Efficacy and safety of moderate-intensity statin with ezetimibe combination therapy in patients after percutaneous coronary intervention: a post-hoc analysis of the RACING trial

Jong-Il Park,[a,b,j] Seung-Jun Lee,[a,j] Bum-Kee Hong,[c,**] Yun-Hyeong Cho,[d] Won-Yong Shin,[e] Sang-Wook Lim,[f] Woong-Chol Kang,[g] Yongwhi Park,[h] Sung-Yoon Lee,[i] Yong-Joon Lee,[a] Sung-Jin Hong,[a] Chul-Min Ahn,[a] Byeong-Keuk Kim,[a] Young-Guk Ko,[a] Donghoon Choi,[a] Myeong-Ki Hong,[a] Yangsoo Jang,[e] and Jung-Sun Kim,[a,*] on behalf of the RACING investigators

[a]Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea
[b]Yeungnam University College of Medicine, Daegu, South Korea
[c]Gangnam Severance Hospital, Seoul, South Korea
[d]Myongji Hospital, Hanyang University College of Medicine, Goyang, South Korea
[e]Soonchunhyang University Cheonan Hospital, Cheonan, South Korea
[f]CHA University College of Medicine, Seongnam, South Korea
[g]Gachon University College of Medicine, Incheon, South Korea
[h]Gyeongsang National University Changwon Hospital, Changwon, South Korea
[i]Inje University Ilsan Paik Hospital, Ilsan, South Korea

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Summary

Background Moderate-intensity statin role with ezetimibe combination therapy following percutaneous coronary intervention (PCI) has not been thoroughly investigated, particularly compared to high-intensity statin monotherapy. We aimed to investigate the effect of ezetimibe combination with moderate-intensity statin in patients with atherosclerotic cardiovascular disease following PCI.

Methods This was a post-hoc analysis of a subset of patients who underwent PCI in the RACING trial. At 26 centres in South Korea, patients with atherosclerotic cardiovascular disease (ASCVD) were randomly assigned to receive either moderate-intensity statin with ezetimibe combination therapy (rosuvastatin 10 mg with ezetimibe 10 mg) or high-intensity statin monotherapy (rosuvastatin 20 mg). The prespecified endpoints of the RACING trial were used. The primary endpoint was the 3-year composite of cardiovascular death, major cardiovascular events, and nonfatal stroke. Event rates between the two groups were compared using log-rank tests, and hazard ratios (HR) with 95% confidence intervals (CI) were estimated using Cox regression analysis. Consistent with the RACING trial, the primary and secondary efficacy endpoints were evaluated using an intention-to-treatment approach, and the safety endpoints were assessed in the safety population. The RACING trial was registered at ClinicalTrials.gov (NCT03044665).

Findings Between Feb 14, 2017, and Dec 18, 2018, 3780 participants were enrolled in the RACING trial. Prior history of PCI was found in 2497 patients (67%, median 64 years, 79% male), and was associated with higher rates of the primary endpoint (hazard ratio [HR], 1.34; 95% confidence interval [CI], 1.06–1.69; p = 0.014). Among patients with prior PCI, moderate-intensity statin therapy with ezetimibe combination versus high-intensity statin therapy did not increase the risk of the primary endpoint (HR, 0.95; 95% CI, 0.74–1.24; p = 0.781). The proportion of patients with low-density lipoprotein cholesterol (LDL-C) <70 mg/dL at 1, 2, and 3 years was 74%, 76%, and 73%, respectively, in the combination therapy group, and was significantly higher than that in the high-intensity statin monotherapy group (57%, 62%, and 59%, respectively, all p < 0.001). Discontinuation of lipid-lowering drugs occurred less frequently in the combination group (4.2% vs. 7.6%, p = 0.001).

Interpretation The effects of ezetimibe combination therapy observed in the RACING trial were consistently preserved among patients with ASCVD following PCI. Ezetimibe combination could be considered as a suitable therapeutic strategy to achieve strict control of LDL-C and reduce drug intolerance in patients who underwent PCI.

*Corresponding author. Division of Cardiology, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, 03722, Seoul, South Korea.
**Corresponding author. Division of Cardiology, Heart Centre, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-Ro, Gangnam-Gu, Seoul, 06273, South Korea.
E-mail addresses: kjs1218@yuhs.ac (J.-S. Kim), bkhong@yuhs.ac (B.-K. Hong).
[j]Contributed equally.

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Research in context

Evidence before this study

We searched PubMed for articles published in English up to July 31, 2022, for randomized trials, meta-analyses, systematic reviews, and observational studies using the search terms "percutaneous coronary intervention (PCI) or PCI", "statin", and "ezetimibe". We aimed to compare clinical outcomes between moderate-intensity statin with ezetimibe combination therapy and high-intensity statin monotherapy in patients with prior PCI. However, data regarding the clinical outcomes of patients with prior PCI are limited.

Added value of this study

Among 3780 patients with established atherosclerotic cardiovascular disease in the RACING trial, 2497 (67%) patients with a history of prior PCI were analyzed to compare the effect of moderate-intensity statin with ezetimibe combination therapy and high-intensity statin monotherapy. Moderate-intensity statin with ezetimibe combination therapy produced 3-year clinical outcomes comparable to high-intensity statin monotherapy in patients with prior PCI and was associated with higher achievement of the target low-density lipoprotein (LDL)-cholesterol goal and less occurrence of drug intolerance.

Implications of all the available evidence

Our findings suggested that moderate-intensity statin with ezetimibe combination therapy could be considered a viable alternative to high-intensity statin monotherapy as a maintenance therapy in patients with atherosclerotic cardiovascular disease (ASCVD) following PCI, achieving more effective LDL-cholesterol reduction and drug adherence without increasing the risk of adverse clinical events.

Introduction

Dyslipidaemia optimal control is the cornerstone of treatment for the prevention of recurrent cardiovascular events in patients with documented atherosclerotic cardiovascular disease (ASCVD).[1] Current guidelines on the management of dyslipidaemia commonly include a history of percutaneous coronary intervention (PCI) as a component of the documented ASCVD and strongly recommend the initial prescription of a high-intensity statin for sufficient reduction of low-density lipoprotein (LDL)-cholesterol.[2,3] Furthermore, the benefit of high-intensity statin treatment following PCI is well established, making it the most frequently used treatment modality in patients following PCI.[4–6] High-intensity statin therapy among patients who underwent PCI have undeniable benefits; however, studies have found significant underuse of high-intensity statins in secondary prevention following PCI in real-world practice.[6,7] This reluctance may be explained by concerns regarding drug-related side effects.[8] The results of the randomised RACING trial (long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease) demonstrated that among the patients with documented ASCVD, moderated-intensity statin with ezetimibe combination therapy was non-inferior to high-intensity statin monotherapy for the occurrence of 3-year adverse cardiovascular events, and was more favourable in LDL-cholesterol reduction and drug adherence.[9] In this post-hoc analysis of the RACING study (long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease), we investigated the effect of ezetimibe in combination with a moderate-intensity statin in patients with ASCVD following PCI.

Methods

Study design and population

This was a post-hoc analysis of the RACING trial that included patients with PCI history. The study design has previously been published and the study protocol is provided in the Appendix.[9] In brief, this trial was an investigator-initiated, multicentre, randomised, open-label clinical trial in 26 clinical centres across South Korea that enrolled 3780 patients with documented ASCVD requiring high-intensity statin therapy and achieved LDL-cholesterol levels <70 mg/dL.[10] This study was approved by the institutional review board at each participating centre (Yonsei University Health System, Institutional Review Board, 4-2016-1025). The study was done in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent.

Randomisation and follow-up

Patients were randomly assigned in a 1:1 manner to receive either ezetimibe/moderate-intensity statin

combination therapy (rosuvastatin 10 mg with ezetimibe 10 mg orally once daily) or high-intensity statin monotherapy (rosuvastatin 20 mg orally once daily). At each participating site, a web-response permuted-block randomisation (mixed blocks of 4 or 6) was used to allocate patients who were stratified by LDL-cholesterol levels <100 mg/dL and the presence of diabetes mellitus at baseline. The initial dose (rosuvastatin 10 mg and ezetimibe 10 mg for combination therapy and rosuvastatin 20 mg for statin monotherapy) was strongly advised to be maintained throughout the entire follow-up period. However, after considering the compliance, tolerance, and clinical situation of the patients, the up or down-titration of dosages in both groups was at the discretion of the physician and required a detailed report of reasons. Guideline-directed medical therapy is strongly recommended for other medical treatments to control the various health conditions of patients (e.g., blood pressure or glycaemia, cessation of smoking, or optimal pharmacologic treatment for heart failure).

The clinical and laboratory reports of the patients were assessed at baseline. Patients were scheduled for follow-up visits at 2, 6 months, and every 1-year after that. At baseline, 2 and 6 months, and 1, 2, and 3 years of follow-up, general health status was assessed, including muscle-related symptoms, medication use, and the occurrence of an endpoint or adverse event. Serial follow-ups of the lipid profile of the patients, including total cholesterol, LDL-cholesterol, high-density lipoprotein cholesterol, and triglyceride levels, were performed at 1, 2, and 3 years. When the study drugs were used for the first time at enrollment or when the dose or type of study medications was changed during follow-up, patients were advised to undergo laboratory tests within 4–6 weeks. Aspartate aminotransferase, alanine aminotransferase, and creatinine kinase levels were assessed to monitor adverse effects related to the study medications.

Study endpoint

In this analysis, the prespecified endpoints of the RACING trial were used.[9] The primary endpoint was the occurrence of cardiovascular death, major cardiovascular events, or nonfatal stroke within 3 years. Coronary or peripheral revascularisation or hospitalisation for cardiovascular events was considered major cardiovascular events. Cardiovascular death was defined as death caused by MI, sudden cardiac death, heart failure, stroke, cardiovascular procedures, cardiovascular haemorrhage, or any other case of death in which a clinical endpoint committee could not exclude a cardiovascular cause.[11] A definition of MI, revascularisation, hospitalisation, and non-fatal stroke of the endpoints has previously been described.[9] Secondary endpoints were the clinical efficacy and safety outcomes. Efficacy endpoints included (1) the proportion of participants who had their LDL-cholesterol levels reduced to <70 mg/dL or <55 mg/dL at 1, 2, and 3 years; (2) the composite of all-cause death, major cardiovascular events, and nonfatal stroke; and (3) any individual component of the primary endpoint. Safety endpoints included (1) study medication discontinuation or dose reduction caused by intolerance and (2) the occurrence of clinical adverse events, including new-onset diabetes mellitus, muscle-, hepatic-, or gallbladder-related adverse effects, or cancer diagnosis. New-onset diabetes mellitus was defined as the initiation of antidiabetic medication during the study period or a fasting plasma glucose level of >125mg/dL in the study.[9]

Statistical analyses

The rationale for determining the sample size for the RACING trial was previously presented.[9] Categorical data on demographics, medication, and procedural characteristics were described as numbers (percentages). Continuous variables were expressed as mean ± standard deviation or median (interquartile range) depending on the normality of data distribution which was assessed by the Kolmogorov–Smirnov test. The time enrollment to the occurrence of the first event of interest during follow-up was used to plot the Kaplan–Meier curves for time-to-event analysis. Event rates between the two groups were compared using log-rank tests, and hazard ratios (HR) with 95% confidence intervals (CI) were estimated using Cox regression analysis, in which the stratification variables (diabetes mellitus and baseline LDL-cholesterol <100 mg/dL) were included. The primary and secondary efficacy endpoints were assessed using an intention-to-treatment manner, while the secondary safety endpoints were assessed in the safety population that excluded the participants who were not given the assigned therapy unless they discontinued or reduced the dose due to intolerance.[9] We performed sensitivity analyses for the primary and secondary efficacy endpoints using a per-protocol population, and for the secondary safety endpoint using the intention-to-treat population. To fill in the missing values, no imputation was used. Those who lacked primary and secondary endpoint data were censored during consent withdrawal or loss to follow-up. All analyses were conducted using SPSS (version 25.0; IBM Corporation, Chicago, IL, USA) and R 3.5.3 software (R Foundation). This trial was registered at ClinicalTrials.gov (NCT03044665).

Role of the funding source

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

Results

Baseline characteristics

Between February 14, 2017, and December 18, 2018, a total of 3780 participants were enrolled in the RACING

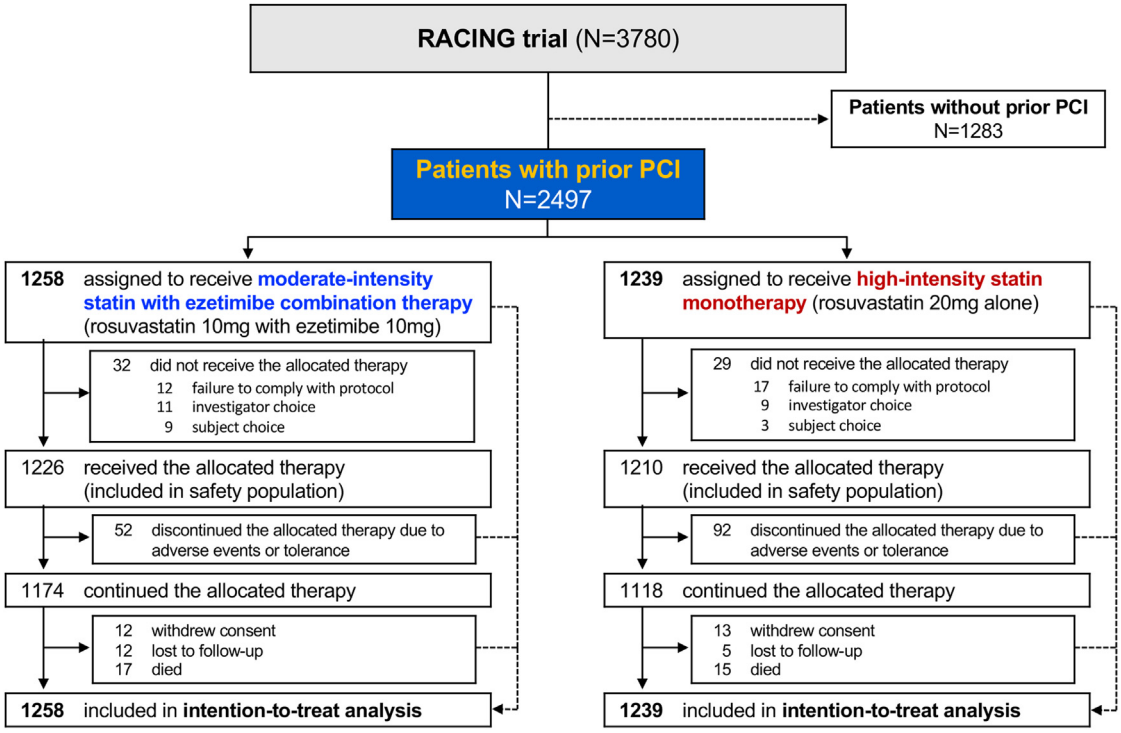

***Fig. 1:* Study profile for this post-hoc analysis of the RACING trial**. RACING, randomised comparison of efficacy and safety of lipid-lowering with statin monotherapy versus statin/ezetimibe combination for high-risk cardiovascular disease; ASCVD, atherosclerotic cardiovascular disease; PCI, percutaneous coronary intervention.

trial, and 2497 patients (67%) had a prior history of PCI at randomisation (Fig. 1). Compared with patients with ASCVD without prior PCI (n = 1283), those with prior PCI were older and more likely to be male. The incidence of myocardial infarction (MI) (49.3% vs. 20.2%), ischaemic stroke (6.3% vs. 4.3%), end-stage kidney disease (1.0% vs. 0.3%), hypertension (69.6% vs. 61.0%), and diabetes mellitus (41.4% vs. 28.4%) was higher in patients with prior PCI. Patients with prior PCI had a higher proportion of previous treatment with high-intensity statins (44.1% vs. 26.3%, p < 0.001) and a lower baseline LDL-cholesterol concentration (77 mg/dL vs. 91 mg/dL, p < 0.001) before randomisation. Table S1 in Appendix shows the other characteristics associated with prior PCI. In patients with or without PCI, the baseline characteristics of patients randomly assigned to moderate-intensity statin with ezetimibe combination therapy and high-intensity statin monotherapy were well balanced (Table 1).

Clinical efficacy outcomes

Fig. 2A depicts the primary endpoint incidence rates in patients with and without prior PCI. The primary endpoint was higher in patients who underwent PCI than in those who did not undergo PCI (10.4% vs. 7.6%; hazard ratio [HR], 1.34; 95% confidence interval [CI], 1.06–1.69; p = 0.014). Among patients who underwent PCI, no significant difference was observed in the occurrence of the primary endpoint based on a history of prior MI (10.1% vs. 11%, p = 0.474) (Fig. 2B). Three-year clinical outcomes of patients with and without prior PCI are presented in Table 2. There was no significant difference in the occurrence of the primary endpoint between the combination therapy and high-intensity statin monotherapy among patients with a history of prior PCI (HR, 0.95; 95% CI, 0.74–1.24; p = 0.781) and without (HR, 0.79; 95% CI, 0.53–1.18; p = 0.253) (Fig. 3). Consistently, the rates of secondary efficacy endpoints were not different between the two treatment groups among patients with and without prior PCI. At sensitivity analyses for patients with prior PCI, the effect of ezetimibe combination therapy versus high-intensity statin monotherapy in terms of the primary and secondary efficacy endpoints appeared consistent throughout the per-protocol analysis (Appendix, Tables S2 and S3), subgroup analyses according to prior coronary revascularisation (Fig. S1 in Appendix), prior MI (Appendix, Table S4 and Fig. S2) or key comorbidities (Appendix, Fig. S3).

Lipid profiles

Table 3 shows the serial changes in serum LDL-cholesterol levels measured at 1, 2, and 3 years after randomisation in patients with and without prior PCI. Among patients with

Characteristics	Prior PCI (N = 2497)			No prior PCI (N = 1283)		
	Moderate-intensity statin with ezetimibe (N = 1258)	High-intensity statin monotherapy (N = 1239)	P-value	Moderate-intensity statin with ezetimibe (N = 636)	High-intensity statin monotherapy (N = 647)	P-value
Age, years	63.8 ± 9.5	64.6 ± 9.6	0.133	63.2 ± 9.5	63.0 ± 9.7	0.799
Female sex	264 (21.0)	268 (21.6)	0.696	210 (33.0)	212 (32.8)	0.485
Male sex	994 (79.0)	971 (78.4)	0.696	426 (67.0)	435 (67.2)	0.485
Height, cm	165.5 ± 8.0	165.1 ± 8.0	0.166	164.1 ± 8.4	163.8 ± 8.6	0.454
Weight, kg	69.1 ± 11.4	68.5 ± 11.0	0.200	67.1 ± 11.2	67.6 ± 10.9	0.409
Body mass index, kg/m^2	25.0 ± 3.1	25.1 ± 3.1	0.585	25.0 ± 3.2	25.1 ± 3.1	0.080
Prior myocardial infarction	623 (49.5)	607 (49.0)	0.810	121 (19.0)	138 (21.3)	0.169
Prior coronary artery bypass surgery	76 (6.0)	64 (5.2)	0.384	56 (8.8)	51 (7.9)	0.614
Acute coronary syndrome	27 (2.1)	20 (1.6)	0.378	0	0	–
Prior ischaemic stroke	73 (5.8)	85 (6.9)	0.286	28 (4.4)	27 (4.2)	0.474
Chronic kidney disease[a]	134 (10.7)	139 (11.2)	0.654	59 (9.3)	60 (9.3)	0.537
End-stage kidney disease on dialysis	11 (0.9)	14 (1.1)	0.552	2 (0.3)	2 (0.3)	0.681
Peripheral artery disease	30 (2.4)	28 (2.3)	0.895	36 (5.7)	41 (6.3)	0.640
Hypertension	868 (69.0)	870 (70.2)	0.514	378 (59.4)	404 (62.4)	0.277
Diabetes mellitus	524 (41.7)	509 (41.1)	0.776	177 (27.8)	188 (29.1)	0.665
Diabetes mellitus with insulin treatment	38 (3.0)	50 (4.0)	0.193	12 (1.9)	20 (3.1)	0.114
Current smoker	211 (16.8)	194 (15.7)	0.480	117 (18.4)	116 (17.9)	0.442
Dyslipidaemia treatment before randomisation			0.154			0.107
High-intensity statin	554 (44.0)	548 (44.2)		157 (24.7)	181 (28.0)	
High-intensity statin with ezetimibe	67 (5.3)	51 (4.1)		18 (2.8)	12 (1.9)	
Moderate-intensity statin	441 (35.1)	481 (38.8)		240 (37.7)	204 (31.5)	
Moderate-intensity statin with ezetimibe	162 (12.9)	134 (10.8)		89 (14.0)	114 (17.6)	
Low-intensity statin	4 (0.3)	2 (0.2)		2 (0.3)	3 (0.5)	
None	30 (2.4)	23 (1.9)		130 (20.4)	133 (20.6)	
Median serum LDL-C level, mg/dL	77 (61–93)	76 (61–92)	0.404	91 (71–115)	90 (72–118)	0.602
No. of patients with LDL-C levels <55 mg/dL (%)	205 (16.3)	199 (16.1)	0.913	50 (7.9)	47 (7.3)	0.752
No. of patients with LDL-C levels <70 mg/dL (%)	494 (39.3)	472 (38.1)	0.287	149 (23.4)	144 (22.3)	0.332

Data are presented as mean ± SD, median (interquartile range), or number (%). PCI, percutaneous coronary intervention; LDL-C, low-density lipoprotein cholesterol. [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.

Table 1: **Baseline characteristics according to treatment assignment and prior PCI status.**

prior PCI, the treatment goal of LDL-cholesterol <70 mg/dL was achieved in 823/1117 (73.6%), 790/1046 (75.5%), and 673/921 (73.1%) patients assigned to the combination therapy group, and 637/1113 (57.2%), 643/1038 (61.9%), and 517/883 (58.6%) patients assigned in the high-intensity statin monotherapy group. Similarly, the proportion of patients with LDL-cholesterol <55 mg/dL was also significantly higher in the combination therapy group. Significant differences in the median LDL-cholesterol concentrations were observed during the follow-up period (57 mg/dL vs. 66 mg/dL at 1 year; 56 vs. 64 at 2 years; 58 vs. 65 at 3 years; all $p < 0.001$). The favourable effect of combination therapy on reducing LDL-cholesterol during the study period was also observed in patients who had not previously undergone PCI.

Safety endpoint

There was no significant difference in the occurrence of death, new-onset diabetes mellitus, muscle-related adverse events, gallbladder-related adverse events, major bleeding, cancer diagnosis, new-onset neurocognitive disorder, or cataract surgery among the patients who underwent PCI who were randomly assigned to either combination therapy or high-intensity statin monotherapy (all $p > 0.05$, Fig. 4). However, 52 patients (4.2%) in the combination therapy group and 92 patients (7.6%) in the high-intensity statin monotherapy group discontinued or reduced the assigned treatment drug due to intolerance or adverse events, with a significantly lower incidence in the combination therapy group (odds ratio [OR], 0.52; 95% CI, 0.37–0.74;

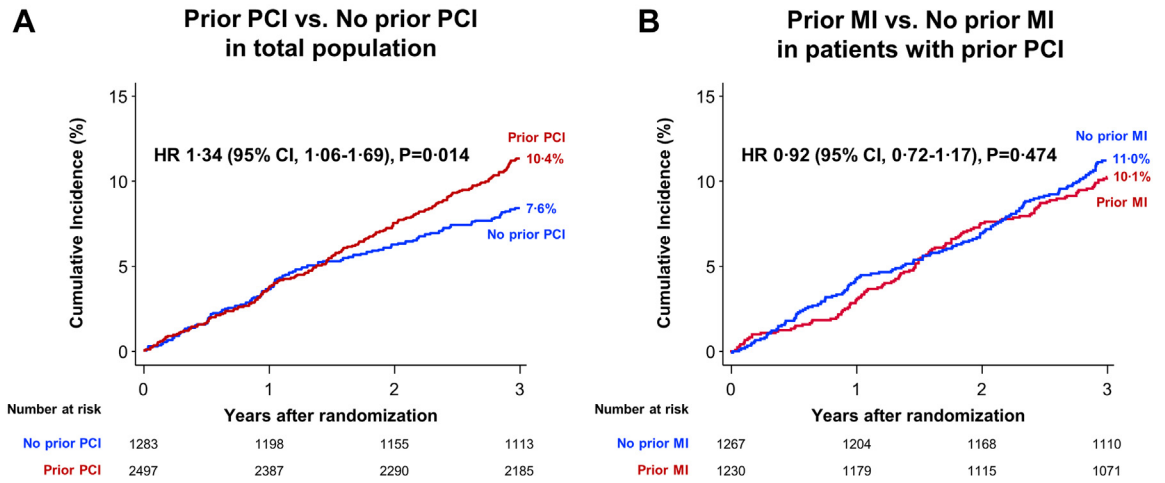

Fig. 2: **Time-to-event curves of the primary endpoint according to (A) prior PCI and (B) history of myocardial infarction among patients with prior PCI**. Time-to-event curves were plotted using Kaplan–Meier survival analysis. HR, hazard ratio; CI, confidence interval; PCI, percutaneous coronary intervention; MI, myocardial infarction.

p = 0.001) (Fig. 4). Similarly, in patients that did not undergo PCI, the occurrence of intolerance leading to discontinuation or dose reduction of the study drug was lower in the combination group (5.8% vs. 9.3%; OR, 0.61; 95% CI, 0.39–0.94; p = 0.023), and there was no difference in the risk of other drug-related adverse events between the treatment groups (Appendix, Fig. S4). As a sensitivity analysis, the secondary safety outcomes of patients with prior PCI according to the intention-to-treat population are presented in Fig. S5 in Appendix.

Discussion

The principal findings were as follows: 1) patients who underwent PCI had a higher risk of recurrent ischaemic events than those without PCI; 2) moderate-intensity statin with ezetimibe combination therapy revealed a similar clinical outcome compared to high-intensity statin monotherapy in terms of a primary endpoint; 3) combination therapy was used to achieve the recommended LDL-cholesterol level more frequently than high-intensity statin monotherapy; 4) statin discontinuation following PCI was less frequently observed in the moderate-intensity statin with ezetimibe combination therapy group compared to the high-intensity statin monotherapy group.

Advances have been made in procedural techniques and the broad adoption of newer-generation drug-eluting stents during contemporary PCI; however, the risk of recurrent adverse cardiovascular outcomes remains considerably high.[12] Therefore, current lipid management guidelines recommend stringent control of LDL-cholesterol in patients with ASCVD with risk factors for recurrent cardiovascular events, such as prior PCI.[2,3] Prior PCI is one of the high-risk conditions constituting the definition criteria of a very high risk of future ASCVD events requiring high-intensity statin in the latest AHA/ACC lipid management guidelines presented in 2018.[2] High-intensity or maximally tolerable doses of statins are strongly recommended for patients with ASCVD at very high risk (Class I), and the addition of ezetimibe should be considered in patients with LDL-cholesterol ≥70 mg/dL (Class IIa). The recent 2019 ESC/EAS guidelines also classified patients with prior PCI as a very high-risk population and strongly recommended intensive lipid-lowering therapy with an LDL-cholesterol goal of <55 mg/dL and ≥50% reduction from baseline (Class Ia).[3] Despite designating patients with prior PCI as very high-risk subset of ASCVD and highlighting the significance of strict LDL-cholesterol lowering, the results of studies investigating the effects of ezetimibe combination in this subgroup are extremely limited. In case of insufficiently reduced LDL-cholesterol levels despite a maximally tolerated dose of statin, combination therapy with ezetimibe should be considered (Class Ia). Prior studies have investigated the effect of strict lipid-lowering therapy with the additional use of non-statin lipid-lowering agents in patients with prior PCI based on the heightened risk of recurrent adverse cardiovascular events.[13–15] A post-hoc analysis of the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in patients with Elevated Risk) trial for patients with prior PCI, revealed that evolocumab significantly reduced the risk of major adverse cardiovascular events, including the risk of coronary revascularisation in patients with prior PCI including patients with complex coronary disease.[13,14] Additionally, in a post-hoc analysis of the REDUCE-IT (Reduction of Cardiovascular Events with Icosapent

	Prior PCI (N = 2497)				No prior PCI (N = 1283)				P for interaction
	Moderate-intensity statin with ezetimibe (N = 1258)	High-intensity statin monotherapy (N = 1239)	HR (95% CI)	P-value	Moderate-intensity statin with ezetimibe (N = 636)	High-intensity statin monotherapy (N = 647)	HR (95% CI)	P-value	
Primary endpoint Composite of cardiovascular death, major cardiovascular event, or nonfatal stroke	129 (10.3)	131 (10.6)	0.95 (0.74–1.24)	0.781	43 (6.8)	55 (8.5)	0.79 (0.53–1.18)	0.253	0.402
Secondary efficacy endpoint Composite of all death, major cardiovascular event, or nonfatal stroke	137 (10.9)	139 (11.2)	0.97 (0.76–1.22)	0.783	49 (7.7)	58 (9.0)	0.86 (0.59–1.25)	0.426	0.592
Individual clinical endpoint									
Cardiovascular death	5 (0.4)	5 (0.4)	1.02 (0.26–3.92)	0.978	3 (0.5)	1 (0.2)	3.08 (0.32–29.63)	0.330	0.401
All-cause of death	17 (1.4)	15 (1.2)	1.12 (0.56–2.24)	0.755	9 (1.4)	7 (1.1)	1.34 (0.50–3.60)	0.564	0.775
Major cardiovascular events	117 (9.3)	118 (9.5)	0.92 (0.71–1.21)	0.564	36 (5.7)	49 (7.6)	0.75 (0.49–1.15)	0.182	0.296
Coronary artery revascularisation	68 (5.4)	64 (5.2)	1.04 (0.74–1.47)	0.801	23 (3.6)	25 (3.9)	0.94 (0.54–1.66)	0.842	0.777
Percutaneous coronary intervention	65 (5.2)	64 (5.2)			22 (3.5)	25 (3.9)			
Coronary artery bypass surgery	3 (0.2)	0			1 (0.1)	0			
Peripheral artery revascularisation	3 (0.2)	5 (0.4)	0.58 (0.24–2.43)	0.457	5 (0.8)	2 (0.3)	2.54 (0.49–13.13)	0.265	0.178
Hospitalisation for ischaemic heart disease	107 (8.5)	109 (8.8)	0.97 (0.74–1.26)	0.810	35 (5.5)	41 (6.3)	0.87 (0.56–1.37)	0.550	0.719
Hospitalisation for heart failure	11 (0.9)	10 (0.8)	1.07 (0.45–2.52)	0.875	3 (0.5)	9 (1.4)	0.35 (0.09–1.28)	0.113	0.145
Hospitalisation for peripheral artery disease	3 (0.2)	5 (0.4)	0.58 (0.14–2.43)	0.457	5 (0.8)	2 (0.3)	2.54 (0.49–13.12)	0.265	0.178
Nonfatal stroke	10 (0.8)	9 (0.7)	1.11 (0.45–2.73)	0.824	5 (0.8)	5 (0.8)	1.02 (0.30–3.53)	0.973	0.923
Ischaemic stroke	7 (0.6)	8 (0.6)	0.87 (0.32–2.40)	0.788	4 (0.6)	3 (0.5)	1.05 (0.23–4.74)	0.950	0.557
Haemorrhagic stroke	3 (0.2)	1 (0.1)	2.79 (0.28–27.51)	0.379	1 (0.2)	2 (0.3)	0.82 (0.05–13.24)	0.887	0.154

Data are the number of events percentages. Hazard ratios were calculated by Cox regression analysis in which the stratification variables (diabetes mellitus and baseline low-density lipoprotein cholesterol <100 mg/dL) were included. PCI, percutaneous coronary intervention.

Table 2: **Three-year clinical efficacy endpoint according to treatment strategy and history of PCI.**

Ethyl-Intervention Trial) study, the addition of icosapent ethyl to statin significantly reduced the risk of coronary revascularisation by 39% in a subset of patients with prior MI, with approximately 80% of patients having a history of prior PCI.[15] Taken together, patients with ASCVD with prior PCI are considered a high-risk population requiring adequate LDL-cholesterol reduction; therefore, high-intensity statin is the guideline-endorsed, and the most common pharmacological therapy in patients with prior PCI.[2,3,6]

However, despite the well-established benefit of high-intensity statins in the secondary prevention of documented ASCVD and prior PCI, there is a significant gap between guideline recommendations and real-world practice.[7,16] Discontinuation of lipid-lowering drugs was observed in 42% of the patients during the 7-year follow-up of the IMPROVE-IT trial (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial), which investigated the additive benefit of ezetimibe combination in addition to a fixed dose of statin (simvastatin 40 mg) after acute coronary syndrome.[17] Only 18 patients at very high risk achieved the target cholesterol level in the DA VINCI registry according to guideline recommendations that included 2794 patients with ASCVD from 18 European countries between 2017 and 2018.[18] Noteworthily, high-intensity statins were used in only 38% of high-risk patients with documented ASCVD; instead, moderate-intensity statin monotherapy was the most frequently used lipid-lowering treatment modality, even in very high-risk patients, and only 16% met the 2019 ESC/EAS guideline LDL-cholesterol goal.[18] Furthermore, the under-utilisation of high-intensity statins following PCI has been consistently observed globally.[6,19–21] In addition to intolerance or poor adherence of the patients based on the concerns for the side effects of high-intensity statin, other numerous factors could contribute to this significant gap between the guidelines and practice, such as

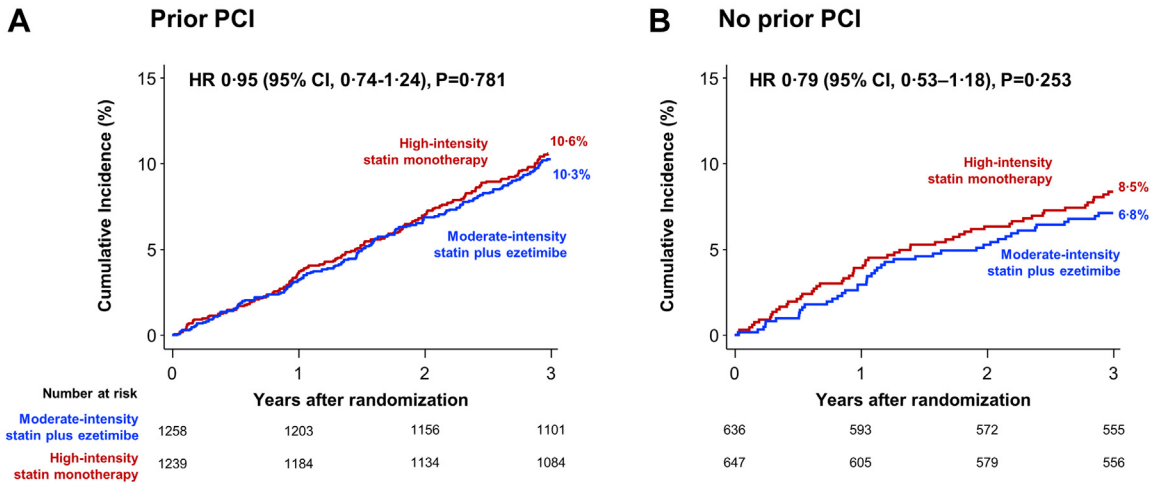

***Fig. 3:* Time-to-event curve of the primary endpoint according to treatment strategy and prior PCI status**. Kaplan–Meier survival curves for the primary outcomes among patients (A) with prior PCI, (B) without prior PCI. HR, hazard ratio; CI, confidence interval; PCI, percutaneous coronary intervention.

reluctance of the physicians to prescribe high-intensity statin or increase the dosage, high drug costs, polypharmacy, a lack of education, socioeconomic environment, caregiver involvement, or insurance issues.[20]

Given the indispensable benefit of strict LDL-cholesterol control by using high-intensity statin following PCI and the contrasting under-utilisation in real-world practice, initial consideration of non-statin lipid-lowering therapy and statin intensity reduction could be a reasonable approach. In contrast to previous randomised controlled trials that investigated the additional benefit of non-statin lipid-lowering modality in addition to a fixed dose of statin[17,22–24] the randomised RACING trial was used to investigate the clinical impact

	Prior PCI (N = 2497)			No prior PCI (N = 1283)		
	Moderate-intensity statin with ezetimibe (N = 1258)	High-intensity statin monotherapy (N = 1239)	P-value	Moderate-intensity statin with ezetimibe (N = 636)	High-intensity statin monotherapy (N = 647)	P-value
1 year						
No. of patients	1117	1113		558	560	
No. of patients with LDL-C levels <70 mg/dL (%)	823 (73.6)	637 (57.2)	<0.001	394 (70.6)	286 (51.1)	<0.001
No. of patients with LDL-C levels <55 mg/dL (%)	475 (42.5)	281 (25.2)	<0.001	220 (39.4)	134 (23.9)	<0.001
LDL-C level (mg/dL)	57 (46–70)	66 (54–79)	<0.001	59 (47–73)	69 (55–83)	<0.001
2 years						
No. of patients	1046	1038		512	501	
No. of patients with LDL-C levels <70 mg/dL (%)	790 (75.5)	643 (61.9)	<0.001	378 (73.8)	281 (56.1)	<0.001
No. of patients with LDL-C levels <55 mg/dL (%)	492 (47.0)	327 (31.5)	<0.001	216 (42.2)	124 (24.8)	<0.001
LDL-C level (mg/dL)	56 (44–69)	64 (52–77)	<0.001	58 (47–71)	66 (55–83)	<0.001
3 years						
No. of patients	921	883		428	432	
No. of patients with LDL-C levels <70 mg/dL (%)	673 (73.1)	517 (58.6)	<0.001	305 (71.3)	242 (56.0)	<0.001
No. of patients with LDL-C levels <55 mg/dL (%)	392 (42.6)	234 (26.5)	<0.001	171 (40.0)	96 (22.2)	<0.001
LDL-C level (mg/dL)	58 (46–70)	65 (54–80)	<0.001	58 (47–72)	67 (55–81)	<0.001

Data are presented as medians (interquartile ranges) or numbers (%). PCI, percutaneous coronary intervention; LDL-C, low-density lipoprotein cholesterol.

***Table 3:* Serial serum LDL cholesterol level during the study period among patients with and without prior PCI.**

Adverse events	Moderate-intensity statin with ezetimibe n/N (%)	High-intensity statin monotherapy n/N (%)	Odds ratio (95% CI)	P-value
Discontinuation or dose reduction of lipid-lowering drug	52/1226 (4·2)	92/1210 (7·6)	0·52 (0·37-0·74)	0·001
New onset diabetes mellitus*	96/723 (13·3)	102/711 (14·3)	0·91 (0·69-1·20)	0·486
New onset diabetes mellitus with requiring medication*	65/723 (9·0)	71/711 (10·0)	0·88 (0·63-1·23)	0·459
Muscle-related adverse events**	15/1226 (1·2)	22/1210 (1·8)	0·66 (0·34-1·28)	0·216
Gallbladder-related adverse events	11/1226 (0·9)	5/1210 (0·4)	2·19 (0·76-6·35)	0·147
Major bleeding	9/1226 (0·7)	7/1210 (0·6)	1·32 (0·49-3·57)	0·581
Cancer diagnosis	25/1226 (2·0)	20/1210 (1·7)	1·30 (0·72-2·36)	0·392
New neurocognitive disorder	4/1226 (0·3)	2/1210 (0·2)	2·42 (0·43-13·56)	0·314
Cataract surgery	15/1226 (1·2)	17/1210 (1·4)	0·92 (0·46-1·86)	0·815

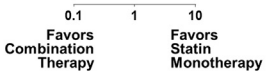

Fig. 4: **Effect of ezetimibe combination therapy on safety endpoint in patients with prior PCI**. *The incidence of new-onset diabetes mellitus was determined specifically for participants who had no prior history of diabetes mellitus at the time of randomisation. **Muscle-related adverse events were defined as a composite of rhabdomyolysis, myopathy, myalgia, and myonecrosis. CI, confidence interval. Odds ratios were calculated by the logistic regression analysis in which age, sex, diabetes mellitus, and baseline low-density lipoprotein cholesterol <100 mg/dL were included for adjustment.

of initial ezetimibe combination with a moderate-potency statin strategy in patients with ASCVD.[9] Consistent with the findings of the main trial, the present secondary analysis for the subset of patients with prior PCI from the RACING trial revealed that moderate-intensity statin with ezetimibe combination versus high-intensity statin found that comparable 3-year clinical outcomes in terms of the primary endpoint and was associated with higher achievement of target LDL-cholesterol goal and lesser occurrence of drug intolerance or dose reduction. Furthermore, these favourable effects of combination therapy were consistently maintained in sensitivity analyses when patients with a history of MI who underwent PCI or prior coronary revascularisation were targeted, implying that moderate-intensity statin with ezetimibe combination therapy could be a feasible treatment modality for patients with coronary artery disease who may not tolerate long-term high-intensity statin therapy.

The present study had some limitations. First, this is an exploratory analysis from the randomised RACING trial; therefore, the results for patients with prior PCI may have limited statistical power and there is a potential for type I error due to multiple comparisons. Second, the current analyses were not pre-specified, the randomisation procedure was not stratified based on prior PCI history, and information regarding the coronary anatomy or procedural complexity was not available. Therefore, the current findings should be considered hypothesis-generating, as it cannot be excluded that the results may have arisen by chance. Third, the proportion of acute coronary syndrome at study randomisation was very small; therefore, our findings may only reflect the clinical impact of the initial combination therapy in stabilised patients following PCI, and caution is warranted when applying it to all patients undergoing PCI. Finally, the 3-year study period was not enough to evaluate whether difference in LDL-cholesterol according to treatment strategy leads to disparities in clinical outcome, therefore long-term follow-up studies are required.

In conclusion, among patients with ASCVD with prior PCI, moderate-intensity statin with ezetimibe combination therapy produced clinical outcomes comparable to high-intensity statin monotherapy and was associated with higher achievement of the target LDL-cholesterol goal and less occurrence of drug intolerance.

Contributors

J-IP, S-JL, B–KH, and J-SK designed this study and participated in the final analyses and data interpretation. All authors participated in enrolment of patients and performed clinical follow-up. This report was drafted by J-IP, S-JL, B–KH, and J-SK. All authors approved the final version of the manuscript and ensured that the accuracy or integrity of any part of the work is appropriately investigated and resolved. All authors accessed and J-IP, S-JL, B–KH, and J-SK verified the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

Data access requests must be made through the corresponding authors of this article to the study steering committee along with a study proposal. Data will only be shared with the approval of the steering committee and institutional review board.

Declaration of interests

B-KK received speaker's fees from Medtronic and Abbott Vascular. M-KH has received speaker's fees from Medtronic, Abbott Vascular and Pfizer, and YJ has received institutional research grants from Biotronik and Hanmi, and J-SK has received proctoring fees from Abbott Vascular. All other authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101933.

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