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Additive effects of ezetimibe, evolocumab, and alirocumab on plaque burden and lipid content as assessed by intravascular ultrasound

A PRISMA-compliant meta-analysis

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Abstract

Background: The additive effects of ezetimibe, evolocumab or alirocumab on lipid level, plaque volume, and plaque composition using intravascular ultrasound (IVUS) remain unclear.

Methods: According to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement, we performed a systematic review and meta-analysis of trials assessing the effects of ezetimibe, evolocumab, and alirocumab on coronary atherosclerosis using IVUS. The primary outcome was change in total atheroma volume (TAV), and the secondary outcomes were changes and differences in plaque composition and lipid content.

Results: Data were collected from 9 trials, involving 917 patients who received ezetimibe, evolocumab or alirocumab in addition to a statin and 919 patients who received statins alone. The pooled estimate demonstrated a significant reduction in TAV with the addition of ezetimibe and favorable effects of evolocumab and alirocumab on TAV. Subgroup analysis also supported favorable effects of evolocumab and alirocumab on TAV, according to baseline TAV, gender, type 2 diabetes mellitus, and prior stain use. Addition of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to statin therapy resulted in significant reductions in low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TG), but not in high-density lipoprotein cholesterol (HDL-C). The pooled estimate also showed significant favorable effects of ezetimibe on LDL-C, TC, and TG, but an insignificant effect on HDL-C. Patients who received ezetimibe showed similar changes in the necrotic core, fibro-fatty plaque, fibrous plaque, and dense calcification compared with patients not treated with ezetimibe.

Conclusions: The addition of ezetimibe to statin therapy may further reduce plaque and lipid burdens but may not modify plaque composition. Although current evidence supports a similar impact from the addition of PCSK9 inhibitors to statin therapy, more evidence is needed to confirm such an effect.

Abbreviations: CI = confidence interval, HDL = high-density lipoprotein, LDL-C = low-density lipoprotein cholesterol, PCSK9 = proprotein convertase subtilisin/kexin type 9, SMD = standardized mean difference, TAV = total atheroma volume, TC = total cholesterol, TG = triglycerides.

Keywords: alirocumab, evolocumab, ezetimibe, intravascular ultrasound, plaque

1. Introduction

Cardiovascular diseases, especially ischemic heart disease, remain the major cause of disease burden in the world.[1] Since 1990, the total number of disability-adjusted life years due to ischemic heart disease has steadily increased, reaching 182 million disability-adjusted life years with 9.14 million deaths in 2019.[2] The 2018 American College of Cardiology and American Heart Association cholesterol guidelines highlighted the addition of non-statins to statin therapy for patients at very high-risk risk of atherosclerotic cardiovascular disease when the low-density lipoprotein cholesterol (LDL-C) level remains ≥70 mg/dL (≥1.8 mmol/L).[3] In addition to the cornerstone lipid-lowering drugs statins, the use of ezetimibe, which targets the Niemann-Pick C1-like 1 intestinal cholesterol transporter protein as well as evolocumab and alirocumab, which target proprotein convertase subtilisin/kexin type 9 (PCSK9), leads to incremental lowering of LDL-C levels and a reduction in cardiovascular events.[4–6]

A thin cap fibroatheroma, referred to as an unstable or vulnerable plaque that is most frequently prone to rupture,

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Ethical approval was not required for this meta-analysis based on public literature.

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is characterized by an overlying thin fibrous cap and a large necrotic core.[7,8] A study based combining near-infrared spectroscopy and intravascular ultrasound showed that non-obstructive mild lesions with a heavy lipid content and high plaque burden are most likely to lead to a future major adverse cardiac event in patients after percutaneous coronary intervention for culprit and hemodynamic lesions.[9–11] Although the study did not endorse intensified pharmacotherapy for non-ischemic vulnerable plaques, the additive effect of non-statin therapy on lipid level and plaque burden needs to be determined.[12] Intravascular ultrasound can be used to image atherosclerotic plaques and measure atheroma burden and plaque dimensions.[13]

Two previous meta-analyses have assessed the effects of non-statin lipid-lowering therapy on atheroma volume using intravascular ultrasound,[14,15] but these studies did not evaluate the effect of such additive therapy on plaque composition or assess the influence of patients' baseline characteristics. Therefore, we performed the present meta-analysis to determine the additive effects of ezetimibe, evolocumab and alirocumab in combination with statins on lipid content and plaque volume and composition.

2. Methods

2.1. Systematic literature search

This study followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement.[16] As a Preferred Reporting Items for Systematic reviews and Meta-Analyses-compliant meta-analysis of published literature, no ethical approval was required for this study. Two independent and blinded reviewers searched for articles in MEDLINE via PubMed, Web of Science and Embase from 1966 through January 2021 using the terms "IVUS, intravascular ultrasound, virtual histology, ezetimibe, evolocumab, alirocumab, proprotein convertase subtilisin/kexin type 9, PCSK9." We also searched the bibliographies of retrieved articles, meta-analyses and systematic reviews. Additional data sources included conference proceedings from major meetings of the American College of Cardiology, European Society of Cardiology, American Heart Association, World Congress of Cardiology and Transcatheter Cardiovascular Therapeutics. We also directly contacted authors for additional information when necessary.

2.2. Study selection

Studies were included if they met the following prespecified criteria: clinical trials reported in peer-reviewed journals with fully available text; studies assessing the additive effects of ezetimibe, evolocumab and alirocumab in comparison with statin therapy alone; primary outcome of change in total atheroma volume between baseline and follow-up; used IVUS to measure atheroma volume; and a minimal 3-month follow-up. Studies were excluded if they met any of the following exclusion criteria: did not have a group that received statin therapy only; did not provide primary outcome and the reported data were incomplete; or serial case and observational studies.

2.3. Data extraction

Two blinded reviewers independently assessed the eligibility of studies using a prespecified standardized form. Disagreements were adjudicated by consensus. Data extraction was completed by the same reviewer. The following information was extracted: study, year, sample size, age, gender, smoking, previous disease, drugs used, lipid level, IVUS outcomes.

2.4. Definition of primary and secondary outcomes

The primary outcome was the change in total atheroma volume (TAV) between baseline and follow-up. Secondary outcomes were: lipid content, including, high-density lipoprotein (HDL), LDL, total cholesterol (TC), and triglycerides (TG); plaque composition, including necrotic core, fibro-fatty plaque, fibrous plaque, and dense calcification; and change in TAV with treatment according to the baseline TAV, gender, type 2 diabetes mellitus, and statin use.

2.5. Risk of bias assessment

The methodological quality of the included studies was evaluated using the Cochrane Collaboration Risk of Bias tool.[17] The risk of bias was evaluated according to incomplete outcome data, selective reporting, blinding of participants and personnel, blinding of outcome assessment, random sequence generation, allocation concealment, and other biases, and each domain was rated as "low risk", "unclear risk", and "high risk".

2.6. Statistical analysis

Traditional meta-analyses were conducted for studies that assessed the additive effects of ezetimibe, evolocumab and alirocumab in comparison with a statin only in terms of plaque burden and lipid level. Standardized mean difference (SMD) with corresponding 95% confidence interval (CI) values were used for continuous outcomes. Heterogeneity was assessed by the Cochran's Q-statistic, and a P value < 0.01 was considered significant. In addition, heterogeneity was quantified using the I^2 test (range, 0%–100%).

An $I^2 > 50\%$ or a $P < .01$ on Q test indicated the existence heterogeneity among the included studies. A random effects model was used to synthesize data in case of heterogeneity. Publication bias was evaluated by funnel plots if there were ≥10 included studies. The meta-analysis was performed using Review Manager (RevMan), version 5.3 (Cochrane Collaboration, Oxford, UK) and Stata 14/MP (StataCorp, College Station, TX).

3. Results

3.1. Characteristics of the included studies

The initial search identified a total of 406 relevant articles. After 317 studies were excluded due to duplication, 125 studies remained after review of the title and abstract. Two studies were excluded due to the absence of the primary outcome.[18,19] Finally, nine studies involving 917 patients were included in the present meta-analysis, including 7 studies evaluating the additive effect of ezetimibe,[20–26] 1 study evaluating the additive effect of evolocumab[27] and 1 study evaluating the effect of alirocumab[28] on plaque burden and lipid levels (Supplemental File 1, http://links.lww.com/MD/H657, Table 1). Most patients included in the meta-analysis were men (72%–91%) and elderly (aged 55–71 years). Cardiovascular risk factors were common, including smoking, hypertension, and diabetes mellitus. The mean range for TC, HDL, LDL, and TG levels were 162 to 220, 92 to 159, 36 to 53, and 66 to 145 mg/mL, respectively (Table 2). The available information indicated that more than half patients were taking an angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor (Table 2). Eight of the nine studies were of moderate to high quality, while one study was of low quality due to its open label, non-randomized study design[25] (Supplemental Files 2–3, http://links.lww.com/MD/H658).

3.2. Meta-analysis of changes in TAV and lipid levels

The pooled estimate for evolocumab and alirocumab demonstrated a significant favorable effect of PCSK9 inhibitors on TAV as measured by IVUS (SMD: –3.63, 95%CI: –4.44, –2.83) with significant heterogeneity ($I^2 = 90.5\%$). The addition of a

Table 1

Characteristics of included studies.

Study	Intensive lipid-lowering treatment	Statin alone treatment	Country	Population	Design	Patients (n)	F/U (mo)
Nicholls (2016)	Statin + Evolucumab 420 mg	Statin + Placebo	United States	ACS	Double-blinded RCT	484/484	19.5
Ako (2019)	Statin + Alirocumab 75/150 mg Q2W	Statin	Japan	ACS	Open-label RCT	93/89	9
Kovarnik (2012)	Atorvastatin 80 mg + Ezetimibe 10 mg/d	Standard statin therapy	Czech Republic	SAP	Single-blinded RCT	42/47	12
Nakajima (2014)	Atorvastatin 20 mg + Ezetimibe 10 mg/d	Atorvastatin 20 mg/d	Japan	ACS	Open label non-randomized	50/45	6
Masuda (2015)	Rosuvastatin 5 mg + Ezetimibe 10 mg/d	Rosuvastatin 5 mg/d	Japan	SAP	Open label randomized	21/19	6
Tsujita (2015)	Atorvastatin + Ezetimibe 10 mg/d	Atorvastatin	Japan	ACS/SAP	Single blinded RCT	100/102	9-12
Hougaard (2016)	Atorvastatin 80 mg + Ezetimibe 10 mg/d	Atorvastatin 80 mg/d + Placebo	Denmark	ACS	Double-blinded RCT	43/44	12
Lee (2016)	Simvastatin 40 mg + Ezetimibe 10 mg/d	Pravastatin 20 mg	Korea	ACS	Open-label RCT	34/36	3
Hibi (2017)	Pitavastatin 2 mg + Ezetimibe 10 mg/d	Pitavastatin 2 mg/d	Japan	ACS	Open-label RCT	50/53	10

ACS = acute coronary syndrome, F/U = follow-up, RCT = randomized control trial, SAP = stable angina pectoris.

Table 2

Baseline demographics and characteristics in patients who received intensive lipid-lowering with a statin or statin alone.

Study	Patients (n)	Male (%)	Age (yr)	BMI (kg/m²)	Smoker (%)	HTN (%)	DM (%)	TC (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TG (mg/dL)	ACEi/ARB, (%)
Nicholls (2016)	484/484	72/72	60/60	29/30	26/23	82/84	20/22	166.1/166.2	92.6/92.4	46.7/45.4	117.0/124.5	72/74
Ako (2019)	93/89	80/81	62/61	25/25	NR	69/71	29/35	168.0/170.5	97.9/95.7	43.9/46.1	115.5/109.0	NR
Kovarnik (2012)	42/47	79/66	64/65	NR	68/62	81/85	29/28	193.3/177.9	119.9/104.4	46.4/46.4	65.7/65.7	75/66
Nakajima (2014)	50/45	80/84	64/61	24/25	64/69	70/69	32/40	NR	116.2/114.3	50.4/45.5	106.3/117.5	68/62
Masuda (2015)	21/19	91/84	64/70	25/24	43/21	62/90	52/42	204.4/194	131.8/123	53.1/47.1	129.7/144.9	10/16
Tsujita (2015)	100/102	78/78	66/67	25/25	20/32	75/66	29/30	177.3/172.7	109.8/108.3	41.1/40	114/116	73/63
Hougaard (2016)	43/44	91/82	55/57	27/27*	58/52	16/18	44/29	204.9/220.4	143.1/158.5	42.5/42.5	NR	9/9
Lee (2016)	34/36	79/75	61/59	NR	44/50	50/58	32/25	190.8/196.8	111.4/119.1	36.0/39.4	120.6/136.8	88/92
Hibi (2017)	50/53	82/77	63/63	NR	44/38	46/64	20/21	191/196	123/126	45/46	109/112	86/82

Data reported as Ezetimibe, Evolucumab, or Alirocumab + Statin/Statin alone.

ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, BMI = body mass index, DM = diabetes mellitus, HDL = high-density lipoprotein, HTN = hypertension, LDL, low-density lipoprotein, TC, total cholesterol, TG = triglycerides, yr = years, NR = not reported.

PCSK9 inhibitor to a statin resulted in a significant reduction in the absolute change between baseline and follow-up for LDL-C (SMD: −30.87, 95%CI: −39.29, −22.45), TC (SMD: −26.04, 95%CI: −36.49, −15.58), and TG (SMD: −3.19, 95%CI: −5.56, −0.82), but not HDL-C (SMD: −1.14, 95%CI: −10.76, 8.49) (Fig. 1).

In contrast, the meta-analysis of 7 studies demonstrated that addition of ezetimibe led to a significant reduction in TAV (SMD: −0.24, 95%CI: −0.40, −0.09) without heterogeneity (I^2 = 2.9%). The pooled estimate also showed a significant favorable effect of ezetimibe in terms of the difference at follow-up in lipid levels for LDL-C (SMD: −0.85, 95%CI: −1.07, −0.63), TC (SMD: −0.60, 95%CI: −0.78, −0.42), and TG (SMD: −1.23, 95%CI: −2.08, −0.39), but an insignificant effect on HDL-C (SMD: 0.06, 95%CI:−0.09, 0.21) (Fig. 2).

3.3. Treatment difference between the effect of evolocumab and alirocumab on TAV

Subgroup analysis showed favorable effects of evolocumab and alirocumab on total atheroma volume according to baseline TAV (<median: −1.07, 95%CI: −2.13, −0.01; ≥median: −1.14, 95%CI: −1.65, −0.62), gender (female: −1.48, 95%CI: −2.17, −0.79; male: −0.87, 95%CI:−1.29, −0.44), type 2 diabetes mellitus (with: −1.26, 95%CI: −2.03, −0.49; without: −1.03, 95%CI: −1.83, −0.23). The addition of a PCSK9 inhibitor led to regression of plaque (SMD: −1.01, 95%CI: −1.40, −0.63) in patients with prior stain use, but not in statin naïve patients (SMD: −0.94, 95%CI: −2.10, 0.23) (Fig. 3). The heterogeneity was significantly reduced in the subgroup for baseline TAV (I^2 = 11.2% vs 0%), gender (I^2 = 0% vs 0%), type 2 diabetes mellitus (I^2 = 0% vs 8.5%), and prior stain use (I^2 = 0% vs 0%).

3.4. Meta-analysis of changes in plaque composition

One study reported the additive effects of evolocumab on plaque composition, and two studies reported the additive effects of ezetimibe on plaque composition. Patients treated with ezetimibe showed similar changes in necrotic core (SMD: 0.04, 95%CI: −0.28, 0.35), fibro-fatty plaque (SMD: −.33, 95%CI−0.74, 0.08), fibrous plaque (−0.22 95%CI: −0.53, 0.10), and dense calcification (SMD: −0.12, 95%CI:−0.46, 0.22) compared with patients not treated with ezetimibe (Fig. 4). Evolocumab had no significant additional effect on the changes in fibrofatty plaque (−3.0 ± 1.0 vs−5.0 ± 1.0 mm^3; P = .49), fibrous plaque (−2.4 ± 0.6 mm^3 vs −3.0 ± 0.6 mm^3; P = .49), necrotic core (0.1 ± 0.5 mm^3 vs 0.6 ± 0.5 mm^3; P = .49), or dense calcification (0.6 ± 0.3 mm^3 vs 1.0 ± 0.3 mm^3; P = .49).[29]

4. Discussion

The present meta-analysis found significant reductions in plaque and lipid burdens in patients who received intensive lipid-lowering treatment with ezetimibe, evolocumab or alirocumab in addition to statin therapy. Subgroup analysis according to baseline total atheroma, gender, and type 2 diabetes mellitus also supported the favorable effect of the PCSK9 inhibitors on TAV. The GLAGOV study revealed that the addition of evolocumab in patients receiving statin therapy had a favorable effect on the progression of atherosclerotic plaques, while the ODYSSEY J-IVUS study found that addition of alirocumab resulted in a numerically greater but not statistically significant reduction in the TAV.[27,28] The lack of a statistically significant difference in the ODYSSEY J-IVUS study may have been due to its limited sample size, the short duration of the treatment period, and the increase in ezetimibe therapy that occurred in the standard care group.[28]

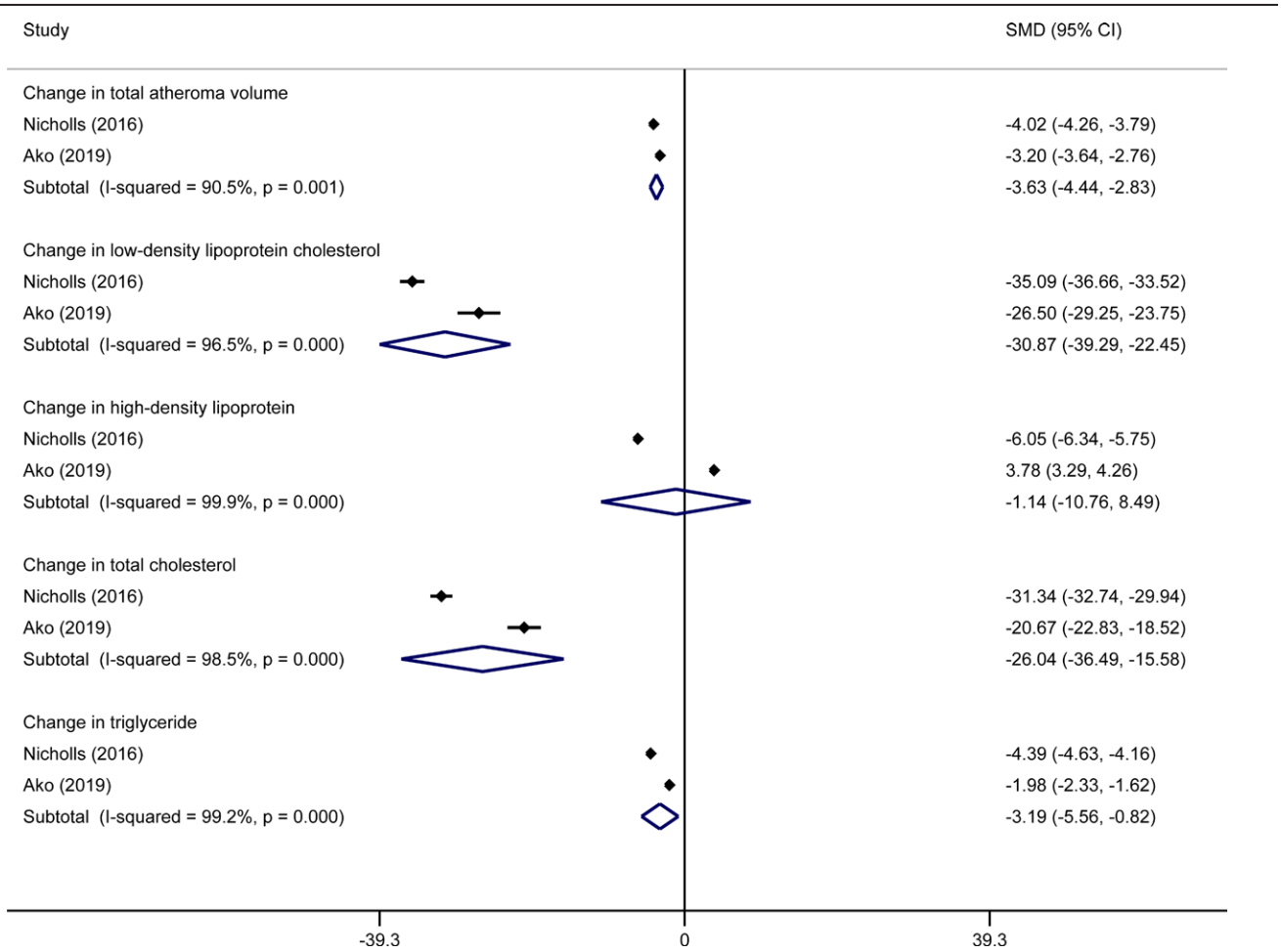

Figure 1. Effects of evolocumab and alirocumab on total atheroma volume and lipid levels. Lipids include low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, and triglycerides.

Addition of a PCSK9 inhibitor and ezetimibe to statin therapy further reduced LDL-C, TC, and TG level, but not HDL-C. Incremental lowering of LDL-C with ezetimibe, alirocumab and evolocumab was shown to improve cardiovascular outcomes in the IMPROVE-IT,[4] ODYSSEY LONG TERM[6] and FOURIER[5] studies. The clinical benefit of LDL-C lowering treatment have also been proven in patients aged 75 years and older.[30] Moreover, the Lipid Rich Plaque (LRP) study indicated that lipid-heavy plaques of non-culprit lesions are associated with subsequent major adverse coronary events in patients with known coronary artery disease.[11,31,32] Therefore, it is necessary to consider tight control of plaque and LDL-C levels by adding PCSK9 inhibitors and ezetimibe for the initiation of rapid and effective plaque modification.

Our findings showed that the addition of ezetimibe did not influence plaque composition, which is consistent with previous results for the addition of evolocumab.[29] In contrast, two meta-analyses showed that long-term and high-intensity statin treatment decreases fibrous tissue and increases dense calcification but does not induce significant changes in necrotic core and fibro-fatty plaque.[33,34] Evolocumab and ezetimibe promote favorable effects on lipid content and plaque atheroma and improve cardiovascular outcomes but fail to improve plaque composition as assessed by IVUS.[4,27,29] There may be two alternative explanations for the contradictory findings. On one hand, the spatial configuration rather than the amount of each type of plaque is the key factor in plaque vulnerability.[33] On the other hand, IVUS is unable to quantify the potential additional benefits of intensive lipid-lowering therapies and to reflect the plaque composition it is purported to measure.[29]

A previous meta-analysis showed that statin treatment induced higher regression of plaque volume in patients with acute coronary syndrome (ACS) than in patients with stable angina pectoris (SAP).[35] Future studies are needed to further investigate the difference in coronary plaque regression between patients with ACS and SAP who received ezetimibe, evolocumab or alirocumab in addition to statin therapy. Although ultrasound has been widely used in the quantification of plaque composition, atherosclerotic plaque composition assessed by computed tomography and magnetic resonance imaging might offer advanced plaque characterization.[36] Large-scale prospective studies are required to demonstrate the incremental value of advanced imaging approaches to plaque burden measurements. The degree of plaque change was associated with the percentage reduction in LDL-C, and no threshold level at which the LDL-C lowering benefit ceases has been established.[37] Although the IMPROVE-IT and FOURIER trials support the additional benefits of ezetimibe and evolocumab regardless of LDL-C levels,[4,38] future studies are required to investigate the effect ezetimibe and PCSK9 inhibitors on coronary plaque in addition to LDL-C levels.

Several limitations of the present study should be noted. First, we must be cautious in extrapolating findings from patients with clinical coronary disease to asymptomatic patients with subclinical atherosclerosis. Second, most composition analyses of plaque were pre-post comparisons of intensive lipid-lowering therapies, which make it difficult to dissect the natural

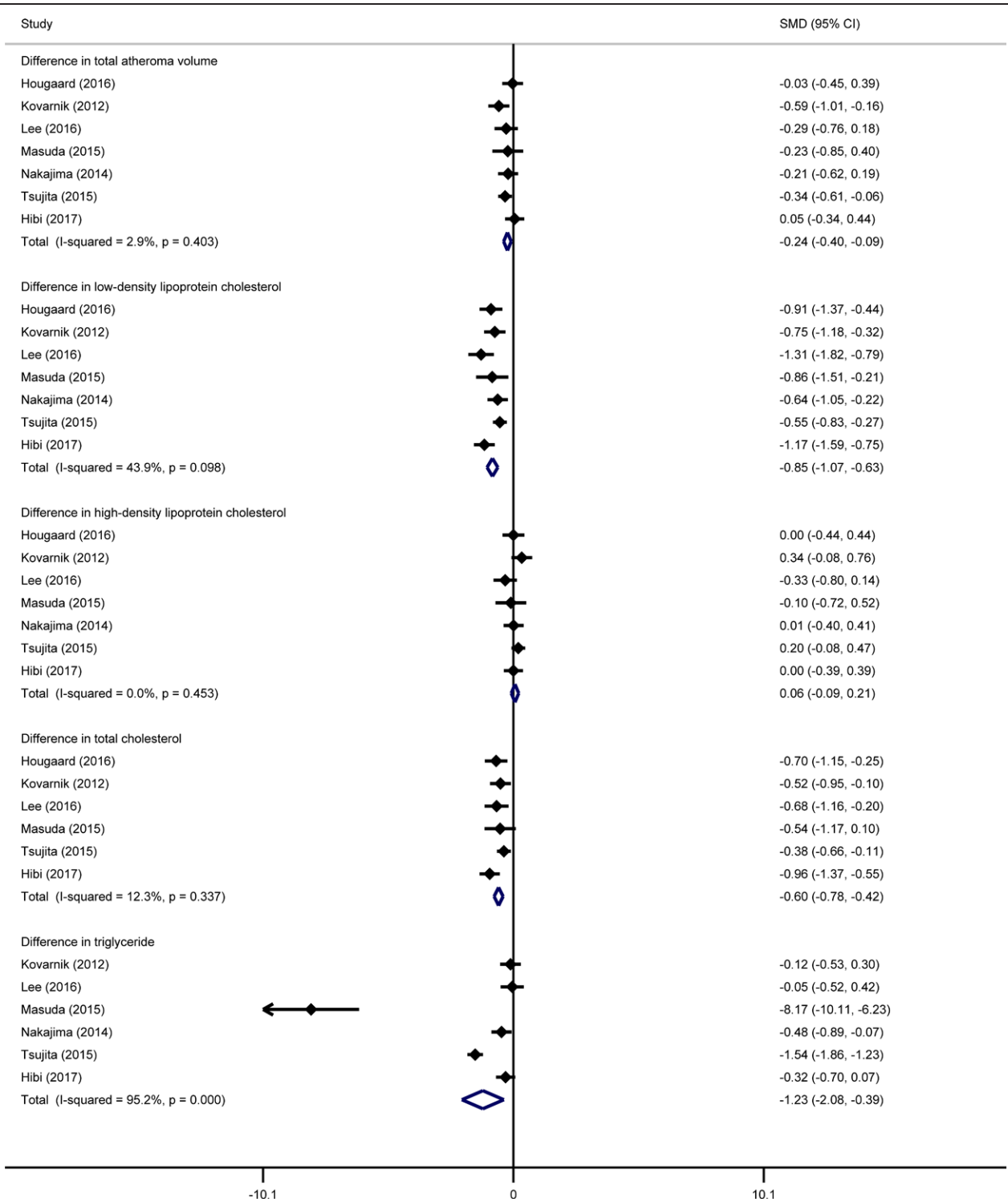

Figure 2. Effect of ezetimibe on total atheroma volume and lipid levels. Lipids include low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, and triglycerides.

progression of plaque composition.[33] Thus, the longitudinal change in plaque composition may be useful for assessing the effect of an intensive lipid-lowering strategy. Third, the lack of remarkable differences in plaque composition with addition of evolocumab and ezetimibe may reflect the potential challenges with measurement of plaque volume due to the generation of acoustic shadows and variable catheter position. Fourth, Hougaard et al provided median and range values for fibrofatty and fibrous plaque as well as dense calcification, which was excluded from the meta-analysis of plaque composition.[21] Fifth, only one study assessed the effect of evolocumab on plaque composition, and no study evaluated the influence of alirocumab on plaque composition. Sixth, only nine papers were included in this meta-analysis and only one study reported data for treatment with evolocumab and alirocumab. Finally, the included studies included patients with different demographics, comorbidities, and baseline drug use in addition to having different study designs and follow-up periods, contributing heterogeneity and possibly weakening the strength of the conclusions.

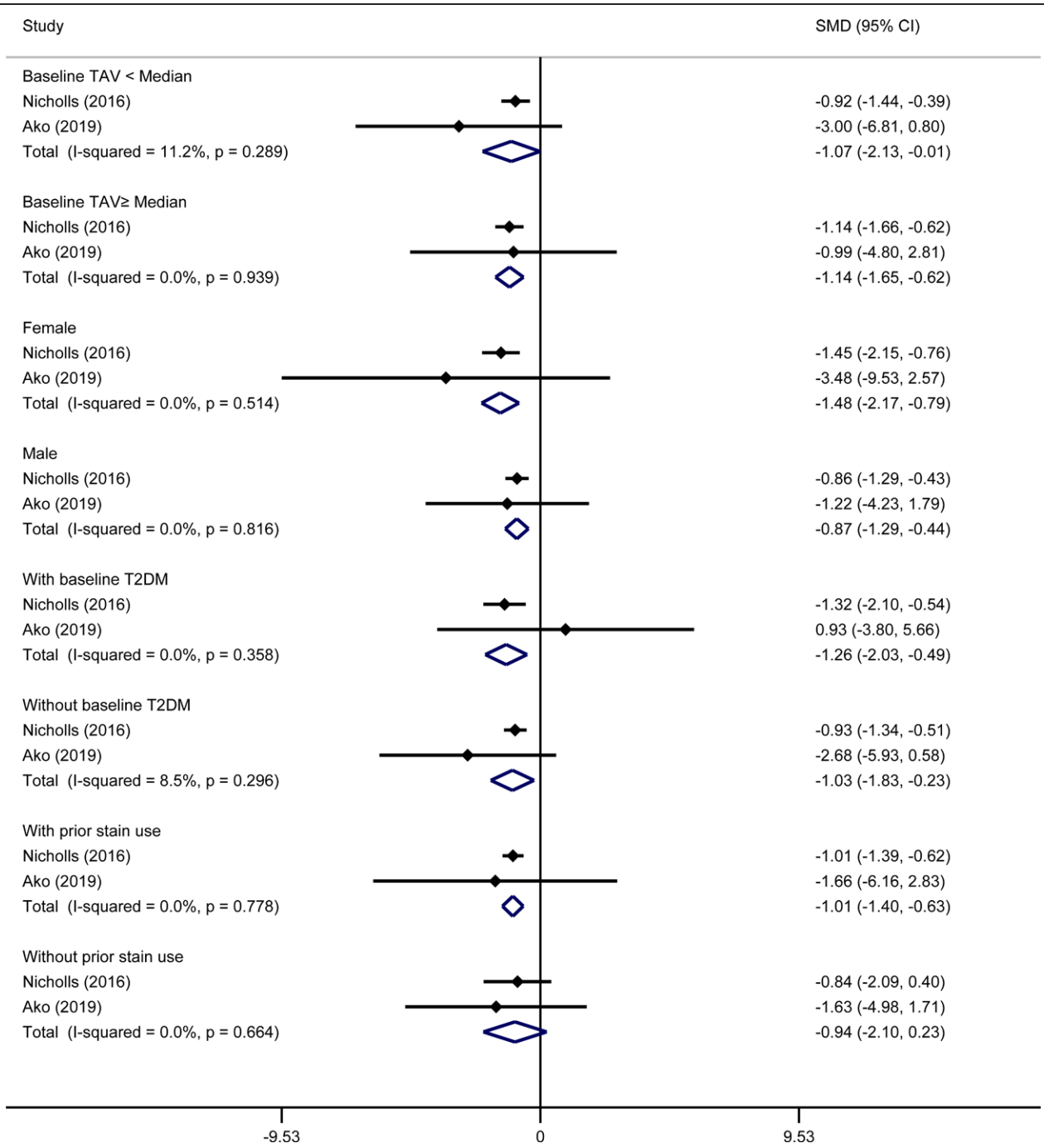

Figure 3. Effects of evolocumab and alirocumab on total atheroma volume according to baseline characteristics. Baseline characteristics include baseline total atheroma volume, gender, type 2 diabetes mellitus, and prior statin use.

In conclusion, the addition of ezetimibe to statin therapy may further reduce plaque and lipid burdens but may not modify plaque composition. Although current evidence supports a similar impact from the addition of PCSK9 inhibitors to statin therapy, more evidence is needed to confirm such an effect.

Author contributions

DL and MZ conceived and designed the research; all authors collected data, conducted the research, and analyzed and interpreted data; DL wrote the initial paper; CL, YT, ZL and MZ revised the paper; MZ had primary responsibility for the final content. All authors read and approved the final manuscript.

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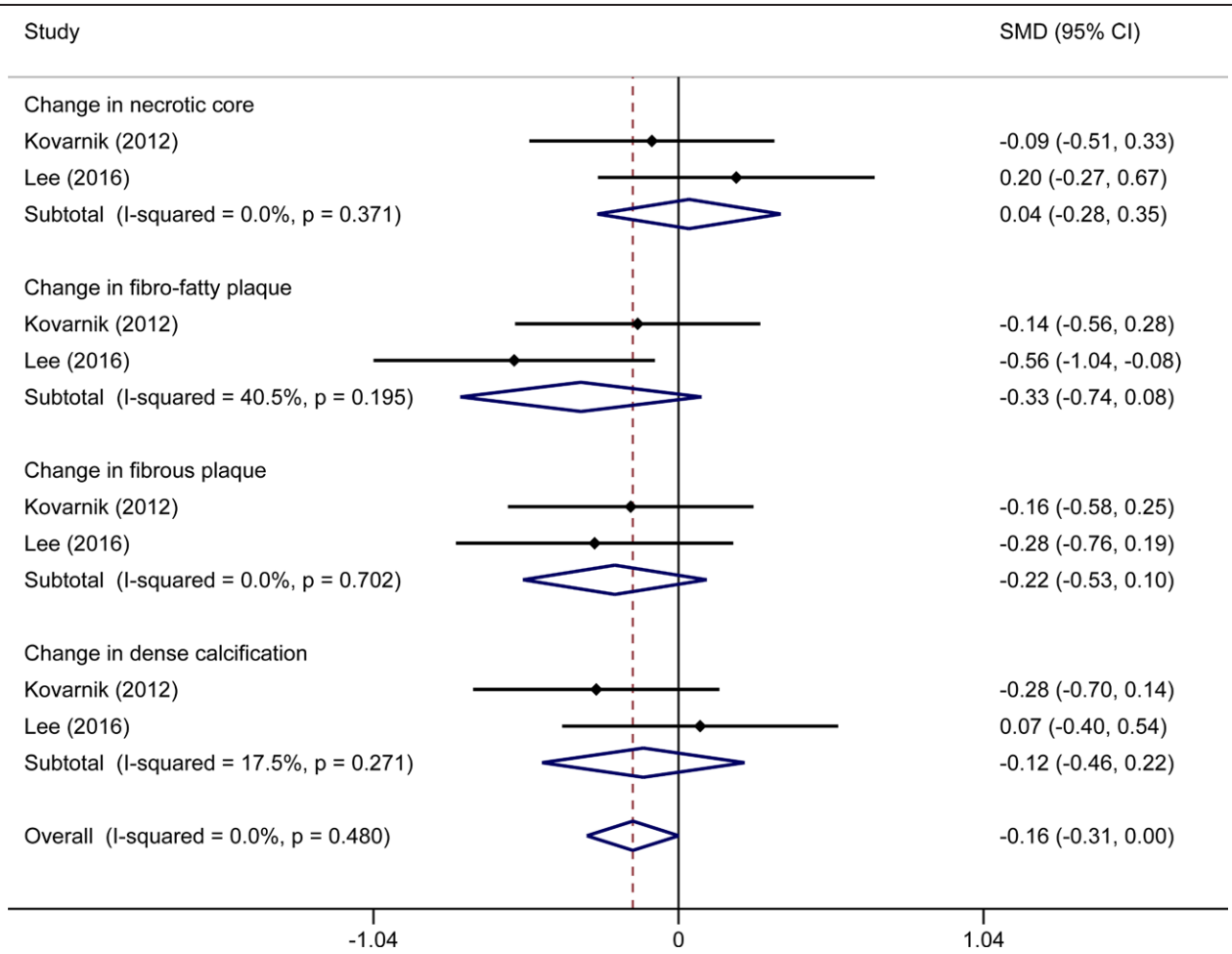

Figure 4. Effect of ezetimibe on plaque composition. Plaque compositions include necrotic core, fibro-fatty plaque, fibrous plaque, and dense calcification.

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