

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 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 $106\pm22 \text{ mg/dL}$. 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 (Cl), 0.64-0.81]; *P*<0.001), stroke (1.0% versus 1.4%; OR: 0.80 [95% Cl, 0.67-0.96]; *P*=0.02), and coronary revascularization (4.2% versus 5.8%; OR: 0.78 [95% Cl, 0.71-0.86]; *P*<0.001). Overall, no significant change was observed in all-cause mortality (OR: 0.71 [95% Cl, 0.47-1.09]; *P*=0.12) or cardiovascular mortality (OR: 1.01 [95% Cl, 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% Cl, 0.88-1.42]; *P*=0.37), myalgia (OR: 0.95 [95% Cl, 0.75-1.20]; *P*=0.65), new onset or worsening of preexisting diabetes mellitus (OR: 1.05 [95% Cl, 0.95-1.17]; *P*=0.32), and increase in levels of creatine kinase (OR: 0.84 [95% Cl, 0.70-1.01]; *P*=0.06) or alanine or aspartate aminotransferase (OR: 0.96 [95% Cl, 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-supple mentary-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.

(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 metaanalysis of RCTs according to established methods and standards recommended by the Cochrane Collaboration⁶ 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 formula¹⁰ 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 \geq 40 mg, rosuvastatin \geq 20 mg, simvastatin \geq 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 \geq 10 mg, pitavastatin \geq 2 mg, rosuvastatin \geq 5 mg, simvastatin \geq 20 mg, lovastatin \geq 40 mg, fluvastatin \geq 80 mg, or any statin \geq 20 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 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 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

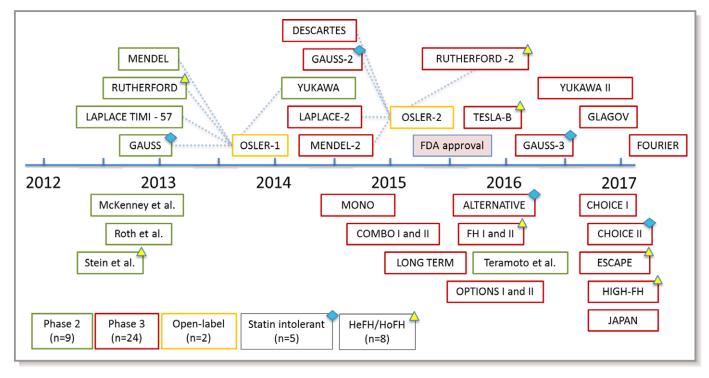


Figure 1. Timeline of randomized controlled trials of alirocumab and evolocumab. FDA indicates US Food and Drug Administration; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia.

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% Cl, 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, 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% Cl, 0.67–0.96]; P=0.02, l²=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% Cl, 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 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, 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, 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% Cl, 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

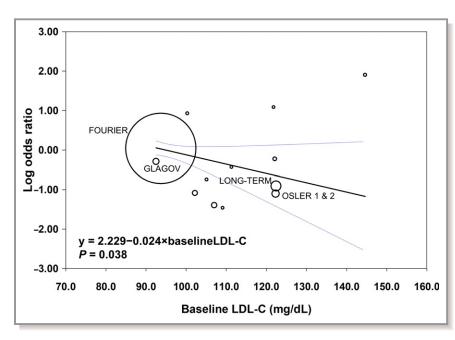
	Antib	ody	No anti	body		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.56.1 Evolocumab							
DESCARTES ¹⁶	2	599	0	302	1.9%	2.53 [0.12, 52.89]	
FOURIER ⁵	444	13784	426	13780	45.9%	1.04 [0.91, 1.19]	•
GAUSS ¹⁷	0	62	0	32		Not estimable	
GAUSS-2 ¹⁸	0	205	0	102		Not estimable	
GAUSS-3 ¹⁹	0	145	0	73		Not estimable	
GLAGOV 20	3	484	4	484	6.8%	0.75 [0.17, 3.36]	
LAPLACE-221	0	1117	1	779	1.7%	0.23 [0.01, 5.71]	
LAPLACE-TIMI57 ²²	1	158	0	155	1.7%	2.96 [0.12, 73.27]	
MENDEL ²⁴	0	90	0	135		Not estimable	
MENDEL-225	0	306	0	308		Not estimable	
OSLER 1 and 2 ³⁸	4	2976	6	1489	9.0%	0.33 (0.09, 1.18)	
RUTHERFORD ⁴⁰	0	56	0	56		Not estimable	
RUTHERFORD 241	0	220	0	109		Not estimable	
TESLA PART B ⁴³	0	33	0	16		Not estimable	
YUKAWA ¹³	0	105	0	102		Not estimable	
YUKAWA II ¹⁴	0	202	0	202		Not estimable	
Subtotal (95% CI)		20542		18124	66.9%	1.03 [0.90, 1.18]	•
Total events	454		437				
Heterogeneity: Tau ² = 0.00;	Chi ² = 4.8	5, df = 5	(P = 0.4)	3); I ² = 09	6		
Test for overall effect: Z = 0.4	11 (P = 0.	68)					
1.56.2 Alirocumab							
McKenney et al. ²³	0	59	0	31		Not estimable	
ODYSSEY ALTERNATIVE 26	0	126	0	124		Not estimable	
ODYSSEY CHOICE I 27	2	573	1	229	2.9%	0.80 (0.07, 8.85)	
ODYSSEY CHOICE II 28	0	173	0	58		Not estimable	
ODYSSEY COMBO I 29	2	207	3	107	4.9%	0.34 [0.06, 2.06]	
ODYSSEY COMBO II 30	2	479	4	241	5.4%	0.25 [0.05, 1.37]	
ODYSSEY ESCAPE 31	0	41	0	21		Not estimable	
ODYSSEY FH 132	6	322	0	163	2.0%	6.72 [0.38, 119.95]	
ODYSSEY FH II32	0	167	0	81		Not estimable	
ODYSSEY HIGH FH 33	0	72	0	35		Not estimable	
ODYSSEY JAPAN ¹¹	0	143	0	72		Not estimable	
ODYSSEY LONG TERM 34	8	1550	10	788	14.3%	0.40 [0.16, 1.03]	
ODYSSEY MONO35	0	52	0	51		Not estimable	
ODYSSEY OPTIONS 136	0	104	2	250	1.8%	0.48 [0.02, 9.99]	
ODYSSEY OPTIONS II 37	0	103	1	202	1.7%	0.65 [0.03, 16.07]	
Roth et al. ³⁹	0	61	0	31		Not estimable	
Stein et al. ⁴²	0	31	0	15		Not estimable	
Teramoto et al. ¹²	0	50	0	25		Not estimable	
Subtotal (95% CI)		4313		2524	33.1%	0.46 [0.24, 0.89]	-
Total events	20		21				
Heterogeneity: Tau ² = 0.00; Toot for overall effect: 7 = 2.2			(P = 0.60	0); I ² = 09	6		
Test for overall effect: Z = 2.3	51 (F = 0.	02)					
Total (95% CI)		24855		20648	100.0%	0.71 [0.47, 1.09]	•
Total events	474		458				
Heterogeneity: Tau ² = 0.10;	Chi ² = 14	61, df=	12 (P = 0	.26); l ² =	18%		0.01 0.1 1 10 100
Test for overall effect: Z = 1.5							0.01 0.1 1 10 100 Favors PCSK9i Favors no PCSK9i
Test for subgroup difference			= 1 (P = 0	0.02), I ² =	81.8%		FAVOIS FUSING FAVOIS NO PUSING

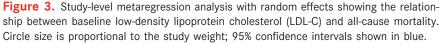
Figure 2. All-cause mortality. Forrest plot showing the odds ratio for all-cause mortality with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (PCSK9i) compared with no PCSK9i. The pooled odds ratio was calculated with random effects according to the Mantel-Haenszel (M-H) method. Marker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

fewer increases in creatine kinase (OR: 0.84 [95% Cl, 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% Cl, 0.75–1.20]; P=0.65), increase in alanine or aspartate aminotransferase (OR: 0.96 [95% Cl, 0.82–1.12]; P=0.61), or treatment-emergent serious adverse events (OR: 0.99 [95% Cl, 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% Cl, -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% Cl, -63.24 to -58.58] versus MD: -31.32% [95% Cl, -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% Cl, 6.10–7.60]; P<0.001), total cholesterol (MD: -34.95 [95% Cl, -37.53 to -32.37]; P<0.001), lipoprotein(a) (MD: -26.45 [95% Cl, -28.88 to -24.03]; P<0.001), and apolipoprotein B (MD: -45.50 [95% Cl, -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 lossof-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 \geq 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,

	Antib	ody	No anti	body		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.59.1 Evolocumab							
DESCARTES 16	2	599	0	302	0.3%	2.53 [0.12, 52.89]	
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Test for overall effect: Z = 0.4			(F = 0.0.	5), 1 = 0	10		
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ODYSSEY JAPAN ¹¹	ŏ	143	ŏ	72		Not estimable	
ODYSSEY LONG TERM ³⁴	4	1550	7	788	1.9%	0.29 [0.08, 0.99]	
ODYSSEY MONO ³⁵	0	52	Ó	51	1.070	Not estimable	
ODYSSEY OPTIONS 136	Ő	104	1	250	0.3%	0.80 [0.03, 19.70]	
ODYSSEY OPTIONS II 37	Ő	103	1	202	0.3%	0.65 [0.03, 16.07]	
Roth et al	0	61	0	31	0.570	Not estimable	
Stein et al. 42	0	31	0	15		Not estimable	
Teramoto et al.	0	50	0	25		Not estimable	
Subtotal (95% CI)	0	3740	0	2295	4.0%	0.48 [0.20, 1.13]	
Total events	10	0140	12	2200	-10 /0	outo [oteo, nito]	
		1 df - 5		s): IZ = 00	6		
Heterogeneity: Tau ² = 0.00; Test for overall effect: 7 = 1.6			(P = 0.7)	0, F = 0;	0		
Test for overall effect: Z = 1.6	ia (r = 0.	09)					
Total (95% CI)		24282		20419	100.0%	1.01 [0.85, 1.19]	+
Total events	271		260				
Heterogeneity: Tau ² = 0.00; •	Chi² = 7.6	7, df = 1	1 (P = 0.)	74); l² = ()%		
Test for overall effect: Z = 0.0	06 (P = 0.	95)					Favors PCSK9i Favors no PCSK9i
Test for subgroup difference	es: Chi ² =	3.01, df	= 1 (P = 1	0.08), I ² =	66.8%		FAVOIS FUONOI FAVOIS 110 FUONOI

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. Cl 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

	Antib	ody	No anti	body		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.57.1 Evolocumab							
DESCARTES ¹⁶	1	599	0	302	0.1%	1.52 [0.06, 37.33]	
FOURIER	468	13784	639	13780	91.4%	0.72 [0.64, 0.82]	
GAUSS 17	1	62	0	32	0.1%	1.59 [0.06, 40.03]	
GAUSS-218	0	205	0	102		Not estimable	
GAUSS-3 ¹⁹	1	145	1	73	0.2%	0.50 (0.03, 8.11)	
GLAGOV ²⁰	10	484	14	484	2.0%	0.71 [0.31, 1.61]	
MENDEL ²⁴	0	90	0	135		Not estimable	
MENDEL-225	0	306	0	308		Not estimable	
OSLER 1 and 2 "	9	2976	5	1489	1.1%	0.90 [0.30, 2.69]	
YUKAWA ¹³	0	105	0	102		Not estimable	
Subtotal (95% CI)		18756		16807	95.0%	0.73 [0.64, 0.82]	♦
Total events	490		659				
Heterogeneity: Tau ² = 0.00; •	Chi ² = 0.8	65, df = 5	(P = 0.9)	9); I ² = 09	6		
Test for overall effect: Z = 5.2	27 (P < 0.	00001)					
1.57.2 Alirocumab							
ODYSSEY ALTERNATIVE 26	1	126	0	124	0.1%	2.98 [0.12, 73.76]	· · · · · · · · · · · · · · · · · · ·
ODYSSEY CHOICE I	1	573	3	229	0.3%	0.13 [0.01, 1.27]	
ODYSSEY CHOICE II 28	1	173	0	58	0.1%	1.02 [0.04, 25.32]	
ODYSSEY COMBO I 29	1	207	1	107	0.2%	0.51 [0.03, 8.31]	
ODYSSEY COMBO II "	12	479	3	241	0.8%	2.04 [0.57, 7.29]	
ODYSSEY FH I 32	1	322	1	163	0.2%	0.50 [0.03, 8.12]	
ODYSSEY FH II 32	0	167	1	81	0.1%	0.16 [0.01, 3.98]	· · · · · · · · · · · · · · · · · · ·
ODYSSEY HIGH FH 33	4	72	0	35	0.2%	4.66 [0.24, 89.09]	
ODYSSEY JAPAN ¹¹	1	143	1	72	0.2%	0.50 [0.03, 8.11]	
ODYSSEY LONG TERM 34	14	1550	18	788	2.7%	0.39 [0.19, 0.79]	
ODYSSEY OPTIONS 136	0	104	0	250		Not estimable	
ODYSSEY OPTIONS II 37	0	103	1	202	0.1%	0.65 [0.03, 16.07]	
Subtotal (95% CI)		4019		2350	5.0%	0.60 [0.34, 1.06]	◆
Total events	36		29				
Heterogeneity: Tau ² = 0.04; •	Chi ² = 10	.42, df =	10 (P = 0)	.40); I ² =	4%		
Test for overall effect: Z = 1.7	77 (P = 0.	08)					
Total (95% CI)		22775		10157	100.0%	0.72 [0.64, 0.81]	
and the second	526	22113	600	19157	100.0%	0.72 [0.04, 0.01]	•
Total events		67 df	688 16 (D = 0	771.17	001		
Heterogeneity: Tau ² = 0.00; ¹			10 (P = 0	(<i>II</i>);I*=	0%		0.01 0.1 1 10 100
Test for overall effect: $Z = 5.6$	•		1 (D		0.07		Favors PCSK9i Favors no PCSK9i
Test for subgroup difference	es: Chi [#] =	U.41, df	= 1 (P = I	J.52), I ² =	:0%		

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

	Antib	ody	No anti	body		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.63.1 Evolocumab							
FOURIER ⁵	207	13784	262	13780	94.4%	0.79 [0.65, 0.95]	
GAUSS-218	0	205	0	102		Not estimable	
GAUSS-319	0	145	0	73		Not estimable	
GLAGOV ²⁰	2	484	3	484	1.0%	0.67 [0.11, 4.00]	
LAPLACE-221	1	1117	0	779	0.3%	2.09 [0.09, 51.48]	
LAPLACE-TIMI5722	0	158	0	155		Not estimable	
MENDEL ²⁴	1	90	0	135	0.3%	4.54 [0.18, 112.74]	
MENDEL-225	0	306	0	308		Not estimable	
OSLER 1 and 2 38	3	2976	2	1489	1.0%	0.75 [0.13, 4.49]	
YUKAWA ¹³	0	105	0	102		Not estimable	
YUKAWA II	0	202	1	202	0.3%	0.33 [0.01, 8.19]	
Subtotal (95% CI)		19572		17609	97.3%	0.79 [0.66, 0.95]	•
Total events	214		268				
Heterogeneity: Tau ² = 0.00; (Chi ² = 1.8	2, df = 5	(P = 0.8)	7); I² = 09	Хо		
Test for overall effect: Z = 2.5	56 (P = 0.	01)					
1.63.2 Alirocumab							
ODYSSEY ALTERNATIVE 26	0	126	0	124		Not estimable	
ODYSSEY CHOICE II 28	0	173	0	58		Not estimable	
ODYSSEY COMBO I29	2	207	0	107	0.3%	2.62 [0.12, 54.97]	
ODYSSEY COMBO II30	1	479	1	241	0.4%	0.50 [0.03, 8.06]	
ODYSSEY FH 132	1	322	0	163	0.3%	1.53 [0.06, 37.66]	
ODYSSEY FH II 32	0	167	0	81		Not estimable	
ODYSSEY HIGH FH 33	0	72	0	35		Not estimable	
ODYSSEY JAPAN ¹¹	0	143	0	72		Not estimable	
ODYSSEY LONG TERM ³⁴	9	1550	2	788	1.4%	2.30 [0.49, 10.65]	
ODYSSEY OPTIONS 136	0	104	0	250		Not estimable	
ODYSSEY OPTIONS II 37	0	103	1	202	0.3%	0.65 [0.03, 16.07]	
Subtotal (95% CI)		3446		2121	2.7%	1.53 [0.52, 4.52]	
Total events	13		4				
Heterogeneity: Tau ² = 0.00;	Chi ² = 1.2	9, df = 4	(P = 0.8)	6); I ² = 09	%		
Test for overall effect: Z = 0.7	78 (P = 0.	44)					
Total (95% CI)		23018		19730	100.0%	0.80 [0.67, 0.96]	◆
Total events	227		272				
Heterogeneity: Tau ² = 0.00;		i1, df = 1		92); I ² = ()%		
Test for overall effect: Z = 2.3			- (. • • •				0.01 0.1 1 10 100
Test for subgroup difference	,	,	= 1 (P = 1	0.24), J ² =	= 29.1%		Favors PCSK9i Favors no PCSK9i
restion subgroup unlefence		1.41, ui		0.247.1 -	20.170		

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. Cl 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 lipidlowering 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

	Antib	ody	No anti	body		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.61.1 Evolocumab							
FOURIER ⁵	759	13784	965	13780	87.1%	0.77 [0.70, 0.85]	
GAUSS ¹⁷ 18	2	62	0	32	0.1%	2.69 [0.13, 57.64]	
GAUSS-2	0	205	0	102		Not estimable	
GAUSS-3	3	145	2	73	0.3%	0.75 [0.12, 4.59]	
GLAGOV ²⁰	50	484	66	484	5.5%	0.73 [0.49, 1.08]	
LAPLACE-TIMI57 ²²	2	158	1	155	0.1%	1.97 [0.18, 22.00]	
MENDEL ²⁴	0	90	0	135		Not estimable	
MENDEL-2	0	306	0	308		Not estimable	
OSLER 1 and 2 ^{°°}	15	2976	17	1489	1.7%	0.44 [0.22, 0.88]	
YUKAWA ¹³	0	105	2	102	0.1%	0.19 [0.01, 4.02]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)		18315		16660	94.8%	0.76 [0.70, 0.84]	•
Fotal events	831		1053				
Heterogeneity: Tau ² = 0.00; •	Chi ² = 4.5	9, df = 6	(P = 0.6)	0); I ² = 09	6		
Test for overall effect: Z = 5.6	60 (P < 0.	00001)					
1.61.2 Alirocumab							
ODYSSEY ALTERNATIVE ²⁶	3	126	1	124	0.2%	3.00 [0.31, 29.24]	
DDYSSEY CHOICE II 28	1	173	0	58	0.1%	1.02 [0.04, 25.32]	
ODYSSEY COMBO I 29	3	207	1	107	0.2%	1.56 [0.16, 15.17]	
ODYSSEY COMBO II30	16	479	4	241	0.7%	2.05 [0.68, 6.19]	
ODYSSEY FH I ³²	2	322	2	163	0.2%	0.50 [0.07, 3.60]	
ODYSSEY FH II 32	2	167	1	81	0.1%	0.97 [0.09, 10.85]	
ODYSSEY HIGH FH ³³	5	72	0	35	0.1%	5.79 [0.31, 107.63]	
ODYSSEY JAPAN ¹¹	2	143	1	72	0.1%	1.01 [0.09, 11.30]	
ODYSSEY LONG TERM 34	48	1550	24	788	3.4%	1.02 [0.62, 1.67]	
ODYSSEY OPTIONS 136	1	104	0	250	0.1%	7.26 [0.29, 179.70]	
ODYSSEY OPTIONS II37	0	103	0	202		Not estimable	
Subtotal (95% CI)		3446		2121	5.2%	1.21 [0.81, 1.81]	*
Fotal events	83		34				
Heterogeneity: Tau ² = 0.00; (Chi ² = 5.1	7. df = 9		2); $ ^2 = 0$?	6		
Test for overall effect: Z = 0.9							
Fotal (95% CI)		21761		18781	100.0%	0.78 [0.71, 0.86]	•
Fotal events	914		1087				
Heterogeneity: Tau ² = 0.00; (Chi ² = 14	45, df =	16(P = 0)	.57); I ² =	0%		
Test for overall effect: Z = 5.2							0.01 0.1 1 10 100 Favors PCSK9i Favors no PCSK9i
Test for subaroup difference	,	,					FAVORS PUSKEL FAVORS NO PUSKEL

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 metaanalysis, 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

	Antib	ody	No anti	body		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl	
1.60.1 Evolocumab								1	
FOURIER ⁵	217	13769	202	13756	74.8%	1.07 [0.89, 1.30]			
GAUSS-2 ¹⁸	0	205	0	102		Not estimable			
GLAGOV 20	7	484	6	484	4.6%	1.17 [0.39, 3.50]			
LAPLACE-221	1	1117	3	779	1.1%	0.23 [0.02, 2.23]			
MENDEL-225	0	306	0	308		Not estimable			
OSLER 1 and 2 ³⁸	27	2976	4	1489	5.0%	3.40 [1.19, 9.73]			
RUTHERFORD 241	0	220	0	109		Not estimable			
TESLA PART B ⁴³	0	33	0	16		Not estimable			
YUKAWA ¹³	0	105	0	102		Not estimable			
YUKAWA II	0	202	0	202		Not estimable			
Subtotal (95% CI)		19417		17347	85.6%	1.26 [0.64, 2.48]		•	
Total events	252		215						
Heterogeneity: Tau ² = 0.24	; Chi ² = 6	.32, df =	3 (P = 0.	10); l² =	53%				
Test for overall effect: Z = 0).68 (P = 1	0.49)							
1.60.2 Alirocumab									
ODYSSEY CHOICE I27	7	573	2	229	2.3%	1.40 [0.29, 6.81]			
ODYSSEY CHOICE II ²⁸	2	173	0	58	0.6%	1.71 [0.08, 36.04]			
ODYSSEY COMBO I29	0	207	1	107	0.6%	0.17 [0.01, 4.24]	•		
ODYSSEY COMBO II30	4	479	3	241	2.5%	0.67 [0.15, 3.01]			
ODYSSEY FH 1 32	2	322	2	163	1.5%	0.50 [0.07, 3.60]			
ODYSSEY FH II ³²	0	167	1	81	0.6%	0.16 [0.01, 3.98]	•		
ODYSSEY HIGH FH ³³	1	72	1	35	0.7%	0.48 [0.03, 7.89]	_		
ODYSSEY LONG TERM 34	18	1550	4	788	4.7%	2.30 [0.78, 6.83]		+	
ODYSSEY OPTIONS 130	0	104	0	250		Not estimable			
ODYSSEY OPTIONS II ³⁷	1	103	2	202	1.0%	0.98 [0.09, 10.94]			
Subtotal (95% CI)		3750		2154	14.4%	1.04 [0.56, 1.94]		•	
Total events	35		16						
Heterogeneity: Tau² = 0.00			8 (P = 0.	65); I² =	0%				
Test for overall effect: Z = 0	0.12 (P = 0	0.90)							
Total (95% CI)		23167		19501	100.0%	1.12 [0.88, 1.42]		•	
Total events	287		231						
Heterogeneity: Tau ² = 0.01		2.33, df		0.42); I ²	= 3%		+		+
Test for overall effect: Z = 0	•		v	-/1.			0.01		100
			df = 1 (P =					Favors PCSK9i Favors no PCSK9i	

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. Cl 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
				Alirocumab 75mg Q2W				
JAPAN ²⁰	2016	3	52	with potential up-titration to	Placebo	HC	Both	NCT02107898
				150 mg Q2W				
LONG TERM ²¹	2015	3	78	Alirocumab 150mg Q2W	Placebo	HC	Both	NCT01507831
				Alirocumab 75mg Q2W				
MONO ²²	2014	3	24	with potential up-titration to	Ezetimibe	HC	None	NCT01644474
				150 mg Q2W				
				Alirocumab 75mg Q2W	Ezetimibe/			
OPTIONS I ²³	2015	3	24	with potential up-titration to	double	HC	Both	NCT01730040
				150 mg Q2W	statin			
				Alirocumab 75mg Q2W	Ezetimibe/			
OPTIONS II ²⁴	2015	3	24	with potential up-titration to	double	HC	Both	NCT01730053
				150 mg Q2W	statin			
OSLER 1 and 2 ²⁵	2015	OL	48	Evolocumab 420 mg	Standard	HC	Both	NCT01439880,
				Q4W/140 mg Q2W	therapy			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	Placebo	HeFH	Both	NCT01763918
				Q4W/140 mg Q2W				
Stein et al. 29	2012	2	12	Alirocumab 150 mg	Placebo	HeFH	Both	NCT01266876
	0040	0	40	Q2W/300 mg Q4W	Disasta	110	D - th	
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
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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%
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

			Moderator variable	;			
			Treatment difference vs.	control			
End point	Baseline LDL-C		in % LDL-C reduction	from	PCSK9i treatment duration		
			baseline				
	Regression coefficient	р	Regression coefficient	n	Regression coefficient	n	
	(95% CI)	Ρ	(95% CI)	р	(95% CI)	р	
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

End point	Population: FH vs	. Non-FH/mixed, OR (9	Statin intolerant/PCSK9i monotherapy, OR (95% CI)				
	Non-FH/mixed	FH	р	No	Yes	р	
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	

Table S4. Subgroup analyses for cardiovascular/safety end points stratified by familial hypercholesterolemia, and background statin therapy

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

		Meta-analysis model									
End point	Fixed-effe	ects	Random effects								
	OR (95% CI)	р	OR (95% CI)	р							
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							

Table S5. Random- and fixed-effects models for cardiovascular/safety end points

CHF, congestive heart failure; CV, cardiovascular

End point	р
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

 Table S6. Egger's regression test for cardiovascular/safety endpoints

CHF, congestive heart failure

Figure S1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) meta-analysis flowchart

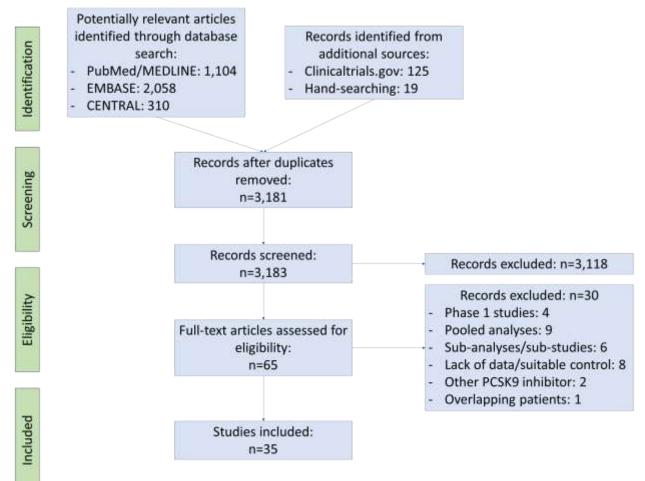




Figure S2. Risk of bias assessment of included studies

Figure S3. Unstable angina

	Antib	ody	No anti	body		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.62.1 Evolocumab						11	
DESCARTES	1	599	0	302	0.3%	1.52 [0.06, 37.33]	0
FOURIER ²	236	13784	239	13780	96.1%	0.99 [0.82, 1.18]	
GAUSS-2	0	205	0	102		Not estimable	T
GAUSS-35	0	145	0	73		Not estimable	
GLAGOV ⁶	3	484	4	484	1.4%	0.75 [0.17, 3.36]	
MENDEL10	Ő	90	Ó	135		Not estimable	
MENDEL-211	Ő	306	Ő	308		Not estimable	
OSLER 1 and 225	3	2976	3	1489	1.2%	0.50 [0.10, 2.48]	
YUKAWA ³²	õ	105	õ	102	1.2.70	Not estimable	
Subtotal (95% CI)	0	18694	Ŭ	16775	99.1%	0.98 [0.82, 1.17]	•
Total events	243		246	02002			
Heterogeneity: Tau ² = 0.00;		8 df = 3		3): I ² = 0.9	%		
Test for overall effect: Z = 0.2			ų – 0.0	o), i = 0.			
	u (i – i.						
1.62.2 Alirocumab							
ODYSSEY ALTERNATIVE12	0	126	0	124		Not estimable	
ODYSSEY CHOICE II 14	Ő	173	ŏ	58		Not estimable	
ODYSSEY COMBO I	ő	207	ő	107		Not estimable	
ODYSSEY COMBO II16	1	479	Ő	241	0.3%	1.51 [0.06, 37.31]	· · · · · · · · · · · · · · · · · · ·
ODYSSEY FH 118	1	322	ŏ	163	0.3%	1.53 [0.06, 37.66]	
ODYSSEY FH II 18	ò	167	0	81	0.070	Not estimable	
ODYSSEY HIGH FH	0	72	ő	35		Not estimable	
ODYSSEY JAPAN ²⁰	0	143	Ő	72		Not estimable	
ODYSSEY LONG TERM ²¹	0	1550	1	788	0.3%	0.17 [0.01, 4.16]	•
ODYSSEY OPTIONS 123	0	104	0	250	0.5%	Not estimable	
ODYSSEY OPTIONS II 24	0	103	0	202		Not estimable	
Subtotal (95% CI)	0	3446		2121	0.9%	0.73 [0.11, 4.65]	
Total events	2	0110	1		01074		
Heterogeneity: Tau ² = 0.00;	~	0 df - 2		5): 12 - 00	K.		
Test for overall effect: Z = 0.3			ų – 0.5.	o, i = 0.			
Total (95% CI)		22140		18896	100.0%	0.97 [0.81, 1.16]	+
Total events	245		247				
Heterogeneity: Tau ² = 0.00;	Chi ² = 2.1	7, df = 6	(P = 0.9	0); l ² = 09	%		
Test for overall effect: Z = 0.3			9850) (1997) 1997)	1889 N 28	17.25		0.01 0.1 1 10 10
Test for subaroup difference		100 C	= 1 (P =)	0.76) IZ-	- 0%		Favours PCSK9i Favours no PCSK9i

Figure S4.	Congestive	heart failure	exacerbation

	Antib	-	No anti			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.64.1 Evolocumab							
DESCARTES	1	599	0	302	0.2%	1.52 [0.06, 37.33]	3
OURIER ²	402	13784	408	13780	96.6%	0.98 [0.86, 1.13]	
DAUSS-2	0	205	0	102		Not estimable	
BAUSS-35	0	145	0	73		Not estimable	
LAGOV ⁶	0	484	0	484		Not estimable	
APLACE-TIMI57 ⁸	1	158	0	155	0.2%	2.96 [0.12, 73.27]	· · · · ·
1ENDEL ¹⁰	0	90	0	135		Not estimable	
IENDEL-2	0	306	0	308		Not estimable	
SLER 1 and 2 ²⁵	1	2976	1	1489	0.2%	0.50 [0.03, 8.00]	8
'UKAWA ³³	0	105	0	102		Not estimable	
subtotal (95% CI)		18852		16930	97.2%	0.99 [0.86, 1.13]	•
otal events	405		409				
leterogeneity: Tau ² = 0.00;	Chi ² = 0.7	75, df = 3	(P = 0.8)	6); I ² = 09	%		
est for overall effect: Z = 0.2		100000					
.64.2 Alirocumab							
DYSSEY ALTERNATIVE ¹²	0	126		124		Not estimable	
DYSSEY CHOICE I	3	573	0	229	0.7%	0.40 [0.08, 1.98]	
	0	173	3	229	0.7%	그 가지 않는 것 같은 것 같은 것 같아요. 이 것 같아요.	
DYSSEY CHOICE II	0	207			0.2%	Not estimable	
DYSSEY COMBO I	1		1	107		0.17 [0.01, 4.24]	
		479	1	241	0.2%	0.50 [0.03, 8.06]	
DYSSEY FH I''	1	322	0	163	0.2%	1.53 [0.06, 37.66]	
DYSSEY FH II 18	0	167	0	81		Not estimable	
DYSSEY HIGH FH ¹⁹	1	72	0	35	0.2%	1.49 [0.06, 37.50]	
DYSSEY JAPAN ²⁰	1	143	0	72	0.2%	1.53 [0.06, 37.94]	
DYSSEY LONG TERM ²¹	9	1550	3	788	1.1%	1.53 [0.41, 5.66]	
DYSSEY OPTIONS 123	0	104	0	250		Not estimable	
DYSSEY OPTIONS II 24	0	103	0	202	0.05	Not estimable	
Subtotal (95% CI)		4019		2350	2.8%	0.84 [0.37, 1.92]	-
otal events	16	an <u>a</u> 14	8		20		
Heterogeneity: Tau² = 0.00; Fest for overall effect: Z = 0.4			(P = 0.8)	0); I² = 09	8		
otal (95% CI)		22871		19280	100.0%	0.98 [0.86, 1.13]	•
otal events	421		417				
leterogeneity: Tau ² = 0.00;	Chi ² = 3.9	99, df = 1	0 (P = 0.9)	95); I ² = (0%		
est for overall effect: Z = 0.2			10				
est for subgroup difference		1 C-17-11	- 1 (P - 1	0 7 2\ IZ -	- 0%		Favours PCSK9i Favours no PCSK9i

Figure S5. Diabetes mellitus

	Antib	ody	No anti	body		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.69.1 Evolocumab					111		C 21
FOURIER ²	677	8337	644	8339	83.9%	1.06 [0.94, 1.18]	
GLAGOV	17	484	18	484	2.3%	0.94 [0.48, 1.85]	
APLACE-TIMI57°	0	158	0	155		Not estimable	
MENDEL'	1	90	0	135	0.1%	4.54 [0.18, 112.74]	· · · · · · · · · · · · · · · · · · ·
DSLER 1 and 2 ²⁵	34	2976	11	1489	2.3%	1.55 [0.78, 3.07]	
/UKAWA II ³³	4	202	4	202	0.5%	1.00 [0.25, 4.05]	1
Subtotal (95% CI)		12247		10804	89.1%	1.06 [0.95, 1.19]	•
Fotal events	733		677				
Heterogeneity: Tau ² = 0.00); Chi ² = 2	2.11, df=	4 (P = 0.	72); 2=	0%		
Test for overall effect: Z = 1	1.13 (P = 1	0.26)					
1.69.2 Alirocumab							
DYSSEY CHOICE 113	12	573	2	229	0.5%	2.43 [0.54, 10.93]	
DYSSEY FH I''	6	322	4	163	0.6%	0.75 [0.21, 2.71]	
DYSSEY FH II18	4	167	2	81	0.4%	0.97 [0.17, 5.41]	
DDYSSEY HIGH FH'	1	72	1	35	0.1%	0.48 [0.03, 7.89]	
DYSSEY JAPAN ²⁰	12	143	4	72	0.8%	1.56 [0.48, 5.01]	1
DDYSSEY LONG TERM ²¹	90	1550	48	788	8.1%	0.95 [0.66, 1.36]	
DYSSEY OPTIONS 123	0	104	5	250	0.1%	0.21 [0.01, 3.90]	
DDYSSEY OPTIONS II24	1	103	6	202	0.2%	0.32 [0.04, 2.70]	
Subtotal (95% CI)		3034		1820	10.9%	0.96 [0.70, 1.32]	•
Total events	126		72				
Heterogeneity: Tau ² = 0.00); $Chi^2 = 4$.54, df=	7 (P = 0.	72); I ² =	0%		
Fest for overall effect: Z = 0	0.24 (P =)	0.81)	2.43	11215			
Fotal (95% CI)		15281		12624	100.0%	1.05 [0.95, 1.17]	•
Total events	859		749				
Heterogeneity: Tau ² = 0.00); Chi ² = 7	.01, df=	12(P = 0).86); l² =	= 0%		
fest for overall effect: Z = 0							0.01 0.1 1 10 10
Test for subaroun differen			Nf - 1 /D -	- 0.66) 1	2 - 0%		Favours PCSK9i Favours no PCSK9i

Test for overall effect: Z = 0.99 (P = 0.32) Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.55), l² = 0%

Figure S6. Increase in creatine kinase

	Antib	-	No anti			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	lotal	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
.66.1 Evolocumab							
ESCARTES ¹	7	599	1	302	0.8%	3.56 [0.44, 29.06]	
OURIER 2	95	13543	99	13523	42.0%	0.96 [0.72, 1.27]	
BAUSS ³	0	62	1	32	0.3%	0.17 [0.01, 4.24]	•
AUSS-24	2	205	3	102	1.0%	0.33 [0.05, 1.98]	
AUSS-3	4	145	1	73	0.7%	2.04 [0.22, 18.61]	
LAGOV ⁶	3	484	3	484	1.3%	1.00 [0.20, 4.98]	
APLACE-2	1	1117	2	779	0.6%	0.35 [0.03, 3.85]	
APLACE-TIMI57 °	2	158	0	155	0.4%	4.97 [0.24, 104.32]	
ENDEL	1	90	2	135	0.6%	0.75 [0.07, 8.36]	
IENDEL-2	2	306	2	308	0.9%	1.01 [0.14, 7.19]	
SLER 1 and 2 ²⁵	17	2976	17	1489	7.4%	0.50 [0.25, 0.98]	
UTHERFORD ²⁷	2	56	0	56	0.4%	5.18 [0.24, 110.45]	
UTHERFORD 228	0	220	2	109	0.4%	0.10 [0.00, 2.05]	• · · · · · · · · · · · · · · · · · · ·
ESLA PART B ³¹	1	33	1	16	0.4%	0.47 [0.03, 8.01]	
UKAWA 32	o	105	1	102	0.3%	0.32 [0.01, 7.96]	
UKAWA II ³³	0	202	1	202	0.3%	0.33 [0.01, 8.19]	
ubtotal (95% CI)	0	20301		17867	57.6%	0.86 [0.68, 1.09]	•
otal events	137	20001	136		0110.1	0.000 [0.000] 1.000]	
leterogeneity: Tau ² = 0.00;		60 df-		1.56\·IE-	0.96		
est for overall effect: Z = 1.			15(1-0		0.0		
corror overall cheet. 2 - 1.	20 (1 - 0.	22/					
.66.2 Alirocumab							
cKenney et al.9	2	59	2	31	0.8%	0.51 [0.07, 3.80]	· · · · · · · · · · · · · · · · · · ·
DYSSEY ALTERNATIVE12	3	126	2	124	1.0%	1.49 [0.24, 9.06]	
DYSSEY CHOICE I	20	573	9	229	5.2%	0.88 [0.40, 1.97]	<u> </u>
DYSSEY CHOICE II14	12	173	1	58	0.8%	4.25 [0.54, 33.41]	· · · · · · · · · · · · · · · · · · ·
DYSSEY COMBO II'	13	479	6	241	3.5%	1.09 [0.41, 2.91]	
DYSSEY ESCAPE ¹⁷	3	41	Ō	21	0.4%	3.91 [0.19, 79.29]	
DYSSEY FH I'	13	322	10	163	4.7%	0.64 [0.28, 1.50]	
DYSSEY FH II ¹⁸	8	167	6	81	2.8%	0.63 [0.21, 1.88]	
DYSSEY HIGH FH	2	72	1	35	0.6%	0.97 [0.09, 11.09]	
DYSSEY JAPAN ²⁰	5	143	O	72	0.4%	5.76 [0.31, 105.59]	
DYSSEY LONG TERM ²¹	56	1550	38	788	18.9%	0.74 [0.49, 1.13]	
DYSSEY MONO ²²	0	52	1	51	0.3%	0.32 [0.01, 8.06]	1
DYSSEY OPTIONS 123	3	104	9	250	1.9%	0.80 [0.21, 3.00]	
DVSSEV OPTIONS II24	0	104	5	202	0.4%		
oth at al ²⁶	0	61	1	31	0.4%	0.17 [0.01, 3.17] 0.17 [0.01, 4.18]	· · · · · · · · · · · · · · · · · · ·
DYSSEY OPTIONS II ²⁴ oth et al. ²⁶ tein et al. ²⁹	0	31	0	15	0.3%	Not estimable	
eramoto et al. ³⁰	2	50	0	25	0.4%		
ubtotal (95% CI)	2	4106	U	2417	42.4%	2.63 [0.12, 56.86] 0.81 [0.61, 1.07]	
	142	4100	91	2411	42.4/0	0.01 [0.01, 1.07]	
otal events otorogonaity: Touri = 0.00:		10 df - 4		021-12-	nov.		
eterogeneity: Tau² = 0.00; est for overall effect: Z = 1.			5 (P = 0.)	02), 17 = 1	0.70		
vieran eneve & - 1.		. 11					
otal (95% CI)		24407		20284	100.0%	0.84 [0.70, 1.01]	•
otal events	279		227				
eterogeneity: Tau ² = 0.00;	Chi ² = 23	.66, df =	31 (P = 0).82); l² =	0%		
est for overall effect: Z = 1.	89 (P = 0.	06)					Favours PCSK9i Favours no PCSK9i
Test for subgroup difference			= 1 (P =	0.75), l²:	= 0%		Favours PCSK91 Favours no PCSK91

Figure S7. Myalgia

	Antibo		No antil			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.53.1 Evolocumab							
DESCARTES	24	599	9	302	6.1%	1.36 [0.62, 2.96]	
GAUSS	7	62	1	32	1.2%	3.95 [0.46, 33.57]	
GAUSS-25	16	205	18	102	6.7%	0.40 [0.19, 0.81]	
GAUSS-3	20	145	16	73	6.6%	0.57 [0.28, 1.18]	
JLAGOV ⁶	34	484	28	484	9.6%	1.23 [0.73, 2.06]	
APLACE-TIMI57 ⁰	1	158	2	155	0.9%	0.49 [0.04, 5.43]	
MENDEL ¹⁰	2	90	1	135	0.9%	3.05 [0.27, 34.09]	
MENDEL-211	3	306	6	308	2.5%	0.50 [0.12, 2.01]	
OSLER 1 and 2 ²⁵	89	2976	43	1489	12.3%	1.04 [0.72, 1.50]	
Subtotal (95% CI)		5025	10.5	3080	46.8%	0.89 [0.62, 1.28]	•
Fotal events	196		124			11	
Heterogeneity: Tau ² = 0.10; (.26. df		.10): I ^z =	= 40%		
Test for overall effect: Z = 0.6			- .				
		,					
1.53.2 Alirocumab							
DDYSSEY ALTERNATIVE 12	31	126	29	124	8.6%	1.07 [0.60, 1.91]	
DDYSSEY CHOICE I 13	19	573	8	229	5.5%	0.95 [0.41, 2.20]	
DDYSSEY CHOICE II 14	10	173	3	58	2.7%	1.12 [0.30, 4.24]	
DDYSSEY COMBO I	7	207	4	107	3.0%	0.90 [0.26, 3.15]	
DYSSEY COMBO 116	21	479	12	241	6.7%	0.88 [0.42, 1.81]	
DDYSSEY ESCAPE ¹⁷	4	41	1	21	1.0%	2.16 [0.23, 20.67]	
DDYSSEY ESCAPE ¹⁷ DDYSSEY FH 1 ¹⁸	6	322	11	163	4.2%	0.26 [0.10, 0.72]	
DYSSEY FH II 18	10	167	5	81	3.7%	0.97 [0.32, 2.93]	
DDYSSEY HIGH FH ¹⁹	4	72	3	35	2.1%	0.63 [0.13, 2.97]	
DYSSEY JAPAN ²⁰	2	143	3	72	1.6%	0.33 [0.05, 2.00]	
DDYSSEY LONG TERM ²¹	84		23	788	10.4%	1.91 [1.19, 3.05]	
DDYSSEY MONO ²²	2	52	1	51	0.9%	2.00 [0.18, 22.77]	
DDYSSEY OPTIONS II 24	4	103	6	202	2.9%	1.32 [0.36, 4.79]	
Subtotal (95% CI)	4	4008	0	2172	53.2%	0.99 [0.71, 1.38]	
Fotal events	204	1000	109	2112	5512 /9	0.00 [0.1 1, 1.00]	Ť
Heterogeneity: Tau² = 0.09; (1868 CONTRACTOR	62 df		0 1 7\- 12	- 27%		
Fest for overall effect: Z = 0.0			- 12 (F =	0.17),1	- 27 30		
estion overall effect. $Z = 0.0$	55 (F = 0.	36)					
Total (95% CI)		9033		5252	100.0%	0.95 [0.75, 1.20]	•
Fotal events	400		233				
Heterogeneity: Tau ² = 0.08; (Chi ² = 30	.61, df	= 21 (P =	0.08); l ^a	= 31%		0.01 0.1 1 10 10
Fest for overall effect: Z = 0.4			<u>.</u>	10			
Test for subgroup difference			if = 1 (P =	0.65). [²= 0%		Favours PCSK9i Favours no PCSK9i

Antibody No antibody Odds Ratio **Odds Ratio** Study or Subgroup Total Weight M-H, Random, 95% Cl Events Total Events M-H, Random, 95% CI 1.67.1 Evolocumab DESCARTES¹ 5 599 3 302 1.2% 0.84 [0.20, 3.53] FOURIER GAUSS³ 240 13543 242 13523 75.4% 0.99 [0.83, 1.19] 0 62 32 0.2% 0.17 [0.01, 4.24] 1 GAUSS-2⁴ GLAGOV⁶ 0 205 0 102 Not estimable 2 484 2 484 0.6% 1.00 [0.14, 7.13] LAPLACE-27 779 0.31 [0.09, 1.00] 4 1117 9 1.8% LAPLACE-TIMI57⁸ MENDEL¹⁰ n 158 1 155 0.2% 0.32 [0.01, 8.04] 0 90 0 135 Not estimable MENDEL-211 1 3% 0.50 [0.12, 2.01] 3 306 6 308 OSLER 1 and 225 31 2976 18 1489 7.2% 0.86 [0.48, 1.54] RUTHERFORD²⁷ 3.05 [0.12, 76.59] 56 0 56 0.2% RUTHERFORD 2²⁸ TESLA PART B³¹ YUKAWA³² 1 0 220 0 109 Not estimable 2 33 0.4% 0.97 [0.08, 11.54] 16 1 0 105 0 102 Not estimable YUKAWA II³³ 202 202 0.50 [0.04, 5.53] 1 2 0.4% Subtotal (95% CI) 0.94 [0.79, 1.11] 20156 17794 88.9% Total events 289 285 Heterogeneity: Tau² = 0.00; Chi² = 6.97, df = 10 (P = 0.73); l² = 0% Test for overall effect: Z = 0.76 (P = 0.45) 1.67.2 Alirocumab McKenney et al.9 Not estimable 0 59 0 31 ODYSSEY ALTERNATIVE¹² 124 Not estimable 0 126 0 ODYSSEY CHOICE I¹³ 3 573 2 229 0.8% 0.60 [0.10, 3.60] ODYSSEY CHOICE II 14 1.02 [0.04, 25.32] 0 1 173 58 0.2% ODYSSEY COMBO II 16 8 479 1 241 0.6% 4.08 [0.51, 32.78] ODYSSEY ESCAPE 17 Not estimable 0 41 0 21 ODYSSEY FH 118 5 322 2 163 0.9% 1.27 [0.24, 6.62] ODYSSEY FH II18 6 167 81 0.5% 2.98 [0.35, 25.19] 1 ODYSSEY HIGH FH 19 3 72 1 35 0.5% 1.48 [0.15, 14.75] ODYSSEY JAPAN 20 5 143 72 0.5% 2.57 [0.29, 22.44] 1 ODYSSEY LONG TERM²¹ ODYSSEY MONO²² 28 0.89 [0.48, 1.65] 1550 16 788 6.4% 0 52 0 51 Not estimable ODYSSEY OPTIONS I 23 0.2% 0.80 [0.03, 19.70] 0 104 250 1 ODYSSEY OPTIONS II 24 Roth et al.26 1 103 0 202 0.2% 5.93 [0.24, 146.78] 1 61 0 31 0.2% 1.56 [0.06, 39.46] Stein et al.29 0 31 0 15 Not estimable Teramoto et al.³⁰ 0 50 0 25 Not estimable Subtotal (95% CI) 4106 2417 11.1% 1.16 [0.72, 1.85] 61 25 Total events Heterogeneity: Tau² = 0.00; Chi² = 5.14, df = 10 (P = 0.88); I² = 0% Test for overall effect: Z = 0.60 (P = 0.55) Total (95% CI) 20211 100.0% 0.96 [0.82, 1.12] 24262 Total events 350 310 Heterogeneity: Tau² = 0.00; Chi² = 12.69, df = 21 (P = 0.92); l² = 0% 0.01 100 0'1 10 Test for overall effect: Z = 0.52 (P = 0.61) Favours PCSK9i Favours no PCSK9i Test for subgroup differences: Chi² = 0.67, df = 1 (P = 0.41), I² = 0%

Figure S8. Alanine/aspartate aminotransferase increase

Antibody No antibody Odds Ratio **Odds Ratio** Total Weight M-H, Random, 95% Cl Study or Subgroup Events Total Events M-H, Random, 95% CI 1.68.1 Evolocumab DESCARTES¹ 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] GAUSS³ 62 0 32 0.0% 1.59 [0.06, 40.03] 1 GAUSS-24 6 205 4 102 0.1% 0.74 [0.20, 2.68] LAPLACE-27 23 1117 15 779 0.6% 1.07 [0.56, 2.07] LAPLACE-TIMI57⁸ MENDEL¹⁰ 1.49 [0.41, 5.39] 6 158 4 155 0.1% 1 90 0 135 0.0% 4.54 [0.18, 112.74] MENDEL-211 4 306 2 308 0.1% 2.03 [0.37, 11.15] OSLER 1 and 225 2976 44% 1.00 [0.79, 1.27] 222 111 1489 RUTHERFORD²⁷ 2 56 0 56 0.0% 5.18 [0.24, 110.45] RUTHERFORD 2²⁸ TESLA PART B³¹ YUKAWA³² 7 220 5 109 0.2% 0.68 [0.21, 2.21] 0 33 0 16 Not estimable 3 105 0 102 0.0% 7.00 [0.36, 137.24] YUKAWA II³³ 1 202 5 202 0.1% 0.20 [0.02, 1.69] Subtotal (95% CI) 19898 17543 88.8% 1.00 [0.95, 1.06] Total events 3719 3563 Heterogeneity: Tau² = 0.00; Chi² = 8.15, df = 12 (P = 0.77); I² = 0% Test for overall effect: Z = 0.14 (P = 0.89) 1.68.2 Alirocumab McKenney et al. 0.0% 1 59 1 31 0.52 [0.03, 8.56] ODYSSEY ALTERNATIVE 12 1.20 [0.50, 2.89] 12 126 10 124 0.3% ODYSSEY CHOICE I 0.77 [0.49, 1.21] 66 573 33 229 1.2% ODYSSEY CHOICE II14 ODYSSEY COMBO I 15 13 173 4 58 0.2% 1.10 [0.34, 3.51] 107 0.95 [0.48, 1.91] 26 207 14 0.5% ODYSSEY COMBO II 16 ODYSSEY ESCAPE¹⁷ 90 479 43 241 1.5% 1.07 [0.71, 1.59] 0.1% 1.03 [0.17, 6.12] 4 41 2 21 ODYSSEY FH 118 44 322 22 163 0.8% 1.01 [0.58, 1.76] ODYSSEY FH II18 15 167 8 81 0.3% 0.90 [0.37, 2.22] ODYSSEY HIGH FH¹⁹ ODYSSEY JAPAN²⁰ 10 72 4 35 0.2% 1.25 [0.36, 4.31] 10 143 9 72 0.3% 0.53 [0.20, 1.36] ODYSSEY LONG TERM²¹ ODYSSEY MONO²² 290 154 5.2% 0.95 [0.76, 1.18] 1550 788 52 51 0.0% 0.98 [0.06, 16.11] 1 1 ODYSSEY OPTIONS 123 0.2% 104 15 250 0.63 [0.20, 1.94] 4 ODYSSEY OPTIONS II 24 6 103 16 202 0.3% 0.72 [0.27, 1.90] Roth et al²³ 1 61 0 31 0.0% 1.56 [0.06, 39.46] Stein et al.24 0 31 1 15 0.0% 0.15 [0.01, 4.00] Teramoto et al.³⁰ 50 25 0.0% 0.49 [0.03, 8.17] 1 1 Subtotal (95% CI) 4313 2524 11.2% 0.93 [0.80, 1.07] Total events 594 338 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) 20067 100.0% 0.99 [0.95, 1.05] 24211 Total events 4313 3901 Heterogeneity: Tau² = 0.00; Chi² = 14.77, df = 30 (P = 0.99); l² = 0% 0.01 100 0'1 10 Test for overall effect: Z = 0.20 (P = 0.84) Favours PCSK9i Favours no PCSK9i

Figure S9. Treatment emergent serious adverse events

Test for subgroup differences: Chi² = 1.00, df = 1 (P = 0.32), I² = 0.5%

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

Study or Subgroup	Mean	ntibody SD		Mean	sD	The second second	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% Cl
1.37.1 vs. Placebo									
DESCARTES ¹	-46.7	37.3	145	10.1	36.7	73	1.7%	-56.80 [-67.18, -46.42]	
DESCARTES	-51.5	20.6	74	4.2	21.3	37	1.8%	-55.70 [-64.01, -47.39]	
DESCARTES	-46.8	33.7	126	1.7	34.1	63	1.7%	-48.50 [-58.77, -38.23]	
DESCARTES	-54.7	23.9	254	6.9	25	129	1.9%	-61.60 [-66.82, -56.38]	
GLAGOV ⁶ 7	0	0	486	0	0	484		Not estimable	
LAPLACE-27	-62.5		110		19.2	55		-62.90 [-69.10, -56.70]	-
LAPLACE-2	-66.2	31	112	3.3	25	56		-69.50 [-78.21, -60.79]	
LAPLACE-2	-59.3		113		18.3	58		-66.90 [-72.75, -61.05]	-
LAPLACE-2	-65.1		110		24.8	55		-74.90 [-82.94, -66.86]	
LAPLACE-2	-61.4		110		16.4	56		-69.90 [-75.23, -64.57]	
LAPLACE-2	-59.1		111		23.2	56		-65.70 [-73.17, -58.23]	
LAPLACE-2	-61.8	29	109	13.1	28.9	55		-74.90 [-84.28, -65.52]	a data da se d
LAPLACE-2	-63.8		115		18.5	57		-66.60 [-72.52, -60.68]	
LAPLACE-2	-62.4		115		35.1	55		-68.40 [-80.34, -56.46]	
LAPLACE-2 LAPLACE-TIMI57 ⁸	-62.9		112		25.9	55		-62.90 [-71.29, -54.51]	
LAPLACE-TIMI57	-63.3 -51.3		78 80		21.2 22.2	78 79		-66.10 [-72.75, -59.45] -50.30 [-57.23, -43.37]	
McKenney et al. 9	-72.4		29	-5.1	17	31		-67.30 [-76.12, -58.48]	
MENDEL ¹⁰	-50.9		45		17.6	45		-47.20 [-54.51, -39.89]	
MENDEL	-48	17	45		17.3	45		-52.50 [-59.59, -45.41]	
MENDEL-2 ¹¹			153	-1.4	12	78		-57.40 [-60.72, -54.08]	-
MENDEL-2	-56.9		153		12.7	76		-56.50 [-60.03, -52.97]	
ODYSSEY CHOICE I 13	-58.8		312	-0.1	28.8	157		-58.70 [-64.19, -53.21]	
ODYSSEY CHOICE I	-52.7	23	146		23.1	73		-52.40 [-58.88, -45.92]	
DDYSSEY CHOICE II ¹⁴	-51.7		59		17.5	58		-56.40 [-65.37, -47.43]	
ODYSSEY COMBOI'S	-48.2		209	-2.3	27.7	107		-45.90 [-52.37, -39.43]	
ODYSSEY ESCAPE ''	-53.7	14.7	41	1.6	14.2	21		-55.30 [-62.86, -47.74]	
DDYSSEY FH I 10	-48.8	28.8	323	9.1	28.1	163	1.9%	-57.90 [-63.24, -52.56]	
DDYSSEY FH II 10	-48.7	24.6	167	2.8	25.4	82	1.9%	-51.50 [-58.14, -44.86]	
ODYSSEY HIGH FH 19	-45.7	29.7	72	-6.6	29	35	1.6%	-39.10 [-50.91, -27.29]	
ODYSSEY JAPAN ²⁰	-62.5	15.6	144	1.6	15.3	72	1.9%	-64.10 [-68.46, -59.74]	100
ODYSSEY LONG TERM ²	-61	27.6	1553	0.8	28.1	788	2.0%	-61.80 [-64.19, -59.41]	-
OSLER 1 and 2 ²⁵	0	0	2976	0	0	1489		Not estimable	
Roth et al. ²⁶ 27	-73.2		30	-17.3		31		-55.90 [-65.61, -46.19]	
RUTHERFORD ²⁷	-55.2		56	1.1	21.7	56		-56.30 [-64.34, -48.26]	
RUTHERFORD 228	-55.7		110		23.7	55		-61.20 [-68.88, -53.52]	
RUTHERFORD 2	-61.3	18	110	-2	18	54		-59.30 [-65.16, -53.44]	
Stein et al. ²⁹	-67.9		16	-10.7		15		-57.20 [-70.93, -43.47]	
Teramoto ³⁰	-71.7		25		15.5	25		-69.00 [-77.59, -60.41]	
TESLA PART B ³¹ YUKAWA ³²	-23.1		33		20.6	16		-31.00 [-43.46, -18.54]	
	-63.9		53		16.3	50 52		-64.00 [-70.37, -57.63]	
YUKAWA YUKAWA II ³³	-71.3 -73.7	10.9	52 50		15.9 15.5	49		-68.60 [-74.71, -62.49] -74.00 [-80.21, -67.79]	
YUKAWA II		14.3	50		14.8	50		-73.90 [-79.60, -68.20]	
YUKAWA II	-74.8	23.3	50		23.5	52		-74.40 [-83.44, -65.36]	
YUKAWA II	-76.9	23.5	51		16.5	52		-74.20 [-80.51, -67.89]	
Subtotal (95% CI)	10.3	10	9474	-4.1	10.0	5377		-60.91 [-63.24, -58.58]	•
Heterogeneity: Tau ² = 47.90;	Chi ² =	249 73		(P < 0	000011			and a second	·
Fest for overall effect: Z = 51	1. C		<u>- 1995</u> - 2997	ų . ų.		a, - 0,			
1.37.2 vs. Ezetimibe									
GAUSS ³	-50.7	21.9	32	-14.8	22	33	1.7%	-35.90 [-46.57, -25.23]	
GAUSS-24	-52.6	15.8	102	-15.1	14.9	51		-37.50 [-42.61, -32.39]	
GAUSS-25	-56.1	18.4	103	-19.2	23.9	51	1.8%	-36.90 [-44.36, -29.44]	
GAUSS-3 [°] 12	-52.8	18.3		-16.7		73	1.9%	-36.10 [-41.12, -31.08]	
ODYSSEY ALTERNATIVE		24.7		-14.6		125		-30.40 [-36.50, -24.30]	
ODYSSEY COMBO II ¹⁶	-50.6			-20.7		241		-29.90 [-34.52, -25.28]	
DDYSSEY MONO ²² 23	-47.2			-15.6		51		-31.60 [-40.04, -23.16]	
UDYSSEY OPTIONS I	-50.5			-29.7		46		-20.80 [-29.67, -11.93]	
ODYSSEY OPTIONS I 24	-48.4			-22.6		53		-25.80 [-36.48, -15.12]	
ODYSSEY OPTIONS II	-49.6			-17.4		47		-32.20 [-43.70, -20.70]	
ODYSSEY OPTIONS II	-32.3	37.9	and the second second	-19.3	38.2	50	1.5%	-13.00 [-27.70, 1.70]	
Subtotal (95% CI)			1241			821	19.6%	-31.32 [-34.83, -27.81]	▼
Heterogeneity: Tau² = 18.64; Fest for overall effect: Z = 17				(P = 0.0	U8); I² :	= 58%			
Total (05% CI)			40745			6400	100 04	EA 77 [EO 07 EA 071	
Total (95% CI) Heterogeneity: Tau² = 159.4		000	10715		00000			-54.77 [-58.27, -51.27]	• · · · ·

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

		ntibody			intiboo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
DESCARTES		14.4	145		13.7	73	2.8%	3.90 [-0.02, 7.82]	
DESCARTES		16.8	126		16.7	63	1.8%	4.00 [-1.06, 9.06]	
DESCARTES		18.9	74		19.5	37	0.9%	11.30 [3.68, 18.92]	
DESCARTES		14.3	254		14.8	129	3.8%	5.30 [2.20, 8.40]	+
GAUSS	7.4	19	32		19.2	33	0.6%	8.50 [-0.79, 17.79]	
GAUSS-2 ⁴	5.3	16.9	103	1.8	15.6	51	1.7%	3.50 [-1.88, 8.88]	T-
GAUSS-2	6.5	16.3	102		15.5	51	1.7%	4.90 [-0.40, 10.20]	-
GAUSS-325		16.4	145		12.4	73	2.8%	4.50 [0.60, 8.40]	
GLAGOV ⁶	0	0	486	0	0	484		Not estimable	
LAPLACE-27		14.3	110	-0.5	14.2	55	2.1%	8.20 [3.59, 12.81]	
LAPLACE-2	6.2	11.6	113	0.9	11.4	58	3.1%	5.30 [1.67, 8.93]	-
LAPLACE-2	4.9	11.7	111	-0.6	11.6	56	3.0%	5.50 [1.76, 9.24]	
LAPLACE-2	10.4		112	0.1	20.4	56	1.1%	10.30 [3.37, 17.23]	
LAPLACE-2	8.4	12.4	109	4.5	12.6	55	2.6%	3.90 [-0.16, 7.96]	-
LAPLACE-2	5.5	11.4	110	-1	11	56	3.1%	6.50 [2.92, 10.08]	-
LAPLACE-2	6.4	13.1	112	-0.4	13.3	55	2.4%	6.80 [2.53, 11.07]	
LAPLACE-2	7.7	19.2	115	-0.9	19	57	1.4%	8.60 [2.55, 14.65]	
LAPLACE-2	7.8	13.8	110	-1.4	13.5	55	2.3%	9.20 [4.80, 13.60]	
LAPLACE-2	6.7	24.1	115	-2.1	19.8	55	1.1%	8.80 [1.96, 15.64]	
LAPLACE-TIMI578	0	0	80	0	0	79		Not estimable	
LAPLACE-TIMI57	0	0	78	0	0	78		Not estimable	
McKenney et al. ⁹	5.5	13.4	29	-1	12.6	31	1.2%	6.50 [-0.09, 13.09]	
MENDEL ¹⁰	11.5	16.1	45	5.7	16.5	45	1.1%	5.80 [-0.94, 12.54]	
MENDEL	11.3	16	45	1.1	15.8	45	1.2%	10.20 [3.63, 16.77]	
MENDEL-2 ¹¹	3.8	45.4	153	-4.7	22.2	78	0.7%	8.50 [-0.22, 17.22]	
MENDEL-2 12	3.9	40.7	153	-1.6	29.3	76	0.6%	5.50 [-3.72, 14.72]	
ODYSSEY ALTERNATIVE	0	0	126	0	0	125		Not estimable	
ODYSSEY CHOICE I	3.6	14.1	312	-1.5	15	157	4.3%	5.10 [2.28, 7.92]	-
ODYSSEY CHOICE I	2.5	14.5	146	-5.3	14.5	73	2.6%	7.80 [3.73, 11.87]	-
ODYSSEY CHOICE IJ	7.7	15.4	59	-2.4	14.5	58	1.6%	10.10 [4.68, 15.52]	
ODYSSEY COMBO I	3.5	15.4	209	-3.8	15.7	107	3.1%	7.30 [3.67, 10.93]	-
ODYSSEY COMBO II	8.6	17.5	479	0.5	17.1	241	4.6%	8.10 [5.43, 10.77]	+
ODYSSEY ESCAPE ''	0	0	41	0	0	21		Not estimable	
ODYSSEY FH I	8.8	16.2	323	0.8	15.3	163	4.1%	8.00 [5.06, 10.94]	+
ODYSSEY FH II 10	6	15.5	167	-0.8	14.5	82	2.8%	6.80 [2.88, 10.72]	
ODYSSEY HIGH FH. 19	7.5	16.1	72	3.9	16	35	1.2%	3.60 [-2.88, 10.08]	
ODYSSEY JAPAN 20	7.9	13.2	144	2.1	12.7	72	3.1%	5.80 [2.16, 9.44]	
ODYSSEY LONG TERM ²¹	4	15.8	1553	-0.6	14	788	8.4%	4.60 [3.35, 5.85]	•
ODYSSEY MONO ²²	6	13.7	52	1.6	13.6	51	1.7%	4.40 [-0.87, 9.67]	<u>+</u>
ODYSSEY OPTIONS I 23	7.7	18.3	46	2	18.3	46	0.9%	5.70 [-1.78, 13.18]	
ODYSSEY OPTIONS I	4.8	14.8	55	-0.1	15.3	53	1.5%	4.90 [-0.78, 10.58]	
ODYSSEY OPTIONS II 24	9.1	16.6	48	4	17.1	47	1.1%	5.10 [-1.68, 11.88]	<u>+</u>
ODYSSEY OPTIONS II	7.2	16.7	53	-1.8	16.3	50	1.2%	9.00 [2.63, 15.37]	
OSLER 1 and 2 ²⁵	0	0	2976	0	0	1489		Not estimable	
Roth et al. ²⁶	5.8	12.6	30	-3.6	12.8	31	1.2%	9.40 [3.03, 15.77]	
RUTHERFORD ²⁷	9.1		56		14.2	56	1.7%	6.80 [1.54, 12.06]	
RUTHERFORD 2 ²⁰	8.1	14	110		13.7	54	2.2%	9.30 [4.81, 13.79]	
RUTHERFORD 2	5.4	17.2	110		17.2	55	1.6%	9.10 [3.53, 14.67]	
RUTHERFORD 2 Stein et al. ²⁹	12.4	14.4	16	2.2	14.3	15	0.5%	10.20 [0.09, 20.31]	
Teramoto et al.	2	0	25	2.1	0	25		Not estimable	
TESLA PART B ³¹		15.7	33		14.8	16	0.7%	-0.10 [-9.12, 8.92]	
YUKAWA ³²		16.6	52		16.6	52	1.2%	9.10 [2.72, 15.48]	
YUKAWA	13.9	16	53		16.3	50	1.3%	13.20 [6.96, 19.44]	
YUKAWA II ³³	14.8	17	50		17.7	50	1.1%	15.20 [8.40, 22.00]	
YUKAWA II		18.4	50		18.2	49	1.0%	13.50 [6.29, 20.71]	
YUKAWA II		16.4	51		17.1	51	1.2%	10.20 [3.70, 16.70]	
YUKAWA II		18.6	51		18.7	52	1.0%	16.90 [9.70, 24.10]	
Total (95% CI)			10715			6100	100.0%		
Total (95% CI)	01.17				. 12 -		100.0%	6.85 [6.10, 7.60]	
Heterogeneity: Tau ² = 1.34; (Fest for overall effect: Z = 17				' = 0.10); I ² = 2	1%		2	-50 -25 0 25 50 Favours [experimental] Favours [control]

Figure S12. Total cholesterol % change from baseline

Study or Subgroup	Mean	ntibody SD		No a Mean	Intiboo SD	The second second	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
1.40.1 vs. Placebo	- avail	50	1.0101	moun	50		reight	in the second se	
DESCARTES	-28.8	26.9	126	22	26.2	63	2 2 %	-31.00 [-38.99, -23.01]	
DESCARTES	-34.7		74		19.5	37		-44.40 [-52.02, -36.78]	5 - 10 - 10 - 10 - 10 - 10 - 10 - 10 - 1
DESCARTES	-32.1		254		20.4	129		-38.90 [-43.24, -34.56]	
DESCARTES	-28		145		28.2	73		-36.40 [-44.40, -28.40]	
GLAGOV ⁶	-20	20.5	486	0.4	20.2	484	2.2 0	Not estimable	
APLACE-27	-35.9	15		-0.5		55	26%	-35.40 [-38.21, -32.59]	
LAPLACE-2			112		1.5				
	-36.2		109		19.4	55		-44.40 [-50.70, -38.10]	
APLACE-2	-40.1		115	1.6	24	55		-41.70 [-49.93, -33.47]	
JAPLACE-2	-39.3		110		13.7	55		-39.70 [-44.15, -35.25]	
JAPLACE-2	-37.6		110		12.1	56		-41.90 [-45.83, -37.97]	
APLACE-2		13.6	111		13.1	56		-36.90 [-41.16, -32.64]	
LAPLACE-2	-36.7		113		11.8	58		-41.80 [-45.59, -38.01]	
LAPLACE-2		16.7	110		16.3	55		-41.50 [-46.82, -36.18]	
LAPLACE-2		13.5	115		13.4	57		-40.40 [-44.66, -36.14]	
JAPLACE-2 8	-42.3		112		18.5	56	2.3%	-41.60 [-48.01, -35.19]	
APLACE-TIMI57	0	0	78	0	0	78		Not estimable	
APLACE-TIMI57	0	0	80	0	0	79		Not estimable	
vlcKenney et al. ⁹	-45.2	12.8	29	-1.6	12.6	31	2.3%	-43.60 [-50.03, -37.17]	
MENDEL ¹⁰	-34	11.8	45	1.4	12	45		-35.40 [-40.32, -30.48]	
MENDEL	-32.9		45		12.5	45		-30.70 [-35.86, -25.54]	2 000-0 0
MENDEL-2 ¹¹	0	0	153	0	0	78		Not estimable	
IENDEL-2	0	0	153	0	0	76		Not estimable	
DDYSSEY CHOICE I 13	-35.8		312		17.5	157	2.6%	-35.00 [-38.37, -31.63]	
DDYSSEY CHOICE I	-33.3		146		16.2	73		-31.40 [-35.91, -26.89]	1
DYSSEY CHOICE 11	-32.3		59		12.2	58		-35.30 [-39.74, -30.86]	-
DYSSEY COMBO 115	-27.9		209	-2.9	18	107		-25.00 [-29.22, -20.78]	
DDYSSEY ESCAPE 17	-36.4		41		11.5	21		-39.50 [-45.55, -33.45]	
DDYSSEY FHI	0	0	323	0	0	163	2.470	Not estimable	
DYSSEY FH II 18	0	0	167	0	0	82			
DYSSEY HIGH FH 19	-33.2		72		21.3	35	2.106	Not estimable	
DDYSSEY JAPAN ²⁰								-28.40 [-37.11, -19.69]	
DVOOEVLONG TED 21	-39.5		144	2	11	72		-41.50 [-44.59, -38.41]	-
DDYSSEY LONG TERM ²¹			1553		19.6	788	2.170	-37.50 [-39.18, -35.82]	
OSLER 1 and 2 ²⁵	0	0	2976	0	0	1489		Not estimable	
Roth et al. ²⁶	0	0	30	0	0	31		Not estimable	and the second sec
RUTHERFORD ²⁷	-42		56		20.2	56	2.0%	-45.00 [-53.98, -36.02]	
RUTHERFORD 228	0	0	110	0	0	54		Not estimable	
RUTHERFORD 2	0	0	110	0	0	55		Not estimable	
Stein et al ²⁹	-43.6	14.8	16	-8.5	14.7	15		-35.10 [-45.49, -24.71]	
Feramoto ³⁰ 31	-41.4	10.5	25	-1.2	10.5	25	2.4%	-40.20 [-46.02, -34.38]	
TESLA PART B	0	0	33	0	0	16		Not estimable	
/UKAWA ³²	-39.4	11.6	53	0.8	12	50	2.5%	-40.20 [-44.76, -35.64]	-
/UKAWA	-45	10.8	52	0.4	10.8	52	2.5%	-45.40 [-49.55, -41.25]	
/UKAWA II ³³	-39.1	11.3	50	2.3	12	50		-41.40 [-45.97, -36.83]	
/UKAWA II	-47.2		50	-1.7	14	49		-45.50 [-51.04, -39.96]	
/UKAWA II		14.3	51		14.4	52		-40.90 [-46.44, -35.36]	~~
/UKAWA II	-40.9		51		12.9	51		-38.50 [-43.51, -33.49]	
Subtotal (95% CI)			9474			5377		-38.54 [-40.11, -36.98]	•
Heterogeneity: Tau ² = 14.23;	Chi ² =	123.85		(P < 0	00001				
est for overall effect: Z = 48.				v		as - 6	2.15		
.40.2 vs. Ezetimibe	~ - -	10.5			40.5				
GAUSS ³	-37.7	1.00		-10.7		33	2.1%	-27.00 [-35.05, -18.95]	
JAUSS-24	0	0	103	0	0	51		Not estimable	
GAUSS-25	0	0	102	0	0	51		Not estimable	
JAUSS-3 12	-36.6	13.1		-11.6	12.9	73	2.6%	-25.00 [-28.65, -21.35]	-
DDYSSEY ALTERNATIVE	0	0	126	0	0	125		Not estimable	
DDYSSEY COMBQ II '	-29.3	19.7	479	-14.6	18.6	241	2.6%	-14.70 [-17.64, -11.76]	-
DDYSSEY MONO ²² 23	-29.6	15.1	52	-10.9	15.7	51	2.4%	-18.70 [-24.65, -12.75]	
DOUSSEY OPTIONS I	-27.1	20		-11.2		53	2.2%	-15.90 [-23.52, -8.28]	
DDYSSEY OPTIONS I 24	-33.6	19.7	46	-15.2	19.7	46	2.1%	-18.40 [-26.45, -10.35]	
DDYSSEY OPTIONS II 24	-20.6			-12.4		50	1.9%	-8.20 [-18.19, 1.79]	
DOYSSEY OPTIONS II	-28.9		48		17.8	47		-20.20 [-27.26, -13.14]	
			1241			821		-18.84 [-22.95, -14.74]	•
Subtotal (95% CI)			df = 7 (F	P = 0.00	03); I² :				
Subtotal (95% CI) Heterogeneity: Tau ² = 23.71;		0.00004	1						
	0 (P < (0.0000	·/						
Heterogeneity: Tau ² = 23.71;	0 (P < (10715			6198	100.0%	-34.95 [-37.53, -32.37]	•
Heterogeneity: Tau ² = 23.71; Fest for overall effect: Z = 9.0			10715	(P < 0	00001			-34.95 [-37.53, -32.37]	-50 -25 0 25 50

Figure S13. Lipoprotein(a) % change from baseline

Study or Subgroup	Mean	ntibody SD	Total	No a Mean	sD		Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% Cl
1.39.1 vs. Placebo		10 NP							
DESCARTES	-20.5	31.4	126	-1.1	31	63	2.1%	-19.40 [-28.82, -9.98]	
DESCARTES	-22.5	31	74	-12.8	30.4	37	1.8%	-9.70 [-21.78, 2.38]	
DESCARTES	-30.1	25.3	145	-10.6	24.8	73	2.5%	-19.50 [-26.52, -12.48]	
DESCARTES	-32.8	25.5	254	-3.6	25	129	2.7%	-29.20 [-34.53, -23.87]	-
GLAGOV ⁶ 7	0	0	486	0	0	484		Not estimable	
LAPLACE-27	-23.2	26.8	115	3.7	26.6	57	2.3%	-26.90 [-35.37, -18.43]	
LAPLACE-2	-24.3	23.3	113	11.4	22.4	58	2.5%	-35.70 [-42.89, -28.51]	
LAPLACE-2 LAPLACE-2	-25 -22.6	22.3 23.5	111 110	8.6	22 23.9	56 55	2.5%	-33.60 [-40.70, -26.50]	
LAPLACE-2	-32.2	47.9	115		18.5	55		-21.80 [-29.49, -14.11] -27.20 [-37.23, -17.17]	
LAPLACE-2	-25.9	25.9	112	6.3	26.3	55		-32.20 [-40.65, -23.75]	
LAPLACE-2	-27.5	24.9	110		24.4	55		-29.00 [-36.95, -21.05]	
LAPLACE-2	-38.6	41.4	112	-10.6	33	56		-28.00 [-39.55, -16.45]	
LAPLACE-2	-24	21.9	109	-3.5	21.8	55	2.5%	-20.50 [-27.58, -13.42]	
LAPLACE-2	-26	21.7	110	6.1	21.1	56	2.5%	-32.10 [-38.95, -25.25]	
LAPLACE-TIMI57 8	0	0	78	0	0	78		Not estimable	
LAPLACE-TIMI57	0	0	80	0	0	79		Not estimable	
McKenney et al. 9 McKenney et al. 9	-28.6	33.7	29	0	31.2	31	1.3%	-28.60 [-45.06, -12.14]	
MENDEL ¹⁰	-19.9	23.8	45	9.2	24	45		-29.10 [-38.98, -19.22]	
MENDEL MENDEL-2 ¹¹	-27.3 -18.4	25.8	45 153	2	26.5 49.5	45 76	1.9% 0.9%	-29.30 [-40.11, -18.49] -18.50 [-40.18, 3.18]	
MENDEL-2	-18.4		153		49.5	78	1.0%	-19.20 [-38.75, 0.35]	
ODYSSEY CHOICE I 13	-19.3	28.3	312	9.7	30.1	157	2.7%	-29.00 [-34.66, -23.34]	
ODYSSEY CHOICE I	-21.3	20.0	146	6.4	29	73	2.3%	-27.70 [-35.85, -19.55]	
ODYSSEY CHOICE II 14	-15.5	28.4	59	4.1	28.2	58	2.0%	-19.60 [-29.86, -9.34]	
ODYSSEY COMBO I ¹⁵	-20.5	28.6	209	-5.9	28.2	107	2.5%	-14.60 [-21.20, -8.00]	
ODYSSEY ESCAPE 17	0	0	41	0	0	21		Not estimable	
ODYSSEY FHI 18	-25.2	25.2	323	-7.5	25.5	163	2.8%	-17.70 [-22.48, -12.92]	
ODYSSEY FH II 18	-30.3	23.3	167	-10	22.6	82	2.6%	-20.30 [-26.33, -14.27]	
ODYSSEY HIGH FH 19	-23.5	31.4	72	-8.7		35	1.7%	-14.80 [-27.00, -2.60]	
ODYSSEY JAPAN ²⁰	-39.5	21.6	144	2.5	21.2	72	2.6%	-42.00 [-48.04, -35.96]	
ODYSSEY LONG TERM ²¹ OSLER 1 and 2 ²⁵	-29.3 0	27.6	1553 2976		28.1 0	788 1489	3.0%	-25.60 [-27.99, -23.21]	
Roth et al. ²⁶	0	0	2970	0	0	31		Not estimable Not estimable	
RUTHERFORD ²⁷	-27.4	23.2	56	4.1		56	2 296	-31.50 [-40.09, -22.91]	
RUTHERFORD 2 28	-21.6	22.5	110	6.7	22.9	55		-28.30 [-35.67, -20.93]	
RUTHERFORD 2	-22.9	24.3	110	8.7	23.6	54		-31.60 [-39.36, -23.84]	
Stein et al 29	0	0	16	0	0	15		Not estimable	
Teramoto 30	0	0	25	0	0	25		Not estimable	
TESLA PART B ³¹	-9.4	23.1	33	2.4	21.5	16	1.6%	-11.80 [-24.96, 1.36]	
YUKAWA 32	-44.3	25.2	52	6.3	25.2	52	2.1%	-50.60 [-60.29, -40.91]	
YUKAWA	-32.1	25.5	53	0.3	25.5	50	2.1%	-32.40 [-42.25, -22.55]	
YUKAWA II 33	-45.7	35.7	51		37.1	51		-40.00 [-54.13, -25.87]	
YUKAWAII	-41.9	36.4	51	10.8	37.5	52	1.5%	-52.70 [-66.97, -38.43]	
	-41.7	37.5 48.8	50 50		38.9 48.3	50		-48.70 [-63.68, -33.72]	
YUKAWA II Subtotal (95% CI)	-45.7	40.0	9474	4.4	40.5	49 5377		-50.10 [-69.23, -30.97] -28.01 [-30.73, -25.30]	•
Heterogeneity: Tau ² = 49.12;	Chi ² = 1	159.99		′P < ∩ ∩	00011				
Test for overall effect: $Z = 20$						1.10	220		
1.39.2 vs. Ezetimibe									
GAUSS ³	-23.6	25.1	32		25.1	33	1.7%	-15.70 [-27.91, -3.49]	
GAUSS-24	-27	28.1	103		25.1	51		-25.30 [-34.07, -16.53]	
GAUSS-2	-22.1	36.9	102		35.9	51		-27.90 [-40.08, -15.72]	
GAUSS-35	-21.1	26.5	145		25.7	73	2.4%	-21.30 [-28.60, -14.00]	
ODYSSEY ALTERNATIVE ¹²		0	126	0	0	125	2.00	Not estimable	<u> </u>
ODYSSEY COMBO II 16 ODYSSEY MONO ²²	-27.8	30.6	479	-6.1 -12.3	31	241		-21.70 [-26.48, -16.92]	
ODYSSEY MONO	-16.7 -30.8	26.7 27.8	52 46	-12.3	26.5	51 46	2.0%	-4.40 [-14.79, 5.99] -31.00 [-42.10, -19.90]	
ODYSSEY OPTIONS I	-23.6	29.7	40	-10.6	20.5	40 53	1.9%	-13.00 [-24.65, -1.35]	
ODYSSEY OPTIONS II ²⁴	-22.7	37.1	53		32.5	50	1.6%	-16.90 [-30.35, -3.45]	
ODYSSEY OPTIONS II	-27.9	28.4	48 1241		30.9	47 821	1.8%	-23.60 [-35.54, -11.66] -20.32 [-24.68, -15.97]	<u> </u>
Subtotal (95% CI)	Chil-	10.21		- 0.025	12 - 64		20.078	-20.32 [-24.00, -13.37]	•
Heterogeneity: Tau² = 23.05; Test for overall effect: Z = 9.1				- 0.03);	17= 51	70			
			10715			6198	100.0%	-26.45 [-28.88, -24.03]	•
Total (95% CI)			10110			v100	100.070	-VITO 1-20,00, -24,0J	
Total (95% CI) Heterogeneity: Tau² = 48.90;	Chi?-		df = 47	Penn	00015		96		-50 -25 0 25 50

Figure S14. Apolipoprotein B % change from baseline

Study or Subgroup	Mean	ntibody SD		Mean	sD	The second second	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
.41.1 vs. Placebo	moun	50	1.7141	mount	30		risignt	in managing work of	
DESCARTES	-43.3	17.2	74	-0.4	17.6	37	1.9%	-42.90 [-49.79, -36.01]	
DESCARTES	-39.2		145		28.2	73		-44.60 [-52.60, -36.60]	1000 C
DESCARTES	-37	28.1	126	0.8	27.8	63	1.8%	-37.80 [-46.24, -29.36]	
DESCARTES	-44.8	20.7	254	2.9	20.4	129	2.0%	-47.70 [-52.04, -43.36]	
GLAGOV ⁶ 7	0	0	486	0	0	484		Not estimable	
LAPLACE-2	-49.1		109		22.2	55		-59.30 [-66.49, -52.11]	
LAPLACE-2	-53.3		110	5.5	20.9	55		-58.80 [-65.60, -52.00]	
LAPLACE-2	-49.8		113		14.8	58		-54.90 [-59.67, -50.13]	
LAPLACE-2 LAPLACE-2	-51 -54.4	14.6 42	110 115	7.6 2.5	14 34	56 55		-58.60 [-63.17, -54.03] -56.90 [-68.72, -45.08]	
LAPLACE-2	-53.6		115		14.1	57		-56.10 [-60.58, -51.62]	-
LAPLACE-2		18.4	112		18.9	55		-55.00 [-61.05, -48.95]	·
LAPLACE-2	-55.7		112		22.4	56		-55.40 [-63.21, -47.59]	(
LAPLACE-2	-51.4		110		15.9	55		-52.20 [-57.35, -47.05]	
LAPLACE-2	-47.1	18.6	111	3.7	18.3	56	1.9%	-50.80 [-56.71, -44.89]	
LAPLACE-TIMI578	-38.8	20.6	80	3.2	20.4	79	1.9%	-42.00 [-48.37, -35.63]	
APLACE-TIMI57	-50.6	19.4	78		19.4	78	1.9%	-56.50 [-62.59, -50.41]	
McKenney et al. ⁹	-56.1		29		15.9	31		-58.30 [-66.40, -50.20]	
MENDEL ¹⁰	-44.5	15	45	-0.3	15	45		-44.20 [-50.40, -38.00]	
MENDEL 211	-42.3		45	0.2	15	45		-42.50 [-48.62, -36.38]	
		14.1	153		12.9	76		-47.10 [-50.76, -43.44]	
MENDEL-2 ODYSSEY CHOICE I 13	-49.4 -45.1	12.5	153 312	1.5 3.1	12.2 22.6	78 157		-50.90 [-54.25, -47.55] -48.20 [-52.56, -43.84]	
ODYSSEY CHOICE I	-40.2		146		19.7	73		-39.50 [-45.00, -34.00]	
DDYSSEY CHOICE II ¹⁴	-38.9		59	7.5	16	58		-46.40 [-52.36, -40.44]	
ODYSSEY COMBO I	-36.7		209		23.2	107		-35.80 [-41.23, -30.37]	
DDYSSEY ESCAPE ¹⁷	-42.8		41		13.7	21		-44.00 [-51.15, -36.85]	
	-41.1	21.6	323	4.7	20.4	163	2.0%	-45.80 [-49.72, -41.88]	-
ODYSSEY FH II 18	-42.8	18.1	167	-3.5	18.1	82	2.0%	-39.30 [-44.08, -34.52]	
DDYSSEY HIGH FH ¹⁹		22.9	72		22.5	35		-30.30 [-39.44, -21.16]	
ODYSSEY JAPAN ²⁰		14.4	144		14.4	72		-53.40 [-57.47, -49.33]	
ODYSSEY LONG TERM ²¹	-52.8	27.6	1553		28.1	788	2.1%	-54.00 [-56.39, -51.61]	-
OSLER 1 and 2 ²⁵ Roth et al. ²⁶ 27	0	0	2976 30	0	0	1489 31		Not estimable	
RUTHERFORD 27	-43.3		56		19.5	56	1 9%	Not estimable -46.20 [-53.42, -38.98]	
RUTHERFORD 228	-49.8		110		16.7	54		-49.10 [-54.59, -43.61]	
RUTHERFORD 2	-44.8		110		19.6	55		-49.40 [-55.69, -43.11]	
Stein et al ²⁹	-50.2	16	16		16.3	15		-43.80 [-55.18, -32.42]	
Teramoto ³⁰ 31	-60	16.5	25	-2.3	16.5	25	1.7%	-57.70 [-66.85, -48.55]	
TESLA PART B	-19.2	54	33	4	18.6	16	1.0%	-23.20 [-43.75, -2.65]	
YUKAWA	-53.2		53		14.1	50		-53.40 [-58.94, -47.86]	
YUKAWA	-47.7		52	-0.9	13	52		-46.80 [-51.93, -41.67]	
YUKAWA II ³³	-64.8	15.6	50		15.4	49	1.9%	-65.50 [-71.61, -59.39]	
YUKAWA II ZUZAVAA II	-58	15	51		15.7	51		-56.10 [-62.06, -50.14]	I
YUKAWA II YUKAWA II	-62.8 -54.8		51 50	-2.5	18 16.3	52 50		-60.30 [-67.23, -53.37] -57.20 [-63.45, -50.95]	
Subtotal (95% CI)	-04.0	13.0	9474	2.4	10.3	5377		-49.73 [-51.79, -47.67]	•
Heterogeneity: Tau ² = 36.54; Test for overall effect: Z = 47			, df = 42	(P < 0.	00001				
1.41.2 vs. Ezetimibe	12.7		2.2			(122)			10000
GAUSS ³	-42.1			-12.2		33		-29.90 [-39.04, -20.76]	
GAUSS-24	-45.9			-13.7		51		-32.20 [-37.48, -26.92]	
GAUSS-2 GAUSS-3 10	-46 -43.5	16.8	102	-11	15.5	51 73		-35.00 [-40.36, -29.64]	
DDYSSEY ALTERNATIVE	-43.5	10.8	145	-11.7	10.5	125	2.070	-31.80 [-36.47, -27.13] Not estimable	
ODYSSEY COMBQ II	-40.7			-18.3		241	2.0%	-22.40 [-26.05, -18.75]	
ODYSSEY MONO ²²	-36.7		52		17.1	51		-25.70 [-32.21, -19.19]	
DDYSSEY OPTIONS I	-41.9			-14.3		46		-27.60 [-36.90, -18.30]	
ODYSSEY OPTIONS I 24	-33.7			-10.1		53		-23.60 [-33.30, -13.90]	
ODYSSEY OPTIONS II 24	-28.3			-11.2	30.4	50	1.5%	-17.10 [-29.02, -5.18]	
ODYSSEY OPTIONS II Subtotal (95% CI)	-36.5		48 1241	-9.7	21.3	47 821	1.8%	-26.80 [-35.41, -18.19] -27.88 [-31.38, -24.38]	
Heterogeneity: Tau² = 18.64; Test for overall effect: Z = 15.				9 = 0.00	3); l²=	64%			
restion overall effect. Z = 15.									
			10745			6400	100.0%	45 50 1 49 35 43 641	▲ I
Total (95% CI) Heterogeneity: Tau ² = 100.41	0.042	- 706 0	10715	2/0-1	0000			-45.50 [-48.35, -42.64]	•

Figure S15. Funnel plot: all-cause mortality

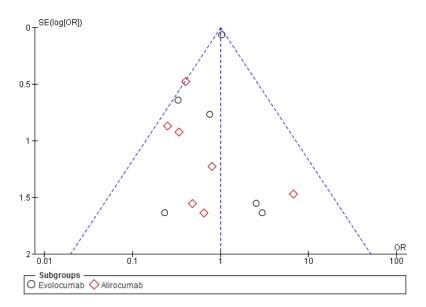


Figure S16. Funnel plot: cardiovascular mortality

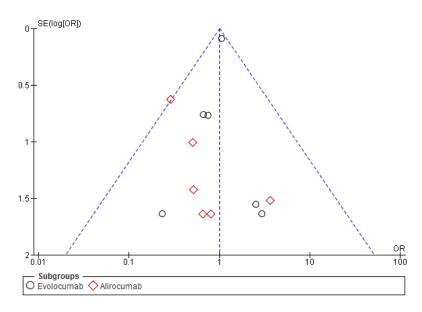
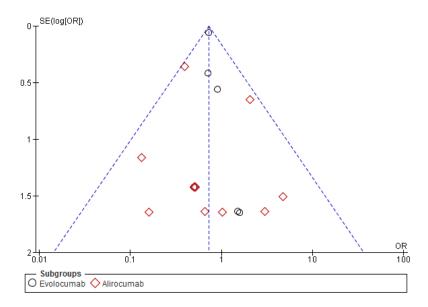


Figure S17. Funnel plot: myocardial infarction





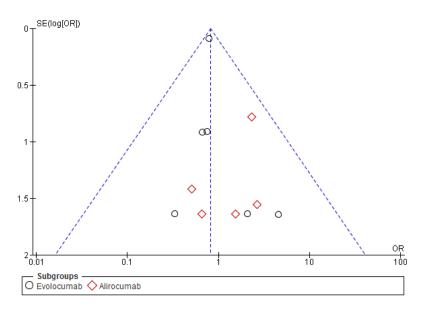


Figure S19. Funnel plot: coronary revascularization

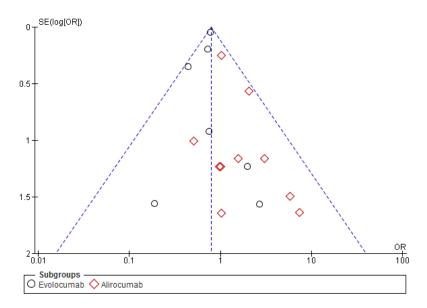


Figure S20. Funnel plot: unstable angina

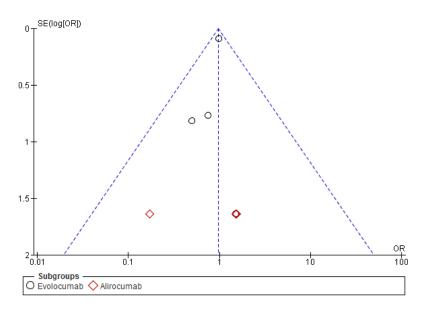
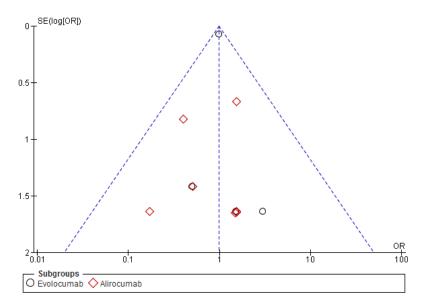


Figure S21. Funnel plot: congestive heart failure exacerbation





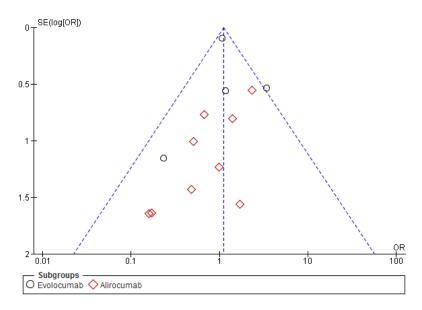
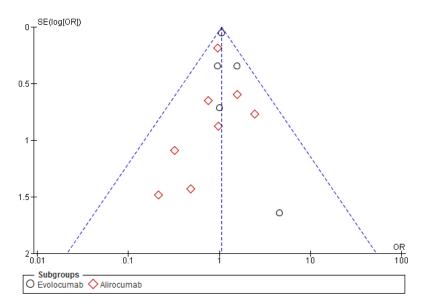
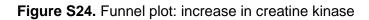


Figure S23. Funnel plot: diabetes mellitus





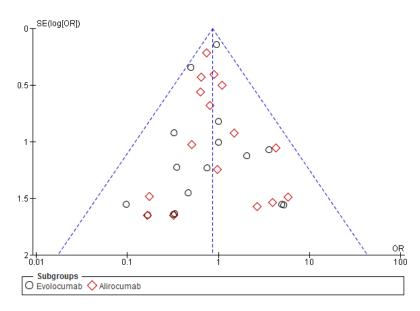
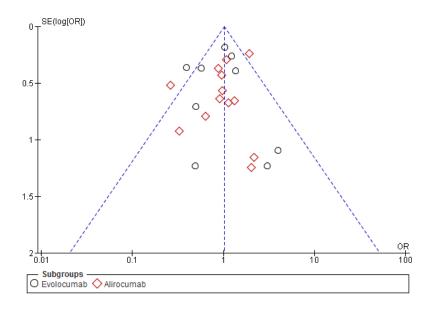


Figure S25. Funnel plot: myalgia



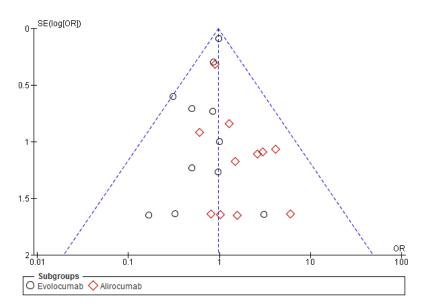


Figure S26. Funnel plot: increase in alanine/aspartate aminotransferase

Figure S27. Funnel plot: treatment emergent serious adverse events

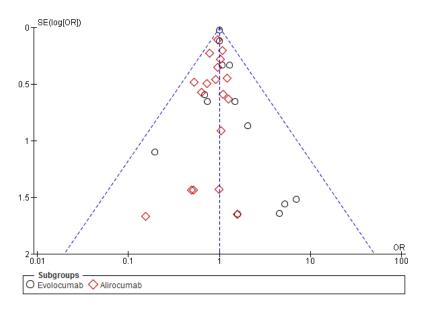


Figure S28. Funnel plot: LDL- Cholesterol

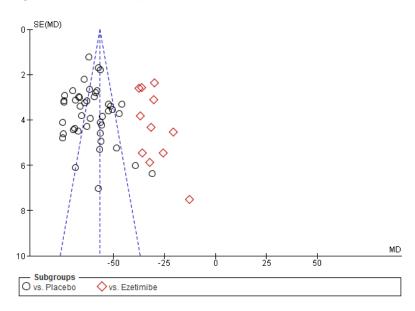


Figure S29. Funnel plot: HDL- cholesterol

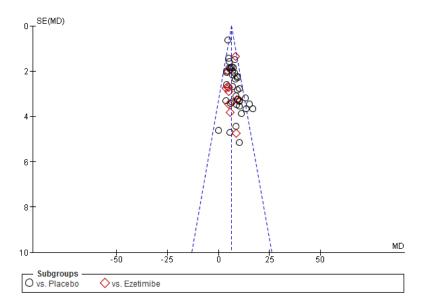


Figure S30. Funnel plot: total cholesterol

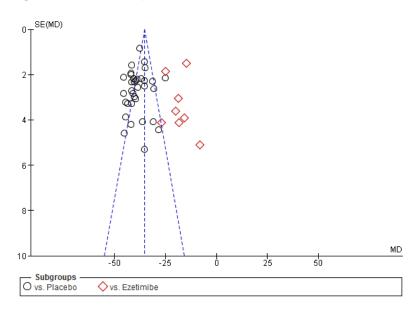


Figure S31. Funnel plot: lipoprotein(a)

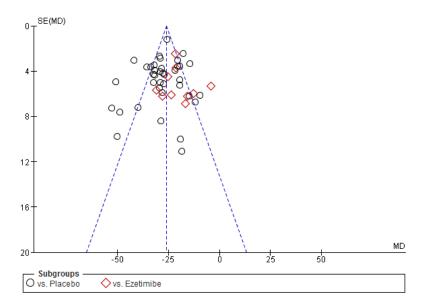
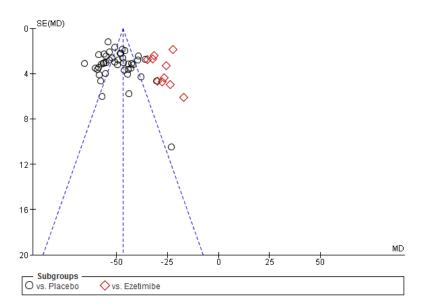


Figure S32. Funnel plot: apolipoprotein B



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