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Statin Therapy in HIGH-Risk Individuals with NORMal Coronary Arteries: The HIGH-NORM Study

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Aims: Mismatches between the risk status of a patient and coronary imaging data can lead to conflicting strategies to prevent a cardiovascular event. We evaluated whether statin use was associated with cardiovascular benefit in high-risk individuals whose coronary computed tomography angiography (CCTA) results showed normal coronary arteries.

Methods: Among asymptomatic individuals whose CCTA showed normal or near normal coronary arteries, 3,389 persons with high- or very-high-risk status were included in this retrospective study. After 1:2 propensity score matching, 906 individuals (302 new statin users and 604 controls; mean age 61 years; male 58%) were analysed. The primary outcome variable was major adverse cardiovascular and cerebrovascular events (MACCEs) that consisted of cardiovascular death, nonfatal myocardial infarction, coronary revascularisation, and nonfatal ischemic stroke.

Results: At a median follow-up of 5.8 years, 20 statin users and 17 controls (7.4 and 5.6 events/1,000 person-year, respectively; hazard ratio [HR] 1.04; $p=0.92$) experienced MACCE. Kaplan–Meier curves showed similar MACCE rates in both groups ($p=0.91$). In separate analyses for persons with normal ($p=0.29$) or near normal coronary arteries ($p=0.67$), MACCE rates did not differ between the groups. Age (HR 1.04; $p=0.044$), male sex (HR 3.06, $p=0.018$), and smoking (HR 2.87, $p=0.019$) were independently associated with MACCEs. In subgroup analyses, no significant factors affected the relationship between statin use and MACCEs.

Conclusions: Statin use was not associated with cardiovascular risk reduction in high-risk persons with normal or near normal coronary arteries. More individualised lipid-lowering therapy may benefit this population.

Key words: Hydroxymethylglutaryl-CoA reductase inhibitors, Outcome assessment, Health care, Coronary artery disease, Risk factors

Abbreviations: CCTA, coronary computed tomography angiography; MACCEs, major adverse cardio- and cerebrovascular events; LLT, lipid-lowering therapy

Introduction

The latest guidelines on lipid-lowering therapy (LLT) recommend intensive statin therapy for patients at high or very-high cardiovascular risk[1-3]. However, if a person is without symptoms and has either normal coronary arteries or 10%–20% luminal narrowing as per coronary computed tomography angiography (CCTA) results, many physicians may hesitate to prescribe statins because they are not confident of the future cardiovascular risk for the patient. A mismatch between patient risk status (as defined by clinical factors) and coronary imaging data can cause conflict in cardiovascular preventive strategies, including LLT. However, supporting data on the use of statin therapy in high-risk patients with normal CCTA results are

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extremely limited.

Approximately half of asymptomatic statin candidates based on the 2013 American College of Cardiology/American Heart Association guidelines for LLT turn out to have normal coronary arteries in CT studies[4, 5]. If statin therapy does not reduce cardiovascular risk in these individuals regardless of the calculated future risk, it is beneficial to differentiate between those who benefit from statins and those who do not.

Usually, CCTA is used to screen coronary artery disease in symptomatic patients and helps to reduce unnecessary invasive coronary angiography[6]. Furthermore, CCTA has been used to identify coronary plaques and help select patients needing statin therapy from the CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter) Registry[7]. A coronary calcium score of zero indicates very low cardiovascular risk, and pharmacotherapy is not commonly recommended in this case[8]. However, when CCTA results show normal or near-normal coronary arteries in a primary prevention setting, there is no appropriate recommendation for preventive measures, including statin use.

The aim of this HIGH-NORM (Statin therapy in HIGH-risk individuals with NORMal coronary arteries) study was to evaluate whether statin use was associated with cardiovascular benefits in high-risk individuals who are candidates for statin therapy, but whose CCTA results show normal or near-normal coronary arteries. This study was conducted by propensity score matching analysis.

Methods

Study Population

The Institutional Review Board of Severance Hospital, Seoul, Korea approved this retrospective study (No. 4-2020-0613). All research was performed in accordance with the Declaration of Helsinki. The Institutional Review Board waived the need for informed consent from the subjects for the following reasons: (i) the research involved no more than minimal risk to the subjects; and (ii) the waiver did not adversely affect the rights or welfare of the subjects. Subjects were selected from among patients who visited the outpatient clinic of the Division of Cardiology, Severance Hospital, Seoul, Korea, between May 2005 and September 2019.

Initially, 55,325 consecutive men and women who visited the outpatient clinic and underwent CCTA for their health check-up were screened. The inclusion criteria were 1) normal or near-normal (luminal stenosis $<30\%$) coronary arteries, and 2) high- or very-high -risk as classified by the 2019 European Society of Cardiology/European Atherosclerosis Society Guidelines for the management of dyslipidaemias (2). Individuals fulfilling both inclusion criteria were eligible for the study. Individuals with the following were excluded: coronary artery stenosis ≥ 30%, a follow-up duration <1 year, a history of cardiovascular disease, missing laboratory values, end-stage renal disease, inconsistent use of statins, or those categorised as moderate- or low-risk groups. History of cardiovascular disease included cerebrovascular, aortic, or peripheral vascular disease or heart failure. Inconsistent statin use was defined as statin use lasting $<80\%$ of the follow-up period. Of the 3,389 persons who were included in the study, 977 used statins on an ongoing basis, 313 newly started statin use, and 2,099 had never used statins. After 1:2 propensity score matching was performed for new statin users and those who had never used statins, 906 patients (302 statin users and 604 controls) were analysed **(Fig. 1)**.

A few previous studies have shown a benefit of statins in persons with non-obstructive coronary lesions in coronary CT angiography. However, "non-obstructive" lesions may vary in luminal stenosis from 1% to 49%. Physicians often consider lesions with 30-49% stenosis closer to being significant ones, although they are still called "non-obstructive". Although there are many cases of coronary stenosis $<$ 30% in CT angiography, no studies have analyzed statin benefits in these people, as well as in those with normal coronary findings. Therefore, we conducted the present study in a population of individuals with normal or near normal coronary findings. We defined normal as coronary arteries with no visible plaques and near normal as coronary arteries with plaques causing 1-29% luminal stenosis. We also obtained information regarding the presence of noncalcified plaque and Agatson score.

Study Protocol

This was a propensity score-matched cohort study. Clinical data, including demographic parameters and medical history, were collected by trained interviewers. Blood samples were collected after a 12-h fast and analysed by the laboratory at Severance Hospital, Seoul, Korea, which was certified by the Korean Society of Laboratory Medicine. The data derived from these samples were used retrospectively for this study. All persons received standard medical therapies at the discretion of their physician. Statin therapy intensity was defined according to the 2018 American College of

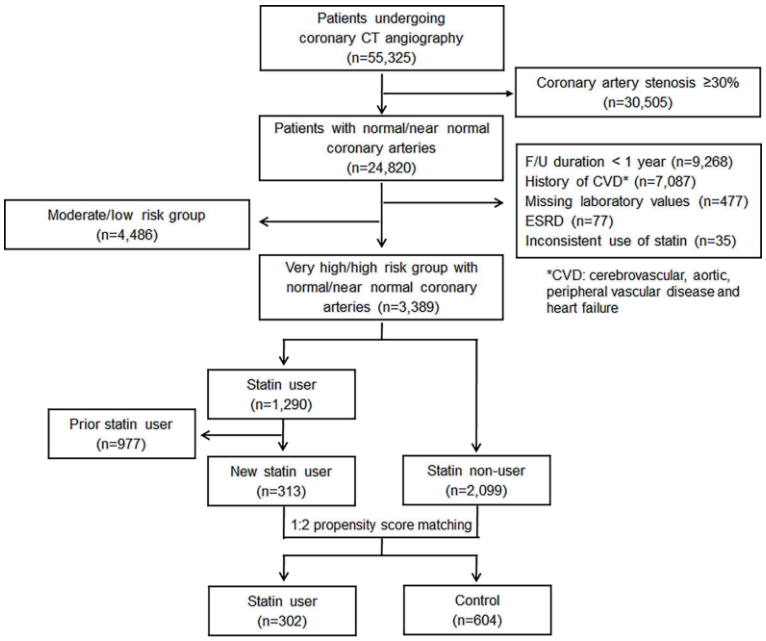

Fig. 1. Patient inclusion flowchart

CT: computed tomography; ESRD: end-stage renal disease

Cardiology/American Heart Association guidelines.

Study population follow-up for risk factor control was performed at the outpatient clinic every 3–6 months. Clinical outcome data were obtained by reviewing medical records or by telephone contact. Primary outcome variables included the rates of major adverse cardiovascular and cerebrovascular events (MACCEs). MACCEs were defined as the composite of cardiovascular death, nonfatal myocardial infarction, coronary revascularisation, nonfatal ischemic stroke, or transient ischemic attack. Secondary outcome variables included the individual components of MACCE.

Previous studies on persons with non-obstructive lesions also included population with near normal findings (1-29% coronary stenosis). Thus, we analyzed our population in total as well as separately (normal vs. near normal) for comparison with previous studies.

Statistical Analysis

Continuous data are reported as the mean ± standard deviation and categorical data are presented as frequencies and percentages. Clinical and laboratory parameter data were compared using chi-square test. Between-group comparisons were conducted using Student's *t*-test. To reduce the effect of selection bias and potential confounders, propensity score matching was performed. The following variables were used for matching: age, sex, hypertension, diabetes mellitus, smoking, atrial fibrillation, chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2), body mass index, baseline total cholesterol, and antiplatelet agent. After matching, validation was performed according to the standardised mean difference of all baseline covariates using a threshold of 0.1 to indicate an imbalance. Cumulative survival curves for each group were built using the Kaplan–Meier method and compared using the log-rank test and Cox-proportional hazard regression. The analysis was also performed in subgroups classified according to statin intensity. Because most study subjects received moderate intensity statins, moderate intensity statins were divided into two groups: atorvastatin 20 mg or similar statins as high moderate intensity, and atorvastatin 10 mg or similar statins as low moderate intensity. Finally, Kaplan-Meier curves were compared between two groups: high or high moderate (higher) versus low or low moderate (lower) intensity. The predictive value of clinical variables on MACCEs was assessed by univariate and multivariate analyses. Subgroup analysis was performed to evaluate the differential effect of statin use according to clinical variables. All analyses used two-tailed tests with a significance level of 0.05. R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for the analyses.

Table 1. Characteristics of the matched study population

	Total statin users (n=302)	Control (n=604)	p	Statin users with normal coronary (n=140)	Control (n=280)	p	Statin users with near-normal coronary (n=162)	Control (n=324)	p
Age, years	60.1±9.6	60.8±10.3	0.29	59.7±10.1	60.1±10.9	0.67	60.5±9.3	61.8±10.1	0.60
Male	173 (57.3)	352 (58.3)	0.83	68 (48.6)	145 (51.8)	0.53	105 (64.8)	201 (62.0)	0.67
Risk factors									
Hypertension	161 (53.3)	322 (53.3)	>0.99	71 (50.7)	129 (46.1)	0.38	90 (55.6)	183 (56.5)	0.79
Diabetes mellitus	81 (26.8)	155 (25.7)	0.77	439 (27.9)	75 (26.8)	0.82	42 (25.9%)	76 (23.5)	0.42
Smoking	33 (10.9)	62 (10.3)	0.85	12 (8.2)	21 (7.5)	0.89	23 (14.2)	41 (12.7)	0.53
Chronic kidney disease	166 (55.0)	326 (54.0)	0.83	10 (7.1)	158 (56.4)	0.78	89 (54.9)	172 (53.1)	0.54
Atrial fibrillation	23 (7.6)	54 (8.9)	0.58	10 (7.1)	24 (8.6)	0.63	13 (8.0)	32 (9.9)	0.74
Risk group			0.51			0.53			0.63
Very high	79 (26.2)	146 (24.2)		39 (27.9)	70 (25.0)		40 (24.7)	76 (23.5)	
High	223 (73.8)	458 (75.8)		101 (72.1)	210 (75.0)		122 (75.3)	248 (76.5)	
Body mass index, kg/m^2	25.2±3.4	25.1±3.2	0.70	24.9±2.9	24.8±3.1	0.73	25.4±3.8	25.4±3.4	0.79
Laboratory values, mg/dL									
Total cholesterol,	199 (169, 221)	196 (172, 215)	0.29	205 (169, 227)	201 (175, 218)	0.49	194 (170, 218)	192 (170, 212)	0.35
Triglyceride	142 (96, 202)	130 (94, 179)	0.068	127 (93, 193)	126 (92, 188)	0.56	144 (97, 203)	132 (96, 176)	0.038
HDL-C	48 (40, 55)	47 (40, 55)	0.92	49 (40, 55)	47 (41, 57)	0.72	47 (40, 54)	46 (40, 54)	0.83
LDL-C	118 (96, 142)	117 (100, 137)	0.66	122 (99, 143)	119 (101, 138)	0.40	114 (95, 138)	114 (95, 136)	0.92
CCTA findings									
Coronary arteries			>0.99			>0.99			>0.99
Normal	140 (46.4)	280 (46.4)		147 (100)	280 (100)		0	0	
Near normal	162 (53.6)	324 (53.6)		0	0		162 (100)	324 (100)	
Noncalcified plaque	76 (25.2)	158 (26.2)	0.81	--	--	--	76 (49.4)	158 (51.5)	0.49
Agatston score	0 (0, 17.3)	0 (0, 11.0)	0.19	0 (0, 0)	0 (0, 0)	0.35	7.6 (0, 32.9)	14.3 (2.8, 35.7)	0.02
Statin intensity									
High	40 (13.2)	0	--	16 (11.4)	0	--	24 (14.8)	0	--
High moderate	99 (32.8)	0		46 (32.9)	0		53 (32.7)	0	
Low moderate	134 (44.4)	0		61 (43.6)	0		73 (45.1)	0	
Low	29 (9.6)	0		17 (12.1)	0		12 (7.4)	0	
Antiplatelet agents	129 (42.7)	248 (41.1)	0.69	52 (37.1)	101 (36.1)	0.83	77 (47.5)	148 (45.7)	0.94

Values are presented as the mean±standard deviation, median (interquartilc range), or number (%).
HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; CCTA: coronary computed tomography angiography

Results

Baseline Characteristics

The characteristics of 906 persons (302 statin users and 604 controls) are presented in **Table 1**. The mean patient age was 61 years and 58% of the study population were male. Approximately half of the subjects in each group had hypertension and chronic kidney disease. The mean level of total cholesterol was 195 mg/dL and 83% of statin users received moderate-intensity statin therapy. All variables were well-matched and did not differ between the groups after propensity score matching. However, triglyceride levels tended to be higher among statin users (p=0.068), particularly those with near normal coronary arteries. About half of the individuals with near normal coronary arteries showed the presence of noncalcified plaques. The median Agatston score was 0, regardless of statin use, in the subjects with normal coronary arteries. Meanwhile, scores were 7.6 and 14.3 in statin users and controls, respectively (p=0.02), among individuals with near normal coronary arteries. Additional comparisons between statin users with normal or near-normal coronary arteries and controls showed similar findings. Specific findings are shown in **Table 1**.

Clinical Outcomes

At a median follow-up of 5.8 years, 20 and 17 individuals in the statin user and control groups, respectively, experienced MACCEs. The incidence of

Table 2. Incidence of events in each group

	Number of events (/1,000 person-years)		HR (95% CI)	*p*	Number of events (/1,000 person-years)		HR (95% CI)	*p*	Number of events (/1,000 person-years)		HR (95% CI)	*p*
	Total statin users (*n* = 302)	Control (*n* = 604)			Statin users with normal coronary arteries (*n* = 140)	Control (*n* = 280)			Statin users with near-normal coronary arteries (*n* = 162)	Control (*n* = 324)		
MACCEs	20 (7.4)	17 (5.6)	1.04 (0.53, 2.01)	0.92	3 (3.2)	7 (4.1)	0.42 (0.08, 2.11)	0.29	14 (11.0)	13 (6.9)	1.25 (0.46, 3.39)	0.67
Cardiovascular death	1 (0.4)	1 (0.3)	1.00 (0.07, 20.5)	>0.99	0 (0)	0 (0)	-	-	1 (0.7)	1 (0.5)	-	-
Myocardial infarction	3 (1.1)	1 (0.3)	3.23 (0.33, 31.7)	0.32	1 (0.8)	0 (0.0)	-	-	2 (1.4)	1 (0.5)	-	-
Coronary revascularisation	12 (4.5)	8 (2.2)	2.19 (0.72, 6.67)	0.17	3 (2.4)	2 (1.2)	-	-	9 (6.3)	6 (3.0)	-	-
Ischemic stroke	4 (1.4)	11 (3.0)	0.38 (0.08, 1.73)	0.21	0 (0)	5 (2.9)	-	-	4 (2.8)	6 (3.0)	-	-

HR: hazard ratio; CI: confidence interval; MACCEs: major adverse cardio- and cerebrovascular events

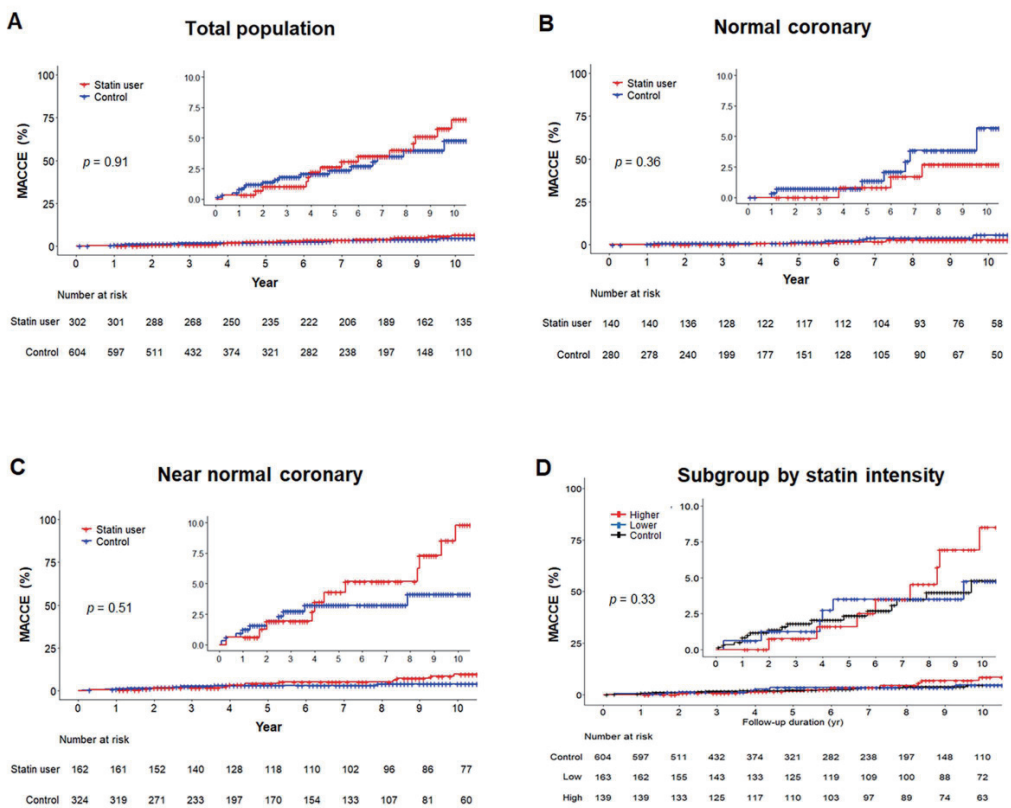

Fig. 2. Kaplan–Meier survival curves for MACCE incidence rates in the total study population (A), patients with normal coronary arteries (B), and patients with near-normal coronary arteries (C) versus matched controls. Curves for MACCE rates in subgroups receiving higher and lower intensity statins and controls (D)

MACCE: major adverse cardiovascular and cerebrovascular event

MACCEs did not differ between the groups (7.4 and 5.6 events/1,000 person-years, respectively; hazard ratio [HR] 1.04; $p=0.92$) (Table 2). Kaplan-Meier curves showed similar rates of MACCEs in statin users and controls ($p=0.91$) (Fig. 2A). The incidence of each MACCE component did not differ between the groups (Table 2).

Upon further analysis of persons with normal

Table 3. Clinical variables associated with MACCEs

	MACCEs			
	Unadjusted HR (95% CI)	*p*	Adjusted HR (95% CI)	*p*
Age	1.04 (0.99, 1.09)	0.082	1.04 (1.00, 1.09)	0.044
Male	3.22 (1.17, 8.86)	0.024	3.06 (1.21, 7.73)	0.018
Hypertension	1.46 (0.65, 3.29)	0.37		
Diabetes mellitus	1.38 (0.56, 3.44)	0.48		
Smoking	4.12 (1.27, 13.38)	0.019	2.87 (1.19, 6.90)	0.019
Chronic kidney disease	2.13 (0.90, 5.01)	0.085		
Atrial fibrillation	1.06 (0.24, 4.65)	0.94		
Body mass index	1.06 (0.94, 1.19)	0.36		
Total cholesterol	0.98 (0.96, 0.99)	0.014	0.99 (0.98, 1.00)	0.11
Triglyceride	1.00 (0.99, 1.01)	0.53		
HDL-C	0.96 (0.92, 0.99)	0.045	0.98 (0.95, 1.02)	0.35
LDL-C	0.99 (0.98, 1.01)	0.37		
Near-normal coronary arteries	2.34 (1.1, 4.97)	0.027	1.70 (0.62, 4.65)	0.30
Noncalcified plaque	1.19 (0.51, 2.78)	0.70		
Agatston score >0	2.22 (0.99, 4.91)	0.050	1.58 (0.64, 3.91)	0.33
Antiplatelet agent	1.40 (0.61, 3.25)	0.43		
Statin use	1.04 (0.53, 2.01)	0.92	1.26 (0.53, 3.03)	0.60

HR: hazard ratio; CI: confidence interval; MACCEs: major adverse cardiovascular and cerebrovascular events; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol

coronary arteries, MACCE rates did not differ between statin users and controls (3.2 and 4.1 events/1,000 person-years, respectively; HR 0.42; $p=0.29$). Likewise, MACCE rates were similar between statin users and controls with near-normal coronary arteries (11.0 and 6.9 events/1,000 person-years, respectively; HR 1.25; $p=0.67$) **(Table 2)**. Kaplan–Meier curves also exhibited similar MACCE rates between statin users and controls with normal and near-normal coronary arteries **(Fig. 2B and 2C)**. Among subgroups classified according to statin intensity, Kaplan-Meier curves did not differ between higher and lower intensity groups and controls **(Fig. 2D)**.

Analysis of Factors Associated with MACCEs

In univariate analysis, male sex (HR 3.22, $p=0.024$), smoking (HR 4.12, $p=0.019$), total cholesterol (HR 0.98, $p=0.014$), high-density lipoprotein-cholesterol (HDL-C) (HR 0.96, $p=0.045$), and near-normal coronary arteries (HR 2.34, $p=0.027$) were associated with higher risk of MACCEs. In multivariate analysis, age (HR 1.04, $p=0.044$), male sex (HR 3.06, $p=0.018$), and smoking (HR 2.87, $p=0.019$) were identified as independent variables associated with MACCEs. Statin use was not correlated with MACCEs in these analyses **(Table 3)**.

Subgroup Analysis

Subgroup analyses identified no significant factors affecting the relationship between statin use and MACCE rate. Risk status (high- versus very-high-risk groups), specific risk factors, and baseline cholesterol levels did not affect the relationship between statin use and MACCEs. Although the p value for the interaction was borderline between individuals aged ≥ 60 years and those aged <60 years, it did not reach statistical significance **(Fig. 3)**. Furthermore, in individuals with Agatston score >0 ($n=422$), there was no significant difference in MACCEs between statin users and controls ($p=0.21$).

Discussion

The major findings of our study were as follows: 1) statin therapy was not associated with a reduction in MACCEs in individuals with normal or near-normal coronary arteries, even with high cardiovascular risk; 2) this finding was consistent with that from a separate analysis of persons with normal and near-normal coronary arteries; 3) clinical factors such as age and male sex were correlated with poorer outcomes; and 4) subgroup analysis showed no observable statin benefit throughout all subgroups classified by conditions including risk status or

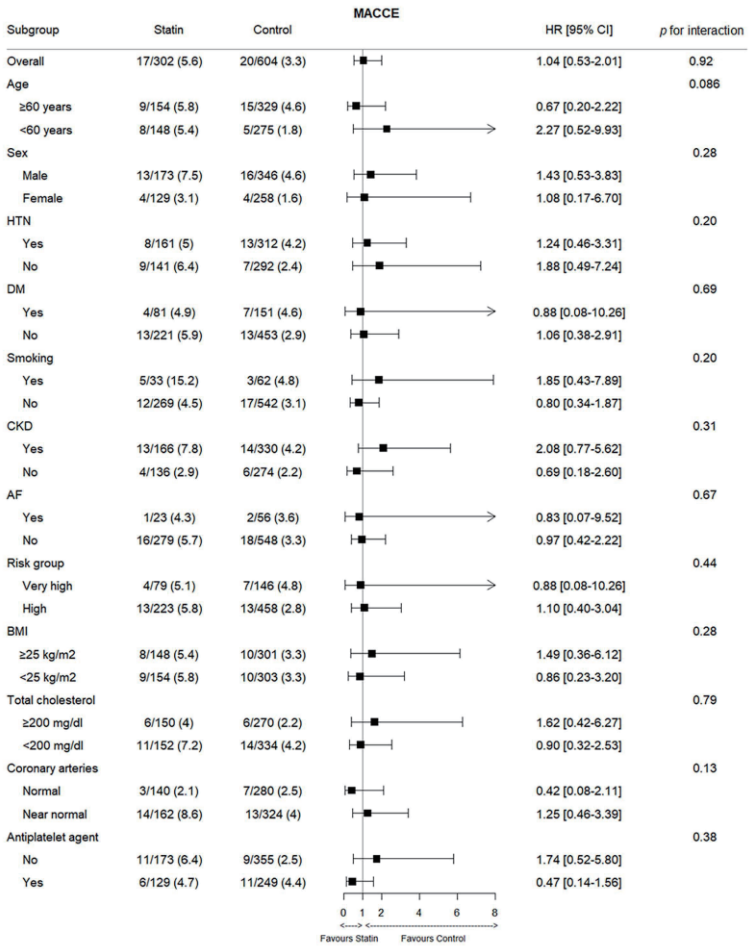

Fig. 3. Forest plot showing subgroup analysis of MACCE

MACCE: major adverse cardiovascular and cerebrovascular events; HTN: hypertension; DM: diabetes mellitus; CKD: chronic kidney disease; AF: atrial fibrillation; BMI: body mass index

baseline cholesterol levels. Of note, the current study is the first to analyse the effect of statins in individuals who had normal or near-normal coronary arteries and were statin-naïve. Our follow-up duration was long enough to evaluate the effect of LLT on clinical outcomes. Our results support more individualised statin therapy for persons classified as being at high cardiovascular risk but who have normal coronary imaging data.

The CONFIRM study reported that statin use had no benefit in patients with normal coronary arteries, whereas it benefited those with non-obstructive plaques. A minor proportion (14%) of enrolled patients in that study was classified as high-risk. Of these, persons with normal coronary arteries showed a HR of 0.25 and p value of 0.068 with statin use[7]. Thus, it has been difficult to confirm the value of statin use in this specific population. A study including Korean individuals replicated the benefit of statins in patients with non-obstructive plaques[9]. However, this study did not include individuals with normal coronary arteries, whereas our study focused on these specific individuals. Another Korean study recognised a benefit of statin use in patients with non-obstructive plaques that was not clearly observed in those with normal coronary arteries who had no subsequent cardiovascular events. However, this study did not include a matching process to compare the effects of statins while minimising bias[5]. Because most people with high cardiovascular risk are candidates for statin therapy in the latest major guidelines regardless of coronary imaging data, the results of the two above-mentioned studies may not considerably change current clinical practice. Furthermore, it is difficult to accurately evaluate the impact of statins on cardiovascular prognosis, including cardiovascular death, using CONFIRM study data because it only assessed total mortality.

However, our finding that statin use was not associated with reduced cardiovascular events in individuals with normal or near-normal CCTA findings, even in high-risk subjects, is clinically relevant. In this regard, the value of coronary imaging data, as shown in our study, is distinctive and may influence clinical practice for these individuals.

The reason for the differences between our findings and those of the CONFIRM study is not completely understood. One possible reason is that our study population consisted of only Korean individuals. Compared to the CONFIRM study that showed an annual mortality of 0.59% in the control group, the event rates were quite low in the present study; thus, it might have been more difficult to demonstrate any statin effect in this population as the absolute risk reduction may be less. In our study, the high mean age and frequency of patients with chronic kidney disease might be additional factors that influenced the results. Furthermore, our study only included individuals who had newly begun statin therapy. In contrast, the CONFIRM study enrolled a substantial number of patients with coronary plaques, even when they were receiving ongoing statin therapy. Therefore, in patients with non-obstructive coronary plaques, the benefit of statins on cardiovascular events might have been greater than that in our study population.

The event rates in our study were lower than expected. Event rates per 1,000 person-years in the control group were 5.6% for the total population, 4.1% for patients with normal coronary arteries, and 6.9% for those with near-normal coronary arteries. These rates are lower than that of the control group in the Heart Outcomes Prevention Evaluation (HOPE)-3 trial, which analysed more limited events as primary outcomes in an intermediate-risk population[10]. In addition, according to the event rate, our population may belong to the borderline risk group as defined by the 2018 American guidelines, which recommend statins for these individuals at a class IIb level only when a patient has risk enhancers[1]. Although the reason for the low event rates in our study is not entirely clear, our rates may be associated with ethnic characteristics[11] or inclusion criteria, such as normal or near-normal coronary arteries. This may suggest that our study population have strong need to adjust cardiovascular risk assessed in the traditional manner. This is in line with previous reports that showed the utility of coronary calcium score of 0 in downgrading an individual's future risk and avoiding unnecessary statin therapy[12]. In this regard, our results indicated that Korean individuals with CCTA results showing normal or near-normal coronary arteries may not benefit from statin use that is recommended based on clinical risk status.

Using CCTA information, some proportion of the intermediate-risk group can be reclassified into high-risk or low-risk groups. However, prior studies did not primarily evaluate the effect of statin use when persons are reclassified according to CCTA results[13, 14]. Risk reclassification is usually performed in individuals for whom the necessity of pharmacotherapy, such as lipid-lowering agents, is uncertain. However, the net reclassification index by CCTA was not sufficiently high in high-risk patients[13]. In another study, statin therapy was not recommended when CCTA results were normal, even for patients with a 10-year risk of 10%–18% calculated using the pooled cohort equation; in this regard, CCTA influences treatment decisions in patients with these specific conditions[15]. Patients with this level of 10-year risk correspond to a relatively high-risk status within an intermediate-risk group as defined by the 2018 American guidelines[1]. Of note, our study evaluated the effect of statin therapy in a risk group that has not been well-assessed in previous research. Furthermore, our study indicated that universal statin use may not be desirable when CCTA results are normal or near-normal, even in high-risk patients.

It is not completely understood what underlies a higher tendency of events after 5 years, although not significant, in statin users among individuals with near-normal coronary arteries. In this subgroup, the proportions of subjects with follow-up duration ≥ 5 years were 88% and 78% for statin users and controls, respectively. Therefore, this difference might have affected the results. However, further investigation is needed to clarify if there are other factors. In the present study, the incidence of ischemic stroke was lower in statin users than in controls (though not significantly), whereas coronary revascularisation occurred in the opposite pattern. We did not have data regarding carotid or cerebral arteries that may impact future cerebrovascular events. It is difficult to make conclusions regarding the benefit of statins on cerebrovascular event risk if the calculated risk is high, even though the coronary arteries are normal.

Our study is not without limitations. Firstly, the power of evidence in our study is limited by its retrospective nature. Nevertheless, our evaluation of the study population included detailed matching and a comprehensive follow-up on clinical outcomes. Secondly, because our study population underwent CCTA for health check-up, it would be difficult to generalize our results to clinical practice where many patients have overt chest symptoms. Thirdly, although statin users and control subjects were largely well-

matched, triglyceride levels tended to be higher in statin users (median difference: 12 mg/dL). However, in our data, it would be difficult to determine whether this difference had any influence on the clinical outcomes. In addition, only 20 and 17 MACCEs were documented in statin users and controls, respectively. Based on these low event rates, our sample size may be insufficient to confirm the difference induced by statins and we cannot rule out type 2 error. The current study does not assert that high-risk patients should be routinely screened using CCTA to select patients who should avoid statin therapy. Such a strategy would require the resolution of other issues including cost-effectiveness. However, it may be acceptable to utilize known CCTA data in this specific population. In addition, the current study adds specific results of an East Asian population in addition to those of other ethnicities that have been partly provided by previous research.

In conclusion, persons with high cardiovascular risk and normal or near-normal coronary arteries (evaluated by CCTA) did not benefit from statin use. To the best of our knowledge, our study is the first to analyse the effect of starting statin therapy under these conditions. These results support the use of more individualised LLT and will help in clinical decision-making for this specific population.

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Conflict of Interest

The authors report no relationships that could be construed as a conflict of interest.

References

1) Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, and Yeboah J: 2018 AHA/ACC/AACVPR/AAPA/ABC/ ACPM/ ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol, 2019; 73: 3168-3209
2) Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O; and ESC Scientific Document Group: 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J, 2020; 41: 111-188
3) Rhee EJ, Kim HC, Kim JH, Lee EY, Kim BJ, Kim EM, Song Y, Lim JH, Kim HJ, Choi S, Moon MK, Na JO, Park KY, Oh MS, Han SY, Noh J, Yi KH, Lee SH, Hong SC, Jeong IK; and Committee of Clinical Practice Guideline of Korean Society of Lipid and Atherosclerosis: 2018 guidelines for the management of dyslipidemia in Korea. J Lipid Atheroscler, 2019; 8: 78-131
4) Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ, Miedema MD, Sibley CT, Shaw LJ, Blumenthal RS, Budoff MJ, and Krumholz HM: Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association Cholesterol Management Guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol, 2015; 66: 1657-1668
5) Seo J, Choi SI, and Kim YK: Subclinical coronary atherosclerosis: implication of coronary computed tomography angiography findings among statin candidates according to the 2013 ACC/AHA Cholesterol Management Guidelines. Korean J Radiol, 2019; 20: 1156-1166
6) Williams MC, Hunter A, Shah ASV, Assi V, Lewis S, Smith J, Berry C, Boon NA, Clark E, Flather M, Forbes J, McLean S, Roditi G, van Beek EJR, Timmis AD, Newby DE; and SCOT-HEART Investigators: Use of coronary computed tomographic angiography to guide management of patients with coronary disease. J Am Coll Cardiol, 2016; 67: 1759-1768
7) Chow BJW, Small G, Yam Y, Chen L, McPherson R, Achenbach S, Al-Mallah M, Berman DS, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng VY, Chinnaiyan K, Cury R, Delago A, Dunning A, Feuchtner G, Hadamitzky M, Hausleiter J, Karlsberg RP, Kaufmann PA, Kim YJ, Leipsic J, LaBounty T, Lin F, Maffei E, Raff GL, Shaw LJ, Villines TC, Min JK; and CONFIRM Investigators: Prognostic and therapeutic implications of statin and aspirin therapy in individuals with nonobstructive coronary artery disease: results from the CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter registry) registry. Arterioscler Thromb Vasc Biol, 2015; 35: 981-989
8) Blaha M, Budoff MJ, Shaw LJ, Khosa F, Rumberger JA, Berman D, Callister T, Raggi P, Blumenthal RS, and Nasir K: Absence of coronary artery calcification and all-cause mortality. JACC Cardiovasc Imaging, 2009; 2: 692-

700
9) Hwang IC, Jeon JY, Kim Y, Kim HM, Yoon YE, Lee SP, Kim HK, Sohn DW, Sung J, and Kim YJ: Statin therapy is associated with lower all-cause mortality in patients with non-obstructive coronary artery disease. Atherosclerosis, 2015; 239: 335-342
10) Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, Pais P, López-Jaramillo P, Leiter LA, Dans A, Avezum A, Piegas LS, Parkhomenko A, Keltai K, Keltai M, Sliwa K, Peters RJ, Held C, Chazova I, Yusoff K, Lewis BS, Jansky P, Khunti K, Toff WD, Reid CM, Varigos J, Sanchez-Vallejo G, McKelvie R, Pogue J, Jung H, Gao P, Diaz R, Lonn E; and HOPE-3 Investigators: Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med, 2016; 374: 2021-2031
11) Cho KH and Jeong MH: Clinical benefit of statins in Korean patients with acute myocardial infarction: experience of the Korea Acute Myocardial Infarction Registry. J Lipid Atheroscler, 2020; 9: 362-379
12) Mortensen MB, Fuster V, Muntendam P, Mehran R, Baber U, Sartori S, Falk E: A simple disease-guided approach to personalized ACC/AHA-recommended statin allocation in elderly people: The BioImage Study. J Am Coll Cardiol, 2016; 68: 881-891
13) Han D, Beecy A, Anchouche K, Gransar H, Dunham PC, Lee JH, Achenbach S, Al-Mallah MH, Andreini D, Berman DS, Bax JJ, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Chinnaiyan K, Chow BJW, Cury RC, DeLago A, Feuchtner G, Hadamitzky M, Hausleiter J, Kaufmann PA, Kim YJ, Leipsic JA, Maffei E, Marques H, de Araújo Gonçalves P, Pontone G, Raff GL, Rubinshtein R, Villines TC, Lu Y, Peña JM, Shaw LJ, Min JK, and Lin FY: Risk reclassification with coronary computed tomography angiography-visualized nonobstructive coronary artery disease according to 2018 American College of Cardiology/American Heart Association Cholesterol Guidelines (from the coronary computed tomography angiography evaluation for clinical outcomes: An international multicenter registry (CONFIRM)). Am J Cardiol, 2019; 124: 1397-1405
14) García-Ortiz L, Barreiro-Perez M, Merchan-Gómez S, Ignacio Recio-Rodriguez J, Sánchez-Aguadero N, Alonso-Dominguez R, Lugones-Sanchez C, Rodríguez-Sanchez E, Sanchez PL, Gómez-Marcos MA; and on behalf EVA investigators: Prevalence of coronary atherosclerosis and reclassification of cardiovascular risk in Spanish population by coronary computed tomography angiography: EVA study. Eur J Clin Invest, 2020; 50: e13272
15) Emami H, Takx RAP, Mayrhofer T, Janjua S, Park J, Pursnani A, Tawakol A, Lu MT, Ferencik M, and Hoffmann U: Nonobstructive coronary artery disease by coronary CT angiography improves risk stratification and allocation of statin therapy. JACC Cardiovasc Imaging, 2017; 10: 1031-1038