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SYSTEMATIC REVIEW AND META-ANALYSIS

Network Meta-Analysis of Randomized Trials Evaluating the Comparative Efficacy of Lipid-Lowering Therapies Added to Maximally Tolerated Statins for the Reduction of Low-Density Lipoprotein Cholesterol

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BACKGROUND: Lowering low-density lipoprotein cholesterol (LDL-C) levels decreases major cardiovascular events and is recommended for patients at elevated cardiovascular risk. However, appropriate doses of statin therapy are often insufficient to reduce LDL-C in accordance with current guidelines. In such cases, treatment could be supplemented with nonstatin lipid-lowering therapy.

METHODS AND RESULTS: A systematic literature review and network meta-analysis were conducted on randomized controlled trials of nonstatin lipid-lowering therapy added to maximally tolerated statins, including statin-intolerant patients. The primary objective was to assess relative efficacy of nonstatin lipid-lowering therapy in reducing LDL-C levels at week 12. Secondary objectives included the following: LDL-C level reduction at week 24 and change in non–high-density lipoprotein cholesterol and apolipoprotein B at week 12. There were 48 randomized controlled trials included in the primary network meta-analysis. All nonstatin agents significantly reduced LDL-C from baseline versus placebo, regardless of background therapy. At week 12, evolocumab, 140 mg every 2 weeks (Q2W)/420 mg once a month, and alirocumab, 150 mg Q2W, were the most efficacious regimens, followed by alirocumab, 75 mg Q2W, alirocumab, 300 mg once a month, inclisiran, bempedoic acid/ezetimibe fixed-dose combination, and ezetimibe and bempedoic acid used as monotherapies. Primary end point results were generally consistent at week 24, and for other lipid end points at week 12.

CONCLUSIONS: Evolocumab, 140 mg Q2W/420 mg once a month, and alirocumab, 150 mg Q2W, were consistently the most efficacious nonstatin regimens when added to maximally tolerated statins to lower LDL-C, non–high-density lipoprotein cholesterol, and apolipoprotein B levels and facilitate attainment of guideline-recommended risk-stratified lipoprotein levels.

Key Words: alirocumab ■ bempedoic acid ■ evolocumab ■ ezetimibe ■ inclisiran

Low-density lipoprotein cholesterol (LDL-C) is an important causal, modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD).[1–3] Evidence from multiple prospective, randomized studies has substantiated that patients achieving the lowest LDL-C levels have the lowest risk of future major adverse

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CLINICAL PERSPECTIVE

What Is New?

- There are few network meta-analyses comparing the efficacy of PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors; this study compared PCSK9 inhibitors and new lipid-lowering therapies (LLTs) (ie, bempedoic acid and inclisiran).
- Primary network meta-analysis found all nonstatin LLTs significantly reduced low-density lipoprotein cholesterol levels versus placebo at week 12; broadly similar results for ranking of the interventions were identified in other lipid end point level changes.
- Evolocumab, 140 mg every 2 weeks/420 mg once a month, and alirocumab, 150 mg every 2 weeks, treatment resulted in >70% of a simulated population achieving the very high-risk cardiovascular disease European guideline goal (<55 mg/dL).

What Are the Clinical Implications?

- Evolocumab and alirocumab, 150 mg every 2 weeks, are the most consistently efficacious nonstatin LLT regimens.
- The network meta-analysis of multiple nonstatin LLTs should help inform physicians' treatment choice for patients who would benefit from lower low-density lipoprotein cholesterol levels and require adjuvant LLTs to statin therapy to achieve current low-density lipoprotein cholesterol goals.

Nonstandard Abbreviations and Acronyms

ESC	European Society of Cardiology
FDC	fixed-dose combination
LLT	lipid-lowering therapy
mAb	monoclonal antibody
MACE	major adverse cardiovascular event
NMA	network meta-analysis
PCSK9	proprotein convertase subtilisin/kexin type 9
Q2W	every 2 weeks
Q3M	every 3 months
Q6M	every 6 months
QD	once a day
QM	once a month
SLR	systematic literature review

cardiovascular events (MACEs), without associated safety concerns/adverse events, even when LDL-C is reduced to very low levels (<40 mg/dL [<1 mmol/L]).[2–5] Managing LDL-C in a risk-stratified manner is particularly important in patients at high or very-high risk of MACEs.[2,3]

European guidelines now recommend even lower LDL-C levels in groups at very-high risk of ASCVD.[3,6,7] The 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society guidelines and the more recent 2021 ESC guidelines recommend an LDL-C goal of <55 mg/dL (<1.4 mmol/L) and ≥50% LDL-C reduction from baseline for very high-risk patients, whereas US guidelines suggest high-intensity or maximal statin therapy, with addition of ezetimibe and/or PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor if LDL-C remains above the threshold of ≥70 mg/dL (≥1.8 mmol/L).[2,3,7]

Although treatment with statins is the predominant treatment for elevated LDL-C, statin therapy does not allow some patients to achieve LDL-C values of <55 mg/dL,[2,7] some patients may not tolerate statins at higher intensities,[8] and there are a minority of others who are reportedly intolerant entirely,[9] although recent data have highlighted an important role for the nocebo effect in patients with perceived adverse effects following statin therapy.[10] In some patients, even high-intensity statins alone may not be enough. Where required, statins can be supplemented by nonstatin agents, such as ezetimibe and/or PCSK9 inhibitors, to further optimize LDL-C reduction.[3,7] Recent real-world European data suggest that LDL-C goals are rarely met among very high-risk patients; only 18% (≈1 of 6) of very high-risk patients achieved the 2019 European guideline LDL-C goal of <55 mg/dL (<1.4 mmol/L), whereas 39% met the 2016 goal of <70 mg/dL (<1.8 mmol/L).[11] A prospective observational study in the United States looking at treatment patterns over 2 years in patients with ASCVD identified that at 2 years of follow-up 31.7% of patients overall had LDL-C levels <70 mg/dL (<1.8 mmol/L).[12] The increased use of nonstatin agents in combination with statins may help higher-risk patients meet the LDL-C levels recommended by current guidelines.

There are limited head-to-head comparative trial data for nonstatin lipid-lowering therapies (LLTs) (focused on PCSK9 inhibitors versus other nonstatin LLTs, including newer agents); therefore, indirect treatment comparisons through network meta-analysis (NMA) may inform evidence-based treatment decisions. We previously used NMA to compare LDL-C reduction in nonstatin LLTs, including evolocumab, alirocumab, and ezetimibe, in patients receiving statin background therapy.[13]

Since this earlier publication, new studies of the approved monoclonal antibody (mAb) PCSK9 inhibitors alirocumab and evolocumab have been published, and 2 new LLTs have emerged: bempedoic acid,[14–18] an ATP citrate lyase inhibitor that has been approved

by the US Food and Drug Administration[19] and the European Medicines Agency[20]; and inclisiran,[21–23] a small interfering RNA (siRNA) PCSK9 inhibitor that has been approved by the European Medicines Agency[24,25] and the US Food and Drug Administration.[26] This systematic review and NMA sought to provide a detailed assessment of the relative efficacy of nonstatin agents in reducing LDL-C.

METHODS

Amgen holds the source data, and all authors had full access to the data. All data are presented in the article and supplementary information.

Objectives

The primary objective of this NMA was to assess the comparative efficacy of nonstatin agents (bempedoic acid, ezetimibe, mAb PCSK9 inhibitors [alirocumab and evolocumab], and siRNA PCSK9 inhibitor [inclisiran]) to reduce LDL-C (percentage change from baseline at week 12) when added to maximally tolerated statins. Secondary objectives of the study were to assess the reduction in LDL-C over a longer follow-up period (percentage change from baseline at week 24), to assess the change in other lipid parameters relevant to ASCVD, including non–high-density lipoprotein cholesterol (HDL-C) and apolipoprotein B (ApoB) (percentage change from baseline at week 12), and to analyze the impact of treating a hypothetical population with each intervention on LDL-C levels to assess the proportion of values that meet the current European guideline-recommended LDL-C goal of <55 mg/dL (<1.4 mmol/L).

Study Design

Systematic Literature Review

The systematic literature review (SLR) adhered to methods published by the Centre for Reviews and Dissemination[27] and the Cochrane Collaboration. The Population, Intervention, Comparison, and Outcomes inclusion/exclusion criteria for the SLR are shown in Table 1. Randomized trials were relevant if they compared at least 2 relevant interventions: alirocumab, bempedoic acid, bempedoic acid/ezetimibe fixed-dose combination (FDC), evolocumab, ezetimibe, inclisiran, or placebo. Trials were included if they enrolled adults (aged ≥18 years) with primary (including familial and nonfamilial) hypercholesterolemia or ASCVD, who require treatment of hyperlipidemia, and were at least 12 weeks in duration with at least 10 patients per study arm.

Databases searched to identify all relevant records were PUBMED, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database (an example search strategy for PUBMED is shown in Data S1). The EMBASE search strategies for each set of searches were independently peer reviewed by a second information specialist, using the Canadian Agency for Drugs and Technologies in Health peer review checklist.[28] All data were extracted by one reviewer and independently checked for errors by a second reviewer during the SLR data extraction. Individual patient data were not available for analysis. The risk of bias was assessed using the Cochrane Risk of Bias Assessment Tool.

Network Meta-Analysis

Trials identified in the SLR were eligible for NMAs if they reported data on LDL-C, non–HDL-C, and/or ApoB. Trials were excluded from NMAs if they were specifically conducted in patients with homozygous familial hypercholesterolemia, if <70% of participants were on moderate-to high-intensity statins (unless apparently statin intolerant), or if insufficient data were available (eg, variability estimates).

Evolocumab doses of 140 mg every 2 weeks (Q2W) and 420 mg once a month (QM) are clinically similar[29–31]; therefore, data for both regimens were combined in a single node in the network. This is not the case for alirocumab, where 75 mg Q2W, 300 mg QM, and 150 mg Q2W regimens are not clinically equivalent[32–35]; hence, these regimens were included as separate nodes.

The primary network was based on the percentage LDL-C reduction achieved at week 12. When week 12 data were not available, the nearest time point after week 12 was used. For evolocumab, data for the mean of weeks 10 and 12 were used to ensure the efficacy of monthly dosing was accurately reflected (representing the average LDL-C reduction across the extended dosing period). Inclisiran is also dosed at extended intervals: days 1 and 90, and in some trials dosing continued on days 270 and 450.[21–23] LDL-C reduction with inclisiran is maximized at day 150 (ie, around week 21).[25] The coprimary end point, time-adjusted LDL-C reduction between days 90 and 540, was used and, given the extended dosing interval, was assumed to provide the most appropriate estimate of inclisiran efficacy rather than using a single time point.

In the NMA focused on time points after week 12 (ie, week 24), data for the nearest time point after the defined follow-up period were used where necessary. Alirocumab trials of 75 mg Q2W, which allowed up titration at week 12, were excluded from the week 24 data set.

Table 1. Inclusion/Exclusion Criteria for the Systematic Literature Review

PICO criteria	Inclusion criteria	Exclusion criteria
Population	Adults (aged ≥18 y) with primary (including familial and nonfamilial) hypercholesterolemia who require treatment of elevated lipid levels (hyperlipidemia) and are receiving maximally tolerated statins (defined as moderate- to high-intensity statin therapy [per AHA-ACC] or where lower-intensity/no statin patients are declared to be statin intolerant*) For the HoFH subgroup only, patients aged ≥12 y were also eligible for inclusion	
Interventions or comparators	Trials comparing at least 2 interventions or comparators of interest: evolocumab, alirocumab, ezetimibe, bempedoic acid, bempedoic acid/ezetimibe fixed-dose combination, inclisiran, placebo	Trials including unlicensed doses or regimens
Outcomes	Trials reporting relevant data for at least one of the following outcomes were considered for inclusion: Lipid outcomes • Percentage reduction from baseline in LDL-C • Absolute reduction in LDL-C from baseline • Percentage reduction from baseline in non–HDL-C • Percentage people achieving LDL-C <70 mg/dL (<1.8 mmol/L) • Percentage reduction from baseline in Lpa • Percentage reduction from baseline in ApoB • Percentage reduction from baseline in total cholesterol • Percentage reduction from baseline in triglycerides Time points • Wk 12 or the nearest time point to 12 wk • Wk 24 or the nearest time point to 24 wk • Wk 48 or the nearest time point to 48 wk Adverse events • Any treatment-emergent AE • Any serious treatment-emergent AE • Any fatal AE • AEs leading to discontinuation • AEs of interest: ◦ Muscle symptoms (specifically, myopathy and rhabdomyolysis) ◦ New-onset diabetes ◦ Elevated creatine kinase ◦ Neurocognitive AEs	
Study design	RCTs of at least 12 wk in duration	Trials with <10 participants and preclinical and animal trials Trials including patients with significant heart failure (NYHA grade III–IV) or significant renal dysfunction (stage 4–5)

ACC indicates American College of Cardiology; AE, adverse event; AHA, American Heart Association; ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Lpa, lipoprotein a; NYHA, New York Heart Association; PICO, Population, Intervention, Comparison, and Outcomes; and RCT, randomized controlled trial.

*Definition of statin intensity is less clear in East Asian countries, and lower doses are generally used compared with Western countries. Trials in which populations received lower-intensity statin therapy than those defined by ACC-AHA were therefore eligible if conducted in East Asian populations.

Trials eligible for the NMAs were assessed for clinical and statistical heterogeneity. In the absence of significant treatment effect modifiers one efficacy for reducing LDL-C, it was considered feasible to combine all eligible trials reporting LDL-C data in a network. Statistical heterogeneity was assessed through visual inspection of forest plots from pairwise direct meta-analyses of agents within the network (overlap of effect sizes and 95% CIs) and through subsequent I^2 and the χ^2 tests (I^2>75% may indicate meaningful heterogeneity). The impact of clinical and statistical heterogeneity was explored through sensitivity analyses that excluded individual trials or groups of trials associated with heterogeneity. Consistency of effect was also explored through subgroup analysis by statin background therapy and ASCVD status by including only trials with at least a 50% ASCVD population.

The NMA was conducted using frequentist methods using the Netmeta R package[36] and Bayesian models[37] in WinBUGS (MRC Biostatistics Unit, Cambridge, UK) version 1.4.3. Bayesian analyses were performed as described previously in Toth et al.[13] All analyses used the mean difference between groups and SE (as opposed to the mean and SE for each group). Where >1 treatment difference was reported for a pair of treatments for a single study (eg, for 2 different statin backgrounds), meta-analysis was used to estimate a single treatment difference for each treatment pair within each study. A random-effects model was used throughout. Local inconsistency was explored using the Netmeta R package by splitting the network estimates into the contribution of direct and indirect evidence. Network graphs were produced to visualize the weight of evidence and number of trials connecting each pair of treatments.

Simulation of LDL-C Lowering With Each Intervention

The impact of treating a population with each intervention was explored using simulation techniques. Using the DA VINCI (The EU-Wide Cross-Sectional Observational Study of Lipid Modifying Therapy Use in Secondary and Primary Care) study,[11] a European Union–wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care, we estimated the mean (and SD) LDL-C for the group of patients with ASCVD receiving stabilized statin therapy without ezetimibe or PCSK9i. Assuming a normal distribution, we simulated 10 000 LDL-C values, and values >70 mg/dL (>1.8 mmol/L) were selected to represent a hypothetical pool of patients requiring additional LLT. We then simulated the LDL-C reduction achieved by each intervention by randomly sampling from a normal distribution with mean estimated from the primary NMA and SD estimate obtained from a specific clinical trial (Table S1). The NMA does not provide any information about the variability between individuals; hence, to estimate the SD, a single clinical trial was selected for each intervention, with a preference given to the largest study with the time point closest to 12 weeks. For ezetimibe, only studies that included patients stabilized on statin at randomization were considered as a source for the SD, because, for the studies that included patients not stabilized on statin at randomization, percentage reduction in LDL-C from baseline of ezetimibe versus placebo had been derived from the data provided (statin plus ezetimibe versus statin plus placebo). The posttreatment LDL-C was calculated, and it was assessed whether each value decreased below 55 mg/dL (1.4 mmol/L), the goal recommended in the 2019 ESC/European Atherosclerosis Society guidelines for very high-risk patients (eg, those who have ASCVD).[3]

RESULTS

Network Construction

The SLR initially identified 5377 records from databases and other sources. This was refined using title and abstract screening and full-text screening to give 55 relevant trials for the SLR. Further refinement excluded 7 trials, resulting in 48 randomized controlled trials for inclusion in the primary NMA (Figure 1). Of these, 10 trials were phase 2 trials, 36 trials were phase 3 trials, 1 trial was a phase 3b/4 trial, and 1 trial was unclear. The reasons for exclusion of the 7 trials from the NMA are outlined in Table S2, with the main reasons being ineligible population and/or study design and insufficient data.

The details of the trials included in the primary NMA are shown in Table 2,[14,16–18,21–23,32,34,38–74] and the overall network diagram is shown in Figure 2.

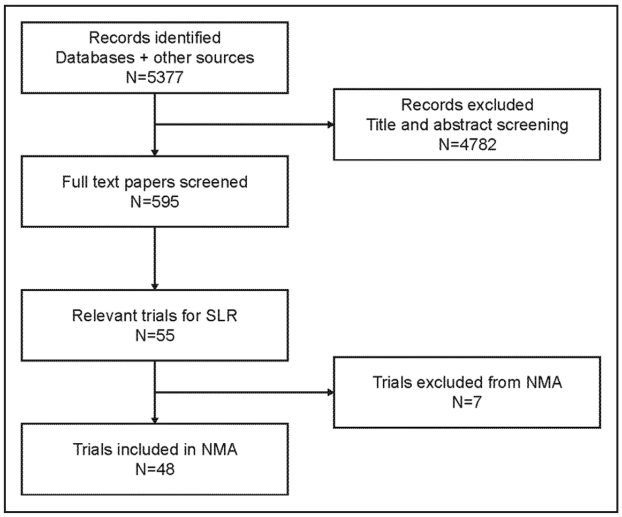

Figure 1. Study flow diagram of the systematic review.
Trials included in the network meta-analysis (NMA) included those with patients either receiving background statin treatment or who were statin intolerant. SLR indicates systematic literature review.

The risk of bias was analyzed to assess the quality of each study. Overall, the risk of bias for the 48 trials in the primary network was generally low or unclear in 31 and 14 trials, respectively. The most common areas where reporting was unclear were allocation of concealment and randomization methods. Some trials (n=4) were observed to have high potential for bias with regard to incomplete reporting of outcomes; however, it was possible to source the required information from ClinicalTrials.gov, and therefore, in practice, risk of bias was low. No studies were excluded from the NMA on the risk of bias. The complete risk of bias assessment is presented in Table S3.

Direct meta-analyses combining specific trials comparing relevant interventions within the network are shown in Figure S1. I^2 values generally indicated high levels of heterogeneity; however, this finding is influenced by narrow CIs from individual trials, resulting in less overlap. Visual inspection indicated some possible heterogeneity associated with East Asian trials and with certain trials in populations with familial hypercholesterolemia. Because this is also clinically plausible, sensitivity analyses for the primary end point excluding these trials were performed.

Table S4 details which trials from the overall network were included in the sensitivity analyses, subgroup analyses, and the secondary objective analyses at week 24 and for the other lipid end points. Although an analysis at week 48 was considered, it was deemed unfeasible because of relatively few data being reported at this time point and, most important, because of differences between trials in approaches to handling missing data over the longer follow-up period.

Table 2. Details of Trials Included in the Primary Network

Study	Arms (number)	Population	Duration
McKenney 2012[38] NCT01288443	Alirocumab, 150 mg Q2W (n=31) vs placebo for alirocumab, Q2W (n=31)	Hypercholesterolemia Background: statins	12 wk
ODYSSEY ALTERNATIVE[39] NCT01709513	Alirocumab, 75 mg Q2W (possible up titration to 150 mg Q2W)+placebo for ezetimibe, QD (n=126) vs ezetimibe, 10 mg QD+placebo for alirocumab, Q2W (n=126)	Hypercholesterolemia Background: NR	24 wk
ODYSSEY CHOICE I[34] NCT01926782	Alirocumab, 75 mg Q2W (possible dose adjustment to 150 mg Q2W) (n=78) vs placebo for alirocumab, QM (results not reported for placebo, Q2W, arm) (n=157)	Hypercholesterolemia Background: statins (maximum tolerated), other LLT (including ezetimibe)	48 wk
ODYSSEY CHOICE II[40] NCT02023879	Alirocumab, 75 mg Q2W (possible up titration to 150 mg Q2W) (n=116) vs placebo for alirocumab, Q2W (n=58)	Hypercholesterolemia Background: ezetimibe	24 wk
ODYSSEY COMBO I[32] NCT01644175	Alirocumab, 75 mg Q2W (possible dose adjustment to 150 mg Q2W) (n=107) vs placebo (n=209)	Hypercholesterolemia Background: statins (maximum tolerated), no statins (statin intolerant)	52 wk
ODYSSEY COMBO II[41] EUCTR2011-004130-34	Alirocumab, 75 mg Q2W (possible dose adjustment to 150 mg Q2W)+placebo for ezetimibe, QD (n=479) vs ezetimibe, 10 mg QD+placebo for alirocumab, Q2W (n=241)	Hypercholesterolemia Background: statins (maximum tolerated), no statin (statin intolerant)	104 wk
ODYSSEY DM INSULIN[42] NCT02585778, EUCTR2015-000799-92	Alirocumab, 75 mg Q2W (possible dose adjustment to 150 mg Q2W) (n=345) vs placebo for alirocumab, Q2W (n=172)	Hypercholesterolemia, diabetes Background: statins (maximum tolerated), other LLT	24 wk
ODYSSEY EAST[43] NCT02715726	Alirocumab, 75 mg Q2W (possibly up titrated to 150 mg Q2W) (n=407) vs ezetimibe, 10 mg QD (n=208)	ASCVD Background: statins (maximum tolerated)	24 wk
ODYSSEY FH I[44] NCT01623115	Alirocumab, 75 mg Q2W (possible dose adjustment to 150 mg Q2W) (n=323) vs placebo for alirocumab, Q2W (n=163)	HeFH Background: statins (maximum tolerated), other LLT (including ezetimibe)	78 wk
ODYSSEY FH II[44] NCT01709500	Alirocumab, 75 mg Q2W (possible dose adjustment to 150 mg Q2W) (n=167) vs placebo for alirocumab, Q2W (n=82)	HeFH Background: statins (maximum tolerated), other LLT (including ezetimibe)	78 wk
ODYSSEY HIGH FH[45] NCT01617655	Alirocumab, 150 mg Q2W (n=72) vs placebo for alirocumab, Q2W (n=35)	HeFH Background: statins (maximum tolerated), other LLT (including ezetimibe)	78 wk
ODYSSEY JAPAN[46] NCT02107898	Alirocumab, 75 mg Q2W (possible dose adjustment to 150 mg Q2W) (n=144) vs placebo (n=72)	Hypercholesterolemia, HeFH Background: statins, other LLT	12 wk
ODYSSEY KT[47] NCT02289963	Alirocumab, 75 mg Q2W (possible dose adjustment to 150 mg Q2W) (n=97) vs placebo for alirocumab, Q2W (n=102)	ASCVD, diabetes, hypercholesterolemia Background: statins (maximum tolerated), other LLT (including ezetimibe)	24 wk
ODYSSEY LONG TERM[48] NCT01507831	Alirocumab, 150 mg Q2W (n=1553) vs placebo for alirocumab, Q2W (n=788)	Hypercholesterolemia Background: statins (maximum tolerated), no statin (statin intolerant), other LLT	78 wk
ODYSSEY NIPPON[49] NCT02584504	Alirocumab, 150 mg Q2W (n=53) vs placebo for alirocumab, Q2W (n=56)	Hypercholesterolemia Background: low/no statin (statin intolerant), ezetimibe, other LLT	12 wk

(*Continued*)

Table 2. Continued

Study	Arms (number)	Population	Duration
ODYSSEY OPTIONS I[50] NCT01730040	Alirocumab, 75 mg Q2W (possible dose adjustment to 150 mg Q2W)+placebo for ezetimibe, QD (n=104) vs ezetimibe, 10 mg QD+placebo for alirocumab, Q2W (n=102) vs placebo for alirocumab, Q2W+placebo for ezetimibe, QD (n=149)	Hypercholesterolemia Background: statins	24 wk
ODYSSEY OPTIONS II[51] NCT01730053	Alirocumab, 75 mg Q2W (possible dose adjustment to 150 mg Q2W)+placebo for ezetimibe, QD (n=103) vs ezetimibe, 10 mg QD+placebo for alirocumab, Q2W (n=101) vs placebo for alirocumab, Q2W+placebo for ezetimibe, QD (n=101)	Hypercholesterolemia Background: statins	24 wk
Stein 2012[52] NCT01266876	Alirocumab, 150 mg Q2W (n=16) vs placebo for alirocumab, Q2W (n=15)	HeFH Background: statins	12 wk
Teramoto 2016[53] NCT01812707	Alirocumab, 75 mg Q2W (n=25) vs alirocumab, 150 mg Q2W (n=25) vs placebo for alirocumab, Q2W (n=25)	Hypercholesterolemia Background: statins	12 wk
Ballantyne 2016[54] NCT02072161	Bempedoic acid, 180 mg QD (n=45) vs placebo (n=45)	Hypercholesterolemia Background: statins	12 wk
CLEAR HARMONY[18] NCT02666664, EUCTR2015-004136-36	Bempedoic acid, 180 mg QD (n=1488) vs placebo for bempedoic acid, QD (n=742)	ASCVD and/or HeFH Background: statins (maximum tolerated), other LLT	52 wk
CLEAR SERENITY[17] NCT02988115	Bempedoic acid, 180 mg QD (n=234) vs placebo for bempedoic acid, QD (n=111)	Hypercholesterolemia Background: none (statin intolerant)	24 wk
CLEAR TRANQUILITY[14] EUCTR2016-004084-39, NCT03001076	Bempedoic acid, 180 mg QD (n=181) vs placebo for bempedoic acid, QD (n=81)	Hypercholesterolemia Background: none (statin intolerant)	12 wk
CLEAR WISDOM[16] NCT02991118	Bempedoic acid, 180 mg QD (n=522) vs placebo (n=257)	ASCVD and/or HeFH Background: LLT (maximum tolerated), statin, no LLT	52 wk
Ballantyne 2020 FDC[55] NCT03337308	Bempedoic acid, 180 mg QD+ezetimibe, 10 mg QD (fixed-dose combination) (n=108 randomized, 86 analyzed) vs bempedoic acid, 180 mg QD (n=110 randomized, 88 analyzed) vs ezetimibe, 10 mg QD (n=109 randomized, 86 analyzed) vs placebo, QD (n=55 randomized, 41 analyzed)	Hypercholesterolemia, high risk Background: all (statin intolerant) after no statins	12 wk
Thompson 2016 (statin-intolerant group only)[56] NCT01941836	Bempedoic acid, 180 mg QD (n=51) vs bempedoic acid, 180 mg QD+ezetimibe, 10 mg QD (n=12) vs ezetimibe, 10 mg QD (n=51)	Hypercholesterolemia Background: none (statin intolerant)	12 wk
BANTING[57] NCT02739984, EUCTR2015-004711-21	Evolocumab, 420 mg QM (n=281) vs placebo for evolocumab, QM (n=143)	Hypercholesterolemia, diabetes Background: statins (maximum tolerated)	12 wk
BERSON[58] NCT02662569	Evolocumab, 140 mg Q2W (n=327) vs placebo for evolocumab, Q2W (n=166) vs evolocumab, 420 mg QM (n=332) vs placebo for evolocumab, QM (n=161)	Hypercholesterolemia, diabetes Background: statins	12 wk

(*Continued*)

Table 2. Continued

Study	Arms (number)	Population	Duration
DESCARTES/Amgen 20110109[59] NCT01516879	Evolocumab, 420 mg QM (n=402) vs placebo for evolocumab, QM (n=202) vs evolocumab, 420 mg QM+ezetimibe, 10 mg QD (n=126) vs ezetimibe, 10 mg QD+placebo for evolocumab, QM (n=63)	Hypercholesterolemia Background: statins	48 wk
FOURIER/Amgen 20160250[60] NCT01764633	Evolocumab, 140 mg Q2W/420 mg QM (n=13 784) vs placebo for evolocumab, Q2W or QM (n=13 780)	ASCVD Background: statins, ezetimibe	Median, 26 mo
GAUSS/Amgen 20090159[61] NCT01375764	Evolocumab, 420 mg QM (n=32) vs evolocumab, 420 mg QM+ezetimibe, 10 mg QD (n=31) vs ezetimibe, 10 mg QD+placebo for evolocumab, QM (n=33)	Hypercholesterolemia Background: none (statin intolerant)	12 wk
GAUSS-2/Amgen 20110116[62] NCT01763905	Evolocumab, 140 mg Q2W+placebo for ezetimibe, QD (n=103) vs ezetimibe, 10 mg QD+placebo for evolocumab, Q2W (n=51) vs evolocumab, 420 mg QM+placebo for ezetimibe, QD (n=102) vs ezetimibe, 10 mg QD+placebo for evolocumab, QM (n=51)	Hypercholesterolemia Background: none (statin intolerant)	12 wk
GAUSS-3 (part B)/Amgen 20120332[63] NCT01984424	Evolocumab, 420 mg QM+placebo for ezetimibe, QD (n=145) vs ezetimibe, 10 mg QD+placebo for evolocumab, QM (n=73)	Hypercholesterolemia Background: none (statin intolerant)	24 wk
GAUSS-4[64] NCT02634580	Evolocumab, 140 mg Q2W+placebo for ezetimibe, QD (n=19) vs ezetimibe, 10 mg QD+placebo for evolocumab, Q2W (n=10) vs evolocumab, 420 mg QM+placebo for ezetimibe, QD (n=21) vs ezetimibe, 10 mg QD+placebo for evolocumab, QM (n=11)	Hypercholesterolemia Background: none (statin intolerant)	12 wk
GLAGOV/Amgen 20120153[65] NCT01813422	Evolocumab, 420 mg QM (n=484) vs placebo for evolocumab, QM (n=486)	ASCVD Background: statins	Median, 78 wk
LAPLACE-2/Amgen 20110115[66] NCT01763866	Evolocumab, 140 mg Q2W+placebo for ezetimibe, QD (n=394) vs placebo for evolocumab, Q2W±placebo for ezetimibe, QD (n=183) vs ezetimibe, 10 mg QD+placebo for evolocumab, Q2W (n=80) vs evolocumab, 420 mg QM±placebo for ezetimibe, QD (n=391) vs placebo for evolocumab, QM±placebo for ezetimibe, QD (n=193) vs ezetimibe, 10 mg QD+placebo for evolocumab, QM (n=68)	Hypercholesterolemia Background: statins	52 wk
LAPLACE-TIMI 57/Amgen 20101155[67] NCT01380730	Evolocumab, 140 mg Q2W (n=78) vs placebo for evolocumab, Q2W (n=78) vs evolocumab, 420 mg QM (n=80) vs placebo for evolocumab, QM (n=79)	Hypercholesterolemia Background: statins	12 wk
RUTHERFORD/Amgen 20090158[68] NCT01375751	Evolocumab, 420 mg QM (n=56) vs placebo for evolocumab, QM (n=56)	HeFH Background: statins, ezetimibe, other LLT	12 wk
RUTHERFORD-2/Amgen 20110117[69] NCT01763918	Evolocumab, 140 mg Q2W (n=111) vs placebo for evolocumab, Q2W (n=55) vs evolocumab, 420 mg QM (n=110) vs placebo for evolocumab, QM (n=55)	HeFH Background: statins, ezetimibe, other LLT	12 wk

(*Continued*)

Table 2. Continued

Study	Arms (number)	Population	Duration
YUKAWA/Amgen 20110231[70] NCT01652703	Evolocumab, 140 mg Q2W (n=52) vs placebo for evolocumab, Q2W (n=52) vs evolocumab, 420 mg QM (n=51) vs placebo for evolocumab, QM (n=53)	Hypercholesterolemia Background: statins, ezetimibe	12 wk
YUKAWA-2/Amgen 20120122[71] NCT01953328	Evolocumab, 140 mg Q2W (n=101) vs placebo for evolocumab, Q2W (n=101) vs evolocumab, 420 mg QM (n=101) vs placebo for evolocumab, QM (n=101)	Hypercholesterolemia Background: statins	12 wk
ENHANCE[72] NCT00552097	Ezetimibe, 10 mg QD (n=357) vs placebo for ezetimibe, QD (n=363)	HeFH Background: statins	104 wk
IMPROVE-IT[73] NCT00202878	Ezetimibe, 10 mg QD (n=9067) vs placebo for ezetimibe, QD (n=9077)	ASCVD Background: statins	Median, 6 y
Masana 2005[74]	Ezetimibe, 10 mg QD (n=355) vs placebo for ezetimibe, QD (n=78)	Hypercholesterolemia Background: statins	48 wk
ORION-1[23] NCT02597127	Inclisiran, 300 mg (n=62) vs placebo for inclisiran (n=65)	Hypercholesterolemia Background: statins (maximum tolerated), other LLT (including ezetimibe)	26.7 wk
ORION-9[21] NCT03397121	Inclisiran-free acid, 284 mg (inclisiran sodium, 300 mg) (n=242) vs placebo (n=240)	HeFH Background: statins (maximum accepted), ezetimibe	77.1 wk
ORION-10[22] NCT03399370	Inclisiran-free acid, 284 mg (inclisiran sodium, 300 mg) (n=781) vs placebo (n=780)	ASCVD Background: statins (maximum tolerated), ezetimibe, other LLT	77.1 wk
ORION-11[22] NCT03400800	Inclisiran-free acid, 284 mg (inclisiran sodium, 300 mg) (n=810) vs placebo (n=807)	ASCVD Background: statins (maximum tolerated), ezetimibe, other LLT	77.1 wk

ASCVD indicates atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; LLT, lipid-lowering therapy; NR, not reported; Q2W, every 2 weeks; QD, once a day; and QM, once a month.

Primary Objective: The Placebo-Corrected LDL-C Reduction at Week 12

All interventions significantly reduced LDL-C when compared with placebo (Figure 3). The treatment differences between LLT and placebo for the percentage reduction in LDL-C from baseline to week 12, or time-average data in the case of inclisiran, show that among the mAb PCSK9 inhibitors, evolocumab, 140 mg Q2W/420 mg QM, reduced LDL-C by a mean of 64.68% (95% CI, 67.37%–62.00%), whereas alirocumab, 150 mg Q2W, reduced LDL-C by a mean of 62.71% (95% CI, 67.56%–57.87%) (Figure 3). Both alirocumab, 75 mg Q2W and 300 mg QM, dosages resulted in a smaller reduction in LDL-C than 150 mg Q2W. Treatment with 300 mg of siRNA PCSK9 inhibitor inclisiran every 3 months and then every 6 months (Q3M to Q6M) was found to reduce LDL-C by a mean of 50.17% (95% CI, 54.99%–45.35%). Treatment with ezetimibe, 10 mg once a day (QD), reduced LDL-C by a mean of 24.49% (95% CI, 27.48%–21.49%) from baseline; and for bempedoic acid, 180 mg QD, LDL-C was reduced by a mean of 22.83% (95% CI, 26.83%–18.82%). The FDC of ezetimibe, 10 mg, and bempedoic acid, 180 mg, was almost 2-fold more efficacious than either treatment individually, reducing LDL-C by a mean of 42.93% (95% CI, 49.96%–35.80%).

The primary analysis was performed using frequentist methods. When Bayesian methods were used, similar results were observed (data not shown), which confirmed the frequentist approach.

A pairwise comparison between the agents in the primary network was performed (Table S5) and identified that the reduction in LDL-C was greater for evolocumab, 140 mg Q2W/420 mg QM, and alirocumab, 150 mg Q2W, compared with each of the other LLTs. Alirocumab, 75 mg Q2W, alirocumab, 300 mg QM, and inclisiran, 300 mg Q3M to Q6M, were not significantly more efficacious than one another. Of these, alirocumab, 75 mg Q2W, was significantly more efficacious than the bempedoic acid/ezetimibe FDC,

whereas alirocumab, 300 mg QM, and inclisiran, 300 mg Q3M to Q6M, were not. All these agents were more efficacious than bempedoic acid and ezetimibe alone.

Subgroup Analyses

In 38 of the trials included in the primary NMA, patients received background statin therapy. A subgroup analysis of these trials looking at the mean difference

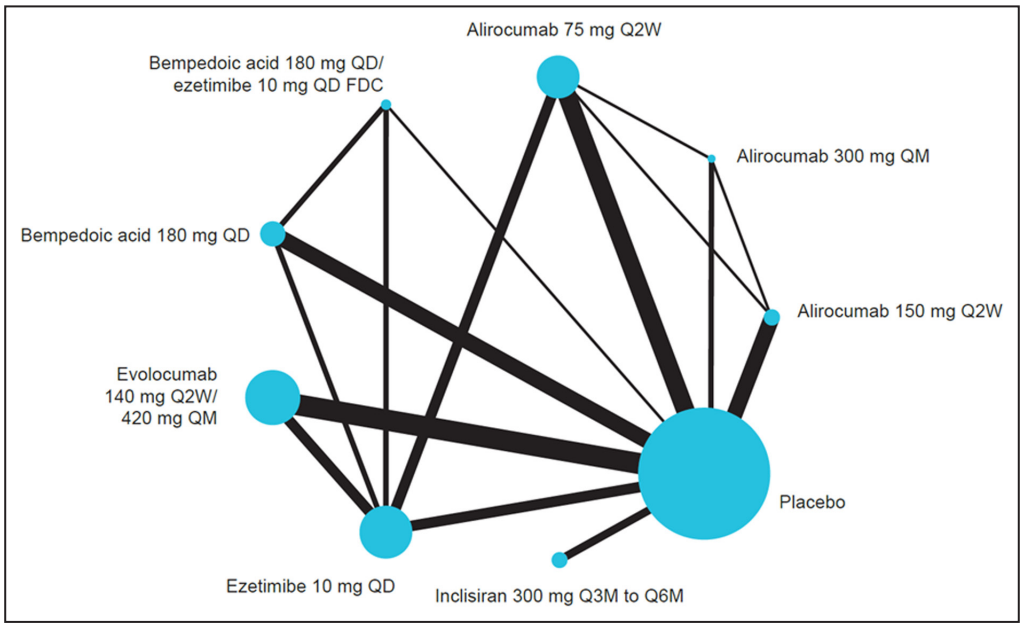

Figure 2. Primary network: connection of eligible randomized controlled trials reporting percentage change in low-density lipoprotein cholesterol from baseline to week 12.
The diameter of each circle represents the proportional total weight of all trials in the network that investigated that intervention. The thickness of each line connecting 2 interventions is proportional to the number of trials that investigated that pair of interventions. FDC indicates fixed-dose combination; Q2W, every 2 weeks; Q3M, every 3 months; Q6M, every 6 months; QD, once a day; QM, once a month; and RCT, randomized controlled trial.

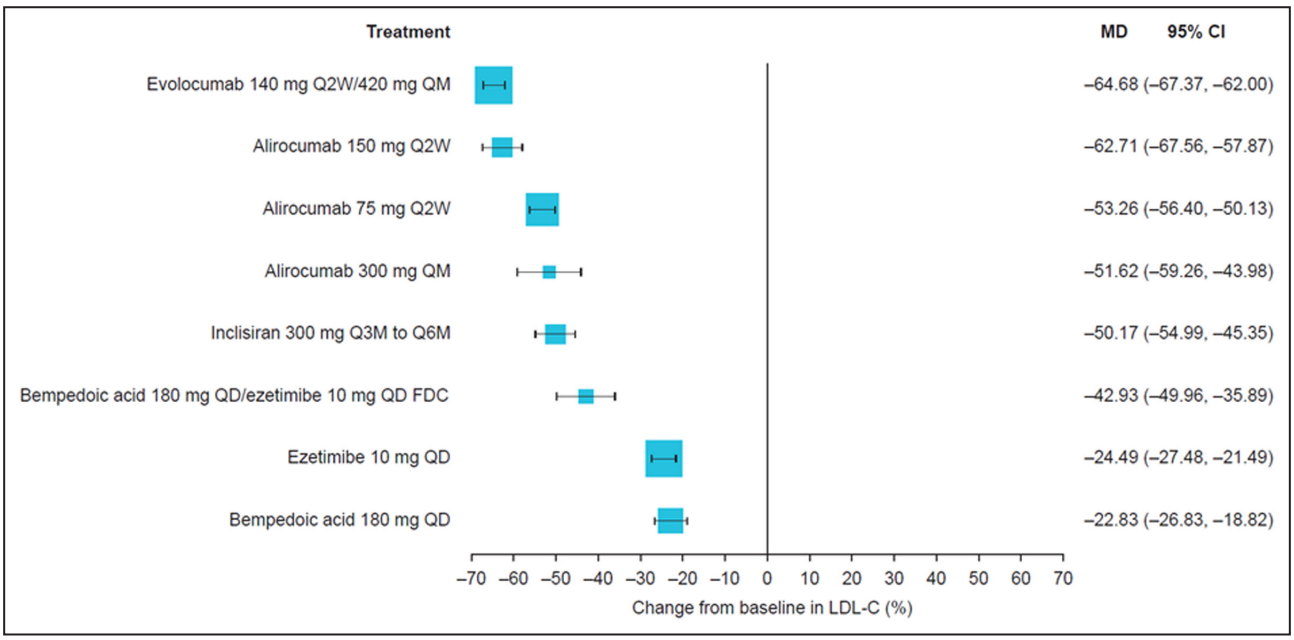

Figure 3. The mean difference (MD) in percentage change in low-density lipoprotein cholesterol (LDL-C) in response to lipid-lowering therapy relative to placebo at week 12.
FDC indicates fixed-dose combination; Q2W, every 2 weeks; Q3M, every 3 months; Q6M, every 6 months; QD, once a day; and QM, once a month.

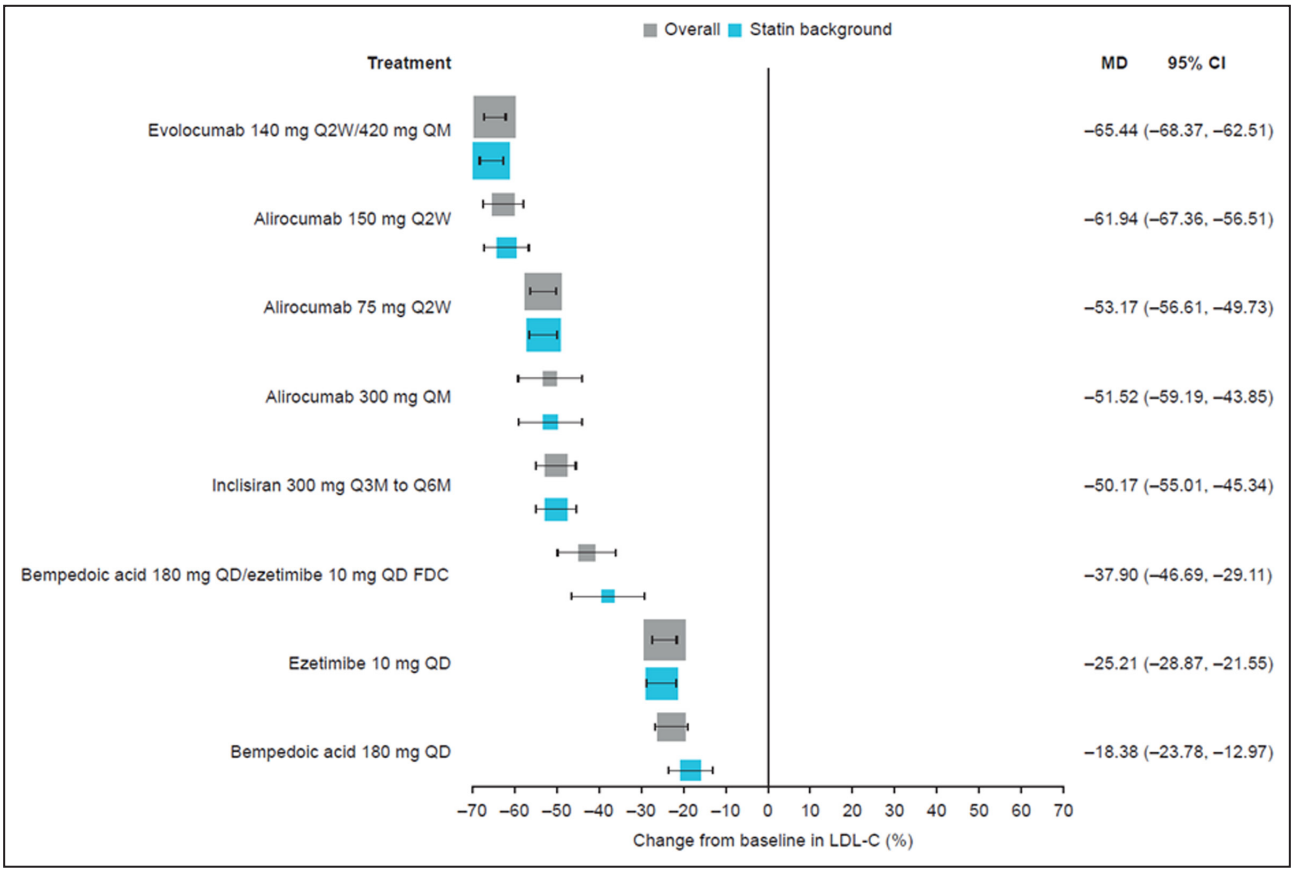

Figure 4. Subgroup analysis: the mean difference (MD) in percentage change in low-density lipoprotein cholesterol (LDL-C) from baseline in response to lipid-lowering therapy relative to placebo at week 12 in patients receiving statin background therapy (moderate-high intensity) (blue), with the primary analysis data plotted for comparison (gray).
FDC indicates fixed-dose combination; Q2W, every 2 weeks; Q3M, every 3 months; Q6M, every 6 months; QD, once a day; and QM, once a month.

in percentage change in LDL-C from baseline relative to placebo at week 12 found similar results to the overall population (Figure 4), with evolocumab, 140 mg Q2W/420 mg QM, and alirocumab, 150 mg Q2W, being the most efficacious (65.44% and 61.94% change in LDL-C from baseline, respectively), followed by other alirocumab doses, inclisiran, and then the bempedoic acid/ezetimibe FDC and its components. A similar pattern was found in an NMA including the 10 trials in patients reporting statin intolerance (Figure S2); however, these findings are based on a much smaller evidence base (lower number of trials and sample size) and a more disconnected network. Furthermore, all the evidence for evolocumab, ezetimibe, and the bempedoic acid/ezetimibe FDC compared with placebo is indirect. These data therefore have greater levels of uncertainty.

Unlike other agents, the percentage reduction of LDL-C levels by bempedoic acid was influenced by statin background therapy. Bempedoic acid reduced LDL-C levels to a lesser extent in the subgroup analysis focusing on trials with moderate- to high-intensity statin background therapy, than it did in the overall analyses, which also included trials that declared lower intensities/no statin patients to be statin intolerant.

A further subgroup NMA included 17 trials that enrolled predominately patient populations with ASCVD (>50% patients with ASCVD included) (Figure 5). Again, analysis of these trials showed a similar trend to the main NMA, with evolocumab, 140 mg Q2W/420 mg QM, and alirocumab, 150 mg Q2W, being most efficacious (62.80% and 64.80% LDL-C reduction, respectively), followed by alirocumab, 75 mg Q2W (53.97%), and inclisiran (52.11%). Bempedoic acid and ezetimibe were least efficacious, with percentage LDL-C reduction of 17.96% and 24.63%, respectively.

Sensitivity Analyses

Sensitivity analyses were conducted for the primary network, excluding potential sources of statistical and clinical heterogeneity (ie, trials in familial hypercholesterolemia or East Asian populations). The 8 trials involving patients with familial hypercholesterolemia and the 8 trials with East Asian populations were excluded in

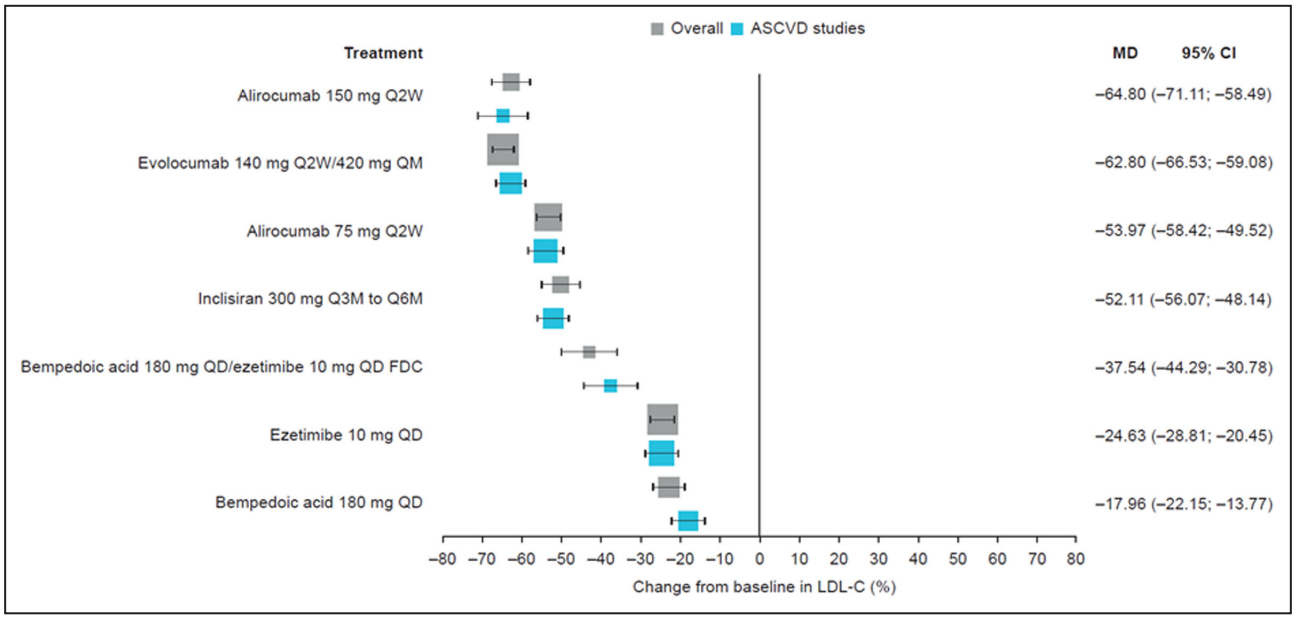

Figure 5. Subgroup analysis: the mean difference (MD) in percentage change in low-density lipoprotein cholesterol (LDL-C) from baseline in response to lipid-lowering therapy relative to placebo at week 12 in predominantly populations with atherosclerotic cardiovascular disease (ASCVD) (blue), with the primary analysis data plotted for comparison (gray). FDC indicates fixed-dose combination; Q2W, every 2 weeks; Q3M, every 3 months; Q6M, every 6 months; QD, once a day; and QM, once a month.

separate analyses. The trials included in the analyses are detailed in Table S4. The exclusion of these trials from the meta-analysis provided similar results to the overall NMA (Figure 6).

Secondary Objectives

Placebo-Corrected LDL-C Reduction at Week 24

Of the 48 trials in the primary NMA, 16 were included in an analysis to assess the reduction in LDL-C levels compared with placebo at week 24 (Table S4). All interventions significantly reduced LDL-C at week 24 (Table 3). Among the PCSK9 inhibitors, evolocumab was the most efficacious (61.84% change from baseline), followed by alirocumab, 300 mg QM, alirocumab, 150 mg Q2W, and inclisiran (58.70%, 57.11%, and 50.07%, respectively). As with the primary NMA, ezetimibe and bempedoic acid were least efficacious.

Percentage Change in Non–HDL-C From Baseline at Week 12 Compared With Placebo

Of the 48 trials in the primary NMA, 44 were included in an analysis to assess the percentage change in non–HDL-C from baseline compared with placebo at week 12 (Table S4). The levels of non–HDL-C were reduced from baseline compared with placebo by all nonstatin agents at week 12 (Table 3). Evolocumab was the most efficacious, with the greatest reduction in non–HDL-C, followed by alirocumab, 150 mg Q2W, in a similar trend to the primary NMA. Inclisiran was more efficacious than alirocumab, 75 mg Q2W and 300 mg QM, at reducing levels of non–HDL-C, in contrast to the findings seen in the primary analysis of LDL-C reduction compared with placebo at week 12. This was followed by bempedoic acid/ezetimibe FDC, which was more efficacious than either treatment individually, as in the primary NMA.

Percentage Change in ApoB From Baseline at Week 12 Compared With Placebo

Of the 48 trials in the primary NMA, 44 were included in an analysis to assess the percentage change in ApoB from baseline compared with placebo at week 12 (Table S4). All nonstatin agents reduced ApoB levels from baseline compared with placebo (Table 3). A similar trend was seen to the primary NMA, with evolocumab as the most efficacious, followed by alirocumab, 150 mg Q2W, and alirocumab, 75 mg Q2W. However, inclisiran was more efficacious than alirocumab, 300 mg QM, at reducing levels of ApoB; these results differed from that seen in the primary analysis of LDL-C reduction compared with placebo at week 12. Following alirocumab, 300 mg QM, were bempedoic acid/ezetimibe FDC, ezetimibe, and bempedoic acid as least efficacious.

Impact of Each Intervention on the LDL-C Levels of a Simulated Population

Of the 10000 simulated LDL-C values ≥70 mg/dL (≥1.8 mmol/L) and thus requiring additional LLT, the proportion of values that achieved the 2019 ESC/European

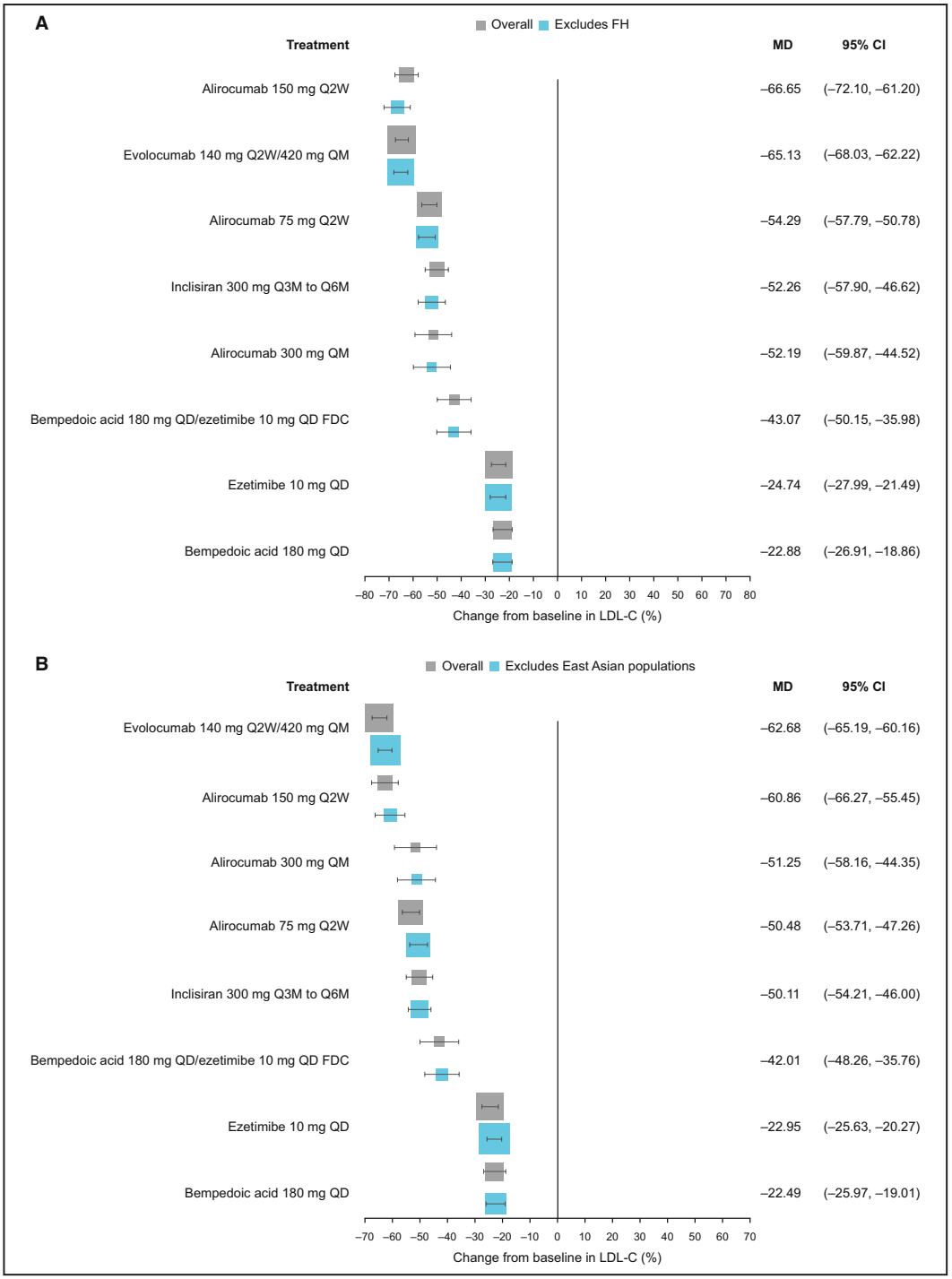

Figure 6. Sensitivity analyses: treatment difference in percentage change in low-density lipoprotein cholesterol (LDL-C) from baseline in response to lipid-lowering therapy relative to placebo at week 12, excluding trials featuring familial hypercholesterolemia (FH) (A) or East Asian populations (B) (blue), with the primary analysis data plotted for comparison (gray).
FDC indicates fixed-dose combination; MD, mean difference; Q2W, every 2 weeks; Q3M, every 3 months; Q6M, every 6 months; QD, once a day; and QM, once a month.

Atherosclerosis Society guideline LDL-C goal of <55 mg/dL (<1.4 mmol/L) was highest for treatment with evolocumab, at 78.41%, followed by alirocumab, 150 mg Q2W, at 74.68% (Figure 7). Alirocumab, 75 mg Q2W, alirocumab, 300 mg QM, and inclisiran achieved proportions of 63.03%, 61.30%, and 60.25%, respectively. This was followed by

Table 3. Relative Efficacy of Nonstatin LLTs When Added to Maximally Tolerated Statins on the Percentage Change in LDL-C at Week 24, on ApoB Levels at Week 12, and on Non–HDL-C Levels at Week 12

Treatment	MD	95% CI
MD in percentage change in LDL-C in response to LLT relative to placebo at wk 24		
Evolocumab, 140 mg Q2W/420 mg QM	−61.84	−65.70 to −57.99
Alirocumab, 300 mg QM	−58.70	−67.30 to −50.10
Alirocumab, 150 mg Q2W	−57.11	−63.39 to −50.83
Inclisiran, 300 mg Q3M to Q6M	−50.07	−53.82 to −46.31
Ezetimibe, 10 mg QD	−25.03	−29.30 to −20.76
Bempedoic acid, 180 mg QD	−16.61	−20.99 to −12.24
MD in percentage change in non–HDL-C in response to LLT relative to placebo at wk 12		
Evolocumab, 140 mg Q2W/420 mg QM	−58.41	−61.19 to −55.63
Alirocumab, 150 mg Q2W	−52.65	−57.97 to −47.32
Inclisiran, 300 mg Q3M to Q6M	−45.07	−50.19 to −39.95
Alirocumab, 75 mg Q2W	−44.80	−48.03 to −41.57
Alirocumab, 300 mg QM	−44.33	−52.04 to −36.62
Bempedoic acid, 180 mg QD/ ezetimibe, 10 mg QD FDC	−34.45	−43.66 to −25.25
Ezetimibe, 10 mg QD	−23.01	−26.38 to −19.64
Bempedoic acid, 180 mg QD	−16.46	−20.89 to −12.04
MD in percentage change in ApoB in response to LLT relative to placebo at wk 12		
Evolocumab, 140 mg Q2W/420 mg QM	−51.16	−53.65 to −48.67
Alirocumab, 150 mg Q2W	−50.08	−54.98 to −45.18
Alirocumab, 75 mg Q2W	−41.46	−44.35 to −38.56
Inclisiran, 300 mg Q3M to Q6M	−39.99	−44.51 to −35.47
Alirocumab, 300 mg QM	−36.12	−43.75 to −28.48
Bempedoic acid, 180 mg QD/ ezetimibe, 10 mg QD FDC	−28.35	−36.82 to −19.88
Ezetimibe, 10 mg QD	−18.86	−21.93 to −15.79
Bempedoic acid, 180 mg QD	−14.53	−18.56 to −10.51

ApoB indicates apolipoprotein B; FDC, fixed-dose combination; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; MD, mean difference; Q2W, every 2 weeks; Q3M, every 3 months; Q6M, every 6 months; QD, once a day; and QM, once a month.

bempedoic acid/ezetimibe FDC with 49.45%, and each monotherapy at 21.87% and 20.75%, respectively.

DISCUSSION

The results of our NMA indicate that all nonstatin agents significantly reduced LDL-C compared with placebo, regardless of background therapy. Evolocumab, 140 mg Q2W/420 mg QM, and alirocumab, 150 mg Q2W, were the most efficacious agents, followed by alirocumab, 75 mg Q2W, alirocumab, 300 mg QM, inclisiran, 300 mg Q3M to Q6M, and bempedoic acid, 180 mg QD/ezetimibe, 10 mg QD FDC. Ezetimibe, 10 mg QD, and bempedoic acid, 180 mg QD, monotherapies were shown to be somewhat less efficacious. The results observed in the primary network at week 12 were generally consistent when a longer time point was analyzed at week 24. The percentage LDL-C reduction achieved with the PCSK9 inhibitor treatments at certain approved dosing regimens compared with placebo indicated that mAb PCSK9 inhibitors were more efficacious at reducing LDL-C than treatment with an siRNA PCSK9 inhibitor. In addition, there was no significant difference between the LDL-C–lowering capacity of alirocumab, 75 mg Q2W, alirocumab, 300 mg QM, and inclisiran, nor was there a significant difference between inclisiran and bempedoic acid/ezetimibe FDC, as shown in the pairwise comparison. Overall, these data could help inform physicians' treatment choice for patients who require additional LLT to lower their LDL-C levels, consistent with current guidelines.

The findings from the primary NMA were consistent regardless of statin background therapy for most interventions, although the analysis in patients who were apparently statin intolerant must be viewed in the context of greater uncertainty. In the case of bempedoic acid, it was shown that the addition of bempedoic acid to moderate- to high-intensity statin therapy resulted in a lower percentage reduction in LDL-C compared with use in statin-intolerant patients. The reduced efficacy of bempedoic acid on top of statin therapy is to be expected, because ATP citrate lyase is 2 steps upstream of statin reductase in the cholesterol synthesis pathway[20,75]; hence, the impact of ATP citrate lyase inhibition can be expected to be greater in the absence of statin reductase inhibition. Findings from the primary NMA were consistent in a subgroup analysis of trials with populations of >50% patients with ASCVD, the most common very high-risk group for whom nonstatin agents are recommended as an adjunct to statins to achieve LDL-C treatment goals.[3] The maximum reduction achieved in the primary NMA by an additional nonstatin agent was 64.68%, which is around 14% higher than the current European guidelines' minimum LDL-C reduction goal of 50%.[3] However, this ≥50% goal reduction is from a baseline of no LDL-C–lowering treatment, not in addition to statins.[3] The benefit of add-on LLT can be estimated by assuming a "pre-PCSK9" LDL-C level of 96.7 mg/dL (2.5 mmol/L), which can be translated into an additional 13.5-mg/dL (0.35-mmol/L) reduction when comparing the reduction goal of 50% with the maximum reduction achieved by a PCSK9 inhibitor of 64.68%. Therefore, assuming the results in the Cholesterol Treatment Trialists' Collaboration meta-analysis, which indicate a 38.7-mg/dL (1.0-mmol/L) reduction in LDL-C reduces MACEs by 21%,[1] this would

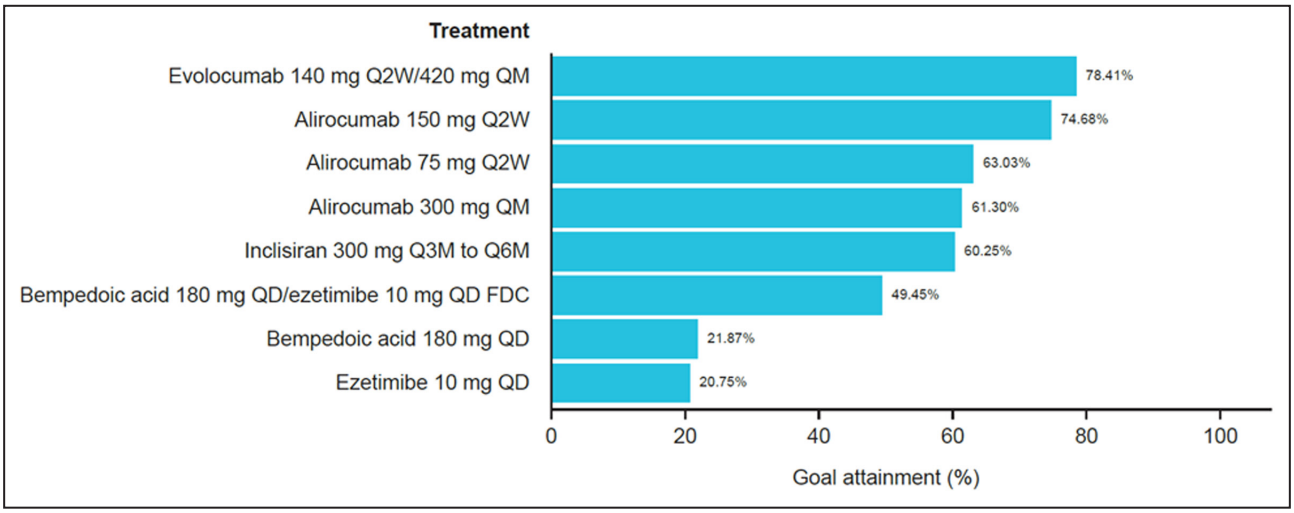

Figure 7. The proportion of simulated values that achieved a low-density lipoprotein cholesterol (LDL-C) level of <55 mg/dL (<1.4 mmol/L) following treatment with each intervention.
The simulation values represent a hypothetical population with atherosclerotic cardiovascular disease, and the <55-mg/dL value is the 2019 European Society of Cardiology/European Atherosclerosis Society guideline-recommended LDL-C level goal for very high-risk patients. FDC indicates fixed-dose combination; Q2W, every 2 weeks; Q3M, every 3 months; Q6M, every 6 months; QD, once a day; and QM, once a month.

imply a reduction in MACEs of ≈7.9% ($1–0.79^{0.35}$), a hypothetical percentage that implies the benefit of the addition of nonstatin LLT agents.

The highest proportion (>70%) of LDL-C values achieved the 2019 ESC/European Atherosclerosis Society LDL-C guideline goal of <55 mg/dL (<1.4 mmol/L) with either evolocumab, 140 mg Q2W/420 mg QM, or alirocumab, 150 mg Q2W, treatment, in a simulated population. These 2 treatments also reduced LDL-C levels by the greatest amount. Studies that also looked at the impact of treatment on whether LDL-C met guidelines looked at the sequential addition of treatment. One study ran a simulation on a population of patients following a myocardial infarction, where the following treatment pathway was used: maximized high-intensity statins, followed by ezetimibe, then an additional mAb PCSK9 inhibitor.[76] In those who had yet to achieve an LDL-C of <55 mg/dL (<1.4 mmol/L) and who already received high-intensity statins (78.3%), the addition of ezetimibe resulted in a further 27.5% achieving the goal.[76] The addition of evolocumab, 140 mg Q2W/420 mg QM, or alirocumab, 75 mg Q2W, to the previous statin and ezetimibe therapy resulted in a further 42.7% and 39.2% of patients achieving an LDL-C of <55 mg/dL (<1.4 mmol/L), respectively.[76] Another study looked at the achievement of an LDL-C of <70 mg/dL (<1.8 mmol/L) using a simulated population with ASCVD, and the following treatments steps sequentially applied with LDL-C measured after each to identify whether LDL-C of <70 mg/dL (<1.8 mmol/L) had been achieved: statin, statin up titration, add-on ezetimibe, add-on alirocumab, 75 mg, and up titration to alirocumab, 150 mg (base-case scenario).[77] The base-case scenario identified that 16.7% people required an ezetimibe add-on therapy, 14% people required an additional add-on alirocumab, 75 mg, therapy or further 150 mg up titration to achieve an LDL-C of <70 mg/dL (<1.8 mmol/L).[77] A related study found that when 10% full and 10% partial statin intolerance were assumed in the simulated population, ezetimibe use was 38.5% and PCSK9 inhibitor use was 21.1% to achieve LDL-C of <70 mg/dL (<1.8 mmol/L).[78] These studies are a sample of those that show the benefits of add-on LLT therapies to achieve an LDL-C consistent with guideline recommendations.

For the time points used in the study, week 12 data were the most reliable to assess relative efficacy. At this time point, most study participants remained on therapy. Fewer trials reported week 24 data. Many alirocumab trials were excluded from analysis at week 24 because the protocol allowed up titration of dose at week 12; hence, week 24 data describe a combination of doses. In clinical practice, the effectiveness of LLT is not only a function of efficacy but also adherence and persistence of patients to treatment in the longer term. The data included in the NMA are drawn from randomized controlled trials in which patients generally adhered to and persisted with treatment. The modes and frequencies of administration differ between LLTs, including oral tablets, Q2W or QM subcutaneous injections (mAb PCSK9 inhibitors), and Q3M to Q6M subcutaneous injection (siRNA PCSK9 inhibitor).[20,25,29,33,79,80]

The NMA reported in this article provides updated information to our previous analysis published in 2017,[13] not only in terms of including new data for established therapies, but also with the introduction of newer agents. In addition, the scope of the analysis was broadened by allowing the inclusion of any study in which nonstatin agents were combined with maximum-tolerated statin background (or in reported statin-intolerant patients). This allowed inclusion of additional trials, such as IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), in which patients were not stabilized on statin dose before randomization.[73] Although there are other NMAs published on this subject, our analysis is differentiated by the granular comparison of PCSK9 inhibitors and by the inclusion of bempedoic acid and inclisiran. Several NMAs have been conducted using clinical studies of mAb PCSK9 inhibitors; however, authors have pooled results together into a single class[81–87] or not made formal indirect comparisons.[88,89]

A recent NMA performed by Burnett et al concluded that inclisiran, alirocumab, and evolocumab are expected to provide similar clinically meaningful improvements in LDL-C in patients with hypercholesterolemia on maximally tolerated statins who were at increased cardiovascular risk.[90] There are, however, important methodologic differences between the Burnett et al study and this study. First, our analysis encompassed a broader population, including a larger number of clinical trials (48 versus 16) in the primary analysis, which reduced overall uncertainty. Second, although the percentage LDL-C reduction reported for evolocumab (≈65%) was consistent in both analyses, Burnett et al reported a larger reduction in LDL-C for inclisiran (57.49%) and a more modest reduction in LDL-C for alirocumab (58.25%) than the analysis presented herein. More important, the reduction in LDL-C for inclisiran was evaluated at day 150, whereas our analysis considered the more appropriate time-adjusted LDL-C reduction between days 90 and 540. Notably, the reduction in LDL-C at day 150 was not a primary or secondary outcome in ORION-10 (Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol) or ORION-11 (Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol)[22]; therefore, Burnett et al also presented a sensitivity analysis considering the time-adjusted LDL-C reduction. The results indicate a reduction in LDL-C for inclisiran of 51.42%, which is closely aligned with the 50.17% reduction reported in our analysis. Finally, alirocumab LDL-C reduction is estimated after dose titration is allowed such that the efficacy estimate is "averaged" over the doses, whereas our analysis considers the 75- and 150-mg Q2W doses separately.

Our analysis of the effect of additional nonstatin agents on the change from baseline in other lipid end points (ApoB and non–HDL-C), compared with placebo at week 12, found broadly similar findings to that of the primary analysis, except for inclisiran. Inclisiran was more efficacious than alirocumab, 300 mg QM, at reducing ApoB levels and more efficacious than alirocumab, 75 mg Q2W and 300 mg QM, at reducing non–HDL-C levels, compared with placebo at week 12.

At present, mAb PCSK9 inhibitors (evolocumab and alirocumab) and ezetimibe have been shown to reduce risk of MACEs in patients with ASCVD or acute coronary syndrome[30,35,60,73,91]; however, bempedoic acid (NCT02993406 and NCT04579367) and inclisiran (NCT03705234) are currently under investigation for their efficacy in reducing cardiovascular events.[92–94] Our NMA did not include a comparison of cardiovascular outcomes, even where data are available for individual interventions, because of differing trial designs and populations. Focusing on LDL-C reduction is therefore currently the best method of comparing the efficacy of LLTs because it is largely unaffected by treatment effect modifiers. In contrast, cardiovascular outcomes are impacted by the duration of follow-up, and the type and recency of qualifying events, as well as the cardiovascular risk of the trial populations. Definition of outcome measures can also complicate comparison between agents.

There are limitations associated with this review and NMA. First, the NMA is limited by the quantity and quality of data available from included trials. Our NMA concentrates on efficacy estimates and does not consider adherence and economic value implications. There are relatively few head-to-head trials of nonstatin agents or regimens; therefore, most comparisons within the network are largely indirect. However, given that LDL-C reductions have been shown to be similar across multiple characteristics, we believe that this limitation does not undermine the analysis. The NMA focuses on week 12 follow-up, which provides the richest data source but could be considered as relatively short-term. However, for most agents, there is evidence that week 12 data are generalizable to the long-term.[18,45,59]

CONCLUSIONS

All nonstatin agents significantly reduced LDL-C levels compared with placebo. However, evolocumab, 140 mg Q2W/420 mg QM, and alirocumab, 150 mg Q2W (mAb PCSK9 inhibitors also shown to reduce MACEs in patients with ASCVD and acute coronary syndrome), were consistently the most efficacious nonstatin agents/regimens, potentially allowing more patients to achieve an LDL-C consistent with the current guidelines.

ARTICLE INFORMATION

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Drs Bray and Villa are Amgen employees and hold Amgen stock. Dr Worth was an employee of Amgen at time of analysis and drafting. Dr Palagashvili was an employee of Amgen at the initiation of analysis and drafting, and holds Amgen stock. Dr Toth reports speakers bureau for Amarin, Amgen, Esperion, and Novo-Nordisk; and consultant for Amarin, Amgen, bio89, Novartis, and Theravance. Dr Sattar reports consulting fees from Affimune, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, MSD, Novo Nordisk, Novartis, Pfizer, and Sanofi; and grants from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics. Dr Stroes reports ad-board/lecturing fees have been paid to his institution by Sanofi-Regeneron, Esperion, Amgen, Novartis, Novo-Nordisk, and Athera.

Supplemental Material

Data S1
Tables S1–S5
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Data S1. Full Search Strategy.

PubMed search only, others available upon request

PubMed **Search terms**
((((((((((((((((((((((((bempedoic acid[MeSH Terms]) OR bempedoic[Title/Abstract]) OR 738606-46-7) OR ESP-55016[Title/Abstract]) OR ESP55016[Title/Abstract]) OR ETC-1002[Title/Abstract]) OR ETC1002[Title/Abstract]) OR 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic[Title/Abstract]) OR inclisiran[MeSH Terms]) OR inclisiran[Title/Abstract]) OR 1499251-18-1) OR ALN-60212[Title/Abstract]) OR ALN60212[Title/Abstract]) OR ALN-PCSSC[Title/Abstract]) OR ALNPCSSC[Title/Abstract])) OR ((("evolocumab"[tiab] OR "AMG145" [tiab] OR "AMG 145" [tiab] OR "repatha"[tiab] OR" LKC0U3A8NJ"[rn] OR "1256937-27-5"[rn]))) OR (("Alirocumab"[tiab] OR "Praluent"[tiab] OR"regn 727"[tiab] OR "regn727"[tiab] OR "sar 236553"[tiab] OR "sar236553"[tiab] OR "1245916-14-6"[rn]))) OR ((ezetimibe[tiab] OR "zetia"[tiab] OR "ezetrol"[tiab] OR "ezedoc"[tiab] OR "ezetib"[tiab] OR "sch 582235"[tiab] OR "sch582235"[tiab] OR "163222-33-1"[rn]))) OR (("anacetrapib"[tiab] OR "mk 0859"[tiab] OR "mk 859"[tiab] OR "mk0859"[tiab] OR "mk859"[tiab] OR 875446-37-0[rn]))) OR (("evacetrapib"[tiab] OR "ly 2484595"[tiab] OR "ly2484595"[tiab] OR "1186486-62-3"[rn]))) OR (("mipomersen"[tiab] OR "isis 301012"[tiab] OR "isis301012"[tiab] OR "kynamro"[tiab] OR 629167-92-6[rn]))) OR (("lomitapide"[tiab] OR "lojuxta"[tiab] OR "Juxtapid"[tiab] OR "aegr 733"[tiab] OR "aegr733"[tiab] OR bms 201038*[tiab] or "182431-12-5"[rn] OR "202833-31-6"[rn] OR "202914-84-9"[rn] OR "210823-48-6"[rn]))))) AND (((((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]))) OR ((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol

assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])))) AND (("2019/05/01"[Date - Publication] : "2020/05/14"[Date - Publication]))

Table S1. The standard deviation and associated literature source for each intervention used in the simulation

Treatment	Mean	SD	SD source
Alirocumab 75 mg	53.26	28.09	ODYSSEY COMBO II
Alirocumab 150 mg	62.71	27.38	ODYSSEY LONG TERM
Alirocumab 300 mg	51.62	26.30	ODYSSEY CHOICE I
Bempedoic acid	22.83	23.43	CLEAR HARMONY
Bempedoic acid/ezetimibe FDC	42.93	23.97	Ballantyne FDC
Evolocumab	64.68	25.06	FOURIER
Ezetimibe	24.49	19.68	LAPLACE-2
Inclisiran	50.17	24.61	ORION 11

FDC indicates fixed-dose combination; and SD, standard deviation.

Table S2. List of SLR Trials Excluded from the NMA and Reason for Exclusion

Study	Reason(s) for Exclusion
RADIOCHOL-1, TESLA, ODYSSEY HoFH	Ineligible population - HoFH
ODYSSEY ESCAPE	Ineligible population/design. Apheresis
ODYSSEY Outcomes	No data available for specific alirocumab dosing regimens (150 mg Q2W or 75 mg Q2W)
ODYSSEY DM Dyslipidemia	Ineligible study design. Control arm allows alteration in LLT
MK 0653H 832	Insufficient data

HoFH indicates homozygous familial hypercholesterolemia; LLT, lipid-lowering therapy; NMA, network meta-analysis; Q2W, every 2 weeks; and SLR, systematic literature review.

Table S3. Risk of Bias Assessment for the 48 Trials Included in the NMA

Trial Name Author (Year)	Information Available	1. Randomization Methods	2. Allocation Concealment	3. Participant Blinding	4. Caregiver Blinding	5. Outcome Assessor Blinding	6. Incomplete Outcome Data	7. Selective Reporting	8. Other Biases	Overall Assessment of Risk of Bias
McKenney 2012 McKenney (2012)[38]	Full publication	U	U	L	L	L	L	L	U	**UNCLEAR RISK**
ODYSSEY ALTERNATIVE Moriarty (2015)[39]	Full publication	U	U	L	L	L	L	L	L	**UNCLEAR RISK**
ODYSSEY CHOICE I Roth (2016)[34]	Full publication	U	U	L	L	L	L	L	L	**UNCLEAR RISK**
ODYSSEY CHOICE II Stroes (2016)[40]	Full publication	U	U	L	L	L	L	L	L	**UNCLEAR RISK**

ODYSSEY COMBO 1 Kereiakes (2015)[32]	Full publication	U	U	L	L	L	L	L	L	**UNCLEAR RISK**
ODYSSEY COMBO II Cannon (2015)[41]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
ODYSSEY DM INSULIN Leiter (2017)[42]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
ODYSSEY EAST Han (2020)[43]	Full publication	U	L	L	L	L	L	L	L	**LOW RISK**
ODYSSEY FH I Kastelein (2015)[44]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
ODYSSEY FH II Kastelein (2015)[44]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
ODYSSEY HIGH FH Ginsberg (2016)[45]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**

ODYSSEY JAPAN NCT02107898[95] Teramoto (2016)[46]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
ODYSSEY KT Koh (2018)[47]	Full publication	U	U	L	L	U	L	L	L	**UNCLEAR RISK**
ODYSSEY LONG TERM Robinson (2015)[48]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
ODYSSEY NIPPON Teramoto (2019)[49]	Full publication	U	U	L	L	L	L	L	L	**UNCLEAR RISK**
ODYSSEY OPTIONS I Bays (2014)[96]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
ODYSSEY OPTIONS II Bays (2014)[96]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**

Stein 2012 Stein (2012)[52]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
Teramoto 2016 Teramoto (2014)[97] /NCT01812707[98]	Mixed publications*	U	U	L	L	U	L	L	L	**UNCLEAR RISK**
Ballantyne 2016 Ballantyne (2016)[54]	Full publication	U	U	L	L	L	L	L	L	**UNCLEAR RISK**
CLEAR HARMONY Ray (2019)[18]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
CLEAR SERENITY Laufs (2019)[17]	Full publication	U	U	L	L	L	L	L	L	**UNCLEAR RISK**
CLEAR TRANQUILITY Ballantyne (2018)[14]	Full publication	L	L	L	L	L	L	U	L	**LOW RISK**
CLEAR WISDOM	Full publication	L	U	L	L	L	L	L	L	**LOW RISK**

Goldberg (2019)[16]										
Ballantyne 2020 FDC NCT03337308 Ballantyne (2020)[55]	Full publication	U	L	L	L	L	H	L	L	**HIGH RISK**
Thompson 2016 SI Thompson (2016)[56]	Full publication	U	U	L	L	L	L	L	U	**UNCLEAR RISK**
BANTING Rosenson (2019)[57]	Full publication	L	L	L	L	U	L	L	L	**LOW RISK**
BERSON Lorenzatti (2019)[58]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
DESCARTES/Amgen 20110109 Blom (2014)[59]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**

FOURIER/Amgen 20160250 Sabatine (2017)[60]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
GAUSS/Amgen 20090159 Sullivan (2012)[61]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
GAUSS-2/Amgen 20110116 Stroes (2014)[62]	Full publication	L	L	L	L	L	H	L	L	**LOW RISK**
GAUSS-3/Amgen 20120332 (Part B) Nissen (2016)[63]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
GAUSS-4 NCT02634580[99]	Trial registry	L	L	L	L	L	L	U	L	**LOW RISK**

GLAGOV/Amgen 20120153 Nicholls (2016)[65]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
LAPLACE-2/Amgen 20110115* Amgen (2014)[100]	Unpublished report; Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
LAPLACE-TIMI 57/ Amgen 20101155 Giugliano (2012)[67]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
RUTHERFORD/ Amgen 20090158 Raal (2012)[68]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
RUTHERFORD-2/ Amgen 20110117 Raal (2015)[69]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**

YUKAWA/Amgen 20110231 Hirayama (2014)[70]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
YUKAWA-2/Amgen 20120122 Amgen (2014)[101]	Unpublished report*	L	L	L	L	L	L	L	L	**LOW RISK**
ENHANCE Kastelein (2008)[72]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
IMPROVE-IT Cannon (2015)[73]	Full publication	L	L	L	L	L	L	L	L	**LOW RISK**
Masana 2005 Masana (2005)[74]	Full publication	U	U	L	U	U	H	L	L	**HIGH RISK**
ORION 1 Ray (2017)[102]	Full publication	L	L	L	L	U	H	L	L	**HIGH RISK**

ORION 9 Raal (2020)[21]	Full publication	U	U	L	L	U	L	L	L	**UNCLEAR RISK**
ORION 10 Ray (2020)[22]	Full publication	U	U	L	L	U	L	L	L	**UNCLEAR RISK**
ORION 11 Ray (2020)[22]	Full publication	U	U	L	L	U	L	L	L	**UNCLEAR RISK**

*Note: published paper available – Kiyosue et al., 2016[71]; Robinson et al., 2014[66]; Teramoto et al., 2016[53].

FDC indicates fixed-dose combination; H, high; L, low; NMA, network meta-analysis; SI, statin intolerant; and U, unclear.

Table S4. Inclusion of Trials in Secondary NMAs and Subgroup/Sensitivity Analyses

	Sensitivity Analyses		Subgroup Scenarios			Secondary Objectives		
Study	**Trials included in the analysis to exclude trials in FH patients**	**Trials included in the analysis to exclude trials in East Asian populations**	**Statin background**	**Statin intolerant**	**ASCVD trials**	**LDL-C Week 24**	**Non-HDL-C Week 12**	**ApoB Week 12**
McKenney 2012	X	X	X				X	X
ODYSSEY ALTERNATIVE	X	X		X			X	X
ODYSSEY CHOICE I	X	X	X			X	X	X
ODYSSEY CHOICE II	X	X		X			X	X
ODYSSEY COMBO I	X	X	X		X		X	X
ODYSSEY COMBO II	X	X	X		X		X	X

	Sensitivity Analyses		Subgroup Scenarios			Secondary Objectives		
Study	**Trials included in the analysis to exclude trials in FH patients**	**Trials included in the analysis to exclude trials in East Asian populations**	**Statin background**	**Statin intolerant**	**ASCVD trials**	**LDL-C Week 24**	**Non-HDL-C Week 12**	**ApoB Week 12**
ODYSSEY DM INSULIN	X	X	X					
ODYSSEY EAST	X		X		X		X	X
ODYSSEY FH I		X	X				X	X
ODYSSEY FH II		X	X				X	X
ODYSSEY HIGH FH		X	X			X	X	X
ODYSSEY JAPAN	X		X				X	X
ODYSSEY KT	X		X		X		X	X
ODYSSEY LONG TERM	X	X	X		X	X	X	X

	Sensitivity Analyses		Subgroup Scenarios			Secondary Objectives		
Study	**Trials included in the analysis to exclude trials in FH patients**	**Trials included in the analysis to exclude trials in East Asian populations**	**Statin background**	**Statin intolerant**	**ASCVD trials**	**LDL-C Week 24**	**Non-HDL-C Week 12**	**ApoB Week 12**
ODYSSEY NIPPON	X			X			X	X
ODYSSEY OPTIONS I	X	X	X		X		X	X
ODYSSEY OPTIONS II	X	X	X		X		X	X
Stein 2012		X	X				X	X
Teramoto 2016	X		X					
Ballantyne 2016	X	X	X				X	X
CLEAR HARMONY	X	X	X		X	X	X	X
CLEAR SERENITY	X	X		X		X	X	X

	Sensitivity Analyses		Subgroup Scenarios			Secondary Objectives		
Study	**Trials included in the analysis to exclude trials in FH patients**	**Trials included in the analysis to exclude trials in East Asian populations**	**Statin background**	**Statin intolerant**	**ASCVD trials**	**LDL-C Week 24**	**Non-HDL-C Week 12**	**ApoB Week 12**
CLEAR TRANQUILITY	X	X		X			X	X
CLEAR WISDOM	X	X	X		X	X	X	X
Ballantyne 2020 FDC	X	X	X		X		X	X
Thompson 2016 SI	X	X		X				
BANTING	X	X	X				X	X
BERSON	X	X	X				X	X
DESCARTES	X	X	X			X	X	X
FOURIER	X	X	X		X	X	X	X

	Sensitivity Analyses		Subgroup Scenarios			Secondary Objectives		
Study	**Trials included in the analysis to exclude trials in FH patients**	**Trials included in the analysis to exclude trials in East Asian populations**	**Statin background**	**Statin intolerant**	**ASCVD trials**	**LDL-C Week 24**	**Non-HDL-C Week 12**	**ApoB Week 12**
GAUSS	X	X		X			X	X
GAUSS-2	X	X		X			X	X
GAUSS-3	X	X		X		X	X	X
GAUSS-4	X	X		X			X	X
GLAGOV	X	X	X		X	X	X	X
LAPLACE-2	X	X	X				X	X
LAPLACE-TIMI 57	X	X	X		X		X	X
RUTHERFORD		X	X				X	X

	Sensitivity Analyses		Subgroup Scenarios			Secondary Objectives		
Study	**Trials included in the analysis to exclude trials in FH patients**	**Trials included in the analysis to exclude trials in East Asian populations**	**Statin background**	**Statin intolerant**	**ASCVD trials**	**LDL-C Week 24**	**Non-HDL-C Week 12**	**ApoB Week 12**
RUTHERFORD-2		X	X				X	X
YUKAWA	X		X				X	X
YUKAWA-2	X		X				X	X
ENHANCE		X	X			X		X
IMPROVE-IT	X	X	X		X	X	X	
Masana 2005	X	X	X				X	X
ORION 1	X	X	X		X	X	X	X
ORION 9		X	X			X	X	X

	Sensitivity Analyses		Subgroup Scenarios			Secondary Objectives		
Study	**Trials included in the analysis to exclude trials in FH patients**	**Trials included in the analysis to exclude trials in East Asian populations**	**Statin background**	**Statin intolerant**	**ASCVD trials**	**LDL-C Week 24**	**Non-HDL-C Week 12**	**ApoB Week 12**
ORION 10	X	X	X		X	X	X	X
ORION 11	X	X	X		X	X	X	X

ApoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; FDC, fixed-dose combination; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NMA, network meta-analysis; and SI, statin intolerant.

Table S5. Treatment Differences Among LLTs in LDL-C Reduction

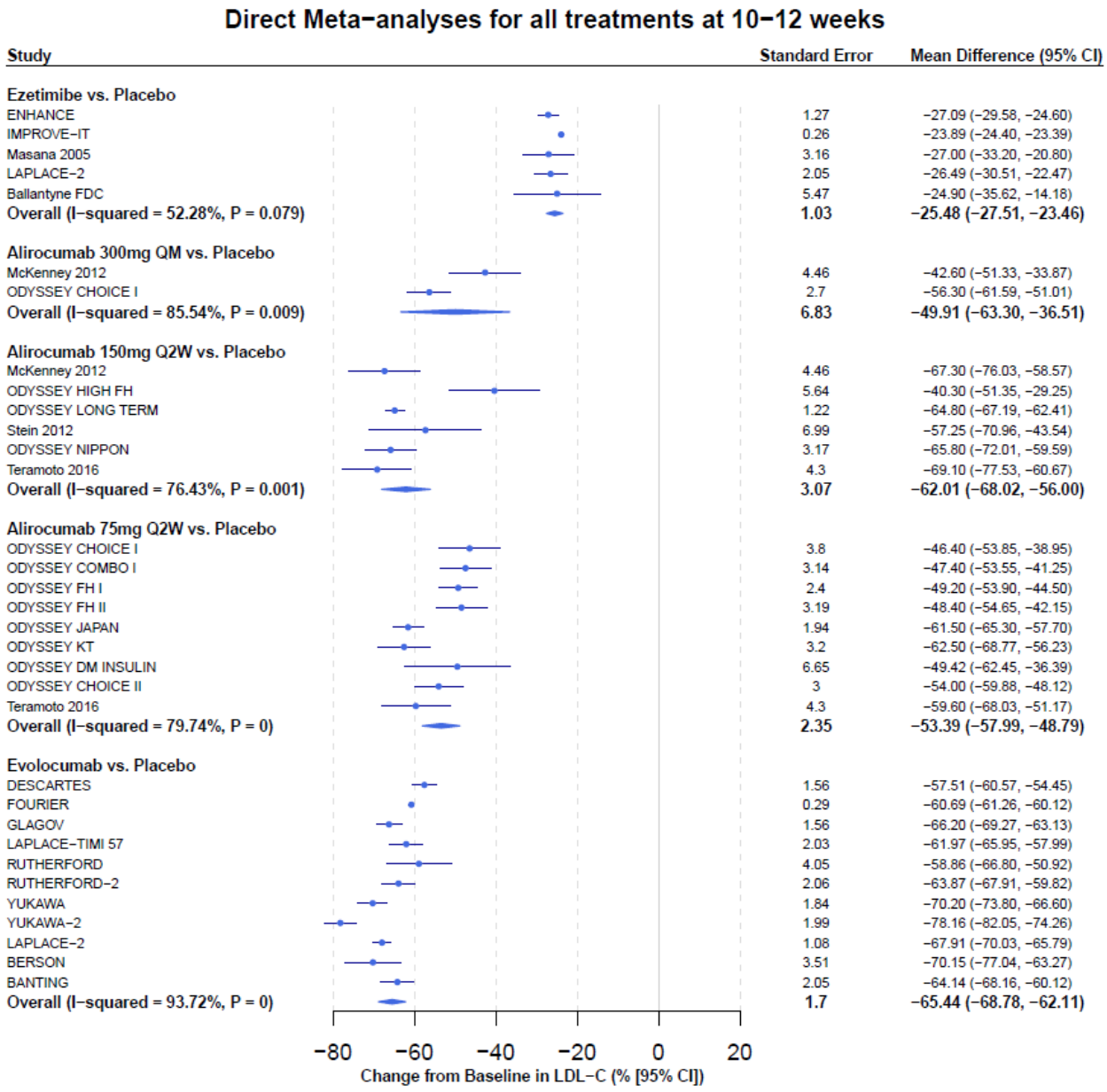
alirocumab 150								
-11.10 [-19.87; -2.33]	alirocumab 300							
-9.45 [-15.13; -3.77]	1.65 [-6.39; 9.69]	alirocumab 75						
-39.89 [-46.16; -33.61]	-28.79 [-37.40; -20.18]	-30.44 [-35.38; -25.50]	bempedoic acid					
1.97 [-3.56; 7.50]	13.07 [4.99; 21.15]	11.42 [7.52; 15.32]	41.86 [37.15; 46.56]	evolocumab				
-38.23 [-43.89; -32.56]	-27.13 [-35.27; -19.00]	-28.78 [-32.27; -25.29]	1.66 [-2.92; 6.25]	-40.20 [-43.55; -36.85]	ezetimibe			
-19.79 [-28.31; -11.26]	-8.69 [-19.05; 1.66]	-10.34 [-17.80; -2.87]	20.10 [12.89; 27.31]	-21.76 [-29.11; -14.41]	18.44 [11.46; 25.43]	BA/EZE FDC		
-12.54 [-19.37; -5.71]	-1.44 [-10.48; 7.59]	-3.09 [-8.84; 2.66]	27.35 [21.08; 33.61]	-14.51 [-20.03; -8.99]	25.69 [20.01; 31.36]	7.25 [-1.28; 15.77]	inclisiran	
-62.71 [-67.56; -57.87]	-51.62 [-59.26; -43.98]	-53.26 [-56.40; -50.13]	-22.83 [-26.83; -18.82]	-64.68 [-67.37; -62.00]	-24.49 [-27.48; -21.49]	-42.93 [-49.96; -35.89]	-50.17 [-54.99; -45.35]	placebo

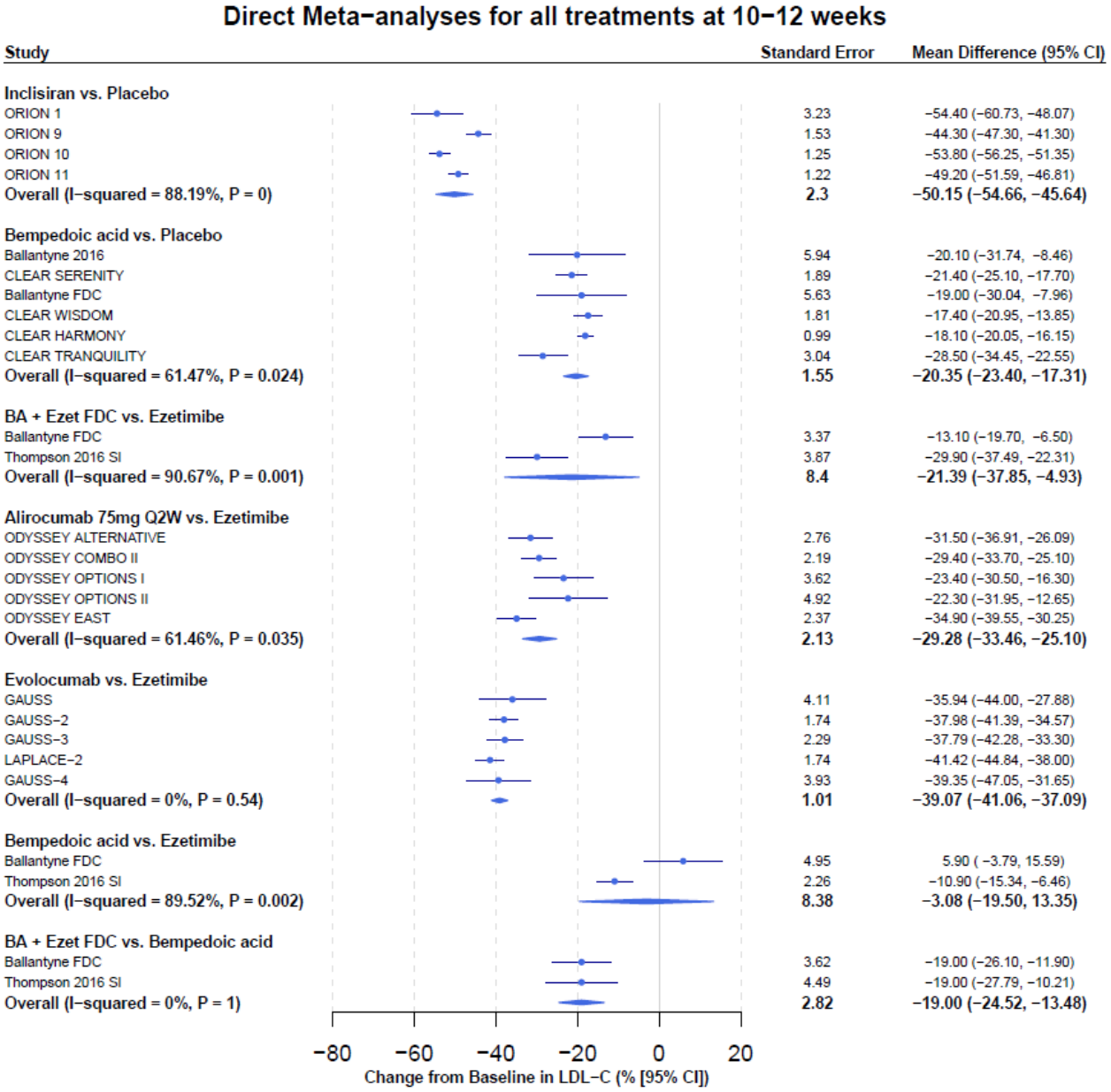
Cells representing data where there is a significant difference between agents has been highlighted.

Positive values indicate greater LDL-C reduction associated with the intervention in the ‘row’ vs the ‘column’. Conversely, negative values indicate greater LDL-C reduction for the intervention in the ‘column’ vs the ‘row’.

BA/EZE FDC indicates bempedoic acid/ezetimibe fixed-dose combination; LDL-C, low-density lipoprotein cholesterol; and LLT, lipid-lowering therapy.

Figure S1. Direct meta-analyses data.





BA indicates bempedoic acid; CI, confidence interval; Ezet, ezetimibe; FDC, fixed-dose combination; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, once a month; and SI, statin intolerant.

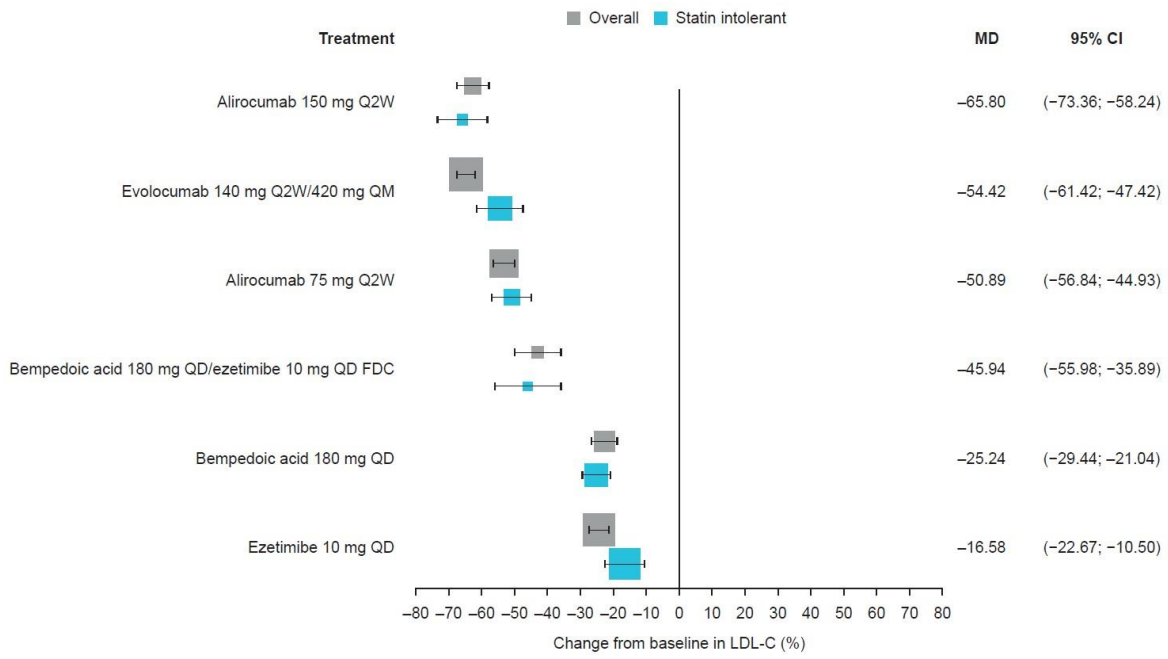


Figure S2. Subgroup analysis: the mean difference in percentage change in LDL-C from baseline in response to lipid-lowering therapy relative to placebo at Week 12 in patients reporting statin intolerance (blue), with primary analysis data plotted for comparison (gray).

CI indicates confidence interval; FDC, fixed-dose combination; LDL-C, low-density lipoprotein cholesterol; MD, mean difference; Q2W, every 2 weeks; QD, once a day; and QM, once a month.