

Efficiency and Safety of Proprotein Convertase Subtilisin/Kexin 9 Monoclonal Antibody on Hypercholesterolemia: A Meta-Analysis of 20 **Randomized Controlled Trials**

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Background—Proprotein convertase subtilisin/kexin9 (PCSK9) monoclonal antibody significantly reduces low-density lipoprotein cholesterol level in patients with hypercholesterolemia. The goal of this study was to review recently reported randomized controlled trials to investigate the therapeutic effects and safety of PCSK9 inhibitors.

Methods and Results—The clinical randomized controlled trials published from inception to March 19, 2015 were identified from The Cochrane Library databases, PUBMED, and EBASE. Randomized controlled trials of at least 8 weeks duration using PCSK9 inhibitors in treating patients with hypercholesterolemia were included. Mean difference (MD) with a 95% CI was used to calculate the continuous data, the standardized mean difference with a 95% CI was used when the unit was not unified, and risk ratio with a 95% CI was used for dichotomous data. After screening, 20 trials fulfilled the inclusion criteria. PCSK9 inhibitors significantly decreased the levels of low-density lipoprotein cholesterol (MD=-65.29 mg/dL, 95% CI: -72.08 to -58.49), total cholesterol (MD=-60.04 mg/dL, 95% CI: -69.95 to -50.13), triglycerides (MD=-12.21 mg/dL, 95% CI: -16.21 to -8.22) and apolipoprotein-B (MD=-41.01 mg/dL, 95% CI: -46.07 to -35.94), lipoprotein(a) (standardized mean difference=-0.94, 95% CI: -1.12 to -0.77) and increased the levels of high-density lipoprotein cholesterol (MD=3.40 mg/dL, 95% CI: 3.12 to 3.68) and apolipoprotein-A1 (MD=6.75 mg/dL, 95% CI: 4.64 to 8.86). There was no significant difference in the incidence of treatmentemergent adverse events (risk ratio=1.01, 95% CI: 0.98 to 1.04), serious treatment-emergent adverse events (risk ratio=1.01, 95% Cl: 0.88 to 1.17), and the discontinuation of treatment between the 2 groups (risk ratio=1.07, 95% Cl: 0.86 to 1.34).

Conclusions—The meta-analysis indicated that PCSK9 inhibitors had a strong effect in lowering low-density lipoprotein cholesterol and other lipid levels with satisfactory safety and tolerability in patients with hypercholesterolemia. (J Am Heart Assoc. 2015;4: e001937 doi: 10.1161/JAHA.115.001937)

Key Words: lipids • lipoproteins • meta-analysis • proprotein convertase subtilisin/kexin9 inhibitor

espite advances in the detection and treatment of ischemic cardiovascular disease (CVD), such as myocardial infarction and stroke in recent years, it remains the leading cause of death worldwide.¹ Low-density lipoprotein

cholesterol (LDL-C) is the primary atherogenic lipoprotein, and LDL-C reduction is the target of primary or secondary prevention of CVD.² Statins are considered the most effective agents for reducing LDL-C and decrease the risk for CVD events.^{3,4} It is recommended to prescribe high-intensity statin therapy for individuals with high risk of CVD.⁵ However, broad spectrums of high-risk patients fail to attain the guidelinerecommended LDL-C goals due to statin intolerance and/or very high baseline levels (eg, familial hypercholesterolemia patients).⁶ Combination therapies that add nonstatin drugs are compromising methods in patients who are intolerant to high-intensity statin therapy.⁷ Recent studies revealed that adding ezetimibe to simvastatin modestly reduced LDL-C (15 mg/dL) and CVD risks.⁸ However, other effective therapies are needed as alternative methods to further decrease LDL-C and finally reduce the mortality and morbidity of CVD.

Proprotein convertase subtilisin/kexin9 (PCSK9) plays a pivotal role in regulating cholesterol homeostasis; it acts by

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binding to the LDL-receptor (LDL-R) at the surface of hepatocytes, hence promoting the clearance of LDL-R in lysosomes/endosomes, and results in decreased amount of LDL-R number and increased plasma HDL-C levels, so it has emerged as an attractive target for lowering LDL-C levels.⁹ The single-nucleotide polymorphism in PCSK9 gene are associated with LDL-C and risk of CVD, making PCSK9 inhibition a potential therapeutic modality.¹⁰⁻¹³ Statin therapy can increase plasma PCSK9 levels to some extent, while combination with PCSK9 inhibitors may compensate this secondary change.¹⁴ Various approaches have been tested to inhibit PCSK9 in active clinical and preclinical trials. Among those strategies, PCSK9 monoclonal antibody is of great interest because it blocks its binding to LDL-R via an allosteric mechanism.¹⁵ The human monoclonal antibodies against PCSK9 primarily include AMG145/Evolocumab, REGN727/SAR236553, and RN316/bococizumab.¹⁶ In the last 2 years, some early clinical trials have shown that PCSK9 inhibitors can reduce the plasma LDL-C level in patients with familial or nonfamilial hypercholesterolemia. The other lipids and lipoproteins such as total cholesterol (TC), triglycerides (TG), high-density lipoprotein-C (HDL-C), apolipoprotein-B (Apo-B), Apo-A1, and lipoprotein(a) could also benefit from this approach.

Because of differences in study design and clinical outcomes, including dyslipidemia types, medicine dosage and therapeutic duration, and the efficiency and safety of PCSK9 inhibitors that each author reported, greatly vary. To date, there is no report of any comprehensive and quantitative evaluation of the efficiency and safety of PCSK9 inhibitors therapy. The purpose of this meta-analysis is to compare the efficiency and safety of all published randomized controlled trials (RCTs) using PCSK9 inhibitors with various background lipid therapies versus placebo for treating patients with familial or nonfamilial hypercholesterolemia. In total, 18 articles were assessed for efficacy and 20 articles were assessed for safety analyses.

Methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (MOOSE group).¹⁷

Data Source, Search Strategy, and Inclusion Criteria

The Cochrane Library databases, PUBMED, and EBASE were searched for original articles from inception to March 19, 2015 to identify all RCTs using PCSK9 inhibitor therapy. The following search items were used: ((((AMG 145*) OR evolocumab*) OR REGN727*) OR SAR236553*) OR RN316*) OR

PF04950615*) OR bococizumab*) OR antibody to proprotein convertase subtilisin/kexin type 9*) OR antibody to PCSK9*) AND (((randomized controlled trial [pt]) OR (controlled clinical trial [pt]) OR (randomized [tiab]) OR (placebo [tiab]) OR (drug therapy [sh]) OR (randomly [tiab]) OR (trial [tiab]) OR (groups [tiab])) NOT (animals[mh] NOT humans [mh])). All the relevant articles were published in English, conducted on human subjects, and classified as RCTs. The references of the studies and trials registries on ClinicalTrial.gov were also searched for additional articles. Original trials were eligible for the present meta-analysis if they met the following criteria: (1) study design: RCT; (2) study population: patients with familial or nonfamilial hypercholesterolemia; (3) study intervention: Patients in the treatment group received PCSK9 inhibitors versus patients in the control group received placebo with or without other lipid-lowering therapy; (4) lipid parameters: Trials in which LDL-C, HDL-C, TC, TG, Apo-B, Apo-A1 and lipoprotein (a) were measured at baseline and during PCSK9 inhibitors therapy in the entire study; and (5) treatment duration: longer than 8 weeks. We excluded the case reports, nonhuman studies, and studies without adequate information on outcomes and lacking control group.

Data Extraction and Study Quality Assessment

Two investigators (C.L., L.L.) individually performed screening the titles and abstracts, duplicate checking, and reviewed full articles that met the inclusion criteria and extracted the data and managed according to the intention-to-treat principle. We extracted data from the published RCTs mainly because it is still controversial to include data from unpublished trials. The following items were extracted from included studies: first author's name, year of publication, study design, characteristic of patients, sample size, duration of intervention and type of control, drug dose, clinical outcomes, and adverse events. If a trial is reported at several time points, we included the final reported follow-up point. We assessed the risk of bias of included studies based on the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The judgments were expressed simply as "low risk," "high risk," or "unclear risk" of bias. Discrepancies were resolved by extensive discussions between the 2 authors or a third person. The last-observation-carried-forward method was used to deal with the missing values. The quality of eligible RCTs was qualified independently using the 5-point Jadad score, which evaluates 3 criteria: basis of randomization (0 to 2 points), double blinding (0 to 2 points), and withdrawals and dropouts (0 to 1 points). Studies with a score \geq 3 points are considered to be high quality.

Outcomes

We calculated the net change in lipid and apolipoprotein levels before and after PCSK9 inhibitors treatment as the primary outcomes. We then compared the clinical and laboratory treatment-emergent adverse events (TEAE)s, serious TEAEs, and the discontinuation of drug treatment between the treatment group and control group. The laboratory adverse events included hepatotoxicity (alanine aminotransferase and aspartate aminotransferase levels ≥3-fold upper limit of normal), musculoskeletal injury (creatine kinase \geq 5-folds upper limit of normal). The most common clinical TEAEs included injection-site reaction (eg, generalized pruritis, hypersensitive reaction, erythema, rash, swelling, discoloration, or pain), nasopharyngitis, upper respiratory tract infections, influenza, cough, nausea, myalgia, myositis, headache, diarrhea, fatigue, abnormal pain, rectal bleeding, dehydration, arthralgia, and back pain.^{18–37} The serious TEAEs were defined as an adverse event that was fatal, life threatening, required admission to the hospital or prolonged stay in the hospital, or that caused persistent or significant disability.³⁵

Data Synthesis and Statistical Analysis

We used mean difference with corresponding 95% CI for continuous outcomes (lipids and apolipoproteins of participants in the trials), standardized mean difference with a 95% Cl for continued outcomes when the unit was not unified (lipoprotein[a]) and relative risk (RR) with 95% CI for dichotomous outcome (TEAEs, serious TEAEs, and discontinuation of participants in the trials). All quantitative variables are listed in the form of mean \pm SD. We contacted the original author of the study to obtain the missing data if necessary. The following data were needed to measure the weighted mean difference: the mean absolute change of lipoproteins and apolipoprotein levels (LDL-C, TC, HDL-C, TG, ApoB, Apo-A1) from baseline to the longest follow-up time point in milligrams per deciliter (mg/dL). All the units of these variables were standardized when TC, HDL-C, and LDL-C are expressed by mmol/L, multiplied by 38.6 to convert to mg/ dL, and TG is converted to mg/dL by multiplying by 88.5. If the results were expressed by median and range, the mean and SD were calculated according to the methods listed in our previous study.^{38–40} Treatment or control groups with multiple doses were combined, respectively, to create a single pairwise comparison, with the primary comparisons being treatment versus placebo. We calculated the average mean and SD of multiple dose-response groups by the methods described in previous studies. If the authors did not list the mean differences but provided the mean and/or SD instead, we calculated the mean difference from the other studies in this review by the methods described previously.³⁸

Heterogeneity and Publication Bias

The results of the included studies were performed with fixedeffect model or random effect in the computer program Review Manager (REVMAN) from the Cochrane Collaboration. We used the Cochrane Q test to measure the heterogeneity across included trials, χ^2 tests, and I² statistics to assess the magnitude of heterogeneity. We selected a fixed-effect model if there was no unexplained statistical heterogeneity. If heterogeneity existed, then the random-effect model was used.⁴¹ We considered I² ≥50% to indicate statistically significant heterogeneity between trials.⁴² When I² ≥50% was observed, we would take some measures to reduce the heterogeneity, such as performed subgroups by age, dyslipidemia types, PCSK9 inhibitor types, treatment duration $(\leq 12 \text{ weeks and } > 12 \text{ weeks})$, monotherapy or coadministration with other therapies, and study quality to identify the reasons for the diverseness. Publication bias, which includes selection bias, performance bias, attrition bias, reporting bias, and other risk of bias, was assessed by using the funnel plots, and Egger's regression test was also used to assay the possibility of publication bias.43 This meta-analysis was performed by REVMAN software, version 5.3 (The Cochrane Collaboration, Nordic Cochrane center, Copenhagen, Den-

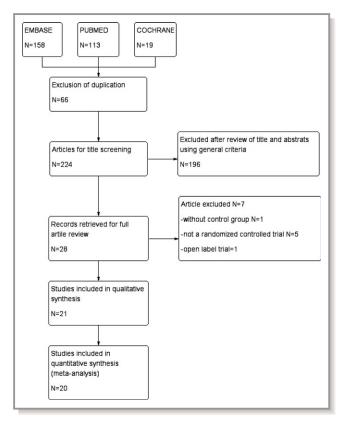


Figure 1. Preferred reporting items for systematic review and meta-analysis (PRISMA) flowchart of the process of study selection.

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Study, Author, Year	Design	Diagnosis	Control	Drug Regimen	Duration	ч	Mean Age (y)
Roth EM, 2012 [18]	M, R, DB, PC, PG	Hypercholesterolemia	Atorvastatin; placebo	A: NR	8 weeks	92	56.9 (9.8)
Stein EA, 2012(1) [19]	M, R, PC, AD, MD	Healthy; HeFH; hypercholesterolemia	Placebo	A: 0.3, 1.0, 3.0, 6.0, 12.0 mg/kg IV and 50, 100, 150, 250 mg SC at days 1, 2, 4, 8, 11, 15, 22, 29, 43, 64, 85, and 106; 50, 100, or 150 mg SC on days 1, 29, and 43	106/148 days	133	41.9
Sullivan D, 2012 [20]	M, R, DB, PC, EC, DR	Hypercholesterolemia	Placebo; ezetimibe	E: 280, 350, or 420 mg SC q4w	12 weeks	157	61.8 (8.4)
Stein EA, 2012(2) [21]	M, R, DB, PC	НеFH	Placebo	E: 150 mg SC q2w;150, 200, or 300 mg SC q4w	12 weeks	22	53.4 (9.7)
Dias CS, 2012 [22]	S, DB, PC, AD	Healthy; hypercholesterolemia, HeFH	Placebo	 E: Healthy adults: 7, 21, 70, 210, or 420 mg SC; 21 or 420 mg IV; hypercholesterolemia adults: 14 or 35 mg SC qw; 140 or 280 mg q2w; 420 mg q4w 	80 days	113	44 (8.5)
Koren MJ, 2012 [23]	M, R, DB, PC	Hypercholesterolemia	Placebo; ezetimibe	E: 70, 105, or 140 mg SC q2w; 280, 350 or 420 mg SC q4w	12 weeks	406	50.6 (11.8)
Cannon CP, 2015 [24]	M, R, DB, PG, AC, DD, EC	High cardiovascular risk and elevated LDL-C	Ezetimibe	A: 75 mg SC q2w	24 weeks	720	61.5 (9.3)
Koren MJ, 2014 [25]	R, DB, PC	Hypercholesterolemia	Placebo; ezetimibe	E: 140 mg SC q2w or 420 mg q4w	12 weeks	614	53.3 (11.8)
Giugliano RP, 2012 [26]	M, R, DB, PC, DR	Hypercholesterolemia	Placebo	E: 70, 105, or 140 mg SC q2w; 280, 350 or 420 mg SC q4w	12 weeks	631	62.0
Raal F, 2012 [27]	M, R, DB, PC, DR	HeFH	Placebo	E: 350 or 420 mg SC q4w	12 weeks	167	49.6 (12.6)
McKenney JM, 2012 [28]	S, R, DB, PC, P	Hypercholesterolemia	Placebo	A: 50, 100, or 150 mg SC q2w; 200, 300 mg SC q4w	12 weeks	183	56.7 (10.0)
Robinson JG, 2014 [29]	M, R, DB, PC, EC	Hypercholesterolemia and mixed dyslipidemia	Placebo; ezetimibe	E: 140 mg SC q2w or 420 mg SC q4w	12 weeks	1896	60.1 (9.8)
Stroes E, 2014 [30]	M, R, DB, PC, EC	Hypercholesterolemia	Placebo; ezetimibe	E: 140 mg SC q2w or 420 mg SC q4w	12 weeks	307	61.5 (9.8)
Hirayama A, 2014 [31]	M, R, DB, PC, DR	High risk for cardiovascular events	Placebo	E: 70 or 140 mg SC q2w; 280 or 420 mg q4w	12 weeks	307	61.5 (9.7)
Blom DJ, 2014 [32]	M, R, DB, PC	Hyperlipidemia	Placebo	E: 420 mg SC q4w	52 weeks	901	56.3 (10.5)
Roth EM, 2014 [33]	M, R, DB, AC, DD	10-year risk of fatal cardiovascular events \geq 1% to b5%, LDL-C 100 to 190 mg/dL	Ezetimibe	A: 75 mg SC q2w with dose up-titrated to 150 mg q2w	24 weeks	103	60.2 (4.9)
Robinson JG, 2015 [34]	M, R, DB, PC,PG	LDL-C >70 mg/dL	Placebo	A: 150 mg SC q2w	24 weeks	2341	60.5 (10.4)
Raal F, 2015 [35]	M, R, DB, PC	НеЕН	Placebo	E: 140 mg SC q2w, 420 mg SC q4w	12 weeks	331	50.6 (12.7)
Raal F, 2015 [36]	M, R, DB, PC	НоЕН	Placebo	E: 420 mg SC q4w	12 weeks	50	31 (13)
Ballantyne CM, 2015 [37]	M, R, DB, PC, DR	LDL-C >80 mg/dL	Placebo	B: 50, 100 or 150 mg SC q2w; 200 or 300 mg SC q4w	24 weeks	354	60.1 (10.1)

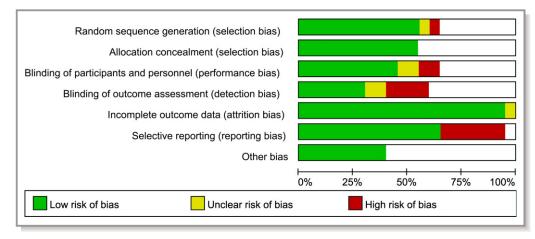


Figure 2. Risk-of-bias graph: review authors' judgments about each risk-of-bias item presented as percentages across all included studies.

mark). A 2-sided *P*-value <0.05 was considered to be statistically significant.

Results

Search Results and Study Characteristics

A total of 290 articles were obtained via searches on the databases, of which 66 records were excluded after determination of duplication and 196 articles were excluded after screening the titles and abstracts. A group of 28 relevant articles were reviewed in-depth by 2 independent authors, of which the following studies were excluded: 5 were not RCTs, 1

lacked a control group, and the other 1 were open-label trials (Figure 1). Finally, 20 RCTs met the eligible criteria including 6464 hypercholesterolemia cases, and 3416 controls were selected into the meta-analysis study.^{18–37} The characteristics of these trials included are shown in Table. Overall, these studies had a relatively high quality judged as by the Jadad score (5 scores=6, 4 scores=5, 3 scores=6, 2 scores=3). The summaries of risk of bias of included studies are shown in Figure 2. The funnel plot results did not show any publication bias in all the analyses performed (data not shown). The enrolled studies included 3 kinds of PCSK9 inhibitors (AMG145/Evolocumab=12, REGN727/SAR236553/Alirocumab=7, RN316/bococizumab=1). Ten studies used PCSK9 inhibitors as

	Expe	rimenta	al	с	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Ballantyne CM 2015	-40.39	31.12	253	-2.04	33.31	101	5.9%	-38.35 [-45.89, -30.81]	-
Blomv DJ 2014	-52.79	30.6	599	6.25	31.12	302	6.2%	-59.04 [-63.32, -54.76]	*
Cannon CP 2015	-54.81	33.2	479	-21.62	30.88	241	6.1%	-33.19 [-38.09, -28.29]	+
Hirayama A 2014	-85.39	30.88	205	-1.97	23.75	102	6.0%	-83.42 [-89.67, -77.17]	-
Jennifer G 2015	-74.85	33.85	1553	0.98	34.22	788	6.2%	-75.83 [-78.75, -72.91]	*
Koren MJ 2012	-61.87	23.72	271	0.51	25.28	135	6.1%	-62.38 [-67.49, -57.27]	-
Koren MJ 2014	-80.86	20.79	306	-13.5	19.79	308	6.2%	-67.36 [-70.57, -64.15]	*
McKenney JM 2012	-67.88	22.09	152	-6.6	22.5	31	5.7%	-61.28 [-69.94, -52.62]	-
Raal F 2012	-73.48	32.36	111	1.9	34.35	56	5.4%	-75.38 [-86.20, -64.56]	-
Raal F 2015(1)	-94.57	20.61	220	-1.88	24.68	109	6.1%	-92.69 [-98.06, -87.32]	÷
Raal F 2015(2)	-82.22	76.81	33	30.11	66.39	16	1.9%	-112.33 [-154.10, -70.56]	
Robinson JG 2014	-65.21	30.66	1117	-0.48	27.35	779	6.3%	-64.73 [-67.36, -62.10]	•
Roth EM 2012	-85.99	23.6	61	-21	23.7	31	5.5%	-64.99 [-75.22, -54.76]	-
Roth EM 2014	-76.34	20.35	52	-23.79	19.75	51	5.8%	-52.55 [-60.29, -44.81]	-
Stein EA 2012(1)	-77.21	16.97	101	-5.99	28.22	32	5.5%	-71.22 [-81.54, -60.90]	-
Stein EA 2012(2)	-65.6	29.91	62	-16.06	29.41	15	4.6%	-49.54 [-66.18, -32.90]	
Stroes E 2014	-104.37	33.66	205	-30.88	31.85	102	5.8%	-73.49 [-81.20, -65.78]	-
Sullivan D 2012	-96.95	42.68	125	-29.97	43.81	32	4.5%	-66.98 [-83.90, -50.06]	
Total (95% CI)			5905			3231	100.0%	-65.29 [-72.08, -58.49]	•
Heterogeneity: Tau ² =	190.15; C	hi² = 43	4.04, df	= 17 (P	< 0.000	001); l²	= 96%	-	
Test for overall effect:	Z = 18.83	(P < 0.0	00001)						-100 -50 0 50 100 Favours [experimental] Favours [control]

Figure 3. Forest plots depicting the effect of PCSK9 monoclonal antibodies on LDL-C. LDL-C indicates low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin9.

	Expe	rimenta	al	С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Ballantyne CM 2015	-40.92	32.69	253	-2.97	35.06	101	8.3%	-37.95 [-45.89, -30.01]	
Blomv DJ 2014	-50.14	35.2	599	9.19	35.33	302	8.6%	-59.33 [-64.21, -54.45]	
Cannon CP 2015	-54.43	36.67	479	-27.02	34.35	241	8.6%	-27.41 [-32.85, -21.97]	+
Hirayama A 2014	-87.37	34.91	205	0	26.44	102	8.4%	-87.37 [-94.38, -80.36]	-
Koren MJ 2012	-64.85	26.16	271	-0.97	27.25	135	8.6%	-63.88 [-69.43, -58.33]	+
McKenney JM 2012	-68.07	25.81	152	-3.3	26.8	31	8.0%	-64.77 [-75.06, -54.48]	-
Raal F 2012	-72.66	35.4	111	6.83	37.02	56	7.8%	-79.49 [-91.21, -67.77]	-
Raal F 2015(2)	-77.97	75.27	33	30.88	66.39	16	3.5%	-108.85 [-150.30, -67.40]	
Robinson JG 2014	-68.3	35.79	1117	-1.39	32.08	779	8.7%	-66.91 [-69.99, -63.83]	•
Roth EM 2012	-89.85	11.85	61	-33.3	22.1	31	8.3%	-56.55 [-64.88, -48.22]	-
Roth EM 2014	-65.62	33.57	52	-24.41	35.18	51	7.6%	-41.21 [-54.49, -27.93]	
Stein EA 2012(2)	-61.7	33.63	62	-19.8	34.59	15	6.6%	-41.90 [-61.30, -22.50]	
Sullivan D 2012	-100.81	46.1	125	-29.37	44.92	32	6.9%	-71.44 [-88.98, -53.90]	
Total (95% CI)			3520			1892	100.0%	-60.04 [-69.95, -50.13]	◆
Heterogeneity: Tau ² =	290.20; C	hi² = 27	7.46, di	f = 12 (P	< 0.000	001); l²	= 96%		
Test for overall effect:	Z = 11.88	(P < 0.0	00001)						-100 -50 0 50 100 Favours [experimental] Favours [control]

Figure 4. Forest plots depicting the effect of PCSK9 monoclonal antibodies on TC. PCSK9 indicates proprotein convertase subtilisin/kexin9; TC, total cholesterol.

monotherapy and another 10 studies were coadministered with statins, ezetimibe, or standard of care. Participants of 16 studies were hypercholesterolemia patients, 2 of these studies contained some heterozygous familial hypercholesterolemia (HeFH) patients. Three studies enrolled HeFH patients and 1 study consisted of homozygous familial hypercholesterolemia patients. Most of the treatment durations ranged from 8 to 24 weeks except for the study of Blom,³² which had treatment durations of as long as 52 weeks.

Lipid-Modifying Effects

Our analysis showed that PCSK9 inhibitors therapy significantly reduced LDL-C levels whether or not in combination with other lipid-lowing therapy. As shown in Figure 3, significant decrease in LDL-C was found in the intervention group; the weighted mean net change was -65.29 mg/dL (95% Cl -72.08 to -58.49). Corresponding changes in TC, HDL-C, TG, Apo-B, and Apo-A1 were -60.04 mg/dL (95% Cl -69.95 to -50.13) (Figure 4), 3.40 mg/dL (95% Cl -16.21 to -8.22) (Figure 5), -12.21 mg/dL (95% Cl -16.21 to -8.22) (Figure 5), -12.21 mg/dL (95% Cl -16.21 to -8.22)

	Exp	eriment	tal	c	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Ballantyne CM 2015	2.26	7.77	253	-0.46	7.17	101	2.7%	2.72 [1.03, 4.41]	
Blomv DJ 2014	2.89	8.11	599	0.03	8.28	302	6.0%	2.86 [1.72, 4.00]	
Cannon CP 2015	3.98	8.11	479	0.23	7.91	241	5.1%	3.75 [2.52, 4.98]	
Hirayama A 2014	5.85	11.99	205	1.97	13.85	102	0.8%	3.88 [0.73, 7.03]	· · · · · · · · · · · · · · · · · · ·
Jennifer G 2015	1.99	7.85	1553	-0.3	7.02	788	19.9%	2.29 [1.66, 2.92]	-
Koren MJ 2012	4.91	8.43	271	1.73	8.36	135	2.6%	3.18 [1.45, 4.91]	
Koren MJ 2014	2.44	2.7	306	-1.51	2.86	308	40.3%	3.95 [3.51, 4.39]	
McKenney JM 2012	3.13	6.64	152	-0.49	6.3	31	1.3%	3.62 [1.16, 6.08]	· · · · ·
Raal F 2012	4.62	6.79	111	1.15	7.14	56	1.5%	3.47 [1.21, 5.73]	
Raal F 2015(1)	3.48	7.74	220	-1.36	7.9	109	2.4%	4.84 [3.04, 6.64]	
Raal F 2015(2)	1.54	6.18	33	1.58	5.04	16	0.7%	-0.04 [-3.29, 3.21]	
Robinson JG 2014	3.83	9.36	1117	0.19	8.5	779	11.9%	3.64 [2.83, 4.45]	-
Roth EM 2012	2.38	7.04	61	-1.9	6.9	31	0.9%	4.28 [1.28, 7.28]	
Roth EM 2014	3.26	7.44	52	0.96	8.13	51	0.9%	2.30 [-0.71, 5.31]	+ · · · ·
Stein EA 2012(2)	4.71	7.26	62	-1.16	7.6	15	0.4%	5.87 [1.62, 10.12]	· · · · · · · · · · · · · · · · · · ·
Stroes E 2014	3.1	8.68	205	0.86	7.74	102	2.1%	2.24 [0.32, 4.16]	
Sullivan D 2012	4.38	11.09	125	-0.67	11.47	32	0.4%	5.05 [0.63, 9.47]	· · · · · · · · · · · · · · · · · · ·
Total (95% CI)			5804			3199	100.0%	3.40 [3.12, 3.68]	♦
Heterogeneity: Chi ² =	31.22, df	f = 16 (F	= 0.0 ⁻	1); I ² = 4	9%				
Test for overall effect:		•							-10 -5 0 5 10
				/					Favours [experimental] Favours [control]

Figure 5. Forest plots depicting the effect of PCSK9 monoclonal antibodies on HDL-C. HDL-C indicates high-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin9.

	Expe	eriment	mental Control					Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ballantyne CM 2015	-13.9	26.48	253	-6.38	29.93	101	7.7%	-7.52 [-14.21, -0.83]	
Blomv DJ 2014	-2.15	42.84	599	10	46.08	302	8.0%	-12.15 [-18.38, -5.92]	
Cannon CP 2015	-17.26	43.54	479	-18.14	43.98	241	7.7%	0.88 [-5.90, 7.66]	
Hirayama A 2014	-23.1	60.98	205	4.34	66.84	102	4.0%	-27.44 [-42.87, -12.01]	
Jennifer G 2015	-20.59	41.61	1553	2.43	45.48	788	9.1%	-23.02 [-26.81, -19.23]	-
Koren MJ 2012	-10.82	42.72	271	-1.86	43.44	135	6.6%	-8.96 [-17.88, -0.04]	
Koren MJ 2014	-13.82	13	306	-0.64	14.25	308	9.6%	-13.18 [-15.34, -11.02]	T
McKenney JM 2012	-13.28	19.52	152	12.03	28.33	31	5.9%	-25.31 [-35.75, -14.87]	
Raal F 2012	-10	38.15	111	11.65	38.06	56	5.1%	-21.65 [-33.89, -9.41]	
Raal F 2015(1)	-12.4	32.31	220	5.33	28.44	109	7.7%	-17.73 [-24.57, -10.89]	
Raal F 2015(2)	-1.5	27.44	33	-1.95	26.55	16	3.8%	0.45 [-15.58, 16.48]	
Robinson JG 2014	-9.84	53.02	1117	6.49	48.26	779	8.7%	-16.33 [-20.93, -11.73]	-
Roth EM 2012	-15.83	27.29	61	-13.4	25.3	31	5.5%	-2.43 [-13.66, 8.80]	
Roth EM 2014	-14.16	36.04	52	-12.64	35.93	51	4.5%	-1.52 [-15.42, 12.38]	
Stein EA 2012(2)	-6.36	27.1	62	-11.59	26.9	15	4.1%	5.23 [-9.96, 20.42]	
Sullivan D 2012	-25.54	62.18	125	-9.01	65.69	32	2.0%	-16.53 [-41.77, 8.71]	
Total (95% CI)			5599			3097		-12.21 [-16.21, -8.22]	
Heterogeneity: Tau ² =				= 15 (P <	< 0.0000	01); l² =	80%	-	-50 -25 0 25 50
Test for overall effect:	Z = 5.99	(P < 0.0	0001)						Favours [experimental] Favours [control]

Figure 6. Forest plots depicting the effect of PCSK9 monoclonal antibodies on TG. PCSK9 indicates proprotein convertase subtilisin/kexin9; TG, triglycerides.

ure 6), -41.01 mg/dL (95% CI -46.07 to -35.94) (Figure 7), and 6.75 mg/dL (95% CI 4.64 to 8.86) (Figure 8), respectively. Also, the standardized mean difference change in lipoprotein(a) was -0.94 (95% CI -1.12 to -0.77) (Figure 9).

We observed significant heterogeneity in the analysis for LDL-C, TC, TG, Apo-B, Apo-A1, and lipoprotein(a) (P<0.00001, I^2 =96%; P<0.00001, I^2 =96%; P<0.00001, I^2 =80%; P<0.00001, I^2 =96%; P=0.001, I^2 =63%; P<0.00001, I^2 =91%, respectively). I^2 from the I^2 test was \geq 50%, so a random-effect model was

used. To investigate the potential discrepancy, we divided subgroups by age, methods of treatment, treatment duration, specific drugs, baseline lipid levels, and study quality, but we failed to find any association with these factors. Fix-effect models were chosen to analyze the HDL-C, because low heterogeneity was obtained (P=0.01, I²=49%). We also performed sensitivity analysis; however, the exclusion of any single study did not change the *P*-value of pooled estimates for either outcome. Heterogeneity was still significant in LDL-

	Exp	eriment	al	с	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Ballantyne CM 2015	-24.95	19.47	253	-1.84	19.49	101	6.2%	-23.11 [-27.60, -18.62]	-
Blomv DJ 2014	-36.11	21.14	599	2.24	21.07	302	6.4%	-38.35 [-41.27, -35.43]	-
Cannon CP 2015	-36.63	21.67	479	-16.47	20.96	241	6.4%	-20.16 [-23.44, -16.88]	~
Hirayama A 2014	-57.4	20.96	205	-5.1	19.9	102	6.2%	-52.30 [-57.11, -47.49]	-
Jennifer G 2015	-53.8	28.11	1553	1.21	28.46	788	6.5%	-55.01 [-57.44, -52.58]	-
Koren MJ 2012	-41.5	16.02	271	-0.06	16.39	135	6.4%	-41.44 [-44.80, -38.08]	-
Koren MJ 2014	-49.95	14.98	306	-6.6	14.29	308	6.5%	-43.35 [-45.67, -41.03]	-
McKenney JM 2012	-40.14	16.59	152	-2.4	17.5	31	5.9%	-37.74 [-44.44, -31.04]	
Raal F 2012	-45.21	23.54	111	3.8	25.3	56	5.7%	-49.01 [-56.95, -41.07]	
Raal F 2015(1)	-54.52	20.75	220	2.18	19.94	109	6.2%	-56.70 [-61.34, -52.06]	-
Raal F 2015(2)	-40.32	41.16	33	8.4	37.64	16	2.8%	-48.72 [-71.90, -25.54]	
Robinson JG 2014	-43.79	21.73	1117	-0.26	18.71	779	6.5%	-43.53 [-45.36, -41.70]	-
Roth EM 2012	-59.25	8.94	61	-12	10.1	31	6.3%	-47.25 [-51.45, -43.05]	-
Roth EM 2014	-38.28	17.3	52	-11.47	17.88	51	5.9%	-26.81 [-33.61, -20.01]	
Stein EA 2012(2)	-38.33	20.01	62	-8.12	20.63	15	4.9%	-30.21 [-41.78, -18.64]	(
Stroes E 2014	-60.74	24.2	205	-16.1	22.66	102	6.1%	-44.64 [-50.15, -39.13]	
Sullivan D 2012	-57.23	26.92	125	-16.84	25.64	32	5.2%	-40.39 [-50.45, -30.33]	
Total (95% CI)			5804			3199	100.0%	-41.01 [-46.07, -35.94]	◆
Heterogeneity: Tau ² =	101.74; (Chi² = 4	48.42, (df = 16 (P < 0.00)));	² = 96%		
Test for overall effect:	Z = 15.80	6 (P < 0	.00001)					-50 -25 0 25 50 Favours [experimental] Favours [control]

Figure 7. Forest plots depicting the effect of PCSK9 monoclonal antibodies on APO-B. APO-B indicates apolipoprotein-B; PCSK9, proprotein convertase subtilisin/kexin9.

	Exp	eriment	tal	c	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Ballantyne CM 2015	7.12	19	253	1.8	17.15	101	9.3%	5.32 [1.24, 9.40]	
Blomv DJ 2014	3.07	17.91	599	-1.5	19.87	302	11.7%	4.57 [1.91, 7.23]	
Hirayama A 2014	11.76	26.15	205	-4.9	23.4	102	6.9%	16.66 [10.88, 22.44]	
Jennifer G 2015	5.86	23.09	1553	1.77	24.81	788	12.6%	4.09 [2.01, 6.17]	
Koren MJ 2012	8.11	18.3	271	-0.76	18.75	135	9.7%	8.87 [5.03, 12.71]	
McKenney JM 2012	2.56	9.9	152	0	8.8	31	10.3%	2.56 [-0.91, 6.03]	—
Raal F 2012	14.6	17.17	111	12.9	18	56	7.0%	1.70 [-3.99, 7.39]	
Raal F 2015(1)	9.1	21.66	220	0.14	21.55	109	8.0%	8.96 [4.00, 13.92]	
Roth EM 2012	-1.47	20.42	61	-8	19.7	31	4.2%	6.53 [-2.09, 15.15]	
Roth EM 2014	7.2	17.66	52	-0.98	17.72	51	5.7%	8.18 [1.35, 15.01]	
Stein EA 2012(2)	6.94	17.31	62	-8.36	18.75	15	3.2%	15.30 [4.88, 25.72]	· · · · ·
Stroes E 2014	8.08	22.14	205	3.15	19.87	102	8.1%	4.93 [0.03, 9.83]	——————————————————————————————————————
Sullivan D 2012	11.52	25.98	125	-2.39	26.06	32	3.3%	13.91 [3.80, 24.02]	
Total (95% CI)			3869			1855	100.0%	6.75 [4.64, 8.86]	•
Heterogeneity: Tau ² =	8.12; Ch	ni² = 32.	55, df =	: 12 (P =	= 0.001)	; l² = 6	3%	-	-20 -10 0 10 20
Test for overall effect:	Z = 6.26	(P < 0.	00001)						-20 -10 0 10 20 Favours [experimental] Favours [control]

Figure 8. Forest plots depicting the effect of PCSK9 monoclonal antibodies on APO-A1. APO-A1 indicates apolipoprotein-A1; PCSK9, proprotein convertase subtilisin/kexin9.

C forest plots after grouping trials by methods of treatment (PSCK9 inhibitor monotherapy or combined therapy) (Figure 10), enrolled patients (HeFH or non-HeFH) (Figure 11), and treatment duration (\leq 12 weeks or >12 weeks) (Figure 12). The LDL-C reduction was more obvious in patients who received PCSK9 inhibitor monotherapy (-69.84 mg/dL, 95% Cl -79.9 to -59.78) than coadministered with other therapy (-60.16 mg/dL, 95% Cl -70.25 to -50.06). Patients with HeFH (-79.02 mg/dL, 95% Cl -99.45 to -58.59) and treatment duration \leq 12 weeks (-70.89 mg/dL, 95% Cl -77.28 to -64.51) also experienced significant reduction in LDL-C levels. We showed no evidence of

publication bias for either outcome as indicated by Egger's linear regression test and funnel plot results. Most of the cholesterol diversities might be ascribed to clinical dissimilarities, as different dyslipidemia types have varying lipid-modifying effects, and different doses of PCSK9 inhibitors may show varying lipid-lowering effects.

Safety and Tolerability Outcomes

The most commonly reported TEAEs in the included studies were nasopharyngitis, upper respiratory tract infections, influenza, cough, headache, and back pain; most of them

	Expe	eriment	al	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Ballantyne CM 2015	-1.48	3.59	253	0.4	3.78	101	6.9%	-0.51 [-0.75, -0.28]	-
Blomv DJ 2014	-23.24	24.77	599	-5.04	25.46	302	7.5%	-0.73 [-0.87, -0.58]	•
Cannon CP 2015	-0.28	0.31	479	-0.05	0.25	241	7.4%	-0.79 [-0.95, -0.63]	•
Jennifer G 2015	-6.5	6.12	1553	-0.77	5.87	788	7.7%	-0.95 [-1.04, -0.86]	•
Koren MJ 2012	-11.16	16.94	271	4.55	21.66	135	7.0%	-0.84 [-1.06, -0.63]	-
Koren MJ 2014	-4.53	3.14	306	-0.15	1.92	308	7.2%	-1.68 [-1.87, -1.50]	•
McKenney JM 2012	-5.18	3.52	152	0	2.3	31	5.4%	-1.54 [-1.96, -1.12]	
Raal F 2012	-8.94	8.76	111	1.85	1.85	56	5.9%	-1.49 [-1.84, -1.13]	*
Raal F 2015(1)	-15.47	16.46	220	4.84	15.88	109	6.8%	-1.25 [-1.49, -1.00]	*
Raal F 2015(2)	-7.14	17.58	33	3.07	26.54	16	4.0%	-0.48 [-1.09, 0.12]	
Robinson JG 2014	-9.25	11.4	1117	1.69	10.51	779	7.7%	-0.99 [-1.09, -0.89]	•
Roth EM 2012	-8.2	3.86	61	-0.5	3.3	31	4.5%	-2.07 [-2.60, -1.54]	-
Roth EM 2014	-2.17	3.47	52	-1.97	4.34	51	5.6%	-0.05 [-0.44, 0.34]	+
Stein EA 2012(2)	-6.06	7.55	62	-2.67	3.2	15	4.2%	-0.48 [-1.05, 0.09]	
Stroes E 2014	-8.7	11.18	205	0.27	12.01	102	6.8%	-0.78 [-1.03, -0.54]	*
Sullivan D 2012	-10.15	11.97	125	-4.62	14.44	32	5.6%	-0.44 [-0.83, -0.05]	7
Total (95% CI)			5599			3097	100.0%	-0.94 [-1.12, -0.77]	•
Heterogeneity: Tau ² =	0.10; Ch	i² = 161	.88, df :	= 15 (P	< 0.000	01); l² =	= 91%		
Test for overall effect:	Z = 10.69) (P < 0	.00001) Ì					-10 -5 0 5 10 Favours [experimental] Favours [control]

Figure 9. Forest plots depicting the effect of proprotein convertase subtilisin/kexin9 monoclonal antibodies on lipoprotein(a).

	Expe	riment	al	c	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	I IV, Random, 95% CI
1.1.1 co-administratio	on -therap	у							
Blomv DJ 2014	-52.79	30.6	599	6.25	31.12	302	6.2%	-59.04 [-63.32, -54.76]	* (
Cannon CP 2015	-54.81	33.2	479	-21.62	30.88	241	6.1%	-33.19 [-38.09, -28.29]	*
Jennifer G 2015	-74.85	33.85	1553	0.98	34.22	788	6.2%	-75.83 [-78.75, -72.91]	· ·
McKenney JM 2012	-67.88	22.09	152	-6.6	22.5	31	5.7%	-61.28 [-69.94, -52.62]	-
Robinson JG 2014	-65.21	30.66	1117	-0.48	27.35	779	6.3%	-64.73 [-67.36, -62.10]	· · · ·
Roth EM 2012	-85.99	23.6	61	-21	23.7	31	5.5%	-64.99 [-75.22, -54.76]	
Stein EA 2012(1)	-77.21	16.97	101	-5.99	28.22	32	5.5%	-71.22 [-81.54, -60.90]	-
Stein EA 2012(2)	-65.6	29.91	62	-16.06	29.41	15	4.6%	-49.54 [-66.18, -32.90]	
Subtotal (95% CI)			4124			2219	46.2%	-60.16 [-70.25, -50.06]	◆
Heterogeneity: Tau ² = Test for overall effect: 2	,		,	f = 7 (P ·	< 0.000	01); I² =	97%		
1.1.2 mono-therapy									
Ballantyne CM 2015	-40.39	31.12	253	-2.04	33.31	101	5.9%	-38.35 [-45.89, -30.81]	
Hirayama A 2014	-85.39	30.88	205	-1.97	23.75	102	6.0%	-83.42 [-89.67, -77.17]	÷
Koren MJ 2012	-61.87	23.72	271	0.51	25.28	135	6.1%	-62.38 [-67.49, -57.27]	*
Koren MJ 2014	-80.86	20.79	306	-13.5	19.79	308	6.2%	-67.36 [-70.57, -64.15]	•
Raal F 2012	-73.48	32.36	111	1.9	34.35	56	5.4%	-75.38 [-86.20, -64.56]	-
Raal F 2015(1)	-94.57	20.61	220	-1.88	24.68	109	6.1%	-92.69 [-98.06, -87.32]	÷
Raal F 2015(2)	-82.22	76.81	33	30.11	66.39	16	1.9%	-112.33 [-154.10, -70.56]	
Roth EM 2014	-76.34	20.35	52	-23.79	19.75	51	5.8%	-52.55 [-60.29, -44.81]	
Stroes E 2014	-104.37	33.66	205	-30.88	31.85	102	5.8%	-73.49 [-81.20, -65.78]	
Sullivan D 2012	-96.95	42.68	125	-29.97	43.81	32	4.5%	-66.98 [-83.90, -50.06]	<u> </u>
Subtotal (95% CI)			1781			1012	53.8%	-69.84 [-79.90, -59.78]	◆
Heterogeneity: Tau ² = 2	228.27; C	hi² = 18	9.89, d	f = 9 (P •	< 0.000	01); I² =	95%		
Test for overall effect: 2	Z = 13.61	(P < 0.0	00001)						
Total (95% CI)			5905			3231	100.0%	-65.29 [-72.08, -58.49]	♦
Heterogeneity: Tau ² =	190.15; C	hi² = 43	4.04, d	f = 17 (P	< 0.00	001); l²	= 96%		-200 -100 0 100 200
Test for overall effect: 2	Z = 18.83	(P < 0.0	00001)						Favours [experimental] Favours [control]
Test for subgroup diffe	rences: C	hi² = 1.7	77. df =	1 (P = 0)	18) I ²	= 43.6%	6		r avours levhenmental i avours [control]

Figure 10. Forest plots depicting the effect on low-density lipoprotein cholesterol for subgroup analysis after grouping by methods of treatment.

were mild or moderate in intensity. There were 4048 patients receiving PCSK9 inhibitor and 3416 patients receiving placebo or statins monotherapy who experienced TEAEs (relative risk: 1.01, 95% CI [0.98 to 1.04]) (Figure 13), which implies that there was no significant difference between the 2 groups, and the serious TEAEs between the 2 groups also did not show a difference (relative risk: 1.01, 95% CI 0.88 to 1.17) (Figure 14). No significant heterogeneity was found in the analysis of TEAEs (P=0.03, I²=41%) and serious TEAEs (P=0.99, I²=0), so the fixed model was chosen. There was no significant difference in the rates of discontinuation of the treatment between the 2 groups (relative risk: 1.07, 95% CI 0.86 to 1.34) (Figure 15).

Discussion

Recently, RCTs indicated that the PCSK9 inhibitors significantly reduced LDL-C levels with or without other lipid-lowing therapies. In the present study, we performed this metaanalysis with a total of 20 studies enrolling 9880 participants with hypercholesterolemia. Our study showed that PCSK9 inhibitor therapy significantly reduced the levels of LDL-C, TC, TG, Apo-B, and lipoprotein(a). We also found that PCSK9 inhibitors not only reduced the absolute LDL-C levels, but also increased the HDL-C and Apo-A1 levels.

The test of heterogeneity of LDL-C, TG, Apo-B, Apo-A1, and lipoprotein(a) failed to reach statistical significance. It may be argued that these studies should not be combined in a meta-analysis because they contained varying interventions and controls. However, the absence of statistical significance does not necessarily rule out clinical diversity in aspects such as study design and dose. Other possible reasons could ascribe the heterogeneity to the selection of enrolled patients, as some enrolled patients had combined statin therapy while others did not. For example, all patients in Stein's²¹ study had experienced a 6-week washout or statin stabilization run-in period, while Raal's²⁷ study did not have the statin run-in period. All patients, whether with or without statin therapy, went into the experimental studies immediately. Thus, Raal's study obtained a significant reduction in the levels of LDL-C, TC, Apo-B, and lipoprotein (a). Therefore, heterogeneity would be expected. Genetic polymorphisms and dietary habits may also influence the response to PSCK9 inhibitors, but they were reported in the research studies. In terms of safety, PCSK9 inhibitors may lead to many TEAEs, such as injection-site reaction, nasopharyn-

	Expe	eriment	al	c	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	I IV, Random, 95% CI
1.1.1 Familial hyperch	holestero	lemia							
Raal F 2012	-73.48	32.36	111	1.9	34.35	56	5.4%	-75.38 [-86.20, -64.56]	-
Raal F 2015(1)	-94.57	20.61	220	-1.88	24.68	109	6.1%	-92.69 [-98.06, -87.32]	÷
Raal F 2015(2)	-82.22	76.81	33	30.11	66.39	16	1.9%	-112.33 [-154.10, -70.56]	
Stein EA 2012(2)	-65.6	29.91	62	-16.06	29.41	15	4.6%	-49.54 [-66.18, -32.90]	
Subtotal (95% CI)			426			196	18.0%	-79.02 [-99.45, -58.59]	◆
Heterogeneity: Tau ² =	342.40; C	hi² = 29	.57, df :	= 3 (P <	0.0000	1); ² = 9	90%		
Test for overall effect:	Z = 7.58 (P < 0.00	0001)						
1.1.2 Non-familial hyp	percholes	terolen	nia						
Ballantyne CM 2015		31.12	253	-2.04	33.31	101	5.9%	-38.35 [-45.89, -30.81]	-
Blomy DJ 2014	-52.79		599		31.12	302	6.2%	-59.04 [-63.32, -54.76]	· ·
Cannon CP 2015	-54.81	33.2	479	-21.62	30.88	241	6.1%	-33.19 [-38.09, -28.29]	*
Hirayama A 2014	-85.39		205		23.75	102	6.0%	-83.42 [-89.67, -77.17]	
Jennifer G 2015	-74.85	33.85	1553	0.98	34.22	788	6.2%	-75.83 [-78.75, -72.91]	· · ·
Koren MJ 2012	-61.87	23.72	271		25.28	135	6.1%	-62.38 [-67.49, -57.27]	*
Koren MJ 2014	-80.86	20.79	306	-13.5	19.79	308	6.2%	-67.36 [-70.57, -64.15]	· ·
McKenney JM 2012	-67.88		152	-6.6	22.5	31	5.7%	-61.28 [-69.94, -52.62]	-
Robinson JG 2014	-65.21	30.66	1117	-0.48	27.35	779	6.3%	-64.73 [-67.36, -62.10]	•
Roth EM 2012	-85.99	23.6	61	-21	23.7	31	5.5%	-64.99 [-75.22, -54.76]	-
Roth EM 2014	-76.34	20.35	52	-23.79	19.75	51	5.8%	-52.55 [-60.29, -44.81]	-
Stein EA 2012(1)	-77.21	16.97	101	-5.99	28.22	32	5.5%	-71.22 [-81.54, -60.90]	-
Stroes E 2014	-104.37	33.66	205	-30.88	31.85	102	5.8%	-73.49 [-81.20, -65.78]	-
Sullivan D 2012	-96.95	42.68	125	-29.97	43.81	32	4.5%	-66.98 [-83.90, -50.06]	
Subtotal (95% CI)			5479			3035	82.0%	-62.38 [-69.21, -55.55]	◆
Heterogeneity: Tau ² =	,		,	f = 13 (P	< 0.00	001); l²	= 96%		
Test for overall effect:	Z = 17.91	(P < 0.0	00001)						
Total (95% CI)			5905			3231	100.0%	-65.29 [-72.08, -58.49]	♦
Heterogeneity: Tau ² =	190.15; C	hi² = 43	4.04, di	f = 17 (P	< 0.00	001); l²	= 96%		-200 -100 0 100 2
Test for overall effect:	Z = 18.83	(P < 0.0	00001)						-200 -100 0 100 2 Favours [experimental] Favours [control]
Test for subaroup diffe	rences: C	hi² = 2.2	29. df =	1 (P = 0)	.13). I ²	= 56.4%	6		Favous [experimental] Favous [control]

Figure 11. Forest plots depicting the effect on low-density lipoprotein cholesterol for subgroup analysis after grouping by enrolled patients.

	Expe	riment	al	с	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	I IV, Random, 95% CI
1.1.1 Duration>12w									
02Stein EA 2012(1)	-77.21	16.97	101	-5.99	28.22	32	5.5%	-71.22 [-81.54, -60.90]	
07Cannon CP 2015	-54.81	33.2	479	-21.62	30.88	241	6.1%	-33.19 [-38.09, -28.29]	÷
15Blomv DJ 2014	-52.79	30.6	599	6.25	31.12	302	6.2%	-59.04 [-63.32, -54.76]	÷
16Roth EM 2014	-76.34	20.35	52	-23.79	19.75	51	5.8%	-52.55 [-60.29, -44.81]	-
17Jennifer G 2015	-74.85	33.85	1553	0.98	34.22	788	6.2%	-75.83 [-78.75, -72.91]	• •
20Ballantyne CM 2015	-40.39	31.12	253	-2.04	33.31	101	5.9%	-38.35 [-45.89, -30.81]	
Subtotal (95% CI)			3037			1515	35.8%	-55.00 [-70.68, -39.31]	◆
Heterogeneity: Tau ² = 37	2.53; Chi ²	= 266.2	25, df =	5 (P < 0	.00001)	; l ² = 9	8%		
Test for overall effect: Z =	= 6.87 (P <	< 0.000	01)	•					
1.1.2 Duration≪12w									
01Roth EM 2012	-85.99	23.6	61	-21	23.7	31	5.5%	-64.99 [-75.22, -54.76]	
03Sullivan D 2012	-96.95			-29.97		32	4.5%	-66.98 [-83.90, -50.06]	<u> </u>
04Stein EA 2012(2)		29.91		-16.06	29.41	15	4.6%	-49.54 [-66.18, -32.90]	
06Koren MJ 2012	-61.87		271	0.51	25.28	135	6.1%	-62.38 [-67.49, -57.27]	÷
08Koren MJ 2012	-80.86		306	-13.5		308	6.2%	-67.36 [-70.57, -64.15]	• ·
10Raal F 2012	-73.48		111		34.35	56	5.4%	-75.38 [-86.20, -64.56]	-
11McKenney JM 2012	-67.88		152	-6.6	22.5	31	5.7%	-61.28 [-69.94, -52.62]	-
12Robinson JG 2014	-65.21		1117		27.35	779	6.3%	-64.73 [-67.36, -62.10]	• •
13Stroes E 2014	-104.37		205	-30.88		102	5.8%	-73.49 [-81.20, -65.78]	-
14Hirayama A 2014	-85.39		205	-1.97		102	6.0%	-83.42 [-89.67, -77.17]	÷
18Raal F 2015(1)	-94.57		200	-1.88		102	6.1%	-92.69 [-98.06, -87.32]	-
19Raal F 2015(2)	-82.22		33	30.11		16		-112.33 [-154.10, -70.56]	
Subtotal (95% CI)	-02.22	70.01	2868	50.11	50.55	1716	64.2%	-70.89 [-77.28, -64.51]	♦
Heterogeneity: Tau ² = 98	69. Chi ² =	= 128 24		1 (P < 0)	00001				
Test for overall effect: Z =						,,	. /0		
									▲
Total (95% CI)			5905				100.0%	-65.29 [-72.08, -58.49]	
Heterogeneity: Tau ² = 19				17 (P <	0.0000	1); l² =	96%		-200 -100 0 100 20
Test for overall effect: Z =	```								Favours [experimental] Favours [control]
Test for subaroup differer	nces: Chi ²	= 3.39.	df = 1	P = 0.07	7). $I^2 = 7$	0.5%			

Figure 12. Forest plots depicting the effect on low-density lipoprotein cholesterol for subgroup analysis after grouping by treatment duration.

Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% Cl Ballantyne CM 2015 207 253 82 101 4.4% 1.01 [0.90, 1.13] Born DJ 2014 448 599 224 302 11.2% 1.01 [0.93, 1.09] Cannon CP 2015 341 479 162 241 8.1% 1.06 [0.95, 1.18] Dias CS 2012 57 85 19 28 1.1% 0.99 [0.74, 1.33] Guigliano RP 2012 277 474 71 157 4.0% 1.29 [1.07, 1.56] Hirayama A 2014 104 205 39 102 2.0% 1.33 [1.00, 1.76] Jennifer G 2015 1255 1553 650 788 32.6% 0.98 [0.82, 1.17] Koren MJ 2012 136 271 67 135 3.4% 1.01 [0.82, 1.41] McKenney JM 2012 91 152 14 31 0.9% 1.33 [0.88, 2.00]		Experime	ental	Risk Ratio				
Blomv DJ 2014 448 599 224 302 11.2% 1.01 [0.93, 1.09] Cannon CP 2015 341 479 162 241 8.1% 1.06 [0.95, 1.18] Dias CS 2012 57 85 19 28 1.1% 0.99 [0.74, 1.33] Guigliano RP 2012 277 474 71 157 4.0% 1.29 [1.07, 1.66] Hirayama A 2014 104 205 39 102 2.0% 1.33 [1.00, 1.76] Jennifer G 2015 1255 1553 650 788 32.6% 0.98 [0.94, 1.02] Koren MJ 2012 136 271 67 135 3.4% 1.01 [0.82, 1.24] Koren MJ 2012 91 152 14 31 0.9% 1.33 [0.88, 2.00] Raal F 2015(1) 124 220 53 109 2.7% 1.16 [0.93, 1.45] Raal F 2015(2) 12 33 10 16 0.5% 0.58 [0.32, 1.05] Roth EM 2012 32 61 19 31	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
Cannon CP 2015 341 479 162 241 8.1% 1.06 [0.95, 1.18] Dias CS 2012 57 85 19 28 1.1% 0.99 [0.74, 1.33] Guigliano RP 2012 277 474 71 157 4.0% 1.29 [1.07, 1.56] Hirayama A 2014 104 205 39 102 2.0% 1.33 [1.00, 1.76] Jennifer G 2015 1255 1553 650 788 32.6% 0.98 [0.94, 1.02] Koren MJ 2012 136 271 67 135 3.4% 1.01 [0.82, 1.24] Koren MJ 2012 91 152 14 31 0.9% 1.33 [0.88, 2.00] Raal F 2015(1) 124 220 53 109 2.7% 1.16 [0.93, 1.45] Raal F 2015(2) 12 33 10 16 0.5% 0.58 [0.32, 1.05] Roth EM 2012 32 61 19 31 1.0% 0.86 [0.70, 1.11] Stein EA 2012(1) 59 101 11 32 <	Ballantyne CM 2015	207	253	82	101	4.4%	1.01 [0.90, 1.13]	+
Dias CS 2012 57 85 19 28 1.1% 0.99 [0.74, 1.33] Guigliano RP 2012 277 474 71 157 4.0% 1.29 [1.07, 1.56] Hirayama A 2014 104 205 39 102 2.0% 1.33 [1.00, 1.76] Jennifer G 2015 1255 1553 650 788 32.6% 0.98 [0.94, 1.02] Koren MJ 2012 136 271 67 135 3.4% 1.01 [0.82, 1.24] Koren MJ 2012 136 271 67 135 3.4% 1.01 [0.82, 1.24] Koren MJ 2012 136 271 67 135 3.4% 1.01 [0.82, 1.24] Koren MJ 2012 91 152 14 31 0.9% 1.33 [0.88, 2.00] Raal F 2015(1) 124 220 53 109 2.7% 1.16 [0.93, 1.45] Raal F 2015(2) 12 33 10 16 0.5% 0.58 [0.32, 1.05] Roth EM 2012 32 61 19 31 1.0% 0.86 [0.59, 1.24] Roth EM 2014 36 52 40	Blomv DJ 2014	448	599	224	302	11.2%	1.01 [0.93, 1.09]	+
Guigliano RP 2012 277 474 71 157 4.0% 1.29 [1.07, 1.56] Hirayama A 2014 104 205 39 102 2.0% 1.33 [1.00, 1.76] Jennifer G 2015 1255 1553 650 788 32.6% 0.98 [0.94, 1.02] Koren MJ 2012 136 271 67 135 3.4% 1.01 [0.82, 1.24] Koren MJ 2012 91 152 14 31 0.9% 1.33 [0.88, 2.00] Raal F 2012 69 111 33 56 1.7% 1.05 [0.81, 1.37] Raal F 2015(1) 124 220 53 109 2.7% 1.16 [0.93, 1.45] Raal F 2015(2) 12 33 10 16 0.5% 0.58 [0.32, 1.05] Robinson JG 2014 406 1117 308 779 13.7% 0.92 [0.82, 1.03] Roth EM 2012 32 61 19 31 1.0% 0.86 [0.59, 1.24] Roth EM 2014 36 52 40 51 1.5% 0.88 [0.70, 1.11] Stein EA 2012(2) 50 62 9	Cannon CP 2015	341	479	162	241	8.1%	1.06 [0.95, 1.18]	
Hirayama A 2014 104 205 39 102 2.0% 1.33 [1.00, 1.76] Jennifer G 2015 1255 1553 650 788 32.6% 0.98 [0.94, 1.02] Koren MJ 2012 136 271 67 135 3.4% 1.01 [0.82, 1.24] Koren MJ 2014 134 306 138 308 5.2% 0.98 [0.82, 1.17] McKenney JM 2012 91 152 14 31 0.9% 1.33 [0.88, 2.00] Raal F 2012 69 111 33 56 1.7% 1.05 [0.81, 1.37] Raal F 2015(1) 124 220 53 109 2.7% 1.16 [0.93, 1.45] Raal F 2015(2) 12 33 10 16 0.5% 0.58 [0.32, 1.05] Roth EM 2012 32 61 19 31 1.0% 0.88 [0.70, 1.11] Stein EA 2012(1) 59 101 11 32 0.6% 1.70 [1.02, 2.82] Stein EA 2012(2) 50 62 9 15 0.5% 1.34 [0.87, 2.07] Stroes E 2014 135 205 74	Dias CS 2012	57	85	19	28	1.1%	0.99 [0.74, 1.33]	
Jennifer G 2015 1255 1553 650 788 32.6% 0.98 [0.94, 1.02] Koren MJ 2012 136 271 67 135 3.4% 1.01 [0.82, 1.24] Koren MJ 2014 134 306 138 308 5.2% 0.98 [0.94, 1.02] McKenney JM 2012 91 152 14 31 0.9% 1.33 [0.88, 2.00] Raal F 2012 69 111 33 56 1.7% 1.05 [0.81, 1.37] Raal F 2015(1) 124 220 53 109 2.7% 1.16 [0.93, 1.45] Raal F 2015(2) 12 33 10 16 0.5% 0.58 [0.32, 1.05] Robinson JG 2014 406 1117 308 779 13.7% 0.92 [0.82, 1.03] Roth EM 2012 32 61 19 31 1.0% 0.86 [0.59, 1.24] Roth EM 2014 36 52 40 51 1.5% 0.88 [0.70, 1.11] Stein EA 2012(2) 50 62 9 15 0.5% 1.34 [0.87, 2.07] Stroes E 2014 135 205 74	Guigliano RP 2012	277	474	71	157	4.0%	1.29 [1.07, 1.56]	_
Koren MJ 2012 136 271 67 135 3.4% 1.01 [0.82, 1.24] Koren MJ 2014 134 306 138 308 5.2% 0.98 [0.82, 1.17] McKenney JM 2012 91 152 14 31 0.9% 1.33 [0.88, 2.00] Raal F 2012 69 111 33 56 1.7% 1.05 [0.81, 1.37] Raal F 2015(1) 124 220 53 109 2.7% 1.16 [0.93, 1.45] Raal F 2015(2) 12 33 10 16 0.5% 0.58 [0.32, 1.05] Robinson JG 2014 406 1117 308 779 13.7% 0.92 [0.82, 1.03] Roth EM 2012 32 61 19 31 1.0% 0.86 [0.59, 1.24]	Hirayama A 2014	104	205	39	102	2.0%	1.33 [1.00, 1.76]	
Koren MJ 2014 134 306 138 308 5.2% 0.98 [0.82, 1.17] McKenney JM 2012 91 152 14 31 0.9% 1.33 [0.88, 2.00] Raal F 2012 69 111 33 56 1.7% 1.05 [0.81, 1.37] Raal F 2015(1) 124 220 53 109 2.7% 1.16 [0.93, 1.45] Raal F 2015(2) 12 33 10 16 0.5% 0.58 [0.32, 1.05] Robinson JG 2014 406 1117 308 779 13.7% 0.92 [0.82, 1.03] Roth EM 2012 32 61 19 31 1.0% 0.86 [0.59, 1.24] Roth EM 2014 36 52 40 51 1.5% 0.88 [0.70, 1.11] Stein EA 2012(1) 59 101 11 32 0.6% 1.70 [1.02, 2.82]	Jennifer G 2015	1255	1553	650	788	32.6%	0.98 [0.94, 1.02]	•
McKenney JM 2012 91 152 14 31 0.9% 1.33 [0.88, 2.00] Raal F 2012 69 111 33 56 1.7% 1.05 [0.81, 1.37] Raal F 2015(1) 124 220 53 109 2.7% 1.16 [0.93, 1.45] Raal F 2015(2) 12 33 10 16 0.5% 0.58 [0.32, 1.05] Robinson JG 2014 406 1117 308 779 13.7% 0.92 [0.82, 1.03] Roth EM 2012 32 61 19 31 1.0% 0.86 [0.59, 1.24] Roth EM 2014 36 52 40 51 1.5% 0.88 [0.70, 1.11] Stein EA 2012(1) 59 101 11 32 0.6% 1.70 [1.02, 2.82] Stein EA 2012(2) 50 62 9 15 0.5% 1.34 [0.87, 2.07] Stroes E 2014 135 205 74 102 3.7% 0.91 [0.78, 1.06]	Koren MJ 2012	136	271	67	135	3.4%	1.01 [0.82, 1.24]	
Raal F 2012 69 111 33 56 1.7% 1.05 [0.81, 1.37] Raal F 2015(1) 124 220 53 109 2.7% 1.16 [0.93, 1.45] Raal F 2015(2) 12 33 10 16 0.5% 0.58 [0.32, 1.05] Robinson JG 2014 406 1117 308 779 13.7% 0.92 [0.82, 1.03] Roth EM 2012 32 61 19 31 1.0% 0.86 [0.59, 1.24] Roth EM 2014 36 52 40 51 1.5% 0.88 [0.70, 1.11] Stein EA 2012(1) 59 101 11 32 0.6% 1.70 [1.02, 2.82] Stein EA 2012(2) 50 62 9 15 0.5% 1.34 [0.87, 2.07] Stroes E 2014 135 205 74 102 3.7% 0.91 [0.78, 1.06] Sullivan D 2012 75 125 19 32 1.1% 1.01 [0.98, 1.04]	Koren MJ 2014	134	306	138	308	5.2%	0.98 [0.82, 1.17]	- + -
Raal F 2015(1) 124 220 53 109 2.7% 1.16 [0.93, 1.45] Raal F 2015(2) 12 33 10 16 0.5% 0.58 [0.32, 1.05] Robinson JG 2014 406 1117 308 779 13.7% 0.92 [0.82, 1.03] Roth EM 2012 32 61 19 31 1.0% 0.86 [0.59, 1.24] Roth EM 2014 36 52 40 51 1.5% 0.88 [0.70, 1.11] Stein EA 2012(1) 59 101 11 32 0.6% 1.70 [1.02, 2.82] Stein EA 2012(2) 50 62 9 15 0.5% 1.34 [0.87, 2.07] Stroes E 2014 135 205 74 102 3.7% 0.91 [0.78, 1.06] Sullivan D 2012 75 125 19 32 1.1% 1.01 [0.73, 1.39]	McKenney JM 2012	91	152	14	31	0.9%	1.33 [0.88, 2.00]	
Raal F 2015(2) 12 33 10 16 0.5% 0.58 [0.32, 1.05] Robinson JG 2014 406 1117 308 779 13.7% 0.92 [0.82, 1.03] Roth EM 2012 32 61 19 31 1.0% 0.86 [0.59, 1.24] Roth EM 2014 36 52 40 51 1.5% 0.88 [0.70, 1.11] Stein EA 2012(1) 59 101 11 32 0.6% 1.70 [1.02, 2.82] Stein EA 2012(2) 50 62 9 15 0.5% 1.34 [0.87, 2.07] Stroes E 2014 135 205 74 102 3.7% 0.91 [0.78, 1.06] Sullivan D 2012 75 125 19 32 1.1% 1.01 [0.73, 1.39]	Raal F 2012	69	111	33	56	1.7%	1.05 [0.81, 1.37]	
Robinson JG 2014 406 1117 308 779 13.7% 0.92 [0.82, 1.03] Roth EM 2012 32 61 19 31 1.0% 0.86 [0.59, 1.24] Roth EM 2014 36 52 40 51 1.5% 0.88 [0.70, 1.11] Stein EA 2012(1) 59 101 11 32 0.6% 1.70 [1.02, 2.82] Stein EA 2012(2) 50 62 9 15 0.5% 1.34 [0.87, 2.07] Stroes E 2014 135 205 74 102 3.7% 0.91 [0.78, 1.06] Sullivan D 2012 75 125 19 32 1.1% 1.01 [0.73, 1.39]	Raal F 2015(1)	124	220	53	109	2.7%	1.16 [0.93, 1.45]	
Roth EM 2012 32 61 19 31 1.0% 0.86 [0.59, 1.24] Roth EM 2014 36 52 40 51 1.5% 0.88 [0.70, 1.11] Stein EA 2012(1) 59 101 11 32 0.6% 1.70 [1.02, 2.82] Stein EA 2012(2) 50 62 9 15 0.5% 1.34 [0.87, 2.07] Stroes E 2014 135 205 74 102 3.7% 0.91 [0.78, 1.06] Sullivan D 2012 75 125 19 32 1.1% 1.01 [0.73, 1.39]	Raal F 2015(2)	12	33	10	16	0.5%	0.58 [0.32, 1.05]	
Roth EM 2014 36 52 40 51 1.5% 0.88 [0.70, 1.11] Stein EA 2012(1) 59 101 11 32 0.6% 1.70 [1.02, 2.82] Stein EA 2012(2) 50 62 9 15 0.5% 1.34 [0.87, 2.07] Stroes E 2014 135 205 74 102 3.7% 0.91 [0.78, 1.06] Sullivan D 2012 75 125 19 32 1.1% 1.01 [0.73, 1.39]	Robinson JG 2014	406	1117	308	779	13.7%	0.92 [0.82, 1.03]	
Stein EA 2012(1) 59 101 11 32 0.6% 1.70 [1.02, 2.82] Stein EA 2012(2) 50 62 9 15 0.5% 1.34 [0.87, 2.07] Stroes E 2014 135 205 74 102 3.7% 0.91 [0.78, 1.06] Sullivan D 2012 75 125 19 32 1.1% 1.01 [0.78, 1.04]	Roth EM 2012	32	61	19	31	1.0%	0.86 [0.59, 1.24]	
Stein EA 2012(2) 50 62 9 15 0.5% 1.34 [0.87, 2.07] Stroes E 2014 135 205 74 102 3.7% 0.91 [0.78, 1.06] Sullivan D 2012 75 125 19 32 1.1% 1.01 [0.73, 1.39] Total (95% Cl) 6464 3416 100.0% 1.01 [0.98, 1.04]	Roth EM 2014	36	52	40	51	1.5%	0.88 [0.70, 1.11]	
Stroes E 2014 135 205 74 102 3.7% 0.91 [0.78, 1.06] Sullivan D 2012 75 125 19 32 1.1% 1.01 [0.73, 1.39] Total (95% Cl) 6464 3416 100.0% 1.01 [0.98, 1.04]	Stein EA 2012(1)	59	101	11	32	0.6%	1.70 [1.02, 2.82]	
Sullivan D 2012 75 125 19 32 1.1% 1.01 [0.73, 1.39] Total (95% Cl) 6464 3416 100.0% 1.01 [0.98, 1.04]	Stein EA 2012(2)	50	62	9	15	0.5%	1.34 [0.87, 2.07]	
Total (95% Cl) 6464 3416 100.0% 1.01 [0.98, 1.04]	Stroes E 2014	135	205	74	102	3.7%	0.91 [0.78, 1.06]	
	Sullivan D 2012	75	125	19	32	1.1%	1.01 [0.73, 1.39]	
Total events 4048 2042	Total (95% CI)		6464		3416	100.0%	1.01 [0.98, 1.04]	+
	Total events	4048		2042				
Heterogeneity: $Chi^2 = 32.27$, df = 19 (P = 0.03); l ² = 41%	Heterogeneity: Chi ² = 3	32.27, df = ²	19 (P =	0.03); l ² =	= 41%			
Test for overall effect: $Z = 0.70$ (P = 0.48) 0.2 0.5 1 $2Favours [experimental] Favours [control]$	Test for overall effect:	Z = 0.70 (P	= 0.48)	,.				

Figure 13. Forest plot depicting the treatment-emergent adverse events of proprotein convertase subtilisin/kexin9 monoclonal antibodies.

gitis, upper respiratory tract infections, influenza, cough, headache, and so on. While none of these TEAEs is life threatening and the serious TEAEs were not increased more

than in the control group, more large RCTs are needed to further confirm the safety. Furthermore, there was also a low rate of TEAEs leading to discontinuation.

Experimental Control Risk Ratio							Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% Cl
Blomv DJ 2014	33	599	13	302	5.4%	1.28 [0.68, 2.40]	- -
Cannon CP 2015	90	479	43	241	17.7%	1.05 [0.76, 1.46]	-
Dias CS 2012	0	85	0	28		Not estimable	
Guigliano RP 2012	11	474	4	157	1.9%	0.91 [0.29, 2.82]	
Hirayama A 2014	4	205	0	102	0.2%	4.50 [0.24, 82.78]	
Jennifer G 2015	290	1553	154	788	63.3%	0.96 [0.80, 1.14]	–
Koren MJ 2012	3	271	0	135	0.2%	3.50 [0.18, 67.28]	
Koren MJ 2014	4	306	2	308	0.6%	2.01 [0.37, 10.91]	
McKenney JM 2012	3	152	1	31	0.5%	0.61 [0.07, 5.69]	· · · · ·
Raal F 2012	2	111	0	56	0.2%	2.54 [0.12, 52.12]	
Raal F 2015(1)	7	220	5	109	2.1%	0.69 [0.23, 2.14]	
Raal F 2015(2)	0	33	0	16		Not estimable	
Robinson JG 2014 23 1117 15				779	5.5%	1.07 [0.56, 2.04]	_
Roth EM 2012	1	61	0	31	0.2%	1.55 [0.06, 36.94]	·
Roth EM 2014	1	52	1	51	0.3%	0.98 [0.06, 15.26]	
Stroes E 2014	6	205	4	102	1.7%	0.75 [0.22, 2.59]	
Sullivan D 2012	4	125	0	32	0.2%	2.36 [0.13, 42.69]	
Total (95% Cl)		6048		3268	100.0%	1.01 [0.88, 1.17]	♦
Total events	482		242				
Heterogeneity: Chi ² =	5.00, df = 1	4 (P = 0	.99); l² =	0%			0.01 0.1 1 10 100
Test for overall effect:	Z = 0.17 (F	= 0.87)				Favours [experimental] Favours [control]	

Figure 14. Forest plots depicting the serious treatment-emergent adverse events of proprotein convertase subtilisin/kexin9 monoclonal antibodies.

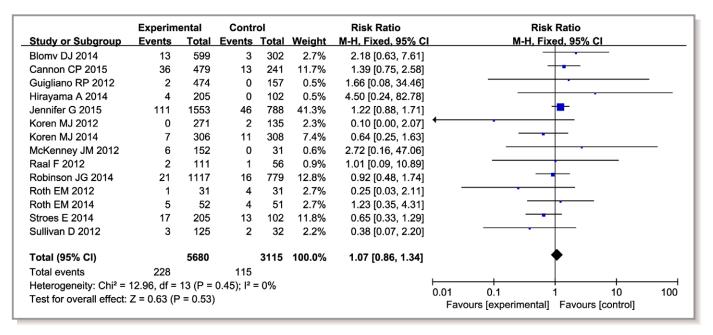


Figure 15. Forest plots depicting the treatment-associated withdrawal.

The causes of CVD are multifactorial, and one of its main risk factors is dyslipidemia. Current guidelines consequently identify TC and LDL-C level as the primary target for lipid-modifying therapy.^{3,44} Statins are by far the most effective lipid-lowering drugs to significantly decrease CVD risk by lowering LDL-C levels.^{45–47} The LDL-C goal is <70 mg/dL and/or a \geq 50% LDL-C reduction in very high CVD risk patients when the target levels cannot be reached.⁴⁸ In order to reach the goal, high-intensity statin therapy is recommended. High-intensity statin was confirmed to be safe and tolerable for most patients, but at least 10% of patients experienced side effects such as myalgia, muscle aches, weakness, or other symptoms. Therefore, some people are unwilling to continue their statin therapy.^{49–51} For these patients, alternative lipid-lowering therapy must be used to obtain their target LDL-C level.

Our meta-analysis revealed that PCSK9 inhibitor treatment received satisfactory lipid-modifying effects with acceptable safety in patients with familial or nonfamilial hypercholesterolemia. Although the current results are encouraging, some issues should be taken into consideration. First, the monoclonal antibody is injected subcutaneously, making it unattractive for long-term treatment. Second, some animal and cellular studies revealed that LDL-R can act as the entry point for some viruses, including hepatitis C virus. It is unknown whether PCSK9 inhibitors would increase the risk of hepatitis C virus infection.⁵² Finally, the main concern of hypercholesterolemia is the increased risk for atherosclerotic disease; it still remains unknown whether the reduced LDL-C with PCSK9 inhibitors can finally improve the clinical outcomes. In our meta-analysis, only Koren's²⁵ phase III clinical trial mentioned that there were no deaths or cardiovascular events in their

trial. Hopefully, some large multicenter RCTs are under investigation, which could provide more evidence to prove its long-term effect, safety, and clinical outcomes.53 In conclusion, PCSK9 inhibitors exert excellent effects on the lipid parameters in patients with familial or nonfamilial hypercholesterolemia even in combination with statin therapy. Given the fact that LDL-C reduction is correlated with reduced CVD mortality, PCSK9 inhibition could potentially be another attractive therapeutic option for CVD treatment. The study has some limitations. We observed significant heterogeneities across most of the reported outcomes, but we failed to reveal the heterogeneities by dividing subgroups or sensitivities methods. Therefore, caution should be used in interpreting the results of the meta-analysis when combining the heterogeneous data sets. Hopefully, more RCTs in progress could add new evidence to PSCK9 inhibitors investigations.

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Disclosures

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