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Combination Moderate-Intensity Statin and Ezetimibe Therapy for Elderly Patients With Atherosclerosis

Sang-Hyup Lee, MD,[a,*] Yong-Joon Lee, MD,[a,*] Jung Ho Heo, MD, PhD,[b] Seung-Ho Hur, MD, PhD,[c] Hyun Hee Choi, MD, PhD,[d] Kyung-Jin Kim, MD, PhD,[e] Ju Han Kim, MD, PhD,[f] Keun-Ho Park, MD, PhD,[g] Jung Hee Lee, MD, PhD,[h,i] Yu Jeong Choi, MD, PhD,[j] Seung-Jun Lee, MD, PhD,[a] Sung-Jin Hong, MD, PhD,[a] Chul-Min Ahn, MD, PhD,[a] Byeong-Keuk Kim, MD, PhD,[a] Young-Guk Ko, MD, PhD,[a] Donghoon Choi, MD, PhD,[a] Myeong-Ki Hong, MD, PhD,[a] Yangsoo Jang, MD, PhD,[k] Jung-Sun Kim, MD, PhD[a]

ABSTRACT

BACKGROUND The routine use of high-intensity statins should be considered carefully in elderly patients because of their higher risk of intolerance or adverse events.

OBJECTIVES We evaluated the impact of moderate-intensity statin with ezetimibe combination therapy compared with high-intensity statin monotherapy in elderly patients with atherosclerotic cardiovascular disease (ASCVD).

METHODS In this post hoc analysis of the RACING (RAndomized Comparison of Efficacy and Safety of Lipid-lowerING With Statin Monotherapy Versus Statin/Ezetimibe Combination for High-risk Cardiovascular Diseases) trial, patients were stratified by age (≥75 years and <75 years). The primary endpoint was a 3-year composite of cardiovascular death, major cardiovascular events, or nonfatal stroke.

RESULTS Among the 3,780 enrolled patients, 574 (15.2%) were aged ≥75 years. The rates of the primary endpoint were not different between the moderate-intensity statin with ezetimibe combination therapy group and the high-intensity statin monotherapy group among patients aged ≥75 years (10.6% vs 12.3%; HR: 0.87; 95% CI: 0.54-1.42; $P = 0.581$) and those <75 years (8.8% vs 9.4%; HR: 0.94; 95% CI: 0.74-1.18; $P = 0.570$) (P for interaction = 0.797). Moderate-intensity statin with ezetimibe combination therapy was associated with lower rates of intolerance-related drug discontinuation or dose reduction among patients aged ≥75 years (2.3% vs 7.2%; $P = 0.010$) and those <75 years (5.2% vs 8.4%; $P < 0.001$) (P for interaction = 0.159).

CONCLUSIONS Moderate-intensity statin with ezetimibe combination therapy showed similar cardiovascular benefits to those of high-intensity statin monotherapy with lower intolerance-related drug discontinuation or dose reduction in elderly patients with ASCVD having a higher risk of intolerance, nonadherence, and discontinuation with high-intensity statin therapy. (RAndomized Comparison of Efficacy and Safety of Lipid-lowerING With Statin Monotherapy Versus Statin/Ezetimibe Combination for High-risk Cardiovascular Diseases [RACING Trial]; NCT03044665)
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From the [a]Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [b]Kosin University Gospel Hospital, Busan, Korea; [c]Keimyung University Dongsan Medical Center, Daegu, Korea; [d]Hallym University Chuncheon Sacred Heart Hospital, Chuncheon, Korea; [e]Ewha Womans University Mokdong Hospital, Seoul, Korea; [f]Chonnam National University Hospital, Gwangju, Korea; [g]Chosun University Hospital, Gwangju, Korea; [h]Yeungnam University Hospital, Daegu, Korea; [i]Wonju Severance Christian Hospital, Wonju, Korea; [j]Daejeon Eulji Medical Center, Eulji University, Daejeon, Korea; and the [k]CHA Bundang Medical Center, CHA University College of Medicine, Seongnam, Korea. *Drs S-H Lee and Y-J Lee contributed equally to this work.
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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

LDL = low-density lipoprotein

MI = myocardial infarction

PCSK9 = proprotein convertase subtilisin-kexin type 9

Among patients with atherosclerotic cardiovascular disease (ASCVD), effective and safe lipid-lowering therapy is required, especially for elderly patients with greater cardiovascular risks.[1] Statin reduces low-density lipoprotein (LDL) cholesterol levels by inhibiting the activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase and exerts additional effect beyond cholesterol lowering by increasing production of nitric oxide, reducing inflammation, improving endothelial function, and inhibiting thrombogenic response, thereby preventing future adverse cardiovascular events.[2-4] To achieve these benefits, high-intensity statin therapy is recommended for patients with ASCVD.[5,6] In the Cholesterol Treatment Trialists' meta-analysis including 28 trials, higher-intensity statin therapy showed further benefits for reducing composite vascular events compared with lower-intensity statin therapy, and the benefit was consistently observed in patients >75 years of age, especially in those with previous vascular diseases.[7] However, as statin-related adverse events are more common with high-intensity statin therapy, high-intensity statins are less likely to be used in elderly patients, and moderate-intensity statins may be preferable to high-intensity statins for patients >75 years of age.[6,8]

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Ezetimibe reduces LDL cholesterol levels by inhibiting the Niemann-Pick C1-Like 1 receptor expression, which leads to inhibition of cholesterol absorption from the intestine.[9,10] The IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) showed that the addition of ezetimibe to moderate-intensity statin therapy provides further benefits in reducing LDL cholesterol levels as well as cardiovascular events compared with moderate-intensity statin monotherapy.[11] In addition, according to the age-based secondary analysis of the IMPROVE-IT, the benefit of ezetimibe addition was greatest in patients aged ≥75 years.[12] However, in IMPROVE-IT, the effect of ezetimibe combination therapy with moderate-intensity statin was compared with that of moderate-intensity statin monotherapy, rather than that of high-intensity statin monotherapy, which is initially recommended for secondary prevention in patients with ASCVD.[6,11-13] Recently, the RACING (Randomized Comparison of Efficacy and Safety of Lipid Lowering With Statin Monotherapy versus Statin-Ezetimibe Combination for High-Risk Cardiovascular Disease) trial demonstrated that moderate-intensity statin with ezetimibe combination therapy could achieve comparable efficacy with that of high-intensity statin monotherapy in terms of long-term composite cardiovascular events and a lower rate of intolerance-related drug discontinuation or dose reduction.[14] In this post hoc analysis of the RACING trial, the efficacy and safety of moderate-intensity statin with ezetimibe combination therapy compared with those of high-intensity statin monotherapy were investigated in elderly patients, especially those aged ≥75 years.

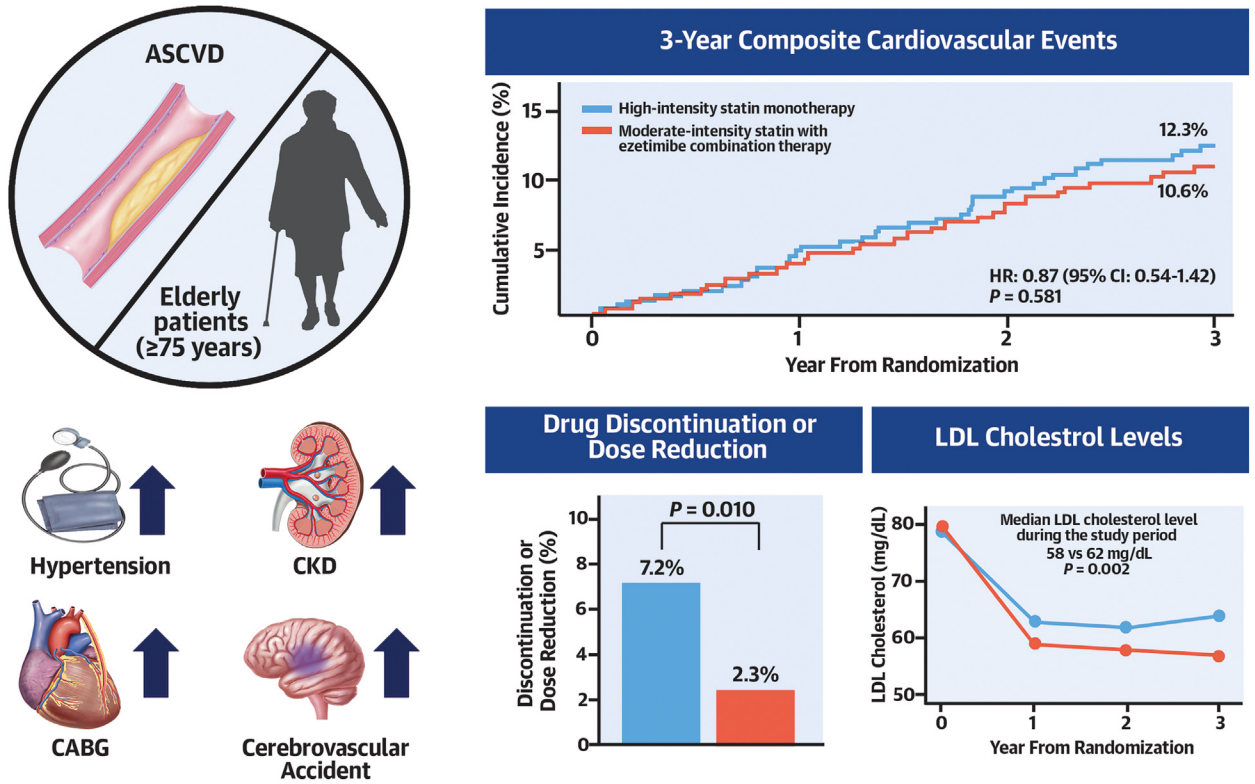
METHODS

STUDY POPULATION AND DESIGN. The RACING trial was a prospective, multicenter, randomized, open-label, noninferiority clinical trial including 3,780 patients from 26 centers in South Korea, and the long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy were compared with those of high-intensity statin monotherapy.[14] Patients with documented ASCVD were enrolled, which was defined as meeting at least 1 of the following criteria: 1) previous myocardial infarction (MI); 2) acute coronary syndrome; 3) history of coronary revascularization (percutaneous coronary intervention or coronary artery bypass surgery) or other arterial revascularization procedures; 4) ischemic stroke; or 5) peripheral artery disease. The detailed study design and rationale for the RACING trial have been published previously.[14]

Patients eligible for the RACING trial were randomly assigned in a 1:1 ratio to the moderate-intensity statin with ezetimibe combination therapy group (rosuvastatin 10 mg plus ezetimibe 10 mg once daily; hereafter, ezetimibe combination therapy group) and the high-intensity statin monotherapy group (rosuvastatin 20 mg once daily). The initial doses of the study drugs were strongly recommended to be maintained during the entire study period. In this post hoc analysis, patients in the RACING trial were stratified by age into those aged ≥75 years and those <75 years. The cutoff value for age (75 years) was selected based on recent dyslipidemia management guidelines and previous studies focusing on age.[6,7,12,13] The trial was approved by the Institutional Review Board of each participating center and followed the ethical principles of the Declaration of Helsinki. All patients provided written informed consent before participating in the trial.

DEFINITION OF STUDY ENDPOINTS. The primary endpoint was a composite of cardiovascular death, major cardiovascular events, or nonfatal stroke within 3 years. Cardiovascular death was defined as death caused by MI, sudden cardiac death, heart

CENTRAL ILLUSTRATION **Age-Stratified Post Hoc Analysis of the Randomized RACING Trial**



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The current study focused on elderly patients, who tended to have higher cardiovascular risks than young patients. Among patients with atherosclerotic cardiovascular disease (ASCVD) aged ≥75 years, ezetimibe combination therapy was shown to have a benefit comparable with that of high-intensity statin monotherapy for the reduction of 3-year composite cardiovascular events. In addition, ezetimibe combination therapy was associated with lower rates of intolerance-related drug discontinuation or dose reduction and greater reduction in low-density lipoprotein (LDL) cholesterol levels. RACING = RAndomized Comparison of Efficacy and Safety of Lipid-lowerING With Statin Monotherapy Versus Statin/Ezetimibe Combination for High-risk Cardiovascular Diseases.

failure, stroke, cardiovascular procedures, cardiovascular hemorrhage, or death for which cardiovascular causes cannot be ruled out.[15] MI was defined as symptoms, typical changes on electrocardiogram, or abnormal imaging findings accompanied by an increase in the creatine kinase myocardial band fraction level above the upper normal limit or an increase in troponin T or I levels above the 99th percentile of the upper normal limit.[15] Major cardiovascular events were defined as revascularization of the coronary or peripheral arteries or hospitalization because of cardiovascular events. The revascularization of the coronary or peripheral arteries included surgical or endovascular revascularization of the coronary arteries, carotid arteries, or arteries of the lower extremities.[16] Hospitalization caused by cardiovascular events included those for ischemic heart disease, heart failure, or peripheral artery disease.[15,17,18] Nonfatal stroke was defined as an acute cerebrovascular event with a neurologic deficit for more than 24 hours or the occurrence of acute infarction documented by imaging studies.[19]

The secondary endpoints were clinical efficacy and safety endpoints. Secondary efficacy endpoints were a composite of all-cause death, major cardiovascular events or nonfatal stroke; individual components of the primary endpoint; and LDL cholesterol levels at years 1, 2, and 3 after randomization. Secondary safety endpoints were the rates of discontinuation or dose reduction of the study drug caused by intolerance and the occurrence of clinical adverse events including new-onset diabetes; adverse events associated with muscles, liver, or gallbladder; cancer diagnosis; or cataract surgery. An independent

TABLE 1 Baseline Characteristics Stratified by Age and Treatment Strategy

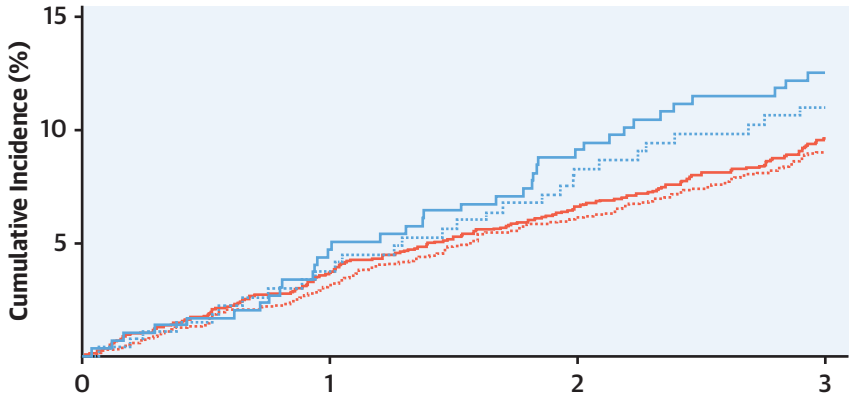
	Age ≥75 Years (n = 574)			Age <75 Years (n = 3,206)		
	Ezetimibe Combination Therapy (n = 273)	High-Intensity Statin Monotherapy (n = 301)	*P* Value	Ezetimibe Combination Therapy (n = 1,621)	High-Intensity Statin Monotherapy (n = 1,585)	*P* Value
Age, y	77 ± 2	77 ± 2	0.085	61 ± 8	62 ± 8	0.442
Male	173 (63.4)	180 (59.8)	0.428	1,247 (76.9)	1,226 (77.4)	0.808
Body mass index, kg/m^2	24.5 ± 3.1	24.6 ± 2.8	0.689	25.1 ± 3.2	25.2 ± 3.1	0.580
Previous myocardial infarction	93 (34.1)	105 (34.9)	0.906	651 (40.2)	640 (40.4)	0.928
Previous percutaneous coronary intervention	185 (67.8)	209 (69.4)	0.733	1,073 (66.2)	1,030 (65.0)	0.494
Previous coronary artery bypass graft surgery	29 (10.6)	29 (9.6)	0.800	103 (6.4)	86 (5.4)	0.298
Previous cerebrovascular accident	26 (9.5)	24 (8.0)	0.610	75 (4.6)	88 (5.6)	0.266
Hypertension	223 (81.7)	232 (77.1)	0.209	1,023 (63.1)	1,042 (65.7)	0.129
Diabetes mellitus	100 (36.6)	131 (43.5)	0.110	601 (37.1)	566 (35.7)	0.443
Chronic kidney disease[a]	56 (20.5)	78 (25.9)	0.153	137 (8.5)	121 (7.6)	0.432
End-stage renal disease requiring dialysis	2 (0.7)	3 (1.0)	>0.999	11 (0.7)	13 (0.8)	0.795
Congestive heart failure	13 (4.8)	7 (2.3)	0.173	58 (3.6)	62 (3.9)	0.686
Peripheral artery disease	11 (4.0)	15 (5.0)	0.728	55 (3.4)	54 (3.4)	>0.999
Current smoker	23 (8.4)	20 (6.6)	0.515	305 (18.8)	290 (18.3)	0.740
Statin therapy before randomization			0.856			0.937
High-intensity statin	105 (38.5)	109 (36.2)		691 (42.6)	683 (43.1)	
Moderate-intensity statin	145 (53.1)	166 (55.1)		787 (48.6)	767 (48.4)	
Low-intensity or no statin	23 (8.4)	26 (8.6)		143 (8.8)	135 (8.5)	
Ezetimibe before randomization	53 (19.4)	42 (14.0)	0.100	283 (17.5)	269 (17.0)	0.750
Serum LDL cholesterol levels, mg/dL	80 (65-99)	79 (62-99)	0.521	80 (64-100)	80 (64-100)	0.721

Values are mean ± SD, n (%), or median (IQR). [a]Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 of body surface area.
LDL = low-density lipoprotein.

clinical endpoint committee blinded to the therapy assignments, and primary results of the trial adjudicated all adverse events including primary and secondary endpoints. Further definitions of the outcomes have been previously described.[14]

STATISTICAL ANALYSES. The assessments of the primary endpoint and secondary efficacy endpoints were analyzed based on the intention-to-treat population, whereas the analyses of secondary safety endpoints were initially performed in the safety population, excluding patients who were not administered the allocated therapy unless they discontinued or reduced the dose because of intolerance.[14] Sensitivity analyses of secondary safety endpoints were performed in the intention-to-treat population. Continuous data are described as the means with standard deviations or medians with interquartile ranges for normal or non-normal distributions, respectively. Categorical data are presented as numbers with percentages. Comparisons of continuous variables between the 2 groups were analyzed using the Student's *t*-test or Mann-Whitney *U* test, and categorical variables were compared using the chi-square test or Fisher exact test, depending on their distribution. Time-to-event data were plotted using Kaplan-Meier survival analysis based on the time from randomization to the occurrence of the first event of interest during follow-up, and the event rates between the 2 groups were compared using log-rank tests. HRs with 95% CIs were estimated using a Cox proportional hazard regression model. To assess whether therapy effects (ezetimibe combination therapy vs high-intensity statin monotherapy) differed according to age (≥75 years vs <75 years), formal interaction tests between age and treatment strategy for the clinical outcomes were performed using Cox proportional hazard or logistic regression models, as appropriate. To evaluate the relationship between age as a continuous variable and the primary endpoint, a Cox proportional hazard regression model with restricted cubic spline was used to explore potential nonlinear relationships.[20] In addition, the 3-way interaction among age group, treatment strategy, and time after randomization (years 1, 2, and 3) for the proportion of patients who achieved LDL cholesterol levels of 70 mg/dL was estimated using a mixed effects logistic regression model with repeated measures. All tests were 2-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using R statistical software version 4.1.2 (R Foundation for Statistical Computing).

FIGURE 1 Time-to-Event Curves of the Primary Endpoint



Number at Risk				
Age ≥75 Years, High-Intensity Statin Monotherapy	301	282	268	255
Age ≥75 Years, Ezetimibe Combination Therapy	273	254	240	227
Age <75 Years, High-Intensity Statin Monotherapy	1,585	1,504	1,443	1,384
Age <75 Years, Ezetimibe Combination Therapy	1,621	1,541	1,484	1,427

Kaplan-Meier curves for the primary endpoint stratified by age (≥75 years vs <75 years) and treatment strategy (ezetimibe combination therapy vs high-intensity statin monotherapy).

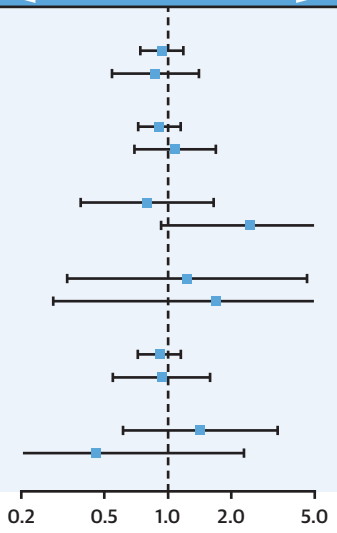
RESULTS

BASELINE CHARACTERISTICS. A total of 3,780 patients were enrolled in the RACING trial, of whom 574 (15.2%) were ≥75 years, and 3,206 (84.8%) were <75 years at randomization. The baseline characteristics stratified by age are presented in Supplemental Table 1. Patients aged ≥75 years were shown to be associated with a lower proportion of male sex (61.5% vs 77.1%) and a lower body mass index (24.6 kg/m^2 vs 25.1 kg/m^2) than those <75 years of age. In addition, patients aged ≥75 years were more likely to have a higher proportion of previous coronary artery bypass surgery (10.1% vs 5.9%), previous cerebrovascular accidents (8.7% vs 5.1%), and predisposing comorbidities including hypertension (79.3% vs 64.4%) and chronic kidney disease (23.3% vs 8.0%) (**Central Illustration**). The proportion of patients with previous MIs (34.5% vs 40.3%) and who received high-intensity statin therapy before randomization was lower (37.3% vs 42.9%) in patients aged ≥75 years than in those <75 years of age. As presented in **Table 1**, the baseline characteristics of patients receiving ezetimibe combination therapy vs high-intensity statin monotherapy were well balanced, irrespective of age.

PRIMARY ENDPOINT AND SECONDARY EFFICACY ENDPOINTS. The incidence of the primary endpoint stratified by age and treatment strategy is shown in **Figures 1** and **2**. Among patients aged ≥75 years, the incidence of the primary endpoint was not different between the ezetimibe combination therapy group and the high-intensity statin monotherapy group (10.6% vs 12.3%; HR: 0.87; 95% CI: 0.54-1.42; $P = 0.581$). Similarly, among patients <75 years of age, the incidence of the primary endpoint was not different between the 2 therapy groups (8.8% vs 9.4%; HR: 0.94; 95% CI: 0.74-1.18; $P = 0.570$). There was no significant interaction between age and treatment strategy (P for interaction [P_{int}] = 0.797) (**Figure 2**). The interaction between age as a continuous variable and treatment strategy for the occurrence of the primary endpoint was also not significant ($P_{int} = 0.283$) (Supplemental Figure 1). The incidences of the secondary efficacy endpoints are shown in **Figure 2**. No significant interactions between age and treatment strategy were observed with regard to secondary efficacy endpoints.

FIGURE 2 Forest Plot for Study Endpoints

	No. of Events/Total No. (Event Rate, %)					
	Ezetimibe Combination Therapy	High-Intensity Statin Monotherapy	HR (95% CI)	*P* Value	Favors Combination Therapy / Favors Monotherapy	P_{int}*
Primary Endpoint†						0.797
Age <75 years	143/1,621 (8.8)	149/1,585 (9.4)	0.94 (0.74-1.18)	0.570		
Age ≥75 years	29/273 (10.6)	37/301 (12.3)	0.87 (0.54-1.42)	0.581		
Secondary Composite Endpoint‡						0.508
Age <75 years	149/1,621 (9.2)	159/1,585 (10.0)	0.91 (0.73-1.14)	0.428		
Age ≥75 years	37/273 (13.6)	38/301 (12.6)	1.08 (0.69-1.70)	0.730		
All-Cause Death						0.070
Age <75 years	13/1,621 (0.8)	16/1,585 (1.0)	0.80 (0.38-1.66)	0.545		
Age ≥75 years	13/273 (4.8)	6/301 (2.0)	2.45 (0.93-6.45)	0.069		
Cardiovascular Death						0.780
Age <75 years	5/1,621 (0.3)	4/1,585 (0.3)	1.23 (0.33-4.57)	0.761		
Age ≥75 years	3/273 (1.1)	2/301 (0.7)	1.70 (0.28-10.2)	0.562		
Major Cardiovascular Events						0.938
Age <75 years	128/1,621 (7.9)	137/1,585 (8.6)	0.91 (0.72-1.16)	0.447		
Age ≥75 years	25/273 (9.2)	30/301 (10.0)	0.93 (0.55-1.59)	0.796		
Nonfatal Stroke						0.221
Age <75 years	13/1621 (0.8)	9/1,585 (0.6)	1.42 (0.61-3.32)	0.420		
Age ≥75 years	2/273 (0.7)	5/301 (1.7)	0.45 (0.09-2.31)	0.336		



The effect of ezetimibe combination therapy compared with high-intensity statin monotherapy on primary and secondary efficacy endpoints are described in terms of event rates, HRs, and interaction terms. *P_{int} indicates the *P* value for the interaction between age and treatment strategy. †Primary endpoint was a 3-year composite of cardiovascular death, major cardiovascular events, or nonfatal stroke. ‡Secondary composite endpoint was a 3-year composite of all-cause death, major cardiovascular events, or nonfatal stroke.

REDUCTION OF LDL CHOLESTEROL. Changes in LDL cholesterol levels during follow-up are shown in Supplemental Table 2. Among patients aged ≥75 years, median LDL cholesterol level during the study period was 58 mg/dL (IQR: 48-71 mg/dL) in the ezetimibe combination therapy group and 62 mg/dL (IQR: 52-76 mg/dL) in the high-intensity statin monotherapy group ($P = 0.002$). Median LDL cholesterol levels were consistently lower in patients in the ezetimibe combination therapy group than in those in the high-intensity statin monotherapy group at year 1 (59 mg/dL vs 63 mg/dL; $P = 0.004$), year 2 (58 mg/dL vs 62 mg/dL; $P = 0.013$), and year 3 (57 mg/dL vs 64 mg/dL; $P = 0.036$) (**Figure 3**). Among patients <75 years of age, median LDL cholesterol level during the study period was 58 mg/dL (IQR: 47-70 mg/dL) in the ezetimibe combination therapy group and 67 mg/dL (IQR: 56-80 mg/dL) in the high-intensity statin monotherapy group ($P < 0.001$), and median LDL cholesterol levels were consistently lower in the ezetimibe combination therapy group at years 1, 2, and 3 (all $P < 0.001$) (Supplemental Figure 2). The proportion of patients who achieved LDL cholesterol levels of 70 mg/dL at years 1, 2, and 3 are shown in Supplemental Table 2, and there was no significant 3-way interaction among age group, treatment strategy, and time ($P_{int} = 0.659$).

SECONDARY SAFETY ENDPOINTS. The secondary safety endpoints stratified by age and treatment strategy are presented in **Table 2**. Among patients aged ≥75 years, ezetimibe combination therapy was associated with a lower rate of intolerance-related discontinuation or dose reduction than high-intensity statin monotherapy (2.3% vs 7.2%; $P = 0.010$) (**Figure 4A**). In addition, the rate of new-onset diabetes was lower in the ezetimibe combination therapy group than in the high-intensity statin monotherapy group (10.0% vs 18.7%; $P = 0.025$) (**Figure 4B**). Among patients <75 years of age, the rate of intolerance-related discontinuation or dose reduction was lower in the ezetimibe combination therapy group (5.2% vs 8.4%; $P < 0.001$), whereas the rate of new-onset diabetes did not differ between the 2 therapy groups (12.8% vs 12.9%; $P = 0.938$) (Supplemental Figure 3). Although no significant interaction between age and treatment strategy was observed for intolerance-related drug discontinuation or dose reduction ($P_{int} = 0.159$), a significant

interaction was noted for new-onset diabetes (P_{int} = 0.041). The rates of other adverse events did not differ between the 2 therapy groups, regardless of age (Table 2). For the sensitivity analysis, the secondary safety endpoints of the intention-to-treat population are shown in Supplemental Table 3.

DISCUSSION

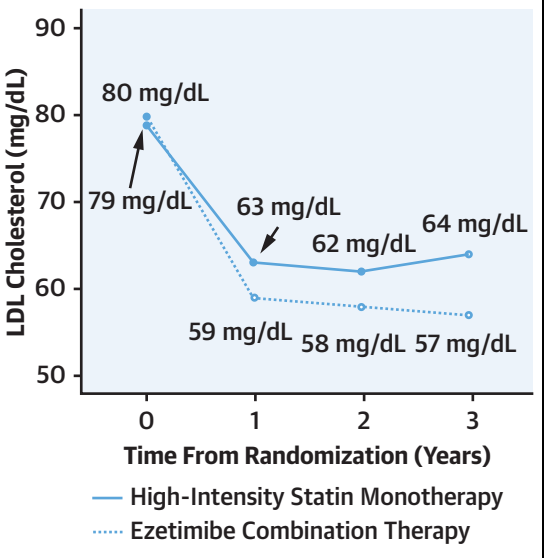
High-intensity statin therapy is a powerful strategy for reducing future cardiovascular events in patients with ASCVD[7]; however, because of poor adherence and concerns regarding statin-related adverse events, the current guidelines do not recommend the routine use of high-intensity statins for secondary prevention in patients >75 years of age.[6] In the recently published RACING trial, moderate-intensity statin with ezetimibe combination therapy was shown to be as effective as high-intensity statin monotherapy in preventing future cardiovascular events, with reduced concerns for intolerance-related drug discontinuation or dose reduction.[14] In this post hoc analysis of the RACING trial stratified by age, the effect of moderate-intensity statin with ezetimibe combination therapy was conserved among patients aged ≥75 years.

Although limited number of elderly patients were included, consistent benefits of statin therapy for elderly patients in reducing cardiovascular risk have been observed in previous studies.[21-23] In addition, intensive lipid-lowering therapy with high-intensity statins has been shown to be associated with further risk reduction compared with moderate-intensity statin therapy.[24-26] The Cholesterol Treatment Trialists' meta-analysis estimated the benefit of intensive lipid-lowering therapy on major vascular events to be 28% per 1 mmol/L of LDL cholesterol level reduction compared with that of less intensive therapy, and this benefit was consistently maintained in elderly patients with previous vascular diseases.[3,7] These studies suggest that intensive lipid-lowering therapy is required to achieve sufficient cardiovascular benefits, even for elderly patients with ASCVD.

Despite the benefits of intensive lipid-lowering therapy, the latest American dyslipidemia management guidelines commented that moderate-intensity statins may be preferable to high-intensity statins for elderly patients, as these patients may be associated with a higher risk of intolerance, nonadherence, and discontinuation due to high-intensity statin therapy.[6] In other words, the decision to initiate or maintain moderate-intensity or high-intensity statin therapy for elderly patients with ASCVD should be made based on the expected efficacy as well as safety of these therapies. The age-stratified secondary analysis of IMPROVE-IT demonstrated that among patients aged ≥75 years, the effect of moderate-intensity statin with ezetimibe combination therapy was superior to that of moderate-intensity statin monotherapy on composite cardiovascular events, and moderate-intensity statin with ezetimibe combination therapy had similar incidences of adverse events to those in moderate-intensity statin monotherapy.[12] However, the high-intensity statin monotherapy arm was not assessed in IMPROVE-IT. In the current analysis, compared with those of high-intensity statin monotherapy, moderate-intensity statin with ezetimibe combination therapy had similar rates of a 3-year composite of cardiovascular death, major cardiovascular events, or nonfatal stroke, regardless of age. Furthermore, the reduction in LDL cholesterol levels achieved by ezetimibe combination therapy was greater than that achieved by high-intensity statin monotherapy, regardless of age, which is in line with previous meta-analysis demonstrating that moderate-intensity statin combined with ezetimibe reduced LDL cholesterol level 5% to 15% more than high-intensity statin monotherapy among patients with ASCVD.[27]

Safety is also a major concern in the clinical application of intensive lipid-lowering therapies.

FIGURE 3 Median LDL Cholesterol Levels in Patients ≥75 Years of Age



Median values of LDL cholesterol levels at years 1, 2, and 3 in patients aged ≥75 years are presented. LDL = low-density lipoprotein.

TABLE 2 Secondary Safety Endpoints of the Safety Population Stratified by Age and Treatment Strategy

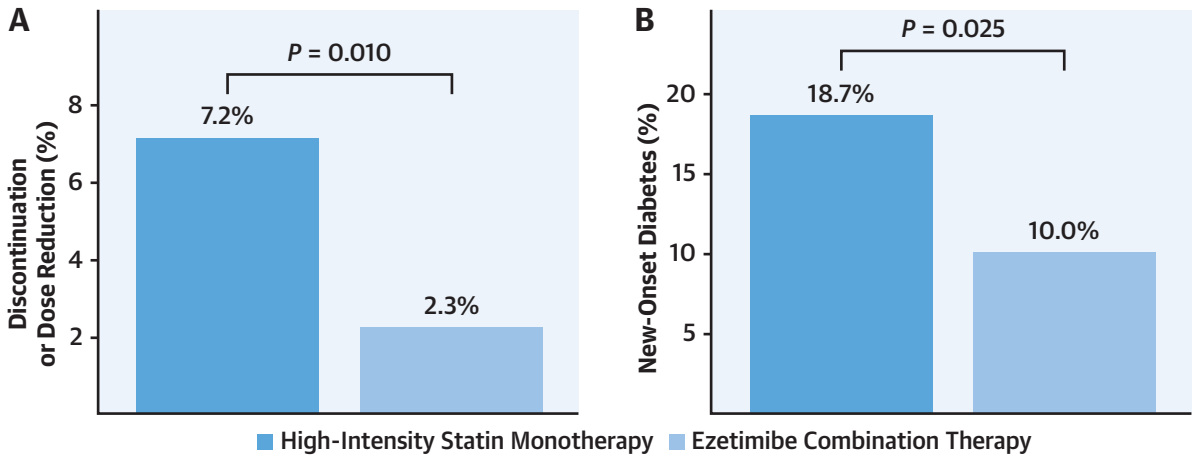
	Age ≥75 Years			Age <75 Years			
	Ezetimibe Combination Therapy (n = 266)	High-Intensity Statin Monotherapy (n = 293)	*P* Value	Ezetimibe Combination Therapy (n = 1,580)	High-Intensity Statin Monotherapy (n = 1,539)	*P* Value	P_{int}[a]
Intolerance-related drug discontinuation or dose reduction	6 (2.3)	21 (7.2)	0.010	82 (5.2)	129 (8.4)	<0.001	0.159
Patients' request							
Dizziness or general weakness	0	3		10	18		
Chest discomfort or headache	1	0		6	12		
Gastrointestinal symptoms	0	0		4	9		
Urticaria or itching sensation	1	3		5	4		
Myalgia	0	4		7	18		
Other	0	1		5	2		
Physicians' decision							
Liver enzyme elevation	1	4		14	28		
Creatine kinase elevation	1	5		24	28		
Fasting glucose level elevation	2	1		2	4		
Other	0	0		5	6		
New-onset diabetes[b]	17 (10.0)	31 (18.7)	0.025	128 (12.8)	128 (12.9)	0.938	0.041
Muscle-related adverse events	2 (0.8)	6 (2.0)	0.216	19 (1.2)	28 (1.8)	0.160	0.496
Myalgia	2 (0.8)	5 (1.7)	0.324	15 (0.9)	24 (1.6)	0.129	0.718
Myopathy	0 (0.0)	1 (0.3)	-	2 (0.1)	3 (0.2)	0.636	-
Myonecrosis[c]	1 (0.4)	1 (0.3)	0.945	10 (0.6)	12 (0.8)	0.625	0.836
Mild	1	1		7	8		
Moderate	0	0		2	3		
Severe	0	0		1	1		
Gallbladder-related adverse events	3 (1.1)	3 (1.0)	0.905	9 (0.6)	4 (0.3)	0.191	0.498
Major bleeding	4 (1.5)	7 (2.4)	0.456	11 (0.7)	6 (0.4)	0.252	0.194
Cancer diagnosis	10 (3.8)	6 (2.0)	0.232	27 (1.7)	20 (1.3)	0.350	0.564
New neurocognitive disorder	2 (0.8)	2 (0.7)	0.923	2 (0.1)	0 (0.0)	-	-
Cataract surgery	4 (1.5)	6 (2.0)	0.629	15 (0.9)	15 (1.0)	0.942	0.700

Values are n (%) or n. [a]P_{int} indicates the *P* value for the interaction between age and treatment strategy. [b]New-onset diabetes was defined as the presence of at least 1 of the following: an adverse event report or a new prescription for medication of diabetes or a fasting glucose level ≥126 mg/dL.[14,39] [c]Severity of myonecrosis was classified by an elevation of creatine kinase level compared with either the baseline level or the upper limit of normal (ULN); mild, 3 to 10 times the ULN; moderate, 10 to 50 times the ULN; severe, >50 times the ULN or rhabdomyolysis.

Statin-related adverse events, such as statin-associated muscle symptoms, new-onset diabetes, and liver enzyme elevation, are more common with use of high-intensity statins.[28] In addition, elderly patients tend to be more susceptible to statin-related adverse events, which may lead to substantially low statin adherence and poor cardiovascular outcomes.[8,29,30] Therefore, alternative strategies using nonstatin agents may be important for elderly patients who are prone to statin-related adverse events or have intolerance to high-intensity statins. In the current analysis, ezetimibe combination therapy was associated with a lower rate of intolerance-related drug discontinuation or dose reduction and adverse events (such as new-onset diabetes) than high-intensity statin monotherapy in patients aged ≥75 years.

New-onset diabetes is an important statin-related adverse event, as diabetes itself is an independent risk factor for cardiovascular events.[31] According to a meta-analysis that included 5 major trials regarding statin therapy, high-intensity statin therapy was associated with a 12% increased risk of new-onset diabetes compared with moderate-intensity statin therapy.[32] In the current study, a significantly lower rate of new-onset diabetes was observed in the ezetimibe combination therapy group than in the high-intensity statin monotherapy group among patients aged ≥75 years, whereas the rates were similar between the 2 therapy groups among patients <75 years of age. A significant interaction was observed between age and treatment strategy regarding new-onset diabetes. This result could be explained by the vulnerability of elderly patients to the development of new-onset diabetes, as shown in a previous meta-analysis.[33] In the current study, patients aged ≥75 years had more comorbidities such as hypertension and chronic kidney disease, which are well-known

FIGURE 4 Drug Intolerance and New-Onset Diabetes in Patients ≥75 Years of Age



(A) The rates of intolerance-related discontinuation or dose reduction of the study drug and **(B)** the rates of new-onset diabetes in patients aged ≥75 years.

risk factors of developing diabetes.[31] Therefore, the addition of ezetimibe to moderate-intensity statin therapy could offset the potential risk of new-onset diabetes resulting from high-intensity statin therapy for elderly patients who are already at a higher risk of developing diabetes.

According to recent studies, a proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor is considered an effective and safe lipid-lowering therapy, and the effect was consistent, regardless of age.[34-37] However, these studies mainly assessed the additive effect of PCSK9 inhibitors rather than the capability of de-escalating the statin dose or intensity. In addition, as PCSK9 inhibitors are only available in the form of injections, the use of PCSK9 inhibitors as an alternative strategy to statins for elderly patients remains questionable. Hence, ezetimibe is still recommended over PCSK9 inhibitors by current guidelines as the first-line nonstatin agent for patients with insufficient reduction of LDL cholesterol levels by high-intensity or maximally tolerated statin therapy.[6,13] Further studies on various nonstatin agents, such as bile acid sequestrants, niacin, lomitapide, and mipomersen, are required to reduce the required dose or intensity of statins while achieving maximal cardiovascular benefits.[13,38]

STUDY LIMITATIONS. First, this study may be underpowered because the number of elderly patients was limited to yield definite conclusions on the effect of ezetimibe combination therapy. Second, the cutoff value of age (75 years) was chosen post hoc; however, it was based on recent dyslipidemia guidelines and previous studies focusing on age.[6,7,12,13] Third, the rate of the all-cause death was numerically higher in the ezetimibe combination therapy group than in the high-intensity monotherapy group among patients aged ≥75 years. However, the difference was not significant, and the comparison of individual component of the primary or secondary composite endpoint was difficult because of the small number of events; therefore, the results should be interpreted with caution. Fourth, considering that the RACING trial enrolled the patients with documented ASCVD, the current study could not address the primary prevention of ASCVD in patients aged ≥75 years. Fifth, although prerandomization prescription of statins or ezetimibe was not different between the 2 therapy groups irrespective of age, further investigations will be required to evaluate the impact of previous prescription of these medications on clinical outcomes. Finally, this analysis for elderly patients with ASCVD should be interpreted cautiously owing to the limited generalizability in patients >80 years of age because of fulfilling the inclusion criteria. Therefore, our findings need to be considered only as hypothesis generating and warrant further prospective confirmation.

CONCLUSIONS

This age-stratified post hoc analysis of the RACING trial indicated that moderate-intensity statin with ezetimibe combination therapy had cardiovascular

benefits comparable with those of high-intensity statin monotherapy, with lower rates of intolerance-related drug discontinuation or dose reduction and greater reduction of LDL cholesterol levels in patients with ASCVD aged ≥75 years (**Central Illustration**). This study suggests that moderate-intensity statin with ezetimibe combination therapy could be a reasonable alternative strategy for elderly patients with ASCVD, in whom a higher risk of intolerance, nonadherence, and discontinuation is expected with high-intensity statin therapy.

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ADDRESS FOR CORRESPONDENCE: Dr Jung-Sun Kim, Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea. E-mail: kjs1218@yuhs.ac. OR Dr Jung Ho Heo, Division of Cardiology, Department of Internal Medicine, Kosin University Gospel Hospital, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea. E-mail: duggymdc@gmail.com. Twitter: @CardioSSoon.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Combination therapy with moderate-intensity statin medication plus ezetimibe is an alternative to high-intensity statin monotherapy for elderly patients with ASCVD.

TRANSLATIONAL OUTLOOK: Further studies of nonstatin lipid-lowering agents are needed to enrich current guidelines for managing dyslipidemia in elderly patients with ASCVD.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.