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

Aris Karatasakis, MD; Barbara A Danek, MD; Judit Karacsonyi, MD; Bavana V Rangan, BDS, MPH; Michele K Roesle, RN, BSN; Thomas Knickelbine, MD; Michael D Miedema, MD, MPH; Houman Khalili; MD; Zahid Ahmad, MD; Shuaib Abdullah, MD; Subhash Banerjee, MD; Emmanouil S. Brilakis, MD, PhD

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 inhibitors; 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

Lipid-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 doses[1]; a high proportion of patients do not achieve adequate reduction of low-density lipoprotein cholesterol (LDL-C), despite high-intensity statin therapy[2]; 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

From the VA North Texas Health Care System and University of Texas Southwestern Medical Center, Dallas, TX (A.K., B.A.D., J.K., B.V.R., M.K.R., H.K., Z.A., S.A., S.B., E.S.B.); Rutgers New Jersey Medical School, Newark, NJ (A.K., B.A.D.); Minneapolis Heart Institute, Minneapolis, MN (T.K., M.D.M., E.S.B.).

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

Correspondence to: Emmanouil S. Brilakis, MD, PhD, Minneapolis Heart Institute, 920 E 28th Street #300, Minneapolis, MN 55407. E-mail: esbrilakis@gmail.com

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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.

(proprotein convertase subtilisin/kexin type 9) inhibitors evolocumab and alirocumab have been associated with reduction of LDL-C levels and recently with improved cardiovascular outcomes in the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial.[5] However, questions remain about the patients who are most likely to derive the greatest clinical benefits and the safety profile of this class of drugs. We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to examine the cumulative evidence on the clinical efficacy and safety of currently available PCSK9 inhibitors, with an emphasis on cardiovascular outcomes.

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[6] and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[7]

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.

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[8,9] 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[10] 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,[11–14] 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.

Statistical Analyses

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

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.[15] Heterogeneity and inconsistency were assessed by using the Cochran Q test and I^2 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 metaregression 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] Alirocumab 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

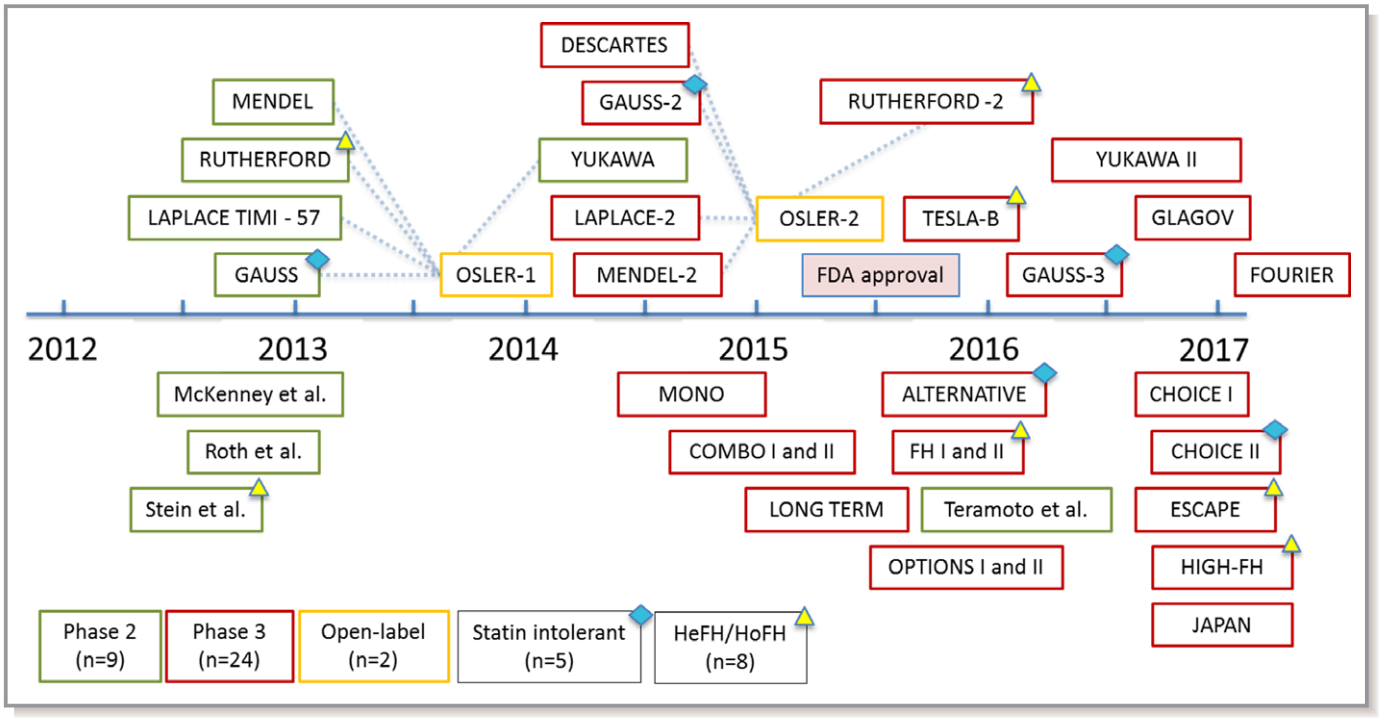

Figure 1. Timeline of randomized controlled trials of alirocumab and evolocumab. FDA indicates US Food and Drug Administration; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia.

available and abstracted for 45 503 (99.9%). Risk of methodological bias was assessed as low in most studies (Figure S2).

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, 1.9% versus 2.2%; OR: 0.71 [95% CI, 0.47–1.09]; P=0.12, I^2=18%, heterogeneity P=0.26). 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 not 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, I^2=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, I^2=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, I^2=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, I^2=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, I^2=0%, heterogeneity P=0.90).

Congestive Heart Failure Exacerbation

Twenty-three RCTs (42 151 participants) were included in the analysis of congestive heart failure exacerbation 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, I^2=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, I^2=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, I^2=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

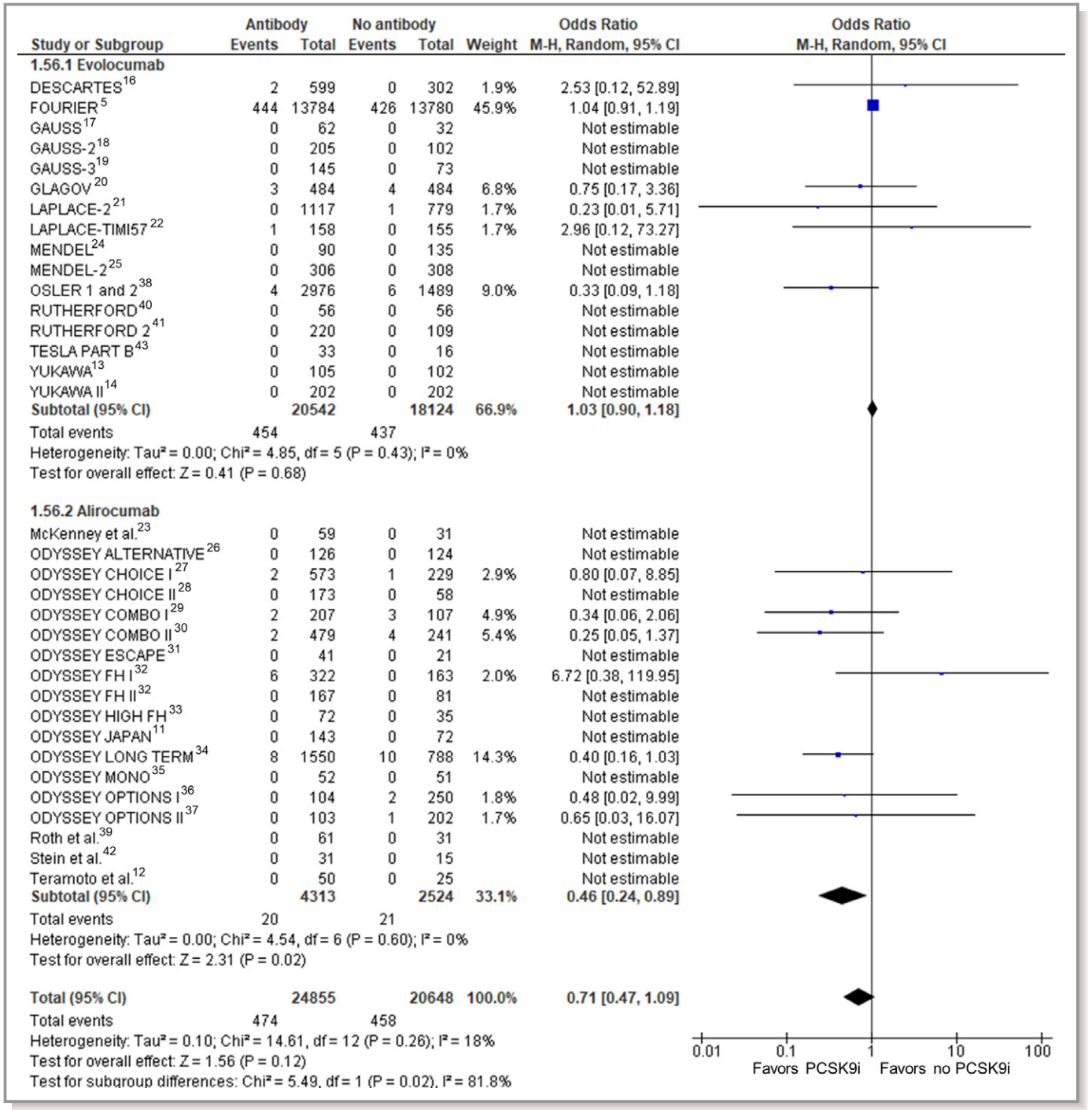

Figure 2. All-cause mortality. Forrest plot showing the odds ratio for all-cause mortality with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (PCSK9i) compared with no PCSK9i. The pooled odds ratio was calculated with random effects according to the Mantel-Haenszel (M-H) method. Marker size is proportional to the study weight. CI indicates confidence interval.

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

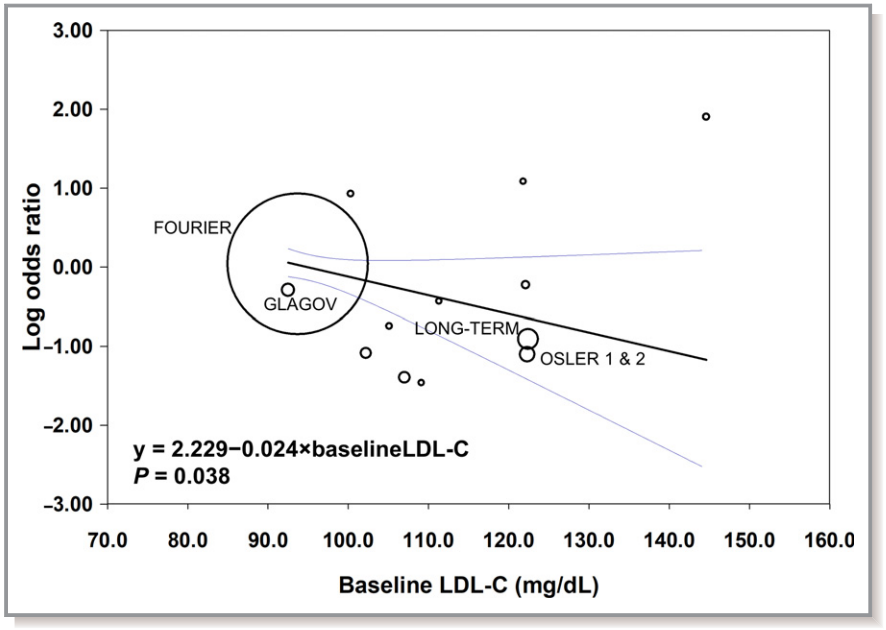

Figure 3. Study-level metaregression analysis with random effects showing the relationship between baseline low-density lipoprotein cholesterol (LDL-C) and all-cause mortality. Circle size is proportional to the study weight; 95% confidence intervals shown in blue.

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,

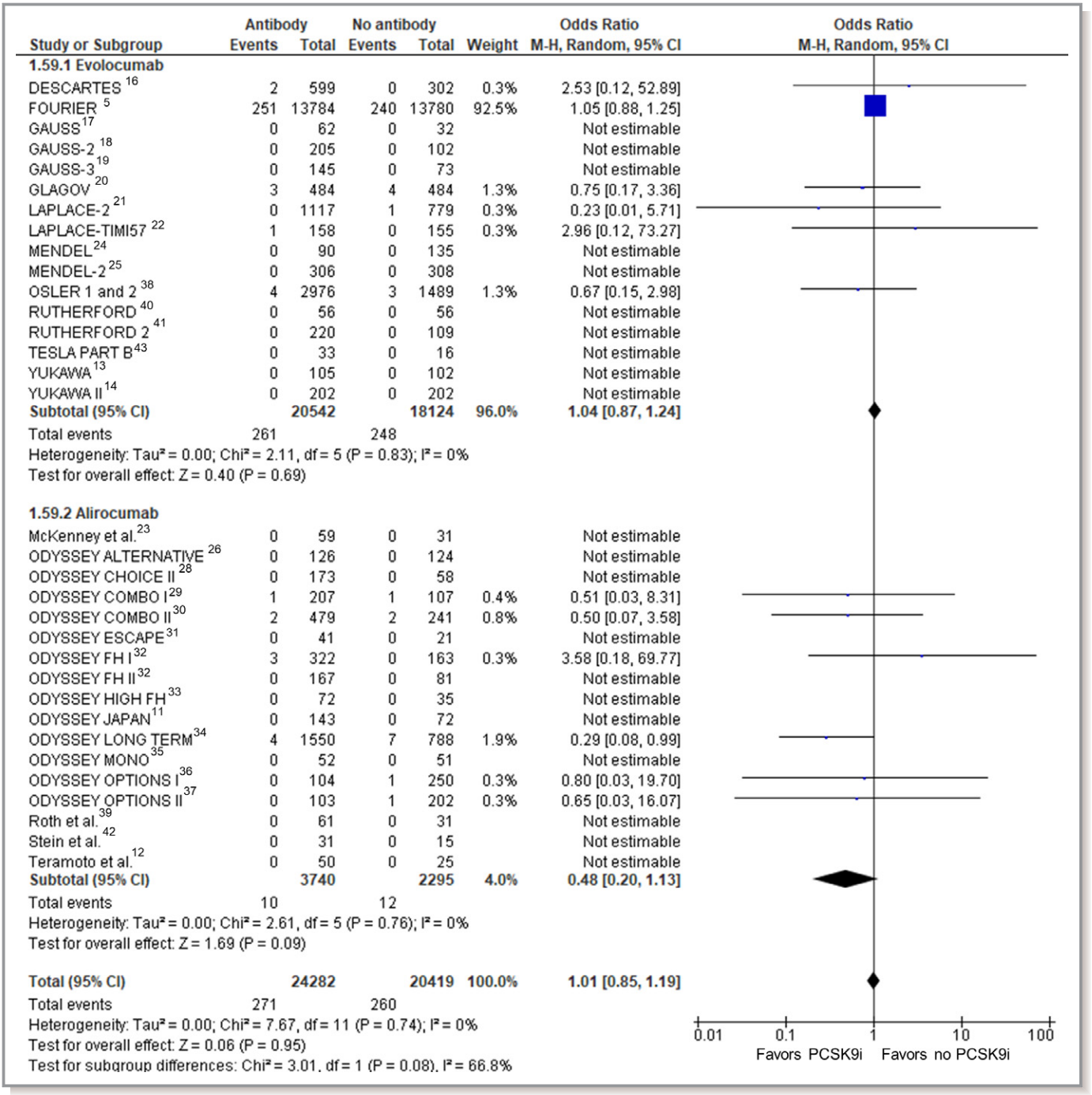

Figure 4. Cardiovascular mortality. Forrest plot showing the odds ratio for cardiovascular mortality with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (PCSK9i) compared with no PCSK9i. The pooled odds ratio was calculated with random effects according to the Mantel-Haenszel (M-H)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

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

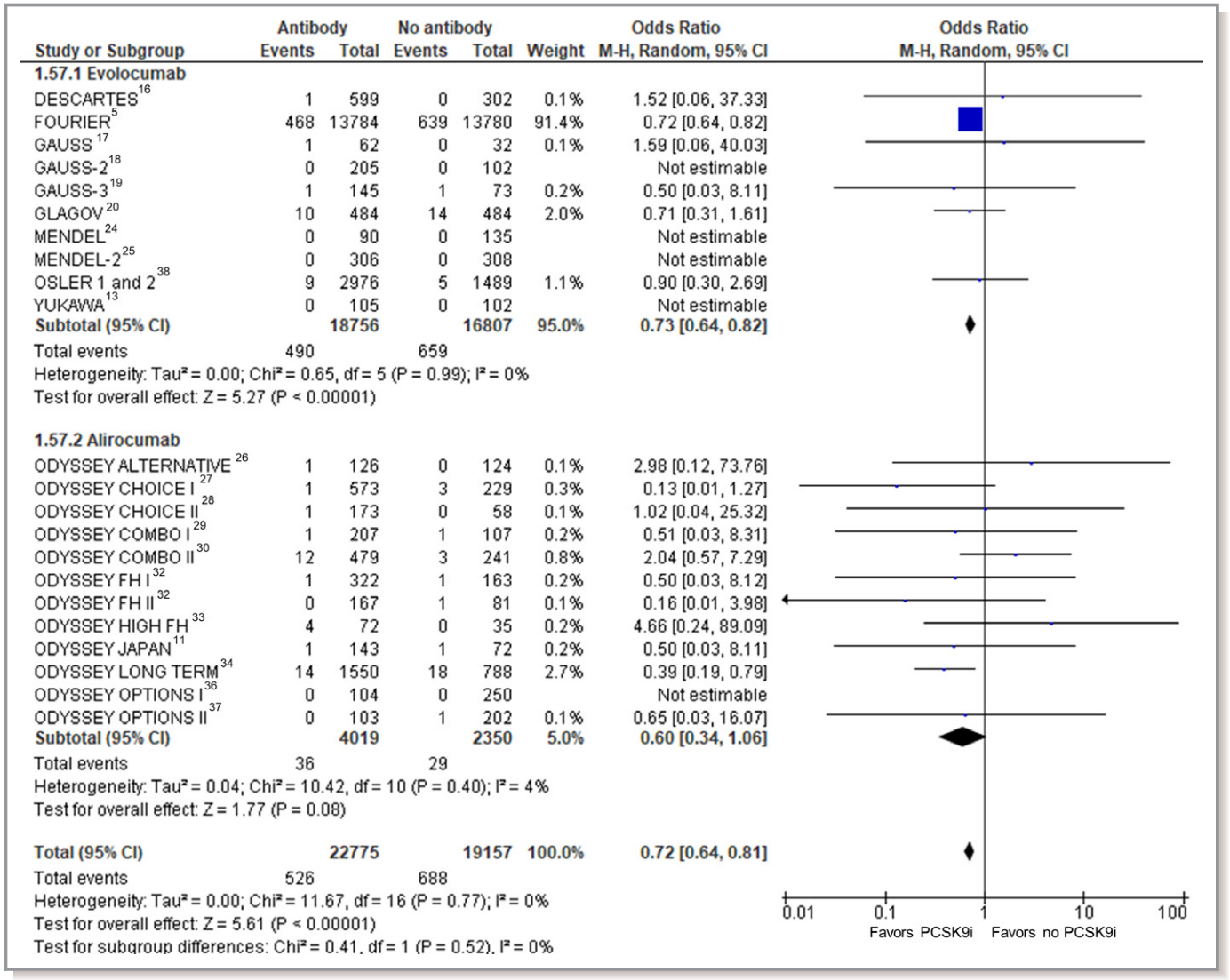

Figure 5. Myocardial infarction. Forrest plot showing the odds ratio for myocardial infarction with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (PCSK9i) compared with no PCSK9i. The pooled odds ratio was calculated with random effects according to the Mantel-Haenszel (M-H) method. Marker size is proportional to the study weight. CI indicates confidence interval.

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

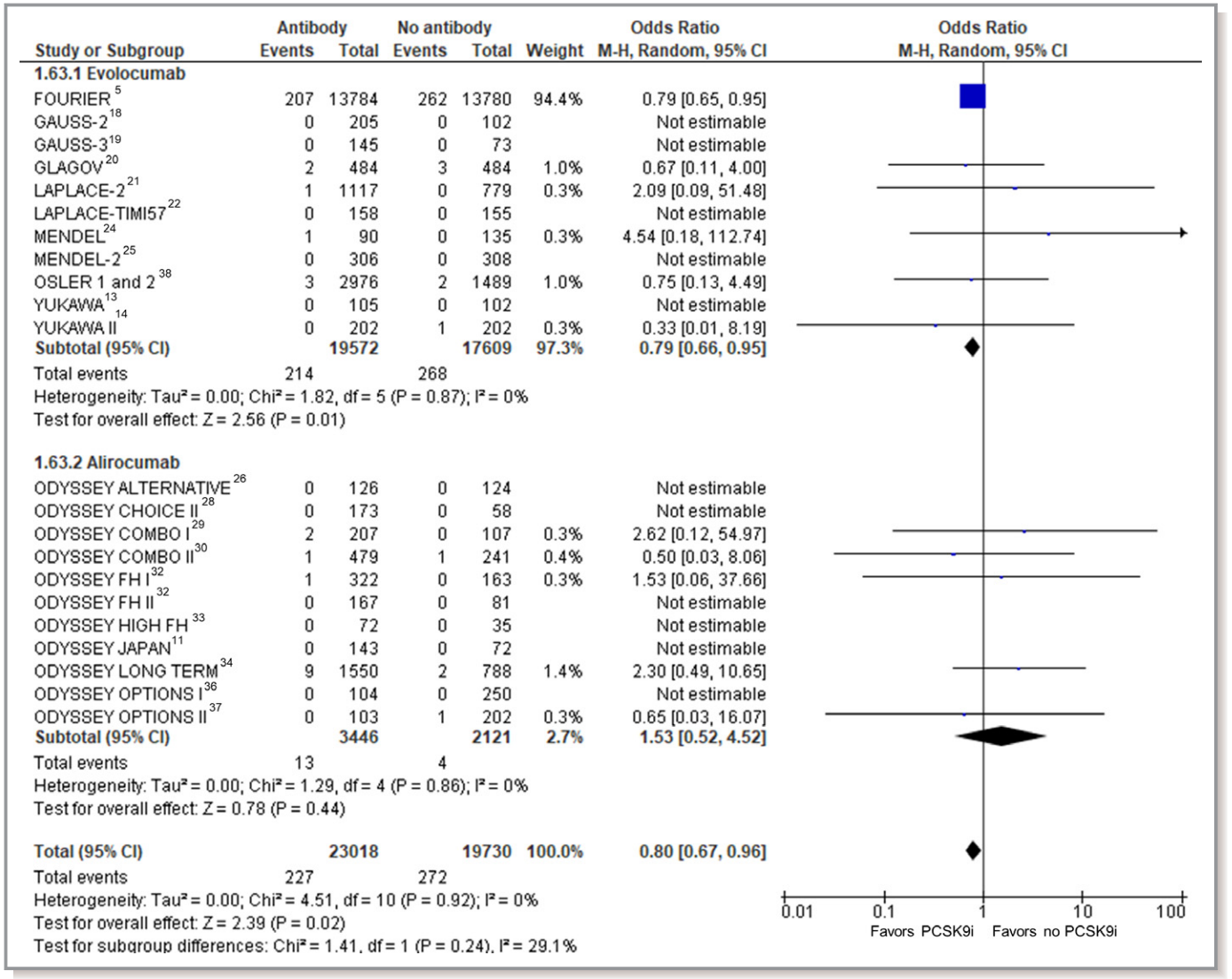

Figure 6. Stroke. Forrest plot showing the odds ratio for stroke with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (PCSK9i) compared with no PCSK9i. The pooled odds ratio was calculated with random effects according to the Mantel-Haenszel (M-H) method. Marker size is proportional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

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

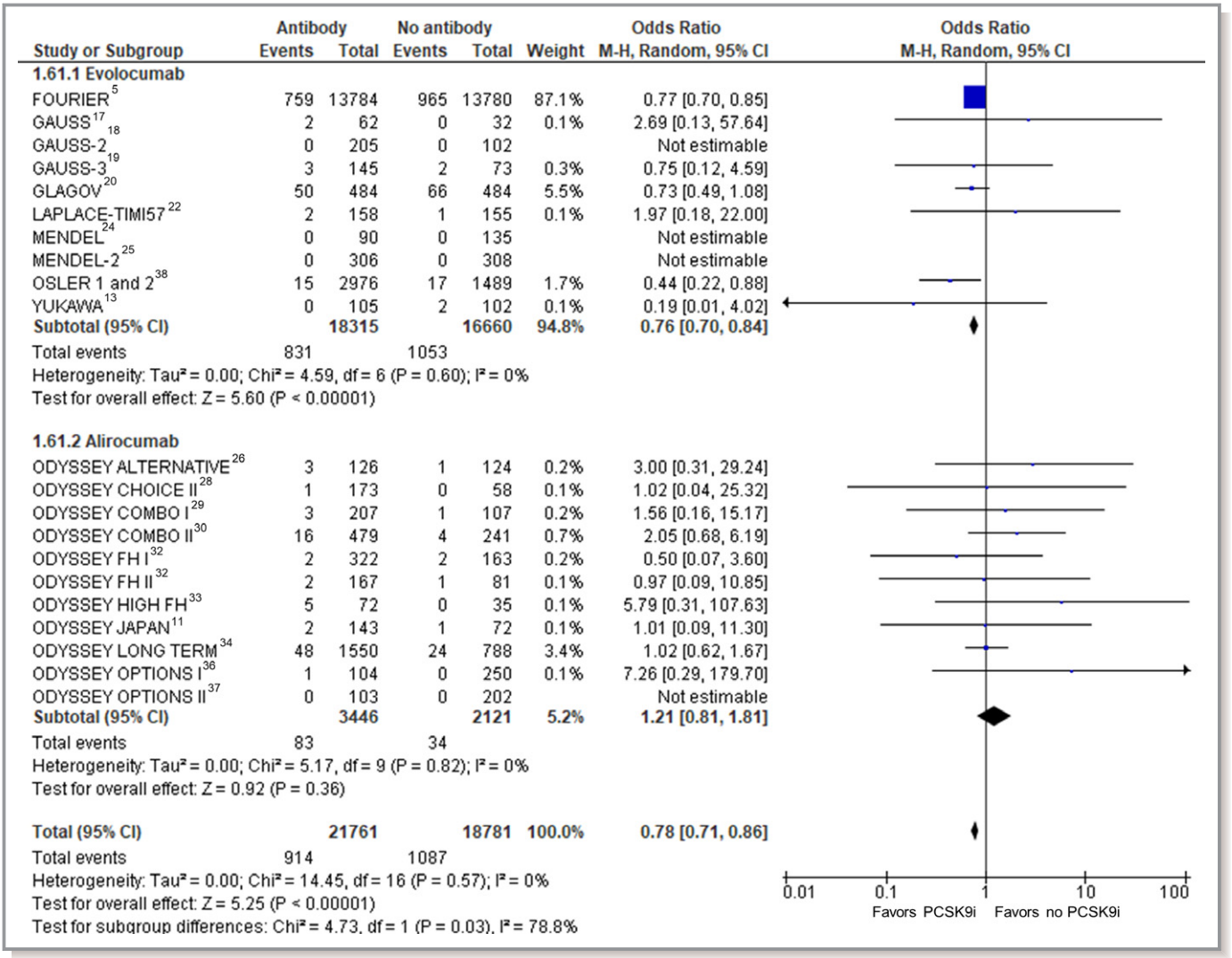

Figure 7. Coronary revascularization. Forrest plot showing the odds ratio for coronary revascularization with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (PCSK9i) compared with no PCSK9i. The pooled odds ratio was calculated with random effects according to the Mantel-Haenszel (M-H) method. Marker size is proportional to the study weight. CI indicates confidence interval.

<25 mg/dL.[57] 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.[58] 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,[59] 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.[60] 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.[9] 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

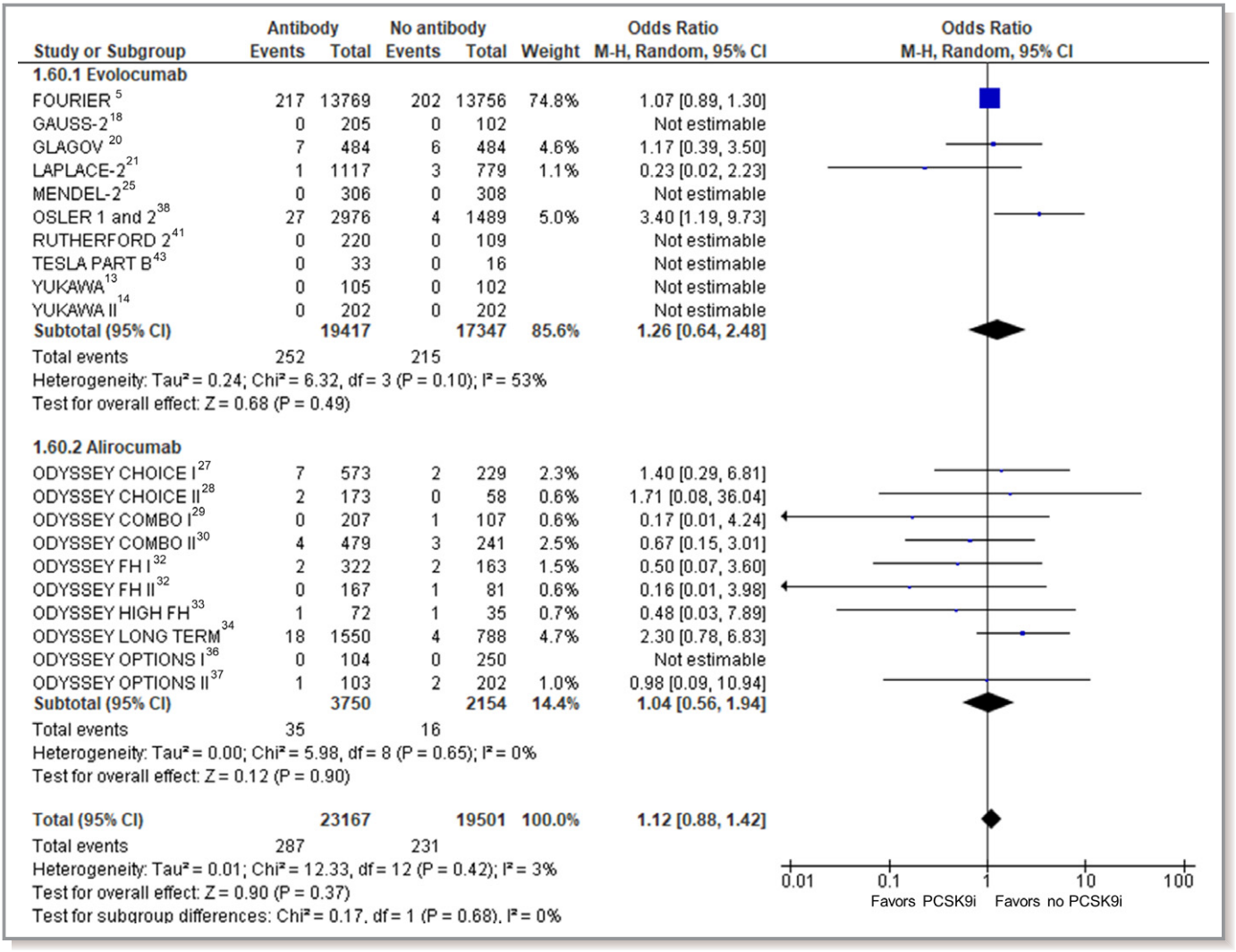

Figure 8. Neurocognitive adverse events. Forrest plot showing the odds ratio for neurocognitive adverse events with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (PCSK9i) compared with no PCSK9i. The pooled odds ratio was calculated with random effects according to the Mantel-Haenszel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

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 heterogeneity 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 administration, treatment with PCSK9 inhibitors results in improvement 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 (significant); and has ownership in HygeiaTel and MDCARE Global (spouse, significant). Dr Brilakis has received research grants

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

Table S1. Study Characteristics

Study	Year	Phase	Treatment duration, weeks	Investigational drug and dose	Control	Population	Statin	clinicaltrials.gov ID
DESCARTES [1]	2014	3	48	Evolocumab 420 mg Q4W	Placebo	HC	Both	NCT01516879
FOURIER[2]	2017	3	113	Evolocumab 420 mg Q4W/140 mg Q2W	Placebo	HC	Both	NCT01764633
GAUSS [3]	2012	2	12	Evolocumab 420 mg Q4W ± Ezetimibe 10 mg	Ezetimibe	HC - Statin intolerant	Non-intensive	NCT01375764
GAUSS-2 [4]	2014	3	12	Evolocumab 420 mg/140 mg Q2W	Ezetimibe	HC - Statin intolerant	Non-intensive	NCT01763905
GAUSS-3 [5]	2016	3	24	Evolocumab 420 mg Q4W	Ezetimibe	HC - Statin intolerant	None	NCT01984424
GLAGOV [6]	2016	3	76	Evolocumab 420 mg Q4W	Placebo	HC - CAD	Both	NCT01813422
LAPLACE-2 [7]	2014	3	12	Evolocumab 420 mg Q4W/140 mg Q2W	Ezetimibe/ placebo	HC	Both	NCT01763866
LAPLACE-TIMI57 [8]	2012	2	12	Evolocumab 420 mg Q4W/140 mg Q2W	Placebo	HC	Both	NCT01380730
McKenney et al. [9]	2012	2	12	Alirocumab 150 mg Q2W/300 mg Q4W	Placebo	HC	Both	NCT01288443
MENDEL[10]	2012	2	12	Evolocumab 420 mg Q4W/140 mg Q2W	Ezetimibe/ placebo	HC	None	NCT01375777
MENDEL-2 [11]	2014	3	12	Evolocumab 420 mg Q4W/140 mg Q2W	Ezetimibe/ placebo	HC	None	NCT01763827

ODYSSEY								
ALTERNATIVE [12]	2015	3	24	Alirocumab 75 mg Q2W with potential up-titration to 150 mg Q2W	Ezetimibe	HC - Statin intolerant	None	NCT01709513
CHOICE I [13]	2016	3	48	Alirocumab 75 mg Q2W/ 300 mg Q4W with potential up-titration to 150 mg Q2W	Placebo	HC	Both	NCT01926782
CHOICE II [14]	2016	3	24	Alirocumab 75 mg Q2W/150 mg Q4Wwith potential up-titration to 150 mg Q2W	Placebo	HC - Statin intolerant	None	NCT02023879
COMBO I [15]	2015	3	52	Alirocumab 75mg Q2W, increased to 150mg Q2W prn	Placebo	HC	Both	NCT01644175
COMBO II [16]	2015	3	104*	Alirocumab 75mg Q2W with potential up-titration to 150 mg Q2W	Ezetimibe	HC	Both	NCT01644188
ESCAPE [17]	2016	3	18	Alirocumab 150mg Q2W	Placebo	HeFH	Both	NCT02326220
FH I [18]	2015	3	78	Alirocumab 75mg Q2W with potential up-titration to 150 mg Q2W	Placebo	HeFH	Both	NCT01623115
FH II [18]	2015	3	78	Alirocumab 75mg Q2W with potential up-titration to 150 mg Q2W	Placebo	HeFH	Both	NCT01709500

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

YUKAWA [32]	2014	2	12	Evolocumab 420 mg Q4W/140 mg Q2W	Placebo	HC	Both	NCT01652703
YUKAWA II [33]	2016	3	12	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; Q2W, 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 UltrasoundLAPLACE-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/m^2	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%
FOURIER[2]	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
MENDEL[10]	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

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	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	51.2	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%

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	Moderator variable					
	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

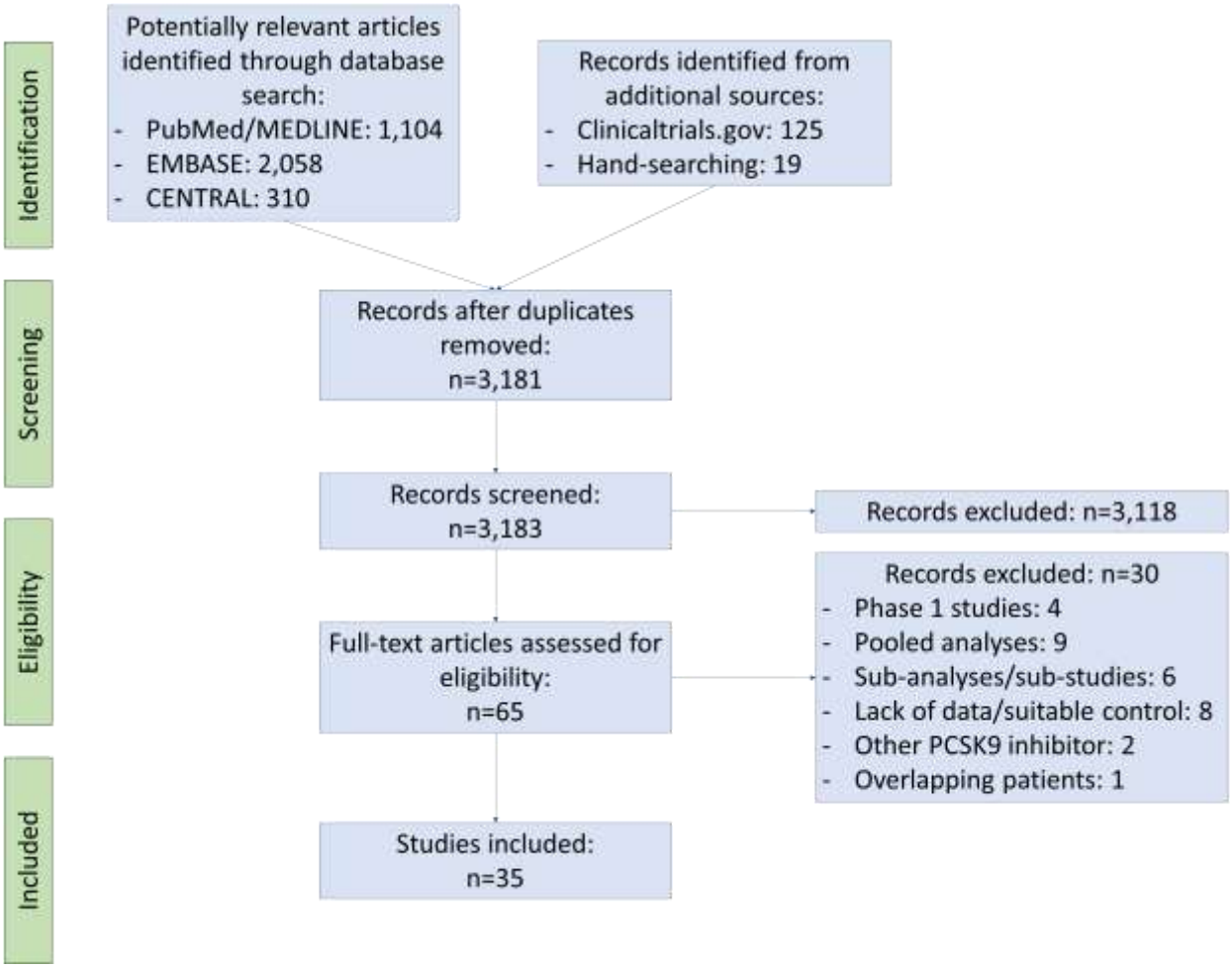


Figure S2. Risk of bias assessment of included studies

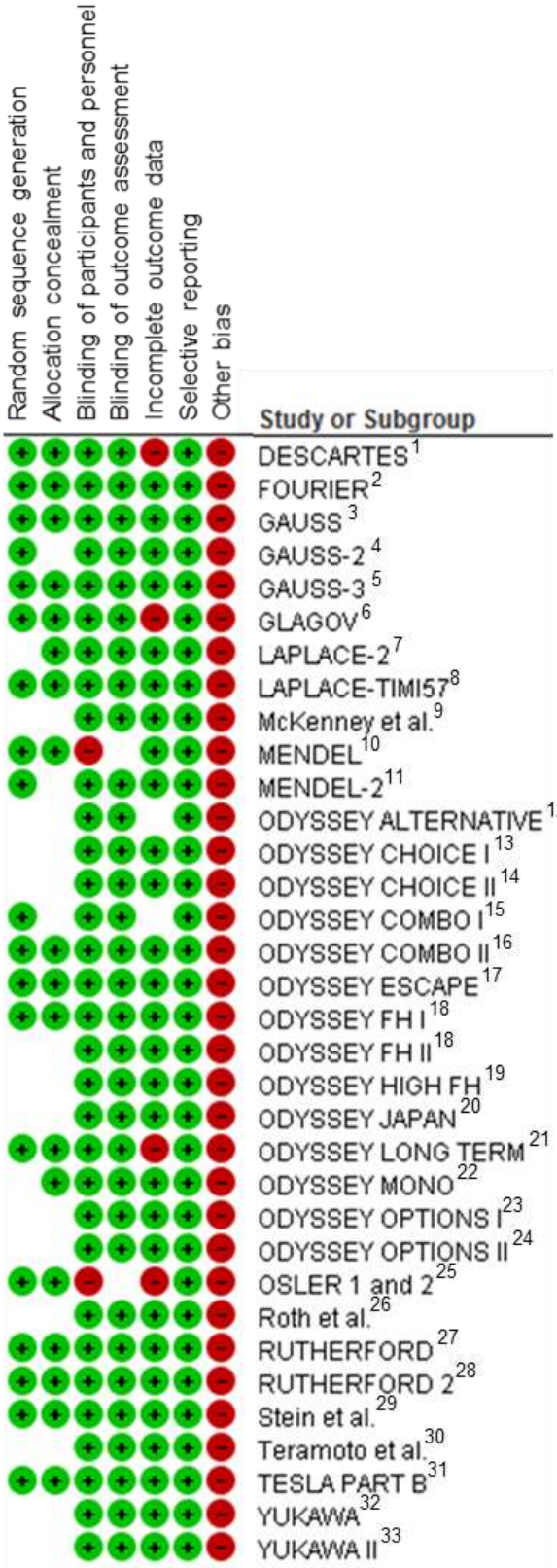


Figure S3. Unstable angina

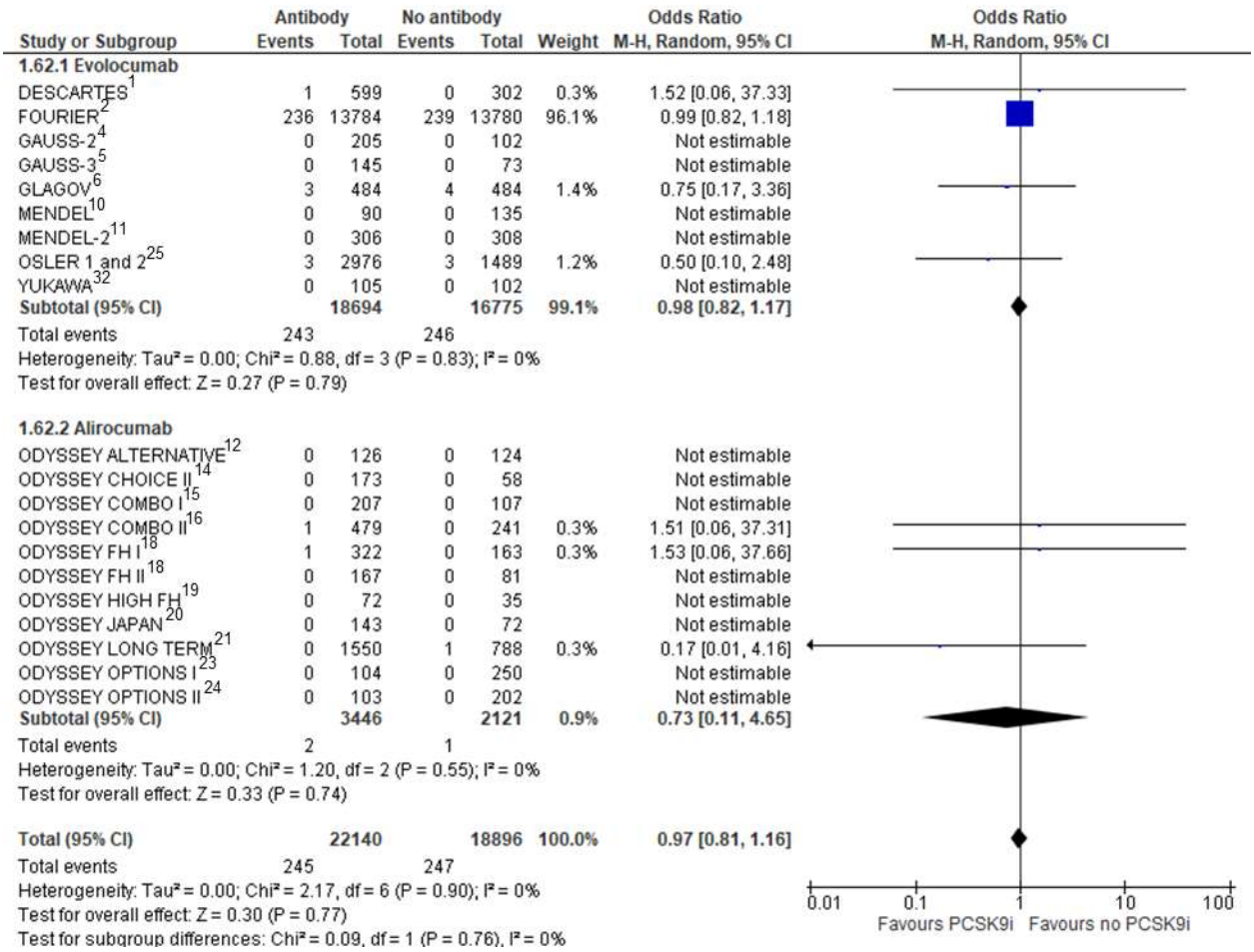


Figure S4. Congestive heart failure exacerbation

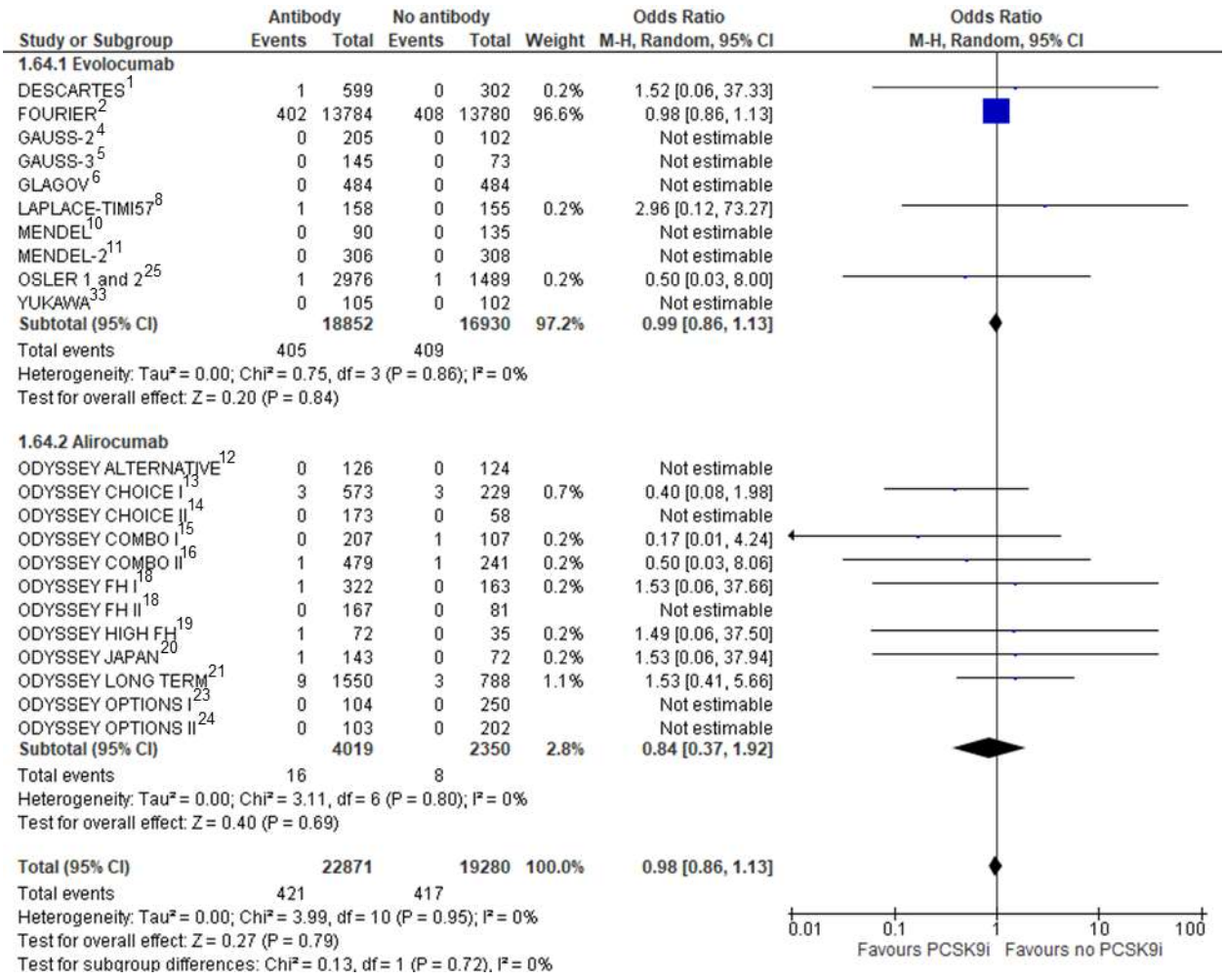


Figure S5. Diabetes mellitus

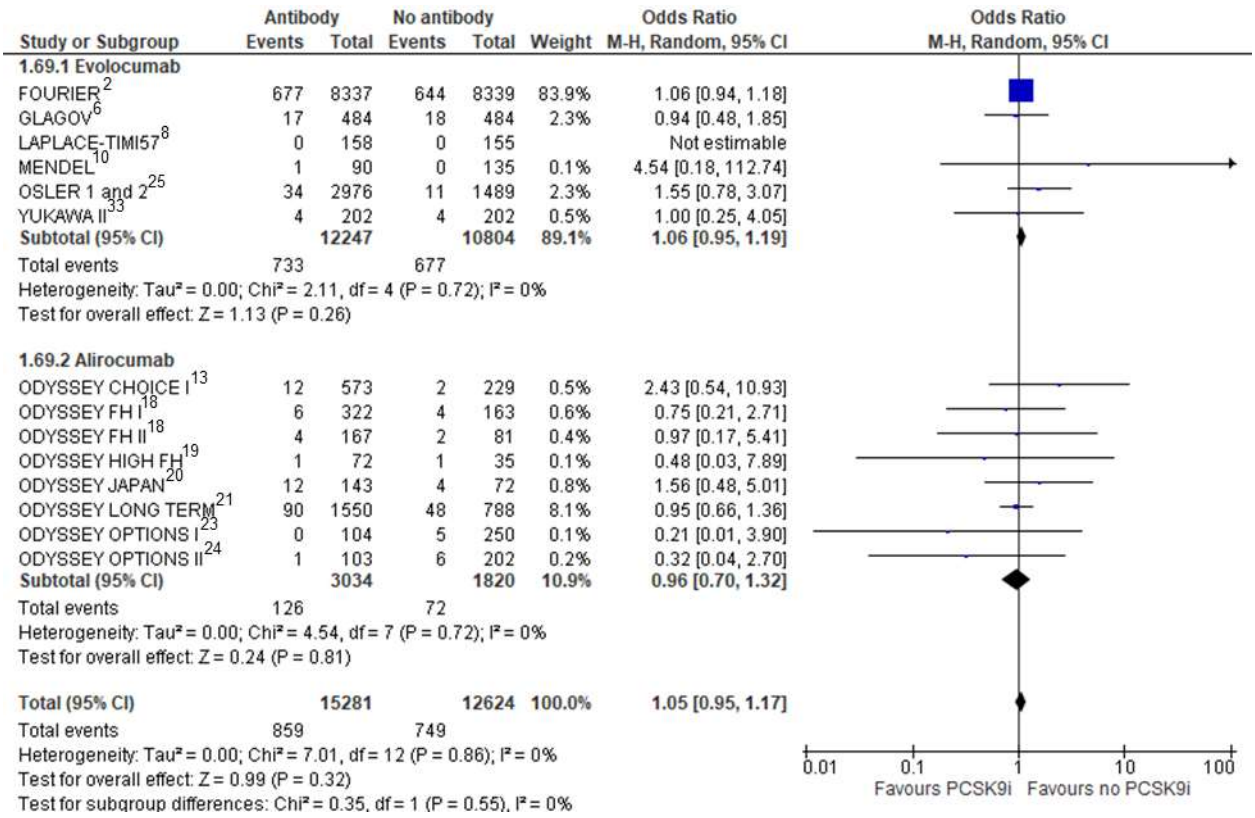


Figure S6. Increase in creatine kinase

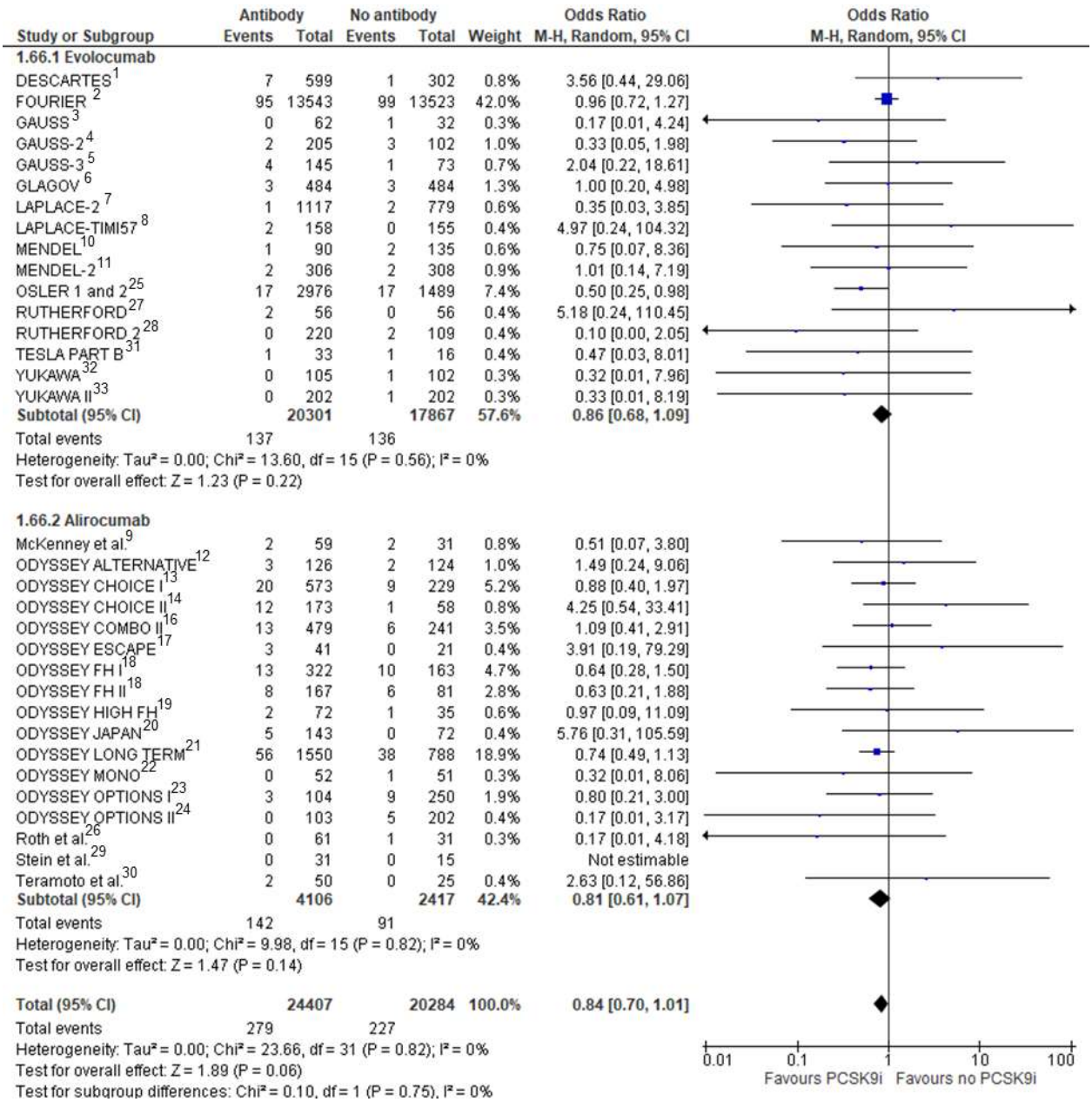


Figure S7. Myalgia

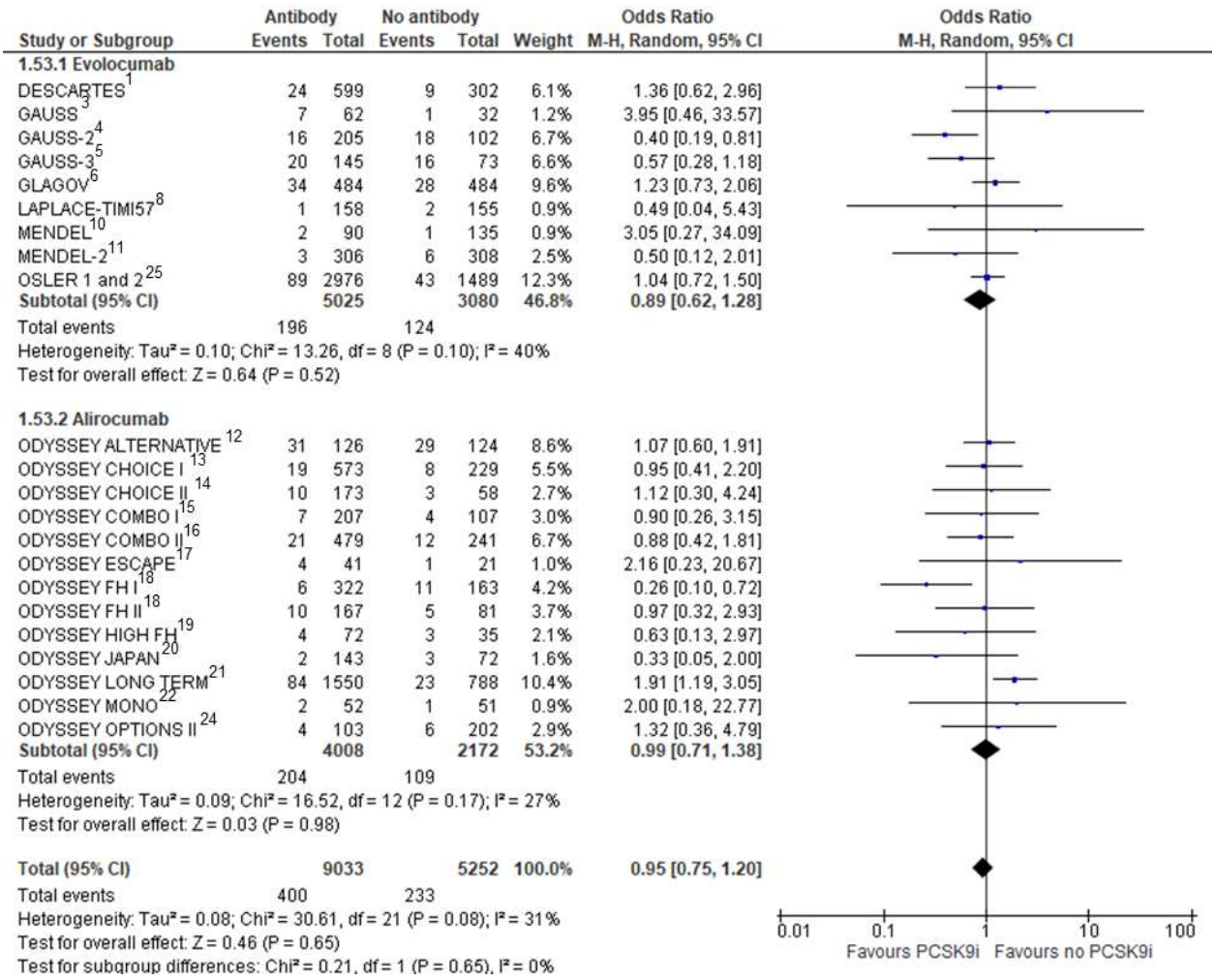


Figure S8. Alanine/aspartate aminotransferase increase

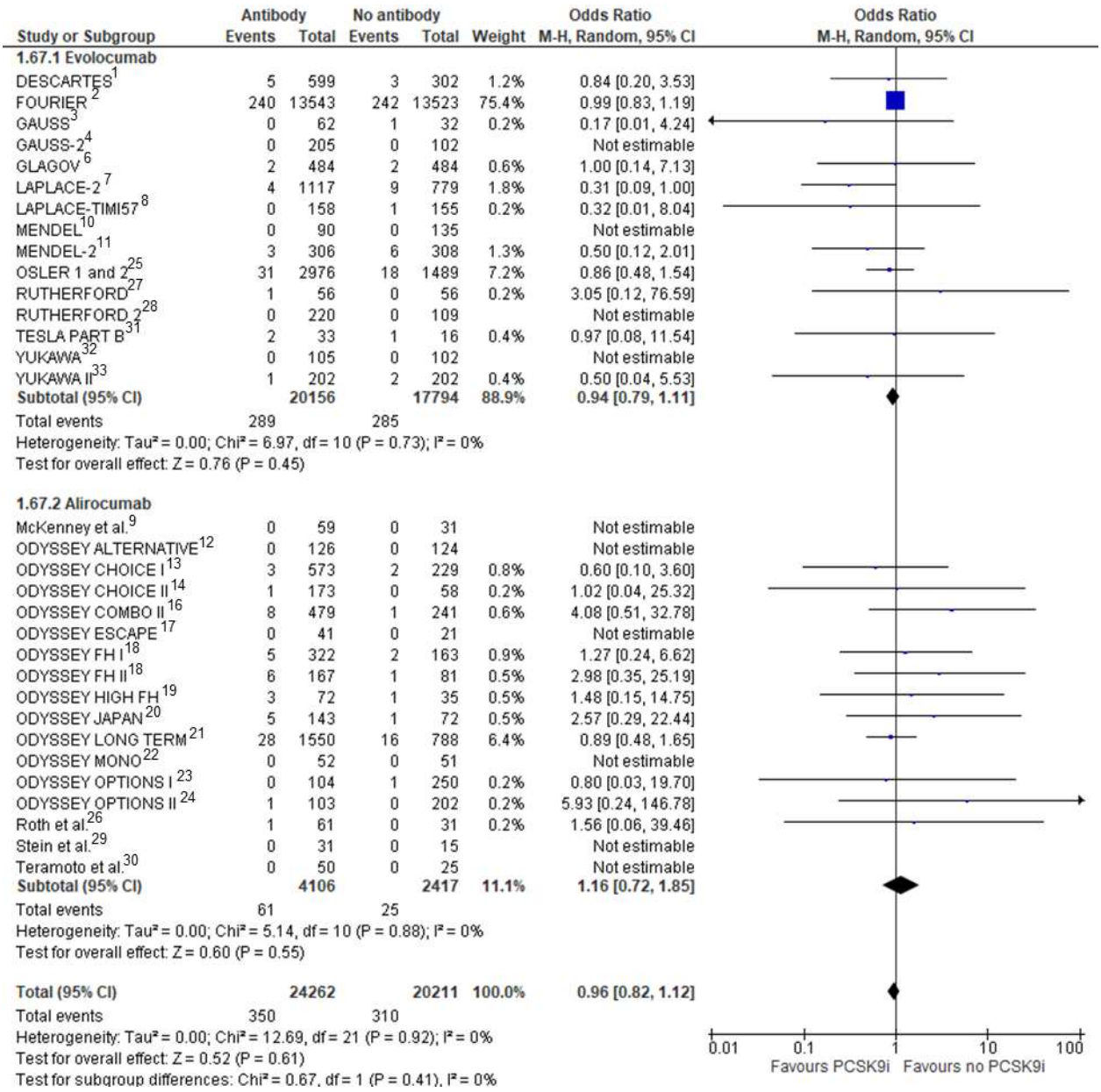


Figure S9. Treatment emergent serious adverse events

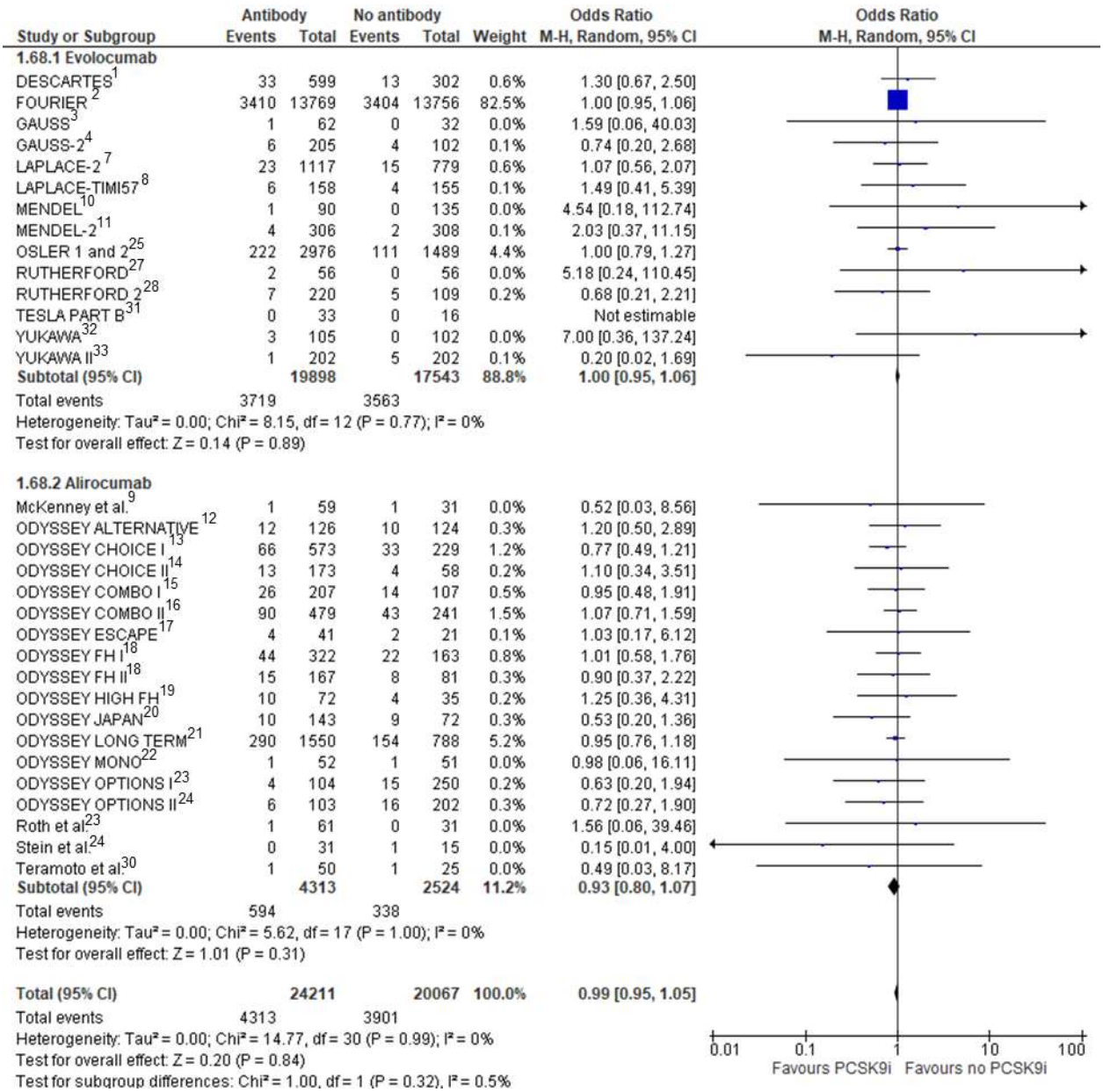


Figure S10. Low-density lipoprotein cholesterol % change from baseline

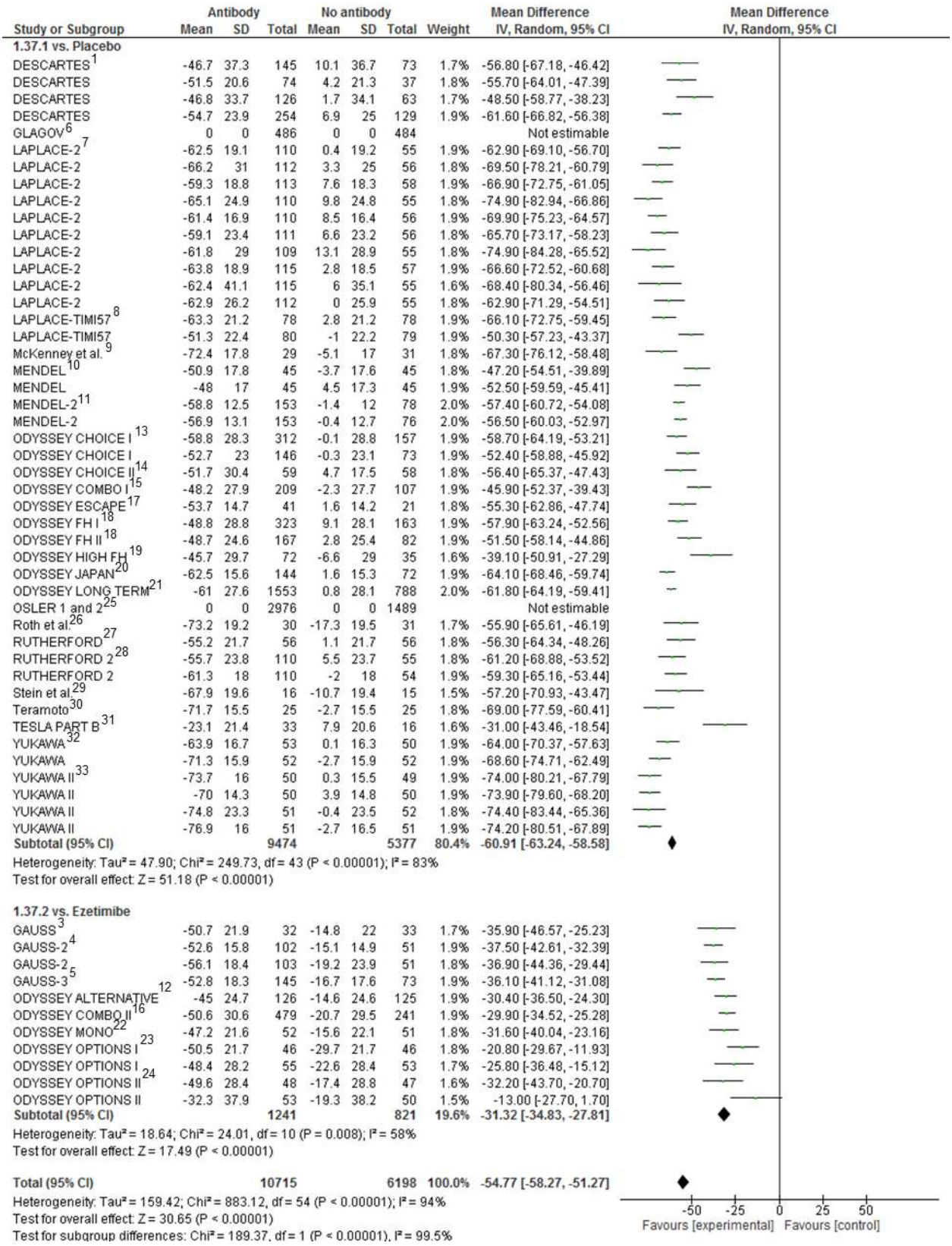


Figure S11. High-density lipoprotein cholesterol % change from baseline

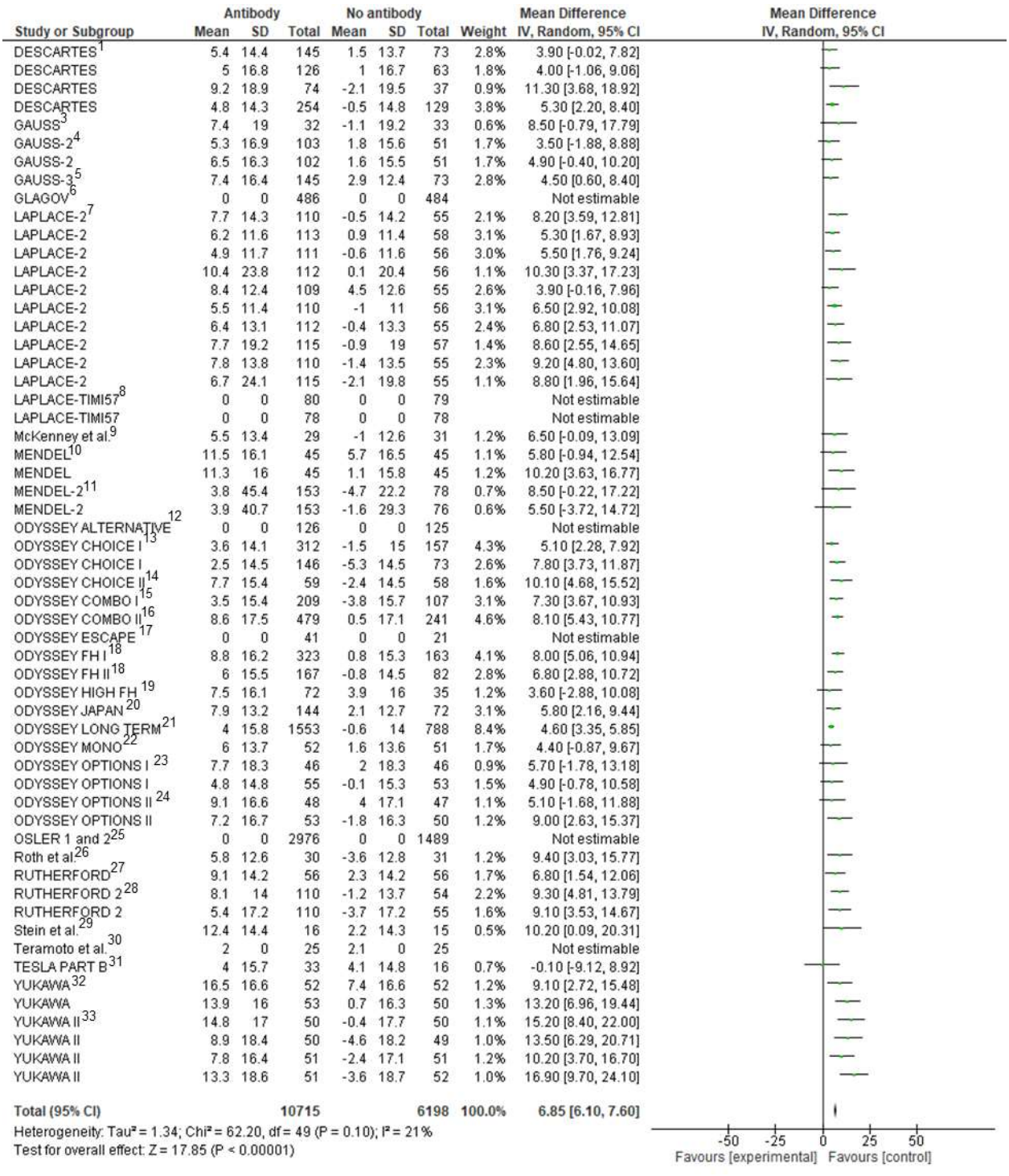


Figure S12. Total cholesterol % change from baseline

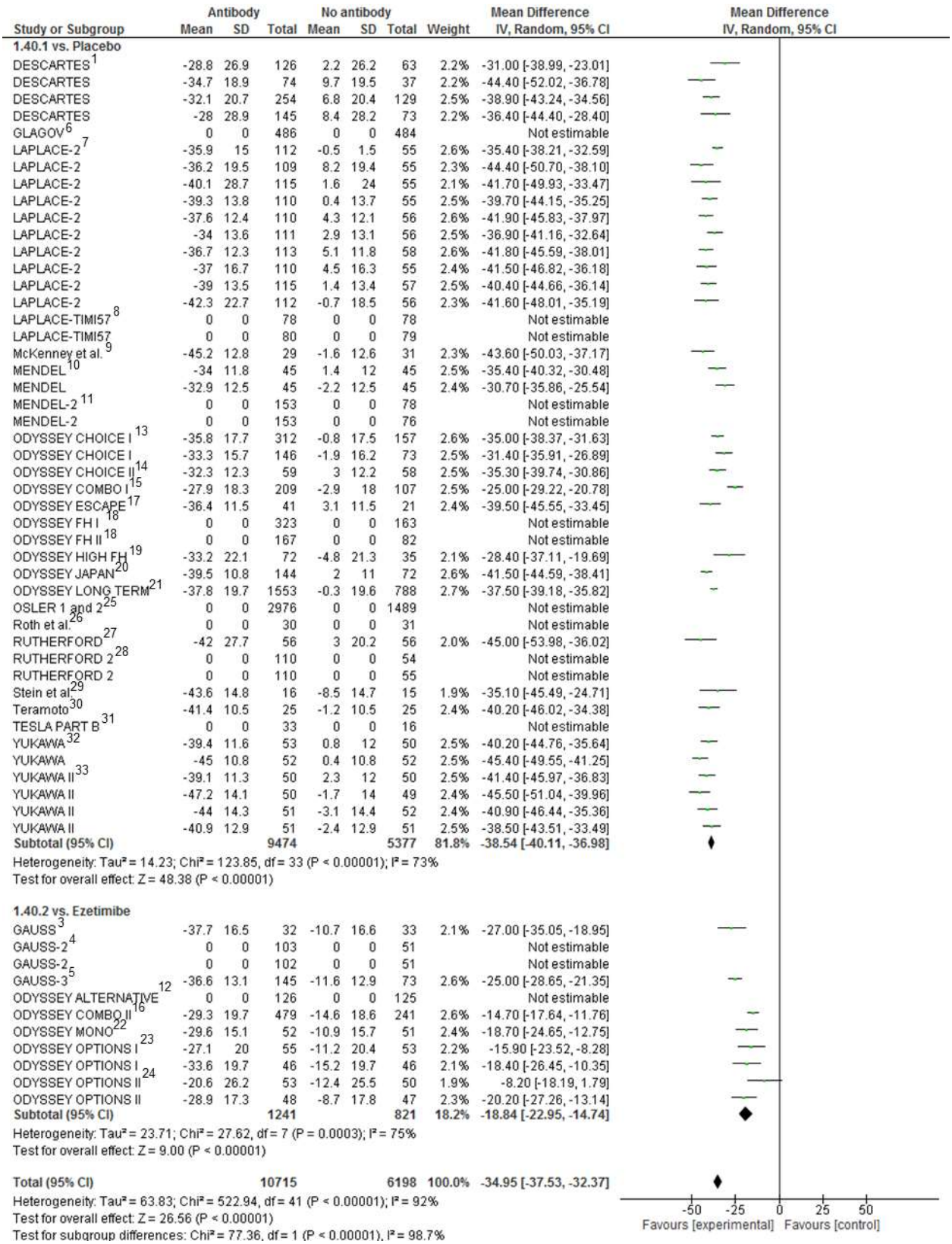


Figure S13. Lipoprotein(a) % change from baseline

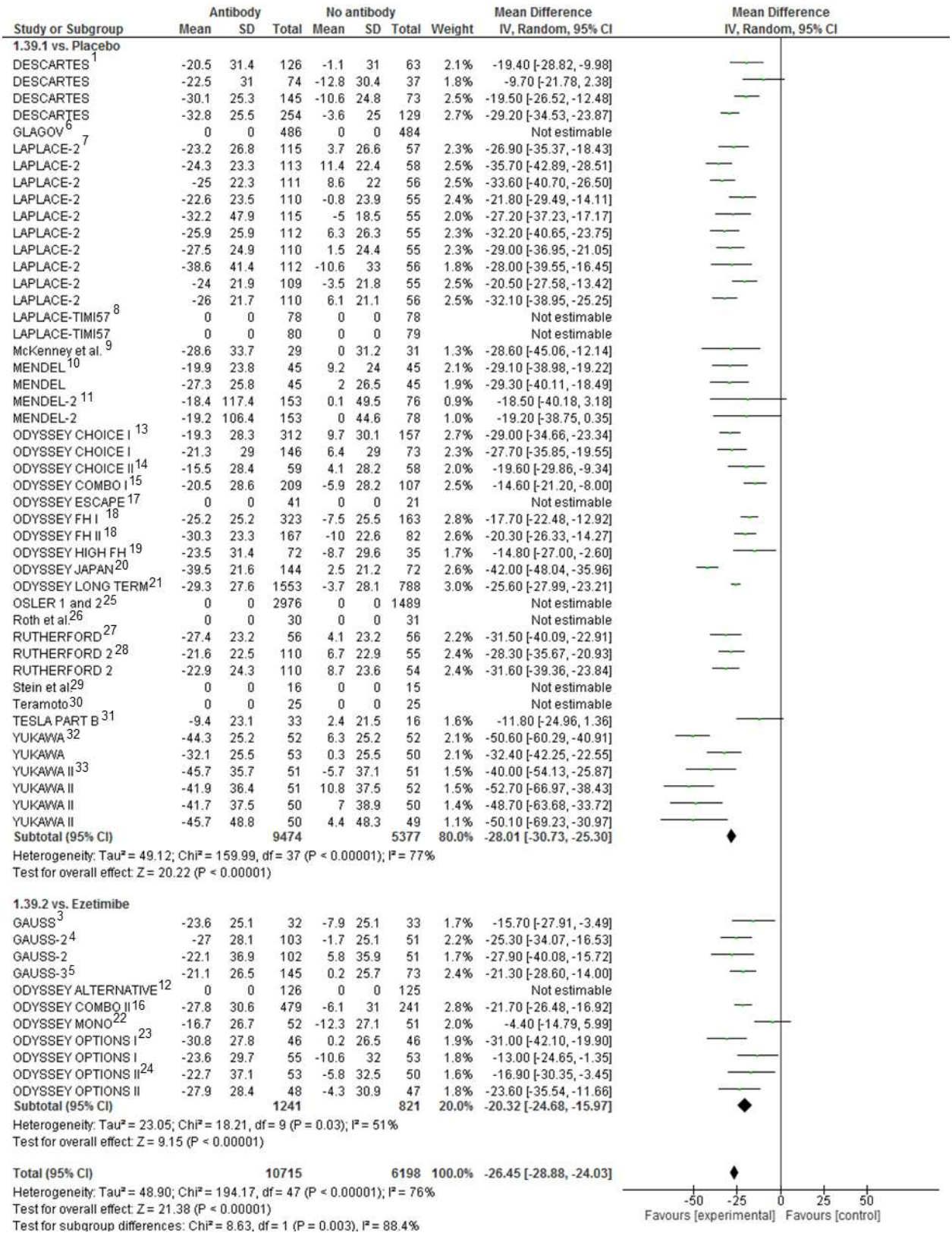


Figure S14. Apolipoprotein B % change from baseline

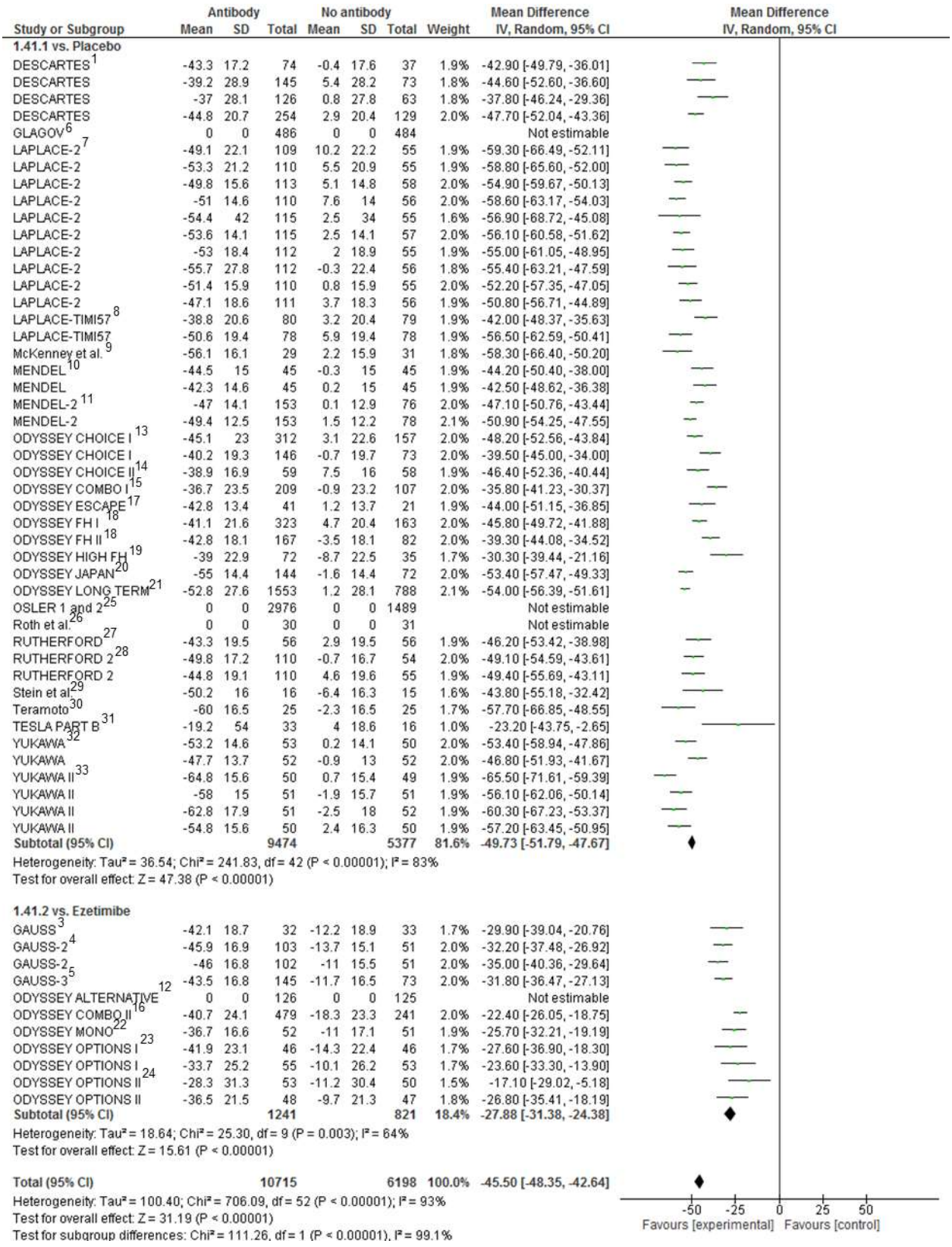


Figure S15. Funnel plot: all-cause mortality

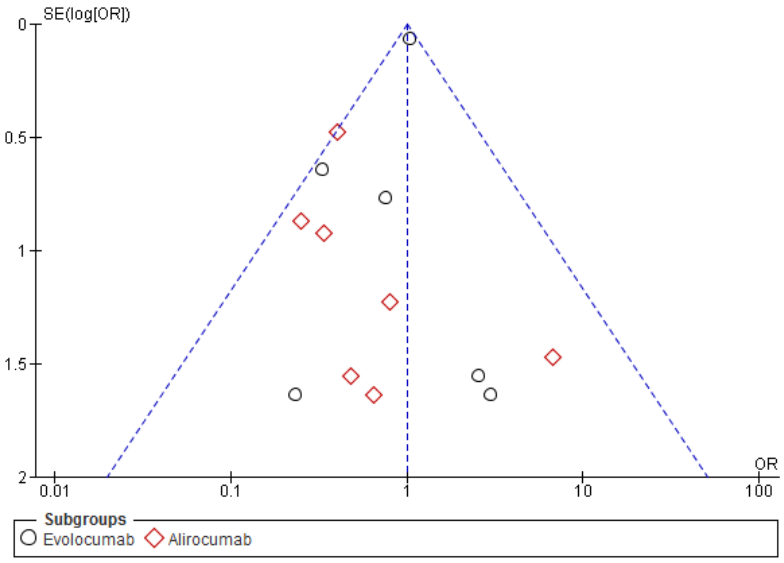


Figure S16. Funnel plot: cardiovascular mortality

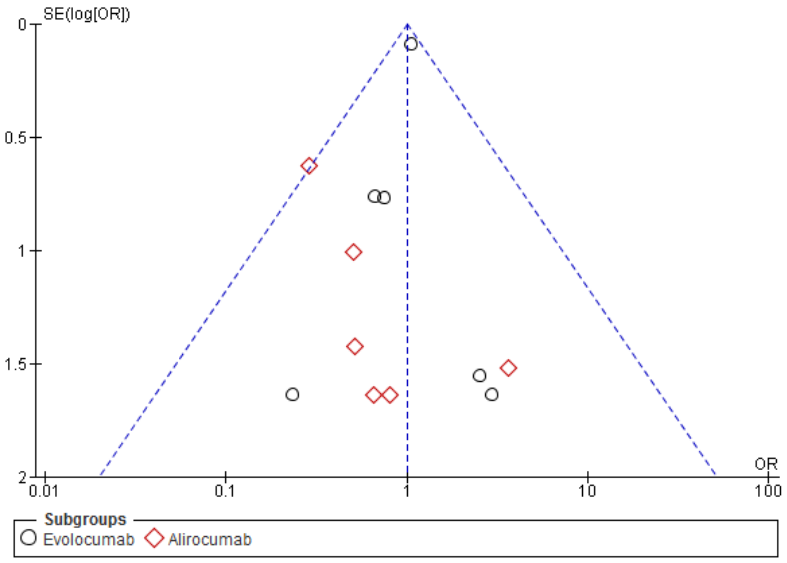


Figure S17. Funnel plot: myocardial infarction

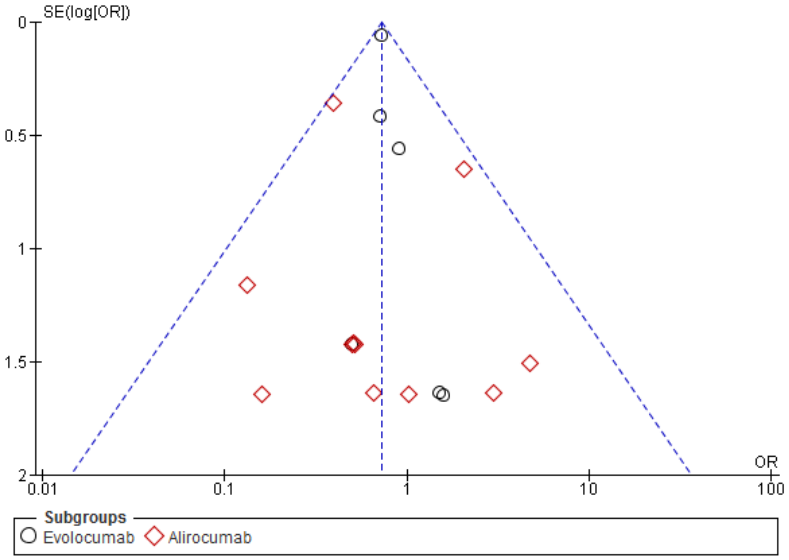


Figure S18. Funnel plot: stroke

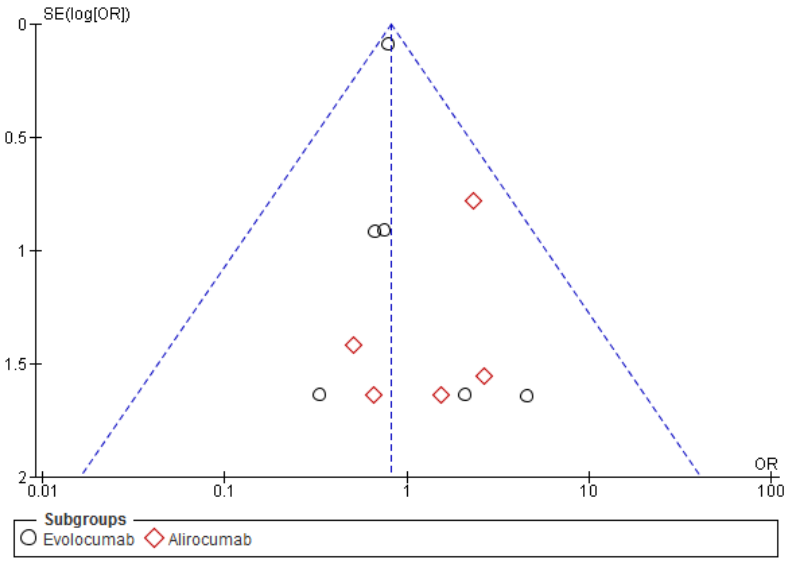


Figure S19. Funnel plot: coronary revascularization

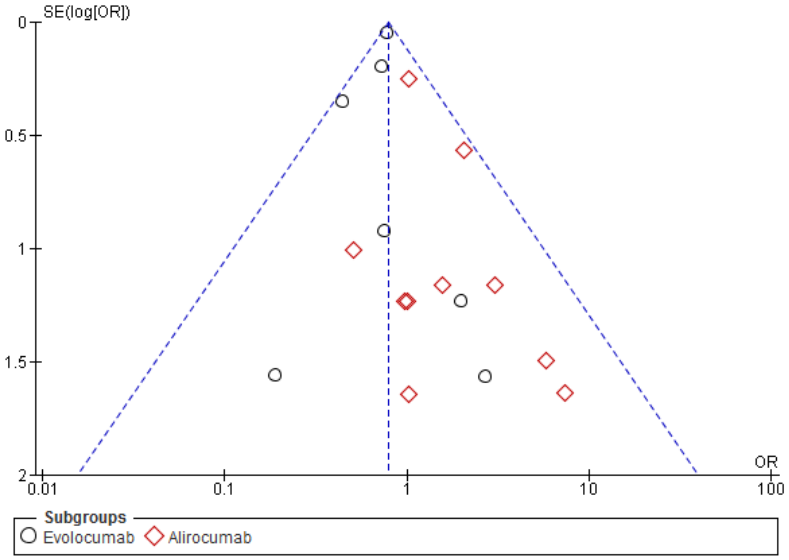


Figure S20. Funnel plot: unstable angina

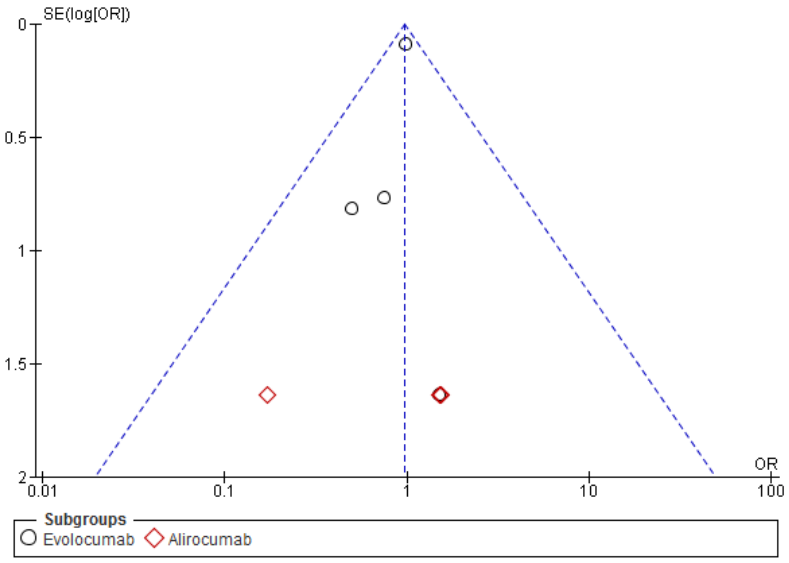


Figure S21. Funnel plot: congestive heart failure exacerbation

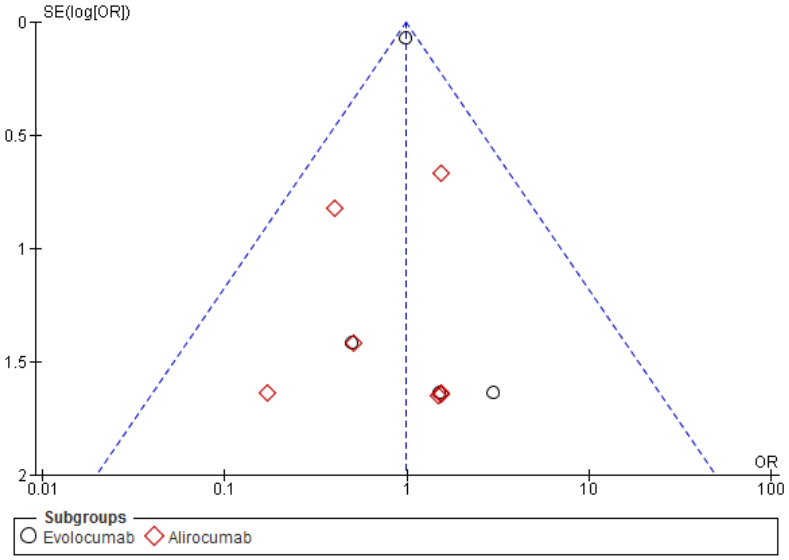


Figure S22. Funnel plot: neurocognitive adverse events

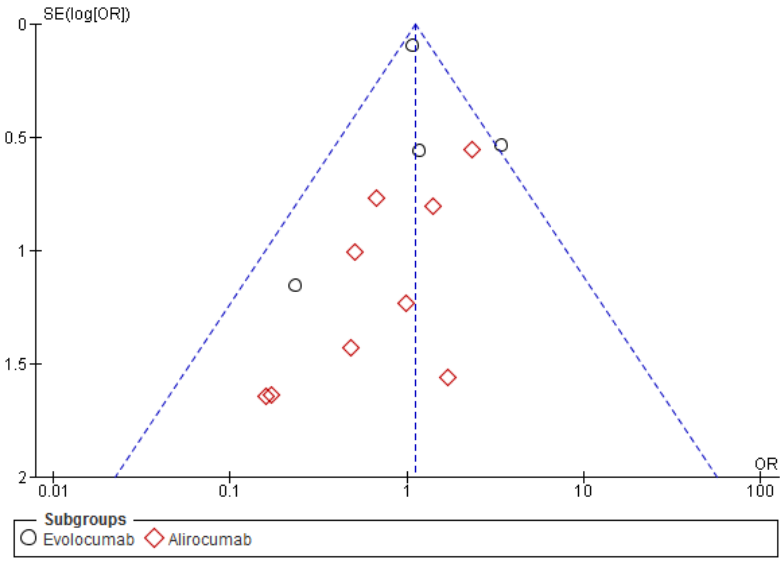


Figure S23. Funnel plot: diabetes mellitus

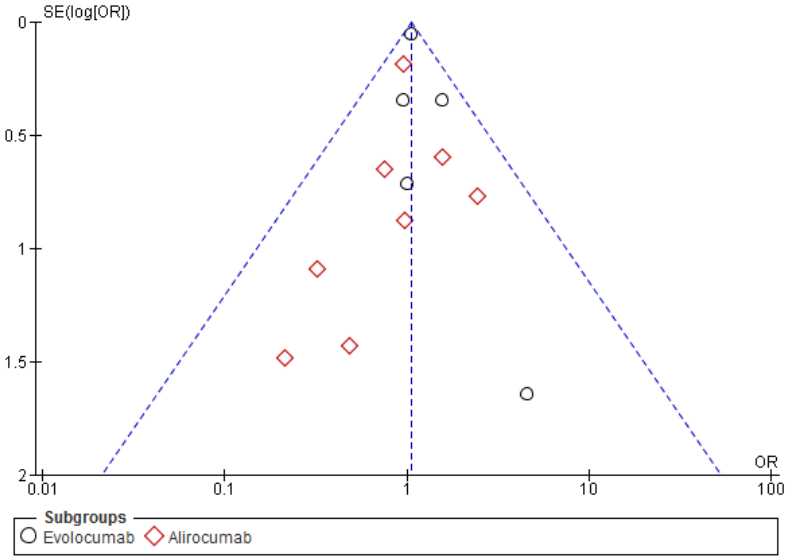


Figure S24. Funnel plot: increase in creatine kinase

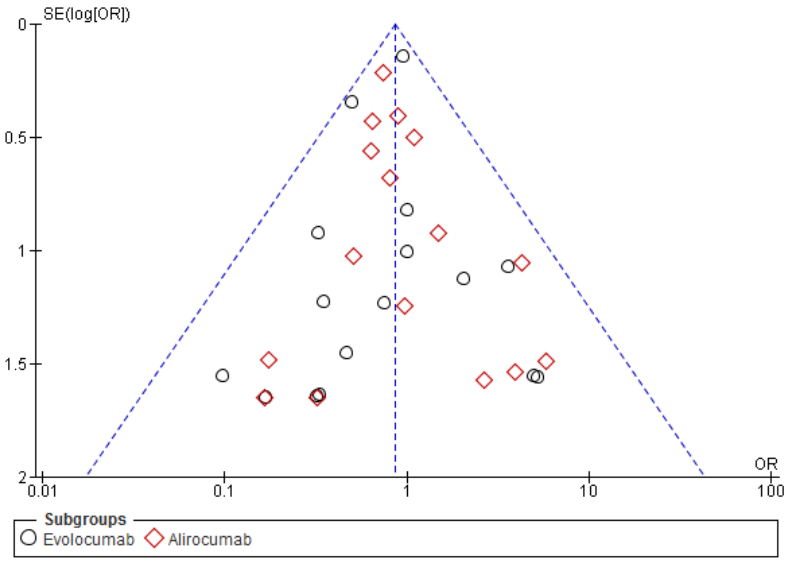


Figure S25. Funnel plot: myalgia

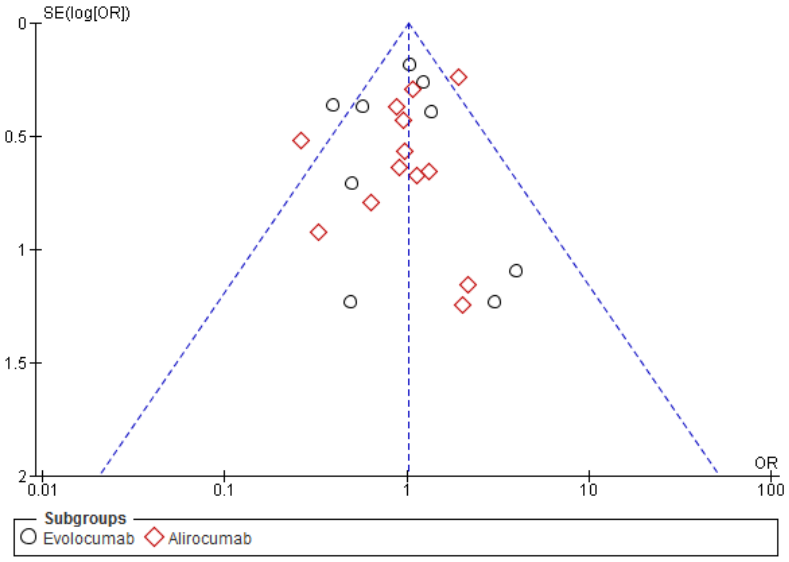


Figure S26. Funnel plot: increase in alanine/aspartate aminotransferase

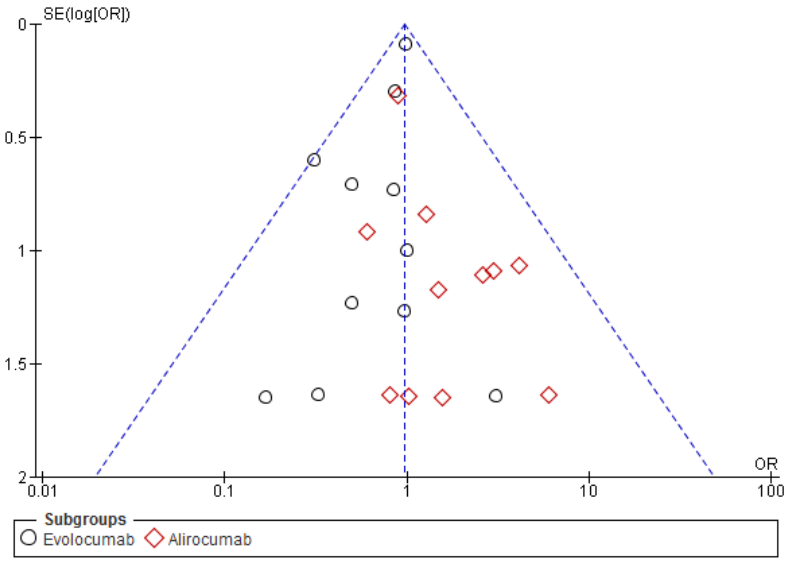


Figure S27. Funnel plot: treatment emergent serious adverse events

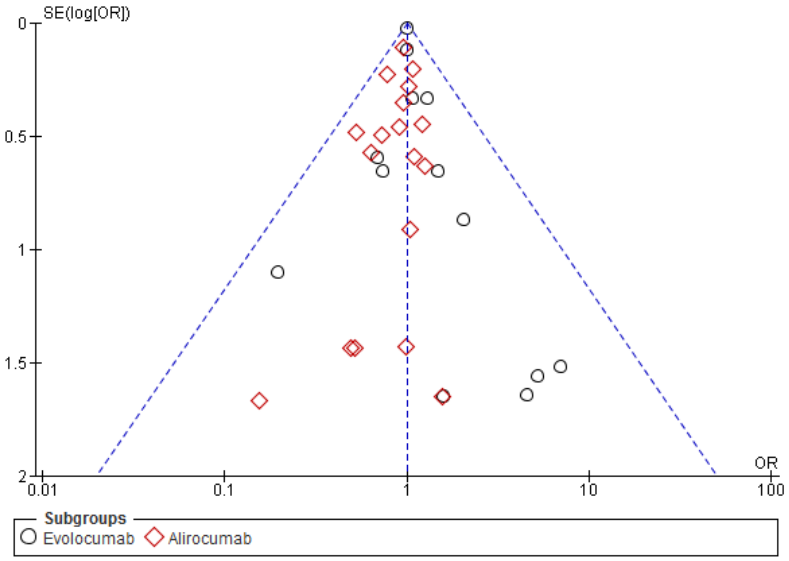


Figure S28. Funnel plot: LDL- Cholesterol

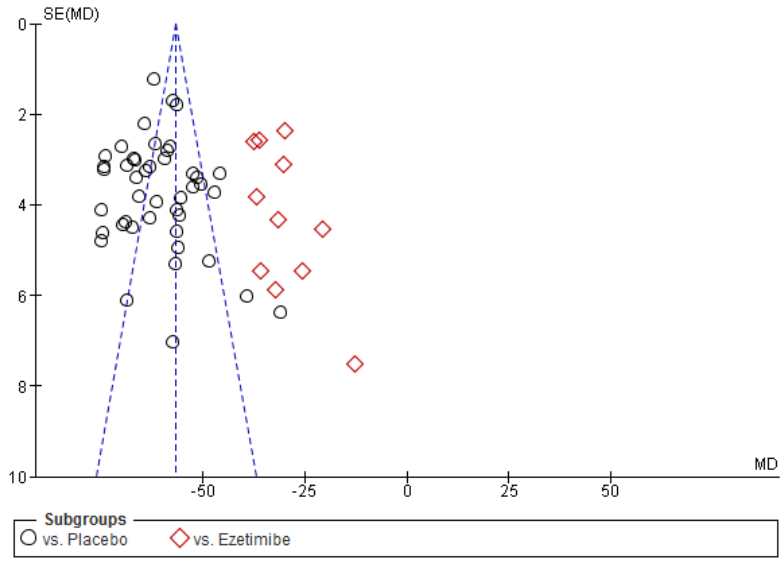


Figure S29. Funnel plot: HDL- cholesterol

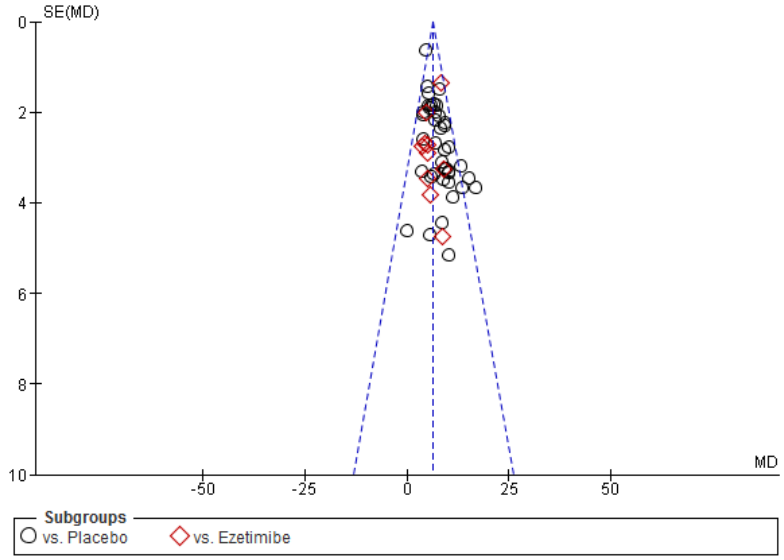


Figure S30. Funnel plot: total cholesterol

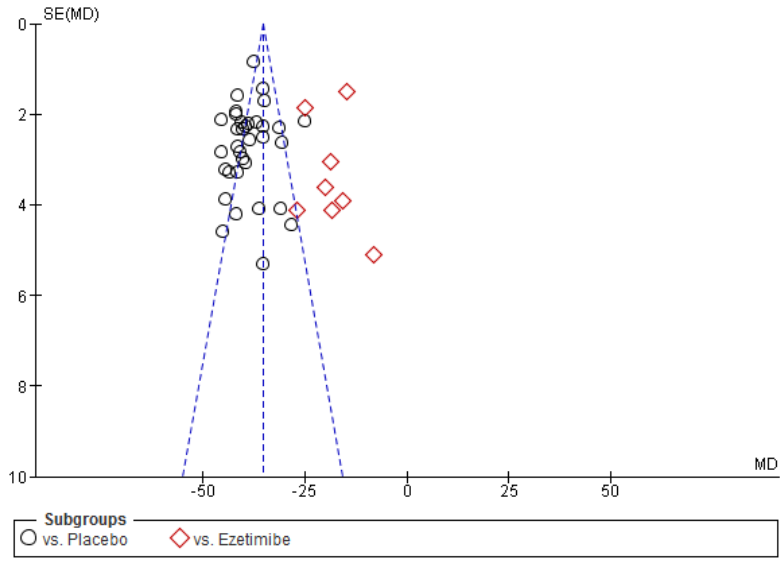


Figure S31. Funnel plot: lipoprotein(a)

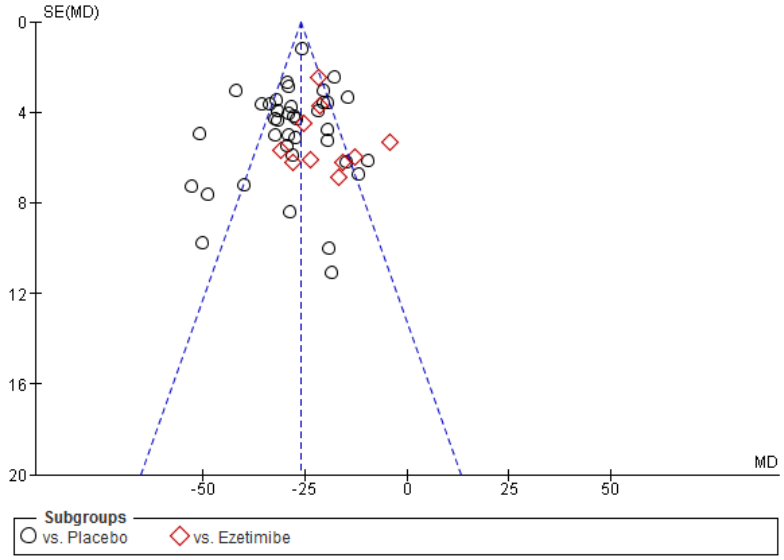
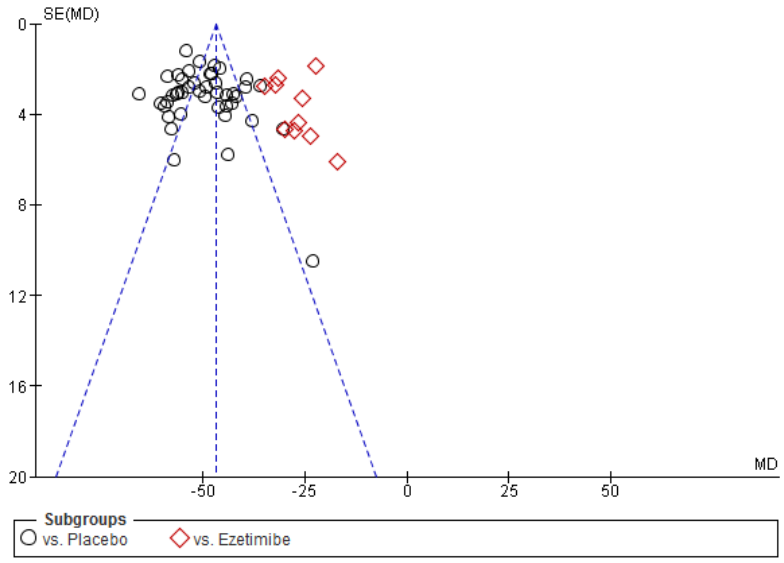


Figure S32. Funnel plot: apolipoprotein B



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