Supplementary Online Content

Lee SJ, Cha JJ, Choi WG, et al; RACING Investigators. Moderate-intensity statin with ezetimibe combination therapy vs high-intensity statin monotherapy in patients at very high risk of atherosclerotic cardiovascular disease: a post hoc analysis from the RACING randomized clinical trial. *JAMA Cardiol*. Published online August 2, 2023. doi:10.1001/jamacardio.2023.2222

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Inclusion and exclusion criteria

Inclusion criteria
1. Age 19–80 years
2. Documented atherosclerotic cardiovascular disease (meeting at least one of the following):
1) Previous myocardial infarction
2) Acute coronary syndrome
3) Coronary revascularization (percutaneous coronary intervention or coronary artery bypass surgery) or other arterial revascularization procedures
4) Ischemic stroke
5) Peripheral artery disease
Exclusion criteria
1. Active liver disease or persistent unexplained elevated AST or ALT levels more than 2-fold the normal upper limit
2. Allergy or hypersensitivity to any statin or ezetimibe
3. Solid-organ transplantation recipient
4. History of any adverse drug reaction requiring discontinuation of statins
5. Pregnant women, potential childbearing women, or lactating women
6. Life expectancy of less than 3 years
7. Inability to follow-up the patient over a period of 1 year after enrollment, as assessed by the investigator
8. Inability to understand or read the informed consent forms

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

eTable 2. Number of VHR patients meeting each of the definition criteria

Major ASCVD events	
History of myocardial infarction	1,281 (84.8%)
History of ischemic stroke	194 (12.8%)
Peripheral artery disease	110 (7.3%)
Recent acute coronary syndrome	43 (2.8%)
High-Risk Conditions	
Prior history of PCI or CABG	1,316 (87.1%)
Hypertension	1,143 (75.6%)
Age ≥65 years	778 (51.5%)
Diabetes mellitus	661 (43.7%)
Current smoking	336 (22.2%)
Chronic kidney disease*	212 (14.0%)
Heart Failure	91 (6.0%)
Persistent LDL-C ≥ 100 mg/dL	91 (6.0%)

*Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 ml per min per 1.73 m^2 of body-surface area.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LDL-C, low density lipoprotein cholesterol

eTable 3. Baseline characteristics of VHR and non-VHR patients

	VHR (N=1,511)	Non-VHR (N=2,269)	P value
Age, years	63.9±10.1	63.7±9.3	.510
Women	295 (19.5)	659 (29.0)	<.001
Body mass index, kg/m^2	25.0±3.1	25.1±3.1	.345
Prior myocardial infarction	1,300 (86.0)	189 (8.3)	<.001
Prior percutaneous coronary intervention	1,280 (84.7)	1,217 (53.6)	<.001
Prior coronary bypass graft surgery	106 (7.0)	141 (6.2)	.363
History of ischemic stroke	194 (12.8)	19 (0.8)	<.001
Chronic kidney disease*	212 (14.0)	180 (7.9)	<.001
End-stage renal disease on hemodialysis	23 (1.5)	6 (0.3)	<.001
Peripheral artery disease	110 (7.3)	25 (1.1)	<.001
Hypertension	1,143 (75.6)	1,377 (60.7)	<.001
Diabetes mellitus	661 (43.7)	737 (32.5)	<.001
Insulin treatment	60 (4.0)	60 (2.6)	.029
Current smoker	336 (22.2)	302 (13.3)	<.001
Dyslipidemia treatment before randomization			<.001
Drug-naive	101 (6.7)	215 (9.5)	
Low-intensity statin	7 (0.5)	4 (0.2)	
Moderate-intensity statin	505 (33.4)	861 (37.9)	
Moderate-intensity statin with ezetimibe	190 (12.6)	309 (13.6)	
High-intensity statin	640 (42.4)	800 (35.3)	
High-intensity statin with ezetimibe	68 (4.5)	80 (3.5)	
Heart Failure	91 (6.0)	49 (2.2)	
Baseline serum LDL-C, mg/dL	82 (65-102)	78 (62-97)	<.001
No. of patients with LDL-C < 70 mg/dL (%)	550 (36.4)	709 (31.2)	<.001

Data are mean ± SD, or number (%).

*Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 ml per min per 1.73 m^2 of body-surface area

Abbreviations: VHR, very high risk; LDL-C, low density lipoprotein cholesterol

eTable 4. Serial changes of the lipid profile among VHR and non-VHR patients

	VHR ASCVD			Non-VHR ASCVD		
	Ezetimibe Combination Therapy	High-Intensity Statin	P value	Ezetimibe Combination Therapy	High-Intensity Statin	P value
1 year	N=673	N=671		N=1,002	N=1,002	
LDL cholesterol	57 (47–71)	65 (53–78)	<.001	58 (47–71)	68 (56–81)	<.001
Total cholesterol	121 (107–138)	130 (115–148)	<.001	124 (109–141)	136 (121–154)	<.001
HDL cholesterol	45 (39–52)	45 (39–54)	.690	47 (41–54)	48 (41–55)	.492
Triglycerides	109 (83-153)	121 (89-169)	.002	108 (80–146)	121 (91–161)	<.001
2 years	N=617	N=618		N=941	N=921	
LDL cholesterol	57 (45–69)	64 (51–78)	<.001	57 (46–70)	66 (53–79)	<.001
Total cholesterol	123 (108–141)	133 (117–152)	<.001	125 (110–142)	135 (120–154)	<.001
HDL cholesterol	45 (38–54)	46 (38–55)	.393	47 (40–56)	49 (41–57)	.283
Triglycerides	114 (87–155)	124 (89–170)	.009	107 (81–150)	118 (88–161)	<.001
3 years	N=530	N=536		N=819	N=779	
LDL cholesterol	57 (46–72)	65 (51–79)	<.001	58 (47–70)	67 (56–81)	<.001
Total cholesterol	124 (108–139)	131 (117–152)	<.001	125 (110–141)	137 (122–153)	<.001
HDL cholesterol	44 (38–51)	45 (38–53)	.235	46 (40–54)	47 (41–55)	.025
Triglycerides	114 (88–153)	121 (89–165)	.108	105 (78–142)	117 (87–163)	<.001

Values (mg/dL) are presented as median (interquartile range).

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VHR, very high risk

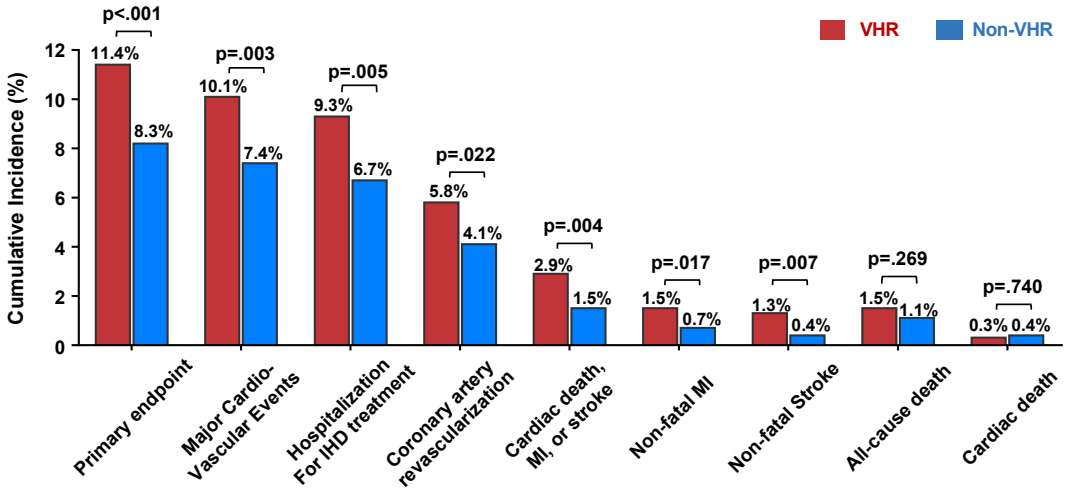
eTable 5. Safety endpoints in VHR and non-VHR Patients (Safety Population)

Characteristics	VHR (N=1,463)			Non-VHR (N=2,219)			
	Moderate-intensity statin with ezetimibe (N=732)	High-intensity statin mono-therapy (N=731)	P value	Moderate-intensity statin with ezetimibe (N=1,114)	High-intensity statin mono-therapy (N=1,105)	P value	P_{int}
Intolerance leading to discontinuation or dose reduction of lipid-lowering drug	34 (4.6)	56 (7.7)	.02	57 (5.0)	100 (8.7)	.001	.80
Participant's subjective symptoms	22	32		27	44		
Physicians' discretion	12	24		27	50		
New-onset diabetes mellitus	57 (7.8)	75 (10.3)	.12	88 (7.9)	84 (7.6)	.87	.16
New-onset diabetes mellitus requiring anti-diabetic medication initiation	42 (5.7)	46 (6.3)	.74	53 (4.8)	61 (5.5)	.46	.83
Muscle-related adverse events including rhabdomyolysis, myopathy, myalgia, and myonecrosis	9 (1.2)	14 (1.9)	.40	12 (1.1)	20 (1.8)	.20	.89
Gallbladder-related adverse events	8 (1.1)	5 (0.7)	.58	4 (0.4)	2 (0.2)	.69	.84
Major bleeding	11 (1.5)	7 (1.0)	.48	4 (0.4)	6 (0.5)	.74	.28
Cancer diagnosis	20 (2.7)	10 (1.4)	.10	17 (1.5)	16 (1.5)	.99	.21
New-onset neurocognitive disorder	2 (0.3)	0	.48	2 (0.2)	2 (0.2)	.99	.99
Cataract surgery	11 (1.5)	8 (1.1)	.65	8 (0.7)	13 (1.2)	.37	.21

Data are number (%). P values for interaction (P*int*) are between the definition of VHR ASCVD and therapy.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; VHR, very high risk

eFigure 1. Clinical endpoints in VHR and non-VHR patients

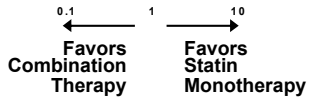


The incidence of primary and each clinical endpoint in VHR (n=1,511) and non-VHR patients (n=2,269) are presented. Major cardiovascular events were defined as coronary or peripheral revascularization or hospitalization for cardiovascular events.

Abbreviations: VHR, very high-risk; IHD, ischemic heart disease; MI, myocardial infarction.

eFigure 2. Clinical endpoints according to statin therapy in VHR and non-VHR patients

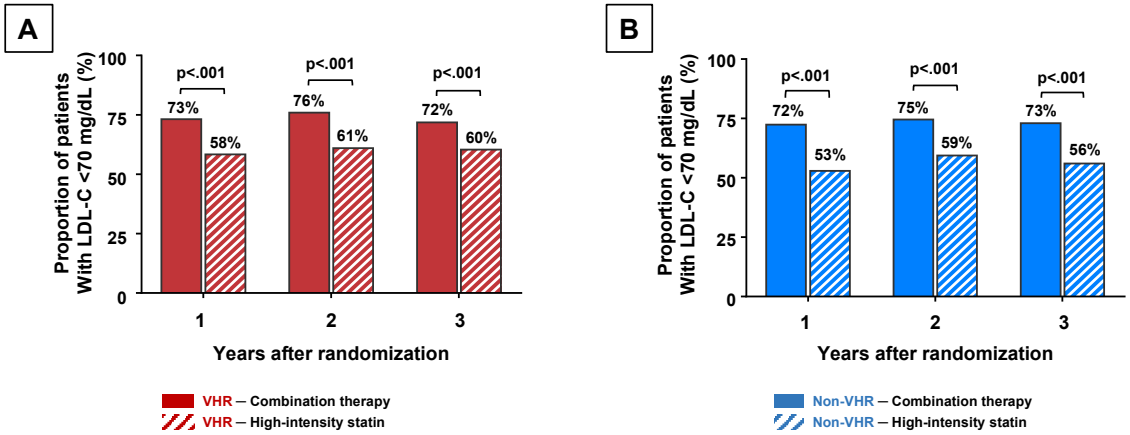
Endpoint	Moderate-intensity statin with ezetimibe n/N (%)	High-intensity statin monotherapy n/N (%)	Hazard ratio (95% CI)	P for interaction
Major cardiovascular events				
VHR ASCVD	74/757 (9.8)	79/754 (10.5)	0.92 (0.67-1.27)	.914
Non-VHR ASCVD	79/1137 (6.9)	88/1132 (7.8)	0.90 (0.67-1.22)	
Coronary revascularization				
VHR ASCVD	43/757 (5.7)	44/754 (5.8)	0.98 (0.67-1.44)	.596
Non-VHR ASCVD	48/1137 (4.2)	45/1132 (4.0)	1.07 (0.71-1.60)	
All-cause death				
VHR ASCVD	13/757 (1.7)	10/754 (1.3)	1.17 (0.52-2.61)	.972
Non-VHR ASCVD	13/1137 (1.1)	12/1132 (1.1)	1.09 (0.50-2.38)	
Cardiovascular death				
VHR ASCVD	4/757 (0.5)	2/754 (0.3)	1.97 (0.36-10.78)	.548
Non-VHR ASCVD	4/1137 (0.4)	4/1132 (0.3)	1.01 (0.25-4.05)	
Non-fatal MI				
VHR ASCVD	14/757 (1.8)	10/754 (1.3)	1.38 (0.61-3.10)	.782
Non-VHR ASCVD	8/1137 (0.7)	7/1132 (0.6)	1.15 (0.42-3.16)	
Cardiovascular death or MI				
VHR ASCVD	16/757 (2.1)	11/754 (1.5)	1.43 (0.66-3.08)	.539
Non-VHR ASCVD	11/1137 (1.0)	11/1132 (1.0)	1.00 (0.43-2.31)	
Cardiovascular death, MI, or stroke				
VHR ASCVD	26/757 (3.4)	21/754 (2.8)	1.21 (0.68-2.16)	.787
Non-VHR ASCVD	16/1137 (1.4)	15/1132 (1.3)	1.07 (0.53-2.17)	
Hospitalization for ischemic heart disease				
VHR ASCVD	67/757 (8.9)	71/754 (9.4)	0.93 (0.67-1.30)	.919
Non-VHR ASCVD	75/1137 (6.6)	79/1132 (7.0)	0.95 (0.69-1.31)	
Hospitalization for heart failure				
VHR ASCVD	6/757 (0.8)	9/754 (1.2)	0.66 (0.23-1.85)	.776
Non-VHR ASCVD	8/1137 (0.7)	10/1132 (0.9)	0.81 (0.32-2.04)	
Non-fatal stroke				
VHR ASCVD	10/757 (1.3)	10/754 (1.3)	0.99 (0.41-2.37)	.758
Non-VHR ASCVD	5/1137 (0.4)	4/1132 (0.4)	1.27 (0.34-4.71)	



The interaction P value (P_{int}) shows no evidence of significant heterogeneity for the treatment effects on the secondary endpoints between the VHR and non-VHR patients with ASCVD.

Abbreviations: VHR, very high-risk; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; MI, myocardial infarction.

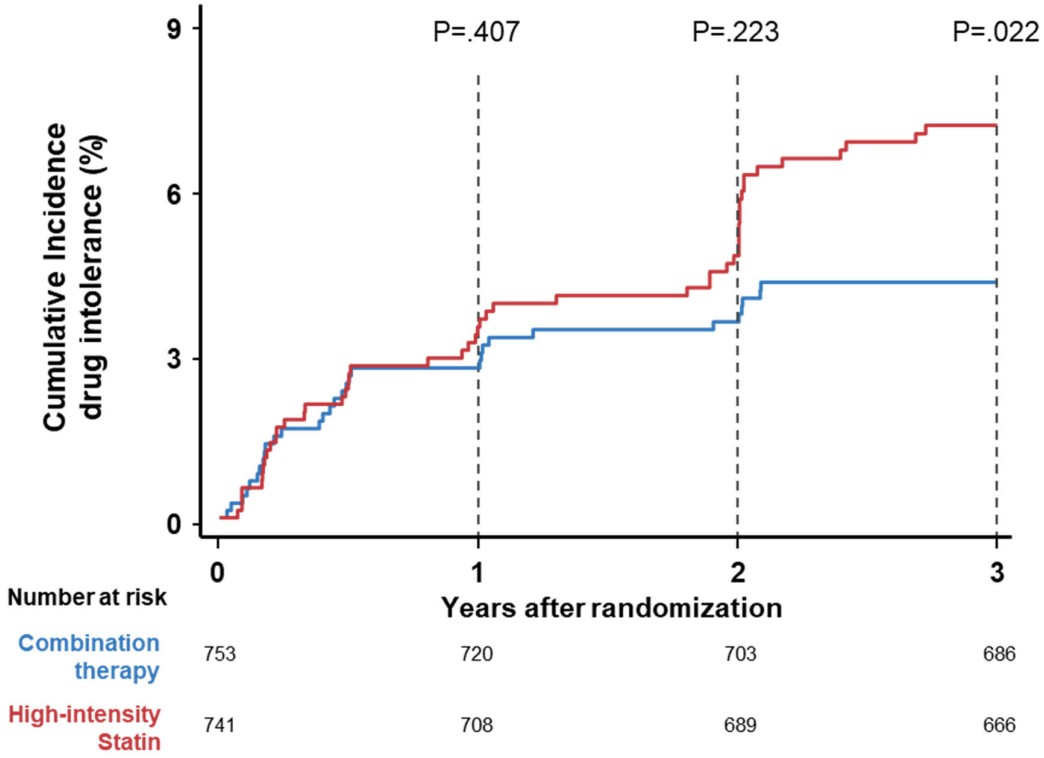
eFigure 3. Proportion of patients with LDL-C <70 mg/dL among VHR and non-VHR ASCVD.



The relative proportion of patients with LDL-C <70 mg/dL at 1, 2, and 3 years after randomization among (**A**) VHR and (**B**) non-VHR ASCVD are presented.

Abbreviations: LDL-C, low-density lipoprotein cholesterol; VHR, very high risk; ASCVD, atherosclerotic cardiovascular disease

eFigure 4. Kaplan-Meier curves of discontinuation or dose reduction of the study drugs by intolerance in VHR patients



The cumulative incidence of drug intolerance leading to drug discontinuation or dose reduction in each treatment group is presented. Comparisons of the intolerance rate at 1, 2, and 3 years after randomization were conducted by chi-square test.