ESC European Society of Cardiology

European Heart Journal (2022) **00**, 1–13
https://doi.org/10.1093/eurheartj/ehac709

CLINICAL RESEARCH
Clinical trials

Moderate-intensity statin with ezetimibe vs. high-intensity statin in patients with diabetes and atherosclerotic cardiovascular disease in the RACING trial

Yong-Joon Lee [1†], Jae Young Cho[2†], Seng Chan You[3], Yong-Ho Lee[1], Kyeong Ho Yun[2]*, Yun-Hyeong Cho[4], Won-Yong Shin[5], Sang Wook Im[6], Woong Chol Kang[7], Yongwhi Park[8], Sung Yoon Lee[9], Seung-Jun Lee[1], Sung-Jin Hong[1], Chul-Min Ahn[1], Byeong-Keuk Kim[1], Young-Guk Ko[1], Donghoon Choi[1], Myeong-Ki Hong[1], Yangsoo Jang[6], and Jung-Sun Kim [1]*

[1]Division of Cardiology, Severance Hospital, Yonsei University College of Medicine, Yonsei-ro 50-1, Seoul 03722, Korea; [2]Department of Cardiovascular Medicine, Wonkwang University Hospital, Muwang-ro 895, Iksan 54538, Korea; [3]Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Yonsei-ro 50-1, Seoul 03722, Korea; [4]Department of Cardiology, Hanyang University College of Medicine, Hwasu-ro 14 beon-gil 55, Goyang 10475, Korea; [5]Department of Cardiology, Soonchunhyang University Cheonan Hospital, Suncheonhyang 6-gil 31, Cheonan 31151, Korea; [6]Department of Cardiology, CHA University College of Medicine, Yatap-ro 59, Seongnam 13496, Korea; [7]Department of Cardiology, Gachon University College of Medicine, Namdong-daero 774 beon-gil 21, Incheon 21565, Korea; [8]Department of Cardiology, Gyeongsang National University Changwon Hospital, Samjeongja-ro 11, Changwon 51472, Korea; and [9]Department of Cardiology, Inje University Ilsan Paik Hospital, Juhwa-ro 170, Ilsan 10380, Korea

Received 22 August 2022; revised 15 October 2022; accepted 17 November 2022

Listen to the audio abstract of this contribution.

Abstract

Aims This study evaluated the effect of moderate-intensity statin with ezetimibe combination therapy vs. high-intensity statin monotherapy among patients with diabetes mellitus (DM) and atherosclerotic cardiovascular disease (ASCVD).

Methods and results This was a pre-specified, stratified subgroup analysis of the DM cohort in the RACING trial. The primary outcome was a 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke. Among total patients, 1398 (37.0%) had DM at baseline. The incidence of the primary outcome was 10.0% and 11.3% among patients with DM randomized to ezetimibe combination therapy vs. high-intensity statin monotherapy (hazard ratio: 0.89; 95% confidence interval: 0.64–1.22; $P = 0.460$). Intolerance-related discontinuation or dose reduction of the study drug was observed in 5.2% and 8.7% of patients in each group, respectively ($P = 0.014$). LDL cholesterol levels <70 mg/dL at 1, 2, and 3 years were observed in 81.0%, 83.1%, and 79.9% of patients in the ezetimibe combination therapy group, and 64.1%, 70.2%, and 66.8% of patients in the high-intensity statin monotherapy group (all $P < 0.001$). In the total population, no significant interactions were found between DM status and therapy regarding primary outcome, intolerance-related discontinuation or dose reduction, and the proportion of patients with LDL cholesterol levels <70 mg/dL.

Conclusion Ezetimibe combination therapy effects observed in the RACING trial population are preserved among patients with DM. This study supports moderate-intensity statin with ezetimibe combination therapy as a suitable alternative to high-intensity statins if the latter cannot be tolerated, or further reduction in LDL cholesterol is required among patients with DM and ASCVD.

Clinical Trial Registration ClinicalTrials.gov, Identifier:NCT03044665.

* Corresponding author. Tel: +(822) 2228 8457, Fax: +(822) 393 2041, Email: kjs1218@yuhs.ac (J.S.-K.); Tel: +(8210) 4330 6049, Fax: +(8263) 858 3922, Email: dryunkh@gmail.com (K.H.Y)
† These authors contributed equally to this work.

Structured Graphical Abstract

Key Question

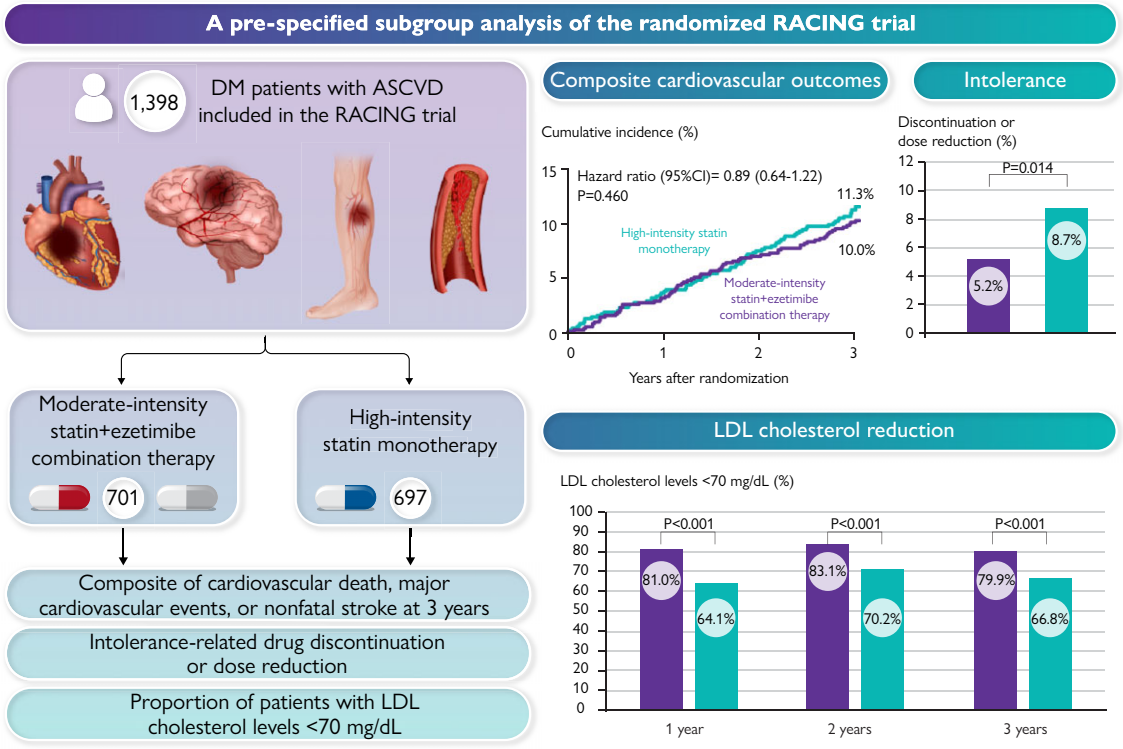
What is an evidence-based, alternative option to high-intensity statins for managing dyslipidaemia among patients with diabetes mellitus (DM) and atherosclerotic cardiovascular disease (ASCVD)?

Key Finding

Among patients with DM and ASCVD, moderate-intensity statin with ezetimibe combination therapy was comparable to high-intensity statin monotherapy regarding 3-year cardiovascular events with lower intolerance-related discontinuation or dose reduction and higher proportion of patients with low-density lipoprotein cholesterol levels <70 mg/dL.

Take Home Message

The use of moderate-intensity statin with ezetimibe combination therapy is a reasonable alternative to high-intensity statin monotherapy, as recommended by the current guidelines for secondary prevention among patients with DM and ASCVD.



Keywords Ezetimibe • Statin • Diabetes mellitus • Atherosclerotic cardiovascular disease

Introduction

The use of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins) has been considered the cornerstone of lipid-lowering therapy for patients with documented atherosclerotic cardiovascular disease (ASCVD).[1–3] Globally, ~537 million adults were estimated to have diabetes mellitus (DM) in 2021.[4] Patients with concomitant DM and ASCVD are considered as having a heightened baseline risk of future cardiovascular events, thus, require intensive efforts to lower LDL cholesterol levels with high-intensity statins according to the current guidelines.[1–6] However, a substantial portion of patients who would benefit from high-intensity statins, including those with DM and ASCVD, may not be able to continue high-intensity statins due to statin-related adverse effects or intolerance.[7–11] In these patients, drug combination therapy with statin and non-statin agents may be a suitable alternative strategy, instead of simply increasing the dose or intensity of statins.[12,13]

Ezetimibe is the most common non-statin agent in lipid-lowering therapy and inhibits cholesterol absorption from the intestine by blocking the Niemann-Pick C1-Like 1 receptor, further reducing LDL cholesterol levels by 23%–24% when used in conjunction with statins.[1–3,12,14,15] Consequently, ezetimibe combination therapy to lower-intensity statins

can be considered as an alternative strategy to high-intensity statins—especially in patients who cannot tolerate high-intensity statin therapy. Although the benefit of adding ezetimibe to moderate-intensity statins in reducing LDL cholesterol levels and adverse cardiovascular events has been shown in the subgroup analysis of the DM cohort in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial, these benefits were mainly due to the add-on effect of ezetimibe to the same statin regimen, in which statin intensity was identical in both the ezetimibe combination therapy and statin monotherapy groups.[16] Therefore, sufficient evidence that directly supports the clinical efficacy and safety of combination therapy with ezetimibe and moderate-intensity statin vs. high-intensity statin monotherapy for patients with DM and ASCVD is lacking. Recently, the Randomized Comparison of Efficacy and Safety of Lipid-lowering with Statin Monotherapy Vs. Statin/ezetimibe Combination for High-risk Cardiovascular Disease (RACING) trial demonstrated the non-inferiority of moderate-intensity statin with ezetimibe combination therapy compared with high-intensity statin monotherapy for the 3-year composite cardiovascular outcomes in patients with ASCVD.[17] Thus, the aim of the present pre-specified, stratified subgroup analysis of the RACING trial was to evaluate the effect of moderate-intensity statins with ezetimibe combination therapy vs. high-intensity statin monotherapy among patients with DM.

Methods

Study design and population

The study design and rationale for the RACING trial have been previously described, in detail.[17] In brief, the multicentre, randomized, open-label, non-inferiority trial evaluated moderate-intensity statin with ezetimibe combination therapy (ezetimibe combination therapy) vs. high-intensity statin monotherapy in 3780 patients, at 26 centres, in South Korea.[17] Patients with documented ASCVD [previous myocardial infarction (MI), acute coronary syndrome, history of coronary revascularization (percutaneous coronary intervention or coronary artery bypass surgery) or other arterial revascularization procedures, ischaemic stroke, or peripheral artery disease) requiring high-intensity statin therapy to achieve LDL cholesterol levels <70 mg/dL were eligible to participate in the trial.[17] The full inclusion and exclusion criteria are provided in Supplementary material online, *Table S1*. The trial was approved by the institutional review board of each participating centre and followed the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before participation in the trial. For this pre-specified subgroup analysis, the effect of ezetimibe combination therapy was evaluated by baseline DM status (*Figure 1*). The presence of DM was determined by the investigators, based on a history of DM, the use of DM medications, a fasting glucose level ≥126 mg/dL, or a haemoglobin A1c level ≥6.5% at randomization.[18]

Study procedures

In the RACING trial, rosuvastatin which has shown efficacy and safety in East Asian patients was given for statin regimen.[17,19] Consenting patients were randomly assigned in a 1:1 manner to receive ezetimibe combination therapy (rosuvastatin 10 mg with ezetimibe 10 mg) or high-intensity statin monotherapy (rosuvastatin 20 mg).[17] Allocation of the patients was performed using a web-response permuted-block randomization (mixed blocks of 4 or 6) at each participating site, with stratification by baseline DM status and LDL cholesterol levels <100 mg/dL.[17] The initial doses of the study drugs were strongly recommended for maintenance during the entire study period.[17] However, considering patients' tolerance, compliance, and diverse clinical situations, the discontinuation or alteration of doses in both therapy groups was at the physicians' discretion and required a detailed report of reasons.[17] Follow-up visits for assessing general health status, medication use, and occurrence of a study outcome or adverse event were performed at 2 and 6 months; and at 1, 2, and 3 years of follow-up.[17] Serial follow-up of the patients' lipid profiles (total cholesterol, LDL cholesterol, high-density lipoprotein cholesterol, and triglyceride levels) and fasting glucose level were performed at 1, 2, and 3 years.[17] Follow-up of haemoglobin A1c level was performed at 1 and 3 years.[17]

Study outcomes and definitions

The primary outcome was a composite of cardiovascular death, major cardiovascular events, or non-fatal stroke at 3 years.[17] Major cardiovascular events included coronary or peripheral artery revascularization, or hospitalization for cardiovascular events.[17]

Cardiovascular death was defined as death owing to MI, heart failure, stroke, cardiovascular procedures, cardiac haemorrhage, sudden cardiac death, and any case of death in which a cardiovascular cause could not be excluded as adjudicated by a clinical endpoints committee.[20] MI was defined as symptoms, changes on electrocardiogram, or abnormal findings on imaging studies, combined with a creatine kinase MB fraction above the upper normal limit or a troponin T or troponin I level greater than the 99th percentile of the upper normal limit.[20] Coronary or peripheral revascularization included endovascular and surgical revascularization of the coronary, carotid, or lower extremity arteries.[1,21] Hospitalization for cardiovascular events included hospitalization for ischaemic heart disease (stable or unstable angina, or acute MI), heart failure, or peripheral artery disease.[20,22,23] Non-fatal stroke was defined as an acute cerebrovascular event resulting in a neurologic deficit more than 24 h or the presence of acute infarction demonstrated by imaging studies.[24]

Secondary outcomes comprised clinical efficacy and safety outcomes. Efficacy outcomes included the following: (i) the proportion of patients whose LDL cholesterol levels were <70 mg/dL at 1, 2, and 3 years; (ii) composite of all-cause death, major cardiovascular events, or non-fatal stroke; and (iii) any individual component of the primary outcome.[17] The proportion of patients whose LDL cholesterol levels were <55 mg/dL was also analyzed as a *post hoc* analysis, since the LDL cholesterol goal of <55 mg/dL was newly recommended for secondary prevention in patients with ASCVD, according to the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines issued after the initiation of the RACING trial.[3,17] Safety outcomes included the following: (i) the discontinuation or dose reduction of the study drug due to intolerance and (ii) the occurrence of clinical adverse events including new-onset DM, muscle-, hepatic-, or gallbladder-associated adverse effects or cancer diagnosis.[17] New-onset DM (for patients without DM at baseline) was defined according to the presence of at least one of the following: (i) an adverse event report, (ii) a new prescription for DM medication, or (iii) a fasting glucose level ≥126 mg/dL.[17,18] A *post hoc* analysis was performed to also include patients identified to have a haemoglobin A1c level ≥6.5% during the study period as having new-onset DM, based on the review of the trial database. Adverse events, including primary and secondary outcomes, were adjudicated by an independent clinical endpoint committee blinded to the therapy assignments and primary results of the trial.

Statistical analyses

Categorical variables were reported as numbers (percentages) and continuous variables were reported as mean ± standard deviation or median (interquartile range), depending on their distribution. As in the primary report of the RACING trial, the assessment of the primary outcome and secondary efficacy outcomes were performed based on the intention-to-treat population, while the assessment of secondary safety outcomes was initially performed in the safety population which excluded the patients who were not given the allocated therapy unless they discontinued or reduced dose due to intolerance.[17] Sensitivity analyses were performed in the intention-to-treat population regarding secondary safety outcomes. Time-to-event curves were plotted using Kaplan–Meier survival analysis based on the time of enrolment to the occurrence of the first event of interest during follow-up,

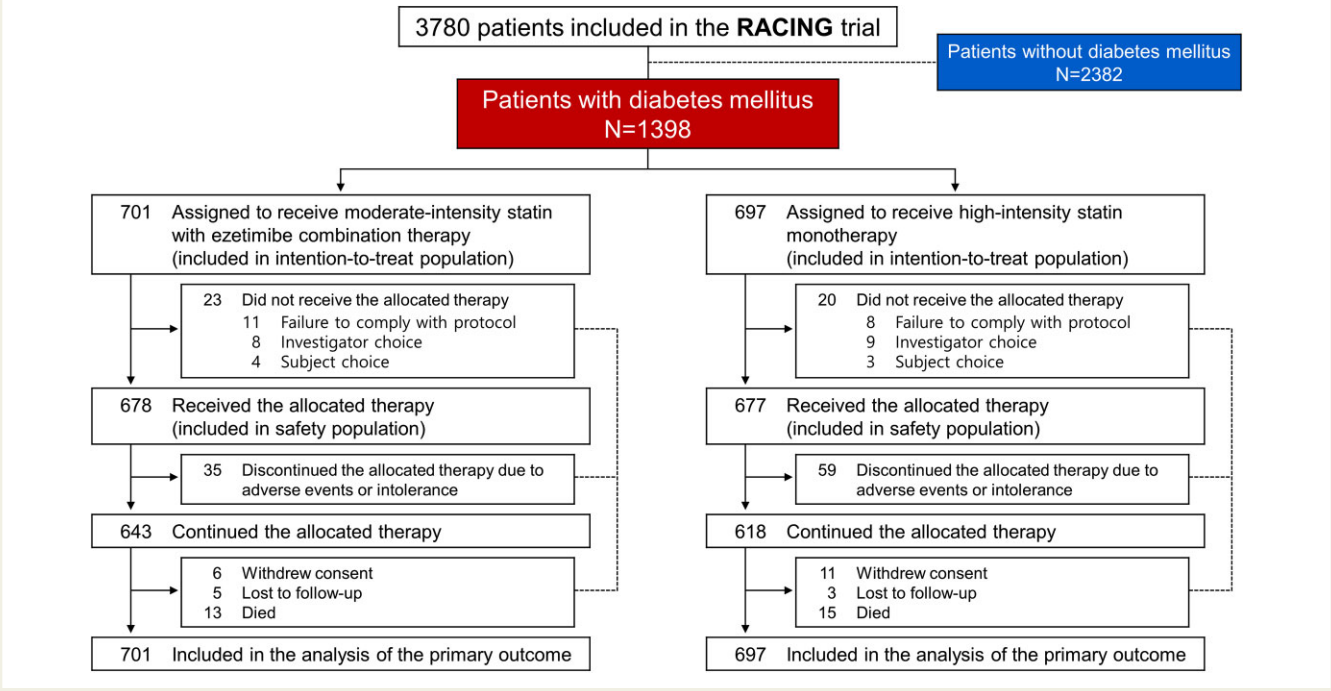


Figure 1 Study flow of participants. RACING, Randomized Comparison of Efficacy and Safety of Lipid-lowering with Statin Monotherapy Versus Statin/ezetimibe Combination for High-risk Cardiovascular Disease.

and the event rates between the two groups were compared using log-rank tests. Hazard ratios (HRs) with 95% confidence intervals (CIs) were computed using Cox regression analysis. To assess whether therapy effects (ezetimibe combination therapy vs. high-intensity statin monotherapy) differ according to DM status, *P*-values for interaction between DM status and therapy were calculated using Cox proportional hazard or logistic regression models, as appropriate. Subgroup analyses were performed among patients with DM regarding primary outcome as *post hoc* analyses. $P < 0.05$ was considered statistically significant, with no adjustment for multiple comparisons. Statistical analyses were performed using IBM SPSS, version 25.0 (IBM Corporation, Chicago, IL, USA) and R 3.5.3 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Between February 2017 and December 2018, 3780 patients were enrolled in the RACING trial, and 1398 patients (37.0%) were identified as having DM at baseline. Baseline clinical characteristics and laboratory findings according to DM status are presented in Supplementary material online, *Table S2*. Compared with patients without DM, patients with DM were more likely to be older (mean 65 vs. 63 years; $P < 0.001$); have a higher body weight (mean 69 vs. 68 kg; $P < 0.001$) and body mass index (mean 25.4 vs. 24.9 kg/m^2; $P < 0.001$); and have a higher proportion of prior percutaneous coronary intervention (73.9 vs. 61.5%; $P < 0.001$), prior coronary artery bypass surgery (10.4 vs. 4.2%; $P < 0.001$), prior ischaemic stroke (7.1 vs. 4.8%; $P = 0.004$), chronic kidney disease (15.3 vs. 7.5%; $P < 0.001$), end-stage renal disease on dialysis (1.5 vs. 0.3%; $P < 0.001$), and hypertension (74.4 vs. 62.1%; $P < 0.001$). Patients with DM were more likely to be treated with high-intensity statins before randomization (40.3 vs. 36.8%; $P = 0.002$); have a higher number of patients with LDL cholesterol levels <70 mg/dL (42.6 vs. 27.9%; $P < 0.001$); and have higher serum fasting glucose (median 133 vs. 103 mg/dL; $P < 0.001$) and haemoglobin A1c (median 7.0 vs. 5.8%; $P < 0.001$) levels. Conversely, serum LDL cholesterol levels were more likely to be lower in patients with DM (median 74 vs. 83 mg/dL; $P < 0.001$). As presented in *Table 1*, the baseline clinical characteristics or laboratory findings of patients receiving ezetimibe combination therapy vs. high-intensity statin therapy were well-balanced among both patients with and without DM—except for age, where patients with DM receiving ezetimibe combination therapy were 1 year younger than those receiving high-intensity statin monotherapy (mean 64 vs. 65 years; $P = 0.012$).

Clinical efficacy and safety

Patients were followed up for a median of 3.0 years (interquartile range, 3.0–3.0 years). The 3-year clinical outcomes are presented in *Table 2* and *Table 3*. Among patients with DM, the rate of primary outcome was 10.0% in the ezetimibe combination therapy group and 11.3% in the high-intensity statin monotherapy group (HR: 0.89; 95% CI: 0.64–1.22; $P = 0.460$) (*Figure 2*). The rate of discontinuation or dose reduction of the study drug due to intolerance was lower in the combination therapy group than in the high-intensity statin monotherapy group (5.2 vs. 8.7%; $P = 0.014$) (*Figure 3*). The rates of other secondary efficacy and safety outcomes were not different between the two therapy groups.

Among patients without DM, the rate of primary outcome was 8.9% in the ezetimibe combination therapy group and 9.4% in the high-intensity statin monotherapy group (HR: 0.94; 95% CI: 0.72–1.23; $P = 0.674$) (see Supplementary material online, *Figure S1*). The rate of discontinuation or dose reduction of the study drug due to intolerance was lower in the combination therapy group than in the high-intensity statin monotherapy group (4.5 vs. 7.9%; $P = 0.001$) (*Figure 3*). The rates of developing other secondary efficacy and safety outcomes were not

Table 1 Baseline characteristics by diabetes mellitus status and therapy strategy

	DM patients (*n* = 1398)		Non-DM patients (*n* = 2382)	
	Moderate-intensity statin with ezetimibe combination therapy (*n* = 701)	High-intensity statin monotherapy (*n* = 697)	Moderate-intensity statin with ezetimibe combination therapy (*n* = 1193)	High-intensity statin monotherapy (*n* = 1189)
Age, years	64 ± 9	65 ± 9	63 ± 10	63 ± 10
Male sex	545 (77.7)	515 (73.9)	875 (73.3)	891 (74.9)
Weight, kg	70 ± 12	69 ± 11	68 ± 11	68 ± 11
Body mass index, kg/m^2	25.3 ± 3.2	25.4 ± 3.0	24.9 ± 3.1	24.9 ± 3.1
Prior myocardial infarction	287 (40.9)	275 (39.5)	457 (38.3)	470 (39.5)
Prior percutaneous coronary intervention	524 (74.8)	509 (73.0)	734 (61.5)	730 (61.4)
Prior coronary artery bypass surgery	75 (10.7)	71 (10.2)	57 (4.8)	44 (3.7)
Acute coronary syndrome	6 (0.9)	9 (1.3)	21 (1.8)	11 (0.9)
Prior ischaemic stroke	48 (6.8)	51 (7.3)	53 (4.4)	61 (5.1)
Chronic kidney disease[a]	107 (15.3)	107 (15.4)	86 (7.2)	92 (7.7)
End-stage kidney disease on dialysis	11 (1.6)	10 (1.4)	2 (0.2)	6 (0.5)
Peripheral artery disease	25 (3.6)	27 (3.9)	41 (3.4)	42 (3.5)
Hypertension	508 (72.5)	532 (76.3)	738 (61.9)	742 (62.4)
Diabetes mellitus with insulin treatment	50 (7.1)	70 (10.0)	-	-
Current smoker	123 (17.5)	99 (14.2)	205 (17.2)	211 (17.7)
Medication for dyslipidaemia before randomization[b]				
High-intensity statin	257 (36.7)	307 (44.0)	454 (38.1)	422 (35.5)
High-intensity statin with ezetimibe	31 (4.4)	24 (3.4)	54 (4.5)	39 (3.3)
Moderate-intensity statin	285 (40.7)	239 (34.3)	396 (33.2)	446 (37.5)
Moderate-intensity statin with ezetimibe	81 (11.6)	82 (11.8)	170 (14.2)	166 (14.0)
Low-intensity statin	2 (0.3)	2 (0.3)	4 (0.3)	3 (0.3)
None	45 (6.4)	43 (6.2)	115 (9.6)	113 (9.5)
Serum LDL cholesterol level, mg/dL	74 (58–94)	74 (60–92)	83 (68–104)	83 (67–104)
Patients with LDL cholesterol levels <70 mg/dL (%)	310 (44.2)	285 (40.9)	333 (27.9)	331 (27.8)
Serum fasting glucose level, mg/dL	133 (117–157)	132 (115–156)	103 (95–111)	103 (96–112)
Serum haemoglobin A1c level, %	7.0 (6.5–7.7)	7.0 (6.5–7.8)	5.8 (5.5–6.0)	5.8 (5.5–6.0)

Data are mean ± SD, median (interquartile range), or number (%). DM, diabetes mellitus.
[a]Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 mL per min per 1.73 m^2 of body-surface area.
[b]The intensity of statin therapy was divided into three categories according the 2018 American Heart Association/American College of Cardiology guidelines on the management of dyslipidaemia.[2]

different between the two therapy groups. The rate of developing new-onset DM did not differ between the two therapy groups (12.4 vs. 13.8%; $P = 0.366$). As a sensitivity analysis, the secondary safety outcomes of the intention-to-treat population are presented in Supplementary material online, *Table S3*. In the total trial population, significant interactions between DM status and therapy regarding primary and secondary outcomes were not observed (*Table 2*, *Table 3*, Supplementary material online, *Table S3*).

Change in lipids

The serial change in LDL cholesterol levels during the study period is presented in *Table 4*. Among patients with DM, the median LDL cholesterol level throughout the study period was 53 (43–64) mg/dL in the ezetimibe combination therapy group and 61 (50–74) mg/dL in the high-intensity statin monotherapy group ($P < 0.001$). Median LDL cholesterol levels were consistently lower in the ezetimibe combination therapy group than in the high-intensity statin

monotherapy group, at 1 (54 vs. 62 mg/dL), 2 (50 vs. 60 mg/dL), and 3 years (54 vs. 62 mg/dL) (all $P < 0.001$) (*Figure 4*). The proportion of patients whose LDL cholesterol levels were <70 mg/dL was consistently higher in the ezetimibe combination therapy group, at 1 (81.0% vs. 64.1%), 2 (83.1% vs. 70.2%), and 3 years (79.9% vs. 66.8%) (all $P < 0.001$).

Among patients without DM, the median LDL cholesterol level throughout the study period was 61 (50–74) mg/dL in the ezetimibe combination therapy group and 69 (58–82) mg/dL in the high-intensity statin monotherapy group ($P < 0.001$). Median LDL cholesterol levels were consistently lower in the ezetimibe combination therapy group than in the high-intensity statin monotherapy group, at 1, 2, and 3 years (all $P < 0.001$) (see Supplementary material online, *Figure S2*). The proportion of patients whose LDL cholesterol levels were <70 mg/dL was consistently higher in the ezetimibe combination therapy group, at 1, 2, and 3 years (all $P < 0.001$). In the total trial population, no significant interaction between DM status and therapy regarding the proportion of patients with LDL cholesterol levels <70 mg/dL was found. As a *post hoc* analysis, the proportion of patients whose LDL cholesterol levels were <55 mg/dL was consistently higher in the ezetimibe combination therapy group than in the high-intensity statin monotherapy group during the study period, irrespective of DM status (see Supplementary material online, *Table S4*). Serial changes in other lipid profiles are presented in Supplementary material online, *Table S5*. The ezetimibe combination therapy was associated with lower total cholesterol and triglyceride levels whereas high-density lipoprotein cholesterol levels did not differ between the two therapy groups, among both patients with and without DM.

Additional analyses

In a *post hoc* analysis using a definition of new-onset DM, which included a haemoglobin A1c level ≥6.5% during the study period, the rate of developing new-onset DM did not differ between the ezetimibe combination therapy group and the high-intensity statin monotherapy group among patients without DM (safety population, 17.1 vs. 16.7%; $P = 0.833$).

The results from subgroup analyses among patients with DM are presented in Supplementary material online, *Figure S3*. The effect of ezetimibe combination therapy vs. high-intensity statin monotherapy was consistent regarding primary outcome across subgroups, including baseline LDL cholesterol levels <100 mg/dL—the other pre-specified stratification criteria in the RACING trial.

Discussion

The main findings of this pre-specified, stratified subgroup analysis that assessed the effect of moderate-intensity statin with ezetimibe combination therapy among patients with DM, randomized in the RACING trial, were as follows: (i) among patients with DM and ASCVD, the risks of 3-year composite cardiovascular outcomes were comparable between those receiving ezetimibe combination therapy vs. high-intensity statin monotherapy; (ii) ezetimibe combination therapy significantly reduced the rate of drug discontinuation or dose reduction due to intolerance; and (iii) ezetimibe combination therapy was associated with lower LDL cholesterol levels and higher proportions of patients with LDL cholesterol levels <70 mg/dL, compared with high-intensity statin monotherapy. Overall, compared with high-intensity statin monotherapy, the clinical efficacy and safety of ezetimibe combination therapy observed in the main RACING trial population were conserved among patients with DM (*Structured Graphical Abstract*).

For patients with ASCVD, current guidelines recommend intensive lowering of LDL cholesterol levels, with statins as the first-line therapy for secondary prevention.[1–3,7,25] Although the use of high-intensity statins is strongly recommended in these patients, patients who cannot tolerate high-intensity statins do exist.[1–3,7–11] Drug combination with lower-intensity statins and non-statin agents, such as ezetimibe, may be considered a reasonable alternative strategy to achieve sufficient LDL cholesterol reduction and reduce adverse cardiovascular outcomes with less concern for drug intolerance or adverse events caused by high-intensity statins.[9–13] Although the effect of ezetimibe combination therapy with statins in patients with acute coronary syndrome was demonstrated in the IMPROVE-IT trial, the same moderate-intensity statin (simvastatin 40 mg) was used in both therapy groups.[12] In other words, it focused on the additive effect of ezetimibe on the same dose of statins, rather than the effect of dose reduction of statins. In contrast, the RACING trial demonstrated the non-inferiority of moderate-intensity statin with ezetimibe combination therapy compared with high-intensity statin monotherapy for 3-year composite cardiovascular outcomes, with a lower intolerance-related drug discontinuation or dose reduction and higher proportion of patients with LDL cholesterol levels <70 mg/dL.[17] Furthermore, the trial included various features of ASCVD, including patients who had not only coronary artery disease, but also stroke or peripheral artery disease, with stratification by DM status during randomization.[17] Compared with those without DM, the patients with DM were characterized by more frequent comorbidities.

The global prevalence of DM was 10.5% in 2021 and is expected to increase to 12.2% by 2045.[4] Patients with DM are at higher risk for developing ASCVD, and patients with concomitant DM and ASCVD are regarded as being at the highest risk for recurrent cardiovascular events, thus requiring secondary prevention with high-intensity statins with the aim of intensive lowering of LDL cholesterol levels.[1–3,5,6] To be specific, according to the 2018 American Heart Association/American College of Cardiology guidelines on the management of dyslipidaemia, high-intensity statin therapy is recommended in a similar manner to recommendations proposed by the American Diabetes Association.[2,6] According to the 2016 ESC/EAS guidelines, intensive lowering of LDL cholesterol levels to the goal of <70 mg/dL is recommended, and an even more intensive goal of <55 mg/dL is recommended in the updated 2019 guidelines with similar recommendation suggested by the European Association for the Study of Diabetes.[1,3,5] Furthermore, these guidelines recommend adding ezetimibe to moderate-intensity statins as a reasonable alternative to high-intensity statins if further reduction in LDL cholesterol levels are required or high-intensity statins cannot be tolerated; however, this recommendation is based only on one prior study: the subgroup analysis of the IMPROVE-IT trial, regarding the DM cohort.[1–3,5,6,16] In the IMPOVE-IT trial, the benefit of adding ezetimibe to moderate-intensity statin, as opposed to the absence of ezetimibe, for reducing primary outcome (a composite of cardiovascular death, major coronary events, or stroke; 40.0% vs. 45.5%; HR: 0.85; 95% CI: 0.78–0.94) and LDL cholesterol levels (median 49 vs. 67 mg/dL) was demonstrated among DM patients with acute coronary syndrome.[16] Despite these benefits, the effect of adding ezetimibe to moderate-intensity statin was compared with moderate-intensity statin rather than high-intensity statin; therefore, additional studies with head-to-head comparisons between moderate-intensity statin with ezetimibe combination therapy vs. high-intensity stain monotherapy have been required to provide direct evidence to current guideline-based recommendations for managing patients with DM and ASCVD.[16] In this study, the effect of

Table 2 Primary and secondary efficacy outcomes by diabetes mellitus status and therapy strategy

	DM patients (*n* = 1398)				Non-DM patients (*n* = 2382)				*P*-value for interaction[b]
	Moderate-intensity statin with ezetimibe combination therapy (*n* = 701)	High-intensity statin monotherapy (*n* = 697)	HR (95% CI)	*P*-value	Moderate-intensity statin with ezetimibe combination therapy (*n* = 1193)	High-intensity statin monotherapy (*n* = 1189)	HR (95% CI)	*P*-value	
Primary outcome									
Composite of cardiovascular death, major cardiovascular events[a], or non-fatal stroke	69 (10.0)	77 (11.3)	0.89 (0.64–1.22)	0.460	103 (8.9)	109 (9.4)	0.94 (0.72–1.23)	0.674	0.765
Secondary outcome									
Composite of all-cause death, major cardiovascular events, or non-fatal stroke	75 (10.8)	84 (12.2)	0.88 (0.65–1.20)	0.427	111 (9.6)	113 (9.7)	0.98 (0.76–1.28)	0.887	0.606
Individual clinical outcome									
Cardiovascular death	6 (0.9)	5 (0.7)	1.19 (0.36–3.90)	0.772	2 (0.2)	1 (0.1)	2.00 (0.18–22.07)	0.563	0.701
All-cause death	13 (1.9)	15 (2.2)	0.86 (0.41–1.81)	0.691	13 (1.1)	7 (0.6)	1.87 (0.75–4.69)	0.174	0.197
Major cardiovascular events	61 (8.9)	64 (9.4)	0.95 (0.67–1.34)	0.751	92 (8.0)	103 (8.9)	0.89 (0.67–1.18)	0.420	0.797
Coronary artery revascularization	43 (6.2)	42 (6.2)	1.02 (0.66–1.56)	0.941	48 (4.2)	47 (4.0)	1.03 (0.69–1.54)	0.897	0.970
Percutaneous coronary intervention	40	42			47	47			
Coronary artery bypass surgery	3	0			1	0			
Peripheral artery revascularization	5 (0.7)	4 (0.6)	1.24 (0.33–4.63)	0.746	3 (0.3)	3 (0.3)	1.01 (0.20–4.98)	0.994	0.844
Hospitalization for ischaemic heart disease	57 (8.3)	58 (8.5)	0.97 (0.68–1.40)	0.885	85 (7.4)	92 (7.9)	0.92 (0.69–1.24)	0.597	0.827
Stable angina or unstable angina	46	47			74	86			
Acute myocardial infarction	11	11			11	5			
Hospitalization for heart failure	7 (1.0)	7 (1.0)	0.99 (0.35–2.83)	0.987	7 (0.6)	12 (1.0)	0.59 (0.23–1.49)	0.256	0.460
Hospitalization for peripheral artery disease	5 (0.7)	4 (0.6)	1.24 (0.33–4.63)	0.746	3 (0.3)	3 (0.3)	1.01 (0.20–4.98)	0.994	0.844
Non-fatal stroke	5 (0.7)	10 (1.5)	0.50 (0.17–1.45)	0.190	10 (0.9)	4 (0.3)	2.52 (0.79–8.04)	0.105	0.063
Ischemic stroke	4	8			7	3			
Hemorrhagic stroke	1	2			3	1			

Data are number (% of the cumulative rates at 3 years according to Kaplan–Meier event rates). CI, confience interval; DM, diabetes mellitus; HR, hazard ratio.
[a]Major cardiovascular events included coronary or peripheral artery revascularization, or hospitalization for cardiovascular events.
[b]P-value for interaction between DM status and therapy.

Table 3 Secondary safety outcomes by diabetes mellitus status and therapy strategy of the safety population

	DM patients (*n* = 1355)			Non-DM patients (*n* = 2323)			*P*-value for interaction[b]
	Moderate-intensity statin with ezetimibe combination therapy (*n* = 678)	High-intensity statin monotherapy (*n* = 677)	*P*-value	Moderate-intensity statin with ezetimibe combination therapy (*n* = 1168)	High-intensity statin monotherapy (*n* = 1155)	*P*-value	
Discontinuation or dose reduction of the study drug due to intolerance	35 (5.2)	59 (8.7)	0.014	53 (4.5)	91 (7.9)	0.001	0.928
Patients' reported symptoms							
Dizziness or general weakness	4	11		6	10		
Chest discomfort or headache	4	4		3	8		
Gastrointestinal symptom	1	5		3	4		
Urticaria or itching sensation	2	1		4	6		
Myalgia	2	11		5	11		
Other	0	1		5	2		
Physicians' discretion							
Liver enzyme elevation	9	9		6	23		
Creatine kinase elevation	9	12		16	21		
Fasting glucose level elevation	4	5		1	1		
Other	0	0		4	5		
New-onset DM	-	-	-	145 (12.4)	159 (13.8)	0.366	-
New-onset DM with initiation of anti-diabetic medication	-	-	-	95 (8.1)	107 (9.3)	0.372	-
Muscle-related adverse events	6 (0.9)	16 (2.4)	0.053	15 (1.3)	18 (1.6)	0.702	0.180
Myalgia	6 (0.9)	13 (1.9)	0.165	11 (0.9)	16 (1.4)	0.422	0.533
Myopathy	2 (0.3)	1 (0.1)	1.000	0	3 (0.3)	0.123	-
Myonecrosis[a]	2 (0.3)	6 (0.9)	0.178	9 (0.8)	7 (0.6)	0.819	0.161
Mild	1	4		7	5		
Moderate	0	1		2	2		
Severe including rhabdomyolysis	1	1		0	0		

Continued

Table 3 *Continued*

	DM patients ($n = 1355$)			Non-DM patients ($n = 2323$)			*P*-value for interaction[b]
	Moderate-intensity statin with ezetimibe combination therapy ($n = 678$)	High-intensity statin monotherapy ($n = 677$)	*P*-value	Moderate-intensity statin with ezetimibe combination therapy ($n = 1168$)	High-intensity statin monotherapy ($n = 1155$)	*P*-value	
Gallbladder-related adverse events	9 (1.3)	5 (0.7)	0.422	3 (0.3)	2 (0.2)	1.000	0.854
Major bleeding	5 (0.7)	5 (0.7)	1.000	10 (0.9)	8 (0.7)	0.831	0.786
Cancer diagnosis	19 (2.8)	14 (2.1)	0.484	18 (1.5)	12 (1.0)	0.375	0.865
New-onset neurocognitive disorder	2 (0.3)	0	0.500	2 (0.2)	2 (0.2)	1.000	-
Cataract surgery	9 (1.3)	14 (2.1)	0.398	10 (0.9)	7 (0.6)	0.643	0.223

Data are number (%). DM, diabetes mellitus.
[a]Severity of myonecrosis was classified by an elevation of creatine kinase level compared with either baseline level or the upper limit of normal (ULN); mild, 3–10 times ULN; moderate, 10–50 times ULN; severe, > 50 times ULN.
[b]P-value for interaction between DM status and therapy.

moderate-intensity statin with ezetimibe combination therapy was evaluated in a pre-specified, stratified DM subgroup of the RACING trial, compared directly with high-intensity statin monotherapy which the IMPROVE-IT trial left out. Compared with high-intensity statin monotherapy, ezetimibe combination therapy demonstrated similar rates of a 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke, with lower LDL cholesterol levels and a higher proportion of patients with LDL cholesterol levels <70 mg/dL during the study period. This observation may directly support current recommendations for patients with DM and ASCVD.[1–3,5,6]

Despite the benefits of statins in reducing LDL cholesterol levels and the risk for future cardiovascular events, statin-related adverse effects or intolerance should also be considered in treatment plans.[9–11] Statin-associated muscle symptoms and other concerning statin-related adverse effects on glucose homeostasis, or liver or kidney function were more common with the use of high-intensity statins.[9–11,26] In addition, DM was associated with an increased risk of statin intolerance, according to a recent meta-analysis.[27] Since these adverse effects or intolerance may decrease patients' compliance, lead to discontinuation or dose reduction of statins, and consequently result in poor reduction in LDL cholesterol levels, appropriate treatment strategies are required in patients who cannot continue high-intensity statins—especially among those with DM and ASCVD, who will benefit from intensive lowering of LDL cholesterol levels by using high-intensity statins.[28] In the current study, compared with high-intensity statin monotherapy, ezetimibe combination therapy demonstrated lower drug discontinuation or dose reduction due to intolerance, while simultaneously achieving similar efficacy for the rate of composite cardiovascular outcomes—an observation that is fully in line with current recommendations for adding ezetimibe to moderate-intensity statin as a suitable alternative to high-intensity statin if high-intensity statins cannot be tolerated when managing patients with DM and ASCVD.[1–3,5,6] The clinical efficacy and safety of adding ezetimibe to moderate-intensity statin with longer follow-up (7 years) and additional results stratified by the Thrombolysis in Myocardial Infarction Risk Score, were presented in the pre-specified DM subgroup of the IMPROVE-IT trial; however, detailed data regarding non-adherence to study drugs due to intolerance were not shown.[16] On the other hand, according to the Statin Web-based Investigation of Side Effects (StatinWISE) and Self-Assessment Method for Statin Side-effects Or Nocebo (SAMSON) trials, patients' reported symptoms and non-adherence to study drugs were not different between the statin and the placebo groups.[29,30] However, only moderate-intensity statin (atorvastatin 20 mg) was used for statin regimens within small number of patients participating in each trial (a total of 200 patients and 60 patients).[29,30] Considering that statin-related adverse effects were more common with the use of high-intensity statins compared to lower-intensity statins, the current study findings regarding non-adherence due to intolerance which were different compared with StatinWISE and SAMSON trials may be explained.[9–11,29,30]

Other than adding ezetimibe, addition of the proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors to statins presented a beneficial effect among patients with DM and ASCVD.[31,32] According to the pre-specified subgroup analyses of the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab trials which evaluated the effect of PCSK9 inhibitors (evolocumab and alirocumab) in patients with ASCVD who were receiving maximally tolerated statin therapy (high-intensity statins, 67% and 88%), adding the

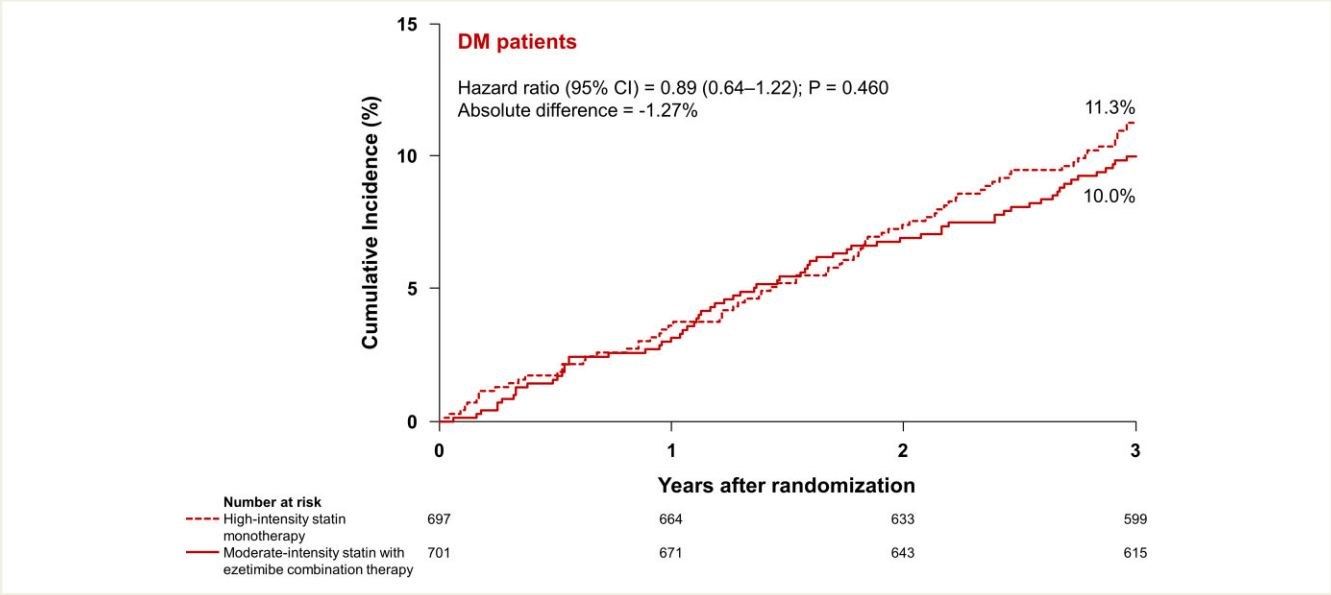


Figure 2 Time-to-event curves of the primary outcome among patients with diabetes mellitus. Kaplan–Meier survival curves for the primary outcome among patients with DM. CI, confidence interval; DM, diabetes mellitus.

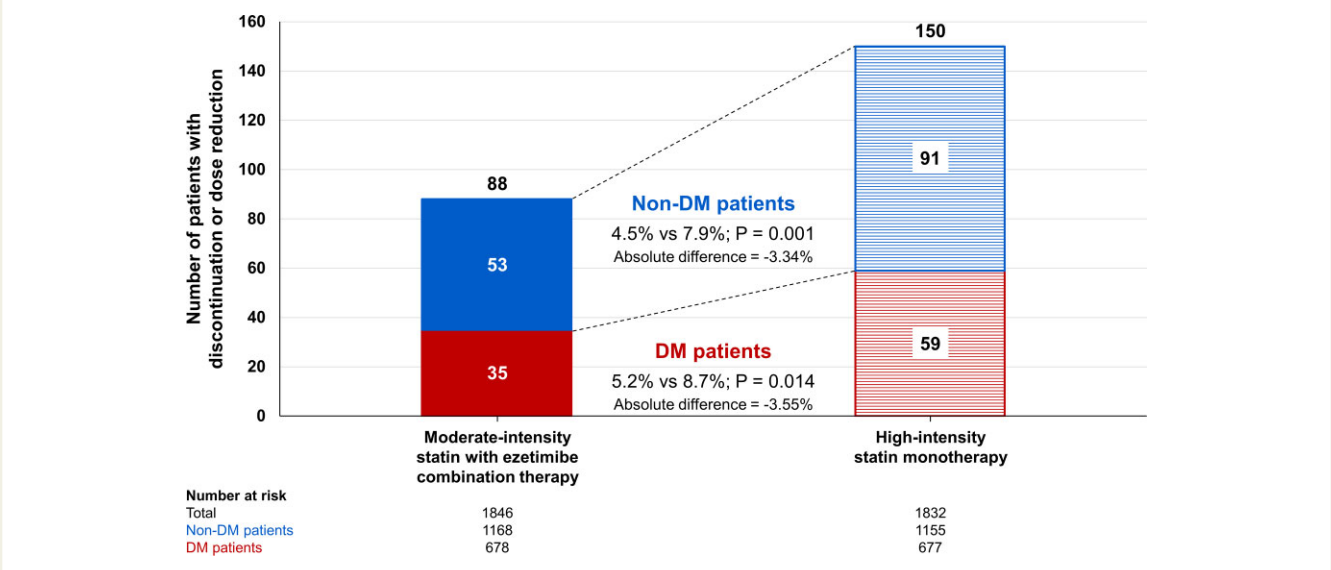


Figure 3 Drug discontinuation or dose reduction due to intolerance by diabetes mellitus status and therapy strategy. Discontinuation or dose reduction of the study drug due to intolerance among patients with (red) and without DM (blue) in the safety population. Between the bars, the rates and *P*-values for the comparison between the ezetimibe combination therapy group (solid colours) and the high-intensity statin monotherapy group (striped colours) are presented. DM, diabetes mellitus.

PCSK9 inhibitors to statins consistently reduced the rate of composite cardiovascular outcomes among patients with DM.[31,32] In both trials, addition of PCSK9 inhibitors was associated with lower LDL cholesterol levels and did not increase the risk of new-onset DM.[31,32] However, similar to the IMPROVE-IT trial, these two trials focused on the additive effect of PCSK9 inhibitors on the same intensity of statins, rather than the effect of reducing the intensity or dose of statins. Further studies evaluating the efficacy and safety of adding PCSK9 inhibitors to moderate-intensity statins compared with high-intensity statins, as well as those evaluating the effect of other novel non-statin agents such as inclisiran or bempedoic acid among patients with DM and ASCVD, are required to enrich the current dyslipidaemia guideline-based recommendations for managing these patients.[33,34]

Study limitations

This study has several limitations. First, although this study was a pre-specified, randomly stratified subgroup analysis, the number of patients

Table 4 Serial LDL cholesterol levels by diabetes mellitus status and therapy strategy

	DM patients ($n = 1398$)			Non-DM patients ($n = 2382$)			*P*-value for interaction[a]
	Moderate-intensity statin with ezetimibe combination therapy	High-intensity statin monotherapy	*P*-value	Moderate-intensity statin with ezetimibe combination therapy	High-intensity statin monotherapy	*P*-value	
1 year							
Number of patients	625	618		1050	1055		
LDL cholesterol level, mg/dL	54 (43–64)	62 (51–75)	$P < 0.001$	61 (50–74)	70 (58–83)	$P < 0.001$	
Patients with LDL cholesterol levels <70 mg/dL (%)	506 (81.0)	396 (64.1)	$P < 0.001$	711 (67.7)	527 (50.0)	$P < 0.001$	0.430
2 years							
Number of patients	590	560		968	979		
LDL cholesterol level, mg/dL	50 (41–63)	60 (48–72)	$P < 0.001$	60 (49–73)	67 (56–82)	$P < 0.001$	
Patients with LDL cholesterol levels <70 mg/dL (%)	490 (83.1)	393 (70.2)	$P < 0.001$	678 (70.0)	531 (54.2)	$P < 0.001$	0.753
3 years							
Number of patients	497	476		852	839		
LDL cholesterol level, mg/dL	54 (43–65)	62 (49–74)	$P < 0.001$	60 (50–74)	69 (57–82)	$P < 0.001$	
Patients with LDL cholesterol levels <70 mg/dL (%)	397 (79.9)	318 (66.8)	$P < 0.001$	581 (68.2)	441 (52.6)	$P < 0.001$	0.914

Data are median (interquartile range) or number (%). DM, diabetes mellitus.
[a]P-value for interaction between DM status and therapy.

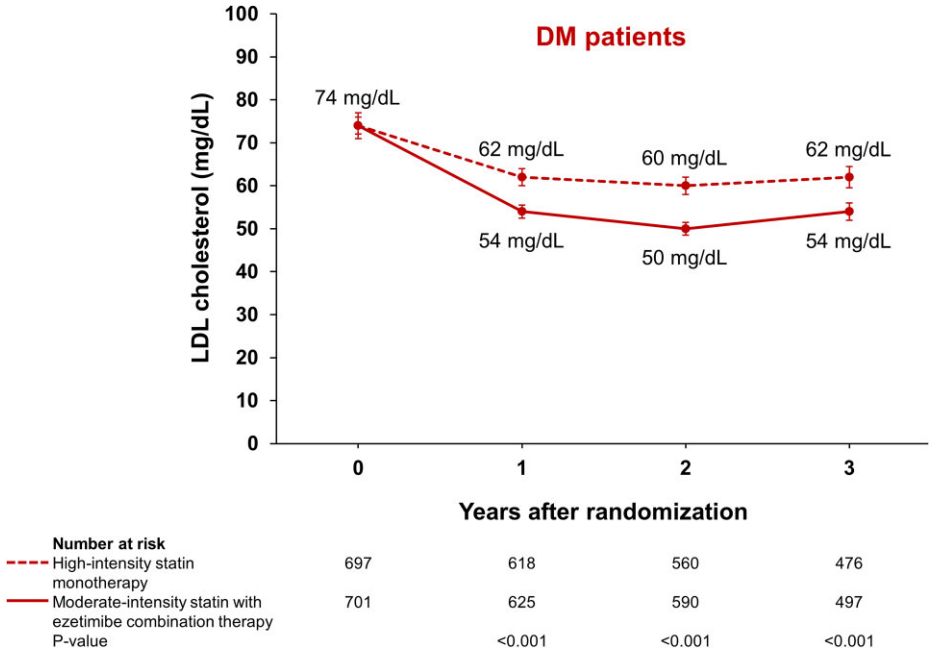


Figure 4 LDL cholesterol levels over time among patients with diabetes mellitus. Serial median values for LDL cholesterol among patients with diabetes mellitus. The I bar indicates 95% confidence intervals. Under the graph, *P*-values for the comparison between the ezetimibe combination therapy group and the high-intensity statin monotherapy group in the LDL cholesterol levels at 1, 2, and 3 years are presented. DM, diabetes mellitus.

included in the DM subgroup may have limited statistical power to yield definite conclusions on the effect of ezetimibe combination therapy. Second, the RACING trial was an open-label trial in which both the patients and physicians were aware of the therapy assignment. Although the nocebo effect (i.e. negative outcome that occurs due to the expectation that the intervention will cause harm) should be considered, this effect may reflect real-world scenarios regarding statin therapy. Third, the comparison of each component of the primary outcome might be difficult due to the small number of events. Fourth, due to the strict fulfilment of inclusion and exclusion criteria in the randomized controlled trials, patients in the present study may have been at lower risk than those in general clinical practice. Fifth, although the benefit of ezetimibe combination therapy in reducing LDL cholesterol levels was shown, the superiority of ezetimibe combination therapy regarding primary outcome was not demonstrated among patients with DM. Sixth, the benefit of ezetimibe combination with lower-intensity statins for reducing the risk of developing new-onset DM compared with higher-intensity statins was not shown. Further studies with a larger number of patients and longer follow-up may be required. Therefore, our findings need to be considered only as hypothesis-generating and warrant further prospective confirmation.

Conclusions

This pre-specified, stratified subgroup analysis of the DM cohort in the RACING trial demonstrated that ezetimibe combination with moderate-intensity statin therapy was comparable with high-intensity statin monotherapy in terms of a 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke. Ezetimibe combination therapy was associated with lower intolerance-related drug discontinuation or dose reduction and a higher proportion of patients achieving LDL cholesterol levels <70 mg/dL. These findings directly support the use of moderate-intensity statin with ezetimibe combination therapy as a suitable alternative to high-intensity monotherapy if high-intensity statins cannot be tolerated or further reduction in LDL cholesterol levels is required, as recommended by the current guidelines for managing dyslipidaemia among patients with DM and ASCVD.

Supplementary data

Supplementary data is available at *European Heart Journal* online.

Acknowledgements

The authors thank Medical Illustration & Design, part of the Medical Research Support Services of Yonsei University College of Medicine, for all artistic support related to this work.

Funding

This work was supported by the Cardiovascular Research Center (Seoul, Korea) and funded by grants from Hanmi Pharmaceutical (Seoul, Korea). No funder/sponsor had any role in the following: design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Conflict of interest: S.C.Y. is a chief technical officer of PHI Digital Healthcare and has received consulting fee from IQVIA; B.-K.K. has received speaker's fees from Medtronic and Abbott Vascular; M.-K.H. has received speaker's fees from Medtronic, Abbott Vascular, and Pfizer, Y.J. has received institutional research grants from Biotronik and Hanmi, and J.-S.K. has received proctoring fees from Abbott Vascular. All other authors declare no competing interests.

Data availability

The data regarding this article will be shared by the corresponding author upon reasonable request.

References

1. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, *et al.* 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J* 2016;**37**:2999–3058. https://doi.org/10.1093/eurheartj/ehw272
2. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, *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. https://doi.org/10.1016/j.jacc.2018.11.003
3. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, *et al.* 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**:111–188. https://doi.org/10.1093/eurheartj/ehz455
4. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, *et al.* IDF Diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract* 2022;**183**:109119. https://doi.org/10.1016/j.diabres.2021.109119
5. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, *et al.* . 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020;**41**:255–323. https://doi.org/10.1093/eurheartj/ehz486
6. American Diabetes Association Professional Practice Committee. 10. Cardiovascular disease and risk management: standards of medical care in diabetes-2022. *Diabetes Care* 2022;**45**:S144–S174. https://doi.org/10.2337/dc22-S010
7. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, *et al.* Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;**352**:1425–1435. https://doi.org/10.1056/NEJMoa050461
8. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, *et al.* High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 2005;**294**:2437–2445. https://doi.org/10.1001/jama.294.19.2437
9. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-Associated Side effects. *J Am Coll Cardiol* 2016;**67**:2395–2410. https://doi.org/10.1016/j.jacc.2016.02.071
10. Adhyaru BB, Jacobson TA. Safety and efficacy of statin therapy. *Nat Rev Cardiol* 2018;**15**:757–769. https://doi.org/10.1038/s41569-018-0098-5
11. Ward NC, Watts GF, Eckel RH. Statin toxicity. *Circ Res* 2019;**124**:328–350. https://doi.org/10.1161/CIRCRESAHA.118.312782
12. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, *et al.* Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;**372**:2387–2397. https://doi.org/10.1056/NEJMoa1410489
13. Ran D, Nie HJ, Gao YL, Deng SB, Du JL, Liu YJ, *et al.* A randomized, controlled comparison of different intensive lipid-lowering therapies in Chinese patients with non-ST-elevation acute coronary syndrome (NSTE-ACS): ezetimibe and rosuvastatin versus high-dose rosuvastatin. *Int J Cardiol* 2017;**235**:49–55. https://doi.org/10.1016/j.ijcard.2017.02.099
14. Sudhop T, Lütjohann D, Kodal A, Igel M, Tribble DL, Shah S, *et al.* Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* 2002;**106**:1943–1948. https://doi.org/10.1161/01.CIR.0000034044.95911.DC
15. Morrone D, Weintraub WS, Toth PP, Hanson ME, Lowe RS, Lin J, *et al.* Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials. *Atherosclerosis* 2012;**223**:251–261. https://doi.org/10.1016/j.atherosclerosis.2012.02.016
16. Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalán R, Špinar J, *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. https://doi.org/10.1161/CIRCULATIONAHA.117.030950
17. Kim BK, Hong SJ, Lee YJ, Hong SJ, Yun KH, Hong BK, *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. https://doi.org/10.1016/S0140-6736(22)00916-3
18. American Diabetes Association. 2. Classification and diagnosis of diabetes. *Diabetes Care* 2016;**39**:S13–S22. https://doi.org/10.2337/dci15-0030

19. Zhang L, Zhang S, Yu Y, Jiang H, Ge J. Efficacy and safety of rosuvastatin vs. Atorvastatin in lowering LDL cholesterol: a meta-analysis of trials with east Asian populations. *Herz* 2020;**45**:594–602. https://doi.org/10.1007/s00059-018-4767-2
20. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, *et al.* 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American college of cardiology/American heart association task force on clinical data standards (writing committee to develop cardiovascular endpoints data standards). *Circulation* 2015;**132**:302–361. https://doi.org/10.1161/CIR.0000000000000156
21. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, *et al.* 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol* 2017;**69**:e71–e126. https://doi.org/10.1016/j.jacc.2016.11.007
22. Zannad F, Garcia AA, Anker SD, Armstrong PW, Calvo G, Cleland JG, *et al.* Clinical outcome endpoints in heart failure trials: a European society of cardiology heart failure association consensus document. *Eur J Heart Fail* 2013;**15**:1082–1094. https://doi.org/10.1093/eurjhf/hft095
23. Patel MR, Conte MS, Cutlip DE, Dib N, Geraghty P, Gray W, *et al.* Evaluation and treatment of patients with lower extremity peripheral artery disease: consensus definitions from peripheral academic research consortium (PARC). *J Am Coll Cardiol* 2015;**65**:931–941. https://doi.org/10.1016/j.jacc.2014.12.036
24. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, *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. https://doi.org/10.1161/STR.0b013e318296aeca
25. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, *et al.* Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;**376**:1670–1681. https://doi.org/10.1016/S0140-6736(10)61350-5
26. Dormuth CR, Filion KB, Paterson JM, James MT, Teare GF, Raymond CB, *et al.* Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases. *BMJ* 2014;**348**:g3244. https://doi.org/10.1136/bmj.g3244
27. Bytyçi I, Penson PE, Mikhailidis DP, Wong ND, Hernandez AV, Sahebkar A, *et al.* Prevalence of statin intolerance: a meta-analysis. *Eur Heart J* 2022;**43**:3213–3223. https://doi.org/10.1093/eurheartj/ehac015
28. Serban MC, Colantonio LD, Manthripragada AD, Monda KL, Bittner VA, Banach M, *et al.* Statin intolerance and risk of coronary heart events and all-cause mortality following myocardial infarction. *J Am Coll Cardiol* 2017;**69**:1386–1395. https://doi.org/10.1016/j.jacc.2016.12.036
29. Herrett E, Williamson E, Brack K, Beaumont D, Perkins A, Thayne A, *et al.* Statin treatment and muscle symptoms: series of randomised, placebo controlled n-of-1 trials. *BMJ* 2021;**372**:n135. https://doi.org/10.1136/bmj.n135
30. Howard JP, Wood FA, Finegold JA, Nowbar AN, Thompson DM, Arnold AD, *et al.* Side effect patterns in a crossover trial of statin, placebo, and No treatment. *J Am Coll Cardiol* 2021;**78**:1210–1222. https://doi.org/10.1016/j.jacc.2021.07.022
31. Sabatine MS, Leiter LA, Wiviott SD, Giugliano RP, Deedwania P, De Ferrari GM, *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. https://doi.org/10.1016/S2213-8587(17)30313-3
32. Ray KK, Colhoun HM, Szarek M, Baccara-Dinet M, Bhatt DL, Bittner VA, *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. https://doi.org/10.1016/S2213-8587(19)30158-5
33. Leiter LA, Teoh H, Kallend D, Wright RS, Landmesser U, Wijngaard PLJ, *et al.* Inclisiran lowers LDL-C and PCSK9 irrespective of diabetes Status: the ORION-1 randomized clinical trial. *Diabetes Care* 2019;**42**:173–176. https://doi.org/10.2337/dc18-1491
34. Leiter LA, Banach M, Catapano AL, Duell PB, Gotto AM Jr, Laufs U, *et al.* Bempedoic acid in patients with type 2 diabetes mellitus, prediabetes, and normoglycaemia: a post hoc analysis of efficacy and glycaemic control using pooled data from phase 3 clinical trials. *Diabetes Obes Metab* 2022;**24**:868–880. https://doi.org/10.1111/dom.14645