TREAT-TO-TARGET VERSUS OTHER APPROACHES OF STATIN THERAPY IN ATHEROSCLEROTIC CARDIOVASCULAR DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of disability and mortality globally. A key strategy to prevent recurrent major adverse cardiovascular events (MACE), through reducing low-density lipoprotein cholesterol (LDL-C) levels, in ASCVD patients is lipid-lowering therapy, with high-intensity statins as the standard approach. However, their use carries potential risks of adverse effects. Treat-to-target statin therapy (TTT), an approach that titrates statin dosage based on the patient's response to achieve a specific LDL-C target, might be an alternative. This systematic review and meta-analysis aimed to compare the efficacy of TTT, fixed-dose high-intensity statin therapy (FH), and no-initial-statin therapy on MACE and LDL-C level in patients with ASCVD. PubMed and Scopus were searched through January 26, 2024, to identify randomized clinical trials (RCTs) evaluating TTT in patients with ASCVD. Two RCTs comparing TTT with target LDL-C of 80-110 mg/dL (TTT110) to no-initial-statin therapy showed a statistically non-significant reduction in risk for MACE (risk ratio [RR] 0.66, 95% confidence interval [CI]: 0.37, 1.16). TTT with target LDL-C of 70 mg/dL (TTT70) resulted in significantly lower risk of MACE than TTT110 (RR 0.86, 95% CI: 0.76, 0.96) in two RCTs. In contrast, the comparison between TTT70 and FH from one RCT suggested no significant difference in the risk of MACE (RR 0.93, 95% CI: 0.77, 1.13). In conclusion, TTT70 appeared to have similar efficacy to FH as an ASCVD secondary prevention strategy.

Keywords: Atherosclerotic Cardiovascular Disease, Low-Density Lipoprotein Cholesterol, Statin, Secondary Prevention

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INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD), caused by plaque accumulation in arterial walls, refers to conditions that include acute coronary syndrome, stroke, transient ischemic attack, and peripheral artery disease. It is a leading cause of disability and mortality globally. In 2019, there were 523 million prevalent cases of total cardiovascular disease (CVD), with 18.6 million deaths attributed to CVD (Roth et al., 2020). Patients with history of ASCVD face a higher risk of recurrent events, making secondary prevention essential. According to the 2018 American Heart Association guidelines, lipid-lowering therapy plays an important role for this purpose, and high-intensity statins are suggested as a standard lipid-lowering therapy for patients with ASCVD, due to their high efficacy in reducing low-density lipoprotein cholesterol (LDL-C) levels (Grundy et al., 2019). However, high-intensity statins carry potentially dose-dependent risks of adverse effects, including muscle symptoms, liver damage, and new-onset diabetes (Ward et al., 2019). A combination of moderate-intensity statin and ezetimibe has been proven as efficacious as a high-intensity statin in preventing major cardiovascular events (MACE), but with better tolerance (Kim et al., 2022). Treat-to-target statin therapy is another strategy of lipid-lowering therapy in which the dose of statin is titrated based on the patient's response until achieving the desired target LDL-C level, which has decreased over time. It aims to optimize the risk-benefit balance for patients with ASCVD. This systematic review and meta-analysis aimed to compare treat-to-target statin therapy to fixed-dose high-intensity statin therapy (FH), fixed-dose low- to moderate-intensity statin therapy (FLM), and expectant management, in which statins were not prescribed at the initial stage but could be added according to subsequent LDL-C levels ("no initial statin" therapy), in terms of MACE and post-treatment LDL-C level among patients with ASCVD.

LITERATURE REVIEWS

A partially relevant systematic review and meta-analysis covered primary studies whose patients received lipid-lowering therapy for all indications, not only ASCVD. The interventions involved various types of lipid-lowering therapy, among which treat-to-target statin therapy was assessed in only one of the 11 studies in this review (Khan et al., 2022). Although another systematic review also considered treat-to-target statin therapy, it regarded different alternative approaches of statin therapy as a single intervention. Thus, it finally included only two randomized controlled trials (RCTs), one involving treat-to-target statin therapy and the other involving combination therapy, in an individual patient data meta-analysis (Lee et al., 2024). There are no systematic reviews and meta-analyses that focus on comparing treat-to-target statin therapy with other approaches of statin therapy in patients with ASCVD.

RESEARCH METHODOLOGY

A literature search was performed in PubMed and Scopus through January 26, 2024. The search terms were constructed based on the following concepts: acute coronary syndrome, myocardial infarction, stroke, peripheral artery disease, atherosclerosis, statins, target, cardiovascular event, and LDL-C.

From the retrieved search results, duplicate reports were removed. Then, the remaining articles were selected using information from the titles and abstracts, based on the following inclusion criteria: 1) RCT; 2) patients with ASCVD, defined as acute coronary syndrome (including unstable angina and myocardial infarction), stroke, transient ischemic attack, or peripheral artery disease; 3) use of treat-to-target statin therapy, compared with no-initial-statin therapy, FLM, FH, or treat-to-target statin therapy of a different target LDL-C level; and 4) MACE or post-treatment LDL-C level reported as an outcome. The studies were excluded if they did not report the outcome data required for data pooling with meta-analysis. When decisions were not reached based on the abstracts alone, the full articles were reviewed.

Data were independently extracted by two reviewers (P.V. and K.T.) using a pre-specified data extraction form. Discrepancies were resolved by consensus after discussion with the third reviewer (S.W.B.). The risk of bias of the eligible studies was assessed by using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (Sterne et al., 2019).

As regards the interventions of interest, no-initial-statin therapy refers to an expectant management in which statins were not prescribed initially but could be added based on subsequent LDL-C levels. FH represents treatment with fixed-dose high-intensity statins, including atorvastatin 40-80 mg/day and rosuvastatin 20-40 mg/day. While TTT70 and TTT110 refer to treat-to-target statin therapy, targeting for serum LDL-C levels < 70 mg/dL and 80-110 mg/dL, respectively.

The effect sizes were risk ratios (RR) for the MACE outcome and mean differences (MD) for the LDL-C level outcome. Random-effects models with the DerSimonian-Laird method were applied. All analyses were performed using the Stata software package, version 18.0 (StataCorp, College Station, TX). Statistical significance was set at p-values < 0.05.

RESEARCH RESULTS

A total of 6,610 articles were assessed for eligibility after removing duplicates, 159 were further reviewed on full text, and five RCTs encompassing 13,023 patients were finally included (Figure 1).

The characteristics of studies and participants are shown in Table 1. Four studies focused on patients with cardiovascular disease, while one on patients with ischemic stroke or transient ischemic attack. The mean age of participants ranged from 58.5 to 66.7 years, and the majority of them were male (67.6%-82.2%). The mean baseline LDL-C levels ranged from 86.5 to 179.5 mg/dL. The prevalence of diabetes mellitus ranged from 19.56% to 33.36%, and hypertension from 65.64% to 67.76%. The risk of bias assessment results are reported in Table 3. Two studies were judged to have low risk of overall bias, two had some concerns due to unclear allocation procedures or early termination, and one was considered at high risk due to differences in the measurement or ascertainment of the outcome between intervention groups.

For the MACE outcome (Figure 2), the pooled RR and 95% confidence intervals (CI) from two RCTs (4,042 patients) showed that TTT110 might result in a lower risk of MACE by 34% relative to no-initial-statin therapy (pooled RR 0.66, 95% CI: 0.37, 1.16); however, the result was not statistically significant (Athyros et al., 2002; Koren & Hunninghake, 2004). Two RCTs (4,581 patients) showed that TTT70 reduced the risk of MACE significantly by 14% compared to TTT110 (pooled RR 0.86, 95% CI: 0.76, 0.96) (Amarenco et al., 2020; Hagiwara et al., 2017). In contrast, the comparison between TTT70 and FH, based on a single RCT (4,400 patients), suggested that the two treatments resulted in similar risks for MACE (RR 0.93, 95% CI: 0.77, 1.13) (Hong et al., 2023). Overall, TTT70 appeared to be more efficacious than TTT110 in reducing the risk of MACE, while no significant difference was observed between TTT70 and FH.

For the LDL-C level outcome (Figure 3), data from two RCTs indicated that TTT110 showed a trend toward lower post-treatment LDL-C levels than no-initial-statin therapy by 43.50 mg/dL (pooled MD -43.50, 95% CI: -99.36, 12.36), although not statistically significant (Athyros et al., 2002; Koren & Hunninghake, 2004). In contrast, TTT70 resulted in significantly lower LDL-C levels by 25.04 mg/dL compared to TTT110 (pooled MD -25.04, 95% CI: -40.43, -9.66), based on two RCTs (Amarenco et al., 2020; Hagiwara et al., 2017). Meanwhile, when comparing TTT70 to FH, the results from one RCT suggested that the two treatments have similar effects on LDL-C levels (MD 0.10, 95% CI: -1.45, 1.65) (Hong et al., 2023). In summary, TTT70 tended to be more efficacious than TTT110 in lowering post-treatment LDL-C levels, while it demonstrated a similar effect to FH, consistent with the findings for MACE.

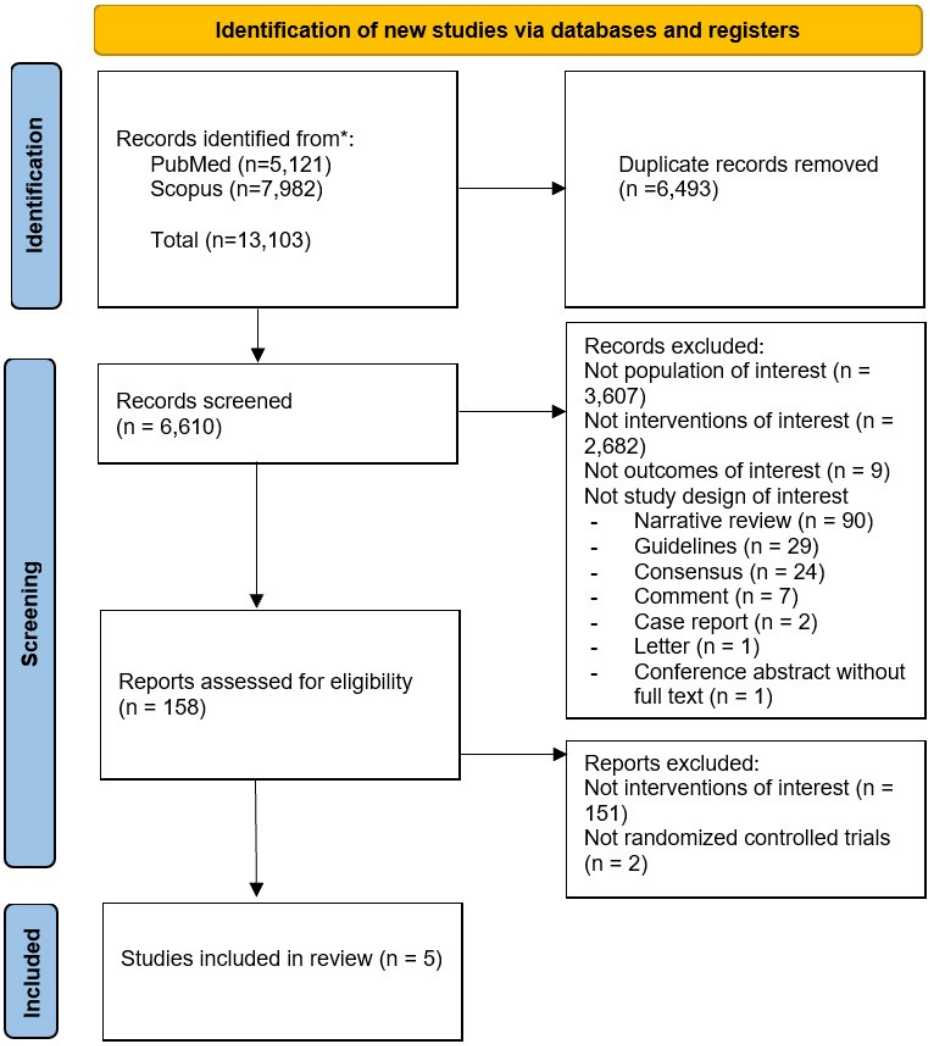

Figure 1 The study selection process

Table 1 Baseline characteristics of studies and participants

Author, year	Country	n	Dx	F/U	Mean age, year	Male, %	Mean BMI, kg/m^2	Mean baseline LDL-C level, mg/dL	DM, %	HTN, %	Current smokers, %
Hong, 2023	South Korea	4,400	Coronary artery disease	3 years	65	72.09	24.7	86.5	33.36	66.75	13.70
Amarenco, 2020	France, South Korea	2,860	TIA, ischemic stroke	Median of 3.5 years	66.7	67.62	25.6	135.5	22.63	65.64	30.34
Hagiwara, 2017	Japan	1,734	Acute coronary syndrome	3 years	65.6	74.97	24.3	135.2	29.99	67.76	34.26
Koren, 2004	USA	2,442	Coronary heart disease	Median of 4.5 years	61.2	82.23	NR	147.1	NR	NR	19.45
Athyros, 2002	Greece	1,600	Coronary heart disease	3 years	58.5	78.50	24.1	179.5	19.56	NR	NR

BMI, body mass index; DM, diabetes mellitus; Dx, diagnosis; F/U, follow-up; HTN, hypertension; LDL-C, low density lipoprotein-cholesterol; n, sample size; NR, not reported; TIA, transient ischemic attack; USA, United States of America.

Table 2 Details of treatments

Author, year	Intervention				Comparator			
	Treatment	LDL-C target level	Type of statin	Type of non-statin	Treatment	LDL-C target level	Type of statin	Type of non-statin
Hong, 2023	TTT	50-70 mg/dL	Rosuvastatin, atorvastatin	-	FH	-	Rosuvastatin, atorvastatin	-
Amarenco, 2020	TTT	< 70 mg/dL	NR	-	TTT	90-110 mg/dL	NR	-
Hagiwara, 2017	TTT	< 70 mg/dL	Pitavastatin	Ezetimibe	TTT	90-100 mg/dL	Pitavastatin	-
Koren, 2004	TTT	< 80 mg/dL	Atorvastatin	-	NIS	-	-	-
Athyros, 2002	TTT	< 100 mg/dL	Atorvastatin	-	NIS	-	-	-

FH, fixed-dose high-intensity statin therapy; LDL-C, low density lipoprotein-cholesterol; NIS, no-initial-statin therapy; NR, not reported; TTT, treat-to-target statin therapy.

Table 3 Risk of bias assessment

Author, year	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Hong, 2023	Low	Low	Low	Low	Low	Low
Amarenco, 2020	Low	Some concerns	Low	Low	Some concerns	Some concerns
Hagiwara, 2017	Some concerns	Low	Low	Low	Low	Some concerns
Koren, 2004	Low	Low	Low	High	High	High
Athyros, 2002	Low	Low	Low	Low	Low	Low

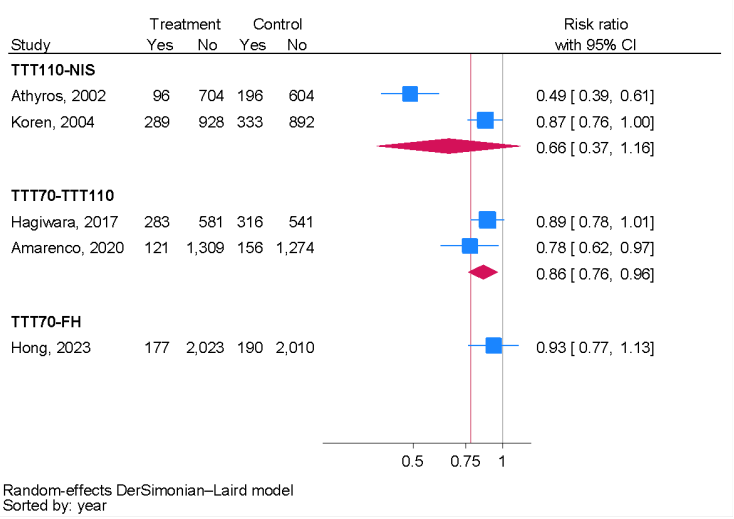

Figure 2 Forest plot for pairwise meta-analysis on MACE outcome. FH, fixed-dose high-intensity statin therapy; NIS, no-initial-statin therapy; TTT70, treat-to-target statin therapy with target serum LDL-C level < 70 mg/dL; TTT110, treat-to-target statin therapy with target serum LDL-C level 80-110 mg/dL.

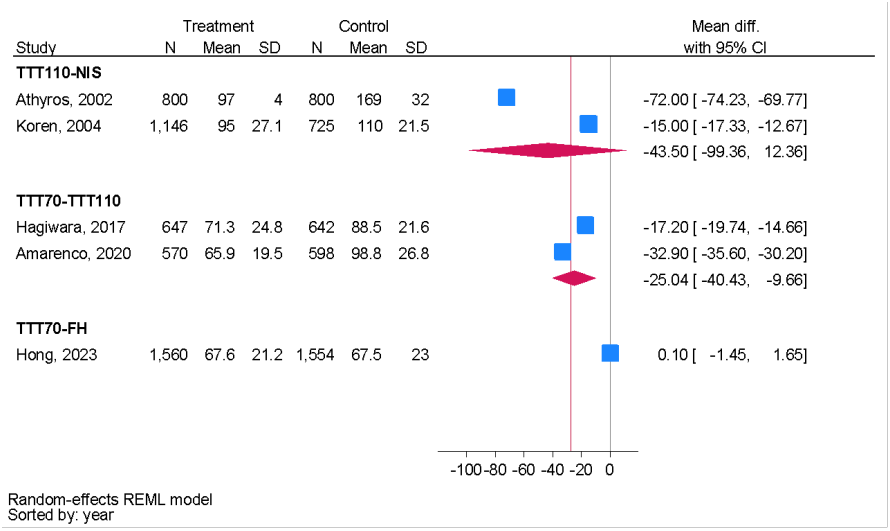

Figure 3 Forest plot for pairwise meta-analysis on post-treatment LDL-C outcome. FH, fixed-dose high-intensity statin therapy; NIS, no-initial-statin therapy; TTT70, treat-to-target statin therapy with target serum LDL-C level < 70 mg/dL; TTT110, treat-to-target statin therapy with target serum LDL-C level 80-110 mg/dL.

DISCUSSION & CONCLUSION

In this systematic review, treat-to-target statin strategies with different LDL-C targets were compared against each other as well as against the FH and no-initial-statin strategies. The results demonstrated that TTT70, while being more efficacious than TTT110 and no-initial-statin therapy, was as efficacious as FH in reducing the risk of MACE and post-treatment LDL-C levels. In a recent systematic review, alternative LDL-C lowering strategies were compared with high-intensity statin therapy in ASCVD patients, with one of the two included trials assessing TTT. Although their intervention of interest does not fully match this systematic review's, the inclusion of a RCT on TTT enables an analogy. Similar findings were reported, as no significant differences in MACE and post-treatment LDL-C levels were observed between alternative approaches and FH (Lee et al., 2024), aligning with the comparison between TTT70 and FH in this analysis. TTT70 should theoretically produce fewer adverse effects than FH, and thus might be the more favorable option. However, further studies are warranted to confirm this hypothesis. The major limitation of this review is the paucity of eligible studies to allow for more precise treatment effect estimates. This suggests that more primary studies in this area are needed. In addition, imbalances in the baseline LDL-C levels across the studies could influence the MACE risk and post-treatment LDL-C levels, but meta-regression or subgroup analysis was not possible because of the limited number of studies. To conclude, in patients with ASCVD, secondary prevention with TTT70 is probably as efficacious as FH, but more efficacious than TTT110 and no-initial-statin therapy, in reducing the risk of MACE and post-treatment LDL-C levels.

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