REVIEW

Annals of Internal Medicine

Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia

A Systematic Review and Meta-analysis

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Background: Guidelines recommend statins as first-line therapy for dyslipidemia. Monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) is a new lipid-lowering approach.

Purpose: To assess the efficacy and safety of PCSK9 antibodies in adults with hypercholesterolemia.

Data Sources: MEDLINE, PubMed Central, and Google Scholar; conference proceedings; and the ClinicalTrials.gov registry through 4 April 2015.

Study Selection: Phase 2 or 3 randomized, controlled trials (RCTs) comparing treatment using PCSK9 antibodies with no anti-PCSK9 therapy in adults with hypercholesterolemia.

Data Extraction: Two investigators independently extracted data on study characteristics and lipid and clinical outcomes, and rated risk of bias of trials. Prespecified primary end points were all-cause and cardiovascular mortality.

Data Synthesis: Twenty-four RCTs comprising 10 159 patients were included. Compared with no antibody, treatment with PCSK9 antibodies led to marked reductions in low-density lipoprotein cholesterol levels (mean difference, −47.49% [95% CI, −69.64% to −25.35%]; $P < 0.001$] and other atherogenic lipid fractions, and it reduced all-cause mortality (odds ratio [OR], 0.45 [CI, 0.23 to 0.86]; $P = 0.015$; heterogeneity $P = 0.63$; $I^2 = 0\%$) and cardiovascular mortality (OR, 0.50 [CI, 0.23 to 1.10]; $P = 0.084$; heterogeneity $P = 0.78$; $I^2 = 0\%$). The rate of myocardial infarction was significantly reduced with use of PCSK9 antibodies (OR, 0.49 [CI, 0.26 to 0.93]; $P = 0.030$; heterogeneity $P = 0.45$; $I^2 = 0\%$), and increases in the serum creatine kinase level were reduced (OR, 0.72 [CI, 0.54 to 0.96]; $P = 0.026$; heterogeneity $P = 0.65$; $I^2 = 0\%$). Serious adverse events did not increase with administration of PCSK9 antibodies.

Limitation: Results were derived from study-level data rather than patient-level data, and clinical outcome data are rare.

Conclusion: PCSK9 antibodies seem to be safe and effective for adults with dyslipidemia.

Primary Funding Source: CRC 1116 Masterswitches in Myocardial Ischemia, German Research Council DFG.

Ann Intern Med. 2015;163:40-51. doi:10.7326/M14-2957 **www.annals.org**

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This article was published online first at www.annals.org on 28 April 2015.

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Hypercholesterolemia contributes substantially to the development of coronary artery disease and the risk for cardiovascular events. Current guidelines from the American College of Cardiology and American Heart Association and from the European Society of Cardiology and European Atherosclerosis Society recommend lipid-lowering for patients with known cardiovascular disease; a 10-year cardiovascular disease risk of 7.5% or greater; diabetes and a low-density lipoprotein (LDL) cholesterol level of 1.8 mmol/L or greater (≥70 mg/dL); or an LDL cholesterol level of 5 mmol/L or greater (≥193 mg/dL) (1, 2). Statins are first-line pharmacotherapy, having shown significant reductions in both LDL cholesterol values and cardiovascular events (1, 2). Yet, despite intensive statin regimens to delay atherosclerotic plaque development and lower the risk for cardiovascular complications (3), a sizable proportion of statin-treated patients does not achieve recommended target LDL cholesterol levels, and some discontinue treatment owing to drug-related side effects (4–6).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme that plays an important role in lipid metabolism by modulating the density of LDL cholesterol receptors in multiple organs. The enzyme is synthesized in the nucleus, and after intramolecular autocatalytic cleavage of its *N*-terminal prosegment in the endoplasmic reticulum, it is secreted from hepatocytes, where it binds to the surrounding LDL cholesterol receptors. The complex is then subject to endocytosis and degradation of its entire structure in lysosomes (7). This physiologic function leads to an inverse relationship between the level of PCSK9 in the blood and the number of LDL receptors; inhibition of PCSK9 prevents LDL receptor degradation within lysosomes and preserves receptor recycling to the hepatocyte surface. Each receptor normally recycles approximately 150 times. Thus, monoclonal antibody binding and inhibition of PCSK9 prevents PCSK9 binding to the LDL cholesterol–LDL receptor complex and subsequent lysosomal degradation of the LDL receptor. The LDL-receptor recycling is preserved, with a consequent increase in receptor density on the hepatocyte surface and LDL cholesterol clearance.

See also:

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Randomized, controlled trials (RCTs) have shown marked reductions in LDL cholesterol levels when PCSK9 antibodies are administered compared with no administration of PCSK9 antibodies (placebo or ezetimibe) (8–10). The PCSK9 inhibitors are currently undergoing regulatory review on the basis of efficacy and safety data from LDL cholesterol–lowering trials. In 2014, pharmaceutical companies submitted a biologics license application to obtain approval from the U.S. Food and Drug Administration for use of the PCSK9 inhibitor alirocumab (SAR236553/REGN727) and evolocumab (AMG 145) in the treatment of high cholesterol. In this context, we performed a systematic review and meta-analysis of RCTs to investigate the safety and efficacy of treatment with PCSK9 antibodies, particularly with respect to their effect on clinical outcomes.

METHODS

We used established methods recommended by the Cochrane guidelines to conduct the meta-analysis and report our findings according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement (11, 12). The review protocol was not registered.

Data Sources and Searches

We searched MEDLINE, the Cochrane Central Register of Controlled Trials, Google Scholar, and Embase; TCTMD (www.tctmd.com), EuroPCR (www.europcr.com), ClinicalTrials.gov, Clinical Trial Results (www.clinicaltrialresults.org), the PCSK9 Education and Research Forum (www.pcsk9forum.org), and the American College of Cardiology Web site (www.cardiosource.com); and major congress proceedings, all until 4 April 2015. The following keywords were used: *PCSK9 antibody*, *evolocumab*, *alirocumab*, *bococizumab*, *randomized controlled trial*, and *hypercholesterolemia*. Citations were screened at the title and abstract level and retrieved as full reports if they were considered relevant.

Study Selection

The main inclusion criterion was a phase 2 or 3 RCT comparing PCSK9 antibodies with no PCSK9 antibody in adults with hypercholesterolemia, with clinical outcomes reported. No restrictions on language, follow-up, or study size were applied. The doses of PCSK9 antibody that had been used in phase 3 RCTs were selected for comparisons; study arms in which doses of PCSK9 antibodies were given that had not been used in phase 3 RCTs were excluded from the analysis.

Primary clinical end points were all-cause mortality and cardiovascular mortality; secondary end points were myocardial infarction, unstable angina, increased serum creatine kinase level, and serious adverse events (as reported in the original trials). Efficacy end points were percent change from baseline in LDL cholesterol and high-density lipoprotein (HDL) cholesterol levels; secondary efficacy end points were changes from baseline in total cholesterol and lipoprotein(a) levels. When LDL cholesterol results were reported by ultracentrifugation and by Friedewald formula calculation, the former was abstracted because we considered it more accurate (13).

Data Extraction and Quality Assessment

Two investigators who were not involved in any of the selected studies independently abstracted data by using prespecified forms. Two investigators then independently appraised the accuracy of the abstractions and resolved any discrepancies by consensus after discussion with a third investigator. Intensive background statin therapy was defined as daily use of atorvastatin, 40 mg or more; rosuvastatin, 20 mg or more (or ≥5 mg for the YUKAWA study, which was defined for a Japanese population); simvastatin, 80 mg or more; or any statin plus ezetimibe at baseline. Other treatment regimens were defined as nonintensive. When patients underwent a statin therapy washout period, the study was classified as "no statin."

Serious adverse events were defined across trials in accordance with the Medical Dictionary for Regulatory Activities. Serious adverse events were predominantly defined as fatal, life-threatening, requiring or prolonging hospital admission, or causing persistent or substantial disability.

Two unblinded investigators independently appraised the potential risk of bias of the RCTs by using methods described in the Cochrane Collaboration guidelines (11).

Data Synthesis and Statistical Analysis

Data were analyzed according to the intention-to-treat principle. Odds ratios (ORs) for dichotomous data and mean difference (MD) of percent change from baseline for continuous variables, with 95% CIs, were used as summary statistics. For clinical outcomes, a continuity correction in case of rare events was applied. If SDs were not reported, they were calculated from CIs or SEs of the mean, according to formulas in the Cochrane Handbook for Systematic Reviews of Interventions (11).

Heterogeneity was assessed by using the Cochran Q test and the I^2 statistic (14, 15). If no or low to moderate inconsistency (<50%) was found, pooled ORs were calculated by using a fixed-effects model (11); otherwise, a random-effects model was used. If there were no outcome events, the software automatically applied a treatment-arm continuity correction approach (16).

Additional analyses included one stratified by the comparator arm for clinical outcomes. To account for the potential differences in follow-up, a prespecified analysis was performed with adjusted models by person-years to obtain pooled log rate ratios and CIs. Rates, rather than number of events, were considered the most appropriate outcome for the person-years analyses because they incorporate the follow-up duration of the trials.

Prespecified sensitivity analyses were conducted for efficacy end points by type and dose of PCSK9 antibody. More specifically, separate analyses were performed for alirocumab, 75 mg every 2 weeks; aliro-

cumab, 150 mg every 2 weeks; evolocumab, 140 mg every 2 weeks; and evolocumab, 420 mg every 4 weeks. Another sensitivity analysis was stratified by intensity of background statin therapy. Potential publication bias was examined by constructing funnel plots in which the SE of the log OR was plotted against the OR of the selected binomial outcomes. For continuous outcomes, the SE was plotted against the MD.

For the summary treatment effect estimate, a 2-tailed *P* value less than 0.05 was considered statistically significant. Analyses were done by using R, version 3.1.3 (R Development Core Team), and Comprehensive Meta-Analysis software, version 2 (Biostat).

Role of the Funding Source

Part of this study was supported by CRC 1116 Masterswitches in Myocardial Ischemia, funded by the German Research Council DFG. The funding source had no role in the study design; collection, extraction, analysis, or interpretation of the data; or the decision to submit the manuscript for publication.

RESULTS

Study Selection and Patient Population

Appendix Figure 1 (available at www.annals.org) shows the PRISMA flow chart of study selection. Twenty-four studies comprising a total of 10 159 patients were included in our final analysis (8–10, 17–35). Study characteristics are shown in Appendix Table 1 (available at www.annals.org). Eight trials were phase 2, and 16 trials were phase 3.

Appendix Table 2 (available at www.annals.org) shows patient characteristics. Twelve trials were of patients with familial hypercholesterolemia, 9 were of nonfamilial or unspecified hypercholesterolemia, 2 were of statin-intolerant hypercholesterolemia, and 1 was of mixed familial and nonfamilial hypercholesterolemia. Patients who did not receive a PCSK9 antibody (control groups) were treated with either placebo or ezetimibe. Seventeen trials were less than 6 months in duration, 2 were 6 to 12 months, and 4 were longer than 1 year. The longest follow-up was 104 weeks. To avoid overlapping patient samples, the OSLER trial was excluded, because the enrolled patients were derived from previous RCTs (36). All included trials were funded by industry.

Risk of Bias in the Included Studies

The risks of bias of the included studies are shown in Appendix Table 3 (available at www.annals.org). No publication bias was suggested by the funnel plots or the Egger regression test (Appendix Figures 2 to 9 and Appendix Table 4, available at www.annals.org).

The RCTs were similar in their risk of bias (Appendix Table 3). All were multicenter trials done according to the intention-to-treat principle. No studies had selective outcome reporting. Risk of bias was considered to be unclear predominantly in studies that were available only as presentation slides rather than full reports (8, 9, 18, 21, 25).

Primary Clinical End Points

All-Cause Mortality

Twenty-four RCTs with a total of 10 159 patients were included in the analysis of all-cause mortality (Figure 1). Overall, there was a statistically significant reduction in mortality with use of PCSK9 antibodies compared with no anti-PCSK9 treatment; the respective mortality rates were 0.31% (19 of 6187 patients) and 0.53% (21 of 3971 patients) (OR, 0.45 [95% CI, 0.23 to 0.86]; $P = 0.015$; heterogeneity $P = 0.63$; $I^2 = 0\%$). No inconsistency was detected across trials ($I^2 = 0\%$). The analysis that was adjusted for follow-up showed the consistency of the results (OR, 0.48 [CI, 0.27 to 0.85]; $P = 0.010$; heterogeneity $P = 0.68$; $I^2 = 0\%$) (Appendix Figure 10, available at www.annals.org). The sensitivity analysis that was stratified by comparator (placebo or ezetimibe) also supported the results (Appendix Table 5, available at www.annals.org).

Cardiovascular Mortality

Twenty-four RCTs comprising 10 159 patients were included in the analysis of cardiovascular mortality (Figure 2). There was a statistically nonsignificant reduction in cardiovascular mortality with use of PCSK9 antibodies compared with no anti-PCSK9 treatment; the respective cardiovascular mortality rates were 0.19% (12 of 6187 patients) and 0.33% (13 of 3972 patients) (OR, 0.50 [CI, 0.23 to 1.10]; $P = 0.084$; heterogeneity $P = 0.78$; $I^2 = 0\%$). The analysis that was adjusted for follow-up showed the consistency of the results (OR, 0.49 [CI, 0.23 to 1.07]; $P = 0.070$; heterogeneity $P = 0.79$; $I^2 = 0\%$) (Appendix Figure 11, available at www.annals.org). The analysis that was stratified by comparator (placebo or ezetimibe) also supported the results (Appendix Table 5).

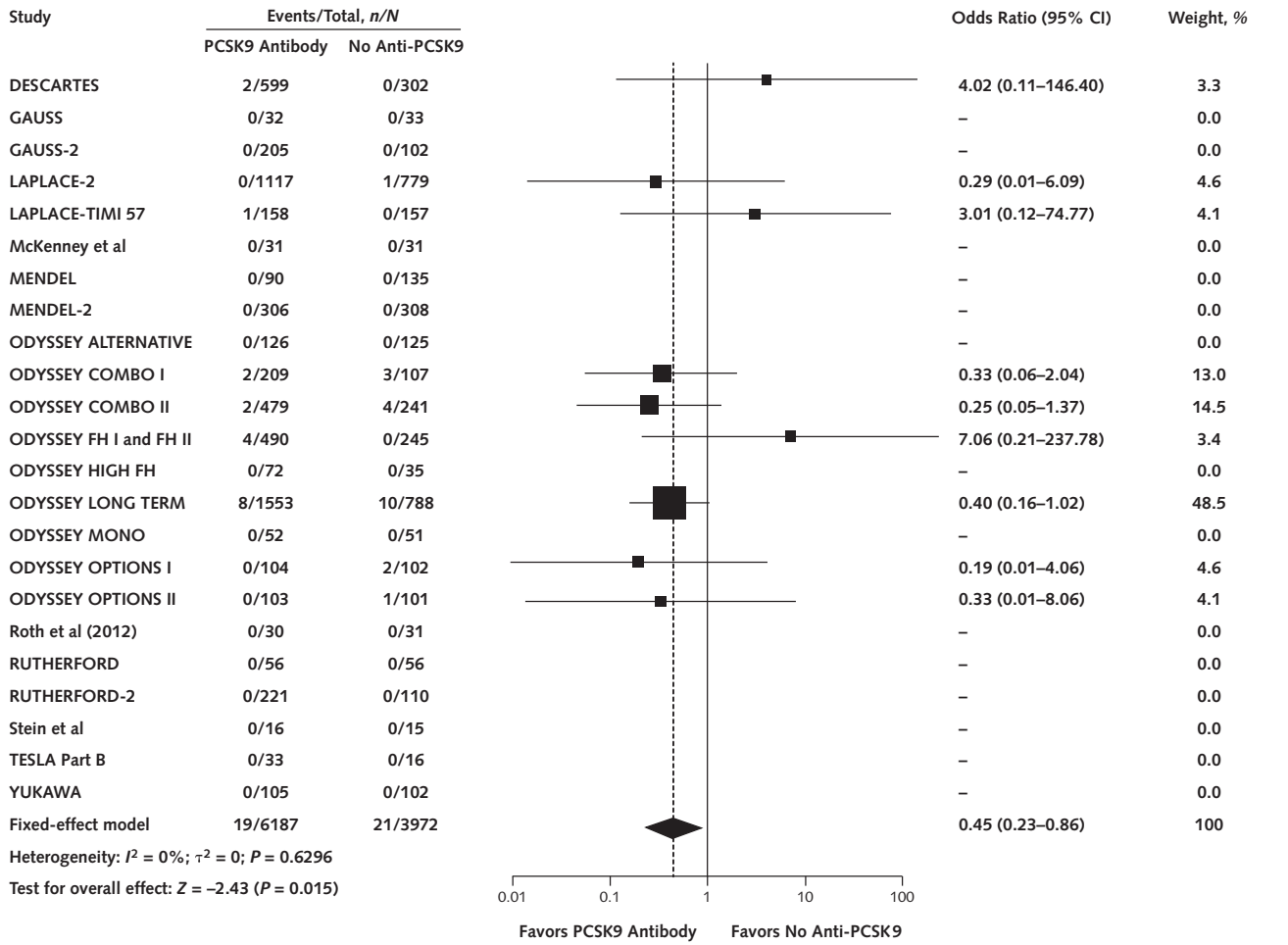
Secondary Safety End Points

Myocardial Infarction and Unstable Angina

Ten RCTs with a total of 5195 patients reported data on myocardial infarction (Figure 3, *top*). Treatment with PCSK9 antibodies resulted in a statistically significant reduction in myocardial infarction compared with no anti-PCSK9 treatment; rates were 0.58% (19 of 3289 patients) and 1.00% (19 of 1906 patients), respectively (OR, 0.49 [CI, 0.26 to 0.93]; $P = 0.030$; heterogeneity $P = 0.45$; $I^2 = 0\%$). The analysis that was adjusted for follow-up showed the consistency of the results (OR, 0.49 [CI, 0.26 to 0.93]; $P = 0.030$; heterogeneity $P = 0.53$; $I^2 = 0\%$) (Appendix Figure 12, available at www.annals.org). The analysis that was stratified by comparator (placebo) also supported the results (Appendix Table 5).

Six RCTs including a total of 3894 patients provided data on unstable angina (Figure 3, *bottom*). The rates were similar between the 2 groups: 0.04% (1 of 2515 patients) who received PCSK9 antibodies and 0.08% (1 of 1379 patients) who did not receive PCSK9 antibodies (OR, 0.61 [CI, 0.06 to 6.14]; $P = 0.676$; heterogeneity $P = 0.34$; $I^2 = 0\%$). The analysis that was adjusted for follow-up showed the consistency of the results (OR, 0.51 [CI, 0.05 to 4.86]; $P = 0.56$;

Figure 1. All-cause mortality.



Expanded study abbreviations are as follows: DESCARTES = Durable Effect of PCSK9 Antibody Compared with Placebo Study; GAUSS = Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects; LAPLACE-2 = LDL-C Assessment with PCKS9 Monoclonal Antibody Inhibition Combined With Statin Therapy-2; LAPLACE-TIMI 57 = LDL-C Assessment with PCKS9 Monoclonal Antibody Inhibition Combined With Statin Therapy = Thrombosis in Myocardial Infarction 57; MENDEL = Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Patients Currently Not Receiving Drug Therapy For Easing Lipid Levels; RUTHERFORD = The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familiar Hypercholesterolemia Disorder; PCSK9 = proprotein convertase subtilisin/kexin type 9; TESLA = Trial Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities; YUKAWA = Study of LDL-Cholesterol Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk.

heterogeneity P = 0.34; I^2 = 0%) (Appendix Figure 13, available at www.annals.org). The analysis that was stratified by comparator (placebo) also supported the results (Appendix Table 5).

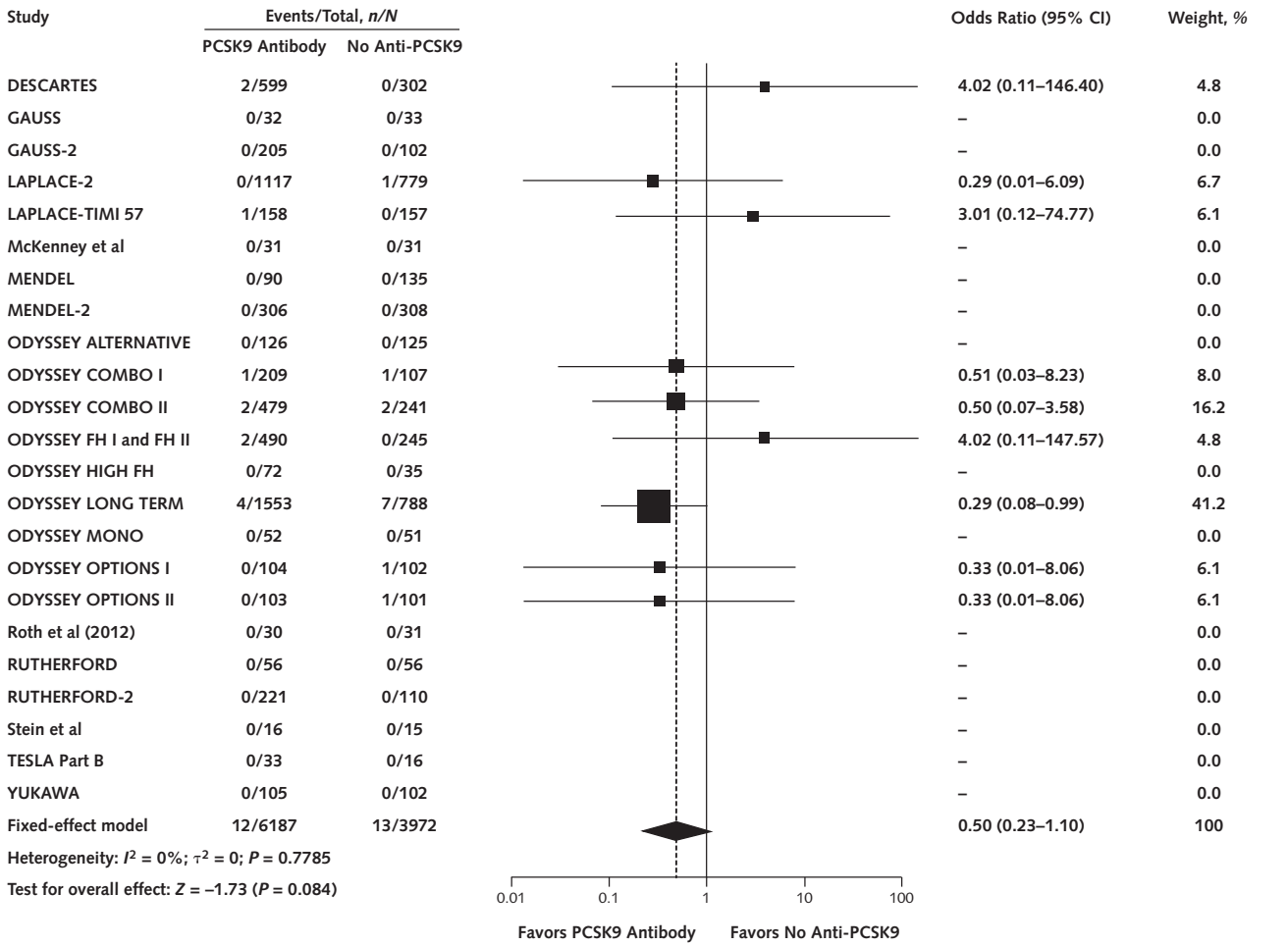
Serum Creatine Kinase Level

Twenty-four RCTs comprising 10 159 patients provided data on serum creatine kinase levels (Figure 4). Treatment with PCSK9 antibodies resulted in statistically significant reductions compared with no anti-PCSK9 treatment; increased creatine kinase levels were found in 1.96% of patients who received PCSK9 antibodies (121 of 6187) and 2.31% of those who did not receive PCSK9 antibodies (92 of 3972) (OR, 0.72 [CI, 0.54 to 0.96]; P = 0.026; heterogeneity P = 0.65; I^2 = 0%). The analysis that was adjusted for follow-up showed the consistency of the results (OR, 0.73 [CI, 0.55 to 0.97]; P = 0.030; heterogeneity P = 0.67; I^2 = 0%) (Appendix Figure 14, available at www.annals.org). The analysis that was stratified by comparator (placebo or ezetimibe) also supported the results (Appendix Table 5).

Serious Adverse Events

Twenty-four RCTs comprising all 10 159 patients were included in the analysis of serious adverse events (Figure 5). The overall incidence was 9.26% (573 of 6187) among patients treated with PCSK9 antibodies and 7.73% (307 of 3972) among patients who were not treated with PCSK9 antibodies (OR, 1.01 [CI, 0.87 to 1.18]; P = 0.879; heterogeneity P = 0.98; I^2 = 0%). Average discontinuation rates were no higher among patients receiving PCSK9 antibodies than among patients receiving placebo or ezetimibe (Appendix Table 6,

Figure 2. Cardiovascular mortality.



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available at www.annals.org). Adjustment for follow-up showed the consistency of the results (OR, 1.01 [CI, 0.88 to 1.16]; P = 0.89; heterogeneity P = 0.98; I^2 = 0%) (Appendix Figure 15, available at www.annals.org). The analysis that was stratified by comparator (placebo or ezetimibe) also supported the results (Appendix Table 5).

Efficacy End Points

LDL Cholesterol

Twenty-four studies comprising 10 159 patients were included in the analysis of LDL cholesterol (Appendix Figure 16, available at www.annals.org). Overall, a reduction in LDL cholesterol levels of almost 50% was observed with use of PCSK9 antibodies compared with no anti-PCSK9 treatment (MD, −47.49% [CI, −69.64% to −25.35%]; P < 0.001). The reduction in LDL cholesterol with anti-PCSK9 therapy compared with placebo was significantly greater than that compared with ezetimibe (placebo: MD, −58.77% [CI, −61.03% to −56.51%]; P < 0.001; ezetimibe: MD, −36.17% [CI, −39.28% to −33.06%]; P < 0.001). Sensitivity analyses stratified by type and dose of PCSK9 antibody showed consistent results (Appendix Table 7, available at www.annals.org).

HDL Cholesterol

Fourteen RCTs comprising 4378 patients were included in the analysis of HDL cholesterol (Appendix Figure 17, available at www.annals.org). Overall, the percentage of increase (MD) with use of PCSK9 antibodies versus no treatment with PCSK9 antibodies was 6.30% (CI, 5.58% to 7.02%; P < 0.001). Similar increases in HDL cholesterol levels were observed when PCSK9 antibodies were compared with placebo (MD, 6.14% [CI, 5.31% to 6.97%]; P < 0.001) or ezetimibe (MD, 6.80% [CI, 5.33% to 8.26%]; P < 0.001) (Appendix Table 7). Findings of sensitivity analyses were consistent with the main results.

Total Cholesterol

Ten studies comprising 5357 patients contributed to the analysis of total cholesterol (Appendix Figure 18, available at www.annals.org). Overall, a 31% reduction

was observed when treatment with PCSK9 antibodies was compared with no anti-PCSK9 treatment (MD, −31.49% [CI, −46.35% to −16.64%]; $P < 0.001$). The reduction in total cholesterol with anti-PCSK9 treatment was greater compared with placebo (MD, −38.99% [CI, −40.72% to −37.26%]; $P < 0.001$) than with ezetimibe (MD, −23.83% [CI, −27.35% to −20.32%]; $P < 0.001$). Sensitivity analyses by type and dose of anti-PCSK9 agent showed consistent results (Appendix Table 7).

Lipoprotein(a)

Twelve RCTs including a total of 6566 patients were included in the analysis of lipoprotein(a) (Appendix Figure 19, available at www.annals.org). Overall, a greater than 25% reduction in lipoprotein(a) levels was observed when anti-PCSK9 treatment was compared with no anti-PCSK9 treatment (MD, −26.45% [CI, −30.19% to −22.71%]; $P < 0.001$). A similar reduction in lipoprotein(a) values was found in placebo-controlled trials (MD, −27.96% [CI, −31.21% to −24.71%]; $P < 0.001$) and in ezetimibe-controlled trials (MD, −24.05% [CI, −28.94% to −19.16%]; $P < 0.001$). Sensitivity analyses for type and dose of PCSK9 antibody showed consistency in the direction and magnitude of the results (Appendix Table 7).

Additional Analyses

Analyses that were stratified by the comparator arm (placebo or ezetimibe) and background statin therapy (no statin vs. not intensive vs. intensive) showed directions that were consistent with those of the main results from a larger sample size (Appendix Tables 5 and 7). Additional analyses by agent and dose of antibody showed that neither a different type nor dose of PCSK9 antibody significantly modified the positive effect on lipid profile.

DISCUSSION

Our main findings are that compared with no anti-PCSK9 treatment, use of PCSK9 antibodies is associated with 1) lower odds of all-cause mortality and myocardial infarction and a statistically nonsignificant

Figure 3. Myocardial infarction (*top*) and unstable angina (*bottom*).

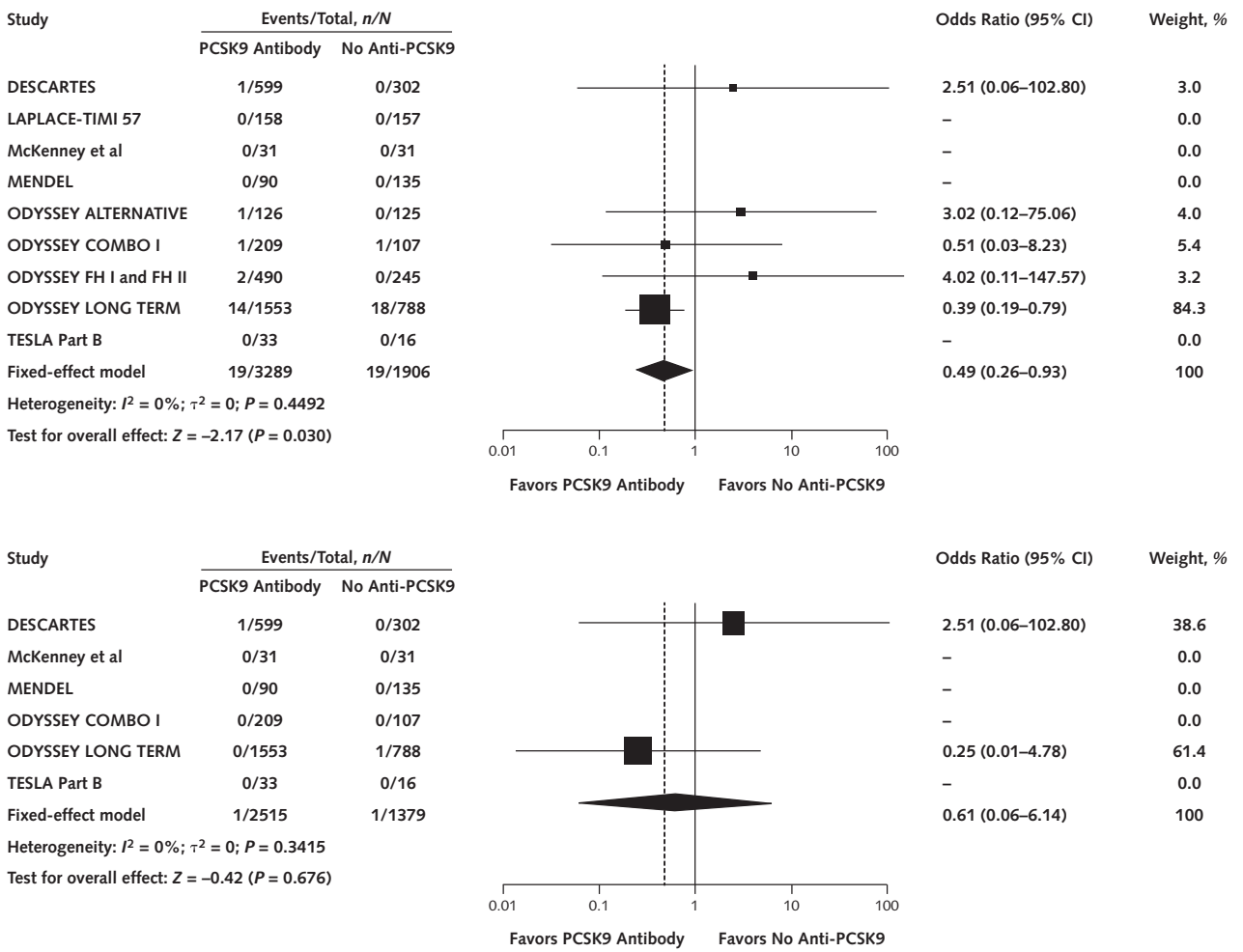

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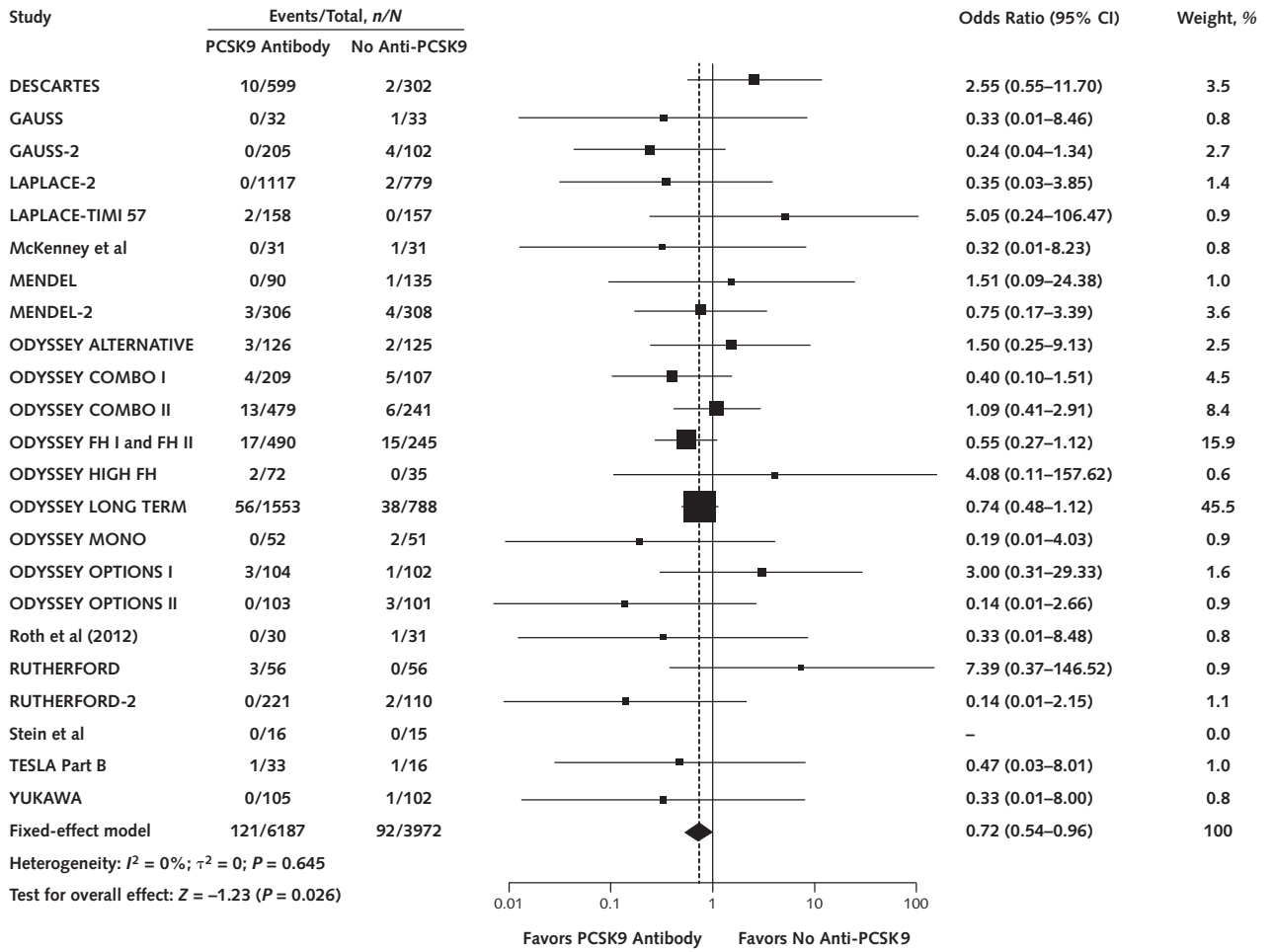
Figure 4. Increase in creatine kinase level.



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reduction in cardiovascular mortality; 2) lower increase in the serum creatine kinase level; 3) no increase in serious adverse events; and 4) a marked reduction in atherogenic lipid fractions. Improvements in clinical outcomes were consistent in multiple sensitivity analyses that used different methods of analysis.

International guidelines to reduce cardiovascular risk have promoted increasingly lower treatment goals for LDL cholesterol (1, 2). Statins are the most prescribed drugs, and evidence shows they reduce cardiovascular risk across all risk factor categories, lending support for widespread use (37). Although statins have acceptable efficacy and safety profiles, more than one half of cardiovascular events are not being prevented by these drugs, owing to either elevated residual cardiovascular risk or statin intolerance. Several reports indicate that up to 40% of patients receiving statins are not able to reach target LDL cholesterol levels with current guideline recommendations (38). Potential reasons are submaximal doses, discontinuation of therapy owing to side effects, pharmacologic interactions, and the limited (about 6%) additional decrease in LDL cholesterol with doubling of the dose (17).

In recent years, novel treatments have actively been sought, and human monoclonal antibodies against PCSK9 have been identified as an innovative lipid-lowering strategy. Several phase 3 studies in different settings showed that use of PCSK9 antibodies combined with statins provided benefits in terms of reducing atherogenic lipid fractions in patients with hyperlipidemia (LAPLACE-2) (29) or heterozygous familial hypercholesterolemia (RUTHERFORD-2) (28), and that PCSK9 antibodies as a stand-alone treatment were beneficial in hyperlipidemia (MENDEL-2) (22).

The DESCARTES trial (17) involved 901 adults with or without coronary heart disease who had an LDL cholesterol level greater than 1.9 mmol/L (>75 mg/dL) despite maximal lipid-lowering therapy. Participants were randomly assigned to receive evolocumab, 420 mg every 4 weeks, or placebo, in addition to background therapy consisting of diet modification alone; atorvastatin, 10 mg, plus diet modification; atorvastatin, 80 mg; or atorvastatin, 80 mg, plus ezetimibe, 10 mg.

In the LAPLACE-2 trial, the efficacy and tolerability of evolocumab were evaluated in addition to either moderate-intensity or high-intensity statin therapy. Evo-

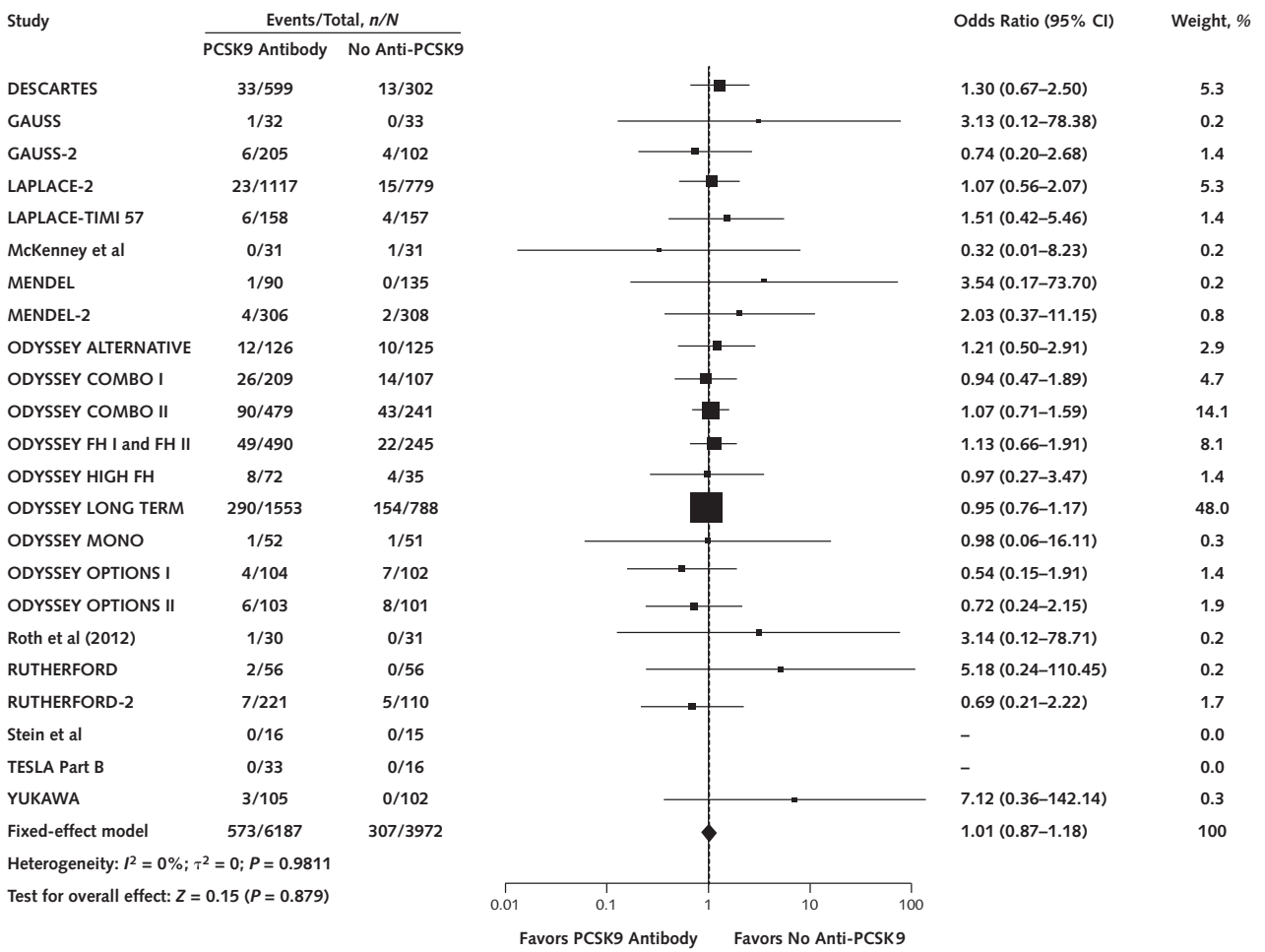
locumab at dosages of 140 mg every 2 weeks or 420 mg every 4 weeks was found to be efficacious and safe. Evolocumab was also found to lower lipoprotein(a) and apoliprotein B levels, and to increase the HDL cholesterol level.

GAUSS and GAUSS-2 differ from the other trials owing to predominant inclusion of statin-intolerant patients, although a substantial proportion of patients actually received a statin during these trials. In those studies, treatment with evolocumab resulted in a 41% to 51% reduction in the LDL cholesterol level, but it had no statistically significant effect on clinical outcomes compared with placebo. These studies demonstrated marked reductions in LDL cholesterol levels with PCSK9 antibody treatment, consistent with the approximate 50% reduction in LDL cholesterol levels in our meta-analysis (Appendix Table 6).

Our large-scale report is the first to show a benefit in mortality with these novel agents. The finding of lower all-cause mortality, although preliminary, is encouraging and is further corroborated by a similar direction of reduction in the odds of cardiovascular mortality, as well as by recent findings of the open-label OSLER-1 and OSLER-2 extension trials that showed reductions in cardiovascular events with evolocumab compared with standard therapy (36). Of note, no signal for heterogeneity was present across trials in the analysis of all-cause and cardiovascular mortality, and there was stability of the direction and magnitude of results in our sensitivity analyses. Moreover, the sensitivity analyses for type and dose of PCSK9 antibody, and the subgroup analyses stratified by placebo or ezetimibe as the control arm and by background statin therapy, all suggest that the overall effect is robust and justified.

The mechanisms of improved survival in patients treated with PCSK9 antibodies are unclear but may be related to the efficacy of these agents in reducing lipid levels (particularly LDL cholesterol, non-HDL cholesterol, and lipoprotein(a)) and may also be influenced by reduced rates of myocardial infarction due to plaque stabilization. However, this encouraging result, which may play a role in the observed survival benefit, should be interpreted with caution.

Figure 5. Serious adverse events.



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Whereas mortality data were frequently reported across studies, fewer studies reported data on myocardial infarction. The most informative study on this outcome—ODYSSEY LONG TERM, which includes the largest patient population studied over 78 weeks of follow-up—demonstrated a reduction in myocardial infarction with PCSK9 antibody therapy (37). Further data from ongoing studies in which the primary end point is cardiovascular events will provide a more definitive answer regarding the effect of profound reduction in LDL cholesterol on myocardial infarction.

The recently presented long-term results of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial), which evaluated the efficacy and safety of ezetimibe plus simvastatin versus simvastatin alone, showed that combination therapy compared with monotherapy not only produced marked reductions in LDL cholesterol but also reduced cardiovascular events in high-risk patients with the acute coronary syndrome (39). IMPROVE-IT reinforces the theory that "lower is better," in terms of LDL cholesterol levels, by resulting in greater clinical benefits. In IMPROVE-IT, adding ezetimibe to statin therapy reduced the LDL cholesterol level by an average of 0.44 mmol/L (17 mg/dL). However, there was no statistically significant effect on mortality.

No single RCT evaluating PCSK9 antibodies has yet been powered to show an effect on mortality and cardiovascular events, but our meta-analysis of 10 159 patients with a mean follow-up of 44.6 weeks found that treatment with PCSK9 antibodies reduced the odds of all-cause death. The magnitude of LDL cholesterol reduction observed with alirocumab and evolocumab was distinctly greater than that with ezetimibe in IMPROVE-IT and in our meta-analysis (**Appendix Table 6**), with an average additional 36% reduction in LDL cholesterol from baseline compared with ezetimibe-treated patients. It should be noted, however, that patient populations differ.

IMPROVE-IT evaluated the combination of ezetimibe with statin for secondary prevention of acute coronary syndromes. In contrast, PCSK9 antibodies have been tested predominantly in adults without the acute coronary syndrome who have hypercholesterolemia. According to the quantitative interaction principle, whereby the benefit of treatment is larger among high-risk patients (40, 41), our preliminary findings on anti-PCSK9 therapy in our mortality analysis might be amplified in higher-risk scenarios characterized by higher baseline mortality rates in both the active treatment (anti-PCSK9) and control arms.

The reduction in lipoprotein(a), another lipid fraction that contributes to atherosclerotic plaque formation (42), may also contribute to the benefits of PCSK9 antibodies in terms of mortality and myocardial infarction rates. The average 25% reduction in lipoprotein(a) levels observed in our meta-analysis was of similar magnitude when PCSK9 antibodies were compared with placebo or ezetimibe. This finding suggests a possible mechanism for long-term cardiovascular benefit with the combination of potent PCSK9 inhibition and pleiotropic statins, especially for patients at high cardiovascular risk.

Of note, in our analysis, increased creatine kinase values occurred significantly less often with PCSK9 antibodies compared with no anti-PCSK9 treatment. Although the majority of included studies involved patients receiving statin therapy, there was a statistically significant 30% reduction in the odds of increased creatine kinase levels with use of PCSK9 antibodies compared with no anti-PCSK9 treatment; this finding suggests that PCSK9 antibodies may have a muscle-sparing effect even in statin-treated patients, which may attenuate statin intolerance. Notably, the rates of serious adverse events reported in the studies did not statistically significantly differ with versus without anti-PCSK9 treatment, confirming the overall comparative safety of the drug. On the basis of these findings of reduced mortality and muscle complications in patients at lower risk (for example, those without or with stable coronary artery disease), PCSK9 inhibition may be even more useful in higher-risk patients, such as those with the acute coronary syndrome, in whom a high dosage of statin is conventionally recommended.

Currently, 4 large cardiovascular outcomes trials (expected completion by 2018) are testing the ability of PCSK9 antibodies to affect clinical outcomes (**Appendix Table 8**). The FOURIER study is assessing whether treatment with evolocumab compared with placebo reduces recurrent cardiovascular events in 27 500 adults with established cardiovascular disease (43). The ODYSSEY Outcomes trial is examining the effect of alirocumab on major adverse cardiovascular events in patients who recently experienced an acute coronary syndrome and is expected to enroll 18 000 patients (44). The phase 3 program of study for bococizumab consists of 2 cardiovascular outcome studies, as well as multiple studies of the change in LDL cholesterol in more than 22 000 patients. One of the 2 cardiovascular outcome studies, SPIRE-1, will assess whether lowering LDL cholesterol to levels well below current guideline-recommended targets will lead to further reduction in cardiovascular events.

Our study has limitations. First, our results are derived from study-level data rather than patient-level data; individual patient data would have improved the accuracy of the analysis by allowing subgroup comparisons. Second, a few studies have only been reported in abstract form or presented at meetings. Third, clinical event outcomes should be interpreted with caution because the data were derived from a small number of events. Fourth, the duration of follow-up in the studies ranged from 2 months to 2 years, but we note that administration of PCSK9 antibodies results in a rapid reduction in lipid subfractions. Finally, the investigated populations represent a broad spectrum of patients with and without known genetic disorders; although our analysis contributes information on the general approach to the management of dyslipidemia, future studies that focus on particular populations will probably refine knowledge about the groups that are most responsive to benefits with small risk for harm.

In conclusion, treatment with PCSK9 antibodies produces profound reductions in LDL cholesterol and lipoprotein(a), with an apparently similar level of safety and an important preliminary signal of survival benefit compared with no anti-PCSK9 treatment. Thus, PCSK9 monoclonal antibody therapy seems to be a safe and effective strategy for patients with dyslipidemia. Ongoing trials should provide further data on the safety of this innovative strategy and on the relationship of lower LDL cholesterol levels and the rate of cardiovascular events (45, 46). In particular, these trials should validate or refute the findings on mortality that, if confirmed, could have a profound effect on public health.

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Note: The study is a project of Systematic Investigation and Research on Interventions and Outcomes (SIRIO)-MEDICINE, a network of senior scientists and fellows collaborating worldwide to pursue research and innovation in medicine.

Financial Support: In part by CRC 1116 Masterswitches in Myocardial Ischemia, funded by the German Research Council DFG.

Disclosures: Dr. Kereiakes has received modest consulting fees from Sanofi. Authors not named here have no conflicts of interest. Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-2957.

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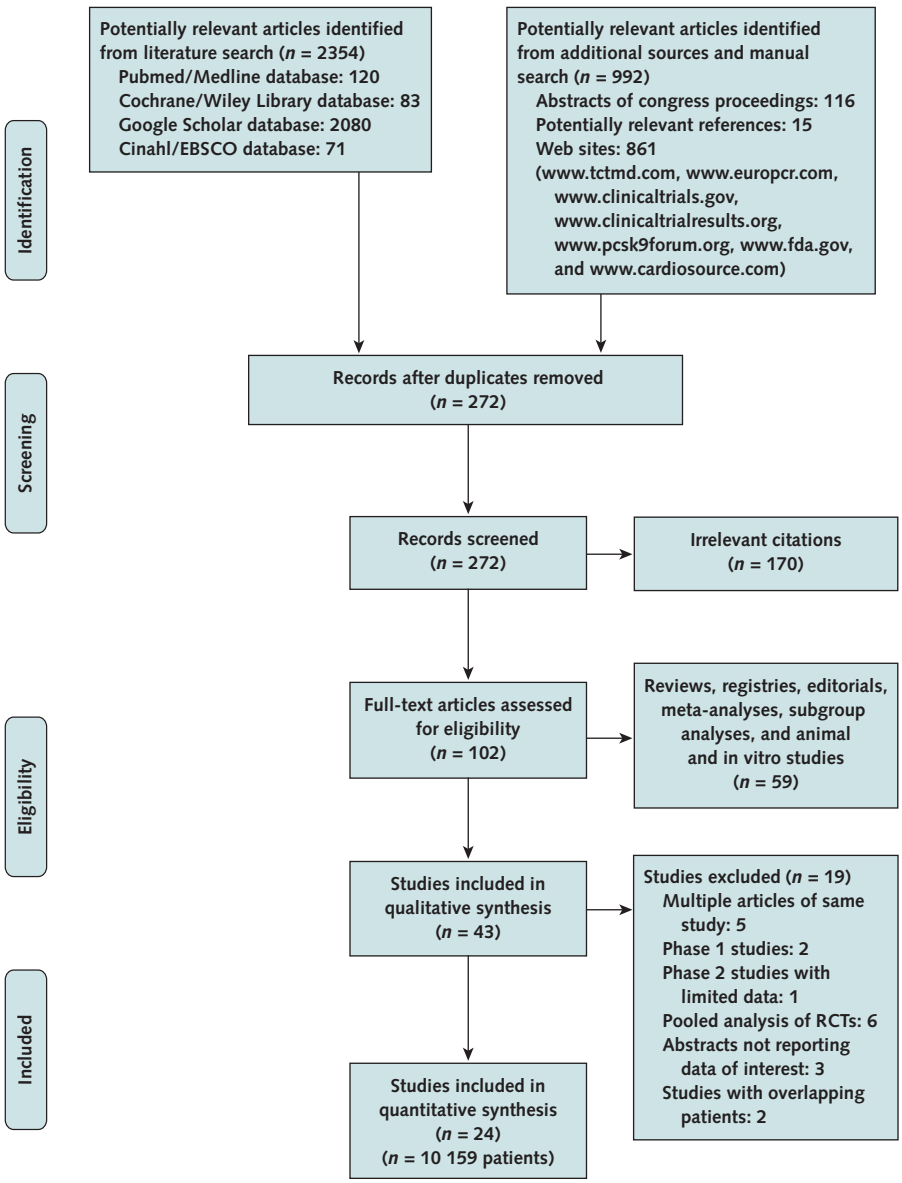
Appendix Figure 1. Summary of evidence search and selection.



RCT = randomized, controlled trial.

Appendix Table 1. Study Characteristics

Study*	Journal, Year	Phase	Follow-up	Investigational Drug and Dose	Control	Population	Statin Therapy	Funding
DESCARTES	NEJM, 2014	3	52 wk	Evolocumab 420 mg Q4W	Placebo	HC	Nonintensive and intensive	Amgen
GAUSS	JAMA, 2012	2	12 wk	Evolocumab 420 mg Q4W	Ezetimibe 10 mg	HC, statin-intolerant	Nonintensive	Amgen
GAUSS-2	JACC, 2014	3	12 wk	Evolocumab 140 mg Q2W and evolocumab 420 mg Q4W	Ezetimibe 10 mg	HC, statin-intolerant	Nonintensive	Amgen
LAPLACE-2	JAMA, 2014	3	12 wk	Evolocumab 140 mg Q2W and Evolocumab 420 mg Q4W	Placebo and ezetimibe 10 mg	HC	Nonintensive Intensive	Amgen
LAPLACE-TIMI 57	Lancet, 2012	2	12 wk	Evolocumab 140 mg Q2W and evolocumab 420 mg Q4W	Placebo	nFH	Intensive	Amgen
McKenney et al	JACC, 2012	2	12 wk	Alirocumab 150 mg Q2W	Placebo	FH	Intensive	Sanofi; Regeneron Pharmaceuticals
MENDEL	Lancet, 2012	2	12 wk	Evolocumab 140 mg Q2W and evolocumab 420 mg Q4W	Placebo and ezetimibe 10 mg	HC	None	Amgen
MENDEL-2	JACC, 2014	3	12 wk	Evolocumab 140mg Q2W and evolocumab 420 mg Q4W	Placebo and ezetimibe 10 mg	FH	None	Amgen
ODYSSEY ALTERNATIVE	AHA Scientific Sessions 2014	3	24 wk	Alirocumab 75 mg with potential up-titration to 150 mg Q2W	Ezetimibe 10 mg	HC	None	Sanofi; Regeneron Pharmaceuticals
ODYSSEY COMBO I	Am Heart J, 2015	3	52 wk	Alirocumab 75 mg with potential up-titration to 150 mg Q2W	Placebo	HC	Intensive	Sanofi; Regeneron Pharmaceuticals
ODYSSEY COMBO II	ESC Congress 2014	3	104 wk	Alirocumab 75 mg with potential up-titration to 150 mg Q2W	Ezetimibe 10 mg	HC	Intensive	Sanofi; Regeneron Pharmaceuticals
ODYSSEY FHI	ESC Congress 2014	3	78 wk	Alirocumab 75 mg with potential up-titration to 150 mg Q2W	Placebo	HeFH	Intensive	Sanofi; Regeneron Pharmaceuticals
ODYSSEY FHII	ESC Congress 2014	3	78 wk	Alirocumab 75 mg with potential up-titration to 150 mg Q2W	Placebo	HeFH	Intensive	Sanofi; Regeneron Pharmaceuticals
ODYSSEY HIGH FH	AHA Scientific Sessions 2014	3	52–78 wk	Alirocumab 150 mg Q2W	Placebo	HeFH	Intensive	Sanofi; Regeneron Pharmaceuticals
ODYSSEY LONG TERM	NEJM, 2015	3	78 wk	Alirocumab 150 mg Q2W	Placebo	HeFH and HC	Intensive	Sanofi; Regeneron Pharmaceuticals
ODYSSEY MONO	Int J Cardiol, 2014	3	24 wk	Alirocumab 75 mg Q2W	Ezetimibe 10 mg	HC	None	Sanofi; Regeneron Pharmaceuticals
ODYSSEY OPTIONS I	AHA Scientific Sessions 2014	3	24 wk	Alirocumab 75 mg with potential up-titration to 150 mg Q2W	Ezetimibe 10 mg	HC	Nonintensive Intensive	Sanofi; Regeneron Pharmaceuticals
ODYSSEY OPTIONS II	AHA Scientific Sessions 2014	3	24 wk	Alirocumab 75 mg with potential up-titration to 150 mg Q2W	Ezetimibe 10 mg	HC	Nonintensive Intensive	Sanofi; Regeneron Pharmaceuticals
Roth et al	NEJM, 2012	2	8 wk	Alirocumab 150 mg Q2W	Placebo	FH	Intensive	Sanofi; Regeneron Pharmaceuticals
RUTHERFORD	Circulation, 2012	2	12 wk	Evolocumab 420 mg Q4W	Placebo	HeFH	Intensive	Amgen
RUTHERFORD-2	Lancet, 2014	3	12 wk	Evolocumab 140 mg Q2W and evolocumab 420 mg Q4W	Placebo	HeFH	Intensive	Amgen
Stein et al	Lancet, 2012	2	12 wk	Alirocumab 150 mg Q2W	Placebo	HeFH	Intensive	Sanofi; Regeneron Pharmaceuticals
TESLA Part B	Lancet, 2014	3	12 wk	Evolocumab 420 mg Q4W	Placebo	HoFH	Intensive	Amgen
YUKAWA	Circ J, 2014	2	12 wk	Evolocumab 140 mg Q2W and evolocumab 420 mg Q4W	Placebo	HC	Intensive	Amgen

AHA = American Heart Association; Am Heart J = *American Heart Journal*; Circ J = *Circulation Journal*; ESC = European Society of Cardiology; FH = familial hypercholesterolemia; HC = hypercholesterolemia; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; Int J Cardiol = *International Journal of Cardiology*; JACC = *Journal of the American College of Cardiology*; JAMA = *Journal of the American Medical Association*; NEJM = *New England Journal of Medicine*; nFH = nonfamilial hypercholesterolemia; Q2W = every 2 weeks; Q4W = every 4 weeks.

* Expanded study names are as follows: DESCARTES = Durable Effect of PCSK9 Antibody Compared with Placebo Study; GAUSS = Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects; LAPLACE-2 = LDL-C Assessment with PCKS9 Monoclonal Antibody Inhibition Combined With Statin Therapy-2; LAPLACE-TIMI 57 = LDL-C Assessment with PCKS9 Monoclonal Antibody Inhibition Combined With Statin Therapy = Thrombosis in Myocardial Infarction 57; MENDEL = Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-CC in Patients Currently Not Receiving Drug Therapy For Easing Lipid Levels; PCSK9 = proprotein; RUTHERFORD = The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder; PCSK9 = proprotein convertase subtilisin/kexin type 9; TESLA = Trial Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities; YUKAWA = Study of LDL-Cholesterol Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk.

Appendix Table 2. Patient Characteristics

Study*	Patients, *n*	Mean Age, *y*	Men, %	CAD, %	HT, %	DM2, %	BMI, *kg/m²*	Mean LDL-C Level at Baseline, *mmol/L (mg/dL)*	Statin Therapy, %	Intensive Statin Therapy, %	Statin and Dose
DESCARTES	111	51.6	45.0	1.8	44.6	3.4	30.3	2.9 (111.8)	0	0	None
	383	57.1	43.8	2.6	41.2	7.3	29.9	2.6 (100.3)	100	0	Atorvastatin 10 mg
	218	54.8	50.0	15.6	57.1	16.2	31	2.5 (95.1)	100	100	Atorvastatin 80 mg
	189	54.8	54.5	47.6	57.2	22.6	29.9	3.0 (117.8)	100	100	Atorvastatin 80 mg (with ezetimibe)
GAUSS	65	61.2	40.6	NA	NA	NA	NA	5.1 (198.4)	16	0	None or ≤ weekly max dose
GAUSS-2	307	61.7	54.0	NA	61	22	NA	5.0 (193.0)	17.9	0	2% Atorvastatin 8.8% Rosuvastatin 2.8% Simvastatin 4.9% Other
LAPLACE-2	1896	59.8	54.3	22.5	NA	16.3	NA	2.8 (109.1)	100	67.1	Atorvastatin 10–80 mg Rosuvastatin 5–40 mg Simvastatin 40 mg
LAPLACE-TIMI 57	315	62.6	45.0	32.0	70.3	16.5	29.4	3.1 (121.8)	99.2	29.3	28.3% Atorvastatin 0.6% Fluvastatin 2.9% Lovastatin 7.6% Pravastatin 17.5% Rosuvastatin 43.2% Simvastatin
McKenney et al	62	56.6	58.6	6.5	40.4	6.5	28.1	3.3 (127.1)	100	24.6	Atorvastatin 10–20-40 mg
MENDEL	225	51.5	34.5	NA	33	0	30.8	3.7 (143.1)	0	0	None
MENDEL-2	614	53.2	34.1	NA	27.2	0.2	NA	3.7 (142.9)	0	0	None
ODYSSEY ALTERNATIVE	251	63.5	54.6	47	64.6	23.9	29	5.0 (192.3)	0	0	None
ODYSSEY COMBO I	316	63.0	65.8	78.2	88.7	43.1	32.3	2.6 (102.1)	99.7	62.7	Atorvastatin 40–80 mg Rosuvastatin 20–40 mg Simvastatin 80 mg and/or appropriate other dose given by investigator
ODYSSEY COMBO II	720	64.9	73.6	90.1	81	30.9	30.2	2.8 (107.7)	99.9	66.7	Atorvastatin 40–80 mg Rosuvastatin 20–40 mg Simvastatin 80 mg
ODYSSEY FHI and FHII	735	52.4	55.1	42.6	37.5	8.2	28.8	3.7 (141.4)	100	83.3	Atorvastatin 40–80 mg Rosuvastatin 20–40 mg Simvastatin 80 mg
ODYSSEY HIGH FH	107	50.6	54.2	49.7	57.1	42.1	28.9	5.1 (197.9)	100	79.4	Atorvastatin 40–80 mg Rosuvastatin 20–40 mg Simvastatin 80 mg and/or appropriate other dose given by investigator
ODYSSEY LONG TERM	2341	60.5	62.3	68.6	NA	34.4	30.4	3.2 (122.4)	99.9	44.1	Atorvastatin 40–80 mg Rosuvastatin 20–40 mg Simvastatin 80 mg
ODYSSEY MONO	103	60.2	53.4	NA	NA	3.9	29.3	3.6 (139.7)	0	0	None
ODYSSEY OPTIONS I	112	63.9	57.1	NA	NA	NA	31.9	2.6 (102.2)	100	0	Atorvastatin 20 mg
	94	64.1	71.3	NA	NA	NA	30.3	2.8 (107.7)	100	100	Atorvastatin 40 mg
ODYSSEY OPTIONS II	97	61.3	50.9	NA	NA	NA	32	2.7 (104.9)	100	0	Rosuvastatin 10 mg
	107	60.5	55.2	NA	NA	NA	30.2	3.1 (118.7)	100	100	Rosuvastatin 20 mg
Roth et al	61	56.4	37.5	1.5	49	16.5	29.6	3.2 (124.0)	100	100	Atorvastatin 80 mg

Continued on following page

Appendix Table 2–Continued

Study*	Patients, *n*	Mean Age, *y*	Men, %	CAD, %	HT, %	DM2, %	BMI, *kg/m²*	Mean LDL-C Level at Baseline, *mmol/L (mg/dL)*	Statin Therapy, %	Intensive Statin Therapy, %	Statin and Dose
RUTHERFORD	112	50.6	52.7	21.5	NA	NA	NA	3.9 (152.7)	100	87.5	Intensive therapy: 31% Atorvastatin ≥40 mg 40.7% Rosuvastatin ≥20 mg 6.6% Simvastatin 80 mg 11.4% lower dose or any other statin with ezetimibe
RUTHERFORD-2	331	51.2	57.3	31.3	NA	NA	NA	4.0 (154.7)	100	87	NA
Stein et al	31	54.2	71.0	35.5	NA	0	30.1	3.8 (145.4)	100	77.4	Stable statin therapy
TESLA Part B	49	31.0	51.0	43.0	NA	NA	NA	9.0 (348.0)	100	93.9	65% Atorvastatin (63% Atorvastatin ≥40 mg) 35% Rosuvastatin (31% Rosuvastatin ≥20 mg)
YUKAWA	207	60.8	67.6	27.0	72.4	35.9	NA	3.6 (141.1)	100	23.7	Stable statin therapy

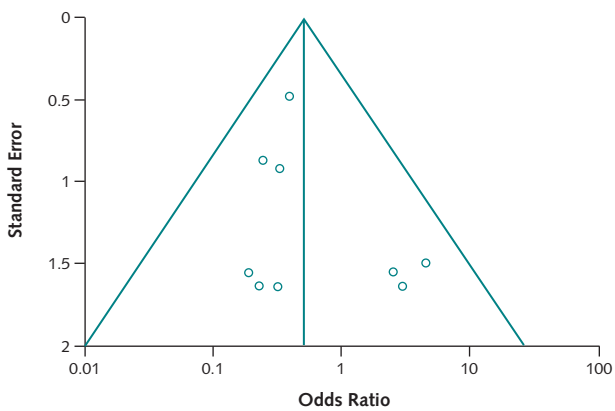
BMI = body mass index; CAD = coronary artery disease; DM2 = type 2 diabetes; HT = hypertension; LDL-C = low-density lipoprotein cholesterol; NA = not available.
* See the legend for **Appendix Table 1** for abbreviation expansions.

Appendix Table 3. Risk of Bias of Individual Randomized, Controlled Trials

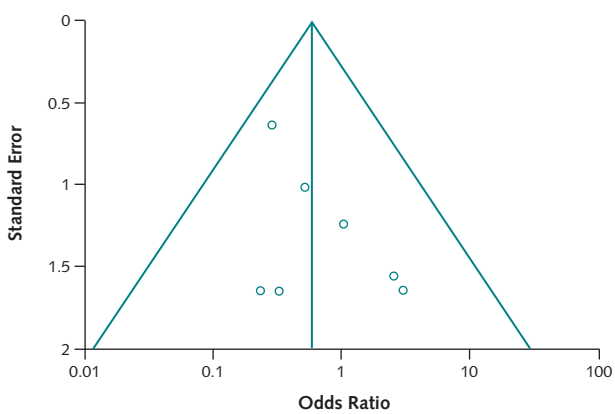
Study	Multicenter Trial	Adequate Sequence Generation	Allocation Concealment	Blinding			Incomplete Data Outcome Addressed?	Selective Outcome Reporting	Free of Other Bias
				Patient	Physician	Adjudication of Outcomes			
DESCARTES	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
GAUSS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
GAUSS-2	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No	Yes
LAPLACE-2	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	Yes
LAPLACE-TIMI 57	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
McKenney et al	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
MENDEL	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
MENDEL-2	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY ALTERNATIVE	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY COMBO I	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY COMBO II	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY FH I and FH II	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY HIGH FH	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY LONG TERM	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY MONO	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY OPTIONS I	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes
ODYSSEY OPTIONS II	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes
Roth et al	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes
TESLA (Part B)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
RUTHERFORD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
RUTHERFORD-2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Stein et al	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
YUKAWA	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Yes

* See the legend for Appendix Table 1 for abbreviation expansions.

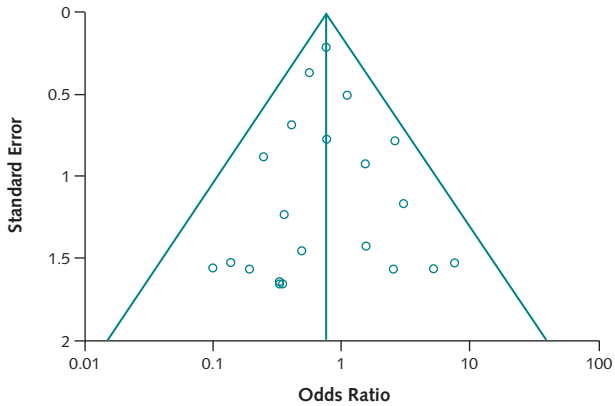
Appendix Figure 2. Funnel plot for all-cause mortality.



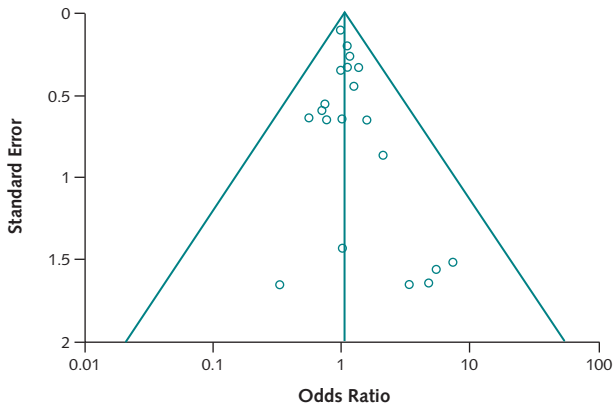
Appendix Figure 3. Funnel plot for cardiovascular mortality.



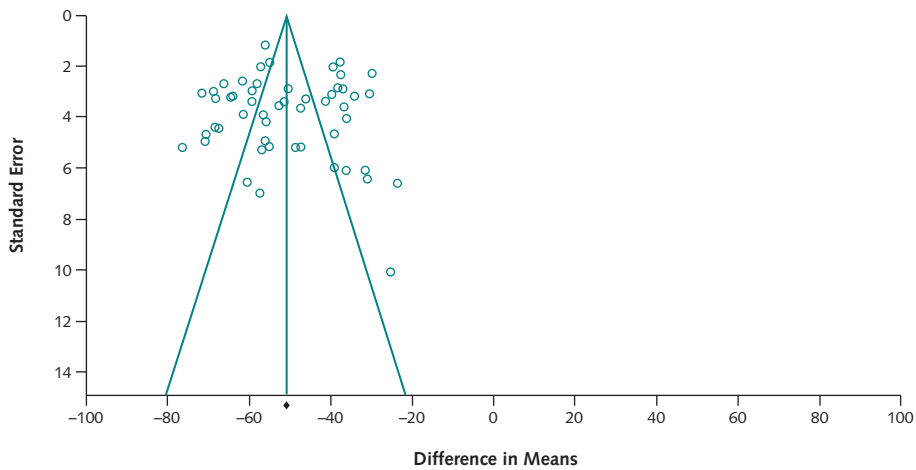
Appendix Figure 4. Funnel plot for increase in creatine kinase.



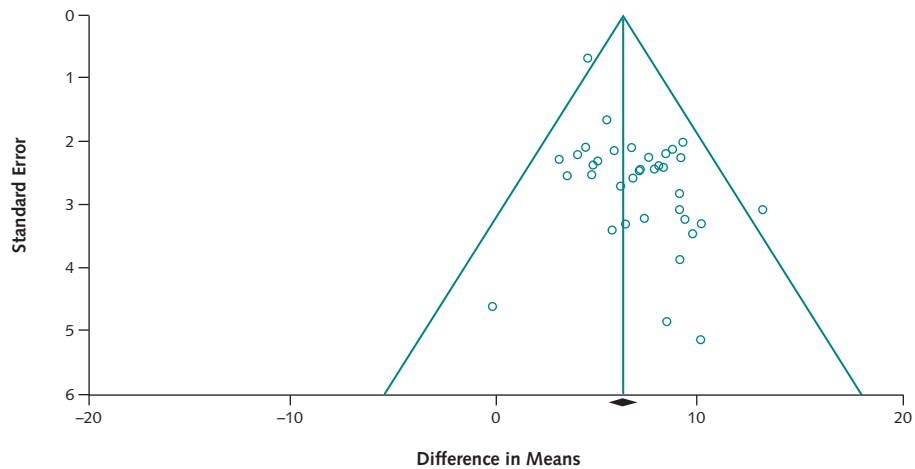
Appendix Figure 5. Funnel plot for serious adverse events.



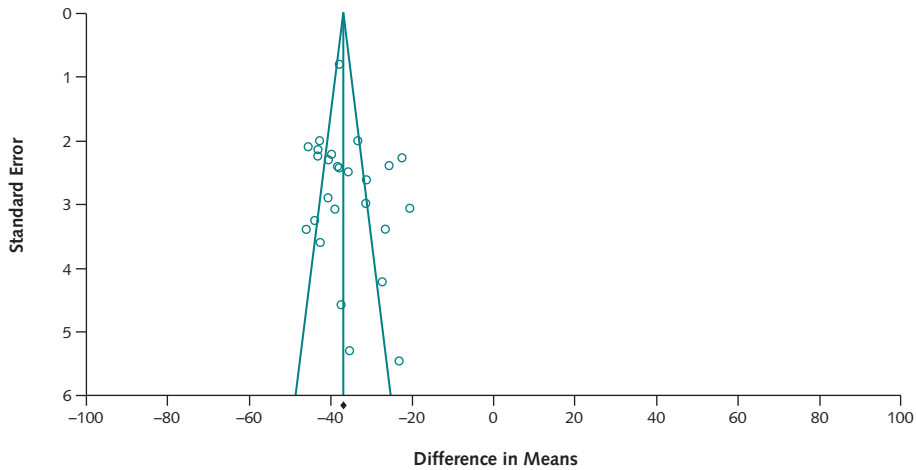
Appendix Figure 6. Funnel plot for low-density lipoprotein cholesterol percentage of change from baseline.



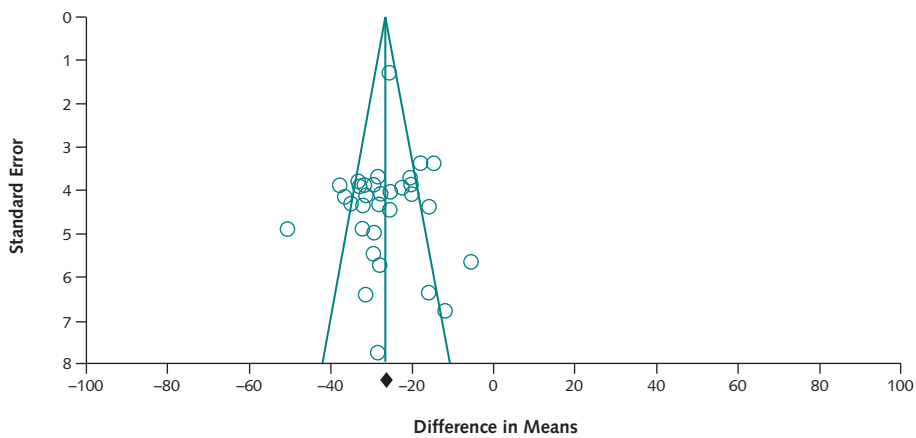
Appendix Figure 7. Funnel plot for high-density lipoprotein cholesterol percentage of change from baseline.



Appendix Figure 8. Funnel plot for total cholesterol percentage of change from baseline.



Appendix Figure 9. Funnel plot for lipoprotein(a) percentage of change from baseline.



Appendix Table 4. Egger Bias Analysis

End Point	Egger 2-Tailed *P* Value
All-cause mortality	0.30
Cardiovascular mortality	0.12
Myocardial infarction	0.11
Unstable angina	NA
Increase of creatinine kinase	0.99
Serious adverse events	0.17
LDL-C percent change from baseline	0.99
HDL-C percent change from baseline	0.12
TC percent change from baseline	0.33
Lp(a) percent change from baseline	0.69

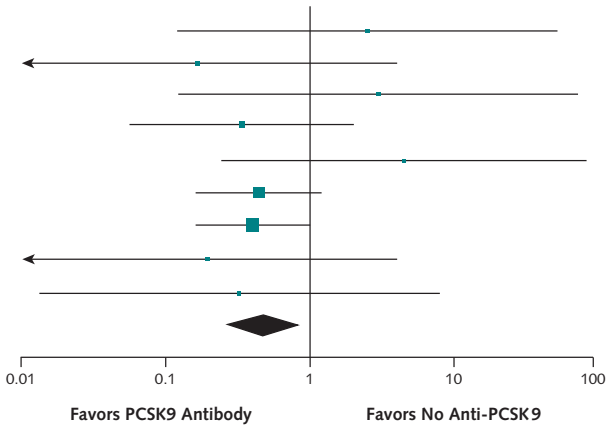
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); NA = not applicable; TC = total cholesterol.

Appendix Figure 10. Analysis of all-cause mortality, adjusted for follow-up.

Study or Subgroup	log(Rate Ratio)	SE	Weight, %	Rate Ratio (95% CI)*
DESCARTES	0.925	1.549	3.5	2.52 (0.12–52.51)
LAPLACE-2	–1.7927	1.633	3.2	0.17 (0.01–4.09)
LAPLACE-TIMI 57	1.092	1.633	3.2	2.98 (0.12–73.16)
ODYSSEY COMBO I	–1.075	0.913	10.2	0.34 (0.06–2.04)
ODYSSEY COMBO II	1.504	1.491	3.8	4.50 (0.24–83.62)
ODYSSEY FH I and FH II	–0.812	0.518	31.6	0.44 (0.16–1.23)
ODYSSEY LONG TERM	–0.902	0.474	37.8	0.41 (0.16–1.03)
ODYSSEY OPTIONS I	–1.629	1.549	3.5	0.20 (0.01–4.08)
ODYSSEY OPTIONS II	–1.118	1.633	3.2	0.33 (0.01–8.03)
Total (95% CI)			100.0	0.48 (0.27–0.85)

Heterogeneity: chi square = 5.75 (P = 0.68); I^2 = 0%

Test for overall effect: Z = 2.51 (P = 0.01)



See the legend for Figure 1 for abbreviation expansions.
* Inverse-variance, fixed-effects model.

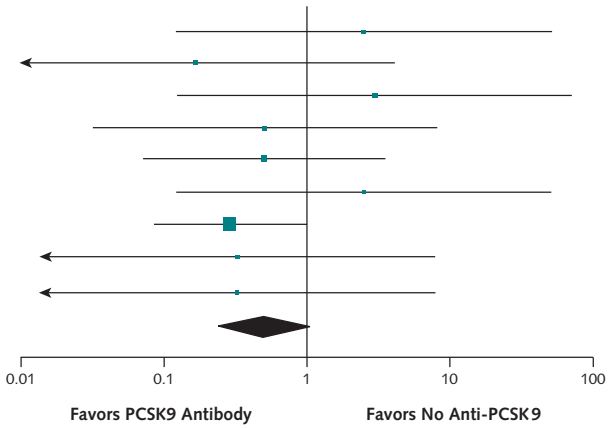
Appendix Table 5. Stratified Analysis of Clinical End Points

Outcome	Comparator	Odds Ratio (95% CI)	*P* Value for Interaction
Mortality	Placebo	0.63 (0.32–1.22)	0.22
	Ezetimibe	0.25 (0.06–0.95)	
Cardiovascular mortality	Placebo	0.59 (0.26–1.33)	0.66
	Ezetimibe	0.41 (0.09–1.77)	
Myocardial infarction	Placebo	0.48 (0.25–0.90)	Not estimable
	Ezetimibe	Not estimable*	
Unstable angina	Placebo	0.51 (0.07–3.60)	Not estimable
	Ezetimibe	Not estimable	
Increase in creatine kinase	Placebo	0.70 (0.52–0.94)	0.62
	Ezetimibe	0.82 (0.46–1.47)	
Serious adverse events	Placebo	1.01 (0.85–1.20)	0.79
	Ezetimibe	1.06 (0.78–1.44)	

* One study only provided data for the stratified analysis.

Appendix Figure 11. Analysis of cardiovascular mortality, adjusted for follow-up.

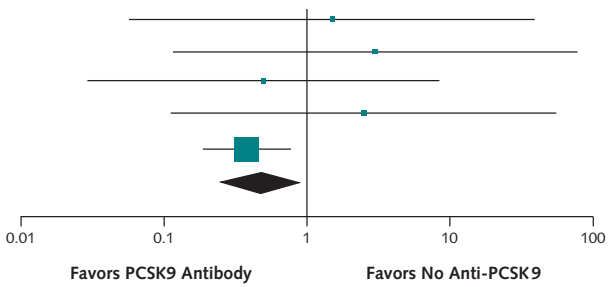
Study or Subgroup	log(Rate Ratio)	SE	Weight, %	Rate Ratio (95% CI)*
DESCARTES	0.925	1.549	6.5	2.52 (0.12–52.51)
LAPLACE-2	–1.793	1.633	5.9	0.17 (0.01–4.09)
LAPLACE-TIMI 57	1.092	1.633	5.9	2.98 (0.12–73.16)
ODYSSEY COMBO I	–0.67	1.414	7.8	0.51 (0.03–8.18)
ODYSSEY COMBO II	–0.687	1	15.7	0.50 (0.07–3.57)
ODYSSEY FH I and FH II	0.916	1.549	6.5	2.50 (0.12–52.4)
ODYSSEY LONG TERM	–1.238	0.627	39.9	0.29 (0.08–0.99)
ODYSSEY OPTIONS I	–1.118	1.633	5.9	0.33 (0.01–8.03)
ODYSSEY OPTIONS II	–1.118	1.633	5.9	0.33 (0.01–8.03)
Total (95% CI)			100.00	0.49 (0.23–1.07)
Heterogeneity: chi square = 4.71 (P = 0.79); I^2 = 0%				
Test for overall effect: Z = 1.78 (P = 0.07)				



See the legend for Figure 1 for abbreviation expansions.
* Inverse variance, fixed-effects model.

Appendix Figure 12. Analysis of myocardial infarction, adjusted for follow-up.

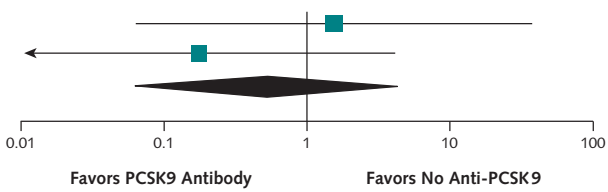
Study or Subgroup	log(Rate Ratio)	SE	Weight, %	Rate Ratio (95% CI)*
DESCARTES	0.414	1.633	3.9	1.51 (0.06–37.14)
ODYSSEY ALTERNATIVE	1.091	1.633	3.9	2.98 (0.12–73.08)
ODYSSEY COMBO I	–0.67	1.414	5.2	0.51 (0.03–8.18)
ODYSSEY FH I and FH II	0.916	1.549	4.4	2.50 (0.12–52.04)
ODYSSEY LONG TERM	–0.93	0.356	82.6	0.39 (0.20–0.79)
Total (95% CI)			100.00	0.49 (0.26–0.93)
Heterogeneity: chi square = 3.17 (P = 0.53); I^2 = 0%				
Test for overall effect: Z = 2.18 (P = 0.03)				



See the legend for Figure 1 for abbreviation expansions.
* Inverse variance, fixed-effects model.

Appendix Figure 13. Analysis of unstable angina, adjusted for follow-up.

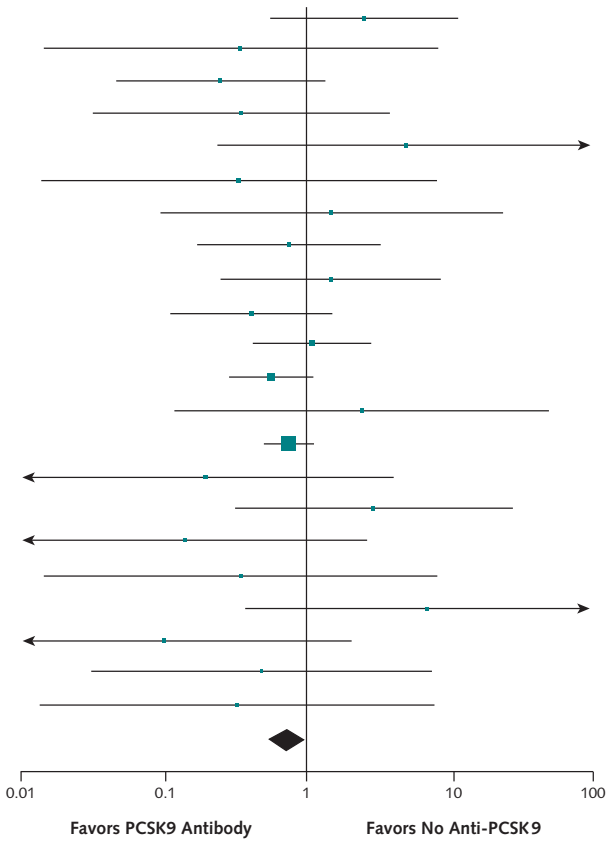
Study or Subgroup	log(Rate Ratio)	SE	Weight, %	Rate Ratio (95% CI)*
DESCARTES	0.414	1.633	50.0	1.51 (0.06–37.14)
ODYSSEY LONG TERM	–1.777	1.633	50.0	0.17 (0.01–4.15)
Total (95% CI)			100.00	0.51 (0.05–4.86)
Heterogeneity: chi square = 90 (P = 0.34); I^2 = 0%				
Test for overall effect: Z = 0.59 (P = 0.56)				



See the legend for Figure 1 for abbreviation expansions.
* Inverse-variance, fixed-effects model.

Appendix Figure 14. Analysis of increase in creatine kinase level, adjusted for follow-up.

Study or Subgroup	log(Rate Ratio)	SE	Weight, %	Rate Ratio (95% CI)*
DESCARTES	0.925	0.775	3.4	2.52 (0.55–11.52)
GAUSS	–1.068	1.633	0.8	0.34 (0.01–8.44)
GAUSS-2	–1.391	0.866	2.7	0.25 (0.05–1.36)
LAPLACE-2	–1.054	1.225	1.4	0.35 (0.03–3.85)
LAPLACE-TIMI 57	1.603	1.549	0.8	4.97 (0.24–103.44)
McKenney et al	–1.099	1.633	0.8	0.33 (0.01–8.18)
MENDEL	0.405	1.414	1.0	1.50 (0.09–23.96)
MENDEL-2	–0.281	0.764	3.5	0.76 (0.17–3.38)
ODYSSEY ALTERNATIVE	0.397	0.913	2.4	1.49 (0.25–8.90)
ODYSSEY COMBO I	–0.893	0.671	4.5	0.41 (0.11–1.53)
ODYSSEY COMBO II	0.086	0.494	8.3	1.09 (0.41–2.87)
ODYSSEY FH I and FH II	–0.568	0.354	16.2	0.57 (0.28–1.13)
ODYSSEY HIGH FH	0.888	1.549	0.8	2.43 (0.12–50.60)
ODYSSEY LONG TERM	–0.291	0.21	46.0	0.75 (0.50–1.13)
ODYSSEY MONO	–1.629	1.549	0.8	0.20 (0.01–4.08)
ODYSSEY OPTIONS I	1.079	1.155	1.5	2.94 (0.31–28.30)
ODYSSEY OPTIONS II	–1.966	1.511	0.9	0.14 (0.01–2.71)
Roth et al (2012)	–1.066	1.633	0.8	0.34 (0.01–8.45)
RUTHERFORD	1.946	1.511	0.9	7.00 (0.36–135.3)
RUTHERFORD-2	–2.307	1.549	0.8	0.10 (0.00–2.07)
TESLA Part B	–0.724	1.414	1.0	0.48 (0.03–7.75)
YUKAWA	1.128	1.633	0.8	0.32 (0.01–7.95)
Total (95% CI)				0.73 (0.55–0.97)
Heterogeneity: chi square = 17.65 (P = 0.67); I^2 = 0%				
Test for overall effect: Z = 2.19 (P = 0.03)				



See the legend for Figure 1 for abbreviation expansions.
* Inverse-variance, fixed-effects model.

Appendix Table 6. LDL Cholesterol Values and Discontinuation Rates

Study	Statin Therapy	Agent	Baseline LDL-C Value, *mmol/L (mg/dL)*	Final LDL-C Value, *mmol/L (mg/dL)*	Patients Reaching LDL-C <3.9 mmol/L (<70 mg/dL), %	Discontinuation Rate, %
DESCARTES	Nonintensive and intensive	Placebo	2.7 (104)	2.8 (107.9)	6.4	7.6
		PCSK9 antibody	2.7 (104.2)	1.3 (50.9)	82.3	12.2
GAUSS	Statin-intolerant	Ezetimibe	4.7 (182.9)	4.0 (154.3)	0	6.1
		PCSK9 antibody	5.3 (203.5)	2.6 (99.0)	NA	3.1
GAUSS-2	Statin-intolerant	Ezetimibe	5.0 (195)	4.2 (161.8)	1	14
		PCSK9 antibody	5.0 (192)	2.3 (89.5)	43.8	4
LAPLACE-2	Nonintensive and Intensive	Placebo	2.8 (107.7)	2.9 (112.5)	12	8.1
		Ezetimibe	2.8 (109.4)	2.3 (88.8)	37.4	12.7
		PCSK9 antibody	2.8 (109.7)	1.1 (43.9)	88.9	5.9
LAPLACE-TIMI 57	Intensive	Placebo	3.2 (123.7)	3.2 (122.5)	0.7	4.5
		PCSK9 antibody	3.1 (119.8)	1.6 (63.4)	82.7	5.7
McKenney et al	Intensive	Placebo	3.4 (130.2)	3.3 (126.8)	3	0
		PCSK9 antibody	3.2 (123.9)	0.9 (34.2)	100	12.9
MENDEL	None	Placebo	3.8 (145)	3.8 (146.9)	NA	12
		Ezetimibe	3.7 (143)	3.2 (122)	NA	2.2
		PCSK9 antibody	3.6 (139.2)	1.8 (71.5)	NA	5.6
MENDEL-2	None	Placebo	3.7 (142)	3.6 (141.1)	0.7	3
		Ezetimibe	3.7 (143.5)	3.0 (117.4)	1.4	3
		PCSK9 antibody	3.7 (143)	1.6 (62.1)	69.2	3
ODYSSEY ALTERNATIVE	None	Ezetimibe	5.0 (193.5)	4.1 (157)	4	33.6
		PCSK9 antibody	4.9 (191.1)	2.4 (92)	42	23.8
ODYSSEY COMBO I	Intensive	Placebo	2.7 (106.0)	2.6 (102.3)	9.0	6.3
		PCSK9 antibody	2.6 (100.2)	1.3 (52.1)	75.0	7.5
ODYSSEY COMBO II	Intensive	Ezetimibe	2.7 (105)	2.1 (82.5)	45.6	5.4
		PCSK9 antibody	2.8 (109)	1.3 (51.6)	77	7.5
ODYSSEY FH I and FH II	Intensive	Placebo	3.6 (139.2)	3.7 (145)	6.9	3.7
		PCSK9 antibody	3.6 (139.7)	1.8 (69.6)	76.8	3.1
ODYSSEY HIGH FH	Intensive	Placebo	5.2 (201.0)	4.9 (188)	3	2.9
		PCSK9 antibody	5.1 (196.3)	2.9 (113)	32	4.2
ODYSSEY LONG TERM	Intensive	Placebo	3.2 (122.0)	3.1 (118.9)	8	24.5
		PCSK9 antibody	3.2 (122.8)	1.2 (48.3)	79.3	28.2
ODYSSEY MONO	None	Ezetimibe	3.6 (138.3)	3.1 (121.1)	NA	13.7
		PCSK9 antibody	3.6 (141.1)	2.2 (87)	NA	15.4
ODYSSEY OPTIONS I	Nonintensive and Intensive	Ezetimibe	2.6 (99.7)	1.4 (52.3)	52.1	4.0
		PCSK9 antibody	2.8 (109.5)	2.0 (78.2)	78.3	6.7
ODYSSEY OPTIONS II	Nonintensive and Intensive	Ezetimibe	2.8 (110.0)	1.1 (43.4)	48.6	7.9
		PCSK9 antibody	2.9 (113.1)	1.8 (69)	68.5	4.9
Roth et al	Intensive	Placebo	3.1 (121.2)	2.7 (103.9)	17	12.9
		PCSK9 antibody	3.3 (126.9)	1.4 (53.7)	90	3
RUTHERFORD	Intensive	Placebo	4.2 (162.4)	4.2 (162.4)	0	5.4
		PCSK9 antibody	3.9 (150.8)	1.8 (69.6)	65	3.6
RUTHERFORD-2	Intensive	Placebo	3.9 (150.8)	3.9 (152.7)	2	1.4
		PCSK9 antibody	4.1 (158.5)	1.8 (67.7)	65.5	1.4
Stein et al	Intensive	Placebo	3.9 (151)	3.5 (136.1)	0	0
		PCSK9 antibody	3.8 (147.4)	1.3 (50.3)	81	0
TESLA Part B	Intensive	Placebo	8.7 (336.4)	9.2 (355.7)	NA	5.9
		PCSK9 antibody	9.2 (355.8)	7.3 (282.3)	NA	6.1
YUKAWA	Intensive	Placebo	3.7 (143.1)	3.6 (139.2)	0	4.8
		PCSK9 antibody	3.6 (139.2)	1.0 (40.6)	85.7	5.7

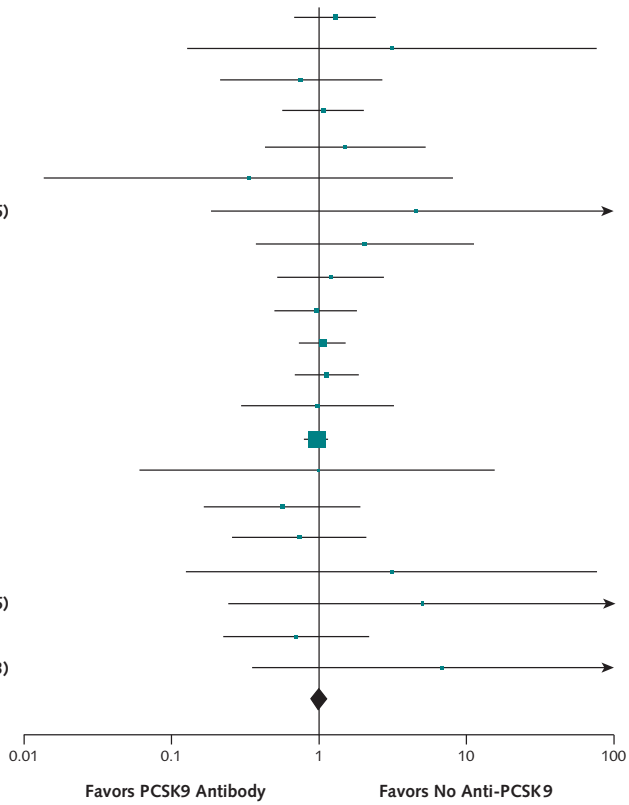
NA = not applicable.
* See the legend for **Appendix Table 1** for abbreviation expansions.

Appendix Figure 15. Analysis of serious adverse events, adjusted for follow-up.

Study or Subgroup	log(Rate Ratio)	SE	Weight, %	Rate Ratio (95% CI)*
DESCARTES	0.247	0.327	4.7	1.28 (0.67–2.43)
GAUSS	1.129	1.633	0.2	3.09 (0.13–75.92)
GAUSS-2	–0.293	0.645	1.2	0.75 (0.21-2.64)
LAPLACE-2	0.067	0.332	4.6	1.07 (0.56-2.05)
LAPLACE-TIMI 57	0.399	0.645	1.2	1.49 (0.42–5.28)
McKenney et al	–1.099	1.633	0.2	0.33 (0.01-8.18)
MENDEL	1.504	1.633	0.2	4.50 (0.18–110.46)
MENDEL-2	0.7	0.866	0.7	2.01 (0.37–10.99)
ODYSSEY ALTERNATIVE	0.174	0.428	2.8	1.19 (0.51–2.75)
ODYSSEY COMBO I	–0.05	0.331	4.6	0.95 (0.50–1.82)
ODYSSEY COMBO II	0.052	0.185	14.8	1.05 (0.73–1.51)
ODYSSEY FH I and FH II	0.108	0.257	7.6	1.11 (0.67–1.84)
ODYSSEY HIGH FH	–0.028	0.612	1.3	0.97 (0.29–3.23)
ODYSSEY LONG TERM	–0.046	0.1	50.5	0.96 (0.79–1.16)
ODYSSEY MONO	–0.019	1.414	0.3	0.98 (0.06–15.68)
ODYSSEY OPTIONS I	–0.579	0.627	1.3	0.56 (0.16–1.92)
ODYSSEY OPTIONS II	–0.307	0.54	1.7	0.74 (0.26–2.12)
Roth et al (2012)	1.131	1.633	0.2	3.10 (0.13–76.07)
RUTHERFORD	1.609	1.549	0.2	5.00 (0.24–104.06)
RUTHERFORD-2	–0.361	0.586	1.5	0.70 (0.22–2.20)
YUKAWA	1.917	1.511	0.2	6.80 (0.35–131.43)
Total (95% CI)			100	1.01 (0.88–1.16)

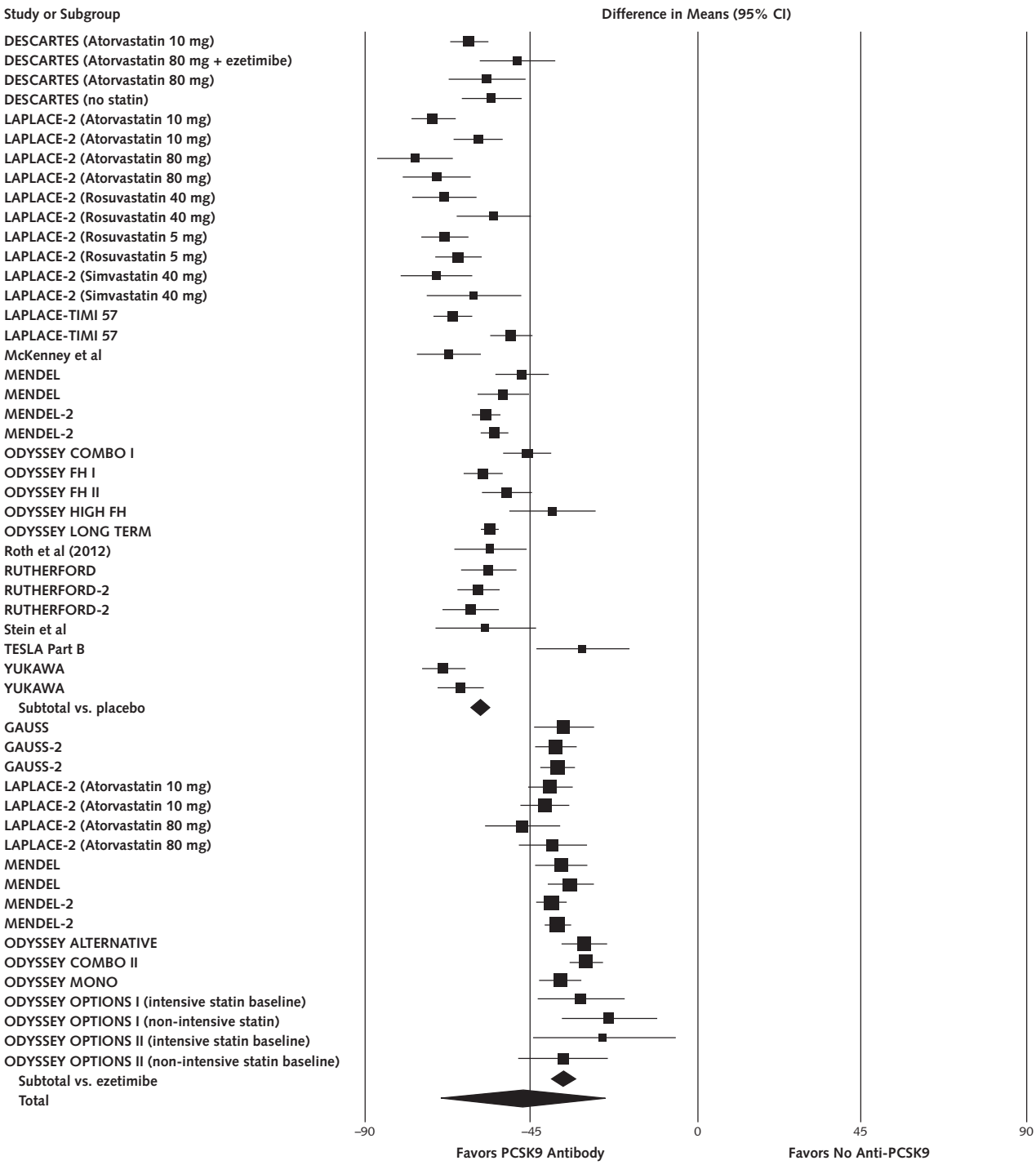
Heterogeneity: chi square = 8.99 ($P = 0.98$); $I^2 = 0\%$

Test for overall effect: $Z = 0.14$ ($P = 0.89$)



See the legend for Figure 1 for abbreviation expansions.
* Inverse-variance, fixed-effects model.

Appendix Figure 16. Low-density lipoprotein cholesterol percentage of change from baseline.



Group	Number of Studies	Effect Size (95% CI) Point Estimate	SE	Variance	Lower Limit	Upper Limit	Test of Null (2-Tail) *Z* Value	*P* Value	Heterogeneity *Q* Value	*P* Value	I^2
Random-effects analysis											
Placebo	34	–58.768	1.154	1.333	–61.031	–56.506	–50.905	0.000	169.290	0.000	80.507
Ezetimibe	18	–36.167	1.586	2.516	–39.276	–33.058	–22.802	0.000	28.847	0.036	41.069
Total between									132.724	0.000	
Overall	52	–47.494	11.301	127.703	–69.643	–25.345	–4.203	0.000	774.133	0.000	93.412

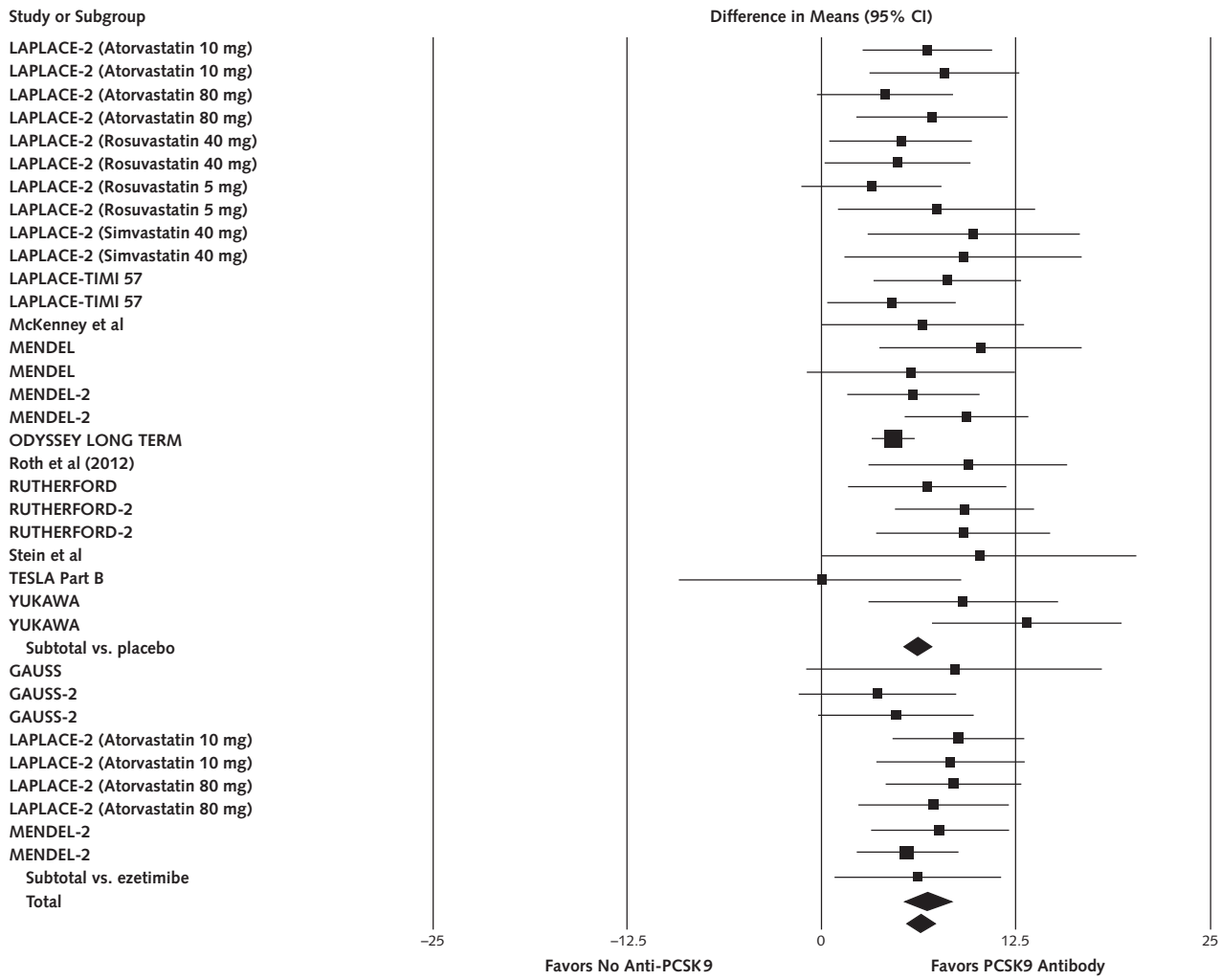
See the legend for Figure 1 for abbreviation expansions.

Appendix Table 7. Sensitivity Analyses for Efficacy

Comparison	Analysis		Efficacy Outcome: Mean Difference (95% CI), %			
			LDL-C	HDL-C	TC	Lp(a)
Placebo	MAb	Alirocumab 75 mg Q2W	−52.63 (−56.12 to −49.14)	–	–	−14.60 (−28.27 to −0.93)
		Alirocumab 150 mg Q2W	−56.15 (−58.29 to −54.00)	4.97 (3.67 to 6.27)	−38.87 (−43.58 to −34.16)	−25.60 (−37.80 to −13.40)
		Evolocumab 140 mg Q2W	−63.46 (−65.41 to −61.51)	6.65 (5.12 to 8.17)	−41.18 (−43.96 to −38.41)	−32.31 (−38.23 to −27.38)
		Evolocumab 420 mg Q4W	−57.26 (−58.97 to −55.54)	7.25 (5.71 to 8.78)	−36.96 (−39.67 to −34.29)	−26.03 (−30.58 to −21.48)
	Background statin	None	−53.65 (−59.51 to −47.78)	7.80 (5.20 to 10.40)	−33.05 (−38.40 to −27.70)	−23.56 (−31.19 to −15.92)
		Nonintensive	−65.24 (−70.46 to −60.02)	6.78 (4.53 to 9.04)	−40.62 (−43.81 to −37.43)	−29.05 (−35.57 to −22.52)
		Intensive	−57.93 (−60.95 to −54.91)	6.18 (5.01 to 7.35)	−39.22 (−41.41 to −37.02)	−28.90 (−33.23 to −24.57)
Ezetimibe	MAb	Alirocumab 75 mg Q2W	−31.67 (−34.45 to −28.90)	6.20 (0.87 to 11.53)	−22.20 (−26.65 to −17.76)	−5.40 (−20.79 to 9.99)
		Evolocumab 140 mg Q2W	−39.27 (−41.84 to −36.70)	7.39 (5.16 to 9.62)	−25.35 (−30.99 to −19.72)	−26.88 (−33.46 to −20.30)
		Evolocumab 420 mg Q4W	−37.49 (−39.74 to −35.25)	6.37 (4.30 to 8.45)	−23.96 (−27.33 to −20.59)	−24.84 (−31.26 to −18.42)
	Background statin	None	−36.23 (−39.24 to −33.26)	6.24 (3.87 to 8.60)	−22.20 (−26.65 to −17.76)	−15.39 (−21.02 to −9.76)
		Nonintensive	−37.49 (−40.81 to −34.16)	6.75 (4.47 to 9.03)	−25.29 (−29.10 to −21.48)	−26.12 (−30.54 to −21.71)
		Intensive	−34.42 (−39.06 to −29.79)	7.92 (4.70 to 11.14)	−23.00 (−27.46 to −18.55)	−33.66 (−40.05 to −27.28)

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); MAb = monoclonal antibody; TC = total cholesterol; Q2W = once every 2 weeks; Q4W = once every 4 weeks.

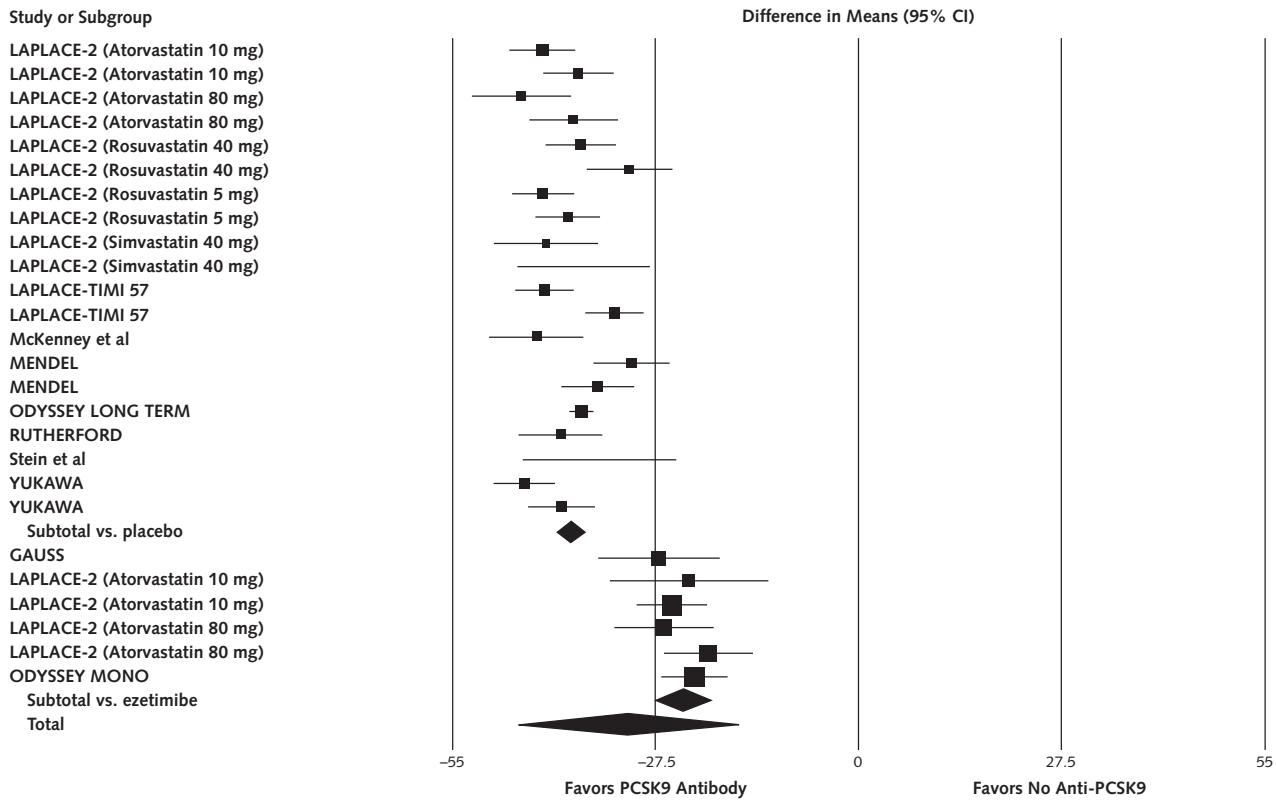
Appendix Figure 17. High-density lipoprotein cholesterol percentage of change from baseline.



Group	Number of Studies	Effect Size (95% CI) Point Estimate	SE	Variance	Lower Limit	Upper Limit	Test of Null (2-Tail) *Z* Value	*P* Value	Heterogeneity *Q* Value	*P* Value	I^2
Fixed-effect analysis											
Placebo	26	6.142	0.424	0.179	5.312	6.973	14.498	0.000	28.132	0.302	11.132
Ezetimibe	10	6.795	0.746	0.557	5.333	8.257	9.107	0.000	4.954	0.838	0.000
Total between									0.579	0.447	
Overall	36	6.301	0.368	0.136	5.579	7.023	17.104	0.000	33.665	0.533	0.000

See the legend for Figure 1 for abbreviation expansions.

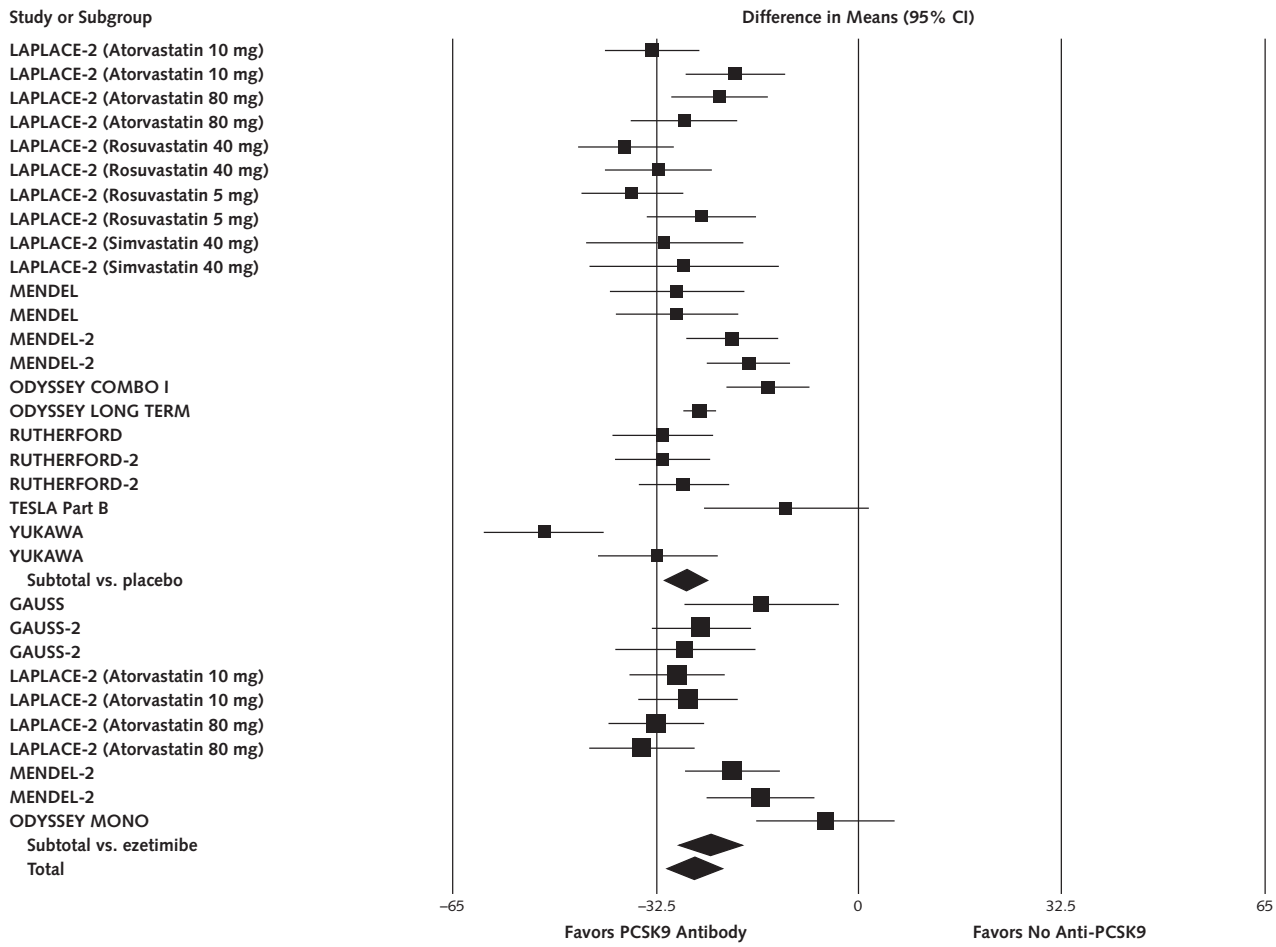
Appendix Figure 18. Total cholesterol percentage of change from baseline.



Group	Effect Size (95% CI)						Test of Null (2-Tail)		Heterogeneity		
Random-effects analysis	Number of Studies	Point Estimate	SE	Variance	Lower Limit	Upper Limit	*Z* Value	*P* Value	*Q* Value	*P* Value	I^2
Placebo	20	–38.992	0.882	0.778	–40.721	–37.263	–44.206	0.000	57.638	0.000	67.036
Ezetimibe	6	–23.831	1.793	3.213	–27.345	–20.318	–13.294	0.000	3.286	0.656	0.000
Total between									57.584	0.000	
Overall	26	–31.492	7.580	57.455	–46.348	–16.635	–4.155	0.000	187.788	0.000	86.687

See the legend for Figure 1 for abbreviation expansions.

Appendix Figure 19. Lipoprotein(a) percentage of change from baseline.



Group	Effect Size (95% CI)						Test of Null (2-Tail)		Heterogeneity		
Random-effects analysis	Number of Studies	Point Estimate	SE	Variance	Lower Limit	Upper Limit	*Z* Value	*P* Value	*Q* Value	*P* Value	I^2
Placebo	22	–27.961	1.658	2.749	–31.211	–24.712	–16.866	0.000	78.837	0.000	73.363
Ezetimibe	10	–24.046	2.495	6.225	–28.937	–19.156	–9.638	0.000	30.611	0.000	70.599
Total between									1.708	0.191	
Overall	32	–26.448	1.906	3.635	–30.185	–22.711	–13.873	0.000	111.060	0.000	72.087

See the legend for Figure 1 for abbreviation expansions.

Appendix Table 8. Randomized, Controlled Trials Comparing Treatment With PCSK9 Antibodies With No Anti-PCSK9 Treatment

Study (ClinicalTrials.gov Registration Number)*	Study Status	Setting	Intervention	Inclusion Criteria†	Exclusion Criteria†	Primary End Point	Duration	Outcome Assessment Method
Phase 2								
GAUSS (NCT01375764)	Completed, results published	Statin therapy intolerance	Evolocumab (AMG145) Ezetimibe Placebo	Age 18–75 y No or ongoing statin therapy (stable for ≥4 wk) Stable lipid modifying therapy before enrollment Triglycerides <400 mg/dL. Patient not at LDL-C goal	NYHA III or IV, or LVEF <30% MI, UA, PCI, CABG or stroke within 3 mo before randomization Uncontrolled cardiac arrhythmia or hypertension Diabetes mellitus (type 1, poorly controlled type 2)	Percent change in baseline LDL-C at 12 wk	12 wk	MedDRA, v 15.0
LAPLACE-TIMI 57 (NCT01380730)	Completed, results published	Hypercholesterolemia, ongoing statin therapy	Evolocumab (AMG145) Placebo (baseline statin)	Age 18–80 y Ongoing statin therapy, with or without ezetimibe (stable for ≥4 wk) LDL-C ≥85 mg/dL Triglycerides ≤400 mg/dL	NYHA III or IV, or LVEF <30% MI, UA, PCI, CABG or stroke within 3 mo before randomization Uncontrolled cardiac arrhythmia or hypertension Diabetes mellitus (type 1, poorly controlled type 2)	Percent change in baseline LDL-C at 12 wk	12 wk	MedDRA, v 14.0
McKenney et al (NCT01288443)	Completed, results published	Primary hypercholesterolemia, ongoing atorvastatin therapy	Alirocumab (SAR236553/REGN727) Placebo (baseline atorvastatin)	Primary hypercholesterolemia Ongoing lipid-lowering treatment other than atorvastatin/ or not at stable dose of atorvastatin (for ≥6 wk before screening period) or drug naive patients LDL-C ≥100 mg/dL at screening visit or at 6-week of run-in atorvastatin treatment	LDL-C <100 mg/dL Patients not previously instructed on a cholesterol-lowering diet Diabetes mellitus (type 1, poorly controlled type 2) Triglycerides >350 mg/dL Females of childbearing potential at pregnancy risk	Percent change in baseline LDL-C at 12 wk	12 wk	MedDRA, v 14.0
MENDEL (NCT01375777)	Completed, results published	Hypercholesterolemia, no statin therapy	Evolocumab (AMG145) Ezetimibe Placebo	Age 18–75 y LDL-C ≥100 mg/dL and <190 mg/dL Framingham risk score ≤10% Triglycerides <400 mg/dL	History of CHD NYHA II–IV Uncontrolled cardiac arrhythmia or hypertension	Percent change in baseline LDL-C at 12 wk	12 wk	MedDRA, v 14.1
Roth et al (2012) (NCT01288469)	Completed, results published	Primary hypercholesterolemia and LDL-cholesterol ≥ 100 mg/dL, co-administered with atorvastatin	Alirocumab (SAR236553/REGN727) Placebo (baseline atorvastatin)	Primary hypercholesterolemia Ongoing lipid-lowering treatment other than atorvastatin/ or not at stable dose of atorvastatin (for ≥6 wk before screening period) or drug naive patients LDL-C ≥100 mg/dL at screening visit or at 6-week of run-in atorvastatin treatment	LDL-C <100 mg/dL Patients not previously instructed on a cholesterol-lowering diet Diabetes mellitus (type 1, poorly controlled type 2) Triglycerides >350 mg/dL Females of childbearing potential at pregnancy risk	Percent change in baseline LDL-C at 8 wk	8 wk	MedDRA, v 14.0
RUTHERFORD (NCT01375751)	Completed, results published	Heterozygous familial hypercholesterolemia	Evolocumab (AMG145) Placebo	Age 18–75 y Heterozygous familial hypercholesterolemia Ongoing statin therapy, with or without ezetimibe (stable for ≥4 wk) LDL-C ≥100 mg/dL Triglycerides ≤400 mg/dL	Homozygous familial hypercholesterolemia LDL or plasma apheresis within 12 mo before randomization NYHA III or IV, or LVEF <30% MI, UA, PCI, CABG or stroke within 3 mo before randomization Uncontrolled cardiac arrhythmia or hypertension Diabetes mellitus (type 1, poorly controlled type 2)	Percent change in baseline LDL-C at 12 wk	12 wk	MedDRA, v 15.0
Stein et al (NCT01266876)	Completed, results published	Heterozygous familial hypercholesterolemia	Alirocumab (SAR236553/REGN727) Placebo	Age 18–75 y Heterozygous familial hypercholesterolemia Ongoing statin therapy, with or without ezetimibe (stable for ≥6 wk) LDL-C ≥100 mg/dL Negative pregnancy test for women of childbearing potential	Homozygous familial hypercholesterolemia LDL plasma apheresis within 12 mo before screening Use of thyroid medication Use of a medication (other than a statin or ezetimibe), nutraceuticals or OTC medications to alter serum lipids within 6 wk before screening Disorders known to influence lipid levels	Percent change in baseline LDL-C at 12 wk	12 wk	NA
YUKAWA (NCT01652703)	Completed, results published	Japanese patients with hypercholesterolemia and high cardiovascular risk	Evolocumab (AMG145) Placebo (baseline statin +/− ezetimibe)	Japanese, age 20–80 y Ongoing statin therapy, with or without ezetimibe (stable for ≥4 wk) LDL-C ≥115 mg/dL Triglycerides ≤400 mg/dL	NYHA III or IV or LVEF <30% MI, UA, PCI, CABG stroke, planned cardiac surgery or revascularization within 6 mo of randomization Uncontrolled cardiac arrhythmia or hypertension Diabetes type 2 (recently diagnosed or poorly controlled)	Percent change in baseline LDL-C at 12 wk	12 wk	MedDRA, v 16.0
NCT01576484	Ongoing, not recruiting participants	Hypercholesterolemia	Alirocumab (SAR236553/ REGN727)	Age 18–75 y Prior participation in and the successful completion of the R727-CL-1003 study Stable daily statin regimen for at least 3 wk before entry Negative urine pregnancy at the screening visit for women of childbearing potential	Early termination or withdrawal from R727-CL-1003 study due to reported drug-related SAE, drug-related clinical or laboratory adverse event Significant protocol deviation in R727-CL-1003 (non-compliance by the investigator or patient) LDL apheresis within 12 mo before the screening visit	Incidence of AEs from baseline to week 218	218 wk	NA

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Appendix Table 8–Continued

Study (ClinicalTrials.gov Registration Number)*	Study Status	Setting	Intervention	Inclusion Criteria†	Exclusion Criteria†	Primary End Point	Duration	Outcome Assessment Method
NCT01812707	Completed, no results available	Primary hypercholesterolemia on stable atorvastatin therapy	Alirocumab (SAR236553/REGN727) Placebo (atorvastatin baseline)	Age 20–75 y Primary hypercholesterolemia - 5-20 mg atorvastatin (stable for ≥6 wk) and LDL-C ≥100 mg/dL or Lipid-lowering treatment other than atorvastatin, or 5-20 mg atorvastatin (stable for ≥6 wk) if likely to have LDL-C ≥100 mg/dL after a 6-week run-in treatment period on atorvastatin therapy	LDL-C <100 mg/dL (at screening with stable dose of atorvastatin 5-20 mg ≥6 weeks before screening or at the end of the 6-week run-in period on atorvastatin) Diabetes mellitus (type 1, poorly controlled type 2)	Percent change in baseline LDL-C at 12 wk	20 wk	NA
NCT01604824	Ongoing, not recruiting participants	Autosomal dominant hypercholesterolemia and gain-of-function mutations in 1 or both alleles of the PCSK9 gene or with a loss-of-function mutation in 1 or more alleles of the apolipoprotein B-100 gene	Alirocumab (SAR236553/REGN727) Placebo	Age 18-70 y A history of molecularly confirmed PCSK9 GOFm for cohort 1 and a history of molecularly confirmed PCSK9 GOFm or ApoB LOFm LDL-C ≥70 mg/dL on a lipid lowering therapy (stable for ≥28 days)	Triglycerides >350 mg/dL Positive for HIV, hepatitis B or C virus Pregnant or breast-feeding women Sexually active man or woman of childbearing potential unwilling to practice adequate contraception during the study	Percent change in baseline LDL-C at day 15	222 wk	NA
NCT01592240	Completed, partial results available	Hypercholesterolemic subjects on a statin	Bococizumab (PF-04950615/RN316) Placebo	Age ≥18 y Statin therapy (stable for ≥6 wk) LDL-C ≥80 mg/dL Triglycerides <400 mg/dL	Severe acute or chronic medical or psychiatric condition or laboratory abnormality Pregnant or breastfeeding females Childbearing potential not using nor willing to use highly effective contraception History of a cardiovascular or cerebrovascular event or procedure during the past 6 mo CHF, NYHA III or IV Poorly controlled hypertension, type 1 or type 2 diabetes mellitus	Percent change from baseline in LDL-C at week 12	24 wk	NA
NCT01350141	Completed, no results available	Hypercholesterolemic subjects on maximum atorvastatin or rosuvastatin dose	Bococizumab (PF-04950615/RN316) Placebo	Age ≥18 y BMI 18.5-40 kg/m^2 Atorvastatin 80 mg or rosuvastatin 40 mg (stable for ≥45 days) LDL-C ≥80 mg/dL Triglycerides <400 mg/dL	History of a cardiovascular or cerebrovascular event or procedure during the past year Poorly controlled hypertension, type 1 or type 2 diabetes mellitus Triglycerides >400 mg/dL 12-lead ECG demonstrating QTcF >455 msec	Percent change in baseline LDL-C at day 85	141 days	NA
NCT01342211	Completed, no results available	Hypercholesterolemic subjects on high doses of statin	Bococizumab (PF-04950615/RN316) Placebo	Age ≥18 y Atorvastatin, rosuvastatin or simvastatin therapy (stable for ≥45 days) LDL-C ≥100 mg/dL Triglycerides <400 mg/dL	History of a cardiovascular or cerebrovascular event or procedure during the past year Poorly controlled hypertension, type 1 or type 2 diabetes mellitus	Percent change in baseline LDL-C at day 85	141 days	NA
NCT02055976	Completed, no results available	Hypercholesterolemic Japanese subjects	Bococizumab (PF-04950615/RN316) Ezetimibe Placebo	Age ≥20 y LDL-C not controlled by a stable dose of atorvastatin (Population A) Naive to lipid lowering drug and with uncontrolled LDL-C (Population B)	Severe acute or chronic medical or psychiatric condition or laboratory abnormality Pregnant, breastfeeding females Childbearing potential subjects unwilling or unable to use a highly effective method of contraception Administration or prior exposure to PF-04950615 and/or anti-body targeting PCSK9	Percent change from baseline in LDL-C at week 12 and 16	24 wk	NA
Phase 3								
ODYSSEY								
ODYSSEY ALTERNATIVE (NCT01709513)	Ongoing, not recruiting participants, results presented	Primary hypercholesterolemia, moderate, high, or very high cardiovascular risk, statin intolerance	Alirocumab (SAR236553/REGN727) Ezetimibe Placebo	Age ≥18 y Primary hypercholesterolemia, moderate, high, or very high cardiovascular risk, statin intolerance	LDL-C <70 mg/dL and very high CV risk LDL-C <100 mg/dL and high or moderate CV risk 10-year fatal cardiovascular disease risk score <1%	Percent change in baseline LDL-C at 24 wk	24 wk	NA

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Appendix Table 8–Continued

Study (ClinicalTrials.gov Registration Number)*	Study Status	Setting	Intervention	Inclusion Criteria†	Exclusion Criteria†	Primary End Point	Duration	Outcome Assessment Method
ODYSSEY CHOICE I (NCT01926782)	Ongoing, not recruiting participants	Primary hypercholesterolemia	Alirocumab (SAR236553/REGN727) Placebo	Age ≥18 y LDL-C≥70 mg/dL and very high cardiovascular risk or LDL-C ≥100 mg/dL and moderate or high cardiovascular risk	MI, UA, PCI, CABG, uncontrolled cardiac arrhythmia, stroke, TIA, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease 3 mo before randomization History HIV positive test Patients considered as inappropriate or with clinically significant abnormality (judgment of the investigator)	Percent change in baseline LDL-C at 24 wk with or without concomitant statins	56 wk	NA
ODDYSEY CHOICE II (NCT02023879)	Ongoing, not recruiting participants	Primary hypercholesterolemia without statin therapy	Alirocumab (SAR236553/REGN727) Placebo	Primary hypercholesterolemia not adequately controlled with non statin lipid modifying therapy or diet	LDL-C <70 mg/dL and very high cardiovascular risk statin intolerant patients LDL-C <100 mg/dL and high or moderate cardiovascular risk patients LDL-C ≥160 mg/dL if receiving diet only or a non-statin lipid modifying therapy	Percent change in baseline LDL-C at week 24	24 wk, optional open-label treatment	NA
ODYSSEY COMBO I (NCT01644175)	Completed, results published	Hypercholesterolemia, high cardiovascular risk ongoing stable maximally tolerated daily statin therapy with or without other lipid-modifying therapy	Alirocumab (SAR236553/REGN727) Placebo (baseline statin ± lipid-modifying therapy)	Age ≥18 y Not adequate control with maximally tolerated daily statin therapy with or without other lipid-modifying therapy Patients with heterozygous familial hypercholesterolemia with established CHD or CHD risk equivalents	Patients without established CHD or CHD risk equivalents LDL-C <70 mg/dL and history of documented CVD LDL-C <100 mg/dL and without history CVD Triglycerides >400 mg/dL No stable dose of lipid-modifying therapy (for ≥4weeks) and/or fenofibrate (for ≥6weeks)	Percent change in LDL-C at week 24 From a mixed-effect model including all LDL-C values collected up to week 52	52 wk	NA
ODYSSEY COMBO II (NCT01644188)	Completed, results presented	Hypercholesterolemia, high cardiovascular risk ongoing stable maximally tolerated daily statin therapy	Alirocumab (SAR236553/REGN727) Ezetimibe baseline statin)	Age ≥18 y Not adequate control with maximally tolerated daily statin therapy Patients with heterozygous familial hypercholesterolemia with established CHD or CHD risk equivalents	Patients without established CHD or CHD risk equivalents LDL-C <70 mg/dL and history of documented CVD LDL-C <100 mg/dL and without history CVD Triglycerides >400 mg/dL	Percent change in LDL-C at week 24 From a mixed-effect model including all LDL-C values collected up to week 52	104 wk	NA
ODYSSEY FH I (NCT01623115)	Completed, results presented	Heterozygous familial hypercholesterolemia with ongoing not sufficient lipid modifying therapy	Alirocumab (SAR236553/REGN727) Placebo	Age ≥18 y Not adequate control with lipid-modifying therapy Patients with heterozygous familial hypercholesterolemia	LDL-C <70 mg/dL and CVD LDL-C <100 mg/dL and without CVD Triglycerides >400 mg/dL History of homozygous familial hypercholesterolemia	Percent change in baseline LDL-C at week 24	24 wk	NA
ODYSSEY FH II (NCT01709500)	Completed, results presented	Heterozygous familial hypercholesterolemia with ongoing not sufficient lipid modifying therapy	Alirocumab (SAR236553/REGN727) Placebo (baseline atorvastatin, simvastatin or rosuvastatin)	Age ≥18 y Not adequate control with lipid-modifying therapy Patients with heterozygous familial hypercholesterolemia	LDL-C <70 mg/dL and CVD LDL-C <100 mg/dL and without CVD Triglycerides >400 mg/dL History of homozygous familial hypercholesterolemia	Percent change in baseline LDL-C at week 24	24 wk	NA
ODYSSEY HIGH FH (NCT01617655)	Completed, results presented	Heterozygous familial hypercholesterolemia with ongoing not sufficient lipid modifying therapy	Alirocumab (SAR236553/REGN727) Placebo	Age ≥18 y Not adequate control with lipid-modifying therapy Patients with heterozygous familial hypercholesterolemia	LDL-C <160 mg/dL Triglycerides >400 mg/dL History of homozygous familial hypercholesterolemia	Percent change in LDL-C at week 24 From a mixed-effect model including all LDL-C values collected up to week 52	52-78 wk	NA
ODYSSEY LONG TERM (NCT01507831)	Completed, results presented	Hypercholesterolemia, high cardiovascular risk with ongoing not sufficient lipid modifying therapy	Alirocumab (SAR236553/REGN727) Placebo	Age ≥18 y Not adequate control with lipid-modifying therapy Patients with heterozygous familial hypercholesterolemia with or without established CHD or CHD risk equivalents or Patients with hypercholesterolemia together with established CHD or CHD risk equivalents	LDL-C <70 mg/dL Triglycerides >400 mg/dL	Assessment of safety parameters (adverse events, laboratory data, vital signs, and ECG)	86 wk	MedDRA
ODYSSEY MONO (NCT01644474)	Completed, results published	Hypercholesterolemia	Alirocumab (SAR236553/REGN727) Ezetimibe	Age ≥18 y Patients with hypercholesterolemia	LDL-C <100 mg/dL or >190 mg/dL Triglycerides >400 mg/dL History of homozygous or heterozygous familial hypercholesterolemia	Percent change in baseline LDL-C at week 24	24 wk	MedDRA

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Appendix Table 8–Continued

Study (ClinicalTrials.gov Registration Number)*	Study Status	Setting	Intervention	Inclusion Criteria†	Exclusion Criteria†	Primary End Point	Duration	Outcome Assessment Method
ODYSSEY OLE (NCT01954394)	Recruiting participants	Hypercholesterolemia with ongoing lipid modifying therapy	Alirocumab (SAR236553/ REGN727)	Age ≥18 y Patients with heterozygous familial hypercholesterolemia who have completed one of the four parent studies (ODYSSEY FH I, ODYSSEY FH II, ODYSSEY HIGH FH, and ODYSSEY LONG TERM).	Significant protocol deviation in the parent study Any permanent treatment discontinuation from the parent study	Assessment of safety parameters (adverse events, laboratory data, vital signs)	120 wk	NA
ODYSSEY OPTIONS I (NCT01730040)	Completed, results presented	Hypercholesterolemia, high cardiovascular risk with ongoing lipid modifying therapy	Alirocumab (SAR236553/REGN727) Ezetimibe (baseline atorvastatin or switch to rosuvastatin)	LDL-C ≥70 mg/dL with documented CVD, no adequate control with a daily dose of atorvastatin or LDL-C ≥100 mg/dL at high risk for CVD, no adequate control with a daily dose of atorvastatin	LDL-C >250 mg/dL LDL-C <70 mg/dL and history CVD LDL-C <100 mg/dL and no history of CHD or non-CHD CVD, but with other risk factors Triglycerides >400 mg/dL Homozygous familial hypercholesterolemia Non-atorvastatin statin therapy Ezetimibe therapy No stable dose of lipid modifying treatments	Percent change in baseline LDL-C at week 24	24 wk	NA
ODYSSEY OPTIONS II (NCT01730053)	Completed, results presented	Hypercholesterolemia, high cardiovascular risk with ongoing lipid modifying therapy	Alirocumab (SAR236553/REGN727) Ezetimibe (baseline rosuvastatin)	LDL-C ≥70 mg/dL, no adequate control with a stable daily dose of rosuvastatin and lipid modifying therapy or LDL-C ≥100 mg/dL, no adequate control with a stable daily dose of rosuvastatin and lipid modifying therapy before the screening visit	LDL-C <70 mg/dL and history CVD LDL-C <100 mg/dL and no history of CHD or non-CHD CVD, but with other risk factors Homozygous familial hypercholesterolemia MI, UA leading to hospitalization, PCI, CABG, uncontrolled cardiac arrhythmia, stroke, transient ischemic attack, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease 3 mo before the screening visit Newly diagnosed (3 mo before randomization visit) or poorly controlled diabetes Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins	Percent change in baseline LDL-C at week 24	24 wk	NA
ODYSSEY OUTCOMES (NCT01663402)	Recruiting participants	Post ACS	Alirocumab (SAR236553/REGN727) Placebo	Age ≥40 y ACS event in the past 52 wk LDL-C ≥70mg/dL	Age <40 y ACS event occurring >52 weeks before randomization LDL-C likely to be <70 mg/dL with evidence-based medical and dietary management of dyslipidemia	Time from randomization to first occurrence of one of: CHD death, any non-fatal MI, fatal and non-fatal ischemic stroke, UA requiring hospitalization	64 mo	NA
PROFICIO DESCARTES (NCT01516879)	Completed, results published	Hypercholesterolemia, a wide range of cardiovascular risk	Evolocumab (AMG145) Placebo (with background statin)	LDL-C ≥75 mg/dL and (while on background lipid-lowering therapy): <100 mg/dL (diagnosed CHD or CHD risk equivalent) <130 mg/dL (no diagnosed CHD or CHD risk equivalent) or On maximal background lipid-lowering therapy (atorvastatin 80 mg QD + ezetimibe 10 mg QD) Triglycerides ≤400 mg/dL	NYHA II–IV or LVEF <30% Uncontrolled cardiac arrhythmia or hypertension MI, UA, PCI, CABG or stroke 3 mo before randomization Diabetes mellitus (type 1, poorly controlled type 2)	Percent change from baseline LDL-C	52 wk	MedDRA, v 16.1

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Appendix Table 8–Continued

Study (ClinicalTrials.gov Registration Number)*	Study Status	Setting	Intervention	Inclusion Criteria†	Exclusion Criteria†	Primary End Point	Duration	Outcome Assessment Method
FOURIER (NCT01764633)	Recruiting participants	High CVD risk, effective statin therapy	Evolocumab (AMG145) Placebo	Age 40–85 y History of clinically evident cardiovascular disease at high risk for a recurrent event LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL Triglycerides ≤400 mg/dL	NYHA III or IV, or LVEF <30% Uncontrolled recurrent ventricular tachycardia or hypertension Untreated hyperthyroidism or hypothyroidism Homozygous familial hypercholesterolemia LDL or plasma apheresis	Time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization (whichever occurs first)	5 years	NA
GAUSS-2 (NCT01763905)	Completed, results published	Statin therapy intolerance	Evolocumab (AMG145) Ezetimibe Placebo	Age 18–80 y No statin or low, stable statin dose (for ≥4 wk) History of statin intolerance (at least 2) Patients not at LDL-C goal Triglycerides ≤400 mg/dL	NYHA III or IV Uncontrolled cardiac arrhythmia, hypertension, hypothyroidism or hyperthyroidism Diabetes mellitus (type 1, poorly controlled type 2)	Mean percent change from baseline LDL-C Percent change from baseline LDL-C	12 wk	MedDRA
GAUSS-3 (NCT01984424)	Ongoing, not recruiting participants	Statin therapy intolerance	Evolocumab (AMG145) Ezetimibe Placebo	Age 18– 80 y Subject not at LDL-C goal History of statin intolerance Stable lipid lowering therapy (for ≥4 wk) Triglycerides ≤400 mg/dL	NYHA III or IV Uncontrolled cardiac arrhythmia, hypertension, hypothyroidism or hyperthyroidism Diabetes mellitus (type 1, poorly controlled type 2)	Mean percent change from baseline LDL-C Percent change from baseline LDL-C	B: 24 wk C: 2 y	
GLAGOV (NCT01813422)	Ongoing, not recruiting participants	Coronary artery disease, ongoing lipid lowering therapy and undergoing coronary catheterization	Evolocumab (AMG145) Placebo	Clinical indication for coronary angiography Stable statin therapy, niacin or ezetimibe (for ≥4 wk) or no statin (if intolerant) LDL-C ≥80 mg/dL (with or without additional risk factors), or, LDL-C ≥60-<80 mg/dL (in the presence of one major or three minor risk factors) Evidence of coronary heart disease or prior PCI LAD <50% reduction in lumen diameter by visual estimation Target coronary artery accessible to the IVUS catheter, with ≤50% reduction in lumen diameter within the target segment and naive to coronary procedures	CABG <6 weeks before the qualifying IVUS NYHA III or IV, or LVEF <30% Uncontrolled cardiac arrhythmia or hypertension Known hemorrhagic stroke Triglycerides ≥400 mg/dL Diabetes mellitus (type 1, poorly controlled type 2) Moderate to severe renal dysfunction (eGFR <30 mL/min/1.73m^2)	Nominal change in PAV from baseline, as determined by IVUS	78 wk	NA
LAPLACE-2 (NCT01763866)	Completed, results published	CVD risk, ongoing statin therapy	Evolocumab (AMG145) Ezetimibe Placebo (with background statin)	Age 18–80 y No statin therapy and LDL-C ≥150 mg/dL Non-intensive statin therapy and LDL-C ≥100 mg/dL Intensive statin therapy and LDL-C ≥80 mg/dL Triglycerides ≤400 mg/dL	Statin intolerance NYHA III or IV Uncontrolled cardiac arrhythmia, hypertension, hypothyroidism or hyperthyroidism Diabetes mellitus (type 1, poorly controlled type 2)	Mean percent change from baseline LDL-C Percent change from baseline LDL-C	12 wk	MedDRA, v 16.1
MENDEL-2 (NCT01763827)	Completed, results published	Hypercholesterolemia, no statin therapy	Evolocumab (AMG145) Ezetimibe Placebo	Age 18– 80 y NCEP ATP III Framingham risk score ≤10% LDL-C ≥100 mg/dL and <190mg/dL Triglycerides ≤400 mg/dL	History of coronary heart disease NYHA III or IV Uncontrolled cardiac arrhythmia, hypertension, hypothyroidism or hyperthyroidism Diabetes mellitus (type 1, poorly controlled type 2)	Mean percent change from baseline LDL-C Percent change from baseline LDL-C	12 wk	MedDRA
OSLER-1 (NCT01439880)	Ongoing, not recruiting participants, results published	Hypercholesterolemia	Evolocumab (AMG145) with standard of care Standard of care	Age 18–75 y Completion of qualifying evolocumab (AMG145) parent study protocol	IP discontinuation from parent study due to TE-SAE Unstable medical condition (investigator's judgment) Sensitivity to any of the administered products Current enrollment in another investigational device or drug study	Incidence of treatment-emergent adverse events at approximately 1 y	52 wk	MedDRA
OSLER-2 (NCT01854918)	Recruiting participants, results published	Hyperlipidemia and mixed dyslipidemia, completion of qualifying evolocumab parent study	Evolocumab (AMG145) Standard of care	Complete a qualifying evolocumab (AMG145) parent study	IP discontinuation from parent study due to TE-SAE Unstable medical condition (investigator's judgment) Sensitivity to any of the administered products Current enrollment in another investigational device or drug study	Incidence of adverse events	104 wk	NA

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Appendix Table 8—Continued

Study (ClinicalTrials.gov Registration Number)*	Study Status	Setting	Intervention	Inclusion Criteria†	Exclusion Criteria†	Primary End Point	Duration	Outcome Assessment Method
RUTHERFORD-2 (NCT01763918)	Completed, results published	Heterozygous familial hypercholesterolemia	Evolocumab (AMG145) Placebo	Age 18– 80 y Diagnosis of heterozygous familial hypercholesterolemia Stable dose of an approved statin and lipid regulating medication LDL-C ≥100 mg/dL Triglycerides ≤400 mg/dL	Homozygous familial hypercholesterolemia LDL or plasma apheresis NYHA III or IV Uncontrolled cardiac arrhythmia, hypertension, hypothyroidism or hyperthyroidism Diabetes mellitus (type 1, poorly controlled type 2)	Mean percent change from baseline LDL-C Percent change from baseline LDL-C	12 wk	MedDRA, v 16.1
TAUSSIG‡ (NCT01624142)	Recruiting participants	Genetic causes of high LDL-C (e.g., mutations in LDL receptor or PCSK9)	Evolocumab (AMG145)	Participation in a qualifying parent protocol *or* Diagnosis of familial hypercholesterolemia 12–80 y of age Stable low-fat diet and lipid-lowering therapies (for ≥4 wk) LDL-C ≥130 mg/dL (no diagnosed CHD/CHD risk equivalent) *or* LDL-C ≥100 mg/dL (diagnosed CHD or CHD risk equivalent) *or* Apheresis patients Triglycerides <400 mg/dL Bodyweight of ≥40 kg (for <18 y of age)	NYHA III or IV, or LVEF <30% MI, UA, PCI, CABG or stroke within 3 mo of screening Planned cardiac surgery or revascularization Uncontrolled cardiac arrhythmia or hypertension	Incidence of treatment emergent adverse events	5 years	NA
TESLA‡ (NCT01588496)	Completed, results published	Homozygous familial hypercholesterolemia	Evolocumab (AMG145) Placebo	Age 12–80 y Diagnosis of homozygous familial hypercholesterolemia Stable lipid-lowering therapies (for ≥4 wk) LDL-C ≥130 mg/dL Triglycerides ≤400 mg/dL Body weight ≥40 kg	LDL or plasma apheresis within 8 weeks prerandomization NYHA III or IV, or LVEF <30% MI, UA, PCI, CABG or stroke within 3 mo of randomization Planned cardiac surgery or revascularization Uncontrolled cardiac arrhythmia or hypertension	Percent change from baseline LDL-C at 12 wk	12 wk	MedDRA, v 16.1
YUKAWA-2 (NCT01953328)	Completed, no results available	Japanese patients at high risk for CVD who are on statin therapy	Evolocumab (AMG145) Statin Placebo	Japanese adult, age 20–85 y Stable statin dose (for ≥4 wk) LDL-C ≥100 mg/dL Triglycerides ≤400 mg/dL High risk for cardiovascular events	NYHA III or IV Uncontrolled cardiac arrhythmia, hypertension, hypothyroidism or hyperthyroidism Diabetes mellitus (type 1, poorly controlled type 2)	Percent change from baseline LDL-C at 12 wk	12 wk	NA
SPIRE								
SPIRE-1 (NCT01975376)	Recruiting participants	High risk, hypercholesterolemic subjects on lipid lowering treatment	Bococizumab (PF-04950615/ RN316) Placebo	Age ≥18 y Background lipid lowering treatment At high risk for a CV event LDL-C ≥70 mg/dL and <100 mg/dL Non–HDL-C ≥100 mg/dL and <130 mg/dL	LDL-C <70 mg/dL or ≥100 mg/dL Non–HDL-C <100 mg/dL or ≥130 mg/dL Planned PCI, CABG or other arterial revascularization NYHA IV CHF or LVEF <25% by cardiac imaging Chronic renal insufficiency with creatinine clearance of <30 mL/min/1.73m^2 or with end state renal disease on dialysis History of hemorrhagic stroke Prior exposure to PCSK9 inhibitor	Major cardiovascular event, up to month 60	60 mo	NA
SPIRE-2 (NCT01975389)	Recruiting participants	High risk, hypercholesterolemic subjects on lipid lowering treatment	Bococizumab (PF-04950615/ RN316) Placebo	Age ≥18 y Background lipid lowering treatment At high risk for a CV event LDL-C ≥100 mg/dL Non–HDL-C ≥130 mg/dL	LDL-C <100 mg/dL Non–HDL-C <130 mg/dL Planned PCI, CABG or other arterial revascularization NYHA IV CHF or LVEF <25% by cardiac imaging Chronic renal insufficiency with creatinine clearance of <30 mL/min/1.73m^2 or with end state renal disease on dialysis History of hemorrhagic stroke Prior exposure to PCSK9 inhibitor	Major cardiovascular event, up to month 60	60 mo	NA
SPIRE-LDL (NCT01968967)	Recruiting participants	Subjects with hyperlipidemia or mixed dyslipidemia at risk of cardiovascular events	Bococizumab (PF-04950615/ RN316) Placebo	Age ≥18 y Statin treatment LDL-C >70 mg/dL Triglyceride ≤400 mg/dL High or very high risk of incurring a cardiovascular event	Pregnant or breastfeeding females Cardiovascular or cerebrovascular event of procedures during the past 30 days NYHA IV CHF Poorly controlled hypertension	Percent change from baseline LDL-C at 12 wk	52 wk	NA
SPIRE-HR (NCT01968954)	Recruiting participants	Subjects with hyperlipidemia or mixed dyslipidemia at risk of cardiovascular events	Bococizumab (PF-04950615/ RN316) Placebo	Age ≥18 y Statin treatment LDL-C >70 mg/dL Triglyceride ≤400 mg/dL High or very high risk of incurring a cardiovascular event	Pregnant or breastfeeding females Cardiovascular or cerebrovascular event of procedures during the past 30 days NYHA IV CHF Poorly controlled hypertension	Percent change from baseline LDL-C at 12 wk	52 wk	NA

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Appendix Table 8–Continued

Study (ClinicalTrials.gov Registration Number)*	Study Status	Setting	Intervention	Inclusion Criteria†	Exclusion Criteria†	Primary End Point	Duration	Outcome Assessment Method
SPIRE-LL (NCT02100514)	Recruiting participants	Subjects with primary hyperlipidemia or mixed dyslipidemia at risk of cardiovascular events	Bococizumab (PF-04950615/ RN316) Placebo	Age ≥18 y Statin treatment LDL-C ≥100 mg/dL Triglyceride ≤400 mg/dL High or very high risk of incurring a cardiovascular event	Pregnant or breastfeeding females Cardiovascular or cerebrovascular event of procedures during the past 30 days NYHA IV CHF Poorly controlled hypertension	Percent change from baseline LDL-C at 12 wk	52 wk	NA
SPIRE-FH (NCT01968980)	Recruiting participants	Subjects with heterozygous familial hyperlipidemia	Bococizumab (PF-04950615/ RN316) Placebo	Age ≥18 y Statin treatment LDL-C >70 mg/dL Triglyceride ≤400 mg/dL High or very high risk of incurring a cardiovascular event Heterozygous familial hyperlipidemia	Pregnant or breastfeeding females Cardiovascular or cerebrovascular event of procedures during the past 30 days NYHA IV CHF Poorly controlled hypertension	Percent change from baseline LDL-C at 12 wk	52 wk	NA
SPIRE-SI (NCT02135029)	Recruiting participants	Subjects intolerant to statins	Bococizumab (PF-04950615/RN316) Placebo	Age ≥18 y Statin intolerant LDL-C ≥70 mg/dL Triglyceride ≤400 mg/dL	Pregnant or breastfeeding females Cardiovascular or cerebrovascular event of procedures during the past 90 days Severe or life-threatening adverse events with past use of statins Poorly controlled hypertension	Percent change from baseline LDL-C at 12 wk	24 wk	NA

ACS = acute coronary syndrome; Apo B = apolipoprotein B; ATP = Adult Treatment Panel; CABG = coronary artery bypass graft; CHD = coronary heart disease; CHF = congestive heart failure; CV = cardiovascular; CVD = cardiovascular disease; ECG = electrocardiography; eGFR = estimated glomerular filtration rate; GOFm = gain of function mutation; HDL-C = high-density lipoprotein cholesterol; IP = Investigational Product; IVUS = intravenous ultrasonography; LAD = left anterior descending; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LOFm = loss of function mutation; LVEF = left ventricular ejection fraction; MedDRA = Medical Dictionary for Regulatory Activities; MI = myocardial infarction; NA = not applicable; NCEP = National Cholesterol Education Program; NYHA = New York Heart Association; PAV = percent atheroma volume; PCI = percutaneous coronary intervention; QTcF = QT interval calculated by using Fridericia's formula; TE-SAE = treatment-emergent serious adverse events; TIA = transient ischemic attach; UA = unstable angina.

* See the legend for **Appendix Table 1** for abbreviation expansions.

† At screening or baseline visit; given lipid parameters are fasting measures.

‡ Phase 2/3 studies.