlled trial. *Circ J*. 2016;80(9):1980-1987.

Systematic Review and Network Meta–Analysis on the Efficacy of Evolocumab and Other Therapies for the Management of Lipid Levels in Hyperlipidemia

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