Am J Transl Res 2023;15(1):452-465
www.ajtr.org /ISSN:1943-8141/AJTR0145181

Review Article

Can proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors regress coronary atherosclerotic plaque? A systematic review and meta-analysis

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Received July 7, 2022; Accepted December 16, 2022; Epub January 15, 2023; Published January 30, 2023

Abstract: Objective: Whether inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes the regression of coronary atherosclerotic plaque in statin-treated individuals remains unclear. This study examined whether PCSK9 inhibitors combined with statin therapy could increase atherosclerotic plaque regression compared with statin therapy alone. Methods: PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), the database Clinical trials, and the Web of Science were searched to report the coronary atherosclerotic plaque of PCSK9 inhibitors using intravascular ultrasonography (IVUS) or optical coherence tomography (OCT) in statin patients. The weighted mean difference (WMD) of the random-effects/fixed-effects model was used to pool data that satisfied our inclusion criteria obtained from the included studies. Results: When compared with statin therapy alone, pooled studies revealed that PCSK9 inhibitors combined with statin therapy significantly decreased percent atheroma volume (PAV) (WMD: -1.06%, 95% confidence interval [CI]: -1.39 to -0.73; P<0.001) and total atheroma volume (TAV) (WMD: -6.38 mm^3, 95% CI: -10.12 to -2.64; P=0.001). Moreover, the fibrous cap thickness (FCT) of the coronary atherosclerotic plaque increases to 21.31 um (WMD: 21.31, 95% CI: 7.08 to 35.53, P<0.001), and the maximum lipid arc decreases 10.9° (WMD: -10.9, 95% CI: -15.24 to -5.34, P<0.001). Conclusion: In our systematic review and meta-analysis, PCSK9 inhibitors combined with statin therapy were found to be more effective than statin therapy alone for slowing coronary plaque progression by decreasing PAV, TAV, and increasing FCT, maximum lipid arc.

Keywords: Coronary atherosclerotic plaque, PCSK9 inhibitors, OCT, IVUS

Introduction

Lowering low-density lipoprotein cholesterol (LDL-C) with statins among coronary artery disease (CAD) patients have been proven in numerous trials to considerably reduce the progression of coronary plaque [1-4], increase the fibrous cap thickness (FCT) to reduce plaque vulnerability [5, 6], and contribute to lower cardiovascular morbidity and mortality [7, 8]. An increase in FCT coupled with plaque regression is thought to be the main mechanism for plaque stabilization. However, a substantial proportion of patients are unable to tolerate high-intensity statin therapy and do not obtain a sufficient decrease in LDL-C levels, which is associated with major adverse reactions, severely limiting the use of maximally tolerated statin therapy [9] and leading to residual cardiovascular risk [10]. Thus, it is urgent to develop an innovative lipid-lowering drug to achieve the goal of lipid levels to reduce cardiovascular events. PCSK9, an enzyme predominantly produced in the liver, binds to the LDL receptor (LDLR) present on the surface of the hepatocytes, induces the degradation of LDLR, and increases plasma LDL-C levels [11, 12]. In addition, as a target of the sterol regulatory element-binding protein (SREBP)-2, the PCSK9 gene expression is enhanced in statin-treated patients via the SREBP-2 pathway, hence weakening the LDL-lowering benefits of HMG-CoA reductase inhibitors. Therefore, combining a PCSK9 inhibitor with a statin leads to an additive (or even synergetic) effect on LDL-C levels, hence minimizing

this undesirable compensatory function [11, 12]. PCSK9 inhibitors (alirocumab and evolocumab) are novel lipid-lowering agents that perform by inhibiting PCSK9, resulting in an increase in LDLR number and rapid and profound decrease in LDL-C levels by a further 50-60% and a lower risk of cardiovascular events [13-15]. For patients with CAD, PCSK9 inhibitors have recently been found to be superior to statin monotherapy for regressing and stabilizing coronary atherosclerosis [16, 17]. However, there is an insufficient number of patients who participated in the study of PCSK9 inhibitors. In addition, the evidence related to the regression of coronary atherosclerotic plaque burden with PCSK9 inhibitors is contradictory and inconclusive [16, 18]. Accordingly, systematic reviews and meta-analyses were conducted to determine whether PCSK9 inhibitors were more effective with regression than statins in coronary atherosclerotic plaques as evaluated by intravascular ultrasonography (IVUS) or optical coherence tomography (OCT).

Methods

Search strategy

This meta-analysis was carried out by the statement on Preferred Reporting Items for Systematic Reviews and Meta-Analyses [19]. Databases searched comprised PubMed, the Cochrane Library, and the Web of Science up to April 2022, with English constraints. The search Medical Subject Headings (MeSH) were "coronary artery disease", "Alirocumab", "Evolocumab", "PCSK9 inhibitor(s)", and optical coherence tomography (OCT), and "intravascular ultrasonography (IVUS)".

The following criteria were utilized to determine inclusion: (a) studies included adult patients over the age of 18 with a diagnosis of CAD or known coronary atherosclerosis. (b) studies comparing PCSK9 inhibitors in combination with statin to statin monotherapy therapy including baseline and follow-up data on percent atheroma volume (PAV), total atheroma volume (TAV), fibrous cap thickness (FCT), and maximum lipid arc. The following criteria were used to exclude candidates: papers were abstracts, reviews, letters to editors, case reports, meta-analyses, or unpublished full-text clinical trials; and insufficient endpoint data were available.

Data collection and extraction

Two authors independently evaluated all titles and abstracts, and entire papers from studies that met the inclusion criteria were received for review. Any discrepancies between the writers were discussed.

Two independently authored (Wu and Gao) articles were used to extract data from the full text. Any disputes were handled either through debate until consensus was attained or through consultation with the senior author (Lin). Each trial's data source included the following: author identification, publication year, the language of publication, study design, study population, patient characteristics, statin type and dose, follow-up duration, coronary risk factors, and intracoronary imaging findings including TAV, PAV, FCT and maximum lipid arc. The primary outcome was the pre-post intervention change in PAV. The secondly outcome was the pre-post intervention change in TAV, FCT, and maximum lipid arc. In addition, the pre-post change of lipid levels was evaluated following the administration of PCSK9 inhibitors.

Quality assessment

Separately, The Cochrane Collaboration Risk of Bias tool was used to assess the risk of bias [20], which assessed the following characteristics: random sequence generation (selection bias), concealment of allocation (selection bias), blinding of participants and employees (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias (**Table 1**).

Data analysis

Stata version 14.0 (Stata Corp. College Station, TX) was used to perform data analysis. Random or fixed effects were used to express continuous outcomes for PAV, TAV, FCT, and lipid levels using WMD with 95% CI. When data were described as the median and interquartile range (IQR) rather than the mean and standard deviation (SD), we calculated the mean and SD based on the study by Luo D et al. and Wan X et

Table 1. Risk of bias assessments for the studies included

Study Name	Random Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective reporting	Other bias	Quality grade
GLAGVO [16]	low	low	low	low	low	low	A
ODYSSEY J [18]	low	low	high	low	low	low	A
PACMAN-AMI [25]	low	low	low	low	low	low	A
HUYGENS [24]	low	low	low	low	low	low	A
Yano [17]	high	high	high	low	low	low	C
ALTAIR [26]	low	low	low	No clear	No clear	No clear	B
Gao [23]	low	high	high	low	low	low	B

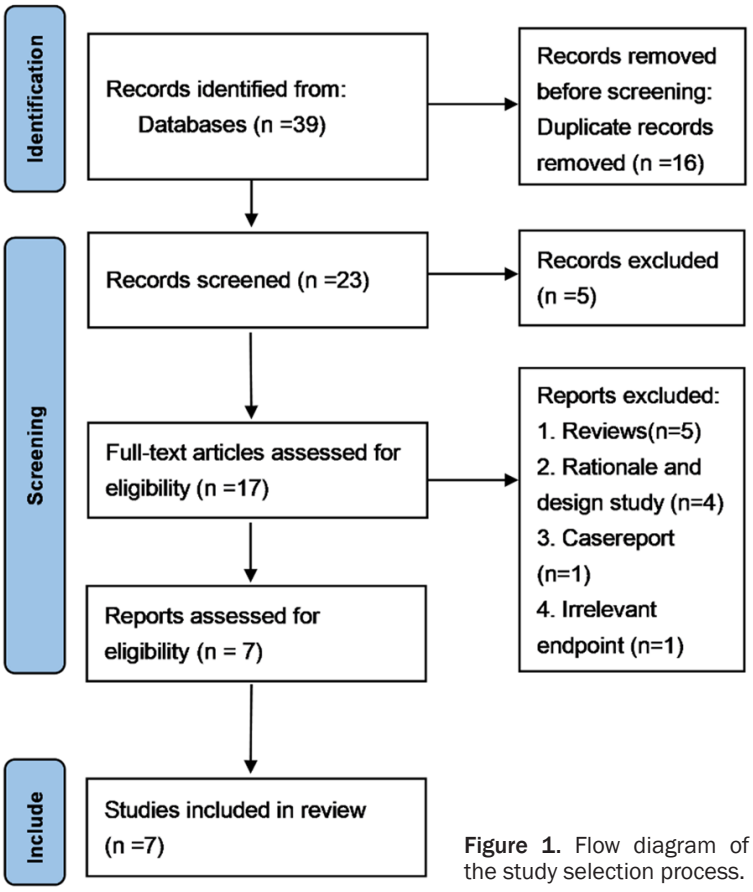

Figure 1. Flow diagram of the study selection process.

Results

Study selection and characteristics

A total of 39 studies were obtained from the searched databases. After screening the title and abstract, 16 duplicates have been removed and 7 studies were excluded since they did not satisfy the inclusion criteria. After another careful review, 15 full-text papers were assessed. Finally, seven trials [16-18, 23-26] evaluating coronary atherosclerotic plaque utilizing OCT and IVUS imaging techniques were selected for this meta-analysis (**Figure 1**). The characteristics of the included studies are presented in **Tables 2** and **3**. Four eligible studies reported changes in PAV and TAV using IVUS [16, 18, 24, 25], while the five studies evaluated FCT with OCT [17, 23-26] between baseline and follow-up. The data of maximum lipid arc was provided in the three studies included [16, 17, 23]. The studies were reported between 2016 and 2022, the sample sizes ranged from 24 to 968. Of them, the ODYSSEY J study and the study conducted by Gao et al. [23] were open-label randomized controlled trials (RCTs). The GLAGOV, PACMAN-AMI, and HUYGENS studies were randomized, multicenter, double-blind trials [16, 24, 25]. Yet, the study reported by Yano et al. [17] was a retrospective, non-randomized, observational, single-center study. In the in-

al. [21, 22]. The I^2 statistic was calculated to quantify heterogeneity and inconsistency between trials. I^2<25% was considered as low heterogeneity, 25%<I^2<50% as moderate, and I^2≥50% as high heterogeneity. By examining the overlap of CIs, the trim-and-fill method was used to screen for suspected publication bias. Sensitivity analysis was performed on the included studies to determine whether or not excluding studies based on different criteria would influence the result.

Table 2. Characteristics of the included studies

Study	Year	Study design	Number (P/C)	PCSK9-inhibitors	Control	Clinical presentation	Follow-up (weeks)
GLAGVO [16]	2016	RCT	484/484	Evolocumab 420 mg qm + Statin	Statin + Placeo	CAD	78
ODYSSEY J [18]	2019	RCT	93/89	Alirocumab 75/150 mg q2w + Statin (Atorvastatin ≥10 mg qd or Rosuvastatin ≥5 mg qd)	Atorvastatin ≥10 mg qd or Rosuvastatin ≥5 mg qd	ACS	36
PACMAN-AMI [25]	2022	RCT	148/152	Alirocumab 150 mg q2w + Rosuvastatin 20 mg qd	Rosuvastatin 20 mg qd + Placebo	AMI	52
HUYGENS [24]	2021	RCT	80/81	Evolocumab 420 mg qm + atorvastatin ≥40 mg	Placebo + atorvastatin ≥40 mg	NSTEMI	48
Yano [17]	2020	Not RCT	18/40	Evolocumab 140 mg q2w + Rosuvastatin 5 mg qd	Rosuvastatin 5 mg qd	ACS	12
ALTAIR [26]	2020	RCT	12/12	Alirocumab 75 mg q2w + Rosuvastatin 10 mg qd	Rosuvastatin 10 mg qd	CAD or ACS	36
Gao [23]	2021	RCT	30/31	Alirocumab 75 mg q2w + Atorvastatin 20 mg qd or Rosuvastatin 10 mg qd	Atorvastatin 20 mg qd or Rosuvastatin 10 mg qd	CAD or ACS	36

RCT: Randomized Clinical Trial; ACS: Acute Coronary Syndrome; AMI: Acute Myocardial Infarction; CAD: Coronary Artery Disease; NSTEMI: Non-ST-Segment Elevation Myocardial Infarction; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; C: Control arm; P: PCSK9-Inhibitors Arm.

Table 3. Subject characteristics

Study	Male N (%)	Age (year)	diabetes mellitus	hypertension	Smoker	ACEI/ARB	β-blocker	DAPT	Target vessel		
									LAD	LCX	RCA
GLAGVO [16]	699 (72%)	59.8	202 (20.8%)	803 (83%)	237 (24.5%)	703 (72.6%)	732 (75.6%)	919 (95%)	NR	NR	NR
ODYSSEY J [18]	146 (80%)	61	58 (31.9%)	127 (69.8%)	NR	NR	NR	180 (99%)	84 (46.2%)	34 (19.2%)	59 (32.4%)
PACMAN-AMI [25]	243 (82%)	58.5	30 (10%)	140 (43.3%)	143 (47.3%)	250 (83.3%)	242 (80.7)	294 (98%)	NR	NR	NR
HUYGENS [24]	118 (72%)	60.5	27 (16.7%)	78 (48.4%)	95 (59%)	140 (89%)	136 (84.5%)	160 (98.8%)	60 (37.6%)	45 (28.3%)	54 (33.7%)
Yano [17]	45 (77%)	65	23 (40%)	41 (71%)	23 (40%)	35 (60%)	8 (14%)	58 (100%)	21 (36%)	11 (19%)	26 (45%)
ALTAIR [26]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gao [23]	43 (70%)	61	15 (25%)	36 (59%)	17 (28%)	38 (62%)	56 (92%)	61 (100%)	26 (43%)	15 (25%)	19 (31%)

N: Numbers; ACEI: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker; LAD: Left Anterior Descending; LCX: Left Circumflex; RCA: Right Coronary; DAPT: Dual Antiplatelet Therapy.

cluded studies, the mean age of the patients was 58.5-65 years, and 70%-82% of patients were male. The follow-up period lasted between 12 and 78 weeks.

The primary outcomes: PAV

Figure 2A illustrates the outcome of the fixed-effects model (I^2=28%) for changing PAV by utilizing IVUS in four included studies [16, 18, 24, 25]. The absolute change in PAV between baseline and follow-up was reported by 765 patients in the PCSK9 inhibitors group (statin plus PCSK9 inhibitors) and 764 patients in the respective control arms (statin monotherapy). When PCSK9 inhibitors are added to statin therapy, the PAV decreases considerably compared to statin therapy alone (WMD: -1.06%, 95% CI: -1.39 to -0.73; P<0.001; I^2=28%).

The second outcome: TAV

Figure 2B depicts the outcome of the random-effects model (I^2=65%) for changing TAV analyzed using IVUS in four included studies [16, 18, 24, 25]. Accordingly, 299 patients receiving PCSK9 inhibitors plus statin and 270 patients receiving statin monotherapy reported an absolute change in TAV between baseline and follow-up. PCSK9 inhibitors in combination with statins reduced TAV considerably (WMD: -6.38 mm^3, 95% CI: -10.12 to -2.64; P=0.001; I^2=65%). It should be noted that significant heterogeneity (I^2=65%) was observed among these studies. A sensitivity analysis was used to identify the potential sources of heterogeneity (**Figure 3B**). In the leave-one-out analysis by omitting one study in turn, the overall combined WMD did not change substantially, with a range from -4.14 (95% CI: -6.27 to -2.01) to -7.53 (95% CI: -13.74 to -1.31), and I^2 varied from 1% to 76%. Therefore, none of the individual studies significantly influenced the overall result.

The second outcome: FCT

Figure 2C below illustrates the outcome of the random-effects model (I^2=75%) for changing FCT measured by OCT between baseline and follow-up reported by 299 patients in the PCSK9 inhibitors group and 270 patients in the statin monotherapy group in five included trials [17, 23-26]. Overall, when compared to statin therapy, the combination of PCSK9 inhibitors and statin therapy was consistently correlated with FCT evolution of coronary plaque (WMD: 21.31 um, 95% CI: 7.08 to 35.53, P<0.001; I^2=75%). However, several studies showed significant heterogeneity, so a sensitivity analysis was conducted (**Figure 3A**). With leave-one-out analysis, the overall combined result remained stable despite omitting one study in turn, ranging from 16.65 (95% CI: 5.05 to 28.24) to 26.37 (95% CI: 5.79 to 41.56), and I^2 varied from 46 to 81%, without individual studies significantly influencing the overall outcome.

The outcome of maximum lipid arc

The pooling of the 3 studies [17, 23, 24] including 280 patients with maximum lipid arc data measured by OCT (**Figure 2D**), reported a significant decrease in maximum lipid arc when CSK9 inhibitors plus statin therapy compared to the statin monotherapy (WMD: -10.9°, 95% CI: -15.24 to -5.34, P<0.001, I^2=6%).

Results of efficacy lipids

As compared to statin therapy alone, PCSK9 inhibitors combined with statin therapy resulted in significant reductions in total cholesterol (TC), LDL-C, apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C) and lipoprotein a (LP(a)); moreover, apolipoprotein A1 (Apo A1) and high-density lipoprotein cholesterol (HDL-C) levels were also significantly elevated (**Table 4**).

Publication bias

The trim-and-fill method indicated a low possibility of publication bias for PAV and TAV was assessed in the included studies (P>0.05). Nevertheless, there is potential publication bias in FCT, but the results remain robust after trimming and filing the data (no trimming performed and data unchanged).

Discussion

This is the first systematic review and meta-analysis that evaluated the influence of PCSK9 inhibitors on coronary atherosclerotic plaque in statin-treated individuals. The key finding of this meta-analysis was that utilizing PCSK9 inhibitors therapy was linked to a considerably higher reduction in PAV, TAV, and maximum

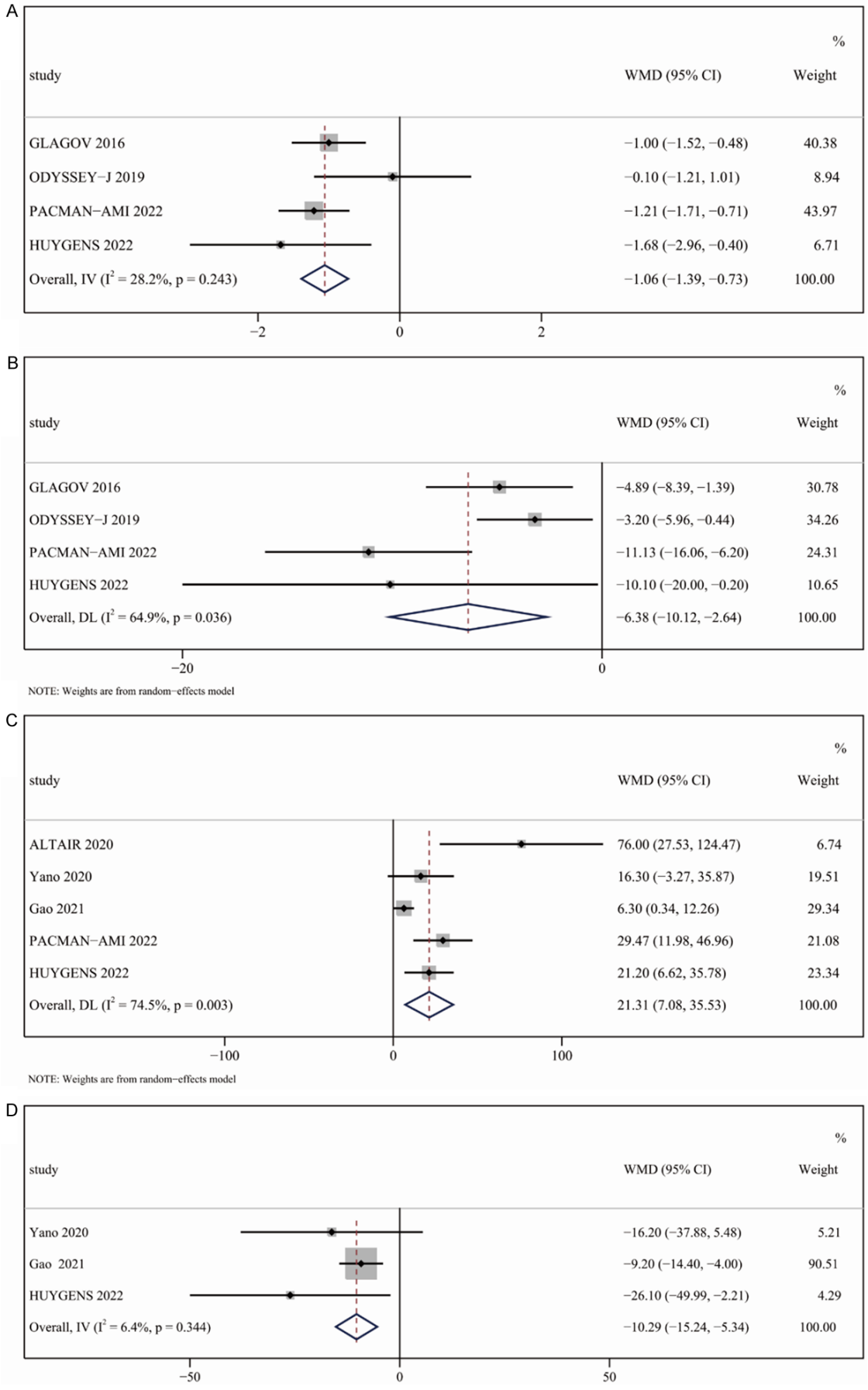
A
study
WMD (95% CI)
%
Weight
GLAGOV 2016
−1.00 (−1.52, −0.48)
40.38
ODYSSEY−J 2019
−0.10 (−1.21, 1.01)
8.94
PACMAN−AMI 2022
−1.21 (−1.71, −0.71)
43.97
HUYGENS 2022
−1.68 (−2.96, −0.40)
6.71
Overall, IV (I² = 28.2%, p = 0.243)
−1.06 (−1.39, −0.73)
100.00
−2
0
2
B
study
WMD (95% CI)
%
Weight
GLAGOV 2016
−4.89 (−8.39, −1.39)
30.78
ODYSSEY−J 2019
−3.20 (−5.96, −0.44)
34.26
PACMAN−AMI 2022
−11.13 (−16.06, −6.20)
24.31
HUYGENS 2022
−10.10 (−20.00, −0.20)
10.65
Overall, DL (I² = 64.9%, p = 0.036)
−6.38 (−10.12, −2.64)
100.00
−20
0
NOTE: Weights are from random−effects model
C
study
WMD (95% CI)
%
Weight
ALTAIR 2020
76.00 (27.53, 124.47)
6.74
Yano 2020
16.30 (−3.27, 35.87)
19.51
Gao 2021
6.30 (0.34, 12.26)
29.34
PACMAN−AMI 2022
29.47 (11.98, 46.96)
21.08
HUYGENS 2022
21.20 (6.62, 35.78)
23.34
Overall, DL (I² = 74.5%, p = 0.003)
21.31 (7.08, 35.53)
100.00
−100
0
100
NOTE: Weights are from random−effects model
D
study
WMD (95% CI)
%
Weight
Yano 2020
−16.20 (−37.88, 5.48)
5.21
Gao 2021
−9.20 (−14.40, −4.00)
90.51
HUYGENS 2022
−26.10 (−49.99, −2.21)
4.29
Overall, IV (I² = 6.4%, p = 0.344)
−10.29 (−15.24, −5.34)
100.00
−50
0
50

Figure 2. The forest plots (A-D) illustrate the effect of combination therapy (PCSK9 inhibitor plus statin) versus statin therapy on the changes in lipid volume and fibrous cap between baseline and follow-up. (A: Percent atheroma volume (PAV); B: Total atheroma volume (TAV); C: Fibrous cap thickness (FCT); D: Lipid arc).

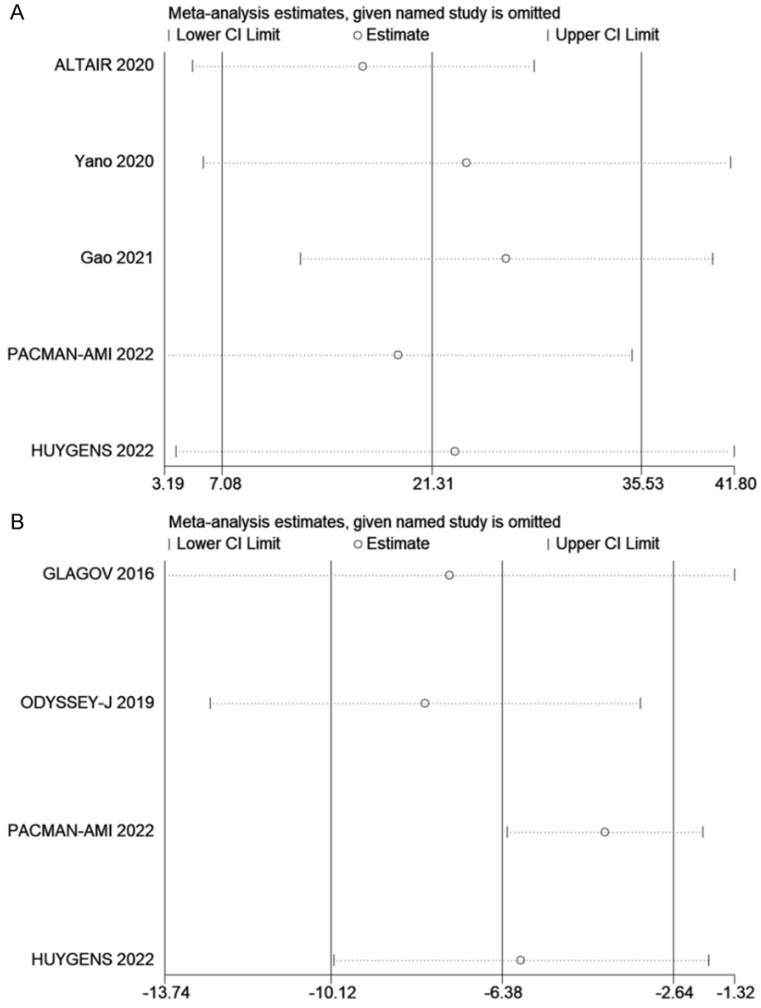

Figure 3. A, B. Illustrate the comparison of fibrous cap thickness (FCT) and total atheroma volume (TAV) between the combination therapy (PCSK9 inhibitor + statin) and the statin therapy (sensitivity analysis).

lipid arc, and a greater increase in FCT as measured by IVUS or OCT. In addition, we discovered that PCSK9 inhibitors increased levels of circulating Apo-A1, and HDL-C and decreased levels of circulating LDL-C, TC, TG, non-HDL-C, LP(a), and Apo B. The results of a systematic review and meta-analysis provide evidence that lower lipid levels in patients with CAD are linked to changes in the phenotype of coronary plaques that may reduce the propensity for rupture.

A previous study has shown that statins induce plaque stabilization by regressing plaque volume and fibrous cap thickening [27]. Patients with a higher plaque volume have a higher cardiovascular risk [28]. Serial IVUS demonstrated that intensive statins lower LDL-C levels, which lower plaque lipid content, stabilizing atherosclerotic plaque in a manner proportional to the reduction of lipids [1, 2]. There is significant evidence of a link between LDL-C levels, atherosclerotic plaque regression, and a reduction in cardiovascular events [8, 15, 29]. However, statin monotherapy results in small reductions in plaque volume (0.3%-1.2% per year) [30, 31], and a subgroup of patients does not achieve their LDL-C targets to achieve regression. Besides, non-HDL-C and triglyceride (TG) levels are considered to also be significant residual risk factors for cardiovascular disease (CVD) [32, 33]. Therefore, new drugs or combination therapies may provide additional benefits in regressing atherosclerosis and reducing the "residual risk" of coronary events. Studies that have been conducted with evinacumab (25 mg/kg/week) [34] and alirocumab (10 mg/kg/week) [35] as a monotherapy in APOE*3-Leiden cholesteryl ester transfer protein (CETP) mice, in which plasma levels of cholesterol and TG were both decreased (by 46% and 52%, respectively), and the size of atherosclerotic lesions was significantly reduced (by 88% and 39%, respectively). The study evaluated the effect of alirocumab and evinacumab in combination with atorvastatin as high-intensive lipid-lowering strategies on the regression of pre-existent atherosclerosis in APOE*3-Leiden. CETP mice [36], which showed atorvastatin reduced LDL-C by 27%, the double treatment of atorvastatin plus alirocumab or evinacumab reduced by

Table 4. Meta analysis results of other efficacy indicators

Lipids	Include studies	I^2	WMD	95% CI	P
LDL-C	6 [16-18, 23-25]	81.7%	-48.7	-55.9, -41.4	0.000
TC	4 [16-18, 24, 25]	79.5%	-53.6	-62.4, -44.7	0.000
ApoB	4 [16, 18, 24, 25]	63.8%	-38.9	-42.9, -34.9	0.000
Lp(a)	4 [16, 18, 24, 25]	73.1%	-7.0	-8.6, -5.3	0.000
Non-HDL-C	4 [16, 18, 24, 25]	81.1%	-59.1	-67.8, -50.4	0.000
TG	5 [16-18, 24, 25]	58.4%	-18.7	-28.2, -9.3	0.000
HDL-C	6 [16-18, 23-25]	0%	2.7	1.9, 3.6	0.000
Apo-A1	4 [16, 18, 24, 25]	0%	5.9	3.9, 7.8	0.000

LDL-C: Low-Density Lipoprotein Cholesterol; TC: Total Cholesterol; Apo B: Apolipoprotein B; Lp(a): Lipoprotein a; non-HDL-C: non-High-Density Lipoprotein Cholesterol; TG: Triglycerides; HDL-C: High-Density Lipoprotein Cholesterol; Apo A1: Apolipoprotein A1.

53% or 47%, and the triple treatment of atorvastatin plus alirocumab and evinacumab reduced by 73% respectively. Both of the studies revealed additional mechanisms of PCSK9 inhibitors reversing plaque [35, 36]. Firstly, by inhibiting the expression of intercellular adhesion molecule 1 (ICAM-1) on the endothelium of activated vessels and consequently reducing the adhesion of monocytes to the endothelium. Secondly, by inhibiting PCSK9, the levels of markers of vascular inflammation, such as T-cell abundance, macrophage content, necrotic content, and cholesterol clefts, were reduced [35, 36]. Finally, the double treatment (atorvastatin plus alirocumab or evinacumab) of APOE*3-Leiden CETP mice completely block the progression of preexistent atherosclerosis, and the triple treatment (atorvastatin plus alirocumab and evinacumab) regressed atherosclerosis in the thoracic aorta by 50% and the aortic root by 36%, making it a promising potential approach for treating atherosclerosis [36]. According to a series of randomized controlled studies, PCSK9 inhibitors appear to decrease LDL-C considerably more effectively than statins alone, leading to plaque volume reduction and possibly plaque reversion, as well as a thicker fibrous cap [16, 18, 23-25]. The GLAGOV trial showed that the evolocumab achieved lower LDL-C levels (36.6 mg/dL), a 0.95% regression in PAV, and a 5.8 mm^3 decrease in TAV as compared with the placebo group. Additionally, Evolocumab caused plaque regression a significantly higher percentage of patients than placebo (64.3% versus 47.3% for PAV and 61.5% versus 48.9% for TAV). The findings of this study provide the first evidence that a nonstatin LDL-C-lowering medication (Evolocumab) can slow the progression of the atherosclerotic disease using IVUS technology in humans [16]. However, according to the ODYSSEY J-IVUS study, normalized TAV and absolute PAV did not achieve statistical significance between alirocumab and SoC (standard of care) [18]. Due to this contradiction, a meta-analysis was conducted to gather convinced conclusive evidence. Finally, in our meta-analysis, the PCSK9 inhibitor plus statin therapy had a higher proportion of lower LDL-C levels (48.7 mg/l), PAV regression (1.09%), and TAV reduction (6.38 mm^3) than statin monotherapy, which indicated that LDL-C lowering has a positive effect on plaque regression, confirming the principle "the lower, the better". In addition, according to the PACMAN-AMI study, the mean change in PAV was -2.13% with alirocumab vs. -0.92% with placebo. Furthermore, alirocumab significantly reduced the maximum lipid core burden index (LCBI) within 4 mm in patients randomized to it in comparison to placebo (difference, -41.24), and a significantly greater increase in minimal FCT (difference, 29.65 μm). Ultimately, PCSK9 inhibitors provide a novel therapy for achieving lipid-lowering goals and have additive advantages over statins in terms of coronary plaque evolution, composition, and phenotype [25]. Considering that the severity and progression of coronary atherosclerosis are associated with adverse cardiovascular outcomes [37], a modest reduction in plaque volume with statins may not be enough to explain the reduced CVD risk, implying an important role in improving lesion stability [38].

Most atherosclerotic plaque ruptures occur in plaques with a substantial lipid pool and macrophage infiltration, which are capped by a thin fibrous cap smaller than 65 um, and which precipitate potentially fatal coronary events [39-41]. OCT is the most common imaging technique for assessing the FCT of coronary plaque in vivo, with a resolution of 10 times that of IVUS [42]. OCT studies have shown that statin therapy increased FCT in patients with CAD by lowering the plasma LDL-C level [43, 44], but the impact of PCSK9 inhibition on plaque phe-

notype has not been clarified. A study directed by Gao demonstrated the absolute changes in the maximum lipid arc (15.1° vs. 8.4°) and minimum FCT (18.0 μm vs. 13.2 μm) were significantly greater in the alirocumab group than in the SOC [23]. Similarly, the same outcome was observed in another study [17]. Additionally, the study also showed that the LDL-C reduction rate significantly correlated with the greater increased rate of FCT in the statin plus evolocumab groups [17]. Due to the relatively small sample size in these studies, we conducted a meta-analysis to gather more conclusive evidence. In view of the significant heterogeneity (I^2=75%), a sensitivity analysis of FCT was also conducted. The overall combined outcome remained stable despite omitting one study in turn, without individual studies significantly influencing the overall outcome. According to the combined analysis, combined treatment induced an increase in minimum FCT of 21.31 um and a decrease in maximum lipid arc of 10.9°. Additionally, analysis of the studies showed a significant decline in macrophage accumulation in patients receiving the combined treatment [17, 24, 25]. The present study showed that administration of PCSK9 inhibitors in combination with statin therapy provided an additional mechanism of stabilizing plaque by enhancing FCT and reducing the macrophage's infiltration.

In the present study, a combination of PCSK9 inhibitors with statin therapy also significantly decreased levels of circulating LDL-C (difference, -48.7) when compared with statin alone. In recent meta-analyses, PCSK9 inhibitor (alirocumab or evolocumab) resulted in a 75 mg/dL absolute reduction in LDL-C levels from baseline when compared to statins alone, consequently, has demonstrated clinical efficacy, leading to significant relative risk reductions in myocardial infarction by 20%, ischaemic stroke by 22%, and coronary revascularization by 17%, with favorable safety profile [45]. These findings show that the combination strategies involving a statin and non-statin agent (alirocumab or evolocumab) have been shown to promote coronary atherosclerosis regression and improve cardiovascular outcomes in patients with moderate-to-high cardiovascular risk.

The 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines recommend the addition of a PCSK9 inhibitor when patients with very-high cardiovascular risk are obtaining a maximum tolerated dosage of statin and ezetimibe or when patients with ACS are taking a maximum tolerated dosage of statin and ezetimibe after 4-6 weeks and are unable to accomplish their goals (an LDL-C reduction of more than 50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL)) [46]. Unfortunately, in clinical reality, the risk of recurrent ischemia episodes is greatest during the initial time following ACS [47]. Even worse, in a real-world study conducted across Europe, 5888 patients were enrolled in the DAVINCI study, and approximately one-fifth of patients with high/very high-risk primary and secondary prevention achieved the LDL-C goals of the 2019 ESC/EAS guidelines [48]. Likewise, in the HEYMANS study, the baseline serum LDL-C levels at evolocumab initiation were about triple the recommended guideline levels, which reflects a gap between clinical practice and guidelines [49]. Therefore, the early addition of PCSK9 inhibitors to statins allows patients whose levels of LDL-C remain uncontrolled despite previous high-intensity statin treatment or who may not achieve recommended treatment targets with such a strategy to achieve risk-based LDL-C goals more rapidly [50].

Numerous clinical trials have demonstrated that despite aggressive LDL-C reduction, atherosclerotic cardiovascular disease (ASCVD) risk persists regardless of statin, nonstatin, or combination therapy. Prospective cohort research involving 108,000 people in Copenhagen found that LDL-C levels and all-cause mortality exhibited a U-shaped relationship, with both high and low LDL-C levels associated with increased all-cause mortality risk [51]. Therefore, lipid levels should be assessed comprehensively rather than simply reducing LDL-C in those at high risk of cardiovascular disease. There is an association between serum levels of Lp a, TG, non-HDL-C, Apo B, and Apo A1 and cardiovascular events, which could be used as an alternative indicator to assess the risk and effectiveness of ASCVD [52-54]. As a result of the reduction in the very low-density lipopro-

tein-cholesterol (VLDL-C)/remnant lipoprotein levels of APOE*3-Leiden CETP mice mode, the dual treatment decreased by 83% with alirocumab and 87% with evinacumab, as compared to 45% with atorvastatin alone, and 93% with the triple treatment [36], It is consistent with previous human pharmacological studies that elevations in hepatic receptors could also remove remnant lipoproteins from the circulation [55]. Our meta-analysis found that PCSK9 inhibitors combined with statin therapy resulted in dramatic reductions in circulating levels of LDL-C, TC, non-HDL-C, Lp a, TG, and Apo-B levels, as well as increased levels of HDL-C and ApoA1, which was consistent with previous studies [15, 56, 57]. In addition, recent studies suggest PCSK9 inhibitors may have some anti-inflammatory properties [58]. This indicates that PCSK9 inhibitors are able to direct patient treatments to achieve optimal serum lipid management and reduce the "residual risk" of CVD.

Limitation

Some limitations were present in our meta-analysis. First of all, some of the included trials are not double-blinded RCTs or are not RCTs at all, which might affect the treatment outcomes. Second, different treatment regimens used different dosages and administration intervals, which resulted in clinical heterogeneity. Third, the follow-up period lasted between 12 and 78 weeks, which may interfere with the observation of changes in coronary plaques. There is a need for a longer follow-up in more trials to determine whether PCSK9 inhibitors will prove beneficial over time.

Conclusions

In our systematic review and meta-analysis, PCSK9 inhibitors combined with statin therapy were found to be more effective than statin therapy alone for regressing coronary plaque progression by decreasing PAV, TAV, and increasing FCT and maximum lipid arc. In the future, a larger number of RCTs with large samples will be required to determine the long-term effects of PCSK9 inhibitors on patients with coronary artery disease.

Disclosure of conflict of interest

None.

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