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

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Summary

Background Drug combinations rather than increasing doses of one drug can achieve greater efficacy and lower risks. Thus, as an alternative to high-intensity statin monotherapy, moderate-intensity statin with ezetimibe combination therapy can lower LDL cholesterol concentrations effectively while reducing adverse effects. However, evidence from randomised trials to compare long-term clinical outcomes is needed.

Methods In this randomised, open-label, non-inferiority trial, patients with atherosclerotic cardiovascular disease (ASCVD) at 26 clinical centres in South Korea were randomly assigned (1:1) 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 primary endpoint was the 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke, in the intention-to-treat population with a non-inferiority margin of 2·0%. This trial is registered with ClinicalTrials.gov, NCT03044665 and is complete.

Findings Between Feb 14, 2017, and Dec 18, 2018, 3780 patients were enrolled: 1894 patients to the combination therapy group and 1886 to the high-intensity statin monotherapy group. The primary endpoint occurred in 172 patients (9·1%) in the combination therapy group and 186 patients (9·9%) in the high-intensity statin monotherapy group (absolute difference −0·78%; 90% CI −2·39 to 0·83). LDL cholesterol concentrations of less than 70 mg/dL at 1, 2, and 3 years were observed in 73%, 75%, and 72% of patients in the combination therapy group, and 55%, 60%, and 58% of patients in the high-intensity statin monotherapy group (all p<0·0001). Discontinuation or dose reduction of the study drug by intolerance was observed in 88 patients (4·8%) and 150 patients (8·2%), respectively (p<0·0001).

Interpretation Among patients with ASCVD, moderate-intensity statin with ezetimibe combination therapy was non-inferior to high-intensity statin monotherapy for the 3-year composite outcomes with a higher proportion of patients with LDL cholesterol concentrations of less than 70 mg/dL and lower intolerance-related drug discontinuation or dose reduction.

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or

Introduction

Guidelines and several studies recommend the intensive lowering of LDL cholesterol concentrations with high-intensity 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) in patients with established atherosclerotic cardiovascular diseases (ASCVD).[1–5] However, rather than increasing doses of one drug, many are now advocating that greater efficacy and lower risks can be achieved by use of drug combinations.[6] Ezetimibe inhibits cholesterol absorption from the intestine by blocking the Niemann-Pick C1-Like 1 receptor, which leads to a decreased delivery of cholesterol to the liver, reduction of hepatic cholesterol stores, and increased clearance of cholesterol from the blood.[7,8] Therefore, compared with high-intensity statin alone, the addition of ezetimibe to lower-intensity statin could provide an alternative strategy to not only achieve adequate LDL cholesterol concentrations but also reduce the required dose of statins. This would contribute to a reduction in the adverse effects or potential intolerances related to high-intensity statin therapy.[9–14] In meta-analyses from several randomised trials, lower-intensity statin with ezetimibe combination therapy showed significantly decreased LDL cholesterol concentrations compared with higher-intensity statin monotherapy.[15,16] However, despite the expectation that lower-intensity statin with ezetimibe

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for articles published in English up to March 31, 2022, to identify relevant published clinical studies using the search terms "randomised", "statin", and "ezetimibe". We aimed to identify randomised clinical trials which compare long-term clinical outcomes (>1 year) between lower-intensity statin with ezetimibe combination therapy and higher-intensity statin monotherapy (not add-on ezetimibe treatment to the same dose statin). However, there were no randomised clinical trials.

Added value of this study

This was a pivotal multicentre, randomised, controlled trial with 3780 patients with established atherosclerotic cardiovascular disease comparing moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy. Moderate-intensity statin with ezetimibe combination therapy was non-inferior to high-intensity statin monotherapy for the 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke (9·1% *vs* 9·9%; difference −0·78%; 90% CI −2·39 to 0·83%; prespecified non-inferiority margin of 2·0% difference) with a higher proportion of patients who achieved LDL cholesterol concentration of less than 70 mg/dL and lower intolerance-related drug discontinuation or dose reduction.

Implications of all the available evidence

Our results support recommending the addition of ezetimibe for patients who are taking moderate-intensity statins at a maximal tolerance. Moreover, these findings suggest that ezetimibe combination therapy might be considered earlier in the use of moderate-intensity statin therapy rather than doubling the statin dose for patients at high risk of adverse effects or statin intolerance with high-intensity statin therapy.

combination therapy would lower LDL cholesterol concentrations more effectively while reducing statin-associated adverse effects, there were no randomised clinical trials that compared the long-term clinical outcomes between these two strategies in patients with established ASCVD.

Therefore, this RACING trial (randomised comparison of efficacy and safety of lipid lowering with statin monotherapy versus statin–ezetimibe combination for high-risk cardiovascular disease) sought to compare 3-year clinical efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients who are at very high risk for cardiovascular diseases. We sought to establish that adding ezetimibe to moderate-intensity statin could be an effective treatment for lowering cholesterol.

Methods

Study design

This trial was an investigator-initiated, multicentre, randomised, open-label, clinical trial done at 26 clinical centres in South Korea. The trial protocol 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. The final study protocol is available in the appendix (pp 15–38). There were no major protocol amendments regarding the sample size, study population, and clinical endpoint. There were no planned trial discontinuation rules. Study coordination, data management, and site management services were done at the Cardiovascular Research Center (Seoul, South Korea). Designated trial monitors reviewed the investigational data at appropriate intervals for accuracy and completeness and to ensure protocol compliance. The data and safety monitoring board (DSMB), which was responsible for ensuring participant safety, acted to monitor patient safety, evaluate study progress, and review the process. For safety monitoring, adverse events were centrally collected, the DSMB reviewed the blinded safety data, and the DSMB statistician provided unblinded summary tables. The DSMB discussed and established whether early stopping was needed or whether there were safety concerns.

Participants

Patients with documented ASCVD requiring high-intensity statin therapy and achievement of LDL cholesterol concentrations of less than 70 mg/dL were enrolled.[2] Documented ASCVD was defined as the presence or occurrence of at least one of the following: previous myocardial infarction (MI), acute coronary syndrome, history of coronary revascularisation or other arterial revascularisation procedures, ischaemic stroke, or peripheral artery disease (PAD).[2] Further details about the inclusion and exclusion criteria are provided in the appendix (p 4). All participants provided written informed consent.

Randomisation

The eligible patients were randomly assigned in a 1:1 manner to receive either ezetimibe and moderate-intensity statin combination therapy (rosuvastatin 10 mg with ezetimibe 10 mg once daily orally) or high-intensity statin monotherapy (rosuvastatin 20 mg once daily orally). A web-response permuted-block randomisation (mixed blocks of 4 or 6) was used at each participating site to allocate the patients, who were stratified by LDL cholesterol concentrations of less than 100 mg/dL and presence of diabetes at baseline. The allocation sequence was computer generated by an external programmer who was not involved in the trial, and physicians or research coordinators accessed the web-response system.

Procedures

Maintenance of the initial dose (rosuvastatin 10 mg and ezetimibe 10 mg for combination therapy and rosuvastatin 20 mg for statin monotherapy) was strongly recommended during the entire follow-up period. However, after considering the patient's compliance, tolerance, and clinical situations, the up-titration or down-titration of doses in both groups was at the physician's discretion and required a detailed report of reasons. For other medical treatments, guideline-directed medical therapy was strongly recommended to control the various health conditions of the patients (eg, blood pressure or glycaemia, cessation of smoking, or optimal pharmacological treatment for heart failure).

Patient clinical and laboratory findings were assessed at baseline. Patients were scheduled for follow-up visits at 2 and 6 months and every 1 year thereafter. Assessment of general health status including muscle-related symptoms, medication use, and the occurrence of an endpoint or adverse event was done at baseline, 2, and 6 months; and at 1, 2, and 3 years of follow-up. Serial follow-up of the patients' lipid profiles, including total cholesterol, LDL cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations, were done at 1, 2, and 3 years. When the study drugs were used for the first time at enrolment or there were changes in the dose or type of study medications during follow-up, patients were recommended to present for a laboratory test within 4–6 weeks. Aspartate aminotransferase, alanine aminotransferase, and creatinine kinase concentrations were assessed to monitor adverse effects related to the study medications.

Outcomes

The primary endpoint was the occurrence of cardiovascular death, major cardiovascular events, or non-fatal stroke within 3 years. Major cardiovascular events included coronary or peripheral revascularisation or hospitalisation for cardiovascular events. Cardiovascular death was defined as death owing to MI, sudden cardiac death, heart failure, stroke, cardiovascular procedures, cardiovascular haemorrhage, and any case of death in which a cardiovascular cause cannot be excluded as adjudicated by a clinical endpoints committee.[17] MI was defined as symptoms, electrocardiographic changes, or abnormal imaging findings, combined with a creatine kinase MB fraction higher than the upper normal limits or a troponin T or troponin I concentration greater than the 99th percentile of the upper normal limit.[17] Coronary or peripheral revascularisation included endovascular and surgical revascularisation of the coronary artery, carotid artery, or lower extremity artery.[2,18] Hospitalisation for any cardiovascular events included hospitalisation for ischaemic heart disease, heart failure, or PAD.[17,19,20] Hospitalisation for ischaemic heart disease was defined as hospitalisation for coronary revascularisation for typical symptoms and signs of electrocardiographic changes, exercise, or pharmacological stress, study evidence for inducible myocardial ischaemia, angiographic evidence for new or worsening coronary artery disease or intracoronary thrombus, or hospitalisation requiring at least an overnight stay because of substantial worsening of ischaemic symptoms and signs (electrocardiographic, echocardiographic, or biomarker changes).[17] Hospitalisation for heart failure was defined as hospitalisation requiring at least an overnight stay in hospital owing to substantial worsening of heart failure symptoms or signs requiring the augmentation of oral medications or new administration of intravenous heart failure therapy including diuretics, inotropes, or vasodilators.[19] Hospitalisation for PAD was defined as hospitalisation for revascularisation or major or minor amputations.[20] Non-fatal stroke was defined as an acute cerebrovascular event resulting in a neurological deficit of more than 24 h or the presence of acute infarction shown by imaging studies.[21]

Secondary endpoints were clinical efficacy and safety. Efficacy endpoints were proportion of participants whose LDL cholesterol concentrations are reduced to less than 70 mg/dL at 1, 2, and 3 years; composite of all-cause death, major cardiovascular events, and non-fatal stroke; drop in the concentrations of LDL cholesterol, that is, the percentage reduction of LDL cholesterol from baseline to follow-up; and any individual component of the primary endpoint. Because an LDL cholesterol goal of less than 55 mg/dL was newly recommended after the start of this trial for secondary prevention in patients at very high-risk according to the latest European guidelines for the management of dyslipidaemia,[1] the proportion of patients whose LDL cholesterol concentrations were less than 55 mg/dL was also analysed as a post-hoc analysis. Safety endpoints included the discontinuation or dose reduction of study medication caused by intolerance and the occurrence of clinical adverse events including new-onset diabetes, muscle-related, hepatic-related, or gallbladder-related adverse effects or cancer diagnosis. An independent clinical endpoint committee masked to the therapy assignment and the primary results of the trial before the locking of the database was responsible for categorising each clinical event.

Statistical analysis

The primary objective of this trial was to establish whether moderate-intensity statin and ezetimibe combination therapy is non-inferior to high-intensity statin monotherapy in the occurrence of the primary endpoint within 3 years of clinical follow-up in the intention-to-treat population. The secondary objective was to test whether the combination therapy group was superior to the high-intensity statin monotherapy group in the efficacy endpoint of achieving an LDL cholesterol value of less than 70 mg/dL. If the primary objective was significant, the secondary objective would be tested. On the basis of the results of the IMPROVE-IT trial, which

revealed primary endpoint rates of 32·7% and 34·7% in the simvastatin–ezetimibe and simvastatin groups, respectively, with a 6-year median follow-up duration, the primary endpoint rate in this study was presumed to be 20%, which was lower than in the same duration of the IMPROVE-IT trial because of our strategy to use a more potent statin.[2,22] Therefore, the expected 3-year event rate was 13% in the combination therapy group and 14% in the high-intensity statin monotherapy group. A non-inferiority margin of 2·0 percentage points was primarily chosen because it was considered to be clinically not different between the two groups. A previous meta-analysis showed a 19% relative risk increase in the moderate-statin therapy versus high-intensity statin therapy for coronary death or any cardiovascular events (MI, stroke, hospitalisation for unstable angina, or any revascularisation) in similar patients.[23] Taking a conservative approach, 7·2% of relative risk increase (38% of the high-intensity statin effect relative to the moderate-intensity statin) in the moderate-intensity statin and ezetimibe combination therapy was thought to be clinically no difference, which corresponds to a 2·0 percentage-point difference between the groups in our study. On the basis of the non-inferiority hypothesis of a 2·0% margin, a total of 1605 patients were required for each group considering a 5% one-sided alpha error rate and 80% power. Considering a 15% loss to follow-up, a total of 3780 patients were required to prove our hypothesis.

For the secondary objective, the achievement of LDL cholesterol of less than 70 mg/dL at 1 year was 31% in the simvastatin and 51% in the simvastatin–ezetimibe groups, in the IMPROVE-IT trial, and the LDL cholesterol-lowering effect of simvastatin–ezetimibe 40–10 mg was known to be similar to that of rosuvastatin 20 mg.[22,24] Therefore, as a clinically important difference, the proportion of participants achieving LDL cholesterol of less than 70 mg/dL was presumed to be 70% in the combination therapy group and 50% in the high-intensity statin monotherapy group. On the basis of the superiority hypothesis with a 5% two-sided alpha error rate, 80% power, and an estimated 15% loss to follow-up, a total of 220 patients were required, which was fulfilled sufficiently by the sample size of 3780 patients for the primary objective of this trial.

Categorical data on demographic, medication, and procedural characteristics are described as numbers (percentages). Continuous variables are expressed as mean (SD) or median (IQR) for normal or skewed distributions. Kaplan-Meier curves for time-to-event

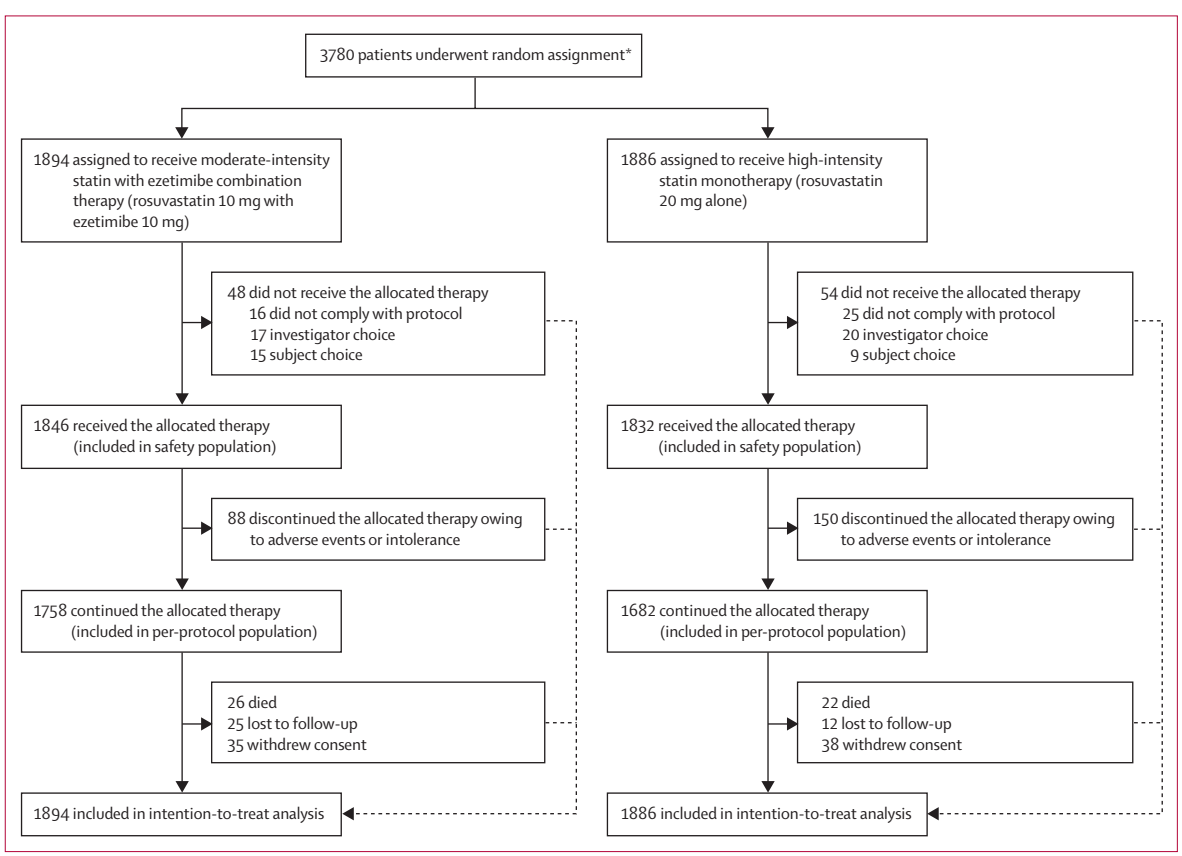

Figure 1: **Trial profile**
*Study sites were not required to provide screening logs. Data regarding reasons for ineligibility are not available.

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analysis were plotted on the basis of the time of enrolment to the occurrence of the first event of interest during follow-up. Event rates between the two groups were compared by means of log-rank tests, and hazard ratios (HRs) with 95% CIs were estimated by means of the Cox regression analysis. A test of non-inferiority was done for the primary endpoint. It was predetermined that non-inferiority would be declared if the upper normal limit of the one-sided 95% CI for the difference in the incidence of the primary endpoint between the two groups was less than 2·0%. The upper normal limit of the one-sided 95% CI was firstly reported because the sample size was calculated for the non-inferiority test with 5% one-sided alpha error rate, and the upper normal limit of the one-sided 97·5% CI for the difference in the incidence of the primary endpoint between the two groups was also calculated as a post-hoc analysis. Secondary endpoints of clinical efficacy (the composite of all-cause death, major cardiovascular events, or non-fatal stroke and the individual components of the primary endpoint) were compared by means of log-rank tests. Analyses of secondary endpoints were not adjusted for multiplicity, and findings should be interpreted as exploratory because of the potential for type I error.

The primary analysis was done in the intention-to-treat population with all patients randomly assigned to a treatment group. Sensitivity analysis was done in the per-protocol population after the exclusion of the patients who were not given the allocated therapy (the total period of the discontinued allocated therapy >5% of the total follow-up period). The assessment of safety outcomes was analysed in a safety population after the exclusion of the patients who were not given the allocated therapy unless they discontinued or reduced dose because of intolerance. A prespecified subgroup analysis was done for clinically relevant factors such as age, sex, body-mass index, hypertension, diabetes, chronic kidney disease, previous MI, stroke, PAD, and baseline LDL cholesterol of less than 100 mg/dL.

Data were collected and analysed according to the predefined statistical analysis plan. No imputation was used to infer missing values. Those with missing primary and secondary endpoint data were censored at the time of withdrawal of consent or loss to follow-up. All analyses were done by means of SAS version 9.2. This trial is registered with ClinicalTrials.gov, NCT03044665.

Role of the funding source

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

Results

Between Feb 14, 2017, and Dec 18, 2018, a total of 3780 patients with documented ASCVD were randomly assigned to receive either combination therapy (n=1894) or high-intensity statin monotherapy (n=1886; figure 1). The baseline characteristics of the patients were not statistically different in the two groups (table 1). The average age was 64 years, 75% were men, 40% had previous MI, 66% had undergone percutaneous coronary intervention, and 37% had diabetes. Before random assignment, 38% were taking high-intensity statin, 36% moderate-intensity statin, and 13% moderate-intensity statin with ezetimibe. All patients were South Korean. The number of patients according to the participating centres is presented in the appendix (p 5). The median follow-up duration was 3 years (IQR 3–3) and 3622 patients (95·8%) completed a 3-year follow-up. In the combination therapy group, 95% were taking the assigned regimen (rosuvastatin 10 mg with ezetimibe 10 mg) at 1 year, 94% at 2 years, and 93% at 3 years; the corresponding rates in the high-intensity statin monotherapy group (rosuvastatin 20 mg) were 94%, 91%, and 90%, respectively (appendix p 6). Other cardiovascular medications were not statistically

	Moderate-intensity statin with ezetimibe combination therapy (n=1894)	High-intensity statin monotherapy (n=1886)
Age, years	64 (10)	64 (10)
Female sex	474 (25%)	480 (25%)
Male sex	1420 (75%)	1406 (75%)
Height, cm	165 (8)	165 (8)
Weight, kg	68 (11)	68 (11)
Body-mass index, kg/m²	25·0 (3·2)	25·1 (3·1)
Previous myocardial infarction	744 (39%)	745 (40%)
Previous percutaneous coronary intervention	1258 (66%)	1239 (66%)
Previous coronary bypass graft surgery	132 (7%)	115 (6%)
Acute coronary syndrome	27 (1%)	20 (1%)
Previous ischaemic stroke	101 (5%)	112 (6%)
Chronic kidney disease*	193 (10%)	199 (11%)
End-stage kidney disease on dialysis	13 (1%)	16 (1%)
Peripheral artery disease	66 (4%)	69 (4%)
Hypertension	1246 (66%)	1274 (68%)
Diabetes	701 (37%)	697 (37%)
Diabetes with insulin treatment	50 (3%)	70 (4%)
Current smoker	328 (17%)	310 (16%)
Medication for dyslipidaemia before randomisation		
High-intensity statin	711 (38%)	729 (39%)
High-intensity statin with ezetimibe	85 (4%)	63 (3%)
Moderate-intensity statin	681 (36%)	685 (36%)
Moderate-intensity statin with ezetimibe	251 (13%)	248 (13%)
Low-intensity statin	6 (<1%)	5 (<1%)
None	160 (8%)	156 (8%)
Serum LDL cholesterol concentration, mg/dL	80 (64–100)	80 (64–100)
Number of patients with LDL cholesterol concentrations <70 mg/dL	643 (34%)	616 (33%)

Data are mean (SD), median (IQR), or n (%). *Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 mL/min per 1·73 m² of body surface area.

Table 1: **Baseline characteristics of the intention-to-treat population**

	Moderate-intensity statin with ezetimibe combination therapy (n=1894)	High-intensity statin monotherapy (n=1886)	Absolute difference (90% CI)	Hazard ratio (95% CI)	p value
Primary endpoint					
Composite of cardiovascular death, major cardiovascular event, or non-fatal stroke	172 (9·1%)	186 (9·9%)	−0·78% (−2·39 to 0·83)	0·92 (0·75 to 1·13)	0·43
Secondary efficacy endpoint					
Composite of all-cause death, major cardiovascular event, or non-fatal stroke	186 (9·8%)	197 (10·4%)	−0·62% (−2·28 to 1·03)	0·94 (0·77 to 1·15)	0·94
Individual clinical endpoint					
Cardiovascular death	8 (0·4%)	6 (0·3%)	0·10% (−0·28 to 0·50)	1·34 (0·46 to 3·85)	0·59
All-cause death	26 (1·4)	22 (1·2)	0·21% (−0·44 to 0·86)	1·19 (0·67 to 2·09)	0·56
Major cardiovascular events	153 (8·1%)	167 (8·9%)	−0·78% (−2·31 to 0·75)	0·91 (0·73 to 1·14)	0·41
Coronary artery revascularisation	91 (4·8%)	89 (4·7%)	0·09% (−1·10 to 1·27)	1·02 (0·76 to 1·37)	0·88
Percutaneous coronary intervention	87	89	..	..	..
Coronary artery bypass surgery	4	0	..	..	..
Peripheral artery revascularisation	8 (0·4%)	7 (0·4%)	0·05% (−0·35 to 0·46)	1·15 (0·42 to 3·16)	0·79
Hospitalisation for ischaemic heart disease	142 (7·5%)	150 (8·0%)	−0·46 (−1·93 to 1·01)	0·94 (0·75 to 1·19)	0·62
Stable angina or unstable angina	120	133	..	..	..
Acute myocardial infarction	22	17	..	..	..
Hospitalisation for heart failure	14 (0·7%)	19 (1·0%)	−0·27% (−0·83 to 0·28)	0·74 (0·37 to 1·47)	0·39
Hospitalisation for peripheral artery disease	8 (0·4%)	7 (0·4%)	0·05% (−0·35 to 0·46)	1·15 (0·42 to 3·16)	0·79
Non-fatal stroke	15 (0·8%)	14 (0·7%)	0·05% (−0·47 to 0·58)	1·07 (0·52 to 2·22)	0·85
Ischaemic stroke	11 (0·6%)	11 (0·6%)	−0·002% (−0·47 to 0·47)	0·99 (0·43 to 2·31)	1·0
Haemorrhagic stroke	4 (0·2%)	3 (0·2%)	0·05% (−0·25 to 0·37)	1·34 (0·30 to 5·97)	0·70

Data are the number of events (%).

Table 2: **3-year clinical endpoint in the intention-to-treat population**

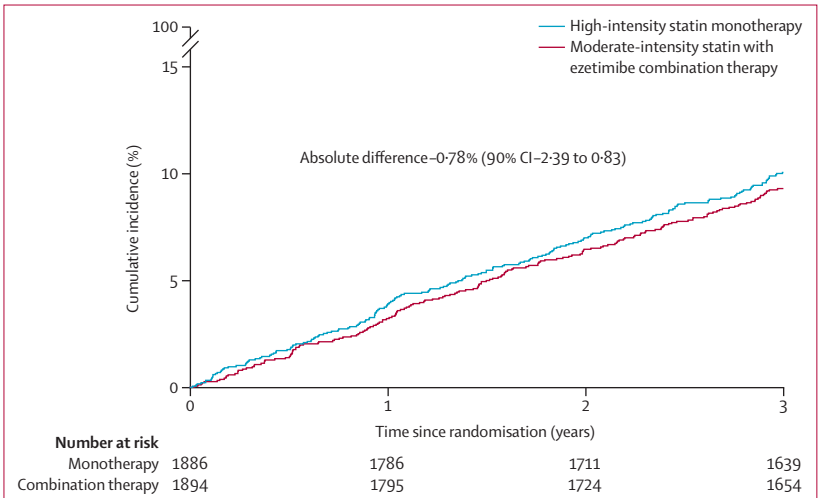

Figure 2: **Kaplan-Meier curves of the primary endpoint of the intention-to-treat population**

different between the two groups during the study period (appendix p 7).

The primary endpoint occurred in 172 patients (9·1%) in the combination therapy group and 186 patients (9·9%) in the high-intensity statin monotherapy group (absolute difference −0·78%; 90% CI −2·39 to 0·83; table 2, figure 2). As a post-hoc analysis, the upper limit of one-sided 97·5% CI of the difference in the primary endpoint was 1·13%, which also met the non-inferiority margin of 2·0% (95% CI −2·69 to 1·13). Cardiovascular death occurred in eight patients (0·4%) in the combination therapy group and six patients (0·3%) in the high-intensity statin monotherapy group (HR 1·34; 95% CI 0·46 to 3·85; p=0·59). Major cardiovascular events were observed in 153 patients (8·1%) in the combination therapy group and 167 patients (8·9%) in the high-intensity statin monotherapy group (HR 0·91; 95% CI 0·73 to 1·14; p=0·41; table 2). The occurrence of non-fatal stroke was not statistically different between the two groups (0·8% *vs* 0·7%; HR 1·07; 95% CI 0·52 to 2·22; p=0·85). As a sensitivity analysis, in the per-protocol population, baseline characteristics and the 3-year clinical endpoint are provided in the appendix (pp 8–9). The primary endpoint occurred in 160 patients (9·1%) in the combination therapy group and 158 patients (9·4%) in the high-intensity statin monotherapy group (absolute difference −0·29%; 90% CI −1·97 to 1·37; appendix pp 9, 12). In post-hoc analyses, the upper limit of one-sided 97·5% CI of the difference in the primary endpoint was 1·69%, which also met the non-inferiority margin of 2·0% (95% CI −2·28 to 1·69).

As for the key secondary endpoint, LDL cholesterol concentrations of less than 70 mg/dL at 1, 2, and 3 years in the intention-to-treat population were observed in

	Moderate-intensity statin with ezetimibe combination therapy	High-intensity statin monotherapy	Absolute differences in proportions, % (95% CI)
1 year			
Number of patients	1675	1673	..
Number of patients with LDL cholesterol concentrations <70 mg/dL	1217 (73%)	923 (55%)	17·5 (14·2 to 20·7)
LDL cholesterol concentration (mg/dL)	58 (47–71)	67 (55–80)	..
2 years			
Number of patients	1558	1539	..
Number of patients with LDL cholesterol concentrations <70 mg/dL	1168 (75%)	924 (60%)	14·9 (11·6 to 18·2)
LDL cholesterol concentration (mg/dL)	57 (45–70)	65 (53–79)	..
3 years			
Number of patients	1349	1315	..
Number of patients with LDL cholesterol concentrations <70 mg/dL	978 (72%)	759 (58%)	14·8 (11·1 to 18·4)
LDL cholesterol concentration (mg/dL)	58 (47–71)	66 (54–80)	..

Data are number of patients (%) or median (IQR).

Table 3: **Proportions of the patients with LDL cholesterol concentrations <70 mg/dL in the intention-to-treat population**

1217 (73%) of 1675, 1168 (75%) of 1558, and 978 (72%) of 1349 patients in the combination therapy group and 923 (55%) of 1673, 924 (60%) of 1539, and 759 (58%) of 1315 patients in the high-intensity statin monotherapy group (table 3; absolute difference 17·5% [95% CI 14·2–20·7] at 1 year; 14·9% [95% CI 11·6–18·2] at 2 years; 14·8% [95% CI 11·1–18·4] at 3 years; all p<0·0001). As a post-hoc analysis, LDL cholesterol concentrations of less than 55 mg/dL at 1, 2, and 3 years were observed in 42%, 45%, and 42% of patients in the combination therapy group and 25%, 29%, and 25% of patients in the high-intensity statin monotherapy group, respectively (absolute difference 17·5% [95% CI 14·3–20·7] at 1 year; 14·9% [95% CI 11·7–18·2] at 2 years; 14·8% [95% CI 11·2–18·3] at 3 years; appendix p 10). The median LDL cholesterol concentration during the study period was 58 (48–71) mg/dL in the combination therapy group and 66 (56–80) mg/dL in the high-intensity statin monotherapy group (p<0·0001). Serial changes in other lipid profiles are provided in the appendix (p 11).

Discontinuation or dose reduction of study medication owing to adverse events or intolerance occurred in 88 patients (4·8%) in the combination therapy group and 150 patients (8·2%) in the high-intensity statin monotherapy group (p<0·0001; table 4; appendix p 13). Other clinical adverse events, which were related to study medications in the two groups are shown in table 4.

The results of prespecified subgroup analyses of the intention-to-treat population are provided in figure 3. The effect of combination therapy versus high-intensity statin monotherapy was consistent as for the primary endpoint across subgroups. These findings were also consistent in the per-protocol population (appendix p 14).

Discussion

Among patients with documented ASCVD who are at very high risk of cardiovascular diseases, moderate-intensity statin with ezetimibe combination therapy was non-inferior to high-intensity statin monotherapy for the 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke. In addition, the non-inferiority of 3-year clinical outcomes was achieved with a higher proportion of LDL cholesterol concentrations of less than 70 mg/dL and a lower prevalence of discontinuation or dose reduction caused by intolerance to the study drug.

A reduction of LDL cholesterol concentrations has been associated with more favourable clinical outcomes, and the use of statins has been recommended as the cornerstone lipid-lowering therapy.[1–5] In particular, patients with documented ASCVD are classified as at very high risk for cardiovascular diseases.[1] For such patients, high-intensity statin therapy with an LDL cholesterol concentration goal of less than 70 mg/dL or a more intensive goal of less than 55 mg/dL is strongly recommended.[1–3] To achieve the LDL cholesterol goals set for patients at very high risk, the use of statins with higher potency, such as rosuvastatin or atorvastatin, was inevitable at the maximum tolerable dose if necessary.[1,2] However, rather than increasing doses of one drug, use of drug combinations can also achieve greater efficacy and lower risks.[6] Ezetimibe could decrease LDL cholesterol concentrations by 13–20%; therefore, the use of ezetimibe plus statins could effectively aid in achieving the target LDL cholesterol concentrations without the need to increase the statin dose.[15,16] Furthermore, as adverse effects of statin therapy are more associated with the use of high-intensity statins, the addition of ezetimibe was consequently expected to reduce the risk of these adverse effects.[9–14] According to the latest dyslipidaemia guidelines issued after the start of the current study, a dual goal of achieving LDL cholesterol concentrations of less than 55 mg/dL and LDL cholesterol reduction of at least 50% from

	Moderate-intensity statin with ezetimibe combination therapy (n=1846)	High-intensity statin monotherapy (n=1832)	Absolute difference (95% CI)
Serious adverse events			
Death	26 (1·4%)	22 (1·2%)	0·21 (−5·88 to 1·01)
Adverse events			
Discontinuation or dose reduction of study drug due to intolerance	88 (4·8%)	150 (8·2%)	−3·42 (−5·07 to −1·80)
Reported symptoms			
Dizziness or general weakness	10	21	..
Chest discomfort or headache	7	12	..
Gastrointestinal symptoms	4	9	..
Urticaria or itching sensation	6	7	..
Myalgia	7	22	..
Other	5	3	..
Physician discretion			
Liver enzyme elevation	15	32	..
Creatine kinase elevation	25	33	..
Fasting glucose concentration elevation	5	6	..
Other	4	5	..
New-onset diabetes	145 (7·9%)	159 (8·7%)	−0·82 (−2·65 to 1·00)
New-onset diabetes with anti-diabetic medication initiation	95 (5·1%)	107 (5·8%)	..
Muscle-related adverse events	21 (1·1%)	34 (1·9%)	0·69 (−2·22 to 0·82)
Myalgia	17 (0·9%)	29 (1·6%)	0·66 (−1·46 to 1·06)
Myopathy	2 (0·1%)	4 (0·2%)	−0·11 (−0·50 to 0·25)
Myonecrosis*	11 (0·6%)	13 (0·7%)	0·11 (−0·72 to 0·48)
Mild	8	9	..
Moderate	2	3	..
Severe including rhabdomyolysis	1	1	..
Gallbladder-related adverse events	13 (0·7%)	7 (0·4%)	0·32 (−0·22 to 0·89)
Major bleeding	17 (0·9%)	13 (0·7%)	0·21 (−0·44 to 0·87)
Cancer diagnosis	37 (2·0%)	28 (1·5%)	0·48 (−0·43 to 0·14)
New-onset neurocognitive disorder	4 (0·2%)	2 (0·1%)	0·11 (−0·25 to 0·50)
Cataract surgery	19 (1·0%)	21 (1·1%)	−0·12 (−0·86 to 0·62)

Data are n (%). These events were adverse events of special interest in this study. ULN=upper limit of normal. *Severity of myonecrosis was classified by an elevation of creatine kinase concentration compared with either baseline concentration or the ULN: mild >3 times ULN; moderate ≥10 times ULN; severe ≥50 times ULN.

Table 4: **Secondary safety endpoint of the safety population**

baseline in patients with documented ASCVD has been recommended, which is more difficult to achieve with mere up-titration of statin monotherapy.[1]

Although the addition of ezetimibe (combination therapy) on clinical outcomes was evaluated in two large randomised trials (the IMPROVE-IT trial and the HIJ-PROPER trial),[22,25] the studies focused on the additive effect of ezetimibe on same-dose statin regimen, but not the dose reduction of statins in the test group. Thus, the clinical benefit was mainly due to the add-on effect of ezetimibe. In addition, the statin intensity was moderate in these two trials, and not a high-intensity statin. When statins are first started in patients with documented ASCVD in current daily clinical practice, high-intensity statins as an initial therapy are usually prescribed. According to the meta-analysis with randomised trials comparing intensive versus moderate intensity statin therapy, intensive statin therapy showed superiority over moderate statin therapy in terms of coronary death or any cardiovascular event.[23] From this result, we firstly hypothesised that high-intensity statin therapy (rosuvastatin 20 mg) would be superior to moderate-intensity statin therapy (rosuvastatin 10 mg), and it would be clinically acceptable when our experimental therapy is at least the moderate-intensity statin therapy, particularly for the clinical outcomes if adverse events can be reduced. Therefore, in our study, we primarily assessed whether moderate-intensity statin and ezetimibe combination therapy was non-inferior to high-intensity statin monotherapy in the context of the primary endpoint. The LDL cholesterol concentration and the event rate of the primary endpoint in the control

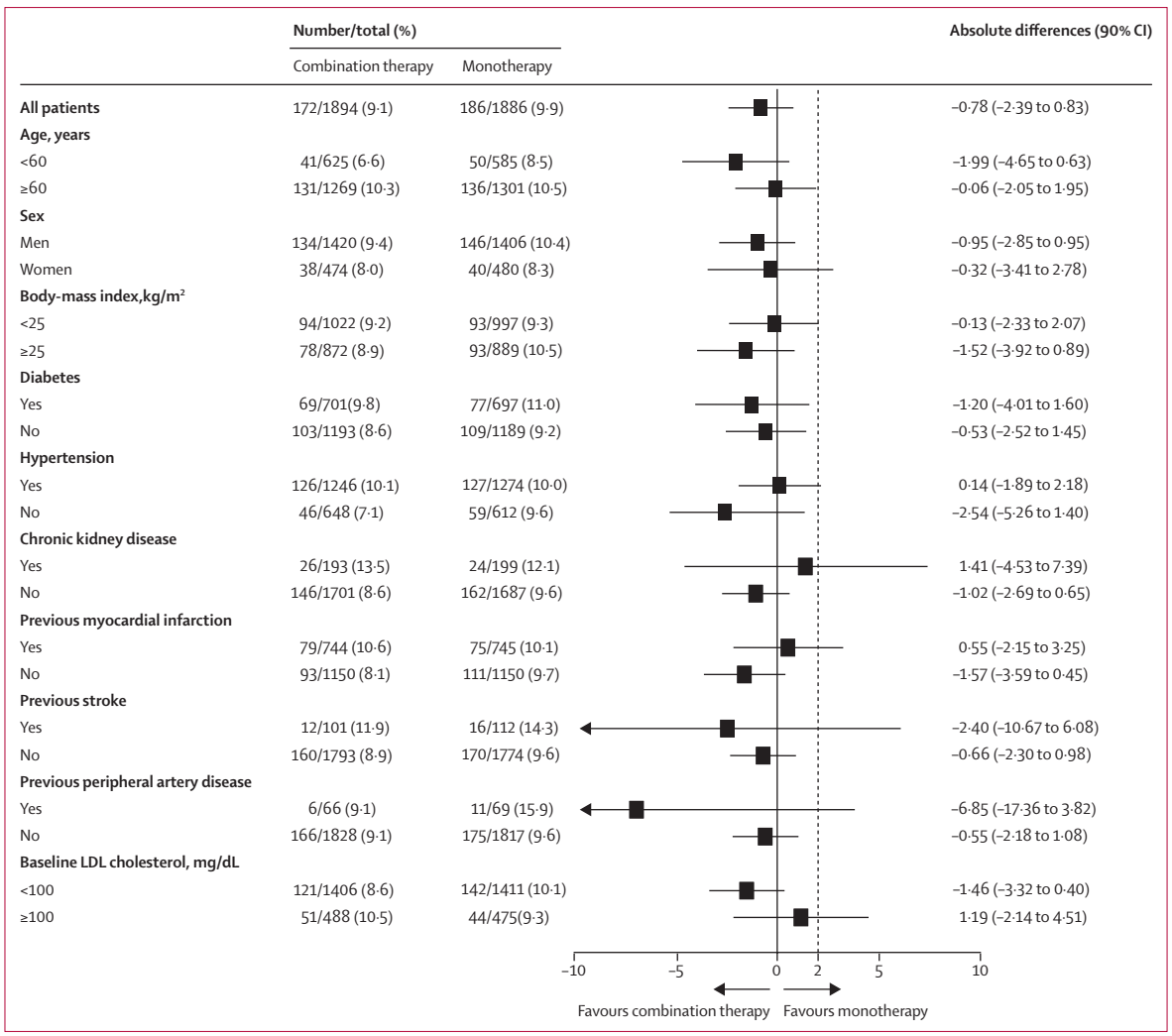

Figure 3: **Subgroup analyses for the primary endpoint of the intention-to-treat population**
The vertical dashed line indicates the prespecified absolute difference 2·0% non-inferiority margin.

group are similar to a previous trial with high-intensity statin therapy.[23] It was also possible to design our trial as a superiority trial considering that initially the greater reduction in the LDL cholesterol concentration was expected in our experimental group. However, the need for a much greater number of patients was a main limitation to evaluating the clinical outcomes as a superiority design. Further studies might be required.

Similar to our design, several randomised trials compared the efficacy of lower-intensity statin with ezetimibe combination therapy versus higher-intensity statin monotherapy,[15,16] but these trials were limited by relatively short-term follow-up of a relatively small number of patients: the longest follow-up was 24 weeks and the largest trial included 891 patients. In addition, these trials had the primary endpoint of surrogate markers or LDL cholesterol concentration,[15,16] not clinical outcomes such as cardiovascular death, MI, stroke, or arterial revascularisation, which are more important endpoints for patients with ASCVD. Thus, even though these meta-analyses with randomised trials showed significantly decreased LDL cholesterol concentrations in patients with moderate-intensity statin and ezetimibe combination therapy versus high-intensity statin monotherapy,[15,16] because of the lack of long-term clinical follow-up evidence, guidelines recommend the use of ezetimibe only in individuals who have high LDL cholesterol concentrations despite a maximal statin monotherapy or are intolerant to statin.[1–3] Our results support the guidelines that recommend the addition of ezetimibe for patients who are taking moderate-intensity statins at a maximal tolerance. Moreover, our results suggest that ezetimibe combination therapy might be considered earlier in the use of moderate-intensity statin therapy instead of doubling the statin dose for patients at high risk of adverse effects or statin intolerance with

high-intensity statin therapy. In a meta-analysis, older age, female sex, obesity, diabetes, hypothyroidism, chronic liver disease, and renal failure were significantly associated with statin intolerance.[11]

In the present study, a significant reduction of LDL cholesterol concentration in the combination therapy group might be one possible explanation for the non-inferiority of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in 3-year clinical outcomes. According to the latest meta-analyses, every 38·7 mg/dL (1 mmol/L) reduction in LDL cholesterol was associated with a risk reduction of major vascular events independent of drug class, suggesting that the benefits from statins, ezetimibe, and PCSK9 inhibitors are probably derived from the cholesterol-lowering effects of these drugs.[26] Importantly, the extent of LDL cholesterol reduction was the strongest independent predictor of a reduction in the risk of major vascular events.[26] The effects of ezetimibe unrelated to cholesterol lowering could be another explanation, for example, ezetimibe-related potentiation of plaque regression, modulation of genes related to inflammation or oxidative stress, inhibition of monocyte or macrophage differentiation, inhibition of smooth muscle cell proliferation, and inhibition of platelet aggregation.[27,28]

Our study has several limitations. First, this was an open-label trial. Physicians and the patients were aware of group assignment, which could potentially have led to bias in reporting patient symptoms. The nocebo effect of the statin therapy should be considered. However, an independent clinical endpoint committee masked to the therapy assignment adjudicated all clinical events including death, MI, stroke, or arterial revascularisation. Second, although our trial showed that moderate-intensity statin with ezetimibe combination therapy was non-inferior to high-intensity statin monotherapy, the lower than anticipated event rates might indicate that the fixed non-inferiority margin of 2·0 percentage points allowed for a more generous CI. Third, although a test for non-inferiority as the primary endpoint was done in this trial, the comparison of the individual clinical outcomes of the primary endpoint might be difficult because of the small number of events.

In conclusion, among patients with documented ASCVD, moderate-intensity statin with ezetimibe combination therapy was non-inferior to high-intensity statin monotherapy in terms of a 3-year composite of cardiovascular death, major cardiovascular events, or non-fatal stroke with a higher proportion of patients who achieved LDL cholesterol concentration of less than 70 mg/dL and lower drug discontinuation or dose reduction owing to intolerance.

Contributors

B-KK, S-JH, YJ, and M-KH designed this study and participated in the final analyses and data interpretation. All authors participated in enrolment of patients and did clinical follow-up, along with revising the draft critically for important intellectual content. This report was drafted by B-KK, S-JH, Y-JL, YJ, and M-KH. All authors approved the final version of the manuscript and ensured that the accuracy or integrity of any part of the work was appropriately investigated and resolved. All authors accessed and verified the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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

Data sharing

Data access will be via application with a study proposal to the study steering committee via the corresponding authors of this Article. Data will only be shared with the approval of the steering committee and institutional review board.

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