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Optimal Target Low-density Lipoprotein Level for Reducing the Risk of Atherosclerotic Cardiovascular Diseases: A Systematic Review and Meta-analysis

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ABSTRACT

Background: As per guidelines for treating dyslipidemia, the recommended low-density lipoprotein cholesterol (LDL-C) level in extremely high-risk patients, including those with coronary artery diseases is <55 mg/dL. Although this recommendation has been adopted in the guidelines for dyslipidemia in various countries, there is limited evidence of its efficacy in reducing cardiovascular diseases (CVDs), especially among East Asian patients. This study aimed to investigate whether an LDL-C value below 55 mg/dL is associated with decreased risk of CVDs. Methods: Seven clinical trials including 50,970 patients that compared intensive lipid-lowering therapy with less therapy or placebo in patients who had >6 months of follow-up, those with a sample size of ≥150 were selected as the final literature for analysis. Risk ratios (RR) using random effects were represented with 95% confidence intervals (CI) for the reliability of the results. Results: An LDL-C level of <55 mg/dL was related to significantly reduced events of major CVDs (RR: 0.88; 95% CI: 0.80-0.98) and myocardial infarction (RR: 0.81; 95% CI: 0.73-0.90) and a reduced risk of ischemic stroke (RR 0.79; 95% CI 0.69-0.89, mean follow-up=2 years). However, an LDL-C level below 55 mg/dL did not reduce the incidence of CVD in intensive therapy in East Asian patients. Conclusions: A goal LDL-C value below 55 mg/dL was identified to be related to a decreased risk of developing CVD. However, the relation to LDL-C below 55 mg/dL with a decreased risk of CVD was not observed in East Asian patients.

KEYWORDS: Cardiovascular diseases, cholesterol, cholesterol-LDL

Reducing the risk of cardiovascular diseases requires effort to determine appropriate target low-density lipoprotein cholesterol (LDL-C) levels. According to the 2019 European Society of Cardiovascular/European Atherosclerosis Society guidelines for managing dyslipidemia, patients diagnosed with atherosclerotic cardiovascular disease (ASCVD), including myocardial infarction (MI), unstable angina, and coronary revascularization, or at risk of developing ASCVD are classified as extremely high-risk patients. For such patients, LDL-C reduction by >50% or a target LDL-C level of <55 mg/dL is recommended[1)]. The 2020 American Association of Clinical Endocrinology Clinical Practice guidelines recommend achieving LDL-C levels <55 mg/dL in diabetic patients with acute ASCVD[2)]. In addition, the 2022 Korean Society of Lipid and Atherosclerosis dyslipidemia treatment guidelines published in November 18, 2022 recommend that patients with coronary artery disease (CAD) reduce their target LDL-C level to 55 mg/dL and by >50%[3)].

Setting a target LDL-C level below 55 mg/dL was based on

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the clinical studies, Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), ODYSSEY OUTCOMES (Effect of Alirocumab on Long-Term Cardiovascular Outcomes Following Acute Coronary Syndromes) and FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk). These clinical studies represented the significant reduction in major adverse cardiovascular events including the coronary events[4-6]. However, no significant reduction of cardiovascular mortality or all-cause mortality was observed despite achieving an LDL-C level of 53.7 mg/dL (hazard ratio [HR] 1.00; 95% confidence interval [95% CI], 0.89-1.13; p=1.00 and HR 0.99; 95% CI 0.91-1.07; p=0.78, respectively)[4]. When LDL-C levels reached 30 mg/dL with evolocumab, one of the types of PCSK9 inhibitors, insignificant reduction of cardiovascular mortality or all-cause mortality was found compared to the placebo group[5]. Additionally, trial participants were mainly Westerners (Caucasian), and it is difficult to determine the efficacy and safety of drug recommendations for Korean or East Asian patients, including Japanese, Chinese, Taiwanese, Hong Kongers, and Mongolians. Although a previous study compared the efficacy of evolocumab intervention for cardiovascular disease risk among Asians and non-Asians, it was limited to confirming the efficacy of the drug for cardiovascular disease or mortality in the East Asian population overall because it included Southeast Asian patients such as those from the Philippines and India.[7] From the perspective of "the lower, the better" LDL-C in a dyslipidemia management strategy,[8] it is essential to examine the effects of low LDL-C levels on mortality and cardiovascular disease in Korean or East Asian patients with similar characteristics. Therefore, this study aimed to investigate whether an LDL-C level of <55 mg/dL can reflect a reduced mortality rate among patients with CAD or dyslipidemia, the risk of cardiovascular diseases, and the risk of occurrence specifically in East Asian patients.

Materials and Methods

Data sources & searches

This study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement for reporting systematic reviews as recommended by the Cochrane review.[9] A comprehensive literature search was performed with language restriction including articles published in only English and Korean because of the researcher's clear understanding of these languages. Articles were searched using electronic databases such as PubMed, EMBASE, and ClinicalTrials.gov up to May 12, 2022. The search strategy included a combination of the following broad search terms: "lipid," "LDL," "cholesterol," "statin," "ezetimibe," and "proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor" (Supplementary Tables 1 and 2). The study protocol for this meta-analysis was registered in the International Prospective Register for Systematic Reviews (PROSPERO) CRD42021247742 on December 13, 2022.

Selection criteria of studies

The prespecified inclusion criteria were as follows: 1) randomized controlled trials with patients with CAD or dyslipidemia using a statin only or statin plus ezetimibe, or statin plus PCSK9 inhibitors as a lipid-lowering therapy; 2) mean/median LDL-C <55 mg/dL achieved with intensive therapy; 3) follow-up period ≥6 months; and 4) sample size ≥150 patients. The exclusion criteria were as follows: 1) patients with heart failure or those requiring hemodialysis[9] 2) therapy with omega 3 fatty acids[10] 3) therapy with fibrates, niacin, cholesteryl ester transfer protein (CETP) inhibitors.[11]

Data extraction, outcomes, and quality assessment

Two investigators (M.G.J. and Y.E.S.) independently extracted the data using prespecified criteria of data collection, evaluated the accuracy of the extraction, and resolved any discrepancies by consensus after discussion with a third investigator (K.H.S.). The extracted data included characteristics of the trial participants, crude point estimates, number of events, sample sizes, and follow-up period. Any key information related to a meta-analysis in this study but not represented in the published manuscript was also determined using clinicaltrials.gov. Two independent investigators (M.G.J. and Y.E.S.) extracted the potential risk of bias in the trials using the Cochrane Risk of Bias Tool at the study level recommended in Cochrane Training[12]. The result of evaluating the risk of bias in studies is represented in Supplementary Figure 1. This study abstracted and analyzed trial-level data according to the original randomization group for which outcomes data were available. The study population was classified into 2 groups: 1) the lower LDL-C group, defined as treatment to achieve mean/median LDL-C levels <55 mg/dL with intensive lipid-lowering therapy, and 2) the higher LDL-C group, defined as treatment with less potent active control or placebo that confers higher achieved LDL-C ≥55 mg/dL. The outcomes were all-cause and cardiovascular

mortality, major adverse cardiovascular events (MACE), MI, revascularization, and ischemic stroke. The meaning of MACE in each study is defined in Supplementary Table 3.

Data synthesis & analysis

Outcomes were pooled using Mantel-Haenszel random-effects model and the DerSimonian and Laird method for estimating the tau. Effect sizes are reported as risk ratios (RRs) with 95% confidence intervals (CIs). I^2 statistics were used to measure the extent of unexplained statistical heterogeneity; I^2 >50% was considered to indicate a high degree of statistical heterogeneity between studies.[13] Publication bias was not evaluated owing to the limited number of studies reviewed because the literatures were only seven.[14] To explore potential sources of heterogeneity, sensitivity and additional subgroup analysis were performed based on the type of drug (e.g., statin+ezetimibe or PCSK9 inhibitor) and population race (e.g., East Asian). Comprehensive meta-analysis was conducted using Review Manager 5.4 recommended by the Cochrane Review Groups.

Results

Searching literatures

A total of 25,064 articles were confirmed, and duplicate documents were excluded. After excluding duplicates, 8843 articles were screened. After confirming the article titles and abstracts, 8532 articles were excluded. A total of 311 articles were full-text screened, and 304 of them were excluded for reasons such as LDL-C levels, outcome/drug ranges, heart failure or hemodialysis patients, sample size, and follow-up periods. Finally, a total of 7 articles were used for the systematic literature review and meta-analysis (Fig. 1). The risk of bias in outcomes across all studies was similar and predominately of some concern and high risk.

Characteristics of included literatures and participants

Table 1 presents the characteristics of clinical trial participants in the seven articles analyzed. Of the seven clinical trials, two used therapies with statin and ezetimibe and five used therapies

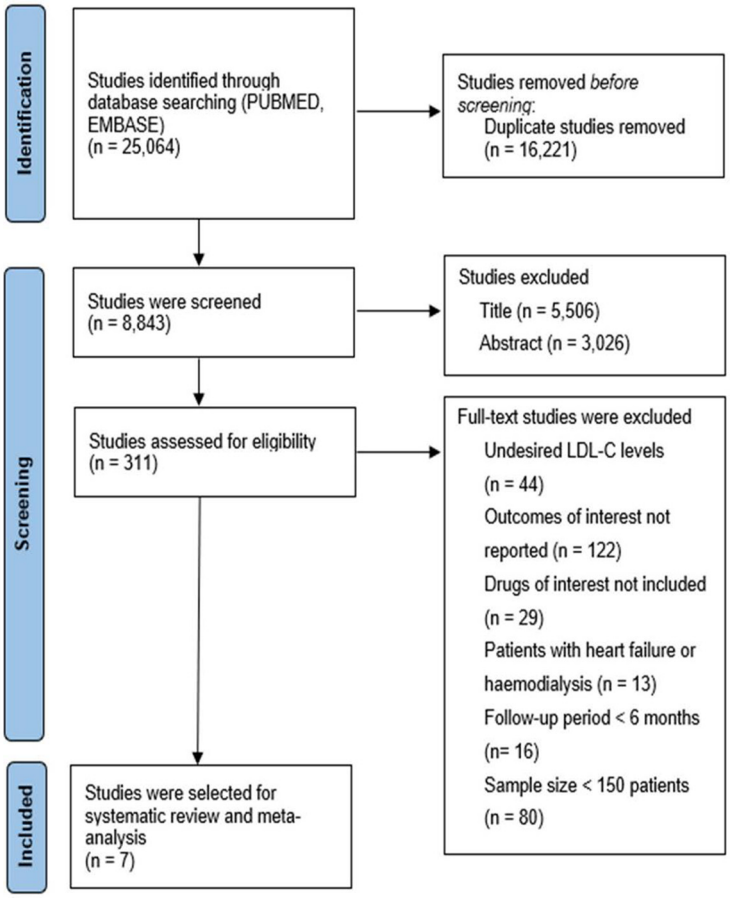

Fig. 1. Workflow of the selecting the literatures for systematic review and meta-analysis

Table 1. Baseline characteristics of trials and participants

Study	N	Age (years)	N (%), Intervention		Intensive therapy				Placebo/less intensive therapy			Follow-up (years)
			Women	Diabetes	Active agent	N	LDL-C	Baseline LDL-C	Active agent	N	LDL-C	
Tamio 2018[23]	163	63.6	20(38.7)	32(60.4)	Alirocumab	53	47.4	149.2	Placebo	56	143.6	1.8
Koh 2017[24]	199	61.2	14(14.4)	32(33.0)	Alirocumab	97	42.7	97.0	Placebo	102	102.9	0.5
Liu 2017[25]	219	84.0	54(47.4)	46(40.4)	Statin+ezetimibe	108	46.4	85.1	Statin	111	54.1	1.0
Sabatine 2017[5]	27,564	62.5	6769(25.0)	10081(37.0)	Evolocumab	13,784	30.0	92.0	Placebo	13,780	92.0	2.2
Tamio 2016[26]	216	60.3	60(41.7)	105(72.9)	Alirocumab	144	53.4	143.1	Placebo	72	135.6	1.8
Cannon 2015[4]	18,144	63.6	4416(24.0)	4933(27.0)	Statin+ezetimibe	9067	54.0	93.8	Statin	9077	70.0	6.0
Sabatine 2015[27]	4465	58.0	2210(49.5)	599(13.4)	Evolocumab	2976	48.0	120.5	Statin	1489	121.0	0.9

with PCSK9 inhibitors, such as evolocumab and alirocumab. The mean patient age was 64.7 years. The proportion of women was ranged 14.4%-49.5% and the mean number of female patients was about 1,935. For the lower LDL-C group (LDL-C <55 mg/dL), the average baseline LDL-C level was 112.5 mg/dL, and the average follow-up period was 2 years.

Meta-analysis of outcomes

All-cause and cardiovascular mortality

Compared with the higher LDL-C group, the lower LDL-C group did not show significantly lower risks of all-cause mortality (RR 1.00; 95% CI, 0.94-1.06; p=0.93; Fig. 2) and cardiovascular mortality (RR 1.02; 95% CI, 0.92-1.13; p=0.70; Fig. 3).

Myocardial infarction, ischemic stroke, and MACE

Compared with the higher LDL-C group, the lower LDL-C group showed significantly lower risks of MI (RR 0.81; 95% CI, 0.73-0.90; p=0.0001; Supplementary Fig. 2), ischemic stroke (RR 0.79; 95% CI, 0.69-0.89; p=0.0002; Supplementary Fig. 3), and MACE (RR 0.88; 95% CI, 0.80-0.98; p=0.01; Supplementary Fig. 4).

Subgroup analysis: Race

No significant differences were observed between both groups in terms of all-cause mortality (RR 1.32; 95% CI, 0.46-3.84; p=0.61; Fig. 4), MI (RR 0.84; 95% CI, 0.40-1.80; p=0.66; Fig. 5) and MACE (RR 1.08; 95% CI 0.68-1.71; p=0.75; Fig. 6) in East Asian patients.

Sensitivity analyses and publication bias

Sensitivity analysis was performed by grouping according to drug type and race. The results were not significantly altered throughout this process.

Discussion

As a result of systematic literature review and meta-analysis of this study, the mean LDL-C level achieved in patients with CAD or dyslipidemia in a mean 2-year follow-up was 102.7 mg/dL in the higher LDL-C group and 45.6 mg/dL in the lower LDL-C group. The risk of myocardial infarction, ischemic stroke, and MACE development was significantly reduced in the Low LDL-C group. However, as a result of meta-analysis of East Asian patients, including Korea, Japan, China, and Taiwan, there was no significant difference between groups in mortality and risk of cardiovascular disease.

LDL-C above a certain level is a representative cause of ASCVD, CAD, which has been repeatedly demonstrated in related previous clinical studies. The slope of the linear graph, which can confirm the association between LDL-C levels and the occurrence of ASCVD, was steep as the follow-up period increased. It can be concluded that the risk of developing ASCVD is determined by LDL-C levels throughout the patient's lifetime.[15,16] The dyslipidemia management strategy called "The lower the better" is a concept supported by clinical studies using ezetimibe and PCSK9 inhibitors based on statin.[17,18] Recommendations of treatment that lower the target LDL-C levels set to reduce the risk of developing cardiovascular disease were presented based on the results of the IMPROVE-IT,

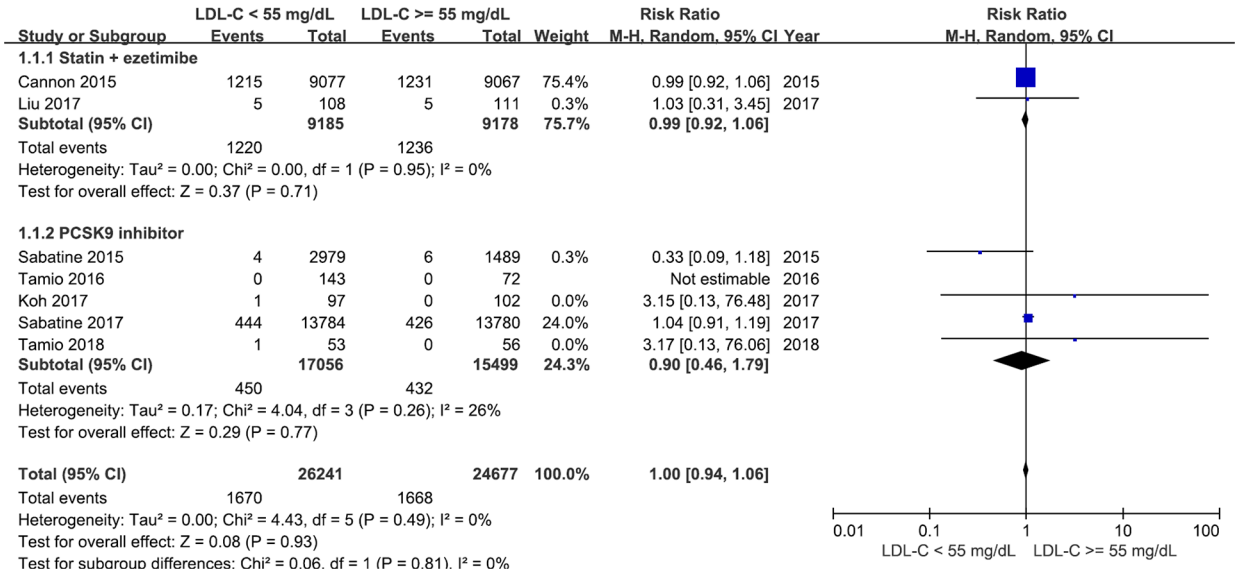

Fig. 2. Effect of treatment to achieve low density lipoprotein (LDL-C, <55 mg/dL) vs higher LDL-C (≥55 mg/dL) on all-cause mortality

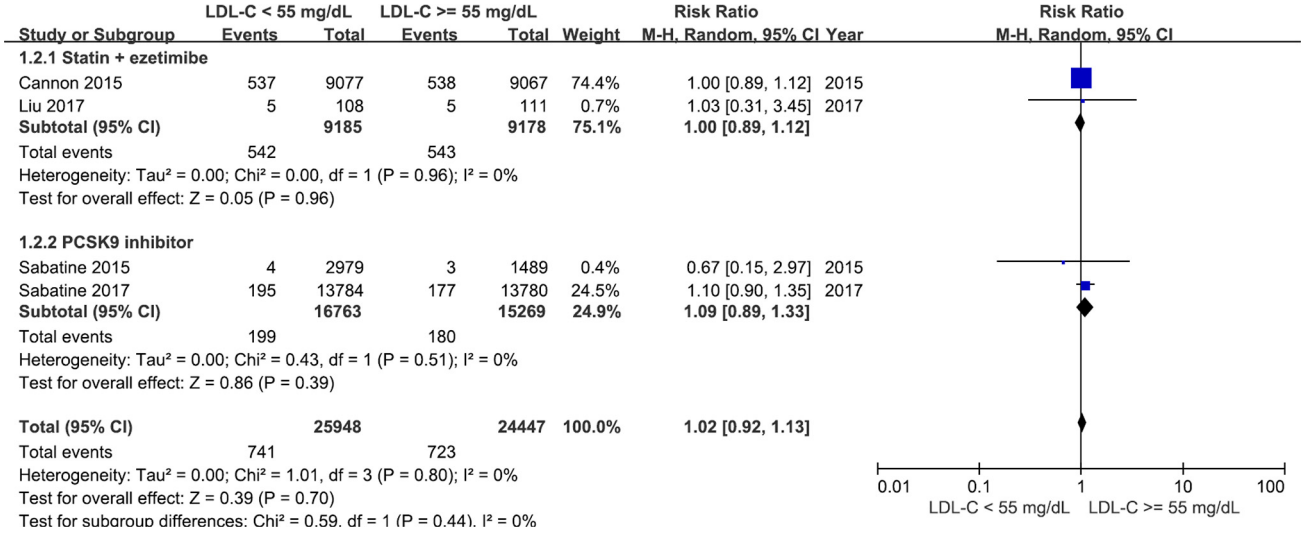

Fig. 3. Effect of treatment to achieve low density lipoprotein (LDL-C, <55 mg/dL) vs higher LDL-C (≥55 mg/dL) on cardiovascular mortality

FOURIER, and ODYSEEY studies.[4,5,19] Based on these studies, the 2017 American Endocrinology Society presented LDL-C target levels of 55 mg/dL in patients with extreme high-risk such as CAD.[20] Subsequently, the 2019 European Heart Association guidelines for dyslipidemia further recommended target LDL-C levels below 40 mg/dL for patients with a 50% reduction from existing LDL-C levels and a secondary vascular disease base within 2 years.[1] However, more than 90% of the IMPROVE-IT, FOURIER, and ODYSSEY studies were white, and their efficacy for mortality was unclear.[4,5,19]

According to the clinical study analyzed in this study, when LDL-C was less than 55 mg/dL, there was no significant decrease in cardiovascular disease mortality or mortality. According to a systematic literature review and meta-analysis that evaluated the validity and safety of target LDL-C levels, below of 70 mg/dL presented in the guidelines for treating dyslipidemia, there was no significant difference in mortality [RR: 0.94 (0.82, 1.08)] and cardiovascular disease mortality [RR: 0.83 (0.61, 1.14)] when compared with LDL-C 55 mg/dL or higher.[10] A meta-analysis of a clinical trial study of a group of patients treated with PCSK9 inhibitors suggested that it was not associated with a decrease in mortality [Relative Risk: 0.94

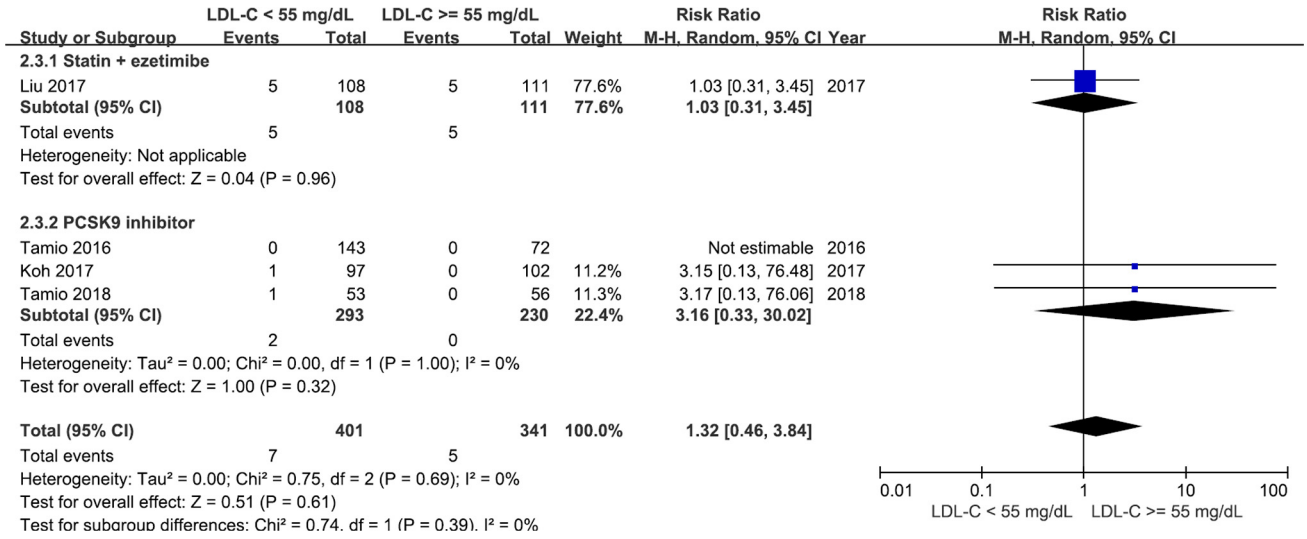

Fig. 4. Effect of treatment to achieve low density lipoprotein (LDL-C, <55 mg/dL) vs higher LDL-C (≥55 mg/dL) on all-cause mortality in East Asian

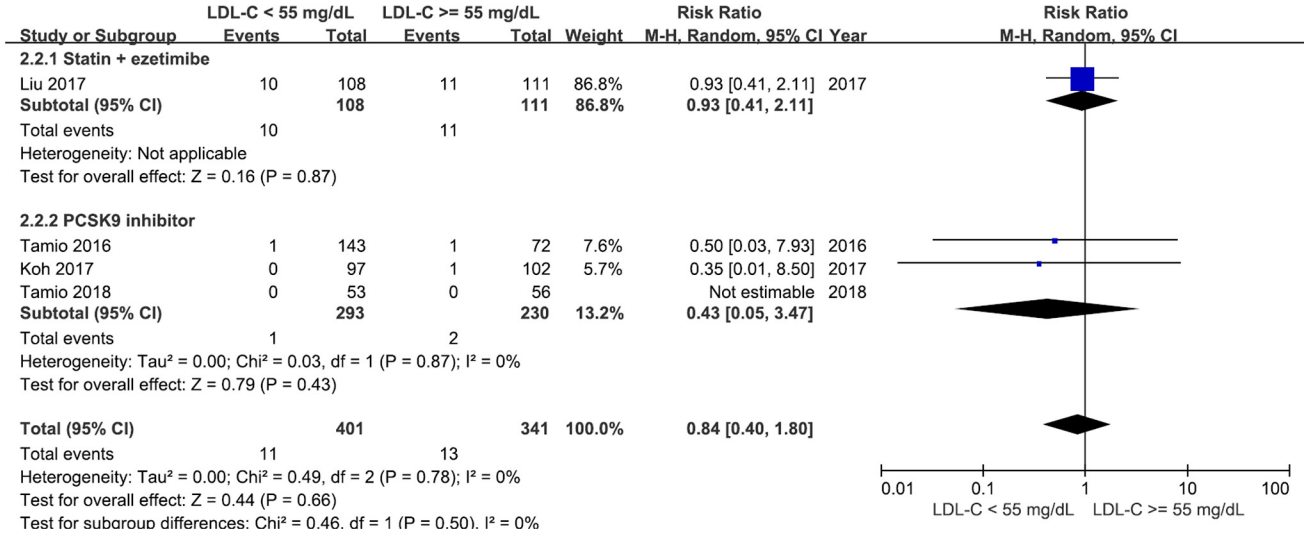

Fig. 5. Effect of treatment to achieve low density lipoprotein (LDL-C, <55 mg/dL) vs higher LDL-C (≥55 mg/dL) on myocardial infarction in East Asian

(0.81, 1.09); p=0.41] regardless of LDL-C achievement levels and baseline LDL-C after follow-up.[21)]

Clinical studies were conducted to find appropriate LDL-C levels for the prevention of secondary occurrence in patients with CAD in East Asia, and there was no significant reduction in the risk of cardiovascular disease when less than LDL-C 55 mg/dL was achieved. As a result of analyzing 10,672 patients with myocardial infarction in Korea, the risk of developing MACE decreased after 3 years of follow-up if the achieved LDL-C level was less than 70 mg/dL and decreased by 50% or more than the base level [HR: 0.73 (0.56, 0.96); p=0.025]. However, compared with those achieved below LDL-C 55 mg/dL and those achieved below 70 mg/dL, the risk of developing MACE after 3 years in the group below 55 mg/dL showed no significant decrease [HR: 0.75 (0.46, 1.22); p=0.247].[19)] A multi-center clinical study based on lipid-lowering therapy in patients of Japanese myocardial infarction suggested that the reduction in cardiovascular disease incidence was not related to the target LDL-C setting.[22)]

This study has the following strengths. First, when LDL-C 55 mg/dL was achieved as a target in patients with dyslipidemia, CAD, and ASCVD, overall clinical results for mortality and

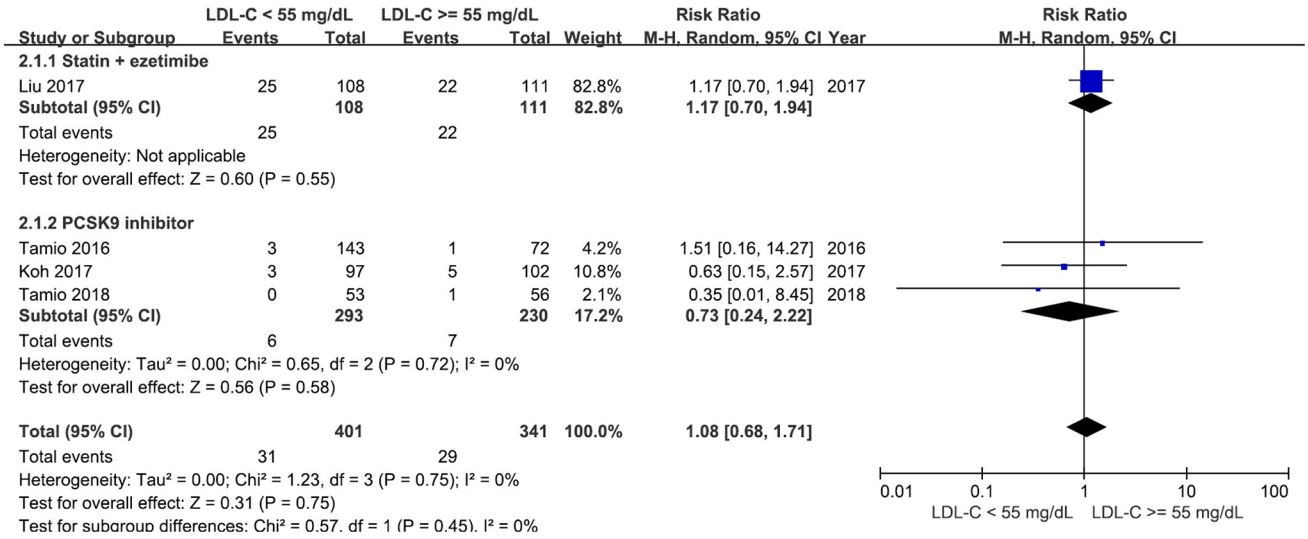

Fig. 6. Effect of treatment to achieve low density lipoprotein (LDL-C, <55 mg/dL) vs higher LDL-C (≥55 mg/dL) on MACE in East Asian

cardiovascular disease were identified. Second, through a sub-analysis of East Asian race, it was confirmed whether the target LDL-C level of less than 55 mg/dL could be applied in the Korean patient group. However, there are also two limitations in this study. First, since the average value of the LDL-C level was confirmed as a target, it is difficult to confirm the trend in the group in which the actual LDL-C level is less than 55 mg/dL. Second, in the case of studies selected as the final literatures, there is a difference in the number of participants for each study, so it is possible that the corresponding part influenced the results. However, analysis through the classification of drug types and races solved the problem of heterogeneity that may occur between studies. Third, the number of East Asian patient groups in the literatures used in the meta-analysis of this study may have affected the results due to the small number of patients despite comprehensive literature searching procedures.

Conclusion

In this study, it was effective to target LDL-C levels below 55 mg/dL to lower the risk of cardiovascular disease. However, in the clinical study of East Asian patients used in systematic literature review and meta-analysis in this study, even if LDL-C levels were less than 55 mg/dL, mortality and cardiovascular disease risk were not lowered. This suggests the need for additional clinical studies aimed at less than LDL-C 55 mg/dL for East Asian patient groups.

Acknowledgments

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Conflicts of Interest

The authors have no conflicts of interest to declare with regards to the contents of this study.

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