Effect of PCSK9 Inhibitors on Clinical Outcomes in Patients With Hypercholesterolemia: A Meta-Analysis of 35 Randomized Controlled Trials

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Background—We sought to examine the efficacy and safety of 2 PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors: alirocumab and evolocumab.

Methods and Results—We performed a systematic review and meta-analysis of randomized controlled trials comparing treatment with and without PCSK9 inhibitor therapy; 35 randomized controlled trials comprising 45 539 patients (mean follow-up: 85.5 weeks) were included. Mean age was 61.0±2.8 years, and mean baseline low-density lipoprotein cholesterol was 106±22 mg/dL. Compared with no PCSK9 inhibitor therapy, treatment with a PCSK9 inhibitor was associated with a lower rate of myocardial infarction (2.3% versus 3.6%; odds ratio [OR]: 0.72 [95% confidence interval (CI), 0.64–0.81]; P<0.001), stroke (1.0% versus 1.4%; OR: 0.80 [95% CI, 0.67–0.96]; P=0.02), and coronary revascularization (4.2% versus 5.8%; OR: 0.78 [95% CI, 0.71–0.86]; P<0.001). Overall, no significant change was observed in all-cause mortality (OR: 0.71 [95% CI, 0.47–1.09]; P=0.12) or cardiovascular mortality (OR: 1.01 [95% CI, 0.85–1.19]; P=0.95). A significant association was observed between higher baseline low-density lipoprotein cholesterol and benefit in all-cause mortality (P=0.038). No significant change was observed in neurocognitive adverse events (OR: 1.12 [95% CI, 0.88–1.42]; P=0.37), myalgia (OR: 0.95 [95% CI, 0.75–1.20]; P=0.65), new onset or worsening of preexisting diabetes mellitus (OR: 1.05 [95% CI, 0.95–1.17]; P=0.32), and increase in levels of creatine kinase (OR: 0.84 [95% CI, 0.70–1.01]; P=0.06) or alanine or aspartate aminotransferase (OR: 0.96 [95% CI, 0.82–1.12]; P=0.61).

Conclusions—Treatment with a PCSK9 inhibitor is well tolerated and improves cardiovascular outcomes. Although no overall benefit was noted in all-cause or cardiovascular mortality, such benefit may be achievable in patients with higher baseline low-density lipoprotein cholesterol. (J Am Heart Assoc. 2017;6:e006910. DOI: 10.1161/JAHA.117.006910.)

Key Words: alirocumab • evolocumab • hyperlipidemia • outcome • PCSK9

L ipid-lowering therapy with statins is highly beneficial for prevention of secondary and high-risk primary atherosclerotic cardiovascular disease (ASCVD). Nevertheless, some patients cannot tolerate recommended statin doses1; a high proportion of patients do not achieve adequate reduction of low-density lipoprotein cholesterol (LDL-C), despite high-intensity statin therapy2; and even patients who achieve guideline recommended reductions may have high residual ASCVD risk.3 Consequently, alternative therapies designed to lower LDL-C and improve outcomes are needed. Improvements in cardiovascular outcomes were observed recently with combination treatment with ezetimibe; however, these improvements were modest, and outcome data on monotherapy with ezetimibe are limited.4 The PCSK9

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Accompanying Tables S1 through S6 and Figures S1 through S32 are available at http://jaha.ahajournals.org/content/6/12/e006910/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors appear safe and are associated with dramatically reduced atherogenic lipid fraction levels and lower incidence of myocardial infarction, stroke, and coronary revascularization.
- Despite favorable early indications from lipid-lowering trials, the available clinical data do not demonstrate a mortality benefit with PCSK9 inhibitors.

What Are the Clinical Implications?

- Whether patient subgroups exist that can derive a significant mortality benefit from PCSK9 inhibitor treatment (eg, patients intolerant to statins or with familial hypercholesterolemia) needs to be further evaluated in randomized controlled trials.

Methods

We conducted a systematic review of the literature and meta-analysis of RCTs according to established methods and standards recommended by the Cochrane Collaboration and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

Data Sources and Searches

We searched PubMed/Medline, Embase, CENTRAL (Cochrane Central Register of Controlled Trials), and ClinicalTrials.gov up to March 18, 2017. The following keywords were used, with the use of wildcard characters to account for variations in spelling and plurals: PCSK9 antibody/inhibitor, evolocumab, alirocumab, bococizumab, AMG145, REGN727, SAR236553, RN 316, and PF-04950615. Citations were screened at the title and abstract levels and retrieved for full-text evaluation if they were considered potentially relevant.

Statistical Analyses

Efficacy outcomes were analyzed according to the intention-to-treat principle. For dichotomous data (cardiovascular and

Study Selection

We included phase 2 or 3 RCTs comparing treatment with and without PCSK9 inhibitors in adults with hypercholesterolemia and reporting clinical outcomes. No restriction on language, follow-up, or study size was applied. For phase 2 studies, only dosing regimens that were also tested in phase 3 studies were included. During the study-selection phase of the trial, the phase 3 clinical development program for the PCSK9 inhibitor bococizumab (SPIRE [Studies of PCSK9 Inhibition and the Reduction of Vascular Events]) was discontinued without plans for future marketing of this drug; therefore, 3 published trials of bococizumab were not included in our quantitative synthesis, so as to maintain the clinical relevance of our findings.

Clinical end points abstracted include all-cause and cardiovascular mortality, myocardial infarction (MI), unstable angina requiring hospitalization, congestive heart failure exacerbation requiring hospitalization, stroke, coronary revascularization, neurocognitive adverse events, new onset or worsening of preexisting diabetes mellitus, increase in serum creatine kinase level (an increase of ≥3 times the upper limit of normal was preferentially abstracted), increase in serum alanine or aspartate aminotransferase levels (an increase in alanine aminotransferase >3 times the upper limit of normal was preferentially abstracted), myalgia, and treatment-emergent serious adverse events. Lipid end points abstracted were percentage changes from baseline in LDL-C, high-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and lipoprotein(a). LDL-C levels calculated using the Friedewald formula were preferentially abstracted.

Data Extraction and Quality Assessment

Two investigators (A.K. and B.A.D.) independently abstracted data by using prespecified data collection forms. In case of discrepancies, consensus was achieved with the help of a third investigator (E.S.B.). Intensive background statin therapy was defined as daily use of atorvastatin ≥40 mg, rosuvastatin ≥20 mg, simvastatin ≥80 mg, or any statin plus ezetimibe. For studies in Japanese populations, a modified definition of intensive background statin therapy was used (atorvastatin ≥10 mg, pitavastatin ≥2 mg, rosuvastatin ≥5 mg simvastatin ≥20 mg, lovastatin ≥40 mg, fluvastatin ≥80 mg, pravastatin ≥40 mg, or any statin plus ezetimibe). Studies were classified as familial hypercholesterolemia (FH) studies if inclusion criteria required diagnosis of FH by genotyping or clinical criteria. The potential risk of bias of the RCTs was assessed using the Cochrane Collaboration guidelines.
safety outcomes), odds ratios (ORs) pooled according to the Mantel-Haenszel method were used as a summary statistic; for continuous data (lipid outcomes), mean difference (MD) of percentage change from baseline was used. Standard deviations were calculated from the standard error or confidence interval (CI) if not reported. Mean baseline LDL-C was estimated from median and interquartile range if not reported. Heterogeneity and inconsistency were assessed by using the Cochran Q test and I² statistic. Because included studies drew samples from clinically different populations, a random-effects model was selected for the primary analysis. Both random- and fixed-effects models were computed and shown as part of the sensitivity analysis. Publication bias was examined by means of funnel plots and the Egger test.

Primary stratification of the analyses was by type of PCSK9 inhibitor for cardiovascular and safety outcomes (alirocumab versus evolocumab) and by control for efficacy outcomes (placebo versus ezetimibe). Additional study-level subgroup analyses by trial population (FH versus non-FH/mixed) and background statin (on stable statin treatment versus statin intolerant/PCSK9 inhibitor monotherapy) were performed. Random-effects metagression was used to estimate the effect of baseline LDL-C and treatment difference in percentage of LDL-C change from baseline on clinical outcomes.

A 2-tailed P value of <0.05 was considered statistically significant. All analyses were performed using Review Manager version 5.3 (RevMan; Cochrane Collaboration) and Comprehensive Meta-Analysis Software version 3.3 (Biostat, Inc).

Results

Study Selection and Patient Population

The PRISMA study identification flowchart for the present analysis is shown in Figure S1. A total of 138 study arms from 35 studies were analyzed, comprising 45 539 patients (Table S1).5,11–14,16–43 Airocumab was used in 18 studies (28 treatment arms), and evolocumab was used in 17 studies (39 treatment arms; Figure 1); placebo was the most common control used (52 control arms), with ezetimibe used in 17 arms, and standard therapy in 2 arms. Eight studies were of an exclusively FH population, and 5 studies included only patients intolerant to statins. Mean treatment duration in the randomized population up to the time of reporting was 85.5 weeks (range: 8–113 weeks).

Baseline patient characteristics for the study arms included are shown in Table S2. Mean age was 61.0±2.8 years, and 67.6% of participants were men; the mean baseline LDL-C was 106.0±22.3 mg/dL (2.7±0.6 mmol/L). The majority of study participants (91.8%) were on stable statin therapy at baseline, and 58.4% were on an intensive statin regimen. From 45 539 total patients in the randomized population, safety data were
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All-Cause Mortality
Thirty-five RCTs (45 503 participants) were included in the analysis of all-cause mortality (Figure 2). Compared with no treatment with a PCSK9 inhibitor, treatment with a PCSK9 inhibitor was not associated with a statistically significant change in mortality (crude rate, 1.6% versus 2.2%; OR: 0.71 [95% CI, 0.54–1.0]; P=0.08, I²=0%, heterogeneity P=0.74). Random effects metaregression showed a significant association between baseline LDL-C and all-cause mortality benefit (P=0.038; Figure 3).

Cardiovascular Mortality
Thirty-four RCTs (44 701 participants) were included in the analysis of cardiovascular mortality (Figure 4). Compared with no treatment with a PCSK9 inhibitor, treatment with a PCSK9 inhibitor was associated with a statistically significant change in cardiovascular mortality (crude rate, 1.1% versus 1.3%; OR: 1.01 [95% CI, 0.85–1.19]; P=0.95, I²=0%, heterogeneity P=0.74).

Myocardial Infarction
Twenty-three RCTs (41 932 participants) were included in the analysis of MI (Figure 5). Compared with no treatment with a PCSK9 inhibitor, treatment with a PCSK9 inhibitor was associated with a statistically significant reduction in MI (crude rate, 2.3% versus 3.6%; OR: 0.72 [95% CI, 0.64–0.81]; P<0.001, I²=0%, heterogeneity P=0.77).

Stroke
Twenty-three RCTs (42 748 participants) were included in the analysis of stroke (Figure 6). Compared with no treatment with a PCSK9 inhibitor, treatment with a PCSK9 inhibitor was associated with a statistically significant reduction in stroke (crude rate, 1.0% versus 1.4; OR: 0.80 [95% CI, 0.67–0.96]; P=0.02, I²=0%, heterogeneity P=0.92).

Coronary Revascularization
Twenty-two RCTs (40 542 participants) were included in the analysis of coronary revascularization (Figure 7). Compared with no treatment with a PCSK9 inhibitor, treatment with a PCSK9 inhibitor was associated with a statistically significant reduction in coronary revascularization (crude rate, 4.2% versus 5.8%; OR: 0.78 [95% CI, 0.71–0.86]; P<0.001, I²=0%, heterogeneity P=0.57). Random-effects metaregression showed a significant association between higher treatment difference versus control in percentage of LDL-C reduction from baseline and benefit in coronary revascularization (P=0.012; Table S3).

Unstable Angina
Twenty-one RCTs (41 036 participants) were included in the analysis of unstable angina requiring hospitalization (Figure S3). Compared with no treatment with a PCSK9 inhibitor, treatment with a PCSK9 inhibitor was not associated with a statistically significant change in unstable angina episodes requiring hospitalization (crude rate, 1.1% versus 1.3%; OR: 0.97 [95% CI, 0.81–1.16]; P=0.77, I²=0%, heterogeneity P=0.90).

Congestive Heart Failure Exacerbation
Twenty-three RCTs (42 151 participants) were included in the analysis of congestive heart failure exacerbations requiring hospitalization (Figure S4). Compared with no treatment with a PCSK9 inhibitor, treatment with a PCSK9 inhibitor was not associated with a statistically significant change in congestive heart failure exacerbations requiring hospitalization (crude rate, 1.8% versus 2.2%; OR: 0.98 [95% CI, 0.86–1.13]; P=0.79, I²=0%, heterogeneity P=0.95).

Neurocognitive Adverse Events
Twenty-one RCTs (42 668 participants) were included in the analysis of neurocognitive adverse events (Figure 8). Compared with no treatment with a PCSK9 inhibitor, treatment with a PCSK9 inhibitor was not associated with a statistically significant change in neurocognitive adverse events (crude rate, 1.2% versus 1.2%; OR: 1.12 [95% CI, 0.88–1.42]; P=0.37, I²=3%, heterogeneity P=0.42).

Diabetes Mellitus
Fifteen RCTs (27 905 participants) were included in the analysis of new onset or worsening of preexisting diabetes mellitus (Figure S5). Compared with no treatment with a PCSK9 inhibitor, treatment with a PCSK9 inhibitor was not associated with a statistically significant change in new onset or worsening of preexisting diabetes mellitus (crude rate, 5.6% versus 5.9%; OR: 1.05 [95% CI, 0.95–1.17]; P=0.32, I²=0%, heterogeneity P=0.86).

Other Safety End Points
Compared with no treatment with a PCSK9 inhibitor, treatment with a PCSK9 inhibitor was associated with a trend of
fewer increases in creatine kinase (OR: 0.84 [95% CI, 0.70–1.01]; \( P=0.06 \)) and was not associated with a statistically significant change in the rates of myalgia (OR: 0.95 [95% CI, 0.75–1.20]; \( P=0.65 \)), increase in alanine or aspartate aminotransferase (OR: 0.96 [95% CI, 0.82–1.12]; \( P=0.61 \)), or treatment-emergent serious adverse events (OR: 0.99 [95% CI, 0.95–1.05]; \( P=0.84 \); Figures S6 through S9).

**Lipid End Points**

Compared with no treatment with a PCSK9 inhibitor, treatment with a PCSK9 inhibitor was associated with a significant percentage of reduction in LDL-C from baseline (MD: −54.77% [95% CI, −58.27% to −51.27%]; \( P<0.001 \); Figure S10). LDL-C reduction was significantly greater in
study arms controlled by placebo compared with those controlled by ezetimibe (MD: −60.91 [95% CI, −63.24 to −58.58] versus MD: −31.32% [95% CI, −34.83 to −27.81]; P<0.001).

Compared with no treatment with a PCSK9 inhibitor, treatment with a PCSK9 inhibitor was also associated with favorable changes in high-density lipoprotein cholesterol (MD: 6.85 [95% CI, 6.10–7.60]; P<0.001), total cholesterol (MD: −34.95 [95% CI, −37.53 to −32.37]; P<0.001), lipoprotein(a) (MD: −26.45 [95% CI, −28.88 to −24.03]; P<0.001), and apolipoprotein B (MD: −45.50 [95% CI, −48.35 to −42.64]; P<0.001; Figures S11 through S14).

Unless specified earlier, other subgroup and sensitivity analyses were consistent with the primary results (Tables S3 through S5). Visual inspection of funnel plots (Figures S15 through S32) and the Egger test did not indicate publication bias (Table S6).

Discussion
The main findings of this meta-analysis are that, compared with no PCSK9 inhibitor use, treatment with PCSK9 inhibitors (1) is associated with a statistically significant reduction in MI, stroke, and coronary revascularization; (2) is not significantly associated with all-cause or cardiovascular mortality, neurocognitive adverse events, incident or worsening of preexisting diabetes mellitus, creatine kinase increase, myalgia, increase in alanine or aspartate aminotransferase, or treatment-emergent serious adverse events; and (3) is associated with consistent and favorable changes in lipid fractions.

In 2006, Cohen et al published initial reports linking loss-of-function genetic variants impairing the PCSK9 protein activity to lifelong reductions in LDL-C and resultant protection against ASCVD.44 In contrast, gain-of-function mutations of PCSK9 resulted in a phenotype similar to FH.45 These findings sparked the development of antibodies against PCSK9, 2 of which (alirocumab and evolocumab) are currently commercially available.

Until recently, the highest quality of evidence surrounding alirocumab and evolocumab stemmed from phase 2 and 3 lipid-lowering trials and their meta-analyses.46,47 The encouraging results led to the 2015 US Food and Drug Administration fast-track approval for use of PCSK9 inhibitors as adjuncts to diet and maximally tolerated statin for patients with FH and clinical ASCVD. In 2016, the American College of Cardiology released an expert consensus decision pathway regarding the role of nonstatin therapies for the treatment of hypercholesterolemia,48 according to which treatment with PCSK9 inhibitors should be considered (as first or second line) for patients with clinical ASCVD and patients with baseline LDL-C ≥190 mg/dL not due to secondary modifiable causes who have not achieved an optimal LDL-C reduction on a maximally tolerated statin therapy (<50% or <70–100 mg/dL).

The recently released results of the FOURIER trial, a cardiovascular outcomes study that randomized 27 564 adults aged 40 to 85 years with clinical ASCVD and baseline LDL-C >70 mg/dL on background statin therapy to evolocumab or placebo, demonstrated a 15% reduction in the primary end point of cardiovascular death, MI, stroke, unstable angina,
or coronary revascularization and a 20% reduction in the key secondary end point of cardiovascular death, MI, or stroke. However, no benefit was observed in all-cause mortality ($P=0.54$) or cardiovascular mortality ($P=0.62$).5

These findings are corroborated by our meta-analysis of 45,539 participants of all available phase 2 and 3 trials of evolocumab and alirocumab. Importantly, although we found significant relative improvement in the risk of MI, stroke, and coronary revascularization, the absolute risk reduction was relatively small, especially for stroke (absolute risk reduction: 0.4%; number needed to treat: 255). No statistically significant differences were identified in study-level subgroup analyses including patients on or off treatment with a background statin and patients with FH. In contrast with a

Figure 4. Cardiovascular mortality. Forrest plot showing the odds ratio for cardiovascular mortality with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (PCSK9i) compared with no PCSK9i. The pooled odds ratio was calculated with random effects according to the Mantel-Haenszel (M-H) method. Marker size is proportional to the study weight. CI indicates confidence interval.

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SYSTEMATIC REVIEW AND META-ANALYSIS
previous meta-analysis from lipid-lowering trials,47 we found no benefit in all-cause mortality with PCSK9 inhibitor therapy. This finding may be attributable to the fact that our analysis included 2 large trials of populations with a baseline LDL-C of <100 mg/dL,5,20 contributing to an overall baseline LDL-C of 106 mg/dL in our pooled sample. Taken in the context of this relatively low baseline LDL-C, this lack of benefit in mortality is concordant with prior studies examining further LDL-C reduction with high-intensity statins 49,50 or ezetimibe. 4 Notably, using random-effects metaregression at the study level, we found that there was a significant association between higher baseline LDL-C levels and all-cause mortality benefit derived. This generates the hypothesis that reduction in all-cause mortality may be possible with PCSK9 inhibitors in patients with higher baseline LDL-C, such as patients with FH or patients with high LDL-C levels who are intolerant to statins. Further research is needed to determine whether there is an LDL-C cutoff at which PCSK9 inhibitors are associated with a mortality benefit.

Our analysis revealed a statistically significant reduction in the odds for coronary revascularization in the evolocumab pool compared with alirocumab. However, this finding should be interpreted in the context of lack of a powered cardiovascular outcome trial for alirocumab, resulting in a much smaller number of coronary revascularization events compared with evolocumab. ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) is an ongoing cardiovascular outcome trial of 18 000 patients investigating alirocumab every 2 weeks versus placebo in patients with

![Table](image)

**Figure 5.** Myocardial infarction. Forrest plot showing the odds ratio for myocardial infarction with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (PCSK9i) compared with no PCSK9i. The pooled odds ratio was calculated with random effects according to the Mantel-Haenszel (M-H) method. Marker size is proportional to the study weight. CI indicates confidence interval.
hospitalization caused by a recent acute coronary syndrome and is expected to clarify the long-term efficacy and safety of alirocumab and any potential differences between the 2 PCSK9 inhibitors.51

In addition to the high cost and uncertainty about the exact benefits in terms of cardiovascular outcomes, other obstacles to expanded use of PCSK9 inhibitors include safety concerns about neurocognitive adverse events and incident diabetes mellitus. De novo glial synthesis of cholesterol in the brain is postulated to be important for synapse formation and function; observational studies and RCTs of statins have been inconsistent in their demonstration of an association between statin utilization and impaired neurocognitive function.52–55 PCSK9 inhibitors are not known to inhibit de novo cholesterol synthesis or to cross the blood–brain barrier; nevertheless, imbalances in neurocognitive side effects between PCSK9 inhibitors and control groups were detected in OSLER (Open-Label Study of Long-Term Evaluation Against LDL-C) 1 and 2 (pooled rate: 0.9% versus 0.3%) and in ODYSSEY LONG-TERM (1.2% versus 0.5%), as well as 2 large meta-analyses of lipid-lowering trials.46,56 However, these findings were limited by heterogeneity of the examined populations, small numbers of events, and differences in the definition and assessment of neurocognitive events. Neurocognitive adverse events were recorded in FOURIER, with no imbalance shown between treatment and control arms. In addition, EBBINGHAUS (Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects), a dedicated noninferiority neurocognitive substudy of FOURIER, assessed neurocognitive function with formal testing and showed no statistically significant difference between evolocumab and placebo, even in patients with a nadir achieved LDL-C

Figure 6. Stroke. Forrest plot showing the odds ratio for stroke with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (PCSK9i) compared with no PCSK9i. The pooled odds ratio was calculated with random effects according to the Mantel-Haenszel (M-H) method. Marker size is proportional to the study weight. CI indicates confidence interval.

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<25 mg/dL. These findings are corroborated by our meta-analysis, which showed no significant association between PCSK9 inhibitors and neurocognitive adverse events, including in metaregression analysis using baseline LDL-C and treatment difference versus control in percentage of LDL-C reduction from baseline as moderator variables.

Given the dramatic decrease in LDL-C achieved with PCSK9 inhibitors, it has been hypothesized that they may adversely affect glycemic control similarly to statins. Although genetic polymorphism data suggest that polymorphisms of PCSK9 are associated with a similar risk for diabetes mellitus as polymorphisms of HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase) for a given decrease in LDL-C, analysis of PCSK9 inhibitor trials does not support this association. A pooled analysis of 10 phase 3 studies from the ODYSSEY program found no significant association between incident diabetes mellitus or diabetic complications and treatment with alirocumab compared with placebo or ezetimibe. Similarly, no statistically significant effect was identified in the present meta-analysis.

SPIRE was the phase 3 clinical trial program incorporating 8 RCTs investigating bococizumab, a humanized monoclonal antibody against PCSK9. The 2 cardiovascular outcome trials, SPIRE-1 and SPIRE-2, collectively enrolled 16 187 patients with variable baseline lipid-lowering therapy (including patients with statin intolerance) and ASCVD status (including patients in the high-risk, primary prevention setting) before the trial was terminated. Bococizumab showed a propensity for development of antidrug antibodies, which may explain the high individual variability in percentage of change in LDL-C, attenuation in LDL-C reduction over time, and comparatively high rate of injection-site reactions. Because this PCSK9

Figure 7. Coronary revascularization. Forrest plot showing the odds ratio for coronary revascularization with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (PCSK9i) compared with no PCSK9i. The pooled odds ratio was calculated with random effects according to the Mantel-Haenszel (M-H) method. Marker size is proportional to the study weight. CI indicates confidence interval.
inhibitor will not become available for clinical use, we elected
to not include bococizumab trials in our study.

Our meta-analysis has several important limitations. First,
pooling of the data was performed at the study level and not
at the patient level, limiting the potential for subgroup
analyses. In addition, despite the low degree of statistical
heterogeneity detected, inherent methodological heterogene-
ity is present because of the pooling of results from studies of
different populations. Some definitions of outcomes were
nonuniform among various trials.

In conclusion, our comprehensive meta-analysis of 35
RCTs shows that, compared with no PCSK9 inhibitor admin-
istration, treatment with PCSK9 inhibitors results in improve-
ment in cardiovascular outcomes, including MI, stroke, and
coronary revascularization; no statistically significant change
in the rate of adverse events, including neurocognitive
adverse events, and incident or worsening of preexisting
diabetes mellitus; and dramatic reductions in atherogenic lipid
fractions. Although there was no statistically significant
improvement in mortality, metaregression analysis revealed
an association between higher baseline LDL-C and an all-
cause mortality benefit, which needs further evaluation in
RCTs.

Disclosures
Dr Ahmad has received research grants from NIH and
Regeneron (modest); honoraria from Genzyme and Sanofi
(modest); and serves as consultant/advisory board for
Genzyme (modest). Dr Banerjee has received research grants
from Boston Scientific and Merck (significant); honoraria from
Medtronic, Cardiovascular Systems, Inc., and Gore (signifi-
cant); and has ownership in HygeiaTel and MDCARE Global
(spouse, significant). Dr Brilakis has received research grants

Figure 8. Neurocognitive adverse events. Forrest plot showing the odds ratio for neurocognitive adverse events with PCSK9 (proprotein
convertase subtilisin/kexin type 9) inhibitors (PCSK9i) compared with no PCSK9i. The pooled odds ratio was calculated with random effects
according to the Mantel-Haenszel (M-H) method. Marker size is proportional to the study weight. CI indicates confidence interval.

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from Boston Scientific and InfraRedx (significant); honoraria from Abbott Vascular and GE Healthcare (significant); honoraria from Asahi, Cardinal Health, and Elsevier (modest); serves as consultant/advisory board for Abbott Vascular (modest); and is employed by Medtronic (spouse, significant).

The remaining authors have no disclosures.

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Supplemental Material
| Study     | Year | Phase | Treatment duration, weeks | Investigational drug and dose | Control | Population | Statin | Statin int tolerant | clinicaltrials.gov ID |
|-----------|------|-------|---------------------------|--------------------------------|---------|------------|--------|---------------------|----------------------|
| DESCARTES | 2014 | 3     | 48                        | Evolocumab 420 mg Q4W          | Placebo | HC         | Both   | None                | NCT01516879          |
| FOURIER   | 2017 | 3     | 113                       | Evolocumab 420 mg Q4W/140 mg Q2W | Placebo | HC         | Both   | None                | NCT01764633          |
| GAUSS     | 2012 | 2     | 12                        | Evolocumab 420 mg Q4W ± Ezetimibe 10 mg | Ezetimibe | HC - Statin intolerant | Non-intensive | NCT01375764          |
| GAUSS-2   | 2014 | 3     | 12                        | Evolocumab 420 mg/140 mg Q2W   | Ezetimibe | HC - Statin intolerant | Non-intensive | NCT01763905          |
| GAUSS-3   | 2016 | 3     | 24                        | Evolocumab 420 mg Q4W          | Ezetimibe | HC - Statin intolerant | None          | NCT01984424          |
| GLAGOV    | 2016 | 3     | 76                        | Evolocumab 420 mg Q4W          | Placebo | HC - CAD   | Both   | None                | NCT01813422          |
| LAPLACE-2 | 2014 | 3     | 12                        | Evolocumab 420 mg Q4W/140 mg Q2W | Ezetimibe/ placebo | HC         | Both   | None                | NCT01763866          |
| LAPLACE-TIMI57 | 2012 | 2     | 12                        | Evolocumab 420 mg Q4W/140 mg Q2W | Placebo | HC         | Both   | None                | NCT01380730          |
| McKenney et al. | 2012 | 2     | 12                        | Alirocumab 150 mg Q2W/300 mg Q4W | Placebo | HC         | Both   | None                | NCT01288443          |
| MENDEL    | 2012 | 2     | 12                        | Evolocumab 420 mg Q4W/140 mg Q2W | Ezetimibe/ placebo | HC         | None   | None                | NCT01375777          |
| MENDEL-2  | 2014 | 3     | 12                        | Evolocumab 420 mg Q4W/140 mg Q2W | Ezetimibe/ placebo | HC         | None   | None                | NCT01763827          |
| Study        | Year | Month | Subjects | Intervention | Comparator | Exclusion Criteria | Control Group | NCT Number |
|--------------|------|-------|----------|--------------|------------|-------------------|---------------|------------|
| ODYSSEY      |      |       |          |              |            |                   |               |            |
| ALTERNATIVE  | 2015 | 3     | 24       | Alirocumab 75 mg Q2W with potential up-titration to 150 mg Q2W | Ezetimibe | HC - Statin intolerant | None | NCT01709513 |
| CHOICE I     | 2016 | 3     | 48       | Alirocumab 75 mg Q2W/300 mg Q4W with potential up-titration to 150 mg Q2W | Placebo | HC | Both | NCT01926782 |
| CHOICE II    | 2016 | 3     | 24       | Alirocumab 75 mg Q2W/150 mg Q4W with potential up-titration to 150 mg Q2W | Placebo | HC - Statin intolerant | None | NCT02023879 |
| COMBO I      | 2015 | 3     | 52       | Alirocumab 75 mg Q2W, increased to 150 mg Q2W prn | Placebo | HC | Both | NCT01644175 |
| COMBO II     | 2015 | 3     | 104*     | Alirocumab 75 mg Q2W with potential up-titration to 150 mg Q2W | Ezetimibe | HC | Both | NCT01644188 |
| ESCAPE       | 2016 | 3     | 18       | Alirocumab 150 mg Q2W | Placebo | HeFH | Both | NCT02326220 |
| FH I         | 2015 | 3     | 78       | Alirocumab 75 mg Q2W with potential up-titration to 150 mg Q2W | Placebo | HeFH | Both | NCT01623115 |
| FH II        | 2015 | 3     | 78       | Alirocumab 75 mg Q2W with potential up-titration to 150 mg Q2W | Placebo | HeFH | Both | NCT01709500 |
| Study Description | Years | Weeks | Patients | Treatment 1 | Treatment 2 | Study Design | Timeframe | Clinical Trials Identifier |
|------------------|-------|-------|----------|-------------|-------------|--------------|-----------|----------------------------|
| HIGH FH 19       | 2016  | 3     | 78       | Alirocumab 150mg Q2W | Placebo | HeFH | Both | NCT01617655 |
| JAPAN 20         | 2016  | 3     | 52       | Alirocumab 75mg Q2W with potential up-titration to 150 mg Q2W | Placebo | HC | Both | NCT02107898 |
| LONG TERM 21     | 2015  | 3     | 78       | Alirocumab 150mg Q2W | Placebo | HC | Both | NCT01507831 |
| MONO 22          | 2014  | 3     | 24       | Alirocumab 75mg Q2W with potential up-titration to 150 mg Q2W | Ezetimibe | HC | None | NCT01644474 |
| OPTIONS I 23     | 2015  | 3     | 24       | Alirocumab 75mg Q2W with potential up-titration to 150 mg Q2W | Ezetimibe/double statin | HC | Both | NCT01730040 |
| OPTIONS II 24    | 2015  | 3     | 24       | Alirocumab 75mg Q2W with potential up-titration to 150 mg Q2W | Ezetimibe/double statin | HC | Both | NCT01730053 |
| OSLER 1 and 2 25 | 2015  | OL    | 48       | Evolocumab 420 mg Q4W/140 mg Q2W | Standard therapy | HC | Both | NCT01439880, NCT01854918 |
| Roth et al. 26   | 2012  | 2     | 8        | Alirocumab 150mg Q2W | Placebo | HC | Both | NCT01288469 |
| RUTHERFORD 27    | 2012  | 2     | 12       | Evolocumab 420 mg Q4W | Placebo | HeFH | Both | NCT01375751 |
| RUTHERFORD 2 28  | 2015  | 3     | 12       | Evolocumab 420 mg Q4W/140 mg Q2W | Placebo | HeFH | Both | NCT01763918 |
| Stein et al. 29  | 2012  | 2     | 12       | Alirocumab 150 mg Q2W/300 mg Q4W | Placebo | HeFH | Both | NCT01266876 |
| Teramoto et al. 30 | 2016  | 2     | 12       | Alirocumab 150 mg Q2W | Placebo | HC | Both | NCT01812707 |
| TESLA PART B 31  | 2015  | 3     | 12       | Evolocumab 420 mg Q4W | Placebo | HoFH | Both | NCT01588496 |
| Trial | Year | Duration | Treatment | Comparator | Condition | Design | Identifier |
|-------|------|----------|-----------|------------|-----------|--------|------------|
| YUKAWA 32 | 2014 | 2-12 weeks | Evolocumab 420 mg Q4W/140 mg Q2W | Placebo | HC, Both | NCT01652703 |
| YUKAWA II 33 | 2016 | 3-12 weeks | Evolocumab 420 mg Q4W/140 mg Q2W | Placebo | HC, Both | NCT01953328 |

CAD, coronary artery disease; HC, hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; Q2W, every four weeks; Q4W, every two weeks. * Results reported up to week 52.

Expanded trial names: DESCARTES = Durable Effect of PCSK9 Antibody Compared with Placebo Study; FOURIER = Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; GAUSS = Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects; GLAGOV = Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound; 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; OSLER = Open-Label Study of Long-term Evaluation Against LDL-C; RUTHERFORD = The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder; 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.
Table S2. Baseline patient characteristics

| Study           | Participants, n | Age, years | Male, % | CAD, % | HTN, % | DM2, % | BMI, kg/m² | LDL-C, mean | Statin, % | Intensive statin, % |
|-----------------|-----------------|------------|---------|--------|--------|--------|------------|-------------|-----------|---------------------|
| DESCARTES ¹     | 901             | 55.4       | 47.7%   | 15.1%  | 48.8%  | 12.2%  | 30.2       | 100.3       | 87.7%    | 45.2%               |
| FOURIER²        | 27,654          | 62.5       | 75.4%   | NA     | 80.1%  | 36.6%  | NA         | 93.7†       | 100.0%   | 69.3%               |
| GAUSS ³         | 94              | 61.5       | 35.1%   | 20.2%  | 48.9%  | 11.7%  | 28.1       | 192.3       | 16.0%    | 0.0%                |
| GAUSS-2 ⁴       | 307             | 61.7       | 54.0%   | 29.0%  | 59.0%  | 20.2%  | NA         | 193.0       | 17.9%    | 0.0%                |
| GAUSS-3 ⁵       | 218             | 58.8       | 51.4%   | 31.7%  | 51.4%  | 11.9%  | 28.0       | 219.8       | 0.0%     | 0.0%                |
| GLAGOV ⁶        | 968             | 59.8       | 72.2%   | 100.0% | 83.0%  | 20.9%  | 29.5       | 92.5        | 98.6%    | 58.9%               |
| LAPLACE-2 ⁷     | 1896            | 59.9       | 54.2%   | 22.5%  | NA     | 15.5%  | NA         | 109.1       | 100.0%   | 40.8%               |
| LAPLACE-TIMI57 ⁸| 315             | 62.6       | 45.4%   | 32.1%  | 70.2%  | 16.5%  | 29.4       | 121.8       | 99.2%    | 29.3%               |
| McKenney et al.⁹| 92              | 56.2       | 43.5%   | 5.4%   | 41.3%  | 14.1%  | 28.8       | 128.6       | 100.0%   | NA                  |
| MENDEL¹⁰        | 225             | 51.2       | 36.4%   | 0.0%   | 32.9%  | 0.0%   | 32.8       | 142.3       | 0.0%     | 0.0%                |
| MENDEL-2 ¹¹     | 614             | 53.2       | 31.1%   | 0.0%   | 28.7%  | 0.2%   | NA         | 142.9       | 0.0%     | 0.0%                |
| ODYSSEY         |                 |            |         |        |        |        |            |             |          |                    |
| ALTERNATIVE ¹²  | 251             | 63.5       | 54.6%   | 47.0%  | 64.6%  | 23.9%  | 29.0       | 191.3       | 0.0%     | 0.0%                |
| CHOICE I ¹³     | 803             | 60.8       | 57.5%   | 52.4%  | NA     | 27.0%  | 31.1       | 122.1       | 68.1%    | NA                  |
| Study                     | Patients | Age Mean | Yearly | 1st Year | 2nd Year | 3rd Year | Sex Male | Sex Female | Pct Markers | Pct Control |
|---------------------------|----------|----------|--------|----------|----------|----------|----------|------------|-------------|-------------|
| **CHOICE II** 14          | 233      | 63.1     | 55.8%  | 49.8%    | 60.9%    | 16.3%    | 28.9     | 157.9      | 0.0%        | 0.0%        |
| **COMBO I** 15            | 316      | 63.0     | 65.8%  | 78.2%    | NA       | 43.1%    | 32.3     | 102.2      | 99.7%       | 62.7%       |
| **COMBO II** 16           | 720      | 61.6     | 73.6%  | 90.1%    | NA       | 30.9%    | 30.2     | 107.0      | 99.9%       | 66.7%       |
| **ESCAPE** 17             | 62       | 58.7     | 58.1%  | NA       | NA       | NA       | NA       | 30.4       | 180.7       | 51.6%       | 40.3%       |
| **FH I** 18               | 486      | 52.0     | 56.4%  | 46.3%    | 43.2%    | 11.7%    | 29.3     | 144.6      | 100.0%      | 83.5%       |
| **FH II** 18              | 249      | 53.2     | 52.6%  | 35.7%    | 32.5%    | 4.0%     | 28.3     | 134.4      | 100.0%      | 88.4%       |
| **HIGH FH** 19            | 107      | 50.6     | 53.3%  | 49.5%    | 57.0%    | 14.0%    | 28.9     | 197.8      | 100.0%      | 72.9%       |
| **JAPAN** 20              | 216      | 60.8     | 60.6%  | NA       | NA       | 68.5%    | 25.5     | 141.2      | 100.0%      | NA          |
| **LONG TERM** 21          | 2341     | 60.5     | 62.2%  | 68.6%    | NA       | 34.6%    | 30.3     | 122.4      | 99.9%       | 46.8%       |
| **MONO** 35               | 103      | 60.2     | 53.4%  | NA       | NA       | 3.9%     | 29.3     | 139.7      | 0.0%        | 0.0%        |
| **OPTIONS I** 23          | 355      | 62.9     | 65.1%  | 56.3%    | 78.3%    | 49.9%    | 31.0     | 105.1      | 100.0%      | 68.5%       |
| **OPTIONS II** 24         | 305      | 60.9     | 61.3%  | 58.0%    | 72.5%    | 41.3%    | 31.3     | 111.3      | 100.0%      | 68.2%       |
| **OSLER 1 and 2** 25      | 4465     | 57.9     | 50.5%  | 20.1%    | 52.0%    | 13.4%    | NA       | 122.3†     | 70.1%       | 27.1%       |
| **Roth et al.** 26        | 92       | 56.9     | 40.2%  | 3.3%     | 51.1%    | 15.2%    | 29.4     | 122.6      | 100.0%      | 66.3%       |
| **RUTHERFORD** 27         | 112      | 50.6     | 52.7%  | 21.5%    | NA       | NA       | NA       | 152.7      | 100.0%      | 87.5%       |
| **RUTHERFORD 2** 28       | 329      | 50.6     | 57.8%  | 31.3%    | NA       | NA       | NA       | 156.0      | 100.0%      | 87.0%       |
| **Stein et al.** 29       | 46       | 54.2     | 63.0%  | 39.1%    | NA       | 0.0%     | 29.5     | 146.1      | 100.0%      | 78.3%       |
| Study                  | N  | BMI | CAD | DM2 | HTN | LDL-C | CAD  | DM2  | HTN  |
|-----------------------|----|-----|-----|-----|-----|-------|------|------|------|
| Teramoto et al. 30    | 75 | 57.7| 52.0%| 0.0%| 34.7%| 14.7% | 24.8 | 120.8| 100.0%| NA |
| TESLA PART B 31       | 49 | 31.0| 51.0%| 43.0%| NA  | NA    | NA   | 348.0| 100.0%| 93.9%|
| YUKAWA 32             | 207| 60.8| 67.6%| 27.1%| 72.9%| 35.3% | NA   | 140.2| 100.0%| 23.7%|
| YUKAWA II 33          | 404| 61.5| 60.4%| 12.9%| 73.5%| 48.8% | NA   | 106.0| 100.0%| 50.7%|
| Overall               | 45,520| 61.0| 67.6%| 39.2%| 73.1%| 30.6% | 30.0 | 106.0| 91.8%| 58.4%|

BMI, body mass index; CAD, coronary artery disease; DM2, diabetes mellitus type 2; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; NA, not available.

See Table S1 for trial name abbreviations

*Estimated from median and interquartile range*
Table S3. Random effects meta-regression analysis showing the study-level association between baseline low-density lipoprotein cholesterol (left) and treatment difference vs. control in percent LDL-C reduction from baseline (right) and cardiovascular/safety end points

| End point                  | Baseline LDL-C | Treatment difference vs. control in % LDL-C reduction from baseline | PCSK9i treatment duration |
|----------------------------|----------------|---------------------------------------------------------------------|----------------------------|
|                            | Regression coefficient (95% CI) | p | Regression coefficient (95% CI) | p | Regression coefficient (95% CI) | p |
| All-cause mortality        | -0.02 (-0.05, 0.00) | 0.038 | -0.02 (-0.07, 0.02) | 0.358 | 0.01 (0.00, 0.02) | 0.012 |
| CV mortality               | -0.02 (-0.05, 0.01) | 0.196 | -0.01 (-0.06, 0.03) | 0.621 | 0.00 (0.00, 0.01) | 0.197 |
| Myocardial infarction      | 0.00 (-0.01, 0.01) | 0.976 | 0.03 (0.00, 0.06) | 0.075 | 0.00 (-0.01, 0.01) | 0.943 |
| Stroke                     | 0.02 (-0.01, 0.05) | 0.166 | 0.00 (-0.06, 0.06) | 0.954 | -0.01 (-0.02, 0.01) | 0.414 |
| Coronary revascularization | 0.00 (0.00, 0.01) | 0.281 | 0.04 (0.01, 0.06) | 0.012 | 0.00 (-0.01, 0.00) | 0.487 |
| Unstable angina            | -0.01 (-0.05, 0.03) | 0.487 | 0.03 (-0.08, 0.14) | 0.612 | 0.01 (-0.01, 0.02) | 0.480 |
| CHF exacerbation           | 0.00 (-0.02, 0.02) | 0.873 | -0.03 (-0.11, 0.04) | 0.400 | 0.00 (-0.01, 0.02) | 0.674 |
| Neurocognitive adverse events | 0.00 (-0.01, 0.02) | 0.862 | -0.03 (-0.07, 0.01) | 0.201 | 0.00 (-0.01, 0.01) | 0.903 |
| Diabetes mellitus          | 0.00 (-0.01, 0.01) | 0.938 | -0.02 (-0.06, 0.02) | 0.236 | 0.00 (-0.01, 0.01) | 0.824 |

CHF, congestive heart failure; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; PCSK9i, PCSK9inhibitor
### Table S4. Subgroup analyses for cardiovascular/safety end points stratified by familial hypercholesterolemia, and background statin therapy

| End point                  | Population: FH vs. Non-FH/mixed, OR (95% CI) | Statin intolerant/PCSK9i monotherapy, OR (95% CI) |
|----------------------------|-----------------------------------------------|-------------------------------------------------|
|                            | Non-FH/mixed  | FH      | p       | No     | Yes  | p       |
|----------------------------|----------------|---------|---------|--------|------|---------|
| All-cause mortality        | 0.99 (0.87, 1.13) | 6.72 (0.38, 119.95) | 0.194   | 1.00 (0.88, 1.14) | 0.79 (0.07, 8.79) | 0.846   |
| CV mortality               | 1.00 (0.84, 1.19) | 3.58 (0.18, 69.77) | 0.401   | 1.01 (0.85, 1.19) | -*   | -       |
| Myocardial infarction      | 0.72 (0.64, 0.81) | 0.99 (0.25, 3.99) | 0.999   | 0.72 (0.64, 0.81) | 0.62 (0.19, 2.00) | 0.999   |
| Stroke                     | 0.81 (0.68, 0.97) | 1.53 (0.06, 37.66) | 0.695   | 0.80 (0.67, 0.96) | 4.54 (0.18, 112.74) | 0.290   |
| Coronary revascularization | 0.78 (0.72, 0.86) | 1.35 (0.39, 4.64) | 0.842   | 0.78 (0.72, 0.86) | 1.48 (0.46, 4.75) | 0.346   |
| Unstable angina            | 0.97 (0.81, 1.16) | 1.53 (0.06, 37.66) | 0.783   | 0.97 (0.82, 1.16) | -*   | -       |
| CHF exacerbation           | 0.98 (0.86, 1.13) | 1.51 (0.16, 14.65) | 0.711   | 0.99 (0.86, 1.13) | 0.19 (0.02, 2.16) | 0.185   |
| Neurocognitive AEs         | 1.14 (0.95, 1.36) | 0.38 (0.09, 1.56) | 0.160   | 1.11 (0.93, 1.33) | 1.45 (0.16, 13.17) | 0.809   |
| Diabetes mellitus          | 1.05 (0.95, 1.17) | 0.78 (0.30, 2.03) | 0.532   | 1.05 (0.95, 1.16) | 3.43 (0.38, 31.41) | 0.278   |

AE, adverse event; CHF, congestive heart failure; CV, cardiovascular; FH, familial hypercholesterolemia; PCSK9i, proprotein convertase subtilisin-kexin type 9 inhibitor; * There were no studies reporting events in these subgroups
Table S5. Random- and fixed-effects models for cardiovascular/safety end points

| End point                          | Meta-analysis model |                  |                  |                  |                  |
|-----------------------------------|---------------------|------------------|------------------|------------------|------------------|
|                                   | Fixed-effects       | Random effects   |                  |                  |                  |
|                                   | OR (95% CI)         | p                | OR (95% CI)      | p                |                  |
| All-cause mortality               | 1.00 (0.88, 1.14)   | 0.999            | 0.71 (0.47, 1.09)| 0.119            |                  |
| CV mortality                      | 1.01 (0.85, 1.19)   | 0.936            | 1.01 (0.85, 1.19)| 0.954            |                  |
| Myocardial infarction             | 0.72 (0.64, 0.81)   | <0.001           | 0.72 (0.64, 0.81)| <0.001           |                  |
| Stroke                            | 0.81 (0.68, 0.97)   | 0.02             | 0.80 (0.67, 0.96)| 0.017            |                  |
| Coronary revascularization        | 0.79 (0.72, 0.86)   | <0.001           | 0.78 (0.71, 0.86)| <0.001           |                  |
| Unstable angina                   | 0.97 (0.82, 1.16)   | 0.762            | 0.97 (0.82, 1.16)| 0.767            |                  |
| CHF exacerbation                  | 0.98 (0.86, 1.13)   | 0.8              | 0.98 (0.86, 1.13)| 0.789            |                  |
| Neurocognitive adverse events     | 1.12 (0.94, 1.33)   | 0.218            | 1.12 (0.88, 1.42)| 0.366            |                  |
| Diabetes mellitus                 | 1.05 (0.95, 1.16)   | 0.337            | 1.05 (0.95, 1.17)| 0.32             |                  |

CHF, congestive heart failure; CV, cardiovascular
**Table S6. Egger's regression test for cardiovascular/safety endpoints**

| End point                        | p    |
|----------------------------------|------|
| All-cause mortality              | 0.131|
| Cardiovascular mortality         | 0.268|
| Myocardial infarction            | 0.937|
| Unstable angina                  | 0.393|
| Stroke                           | 0.186|
| CHF exacerbation                 | 0.734|
| Coronary revascularization       | 0.098|
| Neurocognitive adverse events    | 0.549|
| Diabetes mellitus                | 0.856|

CHF, congestive heart failure
Figure S1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) meta-analysis flowchart

Potentially relevant articles identified through database search:
- PubMed/MEDLINE: 1,104
- EMBASE: 2,058
- CENTRAL: 310

Records identified from additional sources:
- Clinicaltrials.gov: 125
- Hand-searching: 19

Records after duplicates removed: n=3,181

Records screened: n=3,183

Records excluded: n=3,118
- Phase 1 studies: 4
- Pooled analyses: 9
- Sub-analyses/sub-studies: 5
- Lack of data/suitable control: 8
- Other PCSK9 inhibitor: 2
- Overlapping patients: 1

Full-text articles assessed for eligibility: n=65

Studies included: n=35
Figure S2. Risk of bias assessment of included studies

| Study or Subgroup                  | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|-----------------------------------|----------------------------|------------------------|----------------------------------------|-------------------------------|------------------------|---------------------|------------|
| DESCARTES 1                       |                            |                        |                                        |                               |                        |                     |            |
| FOURIER 2                         |                            |                        |                                        |                               |                        |                     |            |
| GAUSS 3                           |                            |                        |                                        |                               |                        |                     |            |
| GAUSS-2 4                         |                            |                        |                                        |                               |                        |                     |            |
| GAUSS-3 5                         |                            |                        |                                        |                               |                        |                     |            |
| GLAGOV 6                          |                            |                        |                                        |                               |                        |                     |            |
| LAPLACE-2 7                       |                            |                        |                                        |                               |                        |                     |            |
| LAPLACE-TIMI5 8                   |                            |                        |                                        |                               |                        |                     |            |
| McKenney et al. 9                 |                            |                        |                                        |                               |                        |                     |            |
| MENDEL 10                         |                            |                        |                                        |                               |                        |                     |            |
| MENDEL-2 11                       |                            |                        |                                        |                               |                        |                     |            |
| ODYSSEY ALTERNATIVE 12            |                            |                        |                                        |                               |                        |                     |            |
| ODYSSEY CHOICE I 13               |                            |                        |                                        |                               |                        |                     |            |
| ODYSSEY CHOICE II 14              |                            |                        |                                        |                               |                        |                     |            |
| ODYSSEY COMBO I 15                |                            |                        |                                        |                               |                        |                     |            |
| ODYSSEY COMBO II 16               |                            |                        |                                        |                               |                        |                     |            |
| ODYSSEY ESCAPE 17                 |                            |                        |                                        |                               |                        |                     |            |
| ODYSSEY FH 18                     |                            |                        |                                        |                               |                        |                     |            |
| ODYSSEY FH II 18                  |                            |                        |                                        |                               |                        |                     |            |
| ODYSSEY HIGH FH 19                |                            |                        |                                        |                               |                        |                     |            |
| ODYSSEY JAPAN 20                  |                            |                        |                                        |                               |                        |                     |            |
| ODYSSEY LONG TERM 21              |                            |                        |                                        |                               |                        |                     |            |
| ODYSSEY MONO 22                   |                            |                        |                                        |                               |                        |                     |            |
| ODYSSEY OPTIONS I 23              |                            |                        |                                        |                               |                        |                     |            |
| ODYSSEY OPTIONS II 24             |                            |                        |                                        |                               |                        |                     |            |
| OSLER 1 and 2 25                  |                            |                        |                                        |                               |                        |                     |            |
| Roth et al. 26                    |                            |                        |                                        |                               |                        |                     |            |
| RUTHERFORD 27                     |                            |                        |                                        |                               |                        |                     |            |
| RUTHERFORD 2 28                   |                            |                        |                                        |                               |                        |                     |            |
| Stein et al. 29                   |                            |                        |                                        |                               |                        |                     |            |
| Teramoto et al. 30                 |                            |                        |                                        |                               |                        |                     |            |
| TESLA PART D 31                   |                            |                        |                                        |                               |                        |                     |            |
| YUKAWA 32                         |                            |                        |                                        |                               |                        |                     |            |
| YUKAWA II 33                      |                            |                        |                                        |                               |                        |                     |            |
Figure S3. Unstable angina

| Study or Subgroup | Antibody Events | Antibody Total | No Antibody Events | No Antibody Total | Weight | M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|----------------|----------------|-------------------|-------------------|--------|---------------------|--------------------------------|
| 1.6.2.1 Evolocumab |                |                |                   |                   |        |                     |                                |
| DESCARTES         | 1              | 598            | 0                 | 302               | 0.3%   | 1.52 [0.06, 37.33]  |                                 |
| FOUWED             | 230            | 13784          | 229               | 13780             | 96.1%  | 0.99 [0.82, 1.19]   |                                 |
| GAUGUS            | 0              | 205            | 0                 | 102               | Not estimable |                                 |
| GAUGUS II         | 0              | 145            | 0                 | 73                | Not estimable |                                 |
| GLAGIOVO          | 3              | 494            | 4                 | 464               | 1.4%   | 0.75 [0.17, 3.38]   |                                 |
| MENDEL            | 0              | 90             | 0                 | 136               | Not estimable |                                 |
| MENDEL 2          | 0              | 306            | 0                 | 308               | Not estimable |                                 |
| OSLER 1 and 2     | 3              | 2976           | 3                 | 1489              | 1.2%   | 0.90 [0.10, 2.48]   |                                 |
| YUKAWA            | 0              | 105            | 0                 | 102               | Not estimable |                                 |
| Subtotal (95% CI) |                | 18894          | 16775             | 99.1%             | 0.98 [0.82, 1.17] |                                 |
| Total events      | 243            | 246            |                   |                   |        |                     |                                |

Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 3 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.27 (P = 0.79)

1.6.2.2 Alirocumab

| Study or Subgroup | Antibody Events | Antibody Total | No Antibody Events | No Antibody Total | Weight | M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|----------------|----------------|-------------------|-------------------|--------|---------------------|--------------------------------|
| ODYSSEY ALTERNATIVE | 0          | 126            | 0                 | 124               | Not estimable |                                 |
| ODYSSEY CHOICE II | 0            | 173            | 0                 | 58                | Not estimable |                                 |
| ODYSSEY COMBO I   | 0            | 207            | 0                 | 107               | Not estimable |                                 |
| ODYSSEY COMBO II  | 1            | 479            | 1                 | 241               | 0.3%   | 1.51 [0.06, 37.31]  |                                 |
| ODYSSEY FH I      | 1            | 322            | 1                 | 163               | 0.3%   | 1.53 [0.06, 37.06]  |                                 |
| ODYSSEY FH II     | 0            | 167            | 0                 | 81                | Not estimable |                                 |
| ODYSSEY HIGH FH   | 0            | 72             | 0                 | 35                | Not estimable |                                 |
| ODYSSEY JAPAN     | 0            | 143            | 0                 | 72                | Not estimable |                                 |
| ODYSSEY LONG TERM | 0            | 1550           | 1                 | 756               | 0.3%   | 0.17 [0.01, 4.18]   |                                 |
| ODYSSEY OPTIONS I | 0            | 104            | 0                 | 250               | Not estimable |                                 |
| ODYSSEY OPTIONS II| 0            | 103            | 0                 | 202               | Not estimable |                                 |
| Subtotal (95% CI) |                | 3446           | 2121              | 9%                | 0.73 [0.11, 4.65] |                                 |
| Total events      | 16            | 1              |                   |                   |        |                     |                                |

Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)

Total (95% CI) 22140 18896 100.0% 0.97 [0.81, 1.16]
Total events 245 247

Heterogeneity: Tau² = 0.00; Chi² = 2.17, df = 6 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.77)
Test for subgroup differences: Chi² = 0.99, df = 1 (P = 0.76); I² = 0%
Figure S4. Congestive heart failure exacerbation

| Study or Subgroup | Antibody | No antibody | Odds Ratio | Odds Ratio |
|-------------------|-----------|-------------|------------|------------|
|                  | Events    | Total       | Events     | Total       | M-H, Random, 95% CI | M-H, Random, 95% CI |
| 1.6.4.1 Evolocumab | 1         | 598         | 0          | 302         | 0.2% | 1.52 [0.06, 37.33] |
|                  | 402       | 13784       | 409        | 13780       | 96.6% | 0.98 [0.86, 1.13] |
|                  | 0         | 205         | 0          | 102         | Not estimable |
|                  | 0         | 145         | 0          | 73          | Not estimable |
|                  | 0         | 494         | 0          | 464         | Not estimable |
|                  | 1         | 158         | 0          | 155         | 0.2% | 2.96 [0.12, 73.27] |
|                  | 0         | 90          | 0          | 135         | Not estimable |
|                  | 0         | 306         | 0          | 308         | Not estimable |
| 1.6.4.2 Allirocumab | 1         | 2976        | 1          | 1489        | 0.2% | 0.50 [0.03, 8.00] |
|                  | 0         | 105         | 0          | 102         | Not estimable |
|                  | 18852     | 16930       | 97.2%      | 0.09 [0.86, 1.13] |
| Total events     | 405       | 409         |           |            |                  |

Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)

Total events: 421, 417
Heterogeneity: Tau² = 0.00; Chi² = 3.99, df = 10 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.27 (P = 0.79)
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%
Figure S5. Diabetes mellitus

| Study or Subgroup | Antibody Events | No antibody Events | Total Events | Total Weight | Odds Ratio M-H, Random, 95% CI |
|-------------------|-----------------|--------------------|--------------|--------------|--------------------------------|
| **1.69.1 Evolocumab** |                |                    |              |              |                                |
| FOURIER          | 677            | 834                | 8330         | 83.9%        | 1.06 [0.94, 1.18]               |
| GLACOV          | 17             | 484                | 484          | 2.3%         | 0.94 [0.48, 1.85]               |
| LAPLACE-TIMI57  | 0              | 159                | 159          | Not estimable |                                |
| MENDEL          | 1              | 90                 | 135          | 0.1%         | 4.54 [0.18, 112.74]             |
| OSELR 1 and 2   | 34             | 2975               | 3009         | 2.3%         | 1.55 [0.78, 3.07]               |
| YUKAWA II       | 4              | 202                | 202          | 0.5%         | 1.00 [0.25, 4.05]               |
| **Subtotal (95% CI)** | 12247         | 10804              | 10330        | 89.1%        | 1.06 [0.95, 1.19]               |
| Total events    | 733            | 677                |              |              |                                |
| Heterogeneity: Tau² = 0.00; Chi² = 2.11, df = 4 (P = 0.72); I² = 0% |
| Test for overall effect: Z = 1.13 (P = 0.26) |

| **1.69.2 Alirocumab** |                |                    |              |              |                                |
| ODYSSEY CHOICE | 12             | 573                | 229          | 0.5%         | 2.43 [0.54, 10.93]             |
| ODYSSEY FHII  | 6              | 322                | 163          | 0.6%         | 0.75 [0.21, 2.71]              |
| ODYSSEY FHIII | 4              | 167                | 81           | 0.4%         | 0.97 [0.17, 5.41]              |
| ODYSSEY HIGH FH | 1             | 72                 | 35           | 0.1%         | 0.48 [0.03, 7.69]              |
| ODYSSEY JAPAN | 12             | 143                | 72           | 0.8%         | 1.56 [0.48, 5.01]              |
| ODYSSEY LONG TERM | 21           | 1550               | 48           | 8.1%         | 0.95 [0.66, 1.36]              |
| ODYSSEY OPTIONS | 0            | 104                | 5            | 0.1%         | 0.21 [0.01, 3.90]              |
| ODYSSEY OPTIONS II | 1          | 103                | 6            | 0.2%         | 0.32 [0.04, 2.70]              |
| **Subtotal (95% CI)** | 3034         | 1820               | 10330        | 10.9%        | 0.96 [0.70, 1.32]              |
| Total events    | 126           | 72                 |              |              |                                |
| Heterogeneity: Tau² = 0.00; Chi² = 4.54, df = 7 (P = 0.72); I² = 0% |
| Test for overall effect: Z = 0.24 (P = 0.81) |

| Total (95% CI) | 15281          | 12624             | 100.0%       | 1.05 [0.95, 1.17] |
| Total events   | 859            | 749               |              |                |
| Heterogeneity: Tau² = 0.00; Chi² = 7.01, df = 12 (P = 0.88); I² = 0% |
| Test for overall effect: Z = 0.99 (P = 0.32) |
| Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.55); I² = 0% |

Favours PCSK9I  Favours no PCSK9I
**Figure S6. Increase in creatine kinase**

| Study or Subgroup | Antibody | No antibody | Odds Ratio | Heterogeneity | Test for overall effect |
|-------------------|----------|-------------|------------|---------------|------------------------|
| **1.6.6.1 Evolocumab** |          |             |            |               |                        |
| DESCARTESE       |          |             |            |               |                        |
| FOURIER          |          |             |            |               |                        |
| GAUSS            |          |             |            |               |                        |
| GAUSS-2          |          |             |            |               |                        |
| GAUSS-3          |          |             |            |               |                        |
| GLAVOS           |          |             |            |               |                        |
| LAPLACE          |          |             |            |               |                        |
| LAPLACE.TIMI57   |          |             |            |               |                        |
| MENDEL           |          |             |            |               |                        |
| MENDEL-11        |          |             |            |               |                        |
| OSLER 1 and 2    |          |             |            |               |                        |
| RUTHERFORD       |          |             |            |               |                        |
| RUTHERFORD-2     |          |             |            |               |                        |
| TESLA PART B     |          |             |            |               |                        |
| YUKAWA           |          |             |            |               |                        |
| YUKAWA-11        |          |             |            |               |                        |
| Subtotal (95% CI)|          |             |            |               |                        |
| **1.6.6.2 Alirocumab** |          |             |            |               |                        |
| Mckinney et al   |          |             |            |               |                        |
| ODYSSEY ALTERNATIVE |      |             |            |               |                        |
| ODYSSEY CHOICE I |          |             |            |               |                        |
| ODYSSEY CHOICE II|          |             |            |               |                        |
| ODYSSEY COMBO II |          |             |            |               |                        |
| ODYSSEY ESCAPE   |          |             |            |               |                        |
| ODYSSEY FH       |          |             |            |               |                        |
| ODYSSEY HIGH FH  |          |             |            |               |                        |
| ODYSSEY JAPAN    |          |             |            |               |                        |
| ODYSSEY LONG TERM|          |             |            |               |                        |
| ODYSSEY MONO      |          |             |            |               |                        |
| ODYSSEY OPTIONS I|          |             |            |               |                        |
| ODYSSEY OPTIONS II|         |             |            |               |                        |
| Roth et al        |          |             |            |               |                        |
| Stein et al       |          |             |            |               |                        |
| Teramoto et al    |          |             |            |               |                        |
| Subtotal (95% CI) |          |             |            |               |                        |

Total events = 137, 136

Heterogeneity: Tau² = 0.00, Chisq = 13.60, df = 15 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.23 (P = 0.22)

For the overall effect, Z = 1.47 (P = 0.14)

Total (95% CI) = 24407, 20284
Total events = 279, 227

Heterogeneity: Tau² = 0.00, Chisq = 23.66, df = 31 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.89 (P = 0.06)
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%
Figure S7. Myalgia

### 1.53.1 Evolocumab

| Study or Subgroup                | Antibody | No antibody | Weight | Odds Ratio M-H, Random, 95% CI |
|----------------------------------|----------|-------------|--------|-------------------------------|
| DESCARTEES                      | 24/599   | 9/302       | 6.1%   | 1.36 (0.62, 2.96)             |
| GAUSS                           | 7/67     | 1/32        | 1.2%   | 3.95 (0.46, 33.57)            |
| GAUSS-2                         | 16/205   | 18/102      | 6.7%   | 0.40 (0.19, 0.81)             |
| GAUSS-3                         | 20/145   | 16/73       | 8.6%   | 0.57 (0.28, 1.18)             |
| GLAASOV                         | 34/484   | 24/484      | 8.6%   | 1.23 (0.73, 2.06)             |
| LAPLACE,TIM57                   | 1/158    | 2/155       | 0.9%   | 0.49 (0.04, 5.43)             |
| MENDEL                          | 2/90     | 1/135       | 0.9%   | 3.05 (0.27, 34.09)            |
| MENDEL-2                       | 3/306    | 6/308       | 2.5%   | 0.50 (0.12, 2.01)             |
| OSLER 1 and 2                   | 89/2976  | 43/1489     | 12.3%  | 1.04 (0.72, 1.50)             |
| Subtotal (95% CI)               | 5025     | 30800       | 46.6%  | 0.89 (0.62, 1.26)             |
| Total events                    | 196      | 124         |        |                               |

Heterogeneity: $\tau^2 = 0.10, \chi^2 = 13.26, df = 8 (P = 0.10); I^2 = 40%$
Test for overall effect: $Z = 0.64 (P = 0.52)$

### 1.53.2 Alirocumab

| Study or Subgroup                | Antibody | No antibody | Weight | Odds Ratio M-H, Random, 95% CI |
|----------------------------------|----------|-------------|--------|-------------------------------|
| ODYSSEY ALTERNATIVE              | 31/126   | 29/124      | 8.6%   | 1.07 (0.60, 1.91)             |
| ODYSSEY CHOICE I                 | 19/573   | 8/229       | 5.5%   | 0.95 (0.41, 2.20)             |
| ODYSSEY CHOICE II                | 10/173   | 3/59        | 2.7%   | 1.12 (0.30, 4.24)             |
| ODYSSEY COMBO I                  | 7/207    | 4/107       | 3.0%   | 0.90 (0.26, 3.15)             |
| ODYSSEY COMBO II                 | 21/479   | 12/241      | 6.7%   | 0.88 (0.42, 1.81)             |
| ODYSSEY ESCAPE                   | 4/41     | 1/21        | 1.0%   | 2.16 (0.23, 20.67)            |
| ODYSSEY FH1                      | 6/322    | 11/163      | 4.2%   | 0.26 (0.10, 0.72)             |
| ODYSSEY FH II                    | 10/167   | 5/81        | 3.7%   | 0.97 (0.32, 2.93)             |
| ODYSSEY HIGH FH1                 | 4/72     | 3/35        | 2.1%   | 0.63 (0.13, 2.97)             |
| ODYSSEY JAPAN                    | 2/143    | 3/72        | 1.6%   | 0.33 (0.05, 2.00)             |
| ODYSSEY LONG TERM                | 64/1550  | 23/788      | 10.4%  | 1.91 (1.19, 3.05)             |
| ODYSSEY MONO                     | 2/52     | 1/51        | 0.9%   | 2.00 (0.18, 22.77)            |
| ODYSSEY OPTIONS II               | 4/103    | 6/202       | 2.9%   | 1.32 (0.36, 4.79)             |
| Subtotal (95% CI)                | 4008     | 2172        | 53.2%  | 0.99 (0.71, 1.38)             |
| Total events                     | 204      | 108         |        |                               |

Heterogeneity: $\tau^2 = 0.09, \chi^2 = 16.52, df = 12 (P = 0.17); I^2 = 27%$
Test for overall effect: $Z = 0.03 (P = 0.96)$

| Total (95% CI)                   | 9033     | 5252        | 100.0% | 0.95 (0.75, 1.20)             |
| Total events                     | 400      | 233         |        |                               |

Heterogeneity: $\tau^2 = 0.08, \chi^2 = 30.61, df = 21 (P = 0.08); I^2 = 31%$
Test for overall effect: $Z = 0.46 (P = 0.65)$
Test for subgroup differences: $\chi^2 = 0.21, df = 1 (P = 0.65), I^2 = 0%$
Figure S8. Alanine/aspartate aminotransferase increase

| Study or Subgroup | Antibody Events | No antibody Events | Odds Ratio M-H, Random, 95% CI |
|-------------------|-----------------|-------------------|--------------------------------|
| DESCARTES         | 5               | 3                 | 1.2%                           | 0.84 [0.20, 3.53] |
| FOURIER           | 240             | 242               | 75.4%                          | 0.99 [0.93, 1.19] |
| GAUSS            | 0               | 1                 | 0.2%                           | 0.17 [0.01, 4.24] |
| GAUSS-2          | 0               | 102               | Not estimable                  |                  |
| GLAGOV           | 4               | 2                 | 6.6%                           | 1.00 [0.14, 7.13] |
| LAPLACE           | 4               | 9                 | 1.8%                           | 0.31 [0.09, 1.00] |
| LAPLACE2-TIMI58  | 0               | 1                 | 0.2%                           | 0.32 [0.01, 8.04] |
| MENDEL           | 0               | 1                 | Not estimable                  |                  |
| MENDEL-2         | 3               | 6                 | 1.3%                           | 0.50 [0.12, 2.01] |
| OSLER 1 and 2    | 31              | 10                | 7.2%                           | 0.66 [0.48, 1.54] |
| RUTHERFORD       | 1               | 5                 | 0.2%                           | 3.05 [0.12, 76.69] |
| TESLA PART B     | 2               | 3                 | 0.4%                           | 0.97 [0.08, 11.54] |
| YUKAWA           | 0               | 1                 | Not estimable                  |                  |
| YUKAWA II        | 1               | 2                 | 0.4%                           | 0.50 [0.04, 5.53] |
| Subtotal (95% CI) | 20/16           | 177/94            | 88.9%                          | 0.84 [0.79, 1.11] |

Total events 289
285
Heterogeneity: Tau² = 0.00, Chi² = 6.97, df = 10 (P = 0.73), I² = 0%
Test for overall effect: Z = 0.76 (P = 0.45)

1.67.2 Alirocumab

| Study or Subgroup | Antibody Events | No antibody Events | Odds Ratio M-H, Random, 95% CI |
|-------------------|-----------------|-------------------|--------------------------------|
| McKenney et al.   | 0               | 50                | Not estimable                  |                  |
| ODYSSEY ALTERNATIVE | 0            | 126               | Not estimable                  |                  |
| ODYSSEY CHOICE II | 3               | 6                 | 0.9%                           | 1.03 [0.16, 6.57] |
| ODYSSEY ESCAPE` | 1               | 1                 | Not estimable                  |                  |
| ODYSSEY FH       | 5               | 2                 | 6.4%                           | 1.27 [0.24, 6.82] |
| ODYSSEY FH II    | 6               | 1                 | 0.5%                           | 2.96 [0.13, 25.19] |
| ODYSSEY JAPAN    | 3               | 1                 | Not estimable                  |                  |
| ODYSSEY LONG TERM | 5               | 1                 | 0.5%                           | 2.57 [0.25, 22.44] |
| ODYSSEY MONO     | 0               | 2                 | Not estimable                  |                  |
| ODYSSEY OPTIONS I| 1               | 1                 | 0.2%                           | 0.60 [0.03, 19.70] |
| ODYSSEY OPTIONS II | 1            | 3                 | 0.2%                           | 5.62 [0.04, 146.78] |
| Stein et al.     | 0               | 1                 | Not estimable                  |                  |
| Subtotal (95% CI) | 4106           | 2417              | 11.1%                          | 1.16 [0.72, 1.85] |

Total events 61
25
Heterogeneity: Tau² = 0.00, Chi² = 5.11, df = 10 (P = 0.88), I² = 0%
Test for overall effect: Z = 0.80 (P = 0.41)

Total (95% CI) 24262
20211
100.0%
0.96 [0.82, 1.12]
**Figure S9. Treatment emergent serious adverse events**

| Study or Subgroup | Antibody | No antibody | Odds Ratio |
|-------------------|----------|-------------|------------|
| **1.68.1 Evolocumab** | | | |
| DESCARTES | 33 | 599 | 13 | 302 | 0.6% | 1.30 (0.67, 2.50) |
| FOURIER | 3410 | 13769 | 3404 | 13756 | 82.5% | 1.00 (0.95, 1.06) |
| GAUSS | 1 | 62 | 0 | 32 | 0.0% | 1.59 (0.68, 4.03) |
| GAUSS-2 | 6 | 206 | 4 | 102 | 0.1% | 0.74 (0.20, 2.69) |
| LAPLACE-2 | 23 | 1117 | 15 | 779 | 0.6% | 1.07 (0.56, 2.07) |
| LAPLACE_TIMI57 | 6 | 158 | 4 | 155 | 0.1% | 1.49 (0.41, 5.39) |
| MENDEL | 1 | 90 | 0 | 135 | 0.0% | 4.54 (0.18, 112.74) |
| MENDEL-2-11 | 4 | 306 | 2 | 306 | 0.1% | 2.03 (0.37, 11.15) |
| OSLER 1 and 2-25 | 222 | 2976 | 111 | 1459 | 4.4% | 1.00 (0.79, 1.27) |
| RUTHERFORD | 2 | 56 | 0 | 56 | 0.0% | 5.18 (0.24, 110.45) |
| RUTHERFORD-226 | 7 | 220 | 5 | 109 | 0.2% | 0.68 (0.21, 2.21) |
| TESLA PART B-27 | 0 | 33 | 0 | 16 | | |
| YUKAWA | 3 | 105 | 0 | 102 | 0.0% | 7.00 (0.36, 137.24) |
| YUKAWA-II-23 | 1 | 202 | 5 | 202 | 0.1% | 0.20 (0.02, 1.89) |
| **Subtotal (95% CI)** | 594 | 330 | | | |
| Total events | 3719 | 3563 | | | |

**1.68.2 Alirocumab**

| Study or Subgroup | Antibody | No antibody | Odds Ratio |
|-------------------|----------|-------------|------------|
| Mckinney et al-12 | 1 | 59 | 1 | 31 | 0.0% | 0.52 (0.03, 8.56) |
| ODYSSEY ALTERNATIVE | 12 | 126 | 10 | 124 | 0.3% | 1.20 (0.50, 2.99) |
| ODYSSEY CHANCE | 66 | 573 | 33 | 229 | 1.2% | 0.77 (0.49, 1.21) |
| ODYSSEY CHANCE-14 | 13 | 173 | 4 | 58 | 0.2% | 1.10 (0.34, 3.51) |
| ODYSSEY COMBO-15 | 26 | 207 | 14 | 107 | 0.5% | 0.95 (0.48, 1.91) |
| ODYSSEY COMBO-16 | 40 | 479 | 43 | 241 | 1.5% | 1.07 (0.71, 1.59) |
| ODYSSEY ESCAPE-17 | 4 | 41 | 2 | 21 | 0.1% | 1.03 (0.17, 6.12) |
| ODYSSEY FH | 44 | 322 | 22 | 163 | 0.8% | 1.01 (0.58, 1.76) |
| ODYSSEY FH-II | 15 | 167 | 9 | 61 | 0.3% | 0.90 (0.37, 2.22) |
| ODYSSEY HIGH FH | 10 | 72 | 4 | 35 | 0.2% | 1.25 (0.36, 4.31) |
| ODYSSEY JAPAN | 20 | 143 | 9 | 72 | 0.3% | 0.53 (0.20, 1.39) |
| ODYSSEY LONG TERM | 290 | 1550 | 154 | 708 | 5.2% | 0.95 (0.76, 1.18) |
| ODYSSEY MONO | 1 | 52 | 1 | 51 | 0.0% | 0.98 (0.06, 16.11) |
| ODYSSEY OPTIONS-23 | 4 | 104 | 15 | 250 | 0.2% | 0.63 (0.20, 1.94) |
| ODYSSEY OPTIONS-24 | 6 | 103 | 16 | 202 | 0.3% | 0.72 (0.27, 1.90) |
| Roth et al | 1 | 61 | 0 | 31 | 0.0% | 1.56 (0.06, 39.48) |
| Stein et al | 14 | 31 | 1 | 15 | 0.0% | 0.15 (0.01, 4.00) |
| Teramoto et al | 1 | 50 | 1 | 25 | 0.0% | 0.49 (0.03, 8.17) |
| **Subtotal (95% CI)** | 4313 | 2524 | | | |

**Heterogeneity**
- Tau² = 0.00, Chi² = 5.62, df = 17 (P = 1.00); I² = 0%
- Test for overall effect: Z = 1.01 (P = 0.31)

**Total (95% CI)**

| Total events | 594 | 330 | | | |

**Heterogeneity**
- Tau² = 0.00, Chi² = 14.77, df = 30 (P = 0.99); I² = 0%
- Test for overall effect: Z = 0.20 (P = 0.84)
- Test for subarous differences: Chi² = 1.00, df = 1 (P = 0.32), I² = 0.5%
Figure S10. Low-density lipoprotein cholesterol % change from baseline

| Study or Subgroup | Antibody | No antibody | Mean Diff. IV, Random, 95% CI |
|-------------------|----------|-------------|-----------------------------|
| DESCARTES        | -45.7    | 37.3        | -1.1                       |
| DESCARTES        | -51.5    | 20.6        | -1.9                       |
| DESCARTES        | -66.8    | 32.7        | -2.2                       |
| DESCARTES        | -54.7    | 23.9        | -1.8                       |
| GLAGOV          | 0        | 0           | 0                          |
| LAPLACE         | -62.2    | 19.1        | -1.0                       |
| LAPLACE         | -58.2    | 31.1        | -1.3                       |
| LAPLACE         | -59.3    | 30.8        | -1.5                       |
| LAPLACE         | -55.1    | 24.9        | -1.8                       |
| LAPLACE         | -61.4    | 16.9        | -1.2                       |
| LAPLACE         | -59.1    | 23.4        | -1.5                       |
| LAPLACE         | -61.6    | 29.0        | -1.7                       |
| LAPLACE         | -63.8    | 19.9        | -1.8                       |
| LAPLACE         | -62.4    | 41.1        | -1.9                       |
| LAPLACE         | -62.9    | 28.2        | -1.9                       |
| LAPLACE         | -63.3    | 21.2        | -1.9                       |
| LAPLACE         | -51.3    | 22.4        | -1.9                       |
| McKuskey et al  | -72.4    | 17.8        | -2.1                       |
| MENDEL          | -50.9    | 17.8        | -1.9                       |
| MENDEL          | -48.7    | 17.5        | -1.9                       |
| MENDEL          | -50.9    | 12.5        | -1.9                       |
| MENDEL          | -59.9    | 13.1        | -2.0                       |
| ODYSSEY CHOICE  | -58.9    | 28.3        | -2.0                       |
| ODYSSEY CHOICE  | -52.7    | 23.3        | -1.5                       |
| ODYSSEY CHOICE  | -51.2    | 30.4        | -1.4                       |
| ODYSSEY CHOICE  | -49.2    | 27.9        | -1.3                       |
| ODYSSEY ESCAPE  | -53.7    | 14.7        | -1.2                       |
| ODYSSEY ESCAPE  | -48.8    | 28.8        | -1.2                       |
| ODYSSEY ESCAPE  | -40.7    | 24.6        | -1.1                       |
| ODYSSEY ESCAPE  | -45.7    | 29.7        | -1.1                       |
| ODYSSEY ESCAPE  | -52.5    | 15.6        | -1.0                       |
| ODYSSEY ESCAPE  | -61.2    | 17.6        | -1.0                       |
| ODYSSEY ESCAPE  | 0        | 0           | 0                          |
| ODYSSEY ESCAPE  | 0        | 0           | 0                          |
| ODYSSEY ESCAPE  | 0        | 0           | 0                          |
| ODYSSEY ESCAPE  | 0        | 0           | 0                          |
| ODYSSEY ESCAPE  | 0        | 0           | 0                          |
| ODYSSEY ESCAPE  | 0        | 0           | 0                          |
| ODYSSEY ESCAPE  | 0        | 0           | 0                          |
| ODYSSEY ESCAPE  | 0        | 0           | 0                          |
| ODYSSEY ESCAPE  | 0        | 0           | 0                          |
| ODYSSEY ESCAPE  | 0        | 0           | 0                          |

Test for overall effect: Z = 51.19 (P < 0.0001)

Heterogeneity: Tau² = 47.90; Chisq = 249.73; df = 43; P < 0.0001; I² = 83%
Figure S11. High-density lipoprotein cholesterol % change from baseline

| Study or Subgroup | Antibody | No antibody | Mean Difference |
|-------------------|----------|-------------|-----------------|
| DESCARTES        | 5.4/14.4 | 145/15.7    | 2.8% / 3.89     |
| DESCARTES        | 9.2/6.9  | 74/1.9      | 2.2% / 3.90     |
| GAUSE            | 4.9/14.3 | 254/14.9    | 3.8% / 5.30     |
| GAUSE-3          | 4.7/16.4 | 145/2.9     | 2.2% / 4.59     |
| LAPLACE-1        | 7.7/14.3 | 110/2.2     | 2.1% / 8.20     |
| LAPLACE-2        | 6.2/11.5 | 113/0.9     | 3.1% / 5.30     |
| LAPLACE-2        | 4.9/11.7 | 111/0.6     | 3.6% / 5.50     |
| LAPLACE-2        | 10.4/23.8 | 112/0.1     | 1.1% / 10.30    |
| LAPLACE-2        | 0.4/12.4 | 109/4.5     | 2.9% / 3.89     |
| LAPLACE-2        | 5.5/11.4 | 110/1.1     | 3.6% / 8.50     |
| LAPLACE-2        | 6.4/13.1 | 112/0.4     | 2.4% / 8.80     |
| LAPLACE-2        | 7.7/19.2 | 115/0.9     | 1.4% / 8.60     |
| LAPLACE-2        | 7.9/13.6 | 110/1.4     | 2.3% / 9.20     |
| LAPLACE-2        | 8.7/21.4 | 115/2.1     | 1.1% / 8.90     |
| LAPLACE-TIM05    | 0/0      | 0/0         | Not estimable   |
| LAPLACE-TIM05    | 0/0      | 0/0         | Not estimable   |
| McKenney et al.  | 5.5/13.4 | 29/1.2     | 1.2% / 6.50     |
| MENDEL          | 11.5/15.6 | 45/6.7    | 1.1% / 5.80     |
| MENDEL          | 11.3/16.4 | 45/1.1     | 1.2% / 10.20    |
| MENDEL          | 3.8/45.4 | 153/4.7    | 0.7% / 8.50     |
| MENDEL          | 3.9/40.7 | 153/1.6    | 0.6% / 5.50     |
| ODYSSEY ALTERNATIVE | 0/0 | 0/0         | Not estimable   |
| ODYSSEY ALTERNATIVE | 3.0/14.1 | 312/1.5     | 4.3% / 5.10     |
| ODYSSEY ALTERNATIVE | 2.5/14.5 | 146/5.3     | 2.6% / 7.60     |
| ODYSSEY ALTERNATIVE | 7.7/15.4 | 59/2.4    | 1.6% / 10.10    |
| ODYSSEY ALTERNATIVE | 3.5/15.4 | 209/3.0  | 1.7% / 7.30     |
| ODYSSEY ALTERNATIVE | 8.6/17.5 | 479/0.5   | 4.6% / 8.10     |
| ODYSSEY ESCAPE | 0/0      | 0/0         | Not estimable   |
| ODYSSEY FH I    | 8.8/16.2 | 323/0.9   | 4.1% / 8.00     |
| ODYSSEY FH II   | 6.5/15.7 | 187/0.8    | 2.8% / 6.80     |
| ODYSSEY FH II   | 7.5/16.1 | 72/3.9    | 1.2% / 3.60     |
| ODYSSEY JAPAN-TEXM | 7.9/13.2 | 144/2.1     | 3.1% / 5.80     |
| ODYSSEY JAPAN-TEXM | 4.5/15.9 | 1553/0.6   | 0.8% / 4.60     |
| ODYSSEY MONO     | 6.6/13.7 | 52/1.6    | 1.7% / 4.40     |
| ODYSSEY OPTIONS  | 7.7/18.3 | 46/2.2   | 0.9% / 5.70     |
| ODYSSEY OPTIONS  | 4.8/14.8 | 55/0.1   | 1.5% / 4.90     |
| ODYSSEY OPTIONS  | 9.1/16.6 | 48/4.7   | 1.1% / 5.10     |
| ODYSSEY OPTIONS  | 7.2/16.7 | 53/1.8   | 1.2% / 6.00     |
| OSLER 1 and 2   | 0/0      | 0/0         | Not estimable   |
| Roth et al.      | 5.8/12.6 | 30/3.6    | 1.2% / 4.90     |
| ROTHERFORD-2    | 9.1/14.2 | 56/2.3    | 1.7% / 8.60     |
| ROTHERFORD-2    | 8.1/14.0 | 110/1.2   | 5.2% / 9.50     |
| ROTHERFORD-2    | 5.4/17.2 | 110/3.7   | 1.8% / 8.10     |
| Stein et al.     | 12.4/14.6 | 14/2.2  | 0.5% / 10.20    |
| Teramoto et al.  | 0/0      | 0/0         | Not estimable   |
| TESLA PART B     | 4.5/15.7 | 33/4.1    | 0.7% / 0.10     |
| YUKAWA          | 13.9/6.5 | 53/0.7   | 1.3% / 13.20    |
| YUKAWA          | 14.8/17  | 50/0.4   | 1.1% / 14.10    |
| YUKAWA          | 8.9/16.4 | 50/4.6   | 1.0% / 13.50    |
| YUKAWA          | 7.6/19.4 | 51/2.4   | 1.2% / 10.10    |
| YUKAWA          | 13.3/18.5 | 51/3.6  | 1.0% / 10.90    |

Heterogeneity: Tau² = 1.34; Chi² = 62.20, df = 49 (P = 0.010); I² = 21%
Test for overall effect: Z = 17.85 (P < 0.0001)
Figure S12. Total cholesterol % change from baseline

| Study or Subgroup | Antibody | No antibody | Mean Difference (IV, Random, 95% CI) |
|-------------------|----------|-------------|-------------------------------------|
| DESCARTES        | -29.9    | 26.9        | 126                                 |
| DESCARTES        | -34.7    | 19.8        | 74                                  |
| DESCARTES        | -32.1    | 20.7        | 254                                 |
| DESCARTES        | -32.1    | 20.7        | 254                                 |
| GLAVERS          | 0        | 0           | 486                                 |
| LALLACE-5        | -36.2    | 19.5        | 109                                 |
| LALLACE-5        | -40.1    | 29.7        | 115                                 |
| LALLACE-2        | -39.3    | 13.8        | 110                                 |
| LALLACE-2        | -37.0    | 12.4        | 110                                 |
| LALLACE-2        | -34.1    | 13.6        | 111                                 |
| LALLACE-2        | -36.7    | 12.3        | 113                                 |
| LALLACE-2        | -37.6    | 17.7        | 110                                 |
| LALLACE-2        | -30.0    | 13.5        | 115                                 |
| LALLACE-2        | -42.5    | 22.7        | 112                                 |
| LALLACE-TIMES    | 0        | 0           | 78                                  |
| MCKINNEY et al.  | -65.2    | 12.8        | 29                                  |
| MENDEL          | -34.1    | 11.8        | 45                                  |
| MENDEL          | -32.9    | 12.5        | 45                                  |
| MENDEL          | 0        | 0           | 153                                 |
| ODYSSEY CHOICE  | -35.8    | 17.7        | 312                                 |
| ODYSSEY CHOICE  | -33.3    | 15.7        | 146                                 |
| ODYSSEY CHOICE  | -32.3    | 12.3        | 59                                  |
| ODYSSEY COMBO   | -27.0    | 18.9        | 209                                 |
| ODYSSEY ESCAPE  | -38.4    | 11.5        | 41                                  |
| ODYSSEY FH I    | 0        | 0           | 323                                 |
| ODYSSEY FH II   | 0        | 0           | 167                                 |
| ODYSSEY JAPAN   | -39.5    | 10.8        | 144                                 |
| ODYSSEY LONG TERM| -37.0   | 19.7        | 1553                                |
| OSLEI et al.    | 0        | 0           | 2976                                |
| ROTH et al.     | 0        | 0           | 30                                  |
| RUTHERFORD      | -42.7    | 27.7        | 58                                  |
| RUTHERFORD      | 0        | 0           | 110                                 |
| SICHEM et al.   | -43.6    | 14.8        | 16                                  |
| TAKAMORI        | -41.1    | 10.5        | 25                                  |
| TESLA PART       | 0        | 0           | 33                                  |
| YUKAWA          | -39.4    | 11.6        | 53                                  |
| YUKAWA          | -45.8    | 10.8        | 52                                  |
| YUKAWA          | -39.1    | 11.2        | 50                                  |
| YUKAWA          | -47.2    | 14.1        | 50                                  |
| YUKAWA          | -44.3    | 14.3        | 51                                  |
| YUKAWA          | -40.9    | 12.9        | 51                                  |
| SubTotal (95% CI)| 9474     | 5377        | 81.8                                |
| Heterogeneity: Tau² = 14.23; Chi² = 123.85, df = 33 (P = 0.00001); I² = 73% |
| Test for overall effect: Z = 48.39 (P = 0.00001) |

| 1.40.2 vs. Ezetimibe |
|----------------------|
| GAUX7               |
| GAUX8               |
| GAUX9               |
| GAUX10              |
| ODYSSEY ALTERNATIVE|
| ODYSSEY COMBO       |
| ODYSSEY MONO        |
| ODYSSEY OPTIONS I   |
| ODYSSEY OPTIONS II  |
| SubTotal (95% CI)   |
| Heterogeneity: Tau² = 23.71; Chi² = 27.62, df = 7 (P = 0.0003); I² = 75% |
| Test for overall effect: Z = 9.00 (P = 0.00001) |

| Total (95% CI) |
|----------------|
| Heterogeneity: Tau² = 63.83; Chi² = 522.94, df = 41 (P = 0.00001); I² = 92% |
| Test for overall effect: Z = 26.56 (P = 0.00001) |

Test for subgroup differences: Chi² = 77.36, df = 1 (P = 0.00001), I² = 98.7%
Figure S13. Lipoprotein(a) % change from baseline
Figure S14. Apolipoprotein B % change from baseline

| Study or Subgroup | Antibody | No antibody | Weight | IV, Random, 95% CI |
|-------------------|----------|-------------|--------|-------------------|
| DESCARTES        | -43.3 17.2 | 74 | 8.4 17.6 37 | 1.9% | -42.90 [40.78, -45.01] |
| DESCARTES        | -39.2 20.8 | 145 | 5.4 26.2 73 | 1.8% | -44.66 [52.82, -38.00] |
| DESCARTES        | -37 28.1 | 126 | 0.8 27.8 83 | 1.8% | -37.80 [46.24, -29.36] |
| GLAGOV           | 0 | 0 | 486 | 0 | Not estimable |
| LAPLACE-5        | -49.3 22.1 | 109 | 10.6 22.2 55 | 1.9% | -59.30 [68.68, -41.11] |
| LAPLACE-2        | -52.3 21.2 | 110 | 5.5 20.9 55 | 1.8% | -50.90 [68.50, -41.46] |
| LAPLACE-2        | -49.0 15.6 | 113 | 5.1 14.8 58 | 2.0% | -54.90 [62.67, -40.53] |
| LAPLACE-2        | -51 15.6 | 110 | 7.6 14 56 | 2.0% | -60.60 [73.17, -44.03] |
| LAPLACE-2        | -54.4 42 | 115 | 2.5 34 55 | 1.6% | -58.70 [69.72, -46.98] |
| LAPLACE-2        | -53.6 41 | 115 | 2.5 14.1 57 | 2.0% | -59.10 [70.58, -50.62] |
| LAPLACE-2        | -53 19.4 | 112 | 2 18.9 55 | 1.9% | -55.00 [61.05, -49.95] |
| LAPLACE-2        | -55.7 27.0 | 112 | 0.3 22.4 56 | 1.8% | -55.40 [63.21, -47.59] |
| LAPLACE-2        | -51.4 15.9 | 110 | 0.8 15.9 55 | 2.0% | -52.20 [57.35, -46.97] |
| LAPLACE-2        | -47.1 18.6 | 111 | 3.7 18.3 56 | 1.9% | -50.80 [56.71, -44.99] |
| LAPLACE-2        | -36.0 20.6 | 70 | 3.2 20.4 79 | 1.9% | -42.00 [48.97, -34.39] |
| LAPLACE-2        | -50.6 19.4 | 78 | 5.9 19.4 78 | 1.9% | -54.50 [68.73, -40.41] |
| McKinney et al.  | -56.1 16.1 | 29 | 2.2 15.9 31 | 1.8% | -59.30 [68.40, -40.20] |
| MENDEL           | -44.5 15 | 45 | 0.3 15 45 | 1.9% | -44.20 [50.40, -38.00] |
| MENDEL           | -59.1 14.6 | 45 | 0.2 15 45 | 1.9% | -52.50 [59.62, -46.39] |
| MENDEL-11        | -47.1 14.1 | 53 | 0.1 12.9 76 | 2.0% | -47.10 [50.76, -43.44] |
| MENDEL-2         | -49.4 12.5 | 153 | 1.5 12.2 78 | 2.1% | -50.90 [54.25, -47.55] |
| ODDYSEY CHOICE 1 | -45.1 23 | 312 | 3.1 22.6 157 | 2.0% | -46.20 [52.56, -39.84] |
| ODDYSEY CHOICE 1 | -40.2 19.3 | 146 | 0.7 19.7 73 | 2.0% | -39.50 [45.00, -34.00] |
| ODDYSEY CHOICE 1 | -39.6 19.9 | 59 | 7.5 16.6 59 | 1.9% | -40.40 [52.58, -30.44] |
| ODDYSEY CHOICE 1 | -36.7 23.5 | 209 | 9.9 23.2 107 | 2.0% | -35.80 [41.23, -30.37] |
| ODDYSEY ESCAPE | -42.6 13.4 | 41 | 1.2 13.7 21 | 1.9% | -40.00 [51.15, -36.85] |
| ODDYSEY FH    | -41.1 21.6 | 323 | 4.7 20.4 183 | 2.0% | -45.80 [49.72, -41.88] |
| ODDYSEY FH    | -42.0 18.1 | 167 | 3.5 18.1 82 | 2.0% | -39.30 [44.06, -34.52] |
| ODDYSEY FH    | -39 22.9 | 72 | 6.4 18.5 35 | 1.7% | -30.30 [36.97, -42.35] |
| ODDYSEY JAPAN | -55 14.4 | 144 | 1.6 14.4 72 | 2.0% | -53.40 [57.47, -49.33] |
| ODDYSEY LONG TERM | -52.9 27.6 | 1553 | 1.2 28.1 789 | 2.1% | -54.00 [56.39, -51.81] |
| OSLER 1 and 2   | 0 | 0 | 2976 | 0 | Not estimable |
| Roth et al.      | 0 | 0 | 30 | 0 | Not estimable |
| RUTHERFORD 3     | -42.3 19.5 | 58 | 2.0 19.5 56 | 1.9% | -46.20 [51.42, -38.98] |
| RUTHERFORD 2     | -49.6 17.2 | 110 | 0.7 16.7 54 | 2.0% | -49.10 [54.69, -43.61] |
| RUTHERFORD 2     | -44.8 19.1 | 110 | 4.6 19.6 55 | 1.9% | -49.40 [55.69, -43.11] |
| Shm et al.       | -50.2 16 | 16 | 6.4 18.3 15 | 1.9% | -49.80 [56.68, -32.42] |
| Teramoto et al.  | -60 19.5 | 25 | -2 16.5 25 | 1.7% | -77.70 [68.68, -45.50] |
| TEILA PAETT     | -19.2 54 | 33 | 4 18.6 16 | 1.0% | -23.20 [43.75, -2.65] |
| YUKAWA 2         | -53.2 14.6 | 53 | 0.2 14.1 50 | 2.0% | -53.40 [58.94, -47.86] |
| YUKAWA 2         | -47.7 13.7 | 52 | 0.9 13 52 | 2.0% | -48.60 [51.93, -41.67] |
| YUKAWA 2         | -64.8 15.6 | 50 | 0.7 15.4 49 | 1.9% | -65.50 [71.81, -59.39] |
| YUKAWA 2         | -58 15 | 51 | 1.0 15.7 51 | 1.9% | -55.10 [52.06, -50.14] |
| YUKAWA 2         | -62.9 17 | 51 | 2.5 18 52 | 1.9% | -60.30 [67.23, -53.37] |
| YUKAWA 2         | -54.8 15.6 | 50 | 2.4 16.3 50 | 1.9% | -57.20 [63.45, -50.95] |

Subtotal (95% CI) 9474 5377 81.6% -49.73 [51.73, -47.57]
Figure S15. Funnel plot: all-cause mortality
Figure S16. Funnel plot: cardiovascular mortality

Figure S17. Funnel plot: myocardial infarction
Figure S18. Funnel plot: stroke

Figure S19. Funnel plot: coronary revascularization
Figure S20. Funnel plot: unstable angina

Figure S21. Funnel plot: congestive heart failure exacerbation
Figure S22. Funnel plot: neurocognitive adverse events

Figure S23. Funnel plot: diabetes mellitus
Figure S24. Funnel plot: increase in creatine kinase

Figure S25. Funnel plot: myalgia
**Figure S26.** Funnel plot: increase in alanine/aspartate aminotransferase

**Figure S27.** Funnel plot: treatment emergent serious adverse events
Figure S28. Funnel plot: LDL- Cholesterol

Figure S29. Funnel plot: HDL- cholesterol
Figure S30. Funnel plot: total cholesterol

Figure S31. Funnel plot: lipoprotein(a)
**Figure S32.** Funnel plot: apolipoprotein B
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