Systematic Review for the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

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Systematic Review for the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

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This document was approved by the American College of Cardiology Clinical Policy Approval Committee, the American Heart Association Science Advisory and Coordinating Committee, American Association of Cardiovascular and Pulmonary Rehabilitation, American Academy of Physician Assistants, Association of Black Cardiologists, American College of Preventive Medicine, American Diabetes Association, American Geriatrics Society, American Pharmacists Association, American Society for Preventive Cardiology, National Lipid Association, and Preventive Cardiovascular Nurses Association in October 2018, and the American Heart Association Executive Committee in October 2018.

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Abstract

Background: The 2013 American College of Cardiology/American Heart Association guidelines for the treatment of blood cholesterol found little evidence to support the use of nonstatin lipid-modifying medications to reduce atherosclerotic cardiovascular disease (ASCVD) events. Since publication of these guidelines, multiple randomized controlled trials evaluating nonstatin lipid-modifying medications have been published.

Methods: We performed a systematic review to assess the magnitude of benefit and/or harm from additional lipid-modifying therapies compared with statins alone in individuals with known ASCVD or at high risk of ASCVD. We included data from randomized controlled trials with a sample size of >1,000 patients and designed for follow-up >1 year. We performed a comprehensive literature search and identified 10 randomized controlled trials for intensive review, including trials evaluating ezetimibe, niacin, cholesterol-ester transfer protein inhibitors, and PCSK9 inhibitors. The prespecified primary outcome for this review was a composite of fatal cardiovascular events, nonfatal myocardial infarction, and nonfatal stroke.

Results: The cardiovascular benefit of nonstatin lipid-modifying therapies varied significantly according to the class of medication. There was evidence for reduced ASCVD morbidity but not mortality with ezetimibe and 2 PSCK9 inhibitors. Reduced ASCVD mortality rate was reported for 1 PCSK9 inhibitor. The use of ezetimibe/simvastatin versus simvastatin in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) reduced the primary outcome by 1.8% over 7 years (hazard ratio: 0.90; 95% CI: 0.84–0.96], 7-year number needed to treat: 56). The PSCK9 inhibitor evolocumab in the FOURIER study (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) decreased the primary outcome by 1.5% over 2.2 years (hazard ratio: 0.80; 95% CI: 0.73–0.88; 2.2=year number needed to treat: 67). In ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), alirocumab reduced the primary outcome by 1.6% over 2.8 years (hazard ratio: 0.86; 95% CI: 0.79–0.93; 2.8-year number needed to treat: 63). For ezetimibe and the PSCK9 inhibitors, rates of musculoskeletal, neurocognitive, gastrointestinal, or other adverse event risks did not differ between the treatment and control groups. For patients at high risk of ASCVD already on background statin therapy, there was minimal evidence for improved ASCVD risk or adverse events with cholesterol-ester transfer protein inhibitors. There was no evidence of benefit for the addition of niacin to statin therapy. Direct comparisons of the results of the 10 randomized controlled trials were limited by significant differences in sample size, duration of follow-up, and reported primary outcomes.

Conclusions: In a systematic review of the evidence for adding nonstatin lipid-modifying therapies to statins to reduce ASCVD risk, we found evidence of benefit for ezetimibe and PCSK9 inhibitors but not for niacin or cholesterol-ester transfer protein inhibitors.

INTRODUCTION

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the treatment of blood cholesterol identified evidence to support the use of moderate- to high-intensity statin therapy in 4 clinical groups: individuals with known atherosclerotic cardiovascular disease (ASCVD), those with diabetes mellitus, those with a low-density lipoprotein cholesterol (LDL-C) level of ≥190 mg/dL (≥4.9 mmol/L), or those with an estimated ASCVD 10-year risk ≥7.5% (1). Despite the presence of residual risk in individuals treated with statin therapy, the 2013 guideline writing committee found little evidence at that time to support the use of nonstatin lipid-modifying therapy to further reduce ASCVD risk.

Since publication of the 2013 ACC/AHA guidelines (1), multiple randomized controlled trials (RCTs) evaluating the efficacy of nonstatin lipid-lowering medications have been published (2-8). The present evidence review committee (ERC) performed a systematic evidence review of recently published RCTs (since 2010) to assess the magnitude of benefit or harm of nonstatin lipid-modifying therapy on a background of statin therapy. The key goal of this review was to provide an evidence document for the "2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol" (9).

Relationships With Industry and Other Entities

The ACC and AHA sponsor the guidelines without commercial support, and members volunteer their time. The ACC/AHA Task Force on Clinical Practice Guidelines avoids actual, potential, or perceived conflicts of interest that might arise through relationships with industry or other entities. All ERC members are required to disclose current industry relationships or personal interests, from 12 months before initiation of the writing effort. The ERC chair and all ERC members may not have any relevant relationships with industry or other entities (Appendix 1). For transparency, ERC members' comprehensive disclosure information is available at http://jaccjacc.acc.org/Clinical_Document/Cholesterol_GL_SR_Author_Comp_RWI.pdf. Comprehensive disclosure information for the Task Force is available at http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/guidelines-and-documents-task-forces.

METHODS

The systematic review addressed the following specific clinical question posed by the guideline writing committee, using the PICOTS format (Population, Intervention, Comparison, Outcomes, Timing, and Setting):

1. In adults ≥20 years of age with clinical ASCVD or at high risk of ASCVD, what is the a) magnitude of benefit in individual endpoints and composite ischemic events and b) magnitude of harm in terms of adverse events derived from LDL-C lowering in large RCTs comparing statin therapy plus a second lipid-modifying agent with statin therapy alone.

The relevant trials of additional lipid-modifying agents included medications from different classes, precluding the ERC from performing a meta-analysis. The systematic review complied with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement recommendations of the "ACC/AHA Clinical Practice Guideline Methodology Summit Report" (10).

Numerical values for triglycerides, total cholesterol (TC), LDL-C, HDL-C and non-HDL-C are given are in both mg/dL and mmol/L. To convert to SI units, the values for TC, LDL-C, HDL-C, and non-HDL-C were divided by 38.6 and for triglycerides, by 88.6.

Study Selection

ERC members compiled a list of relevant clinical trials published in English since December 2, 2009, given that the Cholesterol Treatment Trialists' meta-analysis included reports through 2009 (11). A formal literature search, using PubMed and EMBASE, was performed by an AHA librarian on July 30, 2017. The search strategy is found in Table 1. In total, 199 manuscripts were reviewed independently by 2 members of the ERC. Disagreements were resolved by consensus.

Eligibility Criteria

RCTs were included that enrolled adults ≥20 years of age with clinical ASCVD or at high risk of ASCVD. Clinical ASCVD included acute coronary syndromes (ACS), history of myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease (PAD) presumed to be of atherosclerotic origin. For inclusion, the RCTs needed a minimum sample size of at least 1000 participants and the a priori intention to last at least 12 months. In addition to statin therapy, study participants were treated with placebo versus one of the following drugs/classes: ezetimibe, niacin and niacin/laropiprant, cholesterol-ester transfer protein (CETP) inhibitors, or PCSK9 inhibitors.

The prespecified *PICOTS primary outcome* was a composite of fatal cardiovascular events, nonfatal MI, or nonfatal stroke. The prespecified *PICOTS secondary outcome* was a composite of the primary outcome plus unstable angina or coronary revascularization. Qualitative summary assessment of the relative efficacy of an intervention to reduce clinical events was performed by using the metrics hazard ratio (HR) or relative risk (RR), absolute risk reduction (ARR), and number needed to treat (NNT).

Data Extraction

Data extraction was performed by the ERC. For each included RCT, the following information was abstracted: study design, participant characteristics (e.g., age, race/ethnicity, sex, comorbid conditions), duration of follow-up, adherence to study medication, lipid effects, and adverse side effects. Side effects varied by the drug/class; particular attention was paid to adverse musculoskeletal outcomes, incident diabetes mellitus, incident cancer, cognitive decline, and injection site reactions for biological agents that were injected subcutaneously.

RESULTS

Trials Included in the Systematic Review

Of the 199 publications evaluated, 187 were excluded after abstract review (Figure 1). The majority of publications were excluded because they did not meet inclusion criteria, lacked adequate follow-up, or reported surrogate outcomes rather than ASCVD events. Of the remaining 12 studies, 2 were excluded after full manuscript review. One trial was excluded because it was an open-label study and was not designed to last >1 year (12). A second trial concerning lipid therapy in diabetic patients (ACCORD) was excluded because the contents were already addressed in the 2013 guidelines for the treatment of blood cholesterol (1,13). Two additional trials (Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification [REVEAL], ODYSSEY OUTCOMES [Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab]) that met criteria were published after the literature search was performed and are also included in our review (5,7). Among the 10 trials included in the final review (2-8, 14-15), the sample size ranged from 3,414 to 30,449

subjects. All studies reviewed were planned to last >1 year. The mean study duration ranged from 0.52 to 6 years, and 1 trial (SPIRE 1 [Study of PCSK9 Inhibition and the Reduction of Vascular Events]) was stopped before 1 year for lack of efficacy (Table 2) (3). Results for the present systematic review's PICOTS primary outcome were available for 8 of the studies but were unavailable for HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) or dal-OUTCOMES (Study of R04607381 in Stable Coronary Heart Disease Patients with Recent Acute Coronary Syndrome) (8,14).

Quality Assessment

The RCTs were assessed for potential bias by using the Cochrane Collaboration Risk of Bias Tool. Each trial was reviewed for the quality of randomization (random sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessment), completeness of data (incomplete outcome data), reporting (selective reporting), other bias, relevance (relevance of study sample, intervention, outcome, follow-up period, and setting), and fidelity (assessment of monitoring, protocol adherence, and data validity). The overall results are shown schematically in Figure 2, where the bias risk estimate is color coded: green (<10%, low risk), yellow (10% to 15%, mild risk), and red (>15%, moderate risk).

For the blinding category, mild deficiencies were noted for the SPIRE trials (injection site reaction in 10% for active therapy versus 1.3% for placebo) (3), and moderate deficiencies were observed for the trials that used niacin (AIM-HIGH [Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides Impact on Global Health Outcomes] (15), and HPS2 THRIVE [Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events]) (8). In the relevance category, mild deficiencies were observed for the FOURIER study (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) (12% withdrawal rate) and ODYSSEY OUTCOMES (15% withdrawal rate) (4,5). For relevance, deficiencies were noted for IMPROVE-IT (the Improved Reduction of Outcomes: Vytorin Efficacy International Trial) (19% failure to complete study) (2), AIM-HIGH (8.4% per year discontinuation rate) (15), HPS2 THRIVE (33% withdrawal in lipid run-in phase) (8), and SPIRE (large percentage with antibodies to therapy and loss of effectiveness) (3). For fidelity, moderate deficiencies were seen for AIM-HIGH (25% nonadherence rate). Overall, the RCTs reviewed performed well and had acceptable measures according to the Cochrane Risk of Bias Assessment Tool.

Review of RCTs According to Medication Classes

Ezetimibe

Ezetimibe has been shown to cause a reduction in cholesterol absorption in the intestine by targeting the Niemann-Pick C1-like 1 protein, typically reducing LDL-C by approximately 20%. IMPROVE-IT sought to analyze the impact of ezetimibe on cardiovascular disease (CVD) outcomes when added to moderate-intensity statin therapy in patients experiencing recent ACS (2).

IMPROVE-IT included 18,144 participants >50 years of age and hospitalized for ACS within the previous 10 days (Table 2) (2). Patients taking a moderately potent statin (simvastatin 40 mg) were randomized to ezetimibe 10 mg/d or placebo. Kaplan-Meier event rates were reported over 7 years of follow-up. The median follow-up was 6 years. At baseline, LDL-C levels ranged from 50 to 100 mg/dL (1.3 to 2.6 mmol/L) for patients on lipid-lowering therapy or 50 to 125 mg/dL (1.3 to 3.2 mmol/L) for patients not on lipid-lowering therapy. The mean LDL-C level at baseline was 93.8 mg/dL (2.4 mmol/L) in each group. Baseline lipid levels and change in lipid levels over the course of this RCT and the other trials

reviewed are shown in Table 3. The mean LDL-C levels at 1 year were 24% lower with ezetimibe versus placebo with background therapy of a moderately intensive statin (simvastatin 40 mg/d). The on-treatment mean LDL-C level was 53.2 mg/dL (1.4 mmol/L) with ezetimibe versus 69.9 mg/dL (1.8 mmol/L) on placebo (2). During the trial about half of adults (50.6%) randomized to simvastatin plus ezetimibe reached an LDL-C level of <70 mg/dL (<1.8 mmol/L) and high-sensitivity C-reactive protein <2.0 mg/dL, compared with 30.5% of those randomized to simvastatin plus placebo.

Over 7 years of follow-up, the ARR for the PICOTS primary endpoint was 1.8% (HR: 0.90; 95% CI: 0.84–0.96; NNT: 56 [Table 2]). There were no statistically significant differences in rates of CVD death or death from any cause. Likely because of the long study duration, only 46% to 47% of participants were adherent to medication at the end of the study. The medication adherence rates were similar for both arms of the trial.

Ezetimibe was well tolerated, with no statistically significant differences in adverse effects for myopathy, rhabdomyolysis, liver function test abnormalities, or cancer. In a prespecified safety analysis, IMPROVE-IT participants who achieved an LDL-C level of <30 mg/dL (<0.77 mmol/L) were compared with those achieving higher LDL-C and were found to have no significant increase in risk for 9 prespecified safety outcomes, including muscle, hepatobiliary, and neurocognitive events (2).

Although the net clinical benefit in IMPROVE-IT was modest, several prespecified secondary analyses suggested a more substantial reduction in ASCVD risk among higher-risk participants. For example, there was evidence of effect modification according to age, and individuals >75 years of age appeared to benefit more significantly than those <75 years (*p*-value for interaction, 0.005) (16). Trial participants with diabetes mellitus randomized to ezetimibe experienced a 5.5% ARR compared with placebo (HR: 0.85; 95% CI: 0.78–0.94]), whereas adults without diabetes mellitus experienced a nonsignificant ARR (HR: 0.98; 95% CI: 0.91–1.04; ARR, 0.7%) with ezetimibe (16). In a separate analysis, participants were stratified on the basis of the presence or absence of 9 secondary risk indicators, such as current smoking, renal dysfunction, diabetes mellitus, or PAD (16). The post hoc analysis suggested that adults with the greatest burden of risk factors experienced the largest reduction in ASCVD risk with ezetimibe. About one quarter of the IMPROVE-IT population was identified as high risk, on the basis of the presence of at least 3 risk indicators. High-risk participants experienced anARR of 6.3% (95% CI: 2.3%–9.7%) over 6 years with ezetimibe versus placebo with an NNT of 16. Conversely, 45% of the study population had no more than 1 risk indicator and did not experience a significant reduction in risk with ezetimibe versus placebo (*p*-value for interaction = 0.01). Overall, IMPROVE-IT showed that ezetimibe modestly reduced ASCVD risk over 7 years of follow-up when applied broadly to a post-ACS population treated with background statins.

PCSK9 Inhibitors

PCSK9 is a secreted protein that binds to LDL receptors, accelerating their degradation. Individuals with loss-of-function mutations in the *PCSK9* gene have been shown to have lifelong lower LDL-C levels and markedly reduced rates of ASCVD events (17). Various therapeutic strategies are in development to inhibit PCSK9; however, large-scale RCTs with clinical outcomes have been performed only for monoclonal antibody therapies.

SPIRE-1 and SPIRE-2 enrolled patients with known ASCVD or at high risk of ASCVD to bococizumab 150 mg administered subcutaneously every 2 weeks versus placebo (Table 2) (3). The trials differed slightly in their inclusion criteria. SPIRE-1 enrolled 16,817 individuals with an LDL-C level of ≥70 mg/dL (≥1.8 mmol/L), and SPIRE-2 enrolled 10,621 individuals with an LDL-C level of ≥100 mg/dL (≥2.6 mmol/L). SPIRE-1 required background therapy of at least 40 mg of atorvastatin, 20 mg of rosuvastatin, or 40 mg of simvastatin, whereas 16.8% of SPIRE-2 participants had statin intolerance. As a result, the

baseline LDL-C in SPIRE-1 was lower than that in SPIRE-2 (93.8 mg/dL versus 133.9 mg/dL (2.4 versus 3.5 mmol/L)).

After a median follow-up of 7 months in SPIRE-1 and 12 months in SPIRE-2, the trial sponsor halted development of bococizumab and stopped the trials early because high-titer antidrug antibodies to bococizumab that attenuated LDL-C lowering were detected. In the combined trials, LDL-C was lowered by 56% at 12 weeks but decreased to 41.8% at 52 weeks (Table 3). There was no reduction in event rates with bococizumab in SPIRE-1. However, in SPIRE-2, an ARR of 0.91% (2.66% [active] versus 3.57% [placebo] events per 100 person-years, p=0.007) was seen in the PICOTS primary outcome, and an ARR of 0.87% (3.32% [active] versus 4.19% [placebo], p=0.012) was seen in the PICOTS secondary outcome. The rates of serious adverse events were similar in the 2 groups. However, there was a higher rate of injection site reactions (10.4% active versus 1.3% placebo, p<0.001) with bococizumab. Rates of myalgias, newly diagnosed diabetes mellitus, and cataracts were similar in the 2 groups, as were plasma enzyme levels (aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine kinase).

The FOURIER trial enrolled 27,564 patients 40 to 85 years of age with clinically evident CVD (i.e., MI, nonhemorrhagic stroke, or symptomatic PAD) and additional risk factors. Participants were randomized to evolocumab (140-mg subcutaneous injection every 2 weeks or 420 mg monthly) or matching placebo (Table 2) (4). Patients had to have a fasting LDL-C level of ≥70 mg/dL (≥1.8 mmol/L) or a non–high-density lipoprotein cholesterol (non-HDL-C) level of ≥100 mg/dL (≥2.6 mmol/L) on maximally tolerated statin with or without ezetimibe. Notably, 69% were on a high-intensity statin, 30% were on a moderate-intensity statin, and 5% were on ezetimibe. Participants had stable vascular disease, with MI (81%) or stroke (20%) occurring a median of approximately 3.3 years before enrollment, and were excluded if MI or stroke had occurred within the 4 weeks before enrollment. The median duration of follow-up was 2.2 years.

The baseline median LDL-C level was 92 mg/dL and was reduced by 59% to a median value of 30 mg/dL in the active treatment arm at 48 weeks (Table 3). The evolocumab arm also experienced a reduction in non-HDL-C by 51%, lipoprotein(a) by 27%, and triglycerides by 16%, as well as an increase in HDL-C by 8%. The PICOTS primary outcome occurred in 5.9% of the active treatment arm versus 7.4% of the placebo arm (HR: 0.80; 95% CI: 0.73–0.88; p<0.001; ARR: 1.5%; NNT: 67), with no difference in CVD death or all-cause death. The PICOTS secondary outcome occurred in 9.8% and 11.3% in the evolocumab and placebo arms, respectively (HR: 0.85; 95% CI: 0.79–0.92; p<0.001; ARR: 2.5%; NNT: 40). Serious adverse events were comparable in both trial arms (24.8% versus 24.7%), with only injection site reaction occurring more frequently with evolocumab treatment (2.1% versus 1.6%). There were no differences in the rates of diabetes mellitus, muscle-related events, or elevations in liver function tests (18). Risk of neurocognitive events was similar between groups, both in the overall trial and in a subgroup in which more detailed cognitive testing was performed (19). There was no signal of harm among the 10% of participants with an LDL-C level of <10 mg/dL during the study (20).

The FOURIER trial evaluated a patient population with suboptimal LDL-C levels despite maximally tolerated statin therapy, and high-intensity statins were taken by most. The study had modest dropout rates (12% to 13%) that were similar in the 2 treatment arms, and loss to follow-up was minimal (<0.1%). The reduction in the primary endpoint according to the Cholesterol Treatment Trialists' definition was only 20% despite a 62-mg/dL reduction in the LDL-C level, which was less than would have been predicted on the basis of prior meta-analyses (11).

Additional subgroup analyses from the FOURIER trial have been reported. Patients in the trial with PAD were found to have similar RR reduction, with greater ARR than those without PAD. Evolocumab also reduced major limb events in all subjects (21). Participants with higher C-reactive protein levels similarly had a greater ARR with evolocumab treatment attributable to their higher baseline ASCVD risk. Even at an LDL-C level of <20 mg/dL in FOURIER, there was a monotonic

relationship between achieved LDL-C and ASCVD risk: lower LDL-C on therapy was associated with lower ASCVD risk (20).

The ODYSSEY OUTCOMES trial evaluated patients with recent ACS (within 1 to 12 months [median, 2.6 months] before enrollment) and an LDL-C level of ≥70 mg/dL (≥1.8 mmol/L) or a non-HDL-C level of ≥100 mg/dL (≥2.6 mmol/L) despite predominantly high-intensity statin therapy (89%) (Table 2) (5). A total of 18,924 patients were randomized to biweekly injections of alirocumab 75 mg or 150 mg or matching placebo, targeting an LDL-C level between 25 mg/dL and 50 mg/dL (0.6 and 1.3 mmol/L). Active treatment was blindly switched to placebo for an LDL-C level of <15 mg/dL (<0.4 mmol/L) (7.7%). The median duration of follow-up was 2.8 years, slightly longer than FOURIER.

In ODYSSEY OUTCOMES, the baseline LDL-C level was 92 mg/dL (2.4 mmol/L) and levels were reduced approximately 48% lower at 12 months with relatively persistent effects at 48 months while LDL-C did not change on placebo. Levels of HDL-C increased a few mg/dL with active therapy and the average triglyceride levels were similar at baseline with a mean of approximately 120 mg/dL (3.1 mmol/L) on active therapy versus 140 mg/dL (3.6 mmol/L) over the course of the trial (Table 3) (5). The smaller difference between the on-treatment and intention-to-treat LDL-C levels over the course of the trial is partly attributable to the trial-designed reduction in therapy for those with an LDL-C level of <15 mg/dL (<0.4 mmol/L). The PICOTS primary endpoint occurred in 9.5% and 11.1%, respectively (HR: 0.85; 95% CI: 0.78–0.93; ARR: 1.6%; NNT: 63) based on the median 2.8 years of follow-up without extrapolation. All-cause mortality rate was lower in the alirocumab arm (3.5% versus 4.1%; HR: 0.85; 95% CI: 0.73–0.98; ARR: 0.6%; NNT: 167). In predefined subgroup analyses across three baseline LDL-C cholesterol strata (<80, 80-100, ≥100 mg/dL (<2.1, 2.1-2.6, ≥2.6 mmol/L)) the participants on active therapy in the highest LDL-C group experienced the greatest ARR, but there was no statistically significant difference in relative benefit across the groups (*p* for interaction 0.09). Risks for serious adverse events, muscle-related events, liver function test elevation, and neurocognitive disorders did not differ between alirocumab and placebo. Injection site reactions were more common with alirocumab (3.8% versus 2.1%).

The ODYSSEY OUTCOMES trial confirmed the benefit of PCSK9 human monoclonal antibody therapy to reduce ASCVD risk. The RR reduction of 15% was similar to that observed in FOURIER, despite a slightly longer trial with potent LDL-C lowering. All-cause mortality rate reduction, an important new finding for PCSK9 therapy, was believed to be partly attributable to the inclusion of patients with recent ACS (ODYSSEY OUTCOMES) rather than chronic, stable ischemic disease (FOURIER).

Cholesterol Ester Transfer Protein Inhibitors

CETP facilitates the exchange of triglycerides and cholesterol esters between HDL and atherogenic particles containing apolipoprotein B. Agents that inhibit CETP have been shown to significantly reduce LDL-C and increase HDL-C levels; however, an RCT of torcetrapib was stopped early because of harm from off-target effects (22). For the present analysis, we reviewed trials of 3 additional CETP inhibitors published after December 2009. None of the CETP inhibitors showed a significant reduction in the PICOTS primary outcome (Table 2) (6,7,14).

In dal-OUTCOMES, 15,871 adults who had a recent ACS were randomized to dalcetrapib versus placebo (14). At baseline, the mean LDL-C level was 76 mg/dL (1.9 mmol/L) and the mean HDL-C level was 42 mg/dL (1.1 mmol/L) (Table 3). In the dalcetrapib group, there was a minimal effect on LDL-C; on the other hand, HDL-C increased 31% to 40%. After a median follow-up of 31 months, dal-OUTCOMES was stopped early for futility. Event rates for the PICOTS primary outcome were not reported. The study's primary outcome was a composite of death from coronary heart disease, a major nonfatal coronary event (MI, hospitalization for unstable angina with objective evidence of acute myocardial ischemia, or cardiac arrest with resuscitation), or ischemic stroke (9.1% [placebo] versus 9.2%; HR: 1.04;

95% CI: 0.93–1.16). Adults in the dalcetrapib group had a 0.6-mm Hg higher systolic blood pressure than those randomized to placebo.

Post hoc analyses of dal-OUTCOMES suggest that polymorphisms in the *ADCY9* gene played a significant role in the treatment effect of dalcetrapib. In a genome-wide association study of 5479 participants in dal-OUTCOMES, those with genotype AA at rs1967309 experienced a 39% lower risk of cardiovascular events with dalcetrapib than with placebo, whereas those with genotype GG experienced a 27% increase in events with this agent (23). Dalcetrapib did not significantly reduce ASCVD risk for those with the heterozygous AG genotype. A subsequent study showed that treatment with dalcetrapib compared with placebo resulted in an increase in high-sensitivity C-reactive protein and no improvement in cholesterol efflux among participants with the GG and AG genotypes, but it resulted in stable high-sensitivity C-reactive protein levels and improvement in cholesterol efflux among those with the AA genotype (24). The efficacy and safety of dalcetrapib are now being investigated selectively in the Dal-GenE study (NCT02525939), an RCT of dalcetrapib versus placebo among adults with the AA genotype who were recently hospitalized for ACS. The generalizability of the pharmacogenomic results from dal-OUTCOMES is unclear, as there was no interaction of rs1967309 genotype with ASCVD outcomes in a subsequent nested case–control study within an RCT that used a different CETP inhibitor, evacetrapib (25).

In the ACCELERATE (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with evacetrapib in Patients at a High Risk for Vascular Outcomes) trial, 12,092 adults with high ASCVD risk (an ACS within the previous 30 to 365 days, cerebrovascular atherosclerotic disease, PAD, or diabetes mellitus with coronary heart disease) were randomized to evacetrapib versus placebo, with all patients on background statin therapy (6). At baseline, the mean LDL-C level was 81.3 mg/dL (2.1 mmol/L) and the mean HDL-C level was 41.3 mg/dL (1.1 mmol/L). Despite a 31.1% decrease in LDL-C and a 133% increase in HDL-C with evacetrapib, ACCELERATE was stopped early for futility after a median follow-up of 28 months (event rate of 7.5% versus 7.2%; HR: 0.97; 95% CI: 0.85–1.10). Mean systolic blood pressure increased 1.2 mm Hg with evacetrapib.

The REVEAL study was the largest CETP inhibitor trial and had the longest follow-up to date. In REVEAL, 100 mg of anacetrapib daily was compared with placebo in 30,449 adults with prior MI, cerebrovascular atherosclerotic disease, PAD, or diabetes mellitus with symptomatic coronary heart disease (7). All participants were also treated with atorvastatin, with the goal of reducing the LDL-C level to <77 mg/dL (<1.99 mmol/L). The mean age was 68 years, and 88% of the participants had a history of coronary heart disease. At baseline, the mean LDL-C level was 61 mg/dL (1.5 mmol/L), the mean non-HDL-C level was 92 mg/dL (2.3 mmol/L), and the mean HDL-C level was 40 mg/dL (1.0 mmol/L). With anacetrapib treatment, the mean LDL-C level decreased by 26 mg/dL (0.67 mmol/L) (–41%), the non-HDL-C level decreased by 17 mg/dL (0.43 mmol/L) (–18%), and the HDL-C level increased by 43 mg/dL (1.1 mmol/L) (+103%).

Over 4 years of follow-up, the rate of the PICOTS primary outcome with anacetrapib versus placebo was 9.1% versus 9.7% (HR: 0.93; 95% CI: 0.86–1.00; p=0.052), with an ARR of 0.6% and NNT of 160. Adverse effects in REVEAL included a higher incidence of modest elevations in creatine kinase (10 to 40 times the upper limit of the normal range) with anacetrapib versus placebo and lower rates of more severe creatine kinase elevations (>40 times the upper limit of the normal range). Patients taking anacetrapib experienced slightly higher systolic blood pressure (0.7 mm Hg) and diastolic blood pressure (0.3 mm Hg) than those taking placebo. Incident diabetes mellitus was lower in the anacetrapib group than in the placebo group (5.3% versus 6.0%; rate ratio, 0.89; 95% CI: 0.79–1.00; p=0.05). An estimated glomerular filtration rate of <60 mL/min/1.73 m^2 developed in more patients in the anacetrapib group than in the placebo group (11.5% versus 10.6%;, p=0.04). There were no significant between-group differences in the development of albuminuria. There was also no difference in incident cancer between

groups. In late 2017, the sponsor of anacetrapib withdrew the medication from development because the ASCVD prevention effects observed in REVEAL were modest.

Niacin

Niacin increases HDL-C, decreases LDL-C, and lowers triglycerides. The Coronary Drug Project, an older secondary-prevention trial in men, demonstrated that niacin monotherapy improved long-term risk of ASCVD outcomes compared with placebo (26). Similarly, studies of niacin or extended-release niacin combined with statins have suggested improvements in surrogate outcomes compared with statins alone (27,28). Two large RCTs—AIM-HIGH and HPS2-THRIVE—were recently performed in the past several years to assess the effect of adding niacin to background statin therapy to reduce the risk of ASCVD outcomes (Table 2) (8,29).

The AIM-HIGH trial evaluated the role of extended-release niacin in patients with established ASCVD who had already achieved target LDL-C levels (29). A total of 3414 patients were randomized to niacin (1500 to 2000 mg/d) or placebo in addition to goal-directed LDL management with statin and/or ezetimibe. Patients received 40 to 80 mg of simvastatin, with or without ezetimibe, to maintain an LDL-C level of <80 mg/dL (<2.0 mmol/L). Patients were followed up for approximately 3 years.

Although the niacin arm in AIM-HIGH demonstrated an increase in HDL-C (from 35 to 42 mg/dL (0.9 to 1.08 mmol/L)), along with lowering of triglyceride and LDL-C levels, the trial was stopped because of lack of efficacy (Table 3). No significant risk differences between the active and placebo treatment arms were noted for CVD death or MI. Event rates for a close approximation of the PICOTS primary outcome were 8.1% with placebo and 9.1% with niacin (HR: 1.13; 95% CI: 0.90–1.42. This composite primary endpoint in AIM-HIGH included CHD death, nonfatal MI, ischemic stroke, hospitalization for ACS or symptom-driven coronary or cerebral revascularization, but did not include stroke death. Overall, serious adverse effects in this RCT were rare. More patients receiving niacin discontinued the study medication than did those receiving placebo, predominantly driven by flushing or itching. There were no worrisome significant safety signals in either group.

The second study of niacin was HPS2-THRIVE, which assessed the effects of adding niacin (in combination with laropiprant, a prostaglandin antagonist, to reduce flushing) in patients with established ASCVD who were already on statin and/or ezetimibe (8). A total of 25,673 adults on statin therapy were randomized to receive 2 g of extended-release niacin plus 40 mg/d of laropiprant or matching placebo. Median follow-up was 3.9 years, and the primary endpoint was the first major vascular event (MI, death from coronary disease, stroke, or revascularization).

Similar to AIM HIGH, participants in HPS2-THRIVE experienced an improvement in lipids, with no reduction in CVD events. The combination of niacin and laropiprant resulted in a lower LDL-C level (average reduction of 10 mg/dL (0.25 mmol/L)) and a higher HDL-C level (average increase of 6 mg/dL (0.15 mmol/L), when compared with placebo (Table 3). No significant effects on composite CVD risk were noted (13.2% in treatment group versus 13.7% in placebo group; rate ratio, 0.96; 95% CI: 0.90–1.03; *p*=0.29). Event rates for the PICOTS primary outcome were not reported. Study completion rates were 71.6% on niacin and 82.6% on placebo. The combination of niacin and laropiprant was associated with increased risk of serious side effects, including worsening diabetic control and gastrointestinal, muscle, and skin abnormalities, as well as increased risk of infection and bleeding.

Both HPS2-THRIVE and AIM-HIGH demonstrated no improvement in major vascular events with the addition of extended-release niacin in patients with established atherosclerosis and well-controlled LDL-C levels on statin-based therapy. Furthermore, niacin treatment resulted in an increase in serious side effects. These data significantly curtail the value of niacin as a lipid-modifying agent when added to background statin therapy.

DISCUSSION

The efficacy and safety of statin therapy for secondary prevention of ASCVD events is well established. However, even among patients treated with high-dose statin therapy, in both randomized clinical trials and contemporary cohorts, the 5-year risk of recurrent events ranges from 10% to 30%, depending on the population studied (30-32). As a result, many patients are offered additional lipid therapy to potentially further reduce ASCVD risk. A limited number of event-driven clinical trials have examined the efficacy of various lipid-modifying therapies when added to background statin therapy in persons at high risk of ASCVD events or with established ASCVD. As summarized in the present systematic review, several classes of medications were reviewed, including CETP inhibitors, niacin, ezetimibe, and PCSK9 inhibitors. The unique mechanisms of action of each of these classes precluded a formal meta-analysis, and we have summarized the data according to individual classes of the lipid medications.

Despite generally favorable effects on multiple lipid measures, the net clinical benefit was highly variable across the medications reviewed. Lowering of LDL-C levels was observed with ezetimibe, PCSK9 inhibitors, niacin, and some CETP inhibitors. Increasing HDL-C levels were observed with CETP inhibitors, niacin, and PCSK9 inhibitors. Changes in other lipid markers were not consistently reported. Lipoprotein(a) was reduced with PCSK9 inhibitors, niacin and some CETP inhibitors; some degree of triglyceride lowering was also seen in each medication class.

Studies of ezetimibe (IMPROVE-IT) and PCSK9 inhibitors (FOURIER, ODYSSEY OUTCOMES) showed significant, although modest, reductions in the RR of clinical events (2,4,5). The ARR in the composite ASCVD events ranged from 1.5% to 2%, and the NNT was 50 to 70 over the study intervals reported. An important consideration is that FOURIER and ODYSSEY reported results for only 2.2 and 2.8 years of follow-up, respectively, whereas trials with durations of ≥4 years have historically been used to assess the efficacy of newer pharmaceutical agents to reduce ASCVD events.

The results of both trials that added niacin to background statins (AIM-HIGH, HPS2 THRIVE) demonstrated no reduction in ASCVD events, and niacin increased adverse side effects, such as worsened glycemic control. One CETP inhibitor trial with anacetrapib (REVEAL) was associated with a reduction in events (an ARR of 0.9% in the PICOT secondary outcome) despite a 41% decrease in the LDL-C level with the therapy. Null trial results were reported for evacetrapib (ACCELERATE) and dalcetrapib (dal-OUTCOMES). Whether treatment with dalcetrapib will yield a reduction in ASCVD events in a prospective study targeting patients on the basis of pharmacogenomics is currently being studied.

Adverse events experienced by study participants across the trials were qualitatively reviewed. A higher incidence of myalgias was seen only with niacin. None of the trials reported an increase in creatine kinase levels across multiple lipid medications. Similarly, only niacin therapy was associated with a worsening of glycemic control, whereas a slight improvement was seen with anacetrapib. SPIRE participants experienced a higher incidence of injection site reactions compared with placebo (10.4% versus 1.3%), but the incidence was smaller with evolocumab (2.1% [active] versus 1.6% [placebo]) and alirocumab (3.8% [active] versus 2.1% [placebo]). None of the studies reported an increase in the incidence of cancer.

Importantly, many participants in FOURIER and ODYSSEY achieved LDL-C levels that were substantially lower than previously seen in statin trials, with no evidence of harm. In FOURIER, 10% of participants achieved LDL-C levels <20 mg/dL (0.51 mmol/L). There was no reported increase in the incidence of cataracts or cognitive decline. The FOURIER Open-Label Extension (FOURIER OLE, NCT03080935) study of FOURIER participants with up to 5 years of follow-up should help provide additional insight into longer-term consequences of treatment with evolocumab.

Clinical trial completion rates were assessed for each of the investigations. The trials designed to last 2 years had high completion rates, typically exceeding 95% of those who were randomized at the

start of the trial. Conversely, the IMPROVE-IT trial lasted 7 years, and the overall completion rate was 46% to 47% for those who were randomized.

The reduction in ASCVD risk achieved with novel therapies has traditionally been measured by the HR or RR. However, as high-dose statin therapy has become the standard of care among patients with established ASCVD or at high ASCVD risk, the magnitude of risk reduction was smaller than what was initially seen when statins were compared with placebo. For example, in the Heart Protection Study, treatment with simvastatin 40 mg versus placebo in 20,536 adults with ASCVD or diabetes mellitus achieved a 25% RR reduction and a 5.4% ARR for major vascular events (33). Alternative metrics, including the ARR, NNT, and cost-effectiveness analyses, will become increasingly valuable when trying to determine the overall benefit of novel therapies to reduce ASCVD risk. In an analysis performed before the publication of FOURIER and ODYSSEY, Robinson et al suggested that the incremental benefit, and thus the lowest NNT, of PCSK-9 inhibitors or ezetimibe would likely be greatest among adults with the highest overall risk (34). Although IMPROVE-IT, FOURIER, and ODYSSEY all showed statistically significant reductions in risk for the overall study populations, subgroup analyses demonstrated that highest-risk patients, such as those with multiple risk factors, experienced the greatest reduction in ASCVD events.

The present systematic review was commissioned to evaluate therapies that alter LDL-C levels to improve ASCVD risk in individuals already on statin therapy. It is of interest, however, to consider that additional pathways in the development of atherosclerosis, such as inflammation, are also being actively investigated. For instance, canakinumab is a monoclonal antibody that targets interleukin-1β, an upstream modulator of interleukin-6 and C-reactive protein. The CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) trial enrolled 10,061 adults with a prior MI and high-sensitivity CRP >2 mg/L and randomized them to canakinumab (50 mg, 150 mg, or 300 mg) or placebo injections every 3 months (35). All participants were taking statins at baseline. The trial demonstrated no change in LDL-C levels but a large reduction in C-reactive protein and a 12% reduction in composite ASCVD risk (HR: 0.88;95% CI: 0.79–0.97). At 48 months of follow-up, the absolute ASCVD risk was 4.5% on placebo and 3.95% on active therapy, for an ARR of 0.55% and NNT of 182. Canakinumab was associated with a higher incidence of fatal infection, neutropenia, and thrombocytopenia, with a lower incidence of arthritis and fatal cancer. Two ongoing studies of anti-inflammatory therapies in adults with ASCVD include CIRT (Cardiovascular Inflammation Reduction Trial; NCT01594333) of low-dose methotrexate and COLCOT (Colchicine Cardiovascular Outcomes Trial; NCT02551094) of colchicine. In STRENGTH (A Long-Term Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh Cardiovascular Risk PatienTs With Hypertriglyceridemia; NCT02104817), adults with ASCVD or at high risk with a low HDL-C level and high triglycerides were randomized to epanova versus placebo. Similarly, REDUCE-IT (Reduction of Cardiovascular Events with EPA; NCT 01492361), which is using icosapent ethyl ester, is under way to assess omega-3 fatty acid therapy in study subjects on background statin therapy.

In conclusion, we systematically reviewed recent clinical trial evidence for the magnitude of benefit and harm for the addition of other lipid-modifying agents to background statin therapy. There was little evidence to support use of CETP inhibitors and no evidence for niacin use in persons at high risk of ASCVD and on background statin therapy. For ezetimibe and 2 PCSK9 inhibitors, the trial results demonstrated a modest absolute ASCVD risk reduction and good safety profiles for the medications with successfully completed trials.

Legends for Figures

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram for the evidence review committee selection of the randomized controlled trials. Final number of articles was 8 (SPIRE-1 and SPIRE-2 were published in a single article and discussed as 2 separate studies). ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) has been included.

Figure 2. Cochrane Collaboration risk-of-bias evaluation for the trials reviewed by the evidence review committee. Color coding for bias estimates: Green (<10%, low risk), yellow (10% to 15%, mild risk), and red (>15%, moderate). Clinical trials included:

ACCELERATE (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with evacetrapib in Patients at a High Risk for Vascular Outcomes)

dal-OUTCOMES (Study of R04607381[dalcetrapib] in Stable Coronary Heart Disease Patients with Recent Acute Coronary Syndrome)

REVEAL (Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification)

IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)

AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides Impact on Global Health Outcomes)

HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events)

SPIRE-1 and SPIRE-2 (Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects)

FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk)

ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab)

Figure 1. PRISMA Flow Diagram of the Manuscripts Included in the Analysis

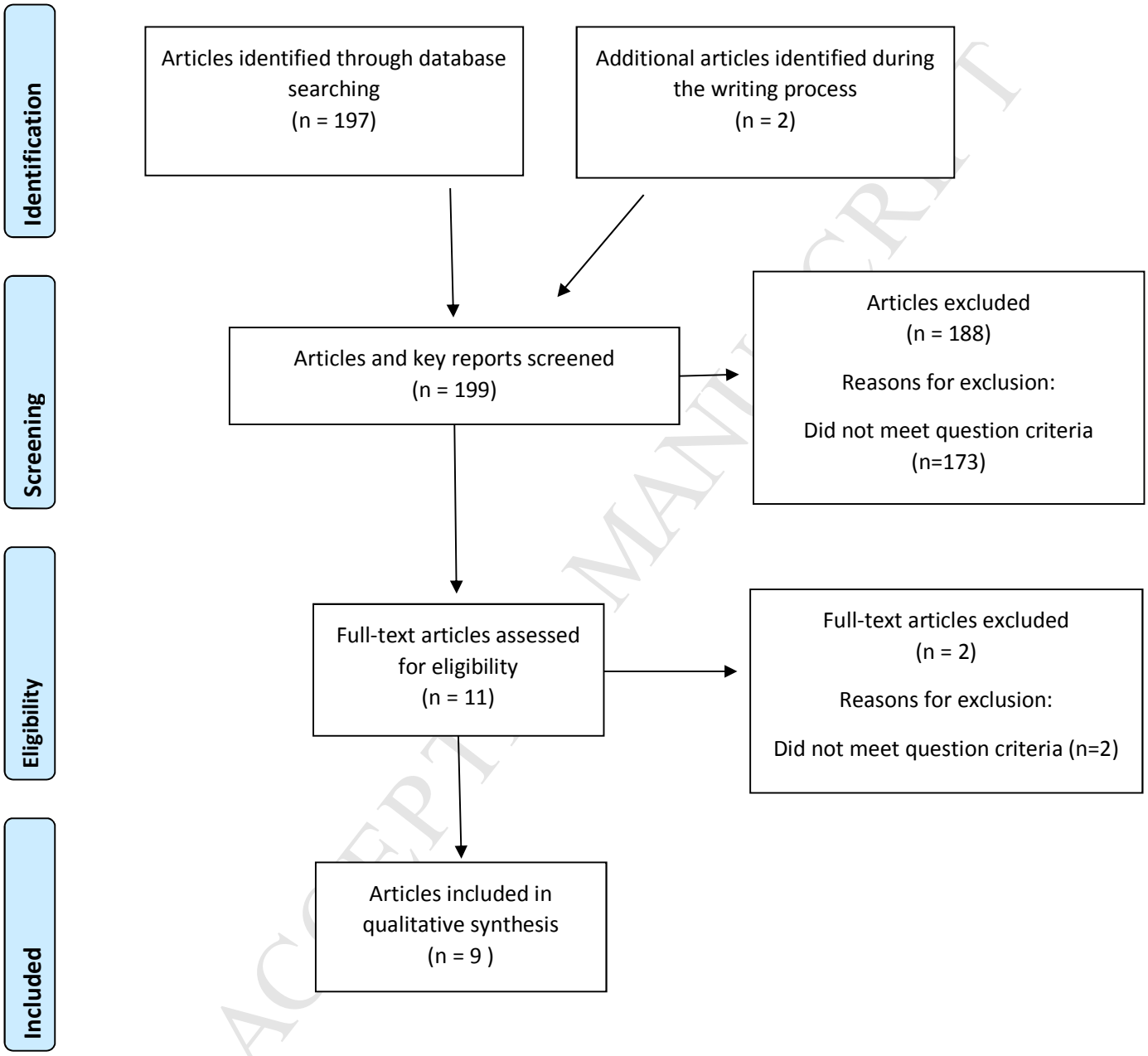

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Figure 2

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Table 1. ACC/AHA Guidelines Literature Search Strategy and Results

Topic/Guideline: **2018 AHA/ACC Cholesterol** Requestor: **Michael D. Miedema**
Database: **Pubmed**
Search conducted **July 30, 2017** by Vanessa Perez, Librarian. American Heart Association Library.

Filters activated: Adult 19+ years, Humans, English language, Randomized Controlled Trial, From 2009/12/01 to 2017/07

Search set	Query	Items found
#1	"Arterial Occlusive Diseases"[Mesh] OR "Arteriolosclerosis"[Mesh] OR "Atherosclerosis"[Mesh] OR "Coronary Artery Disease"[Mesh] OR "Peripheral Arterial Disease"[Mesh] OR "Coronary Disease/blood"[Mesh] OR "Acute Coronary Syndrome"[Mesh] OR "Cardiovascular Diseases/prevention and control"[Mesh] OR “cardiovascular risk” OR “heart disease risk” OR ASCVD[tiab] OR CHD[title] OR PAD[title] OR CVA[title] OR "Angina, Unstable"[Mesh]	7424
#2	"Hypercholesterolemia"[Mesh] OR "Hyperlipidemias"[Mesh] OR "Apolipoproteins/blood"[Mesh] OR "Cholesterol, LDL/blood"[Mesh] OR "Triglycerides/blood"[Mesh]	2282
#3	"Simvastatin/therapeutic use"[Mesh] OR "Anticholesteremic Agents"[Mesh] OR "Ezetimibe, Simvastatin Drug Combination"[Mesh] OR "Cholesterol Ester Transfer Proteins/antagonists and inhibitors"[Mesh] OR “CETP inhibitor”[title] OR "Ezetimibe"[Mesh] OR evolocumab[title] OR anacetrapib[title] or evacetrapib[title] OR "Hypolipidemic Agents/drug therapy"[Mesh] OR PCSK9[title] OR bococizumab[title] OR dalcetrapib[title] OR "Pravastatin"[Mesh] OR "lovastatin-niacin combination" [Supplementary Concept] OR "Niacin/therapeutic use"[Mesh] OR laropiprant[title] OR statin[title]	1751
#4	"Combined Modality Therapy"[Mesh] OR "Double-Blind Method"[Mesh] OR "Drug Therapy, Combination"[Mesh] OR "Delayed-Action Preparations"[Mesh] OR "Drug Combinations"[Mesh] OR "Controlled Before-After Studies"[Mesh] OR "Fatal Outcome"[Mesh] OR non-fatal[title]	38181
#5	#1 AND #2 AND #3 AND #4	174
#6	References cited on literature search form plus manually selected related references.	37
#7	#5 OR #6	197

Table 2. Study Characteristics, Outcomes, and Adverse Event Rates

Study	Sample Size, Study Duration, Adherence	Drug Tested, Statin Used	Study Population	Primary and Secondary Outcomes	Major Adverse Events
ACCELERATE Lincoff et al, 2017 (6) 28514624	12,092 Median follow-up of 26 mo *Adherence* – Active 83% – Placebo 81.2% – Based on % of adults who discontinued drug early; pill counts not reported	Evacetrapib 130 mg daily – 95% receiving any statin – 45%–46% receiving high-dose statin	*Inclusion*: – High-risk vascular disease (ACS within previous 30–365 d, cerebrovascular atherosclerotic disease, PAD, DM, CAD) – HDL-C <80 mg/dL – TG <400 mg/dL – LDL-C <100 mg/dL or 70 mg/dL unless already receiving statin for 30 d, or statin intolerance *Exclusion (cardiovascular)*: ACS, stroke or transient ischemic attack in prior 30 days, planned revascularization Mean age, 64.8 y and 65.0 y 23% women 18% nonwhite	ERC primary outcome – HR: 0.97 (95% CI: 0.85–1.10) – Event rates (7.2% vs. 7.5%), *p*=0.59 – ARR: 0.3% – NNT: 333 ERC secondary outcome – HR: 1.01 (95% CI: 0.91–1.11) – Event rates (12.9% vs. 12.8%), *P*=0.91 – ARR: no reduction in risk – NNT: NA	Hypertension Placebo 10.1% vs. Evacetrapib 11.4%, *p*=0.02 Absolute change in BP Placebo SBP 0±14.3 mm Hg vs. Evacetrapib SBP 1.2±14.4 mm Hg
dal-OUTCOMES Schwartz et al, 2017 (14) 23126252	15,871 Median 31 mo *Adherence* – Active 79% – Placebo 81% – Based on % of participants who continued taking study drug throughout the study	Dalcetrapib 600 mg daily 97% on a statin Intensity or dose not reported	*Inclusion* – Prior hospitalization for ACS, MI with PCI – Target baseline LDL <100 mg/dL, preferably 70 mg/dL, but not excluded if higher *Exclusion (cardiovascular)* – TG >400 mg/dL Mean age 60.3±9.1 y	ERC primary outcome Not reported ERC secondary outcome Not reported Study primary outcome Death from coronary heart disease, nonfatal MI, ischemic stroke, unstable angina, or cardiac arrest with resuscitation)	– Mean SBP remained approximately 0.6 mm Hg higher with dalcetrapib vs. placebo (*p*<0.001) – Greater incidence of hypertension with dalcetrapib (7.3% vs. 6.5%) but smaller difference in report of hypertension as a serious event (0.6% vs. 0.3%) – Greater incidence of

	– 89% of participants in each group had at least 80% adherence to study drug		20% women 12% nonwhite	– HR: 1.04 (0.93–1.16) – Event rates 9.2% vs. 9.1%, *p*=0.52	diarrhea 6.8 vs. 4.3
REVEAL The HPS3/TIMI55–REVEAL Collaborative Group (7) 28847206	30,449 Median follow-up 4.1 y *Adherence* – Active 84.9% – Placebo 84.7% – Based on self-reported adherence to ≥80% of scheduled treatment	Anacetrapib 100 mg daily Atorvastatin was titrated to achieve LDL-C <77 mg/dL	*Inclusion* – Adults age >50 y – History of MI, PAD, cerebrovascular – atherosclerotic disease, or DM with symptomatic coronary heart disease *Exclusion (cardiovascular)* – ACS or stroke <3 mo before randomization – A planned coronary revascularization procedure Mean age 67±8 y 18.1% women Nonwhite participation not reported 28.3% participants in China	ERC primary outcome – HR: 0.93 (95% CI: 0.87–1.00) – Event rates 9.8% vs. 10.5%, *p*=0.05 – ARR: 0.7% – NNT: 142 ERC secondary outcome* – HR: 0.93 (95% CI: 0.88–0.99) – Event rates 13.6% vs. 14.5, *p*=0.02 – ARR: 0.9% – NNT: 111	– Incidence of new-onset DM lower with anacetrapib vs. placebo group (5.3% vs. 6.0%; *p*=0.0496) – Slightly higher rates of moderate elevations in – Creatine kinase (10–40× ULN) with anacetrapib vs. placebo, (14 cases vs. 9 cases, both 0.1%; slightly lower rates of more severe elevations (>40× ULN) 0% vs. 0.1% – Estimated glomerular filtration rate < 60 mL/min/1.73 m^2 Developed in more patients with anacetrapib vs. placebo (11.5% vs. 10.6%, *p*=0.04) – Slightly higher SBP with anacetrapib vs. placebo (by 0.7 mm Hg) and DBP (by 0.3 mm Hg) at the final visit. – No significant difference in rates of serious adverse events attributed to hypertension (1.0% anacetrapib vs. 0.9% placebo group

IMPROVE-IT Cannon et al, 2015 (2) 26039521	18,144 Median follow-up 6 y *Adherence* Active 58% Placebo 58% Adherence reported after a median of 6 y	Ezetimibe 10 mg daily Simvastatin 40 mg, with option of increasing to 80 mg if LDL-C >79 mg/dL. After June 2011, only 40-mg dose allowed given FDA regulations	*Inclusion* – Age ≥50 y – Hospitalized for ACS in prior 10 d – LDL ≥50 mg/dL but ≤125 mg/dL if no prior lipid-lowering therapy – LDL ≥50 mg/dL but ≤100 mg/dL if >4 wk of lipid-lowering therapy – TG ≤350 mg/dL *Exclusion* – Clinical instability – CABG as therapy for the index ACS event – Prior statin therapy of higher intensity than simvastatin 40 mg (ie simvastatin 80 mg, atorvastatin ≥40 mg, or any dose of rosuvastatin) Mean age 63.6±9.8 y 24% women 16% nonwhite	ERC primary outcome – HR: 0.90 (95% CI: 0.84–0.96) – Event rates (20.4% vs. 22.2%), *P*=0.003 – ARR: 1.8% – NNT: 56 ERC secondary outcome – HR: 0.94 (95% CI: 0.89–0.99) – Event rates (32.7% vs. 34.7%) *P*=0.016 – ARR: 2% – NNT: 50	No significant between-group differences were seen in the incidence of elevations in ALT >3× ULN, rates of gallbladder-related adverse events, cholecystectomy, muscle-related adverse events, or new, relapsing, or worsening cancer
AIM-HIGH Boden et al (15) 22085343	3,414 Mean follow-up 3 y *Adherence* – Active 74.6% – Placebo 79.9% – Based on discontinuation rates; of those who remained on drug – 90% of those on	1.5–2 g extended-release niacin Simvastatin, 40–80 mg daily, plus ezetimibe 10 mg daily, if needed, to maintain LDL-C 40–80 mg/dL	*Inclusion* – Age ≥45 y – Established CVD (documented stable coronary heart disease, cerebrovascular or carotid disease, or PAD) – Low HDL (<40 mg/dL for men, <50 mg/dL for women) – TG 150–400 mg/dL – LDL-C <180 mg/dL if not	ERC primary outcome Not reported ERC secondary outcome Not reported Study primary outcome Death from coronary heart disease, nonfatal MI, ischemic stroke, hospitalization for ACS, or symptom-driven coronary or cerebral revascularization	Higher rates with niacin vs. placebo of: – Flushing itching (6.1% vs. 2.5%) – Gastrointestinal symptoms (1.5% vs. 0.7%) – Increased glucose level (1.5% vs. 0.8%)

	niacin and 93.3% on placebo took ≥75% of study drug		taking a statin before study Exclusion Within 4 wk before enrollment, they had been hospitalized for an ACS or had undergone a planned revascularization procedure or if they had had a stroke within the preceding 8 wk	– HR: 1.02 (95% CI: 0.87–1.21) – Event rates (16.4% vs. 16.2%), *p*=0.8 – ARR: No reduction in risk – NNT: NA	
HPS2 THRIVE (HPS2-THRIVE Collaborative Group) (8) 25014686	25,673 Median follow-up 3.9 y *Adherence* – Active 69.9% – Placebo 80.1% – Based on self-reported adherence to ≥80% study drug	2 g extended-release niacin plus 40 mg laropiprant daily	*Inclusion* – Age 50–80 y – Prior MI, cerebrovascular disease, PAD, or DM with evidence of symptomatic coronary disease *Exclusion* – <3 mo since ACS, MI, or stroke – Treatment with simvastatin 80 mg plus ezetimibe, atorvastatin 20–80 mg, or rosuvastatin 10–40 mg	ERC primary outcome Not reported ERC secondary outcome Not reported – need to confirm Study primary outcome First major vascular event, defined as a major coronary event (nonfatal MI or death from coronary causes), stroke of any type, or coronary or noncoronary revascularization – HR: 0.96 (95% CI: 0.90–1.03) – Event rates (13.2% vs. 13.7%), *p*=0.29 – ARR: NA – NNT: NA	Incident DM Worsening glycemic control – Gastrointestinal system (absolute excess, 1.0%; *p*<0.001) – Musculoskeletal system (absolute excess, 0.7%; *p*<0.001) – Skin (absolute excess, 0.3%; *p*=0.003) – Infection (absolute excess, 1.4 %; *p*<0.001) – Bleeding (absolute excess, 0.7%; *p*<0.001)
FOURIER (Sabatine et al) (12) 25773607	27,564 Median follow-up 2.2 y *Adherence* – Active 88% – Placebo 87% – Based on number	Evolocumab either 140 mg every 2 wk or 420 mg monthly – High-intensity statin 69.5% – Moderate-	*Inclusion* – Age 40–85 y – Clinically evident ASCVD (prior MI, nonhemorrhagic stroke, or symptomatic PAD) – Most recent fasting LDL-C ≥70 mg/dL or non-HDL-C	ERC primary outcome – HR: 0.80 (95% CI: 0.73–0.88) – Event rates (5.9% vs. 7.4%), *p*<0.001 – ARR: 1.5% – NNT: 67 ERC secondary outcome	Injection site reactions more frequent with evolocumab (2.1% vs. 1.6%), 90% were considered mild, 0.1% in each group stopped treatment because of a reaction

	taking study drug; specifics of adherence not reported	intensity statin 30.2%	≥100 mg/dL after ≥2 weeks of stable lipid-lowering therapy – Fasting TG <400 mg/dL – PLUS • *At least 1 major risk factor* (DM, age >65 y, prior MI or nonhemorrhagic stroke in the last 6 mo, current daily smoking, prior MI, stroke, symptomatic PAD) • Or *2 minor risk factors* (prior non–MI-related revascularization, residual >40% stenosis in ≥2 large vessels, most recent HDL-C <40 mg/dL for men and <50 mg/dL for women, most recent hsCRP >2.0 mg/L, most recent LDL-C ≥130 mg/dL or non-HDL-C ≥160 mg/dL, metabolic syndrome) <u>*Exclusion (cardiovascular)*</u> – MI or stroke within 4 weeks – NYHA class III or IV or last ejection fraction <30% – Any prior hemorrhagic stroke – Uncontrolled BP – Uncontrolled or recurrent ventricular tachycardia	– HR: 0.85 (95% CI: 0.79–0.92) – Event rates (9.8% vs. 11.3), p<0.001 – ARR: 1.5% – NNT: 67	

			Mean age 62.5±9.1 y 25% women 15% nonwhite		
SPIRE-1 and SPIRE-2 (Ridker et al) (3) 28304242 Study stopped early because of high antidrug antibodies that attenuated LDL-lowering	SPIRE-1 – 16,817 – Median follow-up 7 mo *Adherence* – Not reported SPIRE-2 – 10,621 – Median follow-up 12 mo *Adherence* – Not reported	Bococizumab 150 mg sub-cutaneously every 2 wk SPIRE-1 – 99.1% any statin – 91.7% high-dose statins SPIRE-2 – 83.2% any statin – 73.3% high-dose	*Inclusion both studies* – Previous cardiovascular event or a history of DM, CKD, or PAD with additional cardiovascular risk conditions or a history of FH – If no prior CV event then needed ≥1 additional risk factors (smoking history, HDL-C<40 mg/dL, a high-sensitivity C-reactive protein >2.0 mg/L, lipoprotein(a) >50 mg/dL, microalbuminuria, or evidence of asymptomatic coronary stenosis on cardiac imaging) and an age ≥50 y for men and ≥60 y for women; the age cutoff for patients who had FH was ≥35 y for men and ≥45 y for women SPIRE-1 additional inclusion – Atorvastatin, ≥40 mg daily; rosuvastatin, ≥20 mg daily; or simvastatin, ≥40 mg – LDL-C ≥70 mg/dL	(All event rates per 100 person y) SPIRE-1 ERC primary outcome – HR: 1.03 (95% CI: 0.82–1.30) – Event rates 2.49 vs. 2.59, *p*=0.78 – ARR and NNT: NA ERC secondary outcome – HR: 0.99 (95% CI: 0.80–1.22) – Event rates 3.01 vs. 3.02, *p*=0.94 – ARR and NNT: NA SPIRE-2 ERC primary outcome – HR: 0.74 (95% CI: 0.60–0.92) – Event rates 2.66 vs. 3.57, *p*=0.007 – ARR: 0.91 – NNT: 110 ERC secondary outcome – HR: 0.79 (95% CI: 0.65–0.97) – Event rates 3.32 vs. 4.19, *p*-0.019 – ARR: 0.87 – NNT: 115	Injection site reaction greater with bococizumab 10.2% vs. 1.3%

			SPIRE-2 Statin intolerance allowed LDL-C >100 mg/dL		
ODYSSEY OUTCOMES (Schwartz et al) (5) In Press	18,924 Median follow-up 2.8 y *Adherence* – Active 96.4 % – Placebo 96.6 % – Based on study discontinuation rates	Alirocumab 75–150 mg every 2 wk Drug was titrated to goal LDL 25–50 mg/dL; switched to placebo if LDL<15 mg/dL High-intensity statin in 88.6% Low-moderate intensity in 8.8%	*Inclusion* – Age >40 y – ACS within past 1–12 mo – LDL ≥70 mg/dL or non-HDL ≥100 mg/dL or ApoB ≥80 mg/dL – High-intensity statin ≥2 weeks *Exclusion (cardiovascular)* – Uncontrolled hypertension – NYHA class III or IV heart failure – Ejection fraction <25% – TG >400 mg/dL Mean age 58 y 25% women Nonwhite participation not reported	ERC primary outcome – HR: 0.85 (95% CI: 0.78, 0.93) – Event rates 9.5% vs. 11.1, p<0.001 – ARR: 1.6% – NNT: 63 ERC secondary outcome† – HR: 0.87 (95% CI: 0.81, 0.94) – Event rates 13.7% vs. 15.6%, p<0.001 – ARR: 1.9% – NNT: 53	Injection site reaction 3.8% vs. 2.1%, HR: 1.82 (95% CI: 1.54–2.17)

*Outcomes only included coronary death, not CVD death.
†Includes only coronary heart disease death, not CVD death.
ACC indicates American College of Cardiology; ACS, acute coronary syndrome(s); ALT, alanine aminotransferase; apoB, apolipoprotein B; ARR, absolute risk reduction; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; ERC, evidence review committee; FDA, U.S. Food and Drug Administration; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NNT, number needed to treat; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TG, triglycerides; and ULN, upper limit of normal.

Table 3. Baseline and Change in Lipids and Other Serum Markers With Addition of Lipid-Altering Medication to Statin Therapy

Study	LDL-C* (mg/dL)	HDL-C* (mg/dL)	Triglycerides* (mg/dL)	Additional Serum Markers
dal-OUTCOMES (Schwartz et al) (14)	Baseline Dalcetrapib 76.4±26.4 Placebo 75.8±25.9 No appreciable effect during the study	Baseline Dalcetrapib 42.5±11.7 Placebo 42.2±11.5 % Change Increased from baseline by 4%–11% with placebo vs. 31%–40% with dalcetrapib	Baseline Dalcetrapib 134.2±73.6 Placebo 133.0±73.6 % Change Increased from baseline by 6%–17% with placebo vs. 4%–10% with dalcetrapib	**Median hsCRP % change at 3 mo** 18% increase with dalcetrapib vs. placebo
ACCELERATE (Lincoff et al) (6)	Baseline Evacetrapib 81.6±28.4 Placebo 81.1±27.8 3-mo change Evacetrapib −31.1±27.6% Placebo +6.0±29.0 %	Baseline Evacetrapib 45.3±11.7 Placebo 45.3±11.7 3-mo change Evacetrapib 133.2±57.2 Placebo 1.6±17.5	Baseline median (IQR) Evacetrapib 128 (95–179) Placebo 128 (94–178)	**Lp(a)** Baseline nmol/L (IQR) Evacetrapib 29.1 (11.1–106.8) Placebo 29.1 (10.8–108.1) % Change Evacetrapib −22.3 (−50.6 to 0) Placebo 0 (−15.4 to 14.9) **Median hsCRP % change at 3 months** Evacetrapib 8.6 (−27.0–63.3), Placebo 0 (−32.1–52.4) vs. *P*<0.001
REVEAL (The HPS3/TIMI55–REVEAL Collaborative Group) (7)	Baseline 61±15 for both groups Study midpoint Anacetrapib 38 Placebo 64 41% decrease with anacetrapib	Baseline 40±10 for both groups Study midpoint Anacetrapib 85 Placebo 42 104% increase with anacetrapib	Baseline Not reported Study midpoint Anacetrapib 136 Placebo 146	Baseline levels for **ApoB, Lp(a)** not reported Study midpoint ApoB Anacetrapib 54 mg/dL Placebo 66 mg/dL Study midpoint Lp(a) Anacetrapib 43 nmol/L Placebo 58 nmol/L

HPS-2 THRIVE (HPS2-THRIVE Collaborative Group) (8)	Baseline 63±17 Over 4 y, decreased 10 mg/dL with niacin/laropiprant	Baseline 43.9±11.2 Over 4 y, increased 6 mg/dL with niacin/laropiprant	Baseline values not reported Over 4 y, decreased 33 mg/dL with niacin/laropiprant	**ApoB** baseline levels not reported. Over 4 y, decreased 7 mg/dL with niacin/laropiprant **Lp(a)** baseline values not reported. At 1 y, achieved lower levels with niacin/laropiprant (50.7±2.3) than placebo (60.3±2.6), *p*=0.006
AIM-HIGH (Boden et al) (15)	Baseline 74.0±22.7 Year 3 Niacin 65.2±21.8 Placebo 68.3±19.3	Baseline 34.9±5.6 Year 3 Niacin 44.1±11.3 Placebo 39.1±7.7	Baseline 163 Year 3 Niacin 120 Placebo 152	**ApoB** Baseline 82.9±20.7 Year 3 Niacin 70.4±19.7 Placebo 77.6±16.9 **Lp(a)** Baseline (IQR) Niacin 36.0 (13.4–126.3) Placebo 32.6 (13.1–120.3) **Lp(a)** Year 1 Niacin 27.1 (8.3–106.5) Placebo 30.6 (10.9–121.1)
IMPROVE-IT (Cannon et al) (2)	Baseline median (IQR) for both groups 95.0 (79.0–110.2) 1 y Ezetimibe 50.0 (39.0–62.0) Placebo 67.0 (55.0–81.0) 24% additional lowering with ezetimibe vs. placebo	Baseline median (IQR) for both groups 40.0 (33.0–49.0) 1 y Ezetimibe 47.0 (40.0–56.0) Placebo 46.0 (39.0–55.0)	Baseline median (IQR) Ezetimibe 120.0 (85.0–172.0) Placebo 121.0 (85.0–172.0) 1 y Ezetimibe 104.0 (77.0–143.0) Placebo 116.0 (84.0–165.0) *p*<0.001	**ApoB** Baseline 91.0 (78.0–106.0) for both groups 1 y Ezetimibe 67.0 (56.0–81.0) Placebo 79.0 (67.0–93.0) *p*<0.001

SPIRE-1 and SPIRE-2* (Ridker et al) (3) (Study stopped early because of high antidrug antibodies that attenuated LDL-lowering	Baseline SPIRE-1 93.8 Baseline SPIRE-2 133.9 <u>% Change at 1 y</u> SPIRE-1 -44.9% Bococizumab +6.5% Placebo SPIRE-2 -40.6% Bococizumab + 2.6% Placebo	SPIRE-1 Baseline 47.4 SPIRE-2 Baseline 47.3 <u>% Change at 1 y</u> SPIRE-1 +7.6% Bococizumab +2.5% Placebo SPIRE-2 +8.6% Bococizumab +2.6% Placebo	SPIRE-1 Baseline 124.8 SPIRE-2 Baseline 154 <u>% Change at 1 y</u> SPIRE-1 -4.6% Bococizumab +9.0% Placebo SPIRE-2 -8.0% Bococizumab +4.6% Placebo	**ApoB** Baseline SPIRE-1 80.1 Baseline SPIRE-2 105.8 <u>% Change at 1 y</u> SPIRE-1 -48.4% Bococizumab +5.1% Placebo SPIRE-2 -40.6% Bococizumab +2.6% Placebo **Lp(a)** Baseline SPIRE-1 18.8 Baseline SPIRE-2 19.9 <u>% Change at 1 y</u> SPIRE-1 -23.7% Bococizumab + 5.8% Placebo SPIRE-2 -19.0% Bococizumab + 5.9% Placebo
FOURIER (Sabatine et al) (4)	<u>Baseline (IQR)</u> 92 (80–109) in both groups <u>48-wk median (IQR)</u> Evolocumab 30 (19–46) Placebo 88 <u>48-wk % change</u> Evolocumab 59% decrease (95% CI: 58%–60%) Placebo 4.3% decrease By 48 wk, LDL-C <25 mg/dL in 42% of patients on evolocumab vs. <0.1% on placebo (p<0.001)	Baseline (IQR) 44 (37–53) in both groups <u>48-wk % change median</u> Evolocumab 8.4% increase Placebo 0.3% increase	Baseline (IQR) 134 (101–183) evolocumab 133 (99–181) placebo <u>48-wk % change median</u> Evolocumab 16.2% decrease Placebo 0.7% decrease	**Lp(a*)*** <u>Baseline</u> Placebo 37 (13–164) Evolocumab 37 (13–166) 26.9% decrease with evolocumab, no change with placebo (p<0.001) **ApoB** Increased 2.7% with placebo Reduced by 46% with evolocumab (p<0.001) CRP was 1.7 mg/L (IQR 0.9–3.6) at baseline and by 48 wk was 1.4 mg/L (IQR 0.7–3.1) in both arms.

ODYSSEY OUTCOMES (Schwartz et al) (5)	Baseline Median (IQR) 92±31 both groups 12-mo median Alirocumab 48 Placebo 96 48-mo median Alirocumab 66 Placebo 103	Baseline median (IQR) 43 (37–50) Alirocumab 42 (36–50) Placebo	Baseline median (IQR) 129 (94–181) Alirocumab 129 (95–183) Placebo	**ApoB** Baseline 83±21 Alirocumab 83±22 Placebo **Lp(a)** Baseline Median (IQR) 21 (7–59) Alirocumab 22 (7–60) Placebo

*Levels are mean ± standard deviation, except where noted.
ACC indicates American College of Cardiology; apoB, apolipoprotein B; CI, confidence interval; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; Lp(a), lipoprotein(a); and LDL-C, low-density lipoprotein cholesterol.

Key Words: ACC/AHA Evidence Review Committee ■ ACC/AHA Clinical Practice Guidelines ■ Guidelines ■ biomarkers, coronary artery calcium score ■ pharmacological ■ cardiovascular disease ■ cholesterol, LDL-cholesterol ■ diabetes mellitus ■ drug therapy ■ hydroxymethylglutaryl-CoA reductase inhibitors/statins ■ hypercholesterolemia ■ lipids ■ patient compliance ■ primary prevention ■ risk assessment ■ risk reduction discussion ■ risk treatment discussion, secondary prevention ■ ezetimibe ■ proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9) inhibitors

Appendix 1. Evidence Review Committee Relationships With Industry and Other Entities (Relevant)—2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol (August 2018)

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Peter W. F. Wilson *(Chair)*	Emory University School of Medicine, Department of Medicine	None	None	None	None	None	None
Tamar S. Polonsky *(Vice Chair)*	University of Chicago Medicine	None	None	None	None	• AstraZeneca*	None
Amit Khera	Assistant Professor of Medicine, University of Texas Southwestern Medical Center	None	None	None	None	None	None
Andrzej S. Kosinski	Associate Professor of Biostatistics Duke University Department of Biostatistics and Bioinformatics Durham, NC	None	None	None	None	None	None
Jeffrey T. Kuvin	Section Chief, Cardiovascular Medicine, Dartmouth-Hitchcock Medical Center	None	None	None	None	None	None
Michael D. Miedema	Minneapolis Heart Institute	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the ACC/AHA, a person has a *relevant* relationship IF: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document;* or b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document* or makes a competing drug or device addressed in the *document*; or c) the *person or a member of the person's household*, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the *document*.

*On March 1, 2018 (after writing of this Systematic Review was complete excepting ODYSSEY OUTCOMES inclusion), Dr. Polonsky, after having reviewed her listing on the CMS Open Payments Data website, realized that she had been a local PI in the STRENGTH trial, supported by AstraZeneca, and promptly reported this to the Task Force. Only 1 patient was recruited, and Dr. Polonsky did not receive any direct salary support, but by ACC/AHA standards, this would constitute a relationship with industry (RWI) and thus, in the interest of full transparency, this footnote has been added.

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA, American Academy of Physician Assistants; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; ADA, American Diabetes Association; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASPC, American Society for Preventive Cardiology; PCNA, Preventive Cardiovascular Nurses Association.