JACC: ADVANCES VOL. 4, NO. 2, 2025

ORIGINAL RESEARCH

Impact of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors on Lipoprotein(a)

A Meta-Analysis and Meta-Regression of Randomized Controlled Trials

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ABSTRACT

BACKGROUND Lipoprotein(a) [Lp(a)] has been independently associated with increased cardiovascular risk.

OBJECTIVES The authors examined the effect of monoclonal antibody proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) on plasma Lp(a) levels across multiple trials.

METHODS Studies were retrieved comparing the effect of PCSK9i vs placebo on Lp(a) levels. The primary outcome was percent change in Lp(a) levels. Factors associated with the treatment effect were determined by meta-regression analysis. Subgroup analyses were done to explore potential treatment effect differences.

RESULTS PCSK9i reduced Lp(a) levels on average of −27% (95% CI: −29.8% to −24.1%, $P < 0.001$). Factors associated with the treatment effect included mean percent change in low-density lipoprotein cholesterol ($P = 0.003$, beta coefficient 0.34, 95% CI: 0.11-0.57, $tau^2 = 94.8$, $R^2 = 11.82$) and apolipoprotein B ($P < 0.002$, beta coefficient 0.4, 95% CI: 0.14-0.64, $tau^2 = 93.68$, $R^2 = 11.86$). Subgroup analyses revealed consistent treatment effect amongst comparators vs placebo: −27.69% (95% CI: −30.85% to −24.54%, $P < 0.001$), vs ezetimibe: −24.0% (95% CI: −29.95% to −18.01%, $P < 0.001$), type of PCSK9i, evolocumab: −29.35% (95% CI: −33.56% to −25.14%, $P < 0.001$) vs alirocumab: −24.50% (95% CI: −27.96% to −21.04%, $P < 0.001$), and presence of familial hypercholesterolemia: −25.63% (95% CI: −31.96% to −19.30%, $P < 0.001$ vs no familial hypercholesterolemia: −27.22%; 95% CI: −30.34% to −24.09%, $P < 0.001$). Varying treatment effects were noted in the duration of treatment (12 weeks or shorter: −32.43% [95% CI: −36.63% to −28.23% vs >12 weeks: −22.31%] [95% CI: −25.13% to −19.49%, $P < 0.001$]), P interaction < 0.01.

CONCLUSIONS PCSK9is reduce Lp(a) levels by an average of 27%. Mean percent change in low-density lipoprotein cholesterol and apolipoprotein B were associated with treatment effect. (JACC Adv. 2025;4:101549)

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ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.101549

ABBREVIATIONS AND ACRONYMS

ApoB = apolipoprotein B

FH = familial hypercholesterolemia

LDL-C = low-density lipoprotein cholesterol

Lp(a) = lipoprotein(a)

MD = mean difference

PCSK9 = proprotein convertase subtilisin/kexin type 9

PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor

RCT = randomized controlled trial

Lipoprotein(a) [Lp(a)] is associated with premature and aggressive atherosclerosis across multiple vascular beds,[1,2] along with an increased risk of cardiovascular events.[3,4] Plasma Lp(a) level is genetically determined and elevated in 20% of the general population.[5] Levels >50 mg/dL (or >125 nmol/L) are associated with significantly increased cardiovascular risk, independent of low-density lipoprotein cholesterol (LDL-C) level, hence, Lp(a) is considered a risk enhancer in American College of Cardiology/American Heart Association and European Society of Cardiology/European Atherosclerosis Society guidelines.[5,6] Furthermore, a 3.5-fold higher Lp(a) levels increases the risk of death from myocardial infarction and urgent coronary revascularization.[7] Moreover, elevated Lp(a) is associated with major adverse limb events such as lower extremity amputation and peripheral vascular intervention.[8]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (PCSK9is) have been postulated to lower Lp(a) level by reducing its production and enhancing clearance.[9] Individuals with elevated baseline plasma Lp(a) levels tend to have a more significant reduction in Lp(a) with PCSK9i treatment, and they experience a greater reduction in adverse coronary events.[7] In 2 post hoc analyses of the ODYSSEY Outcomes trial, reduction in Lp(a) by alirocumab contributed to a reduction in major adverse cardiovascular events, independent of LDL-C lowering.[10] These analyses revealed that an elevated baseline Lp(a) level is associated with a more pronounced clinical benefit of major adverse cardiovascular events reduction, as well as greater Lp(a) reduction, from PCSK9i.[10] However, it should be noted that the studies employed LDL-C values adjusted for Lp(a). Additionally, whether PCSK9i therapy lowers Lp(a) consistently across multiple studies is not well established.

Our meta-analysis aims to quantify the extent of Lp(a) reduction that can be achieved with PCSK9i therapy and to provide contribution to the existing body of literature by offering a pooled estimate of the effect of PCSK9i on Lp(a) reduction. While prior studies have examined the impact of individual PCSK9i variants, such as alirocumab and evolocumab, this analysis integrates data across multiple clinical trials to offer a more robust and comprehensive assessment of their effect on Lp(a). By pooling these data, we are able to not only quantify the average percentage reduction in Lp(a) levels but also investigate factors that may alter this effect, including the type of PCSK9i, the comparator used, treatment duration, and the presence of familial hypercholesterolemia (FH). Furthermore, we examined concurrent reductions in other atherogenic lipoproteins. The integration of data from diverse studies in this meta-analysis provides a valuable contribution to advancing the understanding of PCSK9i's role in lipid management.

METHODS

This study was reported under the Preferred Reporting Items for a Review and Meta-Analysis[11,12] (see Supplemental Figure 1). Certainty of evidence was rated using the Grades of Recommendation, Assessment, Development, and Evaluation framework.[13] This study was registered in the International Prospective Register of Systematic Reviews,[14] with the identification number CRD42022378644.

DATA SOURCES AND SEARCHES. The literature search was performed using PubMed/MEDLINE, Ovid/Embase, Web of Science, SCOPUS, and Cochrane databases from database inception until May 2024. Search terms included "PCSK9 inhibitor," "PCSK9 antibody," "Evolocumab," "Alirocumab," "Bococizumab," "AMG145," "Repatha," "REGN727," "SAR236553," "RN 316," "PF-04950615," "LY3015014," "RG7652," "Lipoprotein a," "Lp(a)," "randomized controlled trial," "randomization," "clinical trials," "intervention studies," and synonyms. PCSK9i therapies that are not monoclonal antibodies, such as inclisiran, were not included. Citations of selected articles and any relevant studies that evaluated Lp(a) and LDL-C lowering using PCSK9i were reviewed. After removing duplicates, records were reviewed at the title and abstract level, followed by the screening of full text based on our study criteria.

STUDY SELECTION. Eligible phase II or phase III, double-blind randomized controlled trials (RCTs) comparing treatment with monoclonal antibody PCSK9i with placebo and/or ezetimibe in adult

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received July 31, 2024; revised manuscript received November 24, 2024, accepted December 2, 2024.

patients aged 18 years and above were included. Moreover, the studies must have reported baseline Lp(a) level and Lp(a) reduction in mean percent change, and treatment duration had to be 8 weeks or longer. Additionally, mean percent change in LDL-C and apolipoprotein B (ApoB) from the baseline must have been reported. Studies were excluded if: 1) they did not report a control arm; 2) they reported absolute change; or 3) Lp(a) was reported as median instead of mean. Other agents such as bococizumab and inclisiran were excluded. We also excluded RCTs with participants younger than 18 years, and those reporting interim or post hoc analysis. Cross-over trials were also excluded due to the nature of the outcomes considered. Review articles, case reports, letters to the editor, commentaries, proceedings, laboratory studies, and other nonrelevant studies were excluded as well.

DATA EXTRACTION. Key participant and intervention characteristics and reported data on efficacy outcomes were extracted independently by 2 investigators (J.M. and V.T.) using standard data extraction templates. Any disagreements were resolved by discussion or, if required, by a third author (F.B.R.). Data on the following variables were extracted: first author's name, year of publication, journal, study phase, interventional and control treatments, randomization method, analysis tool, number of randomized patients, and demographic and clinical data (eg, age, sex). In case of uncertainties regarding the study data, we contacted the authors of the specific study for additional information. Quality assessment was performed independently by 2 review authors (J.M. and V.T.) using the Revised Cochrane risk-of-bias tool for randomized trials.

OUTCOME MEASURES. The primary endpoint of this study was percent change from baseline in Lp(a) levels. Secondary endpoints included mean percent change from baseline in LDL-C, non-high-density lipoprotein cholesterol, total cholesterol, triglycerides, high-density lipoprotein cholesterol, ApoB, and apolipoprotein A1. Additionally, subgroup analyses were performed for applicable studies on the: 1) type of PCSK9i; 2) comparator (placebo vs ezetimibe); 3) duration of treatment; and 4) population (FH vs no FH).

BIAS ASSESSMENT. All included studies reported a central randomization process, and outcomes were objectively determined. The included studies reported all primary and secondary outcomes as prespecified in their protocols, so the risk of bias for selective reporting was judged as low. Two authors (J.M. and V.T.) independently assessed the risk of bias based on the Cochrane Risk of Bias Tool (Supplemental Figure 2) for studies that fulfilled the inclusion criteria. Disagreements between the 2 reviewers were resolved by consensus. In case of persistent disagreement, arbitration by a third reviewer (F.B.R.) was performed.

STATISTICAL ANALYSIS. Stata Statistical Software version 18 (StataCorp LLC) was used to conduct the included studies' meta-analysis, heterogeneity tests, and sensitivity analyses. For all outcomes, the significance level was set at a P value of <0.05. Statistical heterogeneity was identified through the forest plots and a standard chi-squared test with a significant level of $P < 0.10$. The extent of heterogeneity was based on the I^2 statistic, wherein a value of more than 50% was interpreted as substantial heterogeneity. We pooled all estimates using a random effects model and utilized the Restricted Maximum Likelihood Estimator for the analysis. Effect sizes were expressed using mean differences (MDs) with 95% CIs. Prespecified subgroup analyses were performed according to the: 1) type of PCSK9i; 2) comparator (placebo versus ezetimibe); 3) duration of treatment; and 4) population (FH vs no FH). Regression analyses were performed to determine baseline factors such as LDL-C and ApoB levels that could affect the point estimate. Changes in mean LDL-C was incorporated as possible covariate because of the reported higher discordance in LDL-C reduction for higher Lp(a) levels[15] and ApoB was incorporated in regression analysis as studies have suggested that it is not always linked on a single Lp(a) particle.[9] Publication bias was assessed using funnel plots and confirmed using Egger and Begg's tests.

RESULTS

A literature search through July 2023, yielded 2,328 potentially relevant references on PCSK9i therapy, focusing on monoclonal antibody-based therapies (Supplemental Figure 1). Of these, 33 duplicates were removed. A total of 2,152 studies with unrelated interventions, outcomes, populations, nonoriginal data (eg, meta-analysis or review), and descriptive or observational study design and study protocols were excluded. A total of 114 studies were left, and 35 pooled analyses were removed for not meeting the eligibility criteria. The remaining 79 related studies were retrieved as full-text publications for detailed evaluation. Overall, 47 studies were included in the final meta-analysis. From the 47 studies, data from 67,057 eligible individuals were included for analysis. Majority of whom are on optimal background lipid

TABLE 1 Characteristics of Included Studies

First Author, Year/Trial Name	Phase	N	Population	Age, y	Baseline Lp(a), Nmol/L	Baseline LDL-C, Mg/dL	Drug (Dose and Frequency)	Duration of Treatment	Comparator	Primary Outcome
Ako et al, 2019/ ODYSSEY J-IVUS TRIAL[16]	4	206	Patients with ACS and hypercholesterolemia	61.2 ± 10.9	(–)	96.8 ± 22.5	Alirocumab 75 min/150 mg every 2 wk	36 wk	Atorvastatin ≥10 mg/d or rosuvastatin ≥5 mg/d	Percent change in normalized total atheroma volume from baseline to wk 36
Bays et al, 2015/ ODYSSEY OPTIONS I[17]	3	355	Hypercholesterolemia on statin and high CV risk	62.9 ± 10.2	72.6 ± 102.5	105.1 ± 34.1	Alirocumab 75 min/150 mg every 2 wk	24 wk	Statin and/or ezetimibe	Percent change in LDL-C from baseline to wk 24
Blom et al, 2014/ DESCARTES[18]	3	905	Hypercholesterolemia	56.2 ± 10.6	63.9 ± 93.6	104.1 ± 21.9	Evolocumab 420 mg every 4 wk	52 wk	Placebo and/or atorvastatin and/or ezetimibe	Percent change in LDL-C from baseline to wk 52
Blom et al, 2020/ ODYSSEY HoFH Trial[19]	3	69	HoFH	43.4 ± 14.7	(–)	282.7 ± 161.9	Alirocumab 150 mg every 2 wk	12 wk	Placebo	Percent change in LDL-C from baseline to wk 12
Boccara et al, 2020/ BEIJERINCK[20]	3	467	People living with HIV and hypercholesterolemia and/or mixed dyslipidemia	56.4 ± 8.7	86.2 ± 124.4	133.3 ± 40.1	Evolocumab 420 mg SC monthly	24 wk	Placebo	Percent change in LDL-C from baseline to wk 24
Cannon et al, 2015/ ODYSSEY COMBO II[21]	3	720	Hypercholesterolemia on statin and high CV risk	61.6 ± 9.3	(–)	107 ± 34.8	Alirocumab 75 min/150 mg every 2 wk	104 wk	Ezetimibe 10 mg/d	Percent change in LDL-C from baseline to week 24
Chao et al, 2019/ ODYSSEY KT-TW[22]	3	116	Taiwanese patients with hypercholesterolemia on statin and high CV risk	60.7 ± 10.0	(–)	102 ± 27	Alirocumab 75 min/150 mg every 2 wk	24 wk	Placebo	Percent change in LDL-C from baseline to wk 24
Farnier et al, 2015/ ODYSSEY OPTIONS II[23]	3	305	Hypercholesterolemia on statin and high CV risk	60.9 ± 10.3	86.8 ± 94.9	111.2 ± 38.8	Alirocumab 75 min/150 mg every 2 wk	24 wk	Statin and/or ezetimibe	Percent change in LDL-C from baseline to wk 24
Ginsberg et al, 2016/ODYSSEY HIGH FH[24]	3	107	HeFH and LDL-C ≥160 mg/dL on statin	50.6 ± 13.3	55.1 ± 60	197.8 ± 53.4	Alirocumab 150 mg every 2 wk	78 wk	Placebo	Percent change in LDL-C from baseline to wk 24
Han et al, 2019/ ODYSSEY EAST[25]	3	615	Hypercholesterolemia on statin and high CV risk	58.6 ± 10.8	71.6 ± 73.7	110.8 ± 48.9	Alirocumab 75 min/150 mg every 2 wk	24 wk	Ezetimibe	Percent change in LDL-C from baseline to wk 24
Hao et al, 2022[26]		136	Extremely high-risk ACS with LDL-C ≥3.0 mmol/L on statin	62.2 ± 11.8	(–)	136.5 ± 19.4	Evolocumab 140 mg every 2 wk	12 wk	Atorvastatin 40 mg/d and ezetimibe 10 mg/d	Major adverse cardiovascular events
Hirayama et al, 2014/ YUKAWA[27]	2	310	Hypercholesterolemia on statin and high CV risk	60.8	40.8 ± 41.9	141.1 ± 21.3	Evolocumab 70 min/140 mg every 2 wk or 280 min/420 mg every 4 wk	12 wk	Placebo	Percent change in LDL-C from baseline to wk 12
Janik et al, 2021[28]	4	2,176	HeFH or non-FH on statin and high CV risk	63 (40-85)	(–)	118.8 ± 41.2	Alirocumab 75 min/150 mg every 2 wk	96 wk	Placebo	Change in CANTAB cognitive domain SWMS *z*-score from baseline to wk 96
Kastelein et al, 2015/ODYSSEY FH I[29]	3	486	HeFH	52 ± 12.7	104.5 ± 106.4	144.6 ± 3.2	Alirocumab 75 min/150 mg every 2 wk	78 wk	Placebo	Percent change in LDL-C from baseline to wk 24

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TABLE 1 Continued

First Author, Year/Trial Name	Phase	N	Population	Age, y	Baseline Lp(a), Nmol/L	Baseline LDL-C, Mg/dL	Drug (Dose and Frequency)	Duration of Treatment	Comparator	Primary Outcome
Kastelein et al, 2015/ODYSSEY FH II[29]	3	249	HeFH	53.2 ± 12.7	105.7 ± 105	134.4 ± 3.7	Alirocumab 75 min/150 mg every 2 wk	78 wk	Placebo	Percent change in LDL-C from baseline to wk 24
Kereiakes et al, 2015/ODYSSEY COMBO I[30]	3	316	Hypercholesterolemia on statin and high CV risk	63 ± 9.3	82.9 ± 107.7	103.4 ± 31.6	Alirocumab 75 min/150 mg every 2 wk	52 wk	Placebo	Percent change in LDL-C from baseline to wk 24
Kiyosue et al, 2016/ YUKAWA-2[31]	3	404	Patients with hyperlipidemia or mixed dyslipidemia and high CV risk	61.5	33.7 ± 31.7	106 ± 31.8	Evolocumab 140 mg every 2 wk/ 420 mg monthly	12 wk	Placebo	Percent change in LDL-C from baseline to wk 12
Koh et al, 2017/ ODYSSEY KT[32]	3	199	Hypercholesterolemia on statin and high CV risk	60.6 ± 9.7	59.7 ± 67.5	98.2 ± 26.5	Alirocumab 75 min/150 mg every 2 wk	24 wk	Placebo	Percent change in LDL-C from baseline to wk 24
Koren et al, 2012/ MENDEL[33]	2	411	Hypercholesterolemia and low CV risk	51.2	73.5 ± 79.1	142.3 ± 22.6	Evolocumab 70 min/105 min/ 140 mg every 2 wk or 280 min/ 350 min/420 mg every 4 wk	12 wk	Placebo or ezetimibe	Percent change in LDL-C from baseline to wk 12
Koren et al, 2014/ MENDEL-2[34]	3	615	Hypercholesterolemia and moderate CV risk	53.2 ± 12.2	37 ± 55.4	142.9 ± 22.7	Evolocumab 140 mg every 2 wk or 420 mg every 4 wk	12 v	Placebo and/or ezetimibe	Percent change in LDL-C from baseline to wk 12
Koskinas et al, 2019/ EVOPACS[35]	3	308	ACS patients	60.7 ± 11.4	68.6 ± 89.3	136.3 ± 38	Evolocumab 420 mg every 4 wk	8 v	Placebo	Percent change in LDL-C from baseline to wk 8
Leiter et al, 2017/ ODYSSEY DM-INSULIN[36]	3b	441	Hypercholesterolemia and insulin-treated patients	62.8 ± 9.5	44.8 ± 66	112 ± 39.8	Alirocumab 75 min/150 mg every 2 wk	24 wk	Placebo	Percent change in LDL-C from baseline to wk 24
Lorenzatti et al, 2019/ BERSON[37]	3	981	T2DM and hypercholesterolemia	61.3	69.4 ± 94	92.8 ± 33.6	Evolocumab 140 mg every 2 wk or 420 mg every 4 wk	12 v	Placebo	Percent change in LDL-C from baseline to wk 12
McKenney et al, 2012[38]	2	183	Hypercholesterolemia on atorvastatin	56.7 ± 10	71.5 ± 111.2	128.5 ± 26.2	Alirocumab 50 min/ 100 min/150 mg every 2 wk or 200/300 mg every 4 wk	12 wk	Placebo	Percent change in LDL-C from baseline to wk 12
Moriarty et al, 2015/ODYSSEY ALTERNATIVE[39]	3	314	Hypercholesterolemia and statin intolerant	63.4 ± 9.4	45.9 ± 57.5	192.3 ± 71.7	Alirocumab 75 min/150 mg every 2 wk	24 wk	Ezetimibe	Percent change in LDL-C from baseline to wk 24
Nicholls et al, 2016/ GLAGOV[40]	3	970	Patient on statin and with coronary disease	59.8 ± 9.2	46.8 ± 76.6	92.5 ± 27.2	Evolocumab 420 mg every 4 wk	78 wk	Placebo	Nominal change in percent atheroma volume from baseline to wk 78
Nissen et al, 2016/ GAUSS-3[41]	3	218	Statin intolerant patients	58.8 ± 10.5	67.6 ± 106.5	219.8 ± 72	Evolocumab 420 mg every 4 wk	24 wk	Ezetimibe	Percent change in LDL-C from baseline to wk 24
Raal et al, 2012/ RUTHERFORD[42]	2	168	HeFH	50.6 ± 13	72.7 ± 112.6	156.6 ± 39.2	Evolocumab (AMG145) 350 mg and 420 mg SC every 4 wk	12 wk	Placebo	Percentage change in LDL-C at wk 12

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TABLE 1 Continued

First Author, Year/Trial Name	Phase	N	Population	Age, y	Baseline Lp(a), Nmol/L	Baseline LDL-C, Mg/dL	Drug (Dose and Frequency)	Duration of Treatment	Comparator	Primary Outcome
Raal et al, 2014/ RUTHERFORD-2[43]	3	331	HeFH	51.2 ± 12.6	93.6 ± 125.8	156 ± 44.3	Evolocumab 140 mg every 2 wk or 420 mg every 4 wk	12 wk	Placebo	Percent change in LDL-C from baseline to wk 12
Raal et al, 2014/ TESLA Part B[44]	3	50	HoFH	31 ± 13	100.7 ± 96.6	348 ± 139.2	Evolocumab 420 mg every 4 wk	12 wk	Placebo	Percent change in LDL-C from baseline to wk 12
Robinson et al, 2014/ LAPLACE-2[45]	3	1,899	Hypercholesterolemia on statin	59.8 ± 9.9	68.9 ± 111.3	109 ± 41.6	Evolocumab 140 mg every 2 wk or 420 mg every 4 wk	12 wk	Placebo and/or ezetimibe	Percent change in LDL-C from baseline to wk 12
Robinson et al, 2015/ODYSSEY LONG TERM[46]	3	2,341	Hypercholesterolemia on statin and high CV risk	60.5 ± 10.4	65.6 ± 92	122.4 ± 42.2	Alirocumab 150 mg every 2 wk	78 wk	Placebo	Percent change in LDL-C from baseline to wk 24
Rosenson et al, 2019/ BANTING[47]	3	421	T2DM and hypercholesterolemia	62.4 ± 8.5	91.8 ± 115.4	109.3 ± 31.6	Evolocumab 420 mg every 4 wk	12 wk	Placebo	Percent change in LDL-C from baseline to wk 12
Roth et al, 2012[48]	2	92	Primary hypercholesterolemia	56.9 ± 9.8	61.2 ± 87.9	122.6 ± 18.7	Alirocumab 150 mg every 2 wk	8 wk	Placebo and/or atorvastatin	Percent change in LDL-C from baseline to wk 8
Roth et al, 2014/ ODYSSEY MONO[49]	3	103	Hypercholesterolemia and moderate CV risk	60.2 ± 5	36.9 ± 48.7	139.7 ± 25.8	Alirocumab 75 min/150 mg every 2 wk	24 wk	Ezetimibe	Percent change in LDL-C from baseline to wk 24
Roth et al, 2016/ ODYSSEY CHOICE I[50]	3	803	Hypercholesterolemia and moderate to high CV risk	60.8 ± 10.1	60.2 ± 82.9	125.4 ± 36.3	Alirocumab 75 min/150 mg every 2 wk or 300 mg every 4 wk	48 wk	Placebo with or without statin	Percent change in LDL-C from baseline to wk 24
Sabatine et al, 2017/ FOURIER[51]	3	27,564	Hypercholesterolemia on statin and high CV risk	62.5 ± 9	71.7 ± 112.6	92 (80-109)	Evolocumab 140 mg every 2 wk or 420 mg every 4 wk	48 wk	Placebo	Major cardiovascular events (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revasculari zation)
Schwartz et al, 2018/ODYSSEY OUTCOMES[52]	3	18,924	Hypercholesterolemia after ACS	58.6 ± 9.4	60.2 ± 81	92 ± 31	Alirocumab 75 mg to 150 mg every 2 wk	64 mo	Placebo	Composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization

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TABLE 1 Continued

First Author, Year/Trial Name	Phase	N	Population	Age, y	Baseline Lp(a), Nmol/L	Baseline LDL-C, Mg/dL	Drug (Dose and Frequency)	Duration of Treatment	Comparator	Primary Outcome
Stein et al, 2012[53]	2	77	HeFH	53.4 ± 9.7	135.8 ± 174.6	146.1 ± 30.1	Alirocumab 150 mg every 2 wk or 150 min/ 200 min/ 300 mg every 4 wk	12 wk	Placebo	Percent change in LDL-C from baseline to wk 12
Stiekema et al, 2018/ ANITSCHKOW[54]	3b	129	Patients ≥50 y old with fasting LDL-C ≥100, Lp(a) ≥125 nmol/L and arterial wall inflammation	60.1	219.4 ± 108.6	145 ± 38.8	Evolocumab 420 mg SC monthly	16 wk	Placebo	Percentage change in MDS TBR of the index vessel at wk 16
Stroes et al, 2014/ GAUSS-2[55]	3	307	Statin intolerant patients	61.7 ± 9.9	57.6 ± 94.4	193 ± 58.5	Evolocumab 140 mg every 2 wk or 420 mg every 4 wk	12 wk	Placebo and/or ezetimibe	Percent change in LDL-C from baseline to wk 12
Stroes et al, 2016/ ODYSSEY CHOICE II[56]	3	233	Hypercholesterolemia and not on statin	63.1 ± 10.1	40.6 ± 56.7	158.1 ± 51.4	Alirocumab 75 min/150 mg every 2 wk or 150 mg every 4 wk	24 wk	Placebo	Percent change in LDL-C from baseline to wk 24
Sullivan et al, 2012/GAUSS[57]	2	160	Statin intolerant patients due to muscle-related side effects	62.2	73.9 ± 119.2	188.5 ± 49.2	Evolocumab 280 min/ 350 min/420 mg every 4 wk	12 wk	Placebo and/or ezetimibe	Percent change in LDL-C from baseline to wk 12
Teramoto et al, 2016/ODYSSEY JAPAN[58]	3	216	HeFH or high CV risk	60.8 ± 9.5	40.4 ± 38	143.1 ± 27.1	Alirocumab 75 min/150 mg every 2 wk	52 wk	Placebo	Percent change in LDL-C from baseline to wk 24
Teramoto et al, 2018/ODYSSEY NIPPON[59]	3	163	Hypercholesterolemia at low intensity statin or nonstatin therapy	63.6 ± 10.1	39.8 ± 41.1	150.9 ± 42.8	Alirocumab 150 mg SC every 2 wk or every 4 wk	12 wk	Placebo	Percentage change in LDL-C at wk 12
Watts et al, 2017/ NCT02189837[60]	3	81	Healthy normolipidemic patients	31.2	21.3 ± 21.3	117.7 ± 19.3	Evolocumab 420 mg every 2 wk	8 wk	Placebo and/or atorvastatin	Apolipoprotein B kinetics

Values are mean ± SD or median (IQR) unless otherwise indicated.

ACS = acute coronary syndrome; CANTAB = Cambridge Neuropsychological Test Automated Battery cognitive domain assessment; CV = cardiovascular; FH = familial hypercholesterolemia; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); MDS TBR = most diseased segment target-to-background ratio; SC = subcutaneous; SWMS = Spatial Working Memory Strategy assessment; T2DM = type 2 diabetes mellitus.

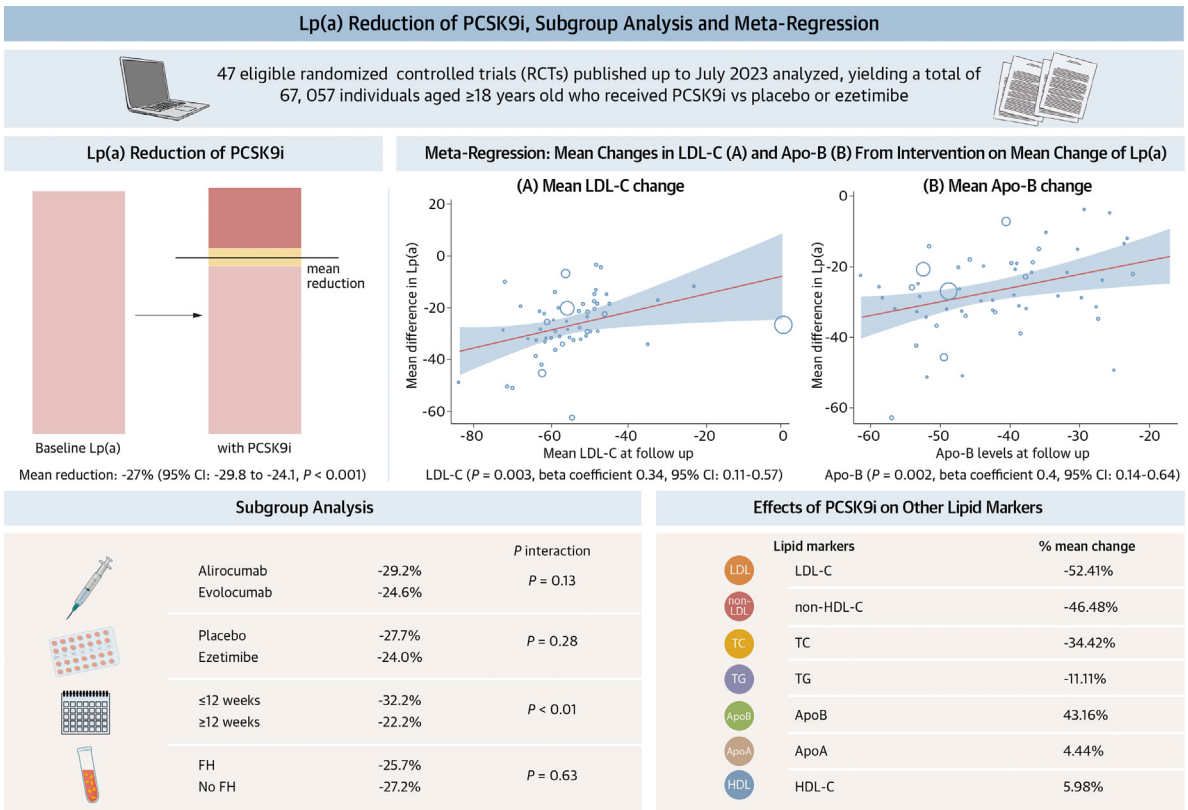
lowering therapy. The study characteristics are shown in **Table 1**.

LP(A) REDUCTION. PCSK9i significantly reduced Lp(a) levels by −27% (95% CI: −29.8% to −24.1%, $P < 0.001$), on average compared with its comparator (placebo or ezetimibe). Significant heterogeneity was noted between the study results (I^2 96.16; $P < 0.001$) (**Central Illustration**), which could be explained by the differences in patient risk profile and population characteristics (ie, comorbidity like FH, race), type of PCSK9i, dose of PCSK9i, and treatment duration, among others. Phase II studies are also included in our study, which makes it difficult to evaluate an average treatment effect. In addition, some studies had patients on background statin and ezetimibe therapy, which could transiently elevate Lp(a) levels.[61] Baseline Lp(a) levels were also variable in the studies included, which could also result in varying reduction in Lp(a): elevated Lp(a) levels are associated with a greater Lp(a) reduction.[10]

Subgroup analyses. PCSK9i significantly reduced Lp(a) by 28% when compared to placebo (MD: 27.69% [95% CI: −30.85% to −24.54%], $P < 0.001$), and 24% when compared to ezetimibe (MD: 24.0% [95% CI: −29.95% to −18.01%], $P < 0.001$). There was no significant difference in the treatment effect of PCSK9i compared with ezetimibe or placebo (p interaction 0.25) (**Figure 1**). The treatment effects of alirocumab and evolocumab on Lp(a) lowering were not significantly different (p interaction 0.06) (**Figure 2**). The achieved Lp(a) reduction by PCSK9i use was significantly different between those who had received treatment for equal to and less than 12 weeks (MD: 32.43% [95% CI: −36.63% to −28.23%]) vs those who received treatment for more than 12 weeks (MD: 22.31% [95% CI: −25.13% to −19.49%, $P < 0.00$]) (P interaction <0.01) (**Figure 3**). PCSK9i reduced Lp(a) for both FH and non-FH cohorts (**Figure 4**).

Meta-regression analysis. Meta-regression analysis revealed that the mean change of LDL-C

CENTRAL ILLUSTRATION Impact of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors on Lipoprotein(a) and Other Lipids



Rivera FB, et al. JACC Adv. 2025;4(2):101549.

Apo-B = apolipoprotein B; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; TC = total cholesterol; TG = triglycerides.

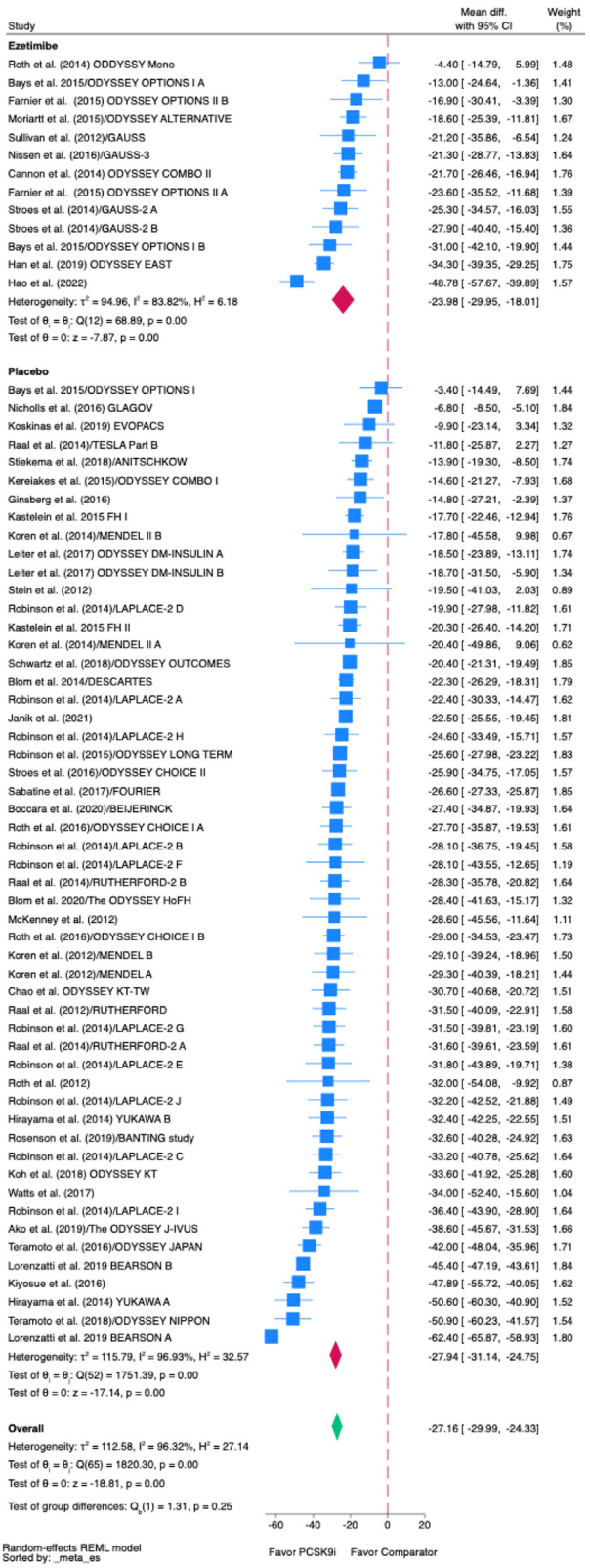
($P = 0.02$, $tau^2 = 177.10$, R^2 analog = 0.00) and ApoB ($P < 0.001$, $tau^2 = 114.20$, R = 1.42) were associated with the mean change in Lp(a) (**Figures 5 and 6**). Baseline LDL-C ($P = 0.14$, Q = 2.17, R^2 analog = 0.00) and baseline mean age ($P = 0.43$, Q = 0.63, R^2analog = 0.00) were not associated with the treatment effect.

Effects of PCSK9is on other lipid markers. PCSK9i reduced LDL-C by 52.41% ([95% CI: 49.54%-55.28%], $P < 0.01$). PCSK9i also reduced non-high-density lipoprotein cholesterol by 46.48%, total cholesterol by 34.42%, triglycerides by 11.11%, and ApoB by 43.16%. PCSK9i increased ApoA-1 by 4.44% and high-density lipoprotein cholesterol by 5.98% (**Figures 7 to 13**). **Table 2** shows the summary results on the effects of PCSK9i on other lipid markers. Please see Supplemental Figure 3 for publication bias analysis.

DISCUSSION

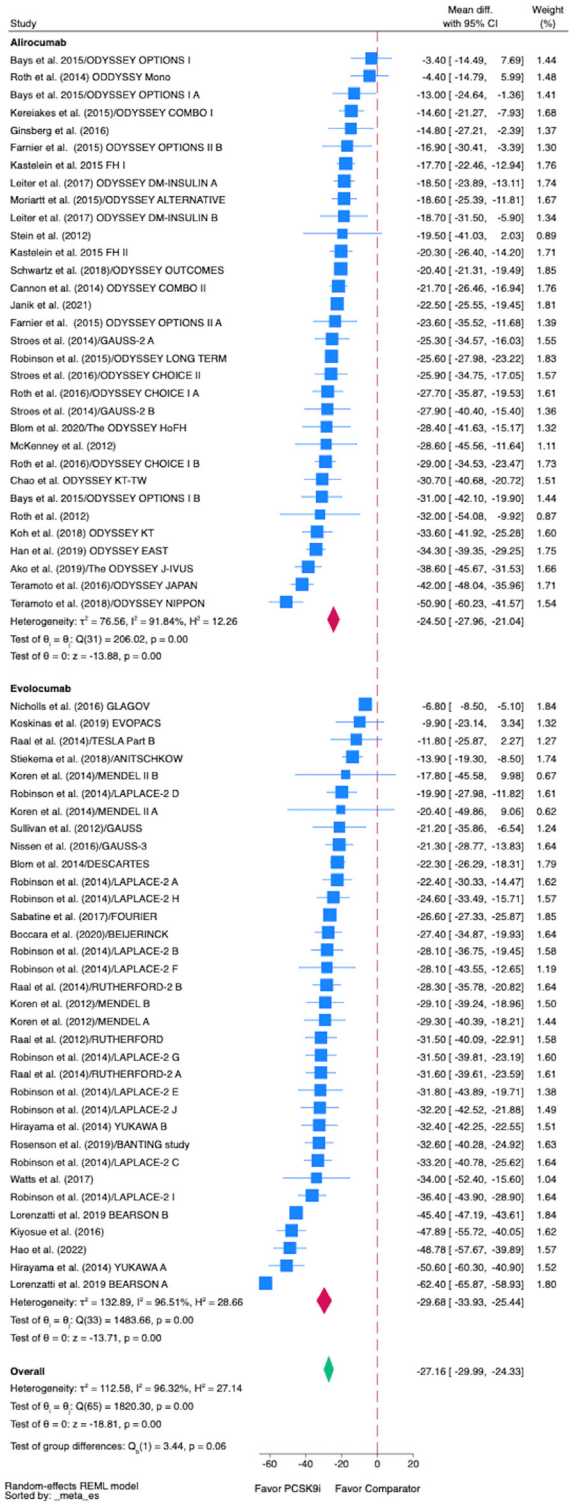
In this meta-analysis evaluating the effect of PCSK9is on Lp(a) levels, we observed that PCSK9i therapy significantly reduced Lp(a) levels, regardless of the comparator (placebo or ezetimibe), treatment duration, type of PCSK9i used, or the presence of FH. This may be attributed to the proposed mechanisms by which PCSK9i lower Lp(a) levels, namely through the reduction of its production and the enhancement of its clearance, as previously suggested in the literature.[9] Other studies suggest that PCSK9i such as evolocumab may further promote Lp(a) catabolism by significantly upregulating LDL receptor expression,

FIGURE 1 **Random Effects Meta-Analysis on the Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors on Lipoprotein(a), Subgroup Analysis Based on Comparator**



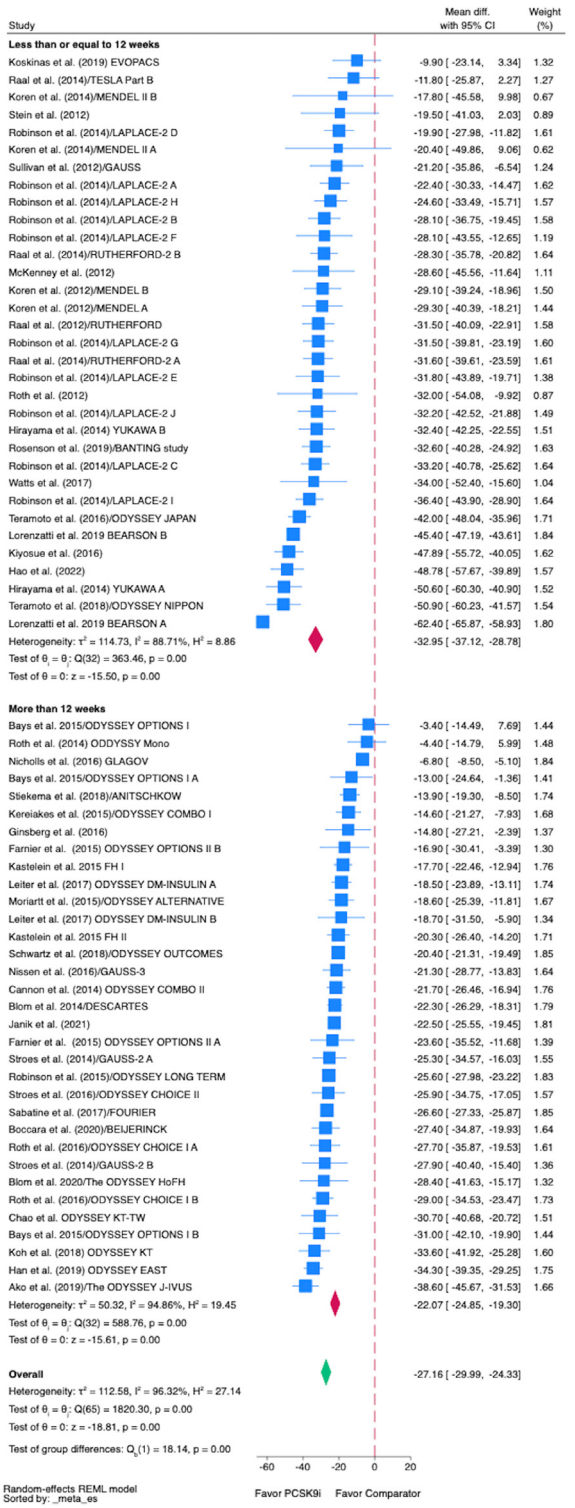
Blue squares indicate point estimates with confidence intervals. Red diamond indicates pooled effect of each subgroup. Green diamond indicates pooled effect of all the studies encompassing both subgroups. PCSK9i = proprotein convertase subtilisin/kexin type 9 tnhibitor; REML = Restricted Maximum Likelihood Estimator.

FIGURE 2 Random Effects Metanalysis on the Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors on Lipoprotein(a), Subgroup Analysis Based on the Type of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors



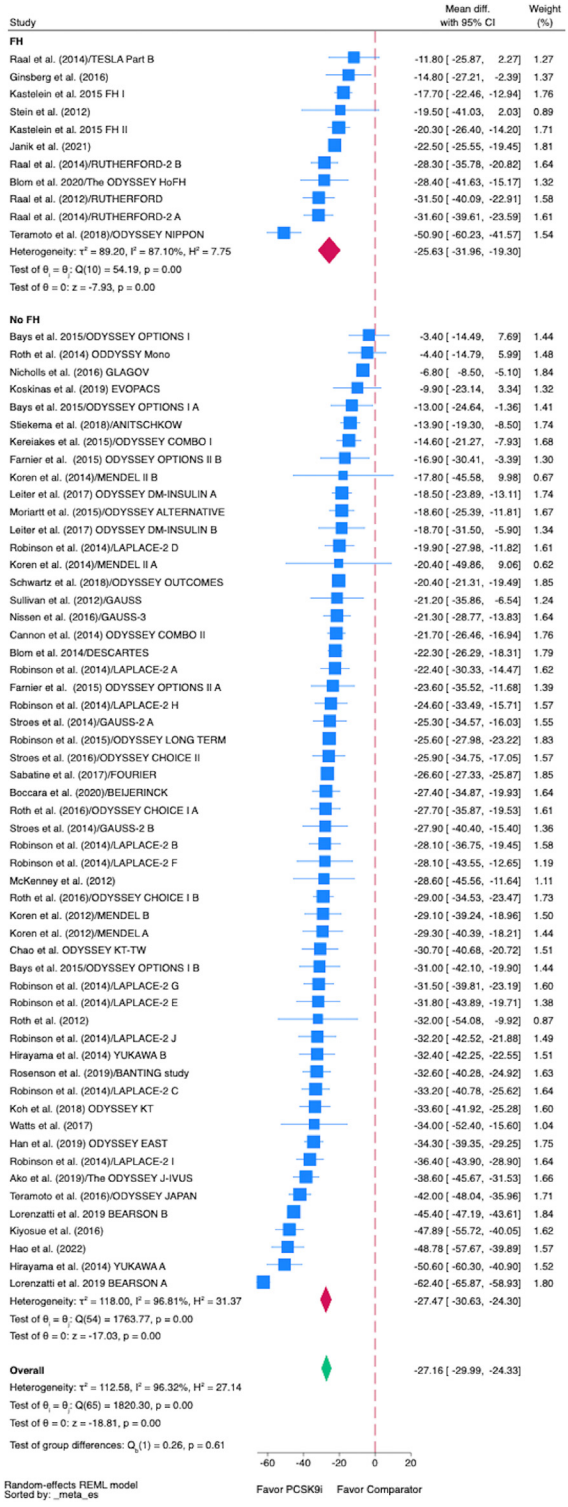
Blue squares indicate point estimates with confidence intervals. Red diamond indicates pooled effect of each subgroup. Green diamond indicates pooled effect of all the studies encompassing both subgroups. PCSK9i = Proprotein convertase subtilisin/kexin type 9 inhibitor; REML = Restricted Maximum Likelihood Estimator.

FIGURE 3 **Random Effects Metanalysis on the Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors on Lipoprotein(a), Subgroup Analysis Based on the Duration of Treatment**



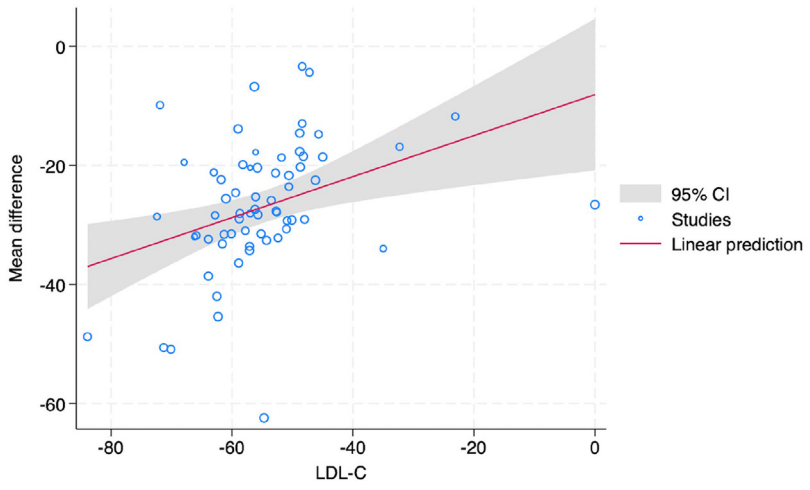
Blue squares indicate point estimates with confidence intervals. Red diamond indicates pooled effect of each subgroup. Green diamond indicates pooled effect of all the studies encompassing both subgroups. PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; REML = Restricted Maximum Likelihood Estimator.

FIGURE 4 Random Effects Metanalysis on the Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors on Lipoprotein(a), Subgroup Analysis Based on the Presence of FH



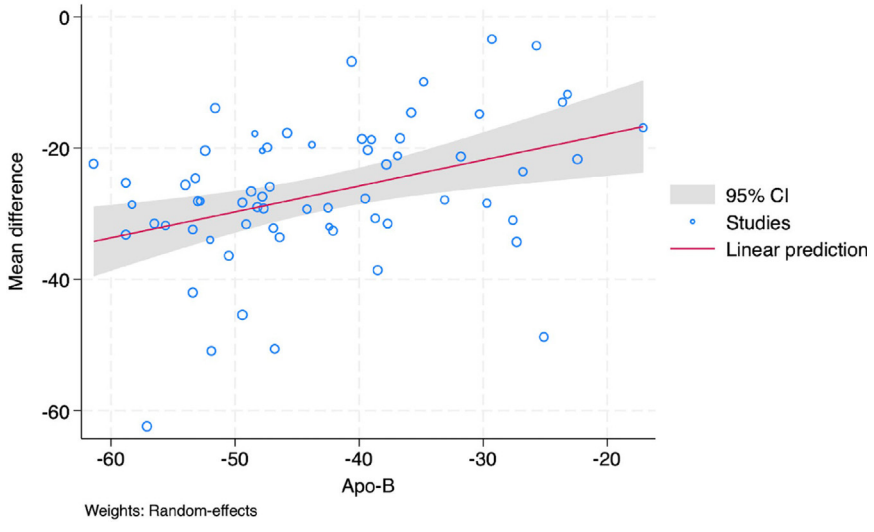
Blue squares indicate point estimates with confidence intervals. Red diamond indicates pooled effect of each subgroup. Green diamond indicates pooled effect of all the studies encompassing both subgroups. FH = familial hypercholesterolemia; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; REML = Restricted Maximum Likelihood Estimator.

FIGURE 5 Scatter Plot Showing the Change in Low-Density Lipoprotein Cholesterol and Its Association With Mean Change in Lipoprotein(a) ($P = 0.003$, Beta Coefficient 0.34, 95% CI: 0.11-0.57, $tau^2 = 94.8$, $R^2 = 11.82$)



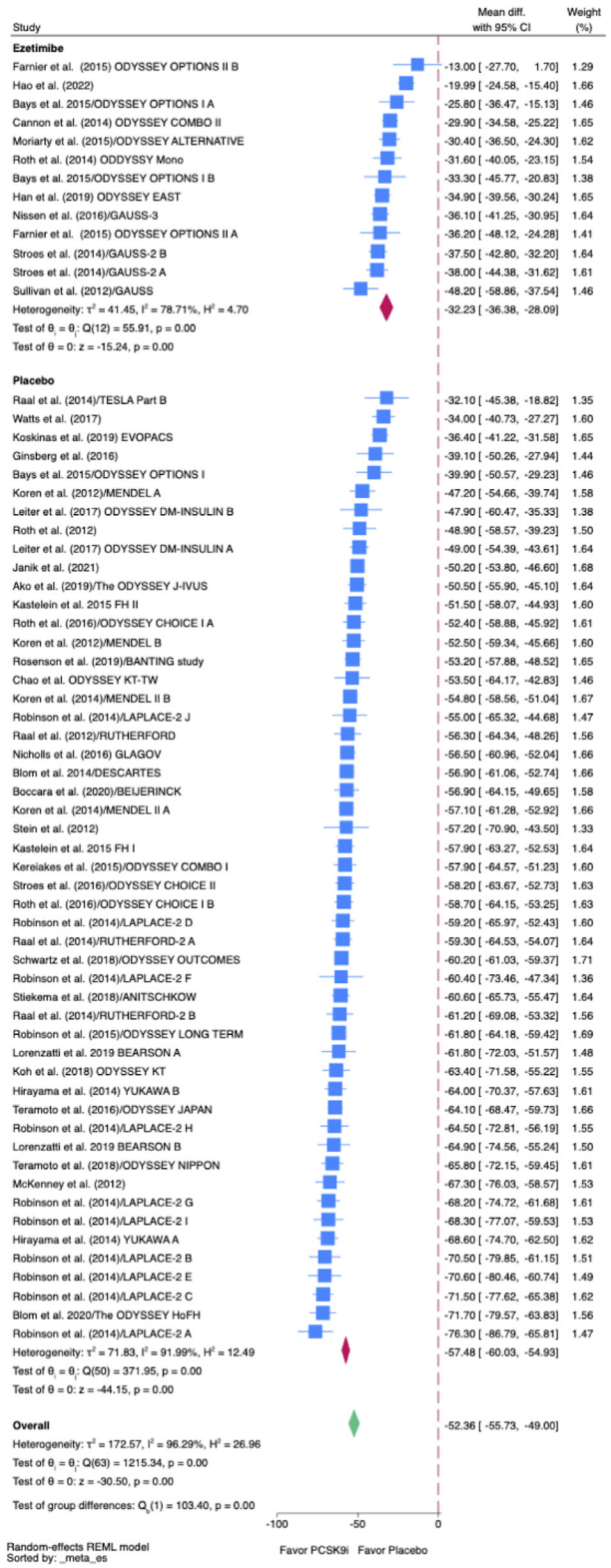
LDL-C = low-density lipoprotein cholesterol.

FIGURE 6 Scatter Plot Showing the Change in Apolipoprotein B and Its Association With Mean Change in Lipoprotein(a) ($P < 0.002$, Beta Coefficient 0.4, 95% CI: 0.14-0.64, $tau^2 = 93.68$, $R^2 = 11.86$)



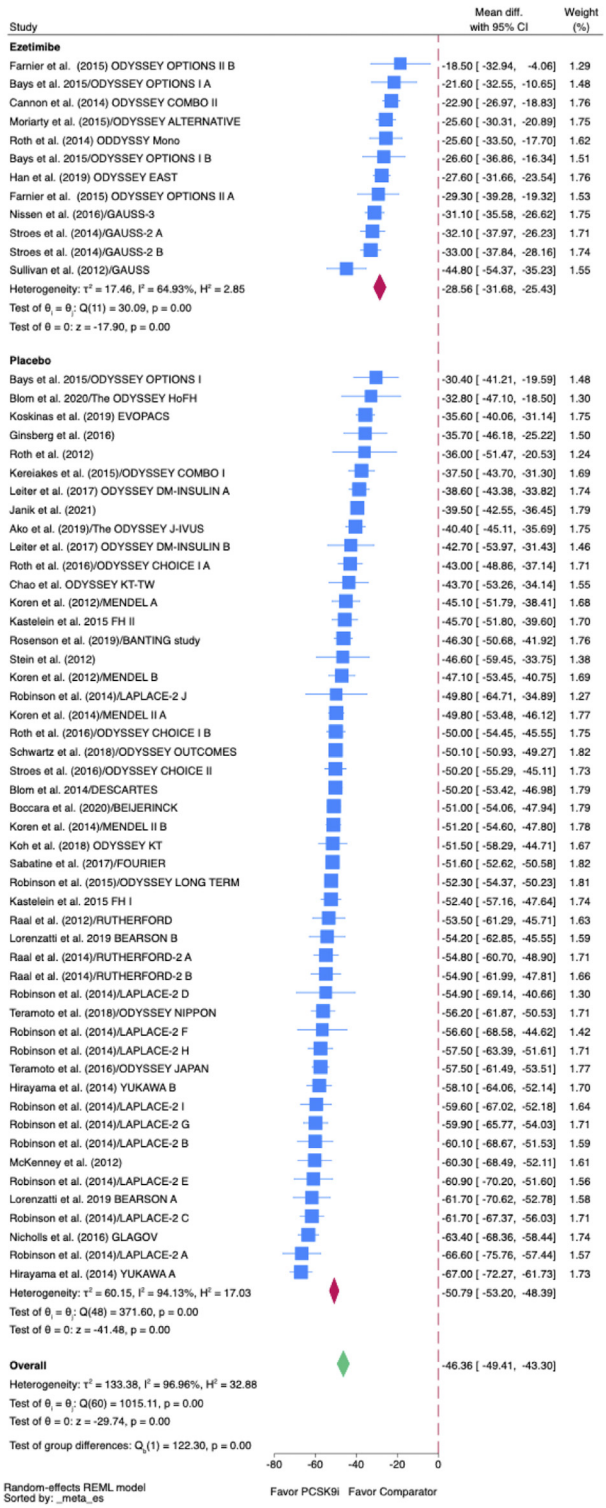
Apo-B = apolipoprotein B.

FIGURE 7 Random Effects Metanalysis on the Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors on Low-Density Lipoprotein Cholesterol



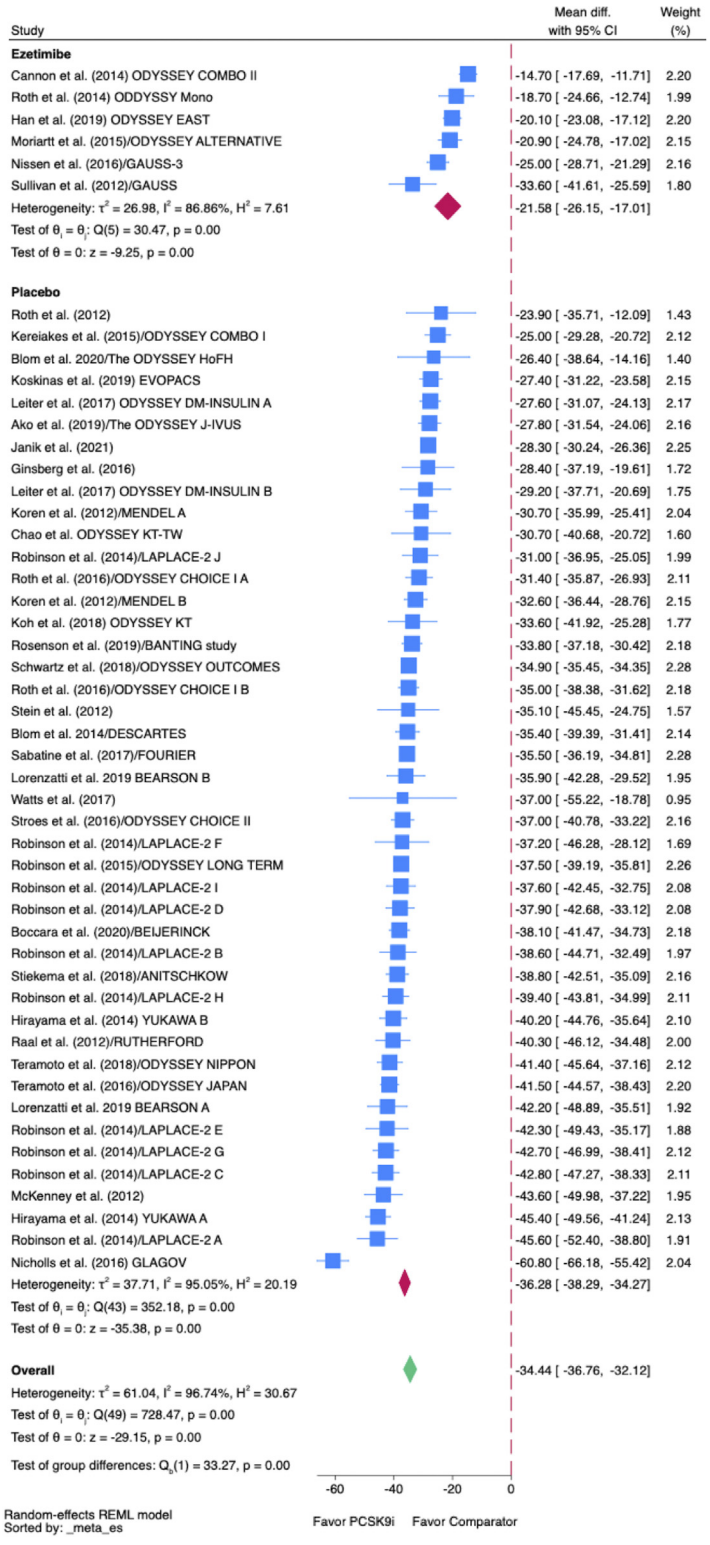
Blue squares indicate point estimates with confidence intervals. Red diamond indicates pooled effect of each subgroup. Green diamond indicates pooled effect of all the studies encompassing both subgroups. PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; REML = Restricted Maximum Likelihood Estimator.

FIGURE 8 **Random Effects Metanalysis on the Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors on Non-High-Density Lipoprotein Cholesterol**



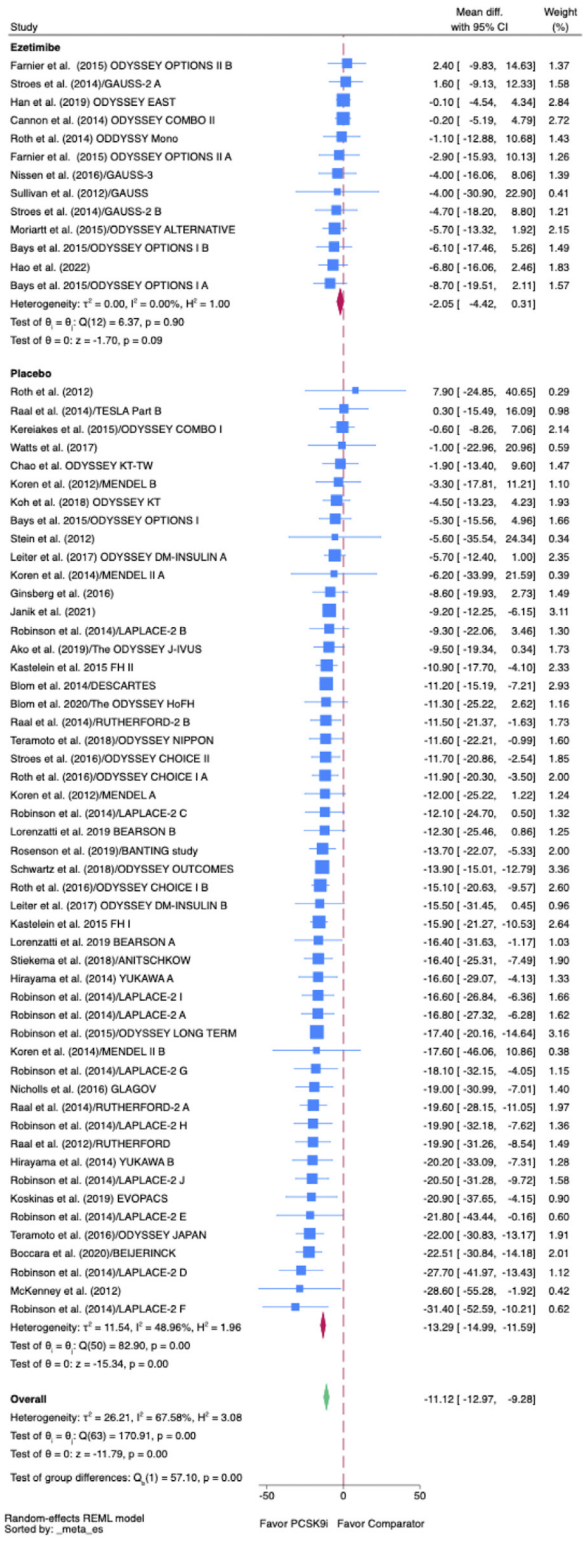
Blue squares indicate point estimates with confidence intervals. Red diamond indicates pooled effect of each subgroup. Green diamond indicates pooled effect of all the studies encompassing both subgroups. PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; REML = Restricted Maximum Likelihood Estimator.

FIGURE 9 Random Effects Metanalysis on the Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors on Total Cholesterol



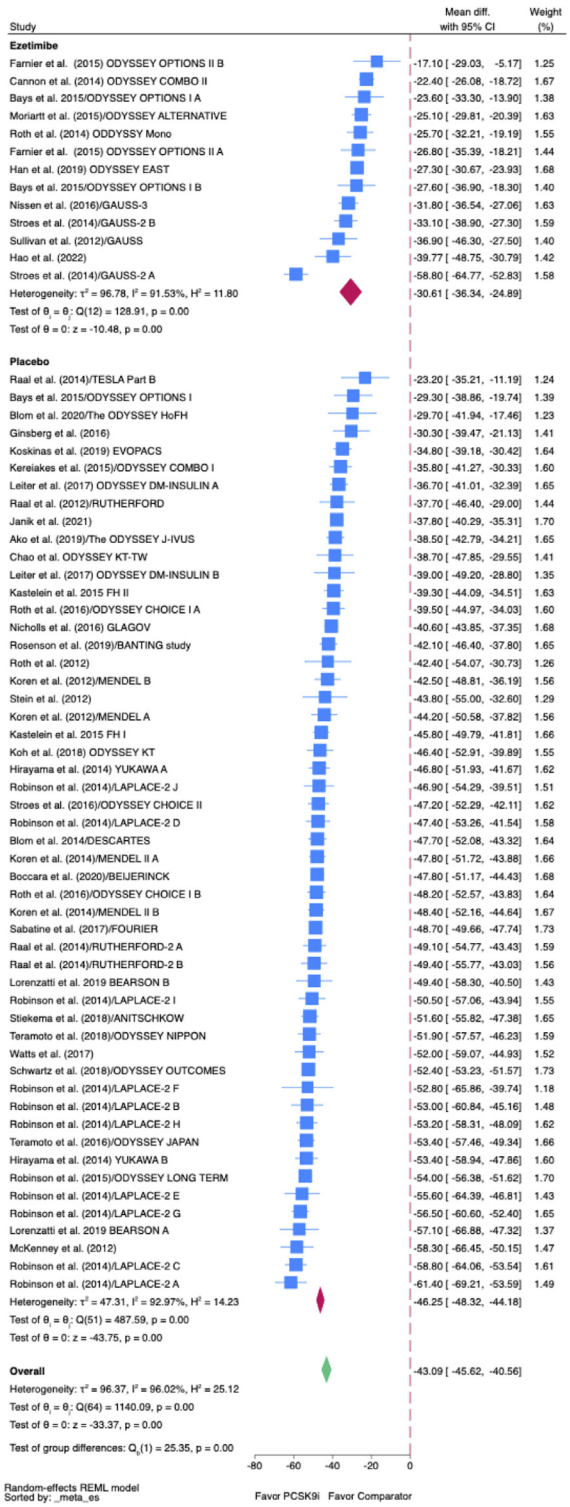
Blue squares indicate point estimates with confidence intervals. Red diamond indicates pooled effect of each subgroup. Green diamond indicates pooled effect of all the studies encompassing both subgroups. PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; REML = Restricted Maximum Likelihood Estimator.

FIGURE 10 Random Effects Metanalysis on the Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors on Triglycerides



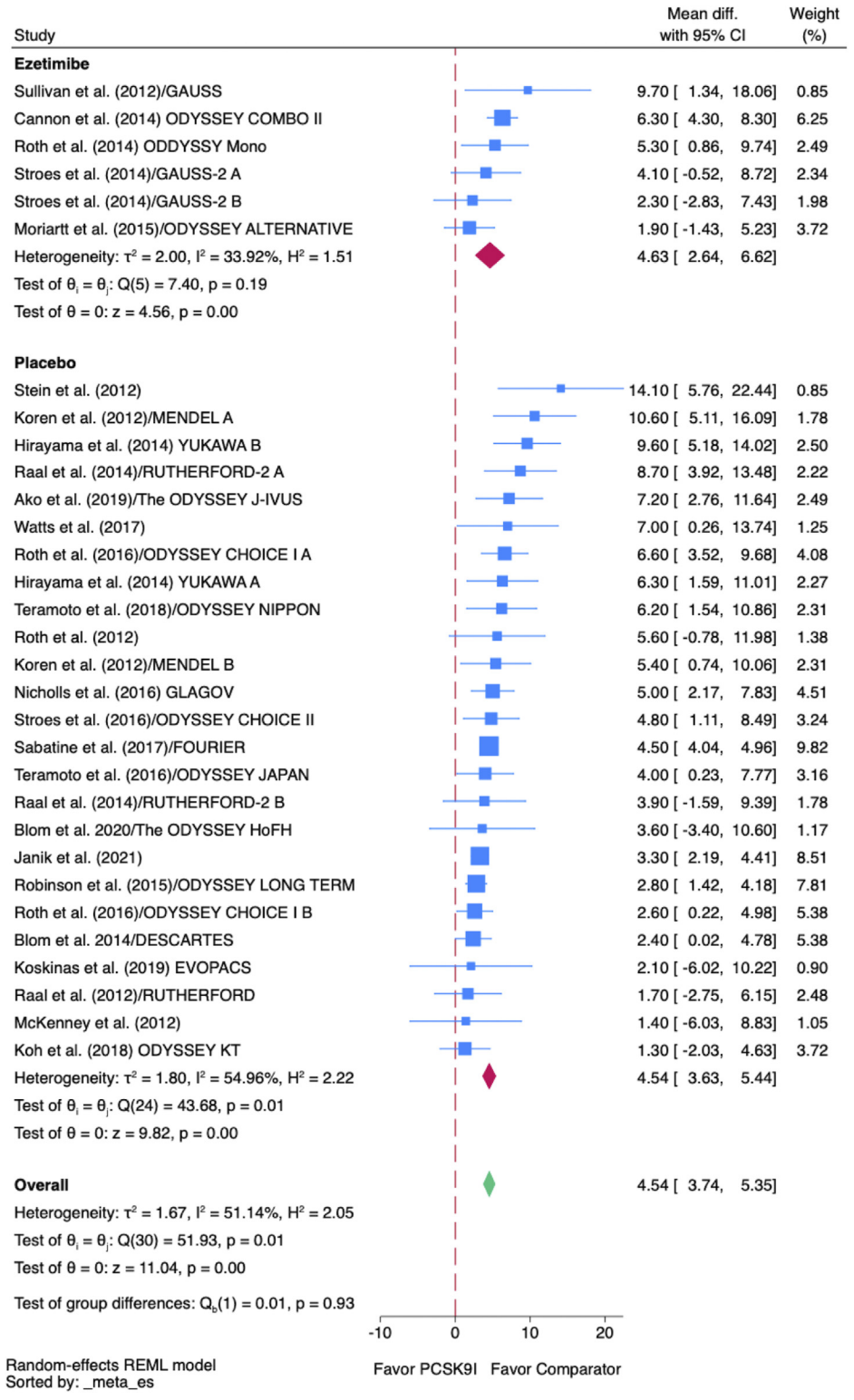
Blue squares indicate point estimates with confidence intervals. Red diamond indicates pooled effect of each subgroup. Green diamond indicates pooled effect of all the studies encompassing both subgroups. PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; REML = Restricted Maximum Likelihood Estimator.

FIGURE 11 Random Effects Metanalysis on the Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors on Apolipoprotein B



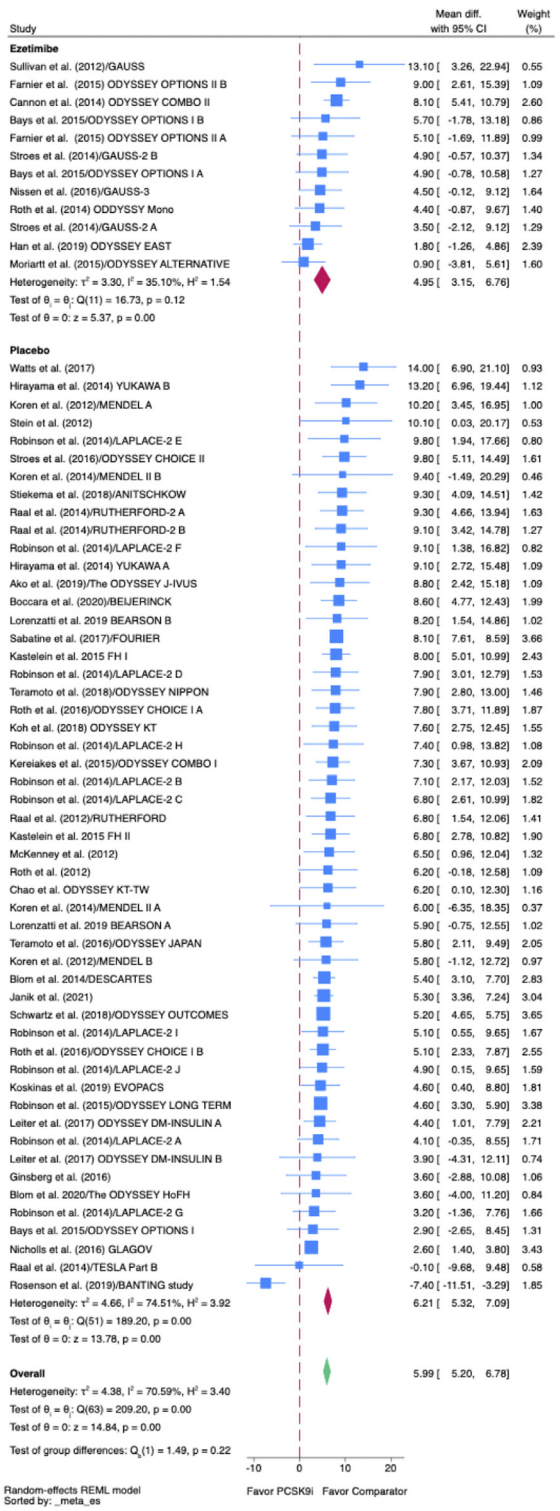
Blue squares indicate point estimates with confidence intervals. Red diamond indicates pooled effect of each subgroup. Green diamond indicates pooled effect of all the studies encompassing both subgroups. PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; REML = Restricted Maximum Likelihood Estimator.

FIGURE 12 Random Effects Metanalysis on the Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors on Apolipoprotein A1



Blue squares indicate point estimates with confidence intervals. Red diamond indicates pooled effect of each subgroup. Green diamond indicates pooled effect of all the studies encompassing both subgroups. PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; REML = Restricted Maximum Likelihood Estimator.

FIGURE 13 Random Effects Metanalysis on the Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors on High-Density Lipoprotein Cholesterol



Blue squares indicate point estimates with confidence intervals. Red diamond indicates pooled effect of each subgroup. Green diamond indicates pooled effect of all the studies encompassing both subgroups. CSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; REML = Restricted Maximum Likelihood Estimator.

TABLE 2 Summary on the Effects of PCSK9i on Other Lipids

Lipids	Overall Mean Percent Change	Mean Percent Change Compared to Placebo	Mean Percent Change Compared to Ezetimibe
LDL-C	−52.41% 95% CI: −55.28% to −49.54%, $P < 0.001$	−57.51% 95% CI: −59.53% to −55.49%, $P < 0.001$	−32.23% 95% CI: −36.36% to −28.1%, $P < 0.001$
Non-HDL-C	−46.48% 95% CI: −48.73% to −44.23%, $P < 0.001$	−50.87% 95% CI: −52.57% to −49.16%, $P < 0.001$	−28.6% 95% CI: −31.62% to −25.49%, $P < 0.001$
Total cholesterol	−34.42% 95% CI: −36.095% to −32.755%, $P < 0.001$	−36.31% 95% CI: −37.68% to −34.94%, $P < 0.001$	−21.47% 95% CI: −25.58% to −17.37%, $P < 0.001$
Triglycerides	−11.11% 95% CI: −12.86% to −9.35%, $P < 0.001$	−13.27% 95% CI: −14.84% to −11.70%, $P < 0.001$	−2.05% 95% CI: −4.42% to −0.31%, $P = 0.09$
ApoB	−43.16% 95% CI: −45.32% to −41.00%, $P < 0.001$	−46.34% 95% CI: −48.08% to −44.60%, $P < 0.001$	−30.62% 95% CI: −36.0% to −25.15%, $P < 0.001$
Apo-A1	4.44% 95% CI: 3.62%-5.26%, $P < 0.001$	4.44% 95% CI: 3.62%-5.26%, $P < 0.001$	4.64% 95% CI: 2.68%-6.60%, $P < 0.001$
HDL-C	5.98% 95% CI: 5.20%-6.77%, $P < 0.001$	6.19% 95% CI: 5.33%-7.06%, $P < 0.001$	4.95% 95% CI: 3.16%-6.75%, $P < 0.001$

ApoB = apolipoprotein B; ApoA1 = apolipoprotein A1; HDL-C = high-density lipoprotein C; non-HDL-C = non-high-density lipoprotein C; PCSK9i = proprotein convertase subtisilin/kexin type 9 inhibitor; other abbreviations as in Table 1.

thereby enhancing the clearance of Lp(a) holoparticles, in the presence of statins.[62] Additionally, PCSK9i treatment also significantly reduced LDL-C and ApoB levels.

Among the subgroup analyses, only the difference in duration of treatment had significant bearing on the treatment effect. Although our study demonstrated that PCSK9i leads to a modest Lp(a) lowering, the treatment effect appears to be higher in the first 12 weeks vs beyond 12 weeks of treatment. Some potential mechanisms underlying this observation have been proposed. Prolonged use of PCSK9i may induce its own resistance, which is thought to be from: 1) increased endogenous PCSK9 triggered by PCSK9i use; and 2) delayed PCSK9 clearance due to accumulation of monoclonal antibody-PCSK9 complexes.[63] However, more data is needed to determine the possible reason of this treatment difference.

Many prospective studies have reported the role of PCSK9i in reducing Lp(a) levels,[64] and prior pooled analyses have supported the efficacy of these agents.[65,66] The results of our meta-analysis showed that the use of PCSK9i resulted in statistically significant reductions in plasma Lp(a) levels vs comparators (placebo and ezetimibe), further increasing our understanding of the effect of PCSK9i on Lp(a) level based on data from multiple clinical trials. Furthermore, this analysis enriches available evidence by providing detailed information on subgroups of interest, based on duration of treatment, comparator, type of PCSK9i, and presence of FH. The 27% reduction in Lp(a) level with PCSK9i compared to comparators (placebo and ezetimibe) in this analysis is consistent with the reports in previous meta-analyses citing on average 26% reduction.[65,66] Beyond confirming this PCSK9i's effect on Lp(a), we also performed robust subgroup analyses with emphasis on duration of treatment and FH status.

Using meta-regression analysis, we were able to determine factors associated with the treatment effect such as percent change of LDL-C and ApoB from baseline. Changes in mean LDL-C was incorporated as possible covariate because of the reported higher discordance in LDL-C reduction for higher Lp(a) levels.[15] While Farmakis et al[65] did not include ApoB in their meta-regression, ApoB was incorporated in our regression analysis as studies have suggested that it is not always linked on a single Lp(a) particle, hence can affect Lp(a) levels after PCSK9i.[9] Our study demonstrated that a greater Lp(a) reduction is associated with more marked LDL-C and ApoB reduction, which indicates a similar effect of PCSK9i on these 2 biomarkers. This is consistent with fact that the LDL receptor plays a role in LDL-C, ApoB, and Lp(a) clearance from the bloodstream, and PCSK9i prevents LDL receptor degradation, thus optimizing its function.[15] Additionally, ApoB is a component of LDL, chylomicrons, and other lipoproteins; therefore, ApoB levels are expected to decrease concurrently with LDL-C. However, the R^2 values in the metaregression analyses were low, which could be explained by discordance between LDL-C reduction and Lp(a) reduction (ie, LDL-C:Lp(a) reduction >3.5:1). This discordance observed in a previous study suggests alternate pathways of Lp(a) clearance beyond the LDL receptor.[15]

In previous studies by Farmakis and Yu, an Lp(a) reduction between 25% and 35% led to a clinically significant coronary heart disease risk reduction,[65,66] and our data show that monoclonal antibody based PCSK9i reduces Lp(a) level in the same range (−27%).

Although studies have shown that a higher degree of absolute Lp(a) lowering (at least 50 mg/dL or 105 nmol/L) may be needed for a significant coronary heart disease risk reduction,[67] data from ODYSSEY Outcomes trial subanalysis showed the contrary.[10] Even a 1 mg/dL reduction in Lp(a) was associated with a HR of 0.99 (95% CI: 0.99-0.00; $P = 0.008$).[10] Trials on cardiovascular outcomes with Lp(a) reduction using directly targeting Lp(a) therapies such as the Lp(a)HORIZON (NCT04023552) and OCEAN(a) Outcomes trial (NCT05581303) are still ongoing, but they have shown reductions in Lp(a) level in the range of 80% to 95%. Findings in these trials will help better understand the optimal absolute reduction in Lp(a) level needed for effective risk reduction.

STUDY LIMITATIONS. There are several limitations that should be noted. This is a study-level meta-analysis, and we could not access individual patient data. Additional limitations include heterogeneity in PCSK9i studies. While we attempted to explain potential reasons for the heterogeneity using subgroup analyses, the lack of disaggregated data precluded further analyses for the matter. Sex and race are important subgroups that were sought from the studies reviewed; unfortunately, our findings show a gross lack of sex disaggregated data to permit subgroup analyses. Future trials should explore these specific disaggregated variables to obtain a deeper understanding of how the treatment effect may vary among these subgroups. Publication bias may also be present, the extent of which could not fully be quantified. Nonetheless, every effort possible was made to limit bias by utilizing a robust analytical approach to adjust for potential moderators through subgroup analyses and meta-regression.

CONCLUSIONS

An elevated level of Lp(a) is an independent highly prevalent risk factor for atherosclerotic cardiovascular disease. In this analysis of 47 RCTs comparing PCSK9i monoclonal antibody therapy vs placebo or ezetimibe, PCSK9is reduced Lp(a) levels by 27% on average. Mean change from the baseline in LDL-C and ApoB positively correlates with Lp(a) reduction. Given the modest but significant reduction in Lp(a) level, further research is needed to evaluate the impact of monoclonal antibody based PCSK9i on cardiovascular outcomes in patients with elevated Lp(a).

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Gulati has received consultant fees/honoraria from Esperion, Novartis, and Boehringer Ingelheim; and has received research/research grants from Congressionally Directed Medical Research Program-Department of Defense (WARRIOR study). Dr Pagidipati has received consulting fees/honoraria from Bayer, Boehringer Ingelheim, CRISPR Therapeutics, Eli Lilly, Esperion, AstraZeneca, Merck, Novartis, and Novo Nordisk; grants to institution from Alnylam, Amgen, Boehringer Ingelheim, Eggland's Best, Eli Lilly, Novartis, and Novo Nordisk; and DSMB for trials sponsored by J + J and Novartis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: PCSK9is reduced lipoprotein(a) levels regardless of comparator, treatment duration, type of PCSK9i used, or the presence of familial hypercholesterolemia.

TRANSLATIONAL OUTLOOK: The impact of PCSK9is on cardiovascular outcomes in patients with elevated lipoprotein(a) needs to be evaluated.

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KEY WORDS alirocumab, apolipoprotein B, atherosclerotic cardiovascular disease, cholesterol, evolocumab, low-density lipoprotein, Lp(a), PCSK9 inhibitors

APPENDIX For supplemental figures, please see the online version of this paper.