Treat-to-target versus high-intensity statin treatment in patients with or without diabetes mellitus: a pre-specified analysis from the LODESTAR trial

Seung-Jun Lee,[a,i] Woong Chol Kang,[b,i] Jong-Young Lee,[c,i] Jin-Bae Lee,[d] Tae-Hyun Yang,[e] Junghan Yoon,[f] Yong-Joon Lee,[a] Sung-Jin Hong,[a] Chul-Min Ahn,[a] Jung-Sun Kim,[a] Byeong-Keuk Kim,[a] Young-Guk Ko,[a] Donghoon Choi,[a] Bum-Kee Hong,[g,**] Yangsoo Jang,[h] and Myeong-Ki Hong,[a,*] for the LODESTAR Investigators

[a]Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[b]Gachon University Gil Medical Center, Incheon, Korea
[c]Kangbuk Samsung Hospital, Sungkyunkwan University Scholl of Medicine, Seoul, Korea
[d]Daegu Catholic University Medical Center, Daegu, Korea
[e]Inje University Busan Paik Hospital, Busan, Korea
[f]Wonju Severance Christian Hospital, Wonju, Korea
[g]Gangnam Severance Hospital, Seoul, Korea
[h]CHA University College of Medicine, Seongnam, Korea

eClinicalMedicine 2023;64: 102227
Published Online 20 September 2023
https://doi.org/10.1016/j.eclinm.2023.102227

Summary

Background The impact of titrated versus fixed intensity statin therapy in patients with coronary artery disease (CAD) and diabetes mellitus (DM) remains to be elucidated.

Methods This was a pre-specified analysis of patients with and without DM from the LODESTAR trial. Patients with CAD were randomly assigned to receive either a treat-to-target strategy with a target LDL-C level of 50–70 mg/dL or a high-intensity statin treatment. Primary outcome was the 3-year composite of all-cause death, myocardial infarction, stroke, or coronary revascularization. Secondary outcomes were safety endpoints. This trial is registered with ClinicalTrials.gov, NCT02579499.

Findings Between September 9, 2016 and November 27, 2019, 4400 patients with CAD were enrolled in the LODESTAR trial. The median age was 65 years (interquartile range, 59–73 years), 3172 (72%) were male, and 1468 (33%) had DM at baseline. There was no significant difference in the occurrence of the primary outcome between the treat-to-target group and high-intensity statin group among patients with DM (10.5% versus 11.1%, hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.69–1.29, p = 0.70) and those without DM (6.9% versus 7.5%, HR 0.93, 95% CI 0.71–1.21, p = 0.58). Among patients without DM, there was a trend towards a lower risk of new-onset DM in the treat-to-target group (8.4% versus 10.4% in the high-intensity statin group, HR 0.79, 95% CI 0.62–1.01; p = 0.06).

Interpretation In patients with CAD, a treat-to-target LDL-C strategy of 50–70 mg/dL as the goal was comparable to high-intensity statin therapy in terms of 3-year clinical efficacy and safety outcomes regardless of the presence of DM.

Funding Sam Jin Pharmaceutical, Seoul, Korea and Chong Kun Dang Pharmaceutical, Seoul, Korea.

Keywords: Coronary artery disease; Atherosclerosis; Cholesterol; Statin; Diabetes

Introduction

Statin therapy is a cornerstone of the management of patients with both diabetes mellitus (DM) and coronary artery disease (CAD), who are considered as the highest risk population among patients with atherosclerotic cardiovascular disease.[1–3] Because the clinical benefits of sufficient lowering of low-density lipoprotein cholesterol (LDL-C) in those patients are well-established,[4–6]

*Corresponding author. Division of Cardiology, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, 03722, Seoul, Korea.
**Corresponding author. Division of Cardiology, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-Ro, Gangnam-Gu, Seoul, 06273, Korea.
E-mail addresses: mkhong61@yuhs.ac (M.-K. Hong), bkhong@yuhs.ac (B.-K. Hong).
[i]These authors contributed equally to this work.

Research in context

Evidence before this study

We searched PUBMED for articles published in English since the inception of the database to June 2, 2023, with the aim of identifying relevant clinical studies. The search terms used were "statin", "intensity", and "diabetes". We retrieved 503 results. Among 503 results, we aimed to identify clinical studies that compare the effects of the treat-to-target strategy to achieve a target low-density lipoprotein cholesterol level with those of high-intensity statin therapy in patients with coronary artery disease (CAD) and diabetes mellitus (DM). However, no relevant clinical studies were found.

Added value of this study

The pre-specified subgroup analysis of the LODESTAR trial in CAD patients with and without DM showed that the treat-to-target strategy showed comparable efficacy and safety outcomes to the high-intensity statin strategy, irrespective of DM status.

Implications of all the available evidence

Despite guidelines recommending high-intensity statins for patients with CAD and DM, real-world practice has shown underutilization of high-intensity statin. This could be due to the risk of drug-related adverse events. Therefore, patients who require very long-term statin therapy may need a tailored approach considering safety issues. The findings of this study support the use of a treat-to-target strategy in patients with CAD regardless of the presence of DM.

high-intensity statin therapy is strongly recommended in most patients with both DM and CAD.[1] However, significant underuse of statins, poor drug adherence, and suboptimal dose titration are still common in real-world clinical practice and are associated with poor future clinical outcomes.[7,8] These findings may be related to concerns regarding the side-effects of high-intensity statin treatment including the potential risk of new-onset DM or worsening of DM.[6,9] Thus, identifying the optimal statin therapy and dose titration strategy to improve drug adherence and to achieve a sufficient reduction in LDL-C level is crucial. Recently, the LODESTAR trial (low-density lipoprotein cholesterol-targeting statin therapy versus intensity-based statin therapy in patients with coronary artery disease) showed that a treat-to-target strategy with a goal LDL-C of 50–70 mg/dL was non-inferior to high-intensity statin therapy in terms of 3-year composite outcomes in patients with CAD.[10] However, it remains unclear whether this treatment effect holds true for CAD patients regardless of DM status. Therefore, as one of the pre-specified analyses of the LODESTAR trial, we evaluated the effects of the treat-to-target strategy versus high-intensity statin therapy among patients with and without DM.

Methods

Study design and population

The present study was a pre-specified analysis of data from the LODESTAR trial, which was an investigator-initiated, multicentre, randomised, open-label, non-inferiority trial for dyslipidaemia management for secondary prevention in patients with CAD conducted at 12 centres in South Korea.[10] Details of the study design and protocols for the LODESTAR trial have been described previously.[10] Patients with documented CAD, including stable ischaemic heart disease or acute coronary syndrome, were enrolled.[10] Full inclusion and exclusion criteria are provided in Supplemental Table S1. The presence of DM at randomisation was defined by the investigators, based on a history of DM, the use of antidiabetic medications, a fasting glucose level ≥126 mg/dL, or a haemoglobin A1c level ≥6.5%.[11] The trial followed the ethical principles of the Declaration of Helsinki and was approved by the institutional review board of each participating centre. All participants provided written informed consent before participation in the trial. Cardiovascular Research Center (Seoul, South Korea) performed study coordination, data management, and site management services.[10] Designated trial monitors reviewed the investigational data at appropriate intervals for accuracy and completeness and ensured protocol compliance. Study safety was monitored by a data and safety monitoring board of independent physicians who acted in an advisory capability to monitor participant safety, evaluate study progress, and review the study process.[10]

Randomisation and masking

Eligible patients were randomised in a 1:1 manner to receive statin therapy by either the treat-to-target strategy or high-intensity statin therapy.[10] Web-response permuted-block randomisation (mixed blocks of 4 or 6) was used to allocate patients at each participating site, and patients were stratified by presence of DM, baseline LDL-C level ≥100 mg/dL, and acute coronary syndrome.[10]

Procedures

Patients received rosuvastatin 10 mg or atorvastatin 20 mg for moderate-intensity statin therapy, and rosuvastatin 20 mg or atorvastatin 40 mg for high-intensity statin therapy.[10,12] In the treat-to-target group, the target LDL-C level was set at below 70 mg/dL, which was the lowest LDL-C level recommended for our population in the latest guidelines at the time of trial design

(August 2015),[13–15] and statin intensity was titrated to achieve this goal, as described previously.[10] In short, for patients who were assigned to the treat-to-target group, statin-naïve patients initially received moderate-intensity statin therapy. For those already on statin therapy, the patients received a dose of study drugs (rosuvastatin or atorvastatin) based on their baseline LDL-C levels; drug dose was maintained at the same intensity for those with an LDL-C level <70 mg/dL but increased for those with an LDL-C level ≥70 mg/dL.[10] During follow-up, up-titration for those with an LDL-C level ≥70 md/dL, maintenance of the same intensity without titration for those with an LDL-C level ≥50 mg/dL and <70 mg/dL, or down-titration for those with an LDL-C level <50 mg/dL was performed.[10] For patients assigned to the high-intensity statin group, high-intensity statin therapy was initiated and maintained regardless of their LDL-C levels at randomisation and follow-up.[10] Adding non-statin agents such as ezetimibe was not strongly recommended to maintain the focus on statin therapy and to avoid introducing confounding effects by imbalances in the use of these non-statin agents.[10] For other medical treatments, guideline-directed medical therapy was strongly recommended and modification of risk factors including blood pressure or glucose control, weight reduction, exercise, dietary changes, and smoking cessation was encouraged.[10]

Follow-up visits to assess general health status, use of drugs, and the occurrence of study outcomes or adverse events were performed at 6 weeks and 3, 6, 12, 24, and 36 months.[10] Serial follow-up of patients' lipid profiles (total cholesterol, LDL-C, high-density lipoprotein cholesterol, and triglyceride levels), aspartate aminotransferase, alanine aminotransferase, creatine kinase, and creatinine levels was performed at 6 weeks and 12, 24, and 36 months.[10] Serial follow-up of plasma glucose and haemoglobin A1c levels was performed at 12, 24, and 36 months.[10]

Outcomes

In accordance with the LODESTAR trial,[10] the primary outcome was major adverse cardiac and cerebrovascular events, defined as the composite of all-cause death, myocardial infarction (MI), stroke, and any coronary revascularisation within 3 years. Death was defined as cardiovascular death and non-cardiovascular death. Cardiovascular death was defined as death caused by MI, sudden cardiac death, heart failure, stroke, cardiovascular procedures, cardiovascular bleeding, and any death for which a cardiovascular cause could not be excluded. MI was defined by clinical symptoms, changes in electrocardiograms, or abnormal findings during imaging studies, along with an increase in the creatine kinase myocardial band fraction above the upper normal limit or an increase in the troponin-T or troponin-I level >99th percentile of the upper normal limit.[10,16] Stroke was defined as an acute cerebrovascular event causing a neurologic deficit for >24 h or the presence of an acute infarction in imaging studies.[10,17] Coronary revascularisation included percutaneous coronary intervention or coronary artery bypass graft surgery, and clinically indicated revascularisation was defined by an invasive angiographic percent diameter stenosis ≥50% with ischaemic symptoms or signs, or a percent diameter stenosis ≥70% even in the absence of symptoms or signs. Secondary outcomes were 1) new-onset diabetes mellitus, 2) hospitalisation due to heart failure, 3) deep vein thrombosis or pulmonary thromboembolism, 4) endovascular revascularisation for peripheral artery disease, 5) aortic intervention or surgery, 6) end-stage kidney disease, 7) discontinuation of study drugs due to intolerance, 8) cataract operation, and 9) a composite of laboratory abnormalities. Secondary outcome definitions are provided in the Supplemental Appendix.

Statistical analysis

Consistent with the primary report of the LODESTAR trial, both primary and secondary outcomes were assessed based on the intention-to-treat population. Sensitivity analyses were conducted in the per-protocol population. Categorical data are presented as numbers with percentages. Continuous data are presented as means (standard deviations) and medians (interquartile ranges) for normal and skewed distributions, respectively. Cumulative incidence of the primary outcome at 3 years was estimated using Kaplan–Meier curves for time-to-event analysis, measured from randomisation to the first occurrence of the event of interest during follow-up, and event rates between the two groups were compared using log-rank tests. Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed using Cox regression analyses. To determine whether therapy effects (treat-to-target strategy versus high-intensity statin therapy) varied by DM status, Cox proportional hazard regression models were used and p-values for interactions between DM status and therapy were calculated. Statistical significance was defined as $p < 0.05$ without adjustment for multiple comparisons. Statistical analyses were conducted using IBM SPSS version 25.0 (IBM Corporation, Chicago, IL, USA) and R 3.5.3 software (R Foundation for Statistical Computing, Vienna, Austria).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between September 9, 2016 and November 27, 2019, a total of 4400 participants with CAD were enrolled in the LODESTAR trial, and 1468 (33%) patients were identified as having DM at baseline (Fig. 1). Baseline clinical

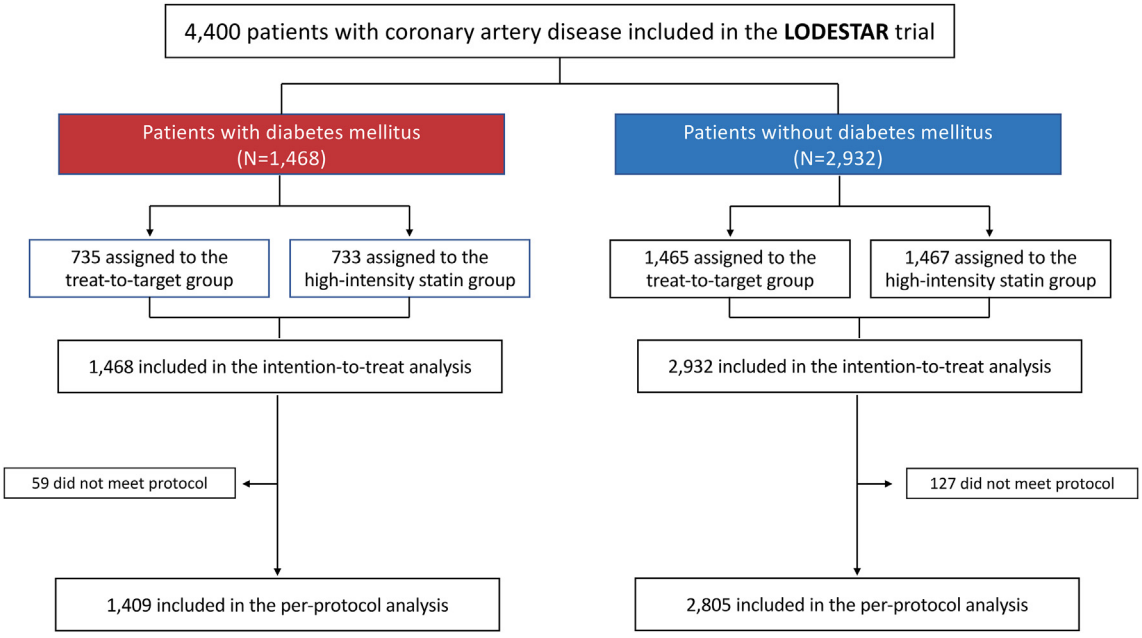

***Fig. 1:* Study flow of participants**. LODESTAR, low-density lipoprotein cholesterol-targeting statin therapy versus intensity-based statin therapy in patients with coronary artery disease.

characteristics and laboratory profiles stratified by DM status are presented in Supplemental Table S2. Patients with and without DM who were allocated to either the treat-to-target group or the high-intensity statin group showed similar baseline clinical characteristics, medication history, baseline haemoglobin A1c, and lipid profiles except for the greater proportion of chronic kidney disease in the high-intensity statin therapy group in patients with DM (Table 1). Patients were followed for a median of 3.0 years (interquartile range, 3.0–3.0 years), and the 3-year clinical outcomes are presented in Table 2. Among patients with DM, the incidence rate of the primary outcome was 10.5% in the treat-to-target group and 11.1% in the high-intensity statin group (HR 0.94, 95% CI 0.69–1.29, p = 0.70). Similarly, among patients without DM, the occurrence of the primary outcome was comparable between the two treatment strategies (6.9% versus 7.5%, respectively, HR 0.93, 95% CI 0.71–1.21, p = 0.58) (Fig. 2). There was no significant heterogeneity in treatment effect according to the presence of DM (p for interaction [p_{int}] = 0.94). Overall occurrences of individual components of the primary outcome were comparable between the two treatment strategies in patients with and without DM (all p > 0.05), with no significant interactions between DM and treatment strategy (all p_{int} >0.05). Serial changes in lipid profiles during the 3-year follow-up are shown in Table 3. In patients with and without DM allocated to either the treat-to-target group or high-intensity statin group, there was no significant difference in LDL-C levels during the 3-year follow-up period. Throughout the study period, mean (SD) LDL-C levels did not differ significantly between treat-to-target strategy and high-intensity statin groups among patients with DM [64.9 (17.7) mg/dL versus 63.7 (19.9) mg/dL, p = 0.19] and those without DM [70.4 (17.3) mg/dL versus 70.4 (20.8) mg/dL, p = 0.97]. The proportions of patients with LDL-C level <70 mg/dL were comparable across the treat-to-target group and high-intensity statin group among patients with and without DM during the 3-year follow-up period (Table 3). During the study period, there was no significant difference in the mean haemoglobin A1c level between the two treatment strategies, both in patients with and without DM (Table 3). The proportions of patients with and without DM who received high-intensity statin treatment and ezetimibe are shown in Fig. 3. Ezetimibe was more frequently prescribed in the treat-to-target group of patients regardless of the presence of DM. Furthermore, in the treat-to-target group of patients with DM, a high-intensity statin was used in 46% at 1 year and in 47% at 2 and 3 years. The incidence of secondary outcomes stratified by DM and treatment strategy are presented in Table 2. Among patients with DM, there was no significant difference in the occurrence of secondary outcomes between the two treatment strategies. Meanwhile, compared with high-intensity statin therapy, the treat-to-target strategy was associated with a substantially lower risk of new-onset DM requiring initiation of medication in patients without DM (7.4% versus 5.1%, HR 0.68, 95% CI 0.51–0.92,

Characteristics	Patients with DM (N = 1468)			Patients without DM (N = 2932)		
	Treat-to-target group (N = 735)	High-intensity statin group (N = 733)	p value	Treat-to-target group (N = 1465)	High-intensity statin group (N = 1467)	p value
Age, mean (SD), y	66.2 (9.4)	66.4 (9.5)	0.70	64.4 (10.2)	64.5 (9.8)	0.73
Male	532 (72.4%)	546 (74.5%)	0.39	1042 (71.1%)	1052 (71.7%)	0.76
Weight, mean (SD), kg	68.1 (11.4)	68.4 (11.2)	0.55	66.5 (10.5)	66.5 (10.2)	0.89
Body-mass index, mean (SD), kg/m^2	25.1 (3.1)	25.1 (3.1)	0.86	24.6 (2.8)	24.5 (2.8)	0.83
Past medical history						
Hypertension	576 (78.4%)	548 (74.8%)	0.12	897 (61.2%)	916 (62.4%)	0.52
Diabetes with insulin treatment	81 (11.0%)	81 (11.1%)	0.99	–	–	–
Chronic kidney disease[a]	82 (11.2%)	110 (15.0%)	0.04	71 (4.8%)	56 (3.8%)	0.20
End-stage kidney disease on dialysis	11 (1.5%)	13 (1.8%)	0.83	2 (0.1%)	3 (0.2%)	0.99
Previous PCI	458 (62.3%)	434 (59.2%)	0.24	785 (53.6%)	780 (53.2%)	0.85
Previous CABG	78 (10.6%)	88 (12.0%)	0.45	76 (5.2%)	92 (6.3%)	0.24
Previous stroke	58 (7.9%)	60 (8.2%)	0.91	77 (5.3%)	68 (4.6%)	0.49
Current smoker	100 (13.6%)	97 (13.2%)	0.90	203 (13.9%)	203 (13.8%)	0.99
Lipids, mean (SD), mg/dl						
Low-density lipoprotein cholesterol	78.4 (31.1)	78.8 (28.8)	0.76	90.4 (32.8)	91.2 (31.9)	0.50
High-density lipoprotein cholesterol	44.4 (11.3)	44.4 (10.8)	0.98	47.9 (11.4)	48.2 (11.7)	0.44
Total cholesterol	145.3 (36.3)	147.4 (33.4)	0.24	161.5 (37.9)	162.3 (37.8)	0.53
Triglycerides	143.2 (90.1)	146.9 (87.9)	0.43	136.0 (79.8)	132.1 (79.8)	0.18
Serum haemoglobin A1c level, %	7.2 (1.2)	7.1 (1.1)	0.11	5.9 (0.5)	5.9 (0.5)	0.86
Clinical presentation at randomisation			0.62			0.74
Acute myocardial infarction within 1 year	49 (6.7%)	63 (8.6%)		110 (7.5%)	116 (7.9%)	
>1 year after myocardial infarction	125 (17.0%)	131 (17.9%)		213 (14.5%)	206 (14.0%)	
Unstable angina or revascularisation within 1 year	132 (18.0%)	131 (17.9%)		249 (17.0%)	276 (18.8%)	
>1 year after unstable angina or revascularisation	331 (45.0%)	309 (42.2%)		579 (39.5%)	565 (38.5%)	
Detection of CAD at screening without symptoms	98 (13.3%)	99 (13.5%)		314 (21.4%)	304 (20.7%)	
Lipid lowering therapy before randomisation						
Statin			0.85			0.11
High-intensity statin	188 (25.6%)	197 (26.9%)		341 (23.3%)	379 (25.8%)	
Moderate-intensity statin	455 (61.9%)	438 (59.8%)		829 (56.6%)	802 (54.7%)	
Low-intensity statin	23 (3.1%)	23 (3.1%)		30 (2.0%)	17 (1.2%)	
None	69 (9.4%)	75 (10.2%)		265 (18.1%)	269 (18.3%)	
Ezetimibe	99 (13.5%)	91 (12.4%)	0.60	154 (10.5%)	135 (9.2%)	0.26

Data are mean (SD), or number (%). Abbreviations: CABG, coronary-artery bypass grafting; CAD, coronary artery disease; PCI, percutaneous coronary intervention. [a]Chronic kidney disease was defined as an estimated glomerular filtration of less than 60 ml per minute per 1.73 m^2 of body-surface area.

Table 1: **Baseline characteristics according to diabetes mellitus and treatment strategy.**

p = 0.01) and there was a trend towards a lower risk of new-onset DM (10.4% versus 8.4%, HR 0.79, 95% CI 0.62–1.01; p = 0.06). In an analysis of the per-protocol population (Supplemental Table S3), the incidence of the primary outcome was also comparable between the two treatment strategies, regardless of DM status, with no heterogeneity in effects of treatment strategy (Supplemental Table S4). Consistent with the primary analysis, the occurrence of new-onset DM requiring initiation of medication was significantly lower in the treat-to-target group than in the high-intensity statin group (5.1% versus 7.5%, HR 0.68, 95% CI 0.50–0.92, p = 0.01) among patients without DM (Supplemental Table S4).

Discussion

This pre-specified analysis of the LODESTAR trial with patients with CAD revealed that among patients with and without DM, the risk of composite adverse events was comparable between the treat-to-target strategy and high-intensity statin therapy, despite less high-intensity statin use in the treat-to-target group. Serial changes in LDL-C level and haemoglobin A1c were also comparable between the two treatment strategies in patients with and without DM. No difference was observed in the proportion of patients achieving LDL-C <70 mg/dL across the treatment strategies regardless of baseline DM status over the study period. Importantly, at the end of 3-year follow-up, 66% of DM patients and 54% of

Outcome	Patients with DM (N = 1468)				Patients without DM (N = 2932)				P_{int}[a]
	Treat-to-target group (N = 735)	High-intensity statin group (N = 733)	HR (95% CI)	p value	Treat-to-target group (N = 1465)	High-intensity statin group (N = 1467)	HR (95% CI)	p value	
Primary outcome									
Death, myocardial infarction, stroke, or coronary revascularisation	76 (10.5%)	81 (11.1%)	0.94 (0.69–1.29)	0.70	101 (6.9%)	109 (7.5%)	0.93 (0.71–1.21)	0.58	0.94
Components of the primary outcome									
Death	27 (3.7%)	25 (3.4%)	1.09 (0.63–1.88)	0.75	27 (1.9%)	29 (2.0%)	0.93 (0.55–1.57)	0.78	0.68
Cardiac death	7 (1.0%)	4 (0.6%)	1.77 (0.52–6.04)	0.36	9 (0.6%)	9 (0.6%)	1.00 (0.40–2.51)	0.99	0.47
Myocardial infarction	14 (2.0%)	14 (2.0%)	1.01 (0.48–2.12)	0.98	20 (1.4%)	12 (0.8%)	1.82 (0.87–3.79)	0.11	0.27
Stroke	7 (1.0%)	16 (2.2%)	0.44 (0.18–1.07)	0.08	10 (0.7%)	11 (0.8%)	0.91 (0.39–2.14)	0.82	0.25
Ischaemic stroke	5	13			7	7			
Hemorrhagic stroke	2	3			3	4			
Coronary revascularisation	45 (6.4%)	41 (5.7%)	1.11 (0.73–1.70)	0.62	67 (4.6%)	73 (5.1%)	0.92 (0.66–1.28)	0.61	0.48
Secondary outcomes									
New-onset DM	–	–	–	–	121 (8.4%)	150 (10.4%)	0.79 (0.62–1.01)	0.06	–
Initiation of anti-diabetic medication	–	–	–	–	73 (5.1%)	105 (7.4%)	0.68 (0.51–0.92)	0.01	–
Discontinuation of statin therapy	14 (1.9%)	16 (2.2%)	0.88 (0.43–1.80)	0.71	17 (1.2%)	30 (2.1%)	0.56 (0.31–1.02)	0.06	0.36
Deep vein thrombosis or pulmonary embolism	1 (0.1%)	1 (0.1%)	1.01 (0.06–16.12)	0.99	3 (0.2%)	4 (0.3%)	0.75 (0.17–3.34)	0.73	0.86
Peripheral artery revascularisation	5 (0.7%)	6 (0.8%)	0.84 (0.26–2.75)	0.77	7 (0.4%)	11 (0.7%)	0.54 (0.20–1.47)	0.23	0.58
Hospitalisation due to heart failure	8 (1.1%)	5 (0.7%)	1.61 (0.53–4.93)	0.40	5 (0.3%)	2 (0.1%)	2.50 (0.48–12.87)	0.27	0.67
Composite of laboratory abnormalities	9 (1.3%)	15 (2.1%)	0.60 (0.26–1.38)	0.23	9 (0.6%)	15 (1.0%)	0.64 (0.28–1.48)	0.22	0.98
Liver enzyme elevation (aminotransferase)	4	4			4	8			
Creatinine kinase elevation	0	1			3	7			
Creatinine elevation	5	10			2	1			
Cataract operation	18 (2.5%)	20 (2.8%)	0.90 (0.48–1.71)	0.74	25 (1.7%)	22 (1.5%)	1.14 (0.64–2.02)	0.77	0.58
End-stage kidney disease on dialysis	3 (0.4%)	9 (1.2%)	0.34 (0.09–1.24)	0.10	0	1 (0.1%)	NA	0.32	0.99

Data are the number of events (%). The percentages shown were calculated using Kaplan–Meier estimates. DM, diabetes mellitus; HR, hazard ratio; CI, confidence interval; NA, not available. [a]P_{int}: p-value for interaction between DM status and treatment strategy.

Table 2: **Primary and secondary outcomes according to diabetes mellitus and treatment strategy.**

non-DM patients in the treat-to-target group achieved the target LDL-C of 50–70 mg/dL. In addition, although the study protocol did not strongly encourage the use of non-statin lipid-lowering agents, the use of ezetimibe was more common in the treat-to-target group than in the high-intensity statin group. These results suggest that achieving optimal LDL-C reduction with statin therapy alone is quite challenging and that there may be physician preference and improved patient tolerability for the addition of ezetimibe over statin intensification to achieve target LDL-C level.

Current lipid management guidelines strongly recommend a stringent reduction in LDL-C level among patients with CAD to prevent recurrent cardiovascular events, and the importance of optimal LDL-C reduction is further emphasized in patients with concurrent cardiovascular risk factors such as DM.[1–3] The 2018 AHA/ACC guidelines for lipid management recommend the use of high-intensity statin therapy to lower LDL-C ≥ 50% from baseline in diabetic patients who have multiple cardiovascular risk factors.[1] Similarly, the American Diabetes Association's 2023 update strongly recommends the use of high-intensity statin therapy for secondary prevention in diabetic patients with atherosclerotic cardiovascular disease.[3] However, despite the well-recognized clinical benefits of high-intensity statin therapy in secondary prevention of adverse cardiovascular events in patients with CAD, concerns regarded statin-related side-effects have posed a considerable hurdle for prescription of high-intensity statins and are associated with low drug adherence in these patients.[18,19] In the 2019 ESC/EAS lipid guidelines, all patients with documented CAD, regardless of diabetes status, are classified as a very high-risk population and it is strongly recommended that these patients achieve at least a 50% reduction in their baseline LDL-C level and maintain their LDL-C level below 55 mg/dL.[2] However, the guidelines also emphasize assessing safety issues and adjusting statin treatment dose accordingly (class of recommendation, IIa).[2] Taken together, two rational therapeutic approaches have been proposed to achieve sufficient LDL-C reduction in high-risk populations: (1) adjusting the statin dose to achieve a target LDL-C level, or (2) initiating treatment with a high-intensity statin until intolerance occurs. However, there is insufficient evidence concerning which approach is most advantageous in terms of efficacy and safety profile in CAD

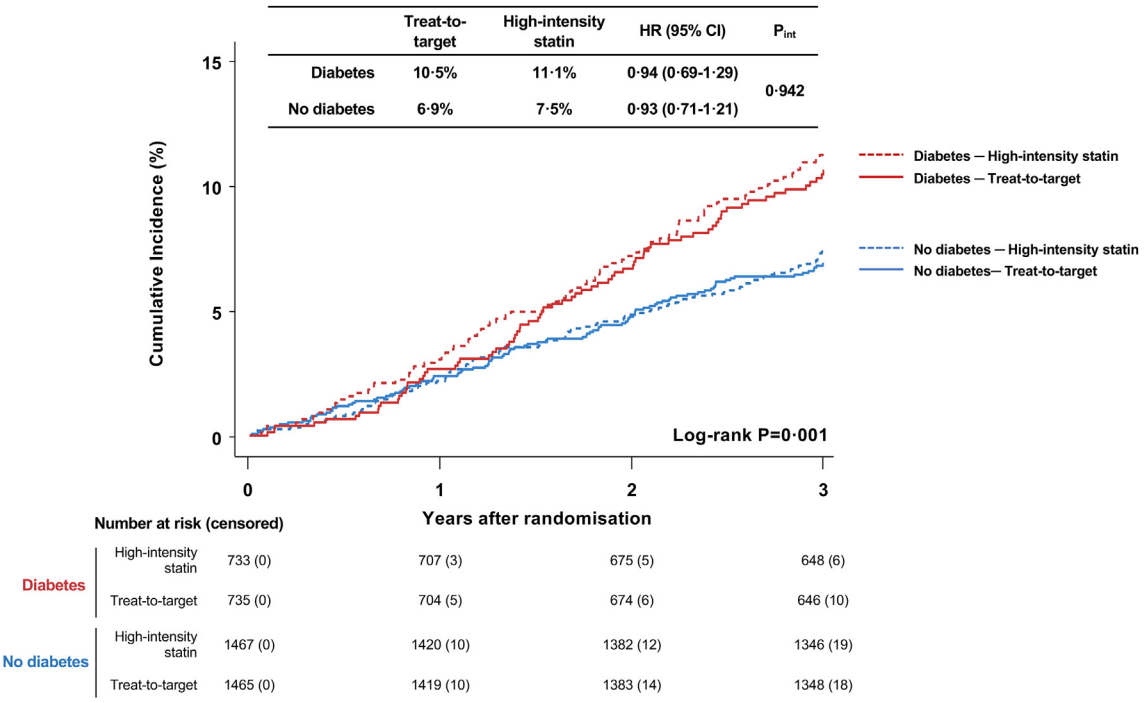

***Fig. 2:* Time-to-event curves of the primary outcome among patients with and without diabetes mellitus.** Kaplan–Meier survival curves for the primary outcome among patients with and without diabetes mellitus according to treatment strategy. HR, hazard ratio; CI, confidence interval; P_{int}, p for interaction. The number of censored patients is shown in brackets at each time point for each group.

patients, particularly those with DM, the most common cardiovascular risk factor.[3,4,20]

In this pre-specified analysis, although less than half of the treat-to-target group in patients with DM received high-intensity statin therapy, the effect of the treat-to-target strategy on the primary outcome was comparable to that of high-intensity statin therapy, with no significant difference in LDL-C levels during the study period. In accordance with our findings, a post-hoc analysis of the IMPROVE-IT trial (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) showed a consistent association between intensive LDL-C reduction and improved clinical outcomes in patients with an acute coronary syndrome, independent of the use of ezetimibe.[21,22] In addition, the favorable impact of aggressive lipid-lowering therapy after acute coronary syndrome was more prominent in patients with DM than in those without DM,[4] implying that achieving an adequate reduction in LDL-cholesterol levels is crucial in patients with DM, irrespective of the treatment strategy employed.

In patients without DM, the occurrence of new-onset DM was not significantly different between the treatment strategies, while the incidence of new-onset DM requiring initiation of anti-diabetic medication was relatively lower in the treat-to-target group. The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial revealed a notable relationship between high-intensity rosuvastatin treatment and new-onset DM.[23] Furthermore, a meta-analysis of 32,752 patients without DM on statin therapy showed a significant association between high-intensity statin therapy and an elevated risk of developing new-onset DM compared to moderate-intensity statin therapy (HR 1.12, 95% CI 1.04–1.22).[24,25] Despite guideline recommendations, underutilization of high-intensity statins in patients with CAD was evident in real-world practice, which could be attributed to the risk of various statin-associated side effects, including new-onset DM, muscle-related symptoms and hepatotoxicity.[26,27] Therefore, patients who require long-term statin therapy need a tailored approach. In this context, starting with a moderate-intensity statin and gradual up-titration, or adopting an early ezetimibe combination strategy is worth consideration. The LIVES (Livalo Effectiveness and Safety) prospective observational study with 20,279 patients with dyslipidemia showed that pitavastatin, a moderate-intensity statin, was not associated with an elevation of hemoglobin A1c or the occurrence of new-onset DM for 2 years of study period.[28] The REAL-CAD (Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy With Pitavastatin in Coronary Artery Disease) trial demonstrated that high-dose pitavastatin, compared with low-dose pitavastatin, significantly reduced adverse cardiovascular events in

	Patients with DM			Patients without DM		
	Treat-to-target group	High-intensity statin group	p-value	Treat-to-target group	High-intensity statin group	p-value
At randomization						
Total number of patients	735	733		1465	1467	
LDL-cholesterol, mg/dL	78.4 (31.1)	78.8 (28.8)	0.76	90.4 (32.8)	91.2 (31.9)	0.50
Total cholesterol, mg/dL	145.2 (36.3)	147.4 (33.4)	0.24	161.5 (37.9)	162.3 (37.8)	0.53
Triglycerides, mg/dL	143.2 (90.1)	146.9 (87.9)	0.43	136.0 (79.8)	132.1 (79.8)	0.18
HDL-cholesterol, mg/dL	44.4 (11.3)	44.4 (10.8)	0.98	47.9 (11.4)	48.2 (11.7)	0.44
Number of patients with LDL cholesterol level <70 mg/dL	315 (42.9%)	298 (40.7%)	0.42	397 (27.1%)	357 (24.3%)	0.10
Serum haemoglobin A1c level, %	7.2 (1.2)	7.1 (1.1)	0.11	5.9 (0.5)	5.9 (0.5)	0.86
At 1-year						
Total number of patients	629	633		1233	1221	
LDL-cholesterol, mg/dL	66.6 (20.3)	64.4 (22.1)	0.07	70.7 (20.6)	70.7 (22.7)	0.98
Total cholesterol, mg/dL	135.9 (27.6)	138.4 (28.4)	0.11	137.7 (27.4)	135.9 (26.8)	0.10
Triglycerides, mg/dL	135.2 (86.6)	133.8 (81.3)	0.78	130.3 (74.4)	128.8 (72.3)	0.58
HDL-cholesterol, mg/dL	47.4 (11.9)	47.4 (11.8)	0.99	47.9 (11.8)	47.7 (11.9)	0.50
Number of patients with LDL cholesterol level <70 mg/dL	395 (62.8%)	416 (65.7%)	0.31	643 (52.1%)	676 (55.4%)	0.12
Serum haemoglobin A1c level, %	7.2 (1.2)	7.2 (1.2)	0.47	5.9 (0.5)	5.9 (0.6)	0.26
At 2 years						
Total number of patients	550	578		1104	1101	
LDL-cholesterol, mg/dL	63.1 (19.9)	63.0 (23.0)	0.94	68.6 (18.9)	69.2 (22.0)	0.47
Total cholesterol, mg/dL	134.6 (26.8)	135.9 (27.5)	0.43	137.2 (26.1)	135.6 (26.0)	0.14
Triglycerides, mg/dL	131.2 (80.1)	130.7 (75.4)	0.91	127.7 (67.4)	122.5 (69.0)	0.08
HDL-cholesterol, mg/dL	47.0 (11.9)	46.6 (12.0)	0.53	47.9 (11.5)	47.3 (11.7)	0.24
Number of patients with LDL cholesterol level <70 mg/dL	380 (69.1%)	386 (66.8%)	0.44	625 (56.6%)	629 (57.1%)	0.84
Serum haemoglobin A1c level, %	7.2 (1.2)	7.2 (1.1)	0.69	5.9 (0.5)	6.0 (0.6)	0.36
At 3 years						
Total number of patients	532	555		1028	999	
LDL-cholesterol, mg/dL	63.6 (19.9)	62.9 (21.7)	0.54	69.6 (21.6)	70.1 (23.3)	0.63
Total cholesterol, mg/dL	133.3 (26.9)	137.3 (28.7)	0.02	136.3 (26.6)	136.0 (26.2)	0.80
Triglycerides, mg/dL	128.9 (71.5)	126.9 (84.7)	0.66	128.0 (73.9)	126.9 (79.5)	0.74
HDL-cholesterol, mg/dL	45.7 (11.2)	46.9 (11.6)	0.09	46.7 (11.6)	47.1 (11.4)	0.41
Number of patients with LDL cholesterol level <70 mg/dL	353 (66.4%)	378 (68.1%)	0.58	555 (54.0%)	549 (55.0%)	0.70
Serum haemoglobin A1c level, %	7.2 (1.2)	7.1 (1.1)	0.11	6.0 (0.5)	6.0 (0.5)	0.86

Data are presented as means (standard deviations) or number (%). DM, diabetes mellitus; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 3: **Serial changes in laboratory profiles and the proportion of patients with LDL-cholesterol level of <70 mg/dL according to diabetes mellitus and treatment strategy.**

patients with and without DM, while not increasing the risk of new-onset DM.[29] Furthermore, a recent study in patients with atherosclerotic cardiovascular disease reported that moderate-intensity statin therapy combined with ezetimibe provided favorable cardiovascular outcomes comparable to those of high-intensity statin therapy along with a significantly lower incidence of drug intolerance.[30] These effects were consistently observed in patients with atherosclerotic cardiovascular disease with and without DM.[20]

In contrast to previous studies that focused primarily on the treatment effects of a particular statin potency, or the additive benefits of 'non-statin agents' in combination with an equivalent statin dose,[4–6,21–23] the LODESTAR trial uniquely evaluated the therapeutic impact of the treat-to-target strategy versus fixed-dose high-intensity statin strategy.[10] Consistent with the primary results of LODESTAR trial, the current study suggested that a treat-to-target strategy could be a reasonable therapeutic approach in patients with CAD, irrespective of their DM status.

The current study had several limitations. First, despite the fact that the current study was based on a pre-specified subgroup analysis, the results derived from the subgroups of patients were not sufficiently powered to draw definite conclusions regarding the impacts of the treat-to-target strategy versus high-intensity statin therapy. Therefore, the possibility of a chance finding cannot be excluded. Second, the target LDL-C level was set below 70 mg/dL, which was the lowest LDL-C level recommended for our population in the latest guidelines at the time of trial design in the treat-to-target group of the present study.[10] However, the latest European guidelines recommend a lower LDL-C

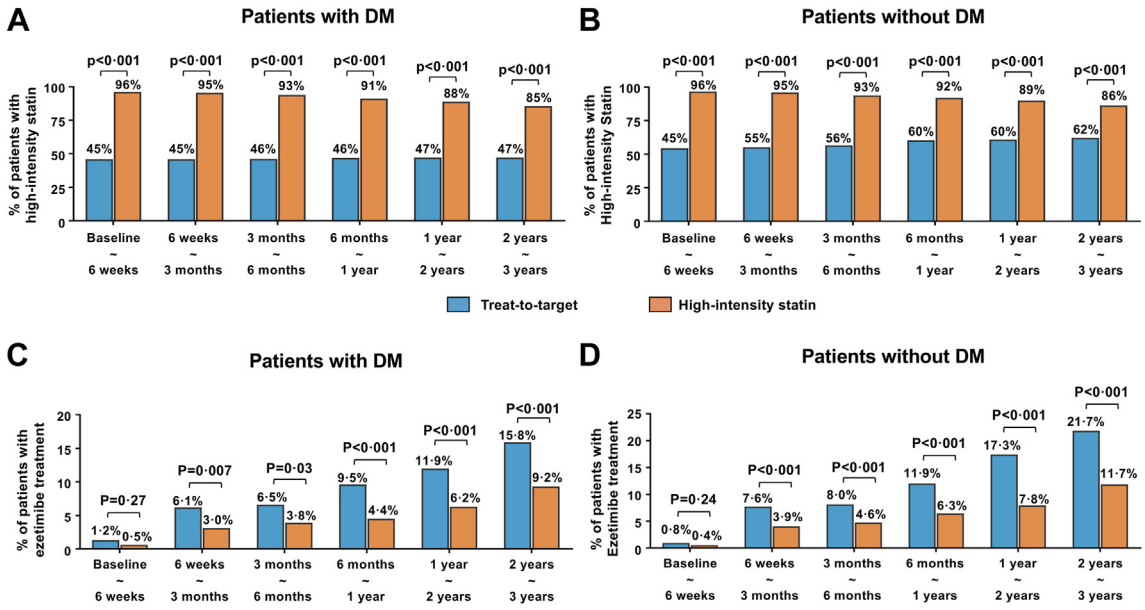

Fig. 3: **Proportion of patients receiving high-intensity statin or ezetimibe therapy**. Serial changes in the proportion of patients prescribed a high-intensity statin (**A** and **B**) or ezetimibe (**C** and **D**) among patients with (**A** and **C**) and without (**B** and **D**) DM. DM, diabetes mellitus.

target of <55 mg/dL in patients with CAD; further research is needed based on this recent change in recommended target LDL-C level. Third, the LODESTAR trial was an open-label study in which both physicians and patients were aware of their assigned treatment arm, which could have introduced bias. Fourth, comparisons of each component of the primary outcome were limited by the small number of events, and there is the possibility of type I error given the multiple comparisons. Fifth, the achievement of the target LDL-C goal in the treat-to-target group was less than optimal, even though not statistically different from the high-intensity statin group.

In conclusion, in patients with CAD, a treat-to-target LDL-C strategy of 50–70 mg/dL as the goal was comparable to high-intensity statin therapy in terms of 3-year efficacy and safety outcomes regardless of the presence of DM.

Contributors

The study was designed by S-JL, WCK, J-YL, B-KH, and M-KH. The final statistical analyses, data interpretation, and manuscript drafting were carried out by S-JL, WCK, J-YL, B-KH, and M-KH. S-JL and M-KH directly accessed and verified the underlying data of the manuscript. Study supervision was provided by B-KH and M-KH. All authors participated in patient enrollment, conducted clinical follow-up, and made significant revisions to the draft for important intellectual content. The final version of the manuscript was approved by all authors, who ensured the accuracy and integrity of all aspects of the work. All authors had full access to the study data and share final responsibility for the decision to submit the manuscript for publication.

Data sharing statement

The data that support the findings of this study may be available from the corresponding author upon reasonable request after all planned manuscripts have been accepted for publication.

Declaration of interests

M-KH has received speaker's fees from Medtronic, Edward Lifesciences, and Viatris Korea and institutional research grants from Sam Jin Pharmaceutical and Chong Kun Dang Pharmaceutical. All other authors declare no competing interests.

Acknowledgements

This study was funded by Sam Jin Pharmaceutical, Seoul, Korea and Chong Kun Dang Pharmaceutical, Seoul, Korea, and supported by the Cardiovascular Research Center, Seoul, Korea.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102227.

References

1 Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2019; 73:e285–e350.
2 Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111–188.
3 ElSayed NA, Aleppo G, Aroda VR, et al. 10. Cardiovascular disease and risk management: standards of care in diabetes-2023. *Diabetes Care*. 2023;46(Suppl 1):S158–S190.
4 Giugliano RP, Cannon CP, Blazing MA, et al. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation*. 2018;137:1571–1582.
5 Sabatine MS, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. *Lancet Diabetes Endocrinol*. 2017;5:941–950.
6 Ray KK, Colhoun HM, Szarek M, et al. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary

syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. *Lancet Diabetes Endocrinol*. 2019;7:618–628.
7 Bin Abdulhak AA, Vaughan-Sarrzin M, Kaboli P, et al. Temporal trends of high-intensity statin therapy among veterans treated with percutaneous coronary intervention. *J Am Heart Assoc*. 2018;7:e007370.
8 Hirsh BJ, Smilowitz NR, Rosenson RS, Fuster V, Sperling LS. Utilization of and adherence to guideline-recommended lipid-lowering therapy after acute coronary syndrome: opportunities for improvement. *J Am Coll Cardiol*. 2015;66:184–192.
9 Crandall JP, Mather K, Rajpathak SN, et al. Statin use and risk of developing diabetes: results from the diabetes prevention program. *BMJ Open Diabetes Res Care*. 2017;5:e000438.
10 Hong SJ, Lee YJ, Lee SJ, et al. Treat-to-target or high-intensity statin in patients with coronaryartery disease: a randomised clinical trial. *JAMA*. 2023;329:1078–1087.
11 American Diabetes Association. 2. Classification and diagnosis of diabetes. *Diabetes Care*. 2016;39:S13–S22.
12 Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation*. 2014;129(25 Suppl 2):S1–S45.
13 Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidaemia: part 1–full report. *J Clin Lipidol*. 2015;9:129–169.
14 Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J*. 2011;32:1769–1818.
15 An International Atherosclerosis Society position paper: global recommendations for the management of dyslipidaemia–full report. *J Clin Lipidol*. 2014;8:29–60.
16 Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020–2035.
17 Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:2064–2089.
18 Ray KK, Reeskamp LF, Laufs U, et al. Combination lipid-lowering therapy as first-line strategy in very high-risk patients. *Eur Heart J*. 2022;43:830–833.
19 Ihm SH, Kim KI, Lee KJ, et al. Interventions for adherence improvement in the primary prevention of cardiovascular diseases: expert consensus statement. *Korean Circ J*. 2022;52:1–33.
20 Lee YJ, Cho JY, You SC, et al. Moderate-intensity statin with ezetimibe versus high-intensity statin in patients with diabetes and atherosclerotic cardiovascular disease in the RACING trial. *Eur Heart J*. 2023;44:972–983.
21 Bohula EA, Giugliano RP, Cannon CP, et al. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. *Circulation*. 2015;132:1224–1233.
22 Giugliano RP, Wiviott SD, Blazing MA, et al. Long-term safety and efficacy of achieving very low levels of low-density lipoprotein cholesterol: a prespecified analysis of the IMPROVE-IT Trial. *JAMA Cardiol*. 2017;2:547–555.
23 Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–2207.
24 Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA*. 2011;305:2556–2564.
25 Adhyaru BB, Jacobson TA. Safety and efficacy of statin therapy. *Nat Rev Cardiol*. 2018;15:757–769.
26 Nelson AJ, Haynes K, Shambhu S, et al. High-intensity statin use among patients with atherosclerosis in the U.S. *J Am Coll Cardiol*. 2022;79:1802–1813.
27 Navar AM, Kolkailah AA, Gupta A, et al. *Gaps in guideline-based lipid-lowering therapy for secondary prevention in the United States: a retrospective cohort study of 322153 patients*. Circ Cardiovasc Qual Outcomes; 2023:e009787.
28 Yokote K, Shimano H, Urashima M, Teramoto T. Efficacy and safety of pitavastatin in Japanese patients with hypercholesterolemia: LIVES study and subanalysis. *Expert Rev Cardiovasc Ther*. 2011;9:555–562.
29 Taguchi I, Iimuro S, Iwata H, et al. High-dose versus low-dose pitavastatin in Japanese patients with stable coronary artery disease (REAL-CAD): a randomized superiority trial. *Circulation*. 2018;137:1997–2009.
30 Kim BK, Hong SJ, Lee YJ, et al. Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. *Lancet*. 2022;400:380–390.