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Statin Use and the Progression of Coronary Artery Calcification in CKD: Findings From the KNOW-CKD Study

Jihyun Yang[1], Kyu-Beck Lee[1], Hyang Kim[1], Soo Wan Kim[2], Yeong Hoon Kim[3], Su Ah Sung[4], Jayoun Kim[5], Kook-Hwan Oh[6], Ji Yong Jung[7,8] and Young Youl Hyun[1,8]

[1]Division of Nephrology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [2]Department of Internal Medicine, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Republic of Korea; [3]Department of Internal Medicine, Inje University Busan Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea; [4]Department of Internal Medicine, Nowon Eulji Medical Center, Eulji University, Seoul, Republic of Korea; [5]Medical Research Collaborating Center, Seoul National University Hospital, Seoul, Republic of Korea; [6]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea; and [7]Division of Nephrology, Department of Internal Medicine, Gachon University Gil Medical Center, Gachon University College of Medicine, Incheon, Republic of Korea

Introduction: Statin treatment can reduce the risk of cardiovascular disease (CVD). Paradoxically, previous studies have shown that the use of statin is associated with the progression coronary artery calcification (CAC), a well-known predictor of CVD, in individuals with preserved renal function or in patients on dialysis. However, little is known about the association in patients with predialysis chronic kidney disease (CKD). The aim of this study was to characterize the relationship between statin use and progression of CAC in a CKD cohort of Korean adults.

Methods: We analyzed 1177 participants registered in the Korean Cohort Study for Outcome in Patients with Chronic Kidney Disease (KNOW-CKD) cohort. Coronary artery calcium score (CACS) was assessed using cardiac computed tomography at baseline and 4 years after enrollment. CAC progression was defined using the Sevrukov method. Statin users were defined as those who used statins for 50% or more of the follow-up period.

Results: The median (interquartile range) of CACS was 0 (0–30.33), and 318 (44.2%) participants had CACS above 0 at baseline. There were 447 (38.0%) statin users and 730 (62.0%) statin nonusers. After 4 years, 374 patients (52.0%) demonstrated CAC progression, which was significantly more frequent in statin users than in statin nonusers (218 [58.3%] vs. 156 [41.7%], $P < 0.001$). The multivariate-adjusted odds ratio for CAC progression in statin users compared to statin nonusers was 1.78 (1.26–2.50).

Conclusion: Statin use, significantly and independently, is associated with CAC progression in Korean patients with predialysis CKD. Further research is warranted to verify the prognosis of statin-related CAC progression.

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As renal function decreases or proteinuria increases, the incidence of CVD increases, and CVD is the leading cause of death in CKD.[1] Therefore, reducing cardiovascular complications is an important therapeutic goal in addition to preserving renal function in CKD.

Statins are a group of medications that lower the risk of major cardiovascular events such as coronary artery disease or stroke by lowering low-density lipoprotein cholesterol.[2] Statin use is a mainstay treatment modality for dyslipidemia in the general population.[3–5] The cardiovascular protective effects of statins are also verified in CKD,[6] and the 2013 Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Lipid Management in CKD recommends the use of statins in patients with CKD who are aged 50 years or older and in patients with CKD with high cardiovascular risk.[7]

Correspondence: Ji Yong Jung, Division of Nephrology, Department of Internal Medicine, Gachon University Gil Medical Center, Gachon University College of Medicine, 21 Namdong-daero 774 Beon-gil, Namdonggu, Incheon, 21565, Republic of Korea. E-mail: jyjung@gachon.ac.kr; or Young Youl Hyun, Division of Nephrology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongnogu, Seoul 03181, Republic of Korea. E-mail: femur0@naver.com

[8]JYJ and YYH contributed equally to this work.

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In the general population, CAC is a well-known risk factor for CVD and can improve cardiovascular risk prediction.[8,9] The prevalence of CAC is higher in patients with CKD than in control patients, and lower renal function is a risk factor for more severe CAC in CKD even after correcting for various risk factors.[10,11] Although data are scarce in the general population, CAC is a risk factor for increased cardiovascular events and mortality in CKD.[12–14]

Interestingly, statin use was associated with progression of CAC in previous studies conducted in the non-CKD population, and the cause of this paradoxical relationship is not clear. In addition, little is known about the effect of statin use on CAC in CKD. In CKD, nontraditional risk factors such as anemia, proteinuria, or abnormal mineral metabolism can increase cardiovascular risk and influence the effect of statins.

We hypothesized that statins promote CAC in patients with CKD. The purpose of this study was to test our hypothesis by analyzing the relationship between statin use and progression of CAC in a CKD cohort of Korean adults.

METHODS

Study Design and Population

This is a cohort study designed to examine the association between statin use and CAC progression in patients with CKD. The study subjects were participants in the prospective KNOW-CKD. A detailed protocol of this study has been published.[15] The study protocol was approved by the institutional review board at each participating clinical center in 2011. In brief, KNOW-CKD is a prospective cohort study that enrolls subjects with predialysis CKD stages 1 to 5 and who are aged between 20 and 75 years. Among a total of 2238 participants at baseline, 684 (30.5%) patients had preserved renal function (CKD stage 1 and 2) and other evidence of CKD such as proteinuria. Nine nephrology centers at major university hospitals throughout Korea enrolled 2238 adults with CKD over a 5-year period, from 2011 to 2016. The participating individuals will be monitored for more than 10 years until death or end-stage renal disease occurs. Among the cohort, 1177 patients underwent coronary multidetector computed tomography at baseline and 4 years. Coronary multidetector computed tomography was performed at baseline and at 4 years according to the KNOW-CKD study protocol. However, due to budget limitations, changes in the examination protocol occurred during the study, and only about half of the patients underwent a second coronary multidetector computed tomography. Because this was applied randomly to all patients, we do not think it would have caused any bias. Participants were divided into 2 groups according to the state of statin usage, and statin users were defined as those who used statins for 50% or more of the follow-up period. (Figure 1). We conducted further sensitivity analysis by defining statin use with more strict definition. In this analysis, we excluded patients who did not use statins for the first 6 months in the statin user group and excluded patients who used statins for the first 6 months in the statin nonuser group. In another sensitivity analysis, we analyzed patients according to whether they had taken statin for the first 6 months (intention-to-treat approach).

Clinical and Laboratory Measurements

Data on sociodemographic information, medical history, medication use, and health-related behavior were collected using a self-administered questionnaire, with the assistance of trained staff. Anthropometric data and resting blood pressure were measured by trained nurses. Blood samples were collected after fasting for at least 8 hours. Second voided or random urine samples from midstream collection were used to measure urine protein-to-creatinine ratio. Serum creatinine, cystatin C, 25-hydroxyvitamin D (25-[OH]-vit), intact parathyroid hormone, and vitamin D were measured at a central laboratory. Additional biochemical analyses were conducted at the local laboratory of each participating center. Serum creatinine level was measured using the isotope dilution mass spectroscopy-traceable method. Hypertension was defined as a systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or a history of hypertension. Diabetes mellitus was defined as a fasting serum glucose >126 mg/dl or a history of diabetes.

Measurement of CAC

Electrocardiography-gated coronary multidetector computed tomography scans were conducted following the standard protocol of each center. The quantitative CACS was calculated according to the method described by Agatston *et al.*[16]

Definition of CAC Progression

The progression of CAC at 4 years was defined using the method by Sevrukov *et al.*[17] If baseline CACS was 0, a follow-up CACS > 11.6 qualified for progression. In subjects with a baseline CACS above 0, an increase of follow-up CACS > 4.930 times the square root of the baseline CACS was defined as statistically significant progression. We used 3 other definitions of CAC progression in sensitivity analysis. The first was an increase in CACS ≥ 200 during the 4-year follow-up period, which is the definition used in KNOW-

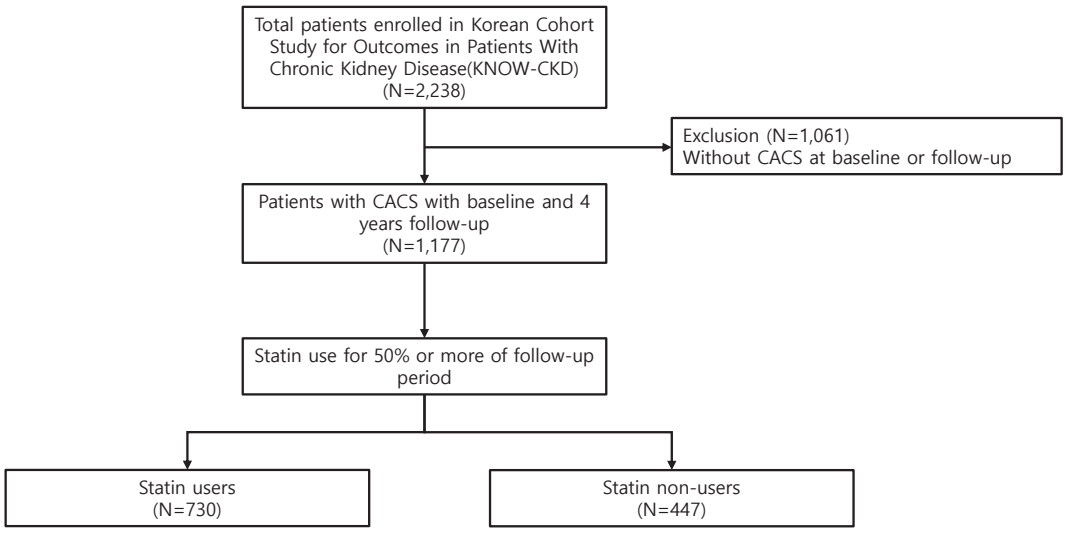

Figure 1. Flow diagram for selection of study subjects. CACS, coronary artery calcium score.

CKD.[18,19] The second was based on the Hokanson method, defined as a difference between the follow-up and baseline square root transformed CACS > 2.5.[20] The third was based on the Berry method, which depends on the baseline CACS (CACS baseline 0: CACS follow-up > 0; CACS baseline 1–100: [CACS follow-up − CACS baseline] $\geq$ 10/yr; CACS baseline > 100: [CACS follow-up − CACS baseline]/CACS baseline $\geq$ 10%/yr).[21]

Statistical Analysis

Continuous variables are expressed as the mean ± SD or median (interquartile range) and were compared between 2 groups using a *t* test or the Mann-Whitney U test and among 4 groups using analysis of variance or the Kruskal-Walli's test. Categorical variables are expressed as percentage and compared between groups using the $\chi 2$ test.

Further logistic regression analysis was conducted to evaluate the association between statin use and CAC progression and to calculate the odds ratio and confidence interval for CAC progression in statin users compared to statin nonusers. Multivariate models were adjusted for age, sex, waist-to-hip ratio, systolic blood pressure, diabetes, CVD, antiplatelet agent, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate, calcium, phosphorus, high-sensitivity C-reactive protein, vitamin D and parathyroid hormone, smoking, alcohol intake, metabolic equivalent, and baseline CACS. To test the robustness of the association, we further analyzed clinically relevant subgroups and with different definitions of CAC progression as sensitivity analysis. Statistical analyses were performed using Stata Version 18.0 (StataCorp LLC, College Station, TX).

RESULTS

The baseline characteristics of the study participants according to statin use are described in Table 1. In general, statin users had worse cardiometabolic profiles, with higher body mass index, waist-to-hip ratio, glucose, urine protein-to-creatinine ratio, phosphorus, and baseline CACS. In addition, diabetes and CVD were more common in statin users. However, statin users had lower estimated glomerular filtration rate. After 4 years, follow-up CACS was higher in statin users ($P < 0.001$), as was change of CACS at 4 years ($P < 0.001$, Table 1). CAC progression was observed in 449 (38.2%) patients. Compared to statin nonusers, statin users had more frequent CAC progression (342 [46.9%] vs. 107 [23.9%], $P < 0.001$).

In multivariate logistic analysis, statin use was independently associated with increased risk of CAC progression. The odds ratio (95% confidence interval) for CAC progression was 1.78 (1.26–2.50) in statin users compared to statin nonusers (Table 2). In sensitivity analysis with strict definition of statin use, there was no change in the main outcome. In further sensitivity analysis, this association was preserved when we used 3 different definitions of CAC progression (Table 3). In subgroup analysis, the association of statin use with CAC progression was not modified by age, body mass index, diabetes, estimated glomerular filtration rate, proteinuria, high-sensitivity C-reactive protein, parathyroid hormone and calcium, but modified by phosphorus. However, the trend was in the same direction regardless of the phosphorus level (Figure 2).

DISCUSSION

In this predialysis CKD cohort of Korean adults, increase in CACS after 4 years was higher, and CAC

Table 1. Baseline characteristics of study participants according to statin use

Characteristics	Overall	Statin use		*P*-value
		Nonuser	User	
Number	1177	447 (38.0)	730 (62.0)	
Age (yr)	52.55 ± 11.85	48.38 ± 12.25	55.1 ± 10.84	<0.001
Male	481 (40.9)	180 (40.3)	301 (41.2)	0.744
Body mass index (kg/m^2)	24.6 ± 3.4	23.8 ± 3.5	25.1 ± 3.2	<0.001
Waist-to-hip ratio	0.89 ± 0.07	0.88 ± 0.07	0.90 ± 0.06	<0.001
Systolic BP (mm Hg)	127.0 ± 14.7	125.8 ± 14.8	126.1 ± 14.6	0.671
Diastolic BP (mm Hg)	76.9 ± 10.4	77.9 ± 10.7	76.3 ± 10.1	0.008
Diabetes	301 (25.6)	66 (14.8)	235 (32.2)	<0.001
Cardiovascular disease	89 (7.6)	22 (4.9)	67 (9.2)	0.007
Antiplatelet agent	311 (26.4)	71 (15.9)	240 (32.9)	<0.001
Glucose (mg/dl)	106.7 ± 30.4	100.0 ± 21.9	110.8 ± 33.9	<0.001
LDL cholesterol (mg/dl)	97.2 ± 30.2	101.2 ± 26.1	94.9 ± 32.1	<0.001
HDL cholesterol (mg/dl)	50.9 ± 15.0	51.8 ± 16.1	50.3 ± 14.4	0.122
CRP (mg/l)	1.94 ± 5.53	1.74 ± 4.36	2.05 ± 6.11	0.230
eGFR (ml/min per 1.73 m^2)	63.0 ± 29.0	69.5 ± 31.6	59.0 ± 26.5	<0.001
CKD stage				<0.001
1	255 (21.7)	137 (30.7)	118 (16.2)	
2	298 (25.3)	106 (23.7)	192 (26.3)	
3A	227 (19.3)	74 (16.6)	153 (21.0)	
3B	262 (22.3)	89 (19.9)	173 (23.7)	
4	127 (10.8)	38 (8.5)	89 (12.2)	
5	8 (0.7)	3 (0.7)	5 (0.7)	
Urine PCR (g/gCr)	0.74 ± 1.14	0.46 ± 0.77	0.91 ± 1.28	<0.001
Calcium (mg/dl)	9.23 ± 0.42	9.21 ± 0.41	9.25 ± 0.44	0.198
Phosphorus (mg/dl)	3.54 ± 0.56	3.45 ± 0.56	3.59 ± 0.56	<0.001
25-(OH)-vitamin D (ng/ml)	18.3 ± 7.3	18.7 ± 7.6	18.1 ± 7.2	0.151
PTH (pg/ml)	53.2 ± 37.2	51.4 ± 37.0	54.3 ± 37.2	0.073
Smoking status				0.471
Never	595 (50.6)	227 (50.8)	368 (50.4)	
Former	383 (32.5)	138 (30.9)	245 (33.6)	
Current	199 (16.9)	82 (18.3)	117 (16.0)	
Alcohol intake				0.057
No	370 (31.4)	120 (26.9)	250 (34.3)	
<6 standard drinks/wk	362 (30.8)	143 (32.0)	219 (30.0)	
≥6 standard drinks/wk	351 (29.8)	147 (32.9)	204 (28.0)	
Unknown	94 (8.0)	37 (8.3)	57 (7.8)	
Physical activity (MET-min/wk)	2256 ± 3525	2171 ± 3647	2309 ± 3449	0.124
CACS baseline	0.0 (0.0–37.2)	0.0 (0.0–4.0)	2.9 (0–84.6)	<0.001
CACS 4 yrs	3.6 (0.0–107.0)	0.0 (0.0–28.5)	20.1 (0.0–185.4)	<0.001
CACS change for 4 yrs	1.0 (0.0–59.6)	0.0 (0.0–13.7)	12.7 (0.0–94.2)	<0.001

BP, blood pressure; CACS, coronary artery calcium score; CKD, chronic kidney disease; CRP, c-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent; PCR, protein to creatinine ratio; PTH, parathyroid hormone.
Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± SD or median (interquartile range).

progression was more frequent in patients taking statins than in those who were not. Baseline statin use is associated with CAC progression, and this association was preserved after adjustment of various cardiovascular risk factors in different subgroup analysis and in sensitivity analysis.

Our finding is like the results of previous studies that have shown an association between statin use and progression of CAC in non-CKD populations. Initial studies were conducted in patients with diabetes. Anand *et al*. prospectively observed volumetric CACSs of 398 patients with type 2 diabetes without prior coronary disease or symptoms for 2.5 years. In their study, statin use was an independent predictor of CAC progression. Another study was a substudy of the Veterans Affairs Diabetes Trial, which analyzed 197 patients with type 2 diabetes and their volumetric CACS.[22] The authors found that frequent statin use was associated with accelerated CAC.

In a reanalysis of the St. Francis Heart Study and EBEAT Study clinical trials, 80 mg of daily atorvastatin increased CACS by 12% to 14% over that of the placebo.[23] However, this statin therapy did not increase cardiovascular events. Puri *et al*.[24] conducted a *post hoc* analysis of 8 prospective randomized trials using serial coronary intravascular ultrasound. They compared

Table 2. Association between statin use and CAC progression

Statin use	Model 1	Model 2	Model 3
Statin use			
Nonuser ($n = 447$)	Reference	Reference	Reference
User ($n = 730$)	2.80 (2.16–3.64)	1.81 (1.29–2.54)	1.78 (1.26–2.50)
Statin use (strict definition[a])			
Nonuser ($n = 432$)	Reference	Reference	Reference
User ($n = 578$)	3.08 (2.34–4.06)	1.92 (1.32–2.79)	1.89 (1.29–2.78)
Statin use for the first 6 mo			
Nonuser ($n = 636$)	Reference	Reference	Reference
User ($n = 541$)	2.25 (1.77–2.87)	1.73 (1.25–2.38)	1.74 (1.25–2.41)

CAC, coronary calcification; CACS, coronary artery calcium score.
[a]In the strict definition, we excluded patients who did not use statins for the first 6 months in the statin user group and excluded patients who used statins for the first 6 months in the statin nonuser group.
Model 1: no adjustment.
Model 2: adjusted for age, sex, waist-to-hip ratio, systolic blood pressure, diabetes, cardiovascular disease, antiplatelet agent, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate, calcium, phosphorus, urine protein to creatinine ratio, C-reactive protein, vitamin D, and parathyroid hormone.
Model 3: adjusted for model 2 + smoking, alcohol intake, metabolic equivalent, and baseline CACS.

calcium indices and coronary atheroma volume and found that high-intensity statin therapy promoted coronary atheroma calcification compared to low-intensity statin therapy or no-statin therapy. Interestingly, high-intensity statin therapy regressed atheroma volume.

In renal patients, Yazbek *et al.*[25] randomized 120 kidney transplant recipients to statin and control groups. In that study, there was no difference in CAC progression between the 2 groups although statin improved the lipid profile. In another study by Zhimin *et al.*, 35 patients with end-stage renal disease underwent repeated cardiac CT scans after 1.5 years.[26] In this study, statin therapy was an independent predictor of CACS increase. However, these studies were small and did not consider various confounders and risk factors. In addition, they analyzed only patients with end-stage renal disease, in whom current guidelines do not recommend starting statin treatment.[7] To the best of our knowledge, ours is the only relatively large and well-organized study that demonstrated an association between statin use and CAC progression in patients with predialysis CKD.

The mechanism underlying the association between statin use and the CAC progression is uncertain; however, there are possible explanations. The most important action of statin is to improve lipid profiles to regress atherosclerosis.[27,28] In addition, statins have been shown to have beneficial cardiovascular protection through pleiotropic effects such as plaque stabilization, improving endothelial function, decreasing oxidative stress and inflammation, and decreasing thrombogenicity.[29,30] Statins reduce plaque volume, decrease inflammation and vulnerable lipid cores, and increase collagen content within the plaque, contributing to plaque stabilization.[31–33] Statins increase calcium content in plaque, and this procalcific effect itself also stabilizes the plaque.[31,33,34] In terms of CACS, progression is significantly associated with an increase in both calcified and noncalcified plaque volume in nonstatin groups. However, CACS progression is associated with only calcified plaque volume progression in statin users.[35] In a more recent study, 857 patients underwent serial coronary computed tomography angiography and quantitative measurements of coronary plaque. The study found that statin therapy was

Table 3. Association between statin use and CAC progression by definition

CAC progression	Model 1	Model 2	Model 3
CACS increase ≥ 200			
Nonuser	Reference	Reference	Reference
User	4.08 (2.47–6.74)	2.80 (1.48–5.30)	2.29 (1.16–4.55)
Hokanson method			
Nonuser	Reference	Reference	Reference
User	2.82 (2.15–3.68)	1.88 (1.33–2.65)	1.83 (1.30–2.59)
Berry method			
Nonuser	Reference	Reference	Reference
User	2.23 (1.71–2.89)	1.36 (0.98–1.88)	1.39 (1.003–1.93)

CAC, coronary calcification; CACS, coronary artery calcium score.
Model 1: no adjustment.
Model 2: adjusted for age, sex, waist-to-hip ratio, systolic blood pressure, diabetes, cardiovascular disease, antiplatelet agent, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate, calcium, phosphorus, urine protein to creatinine ratio, C-reactive protein, vitamin D, and parathyroid hormone.
Model 3: adjusted for model 2 + smoking, alcohol intake, metabolic equivalent, and baseline CACS.

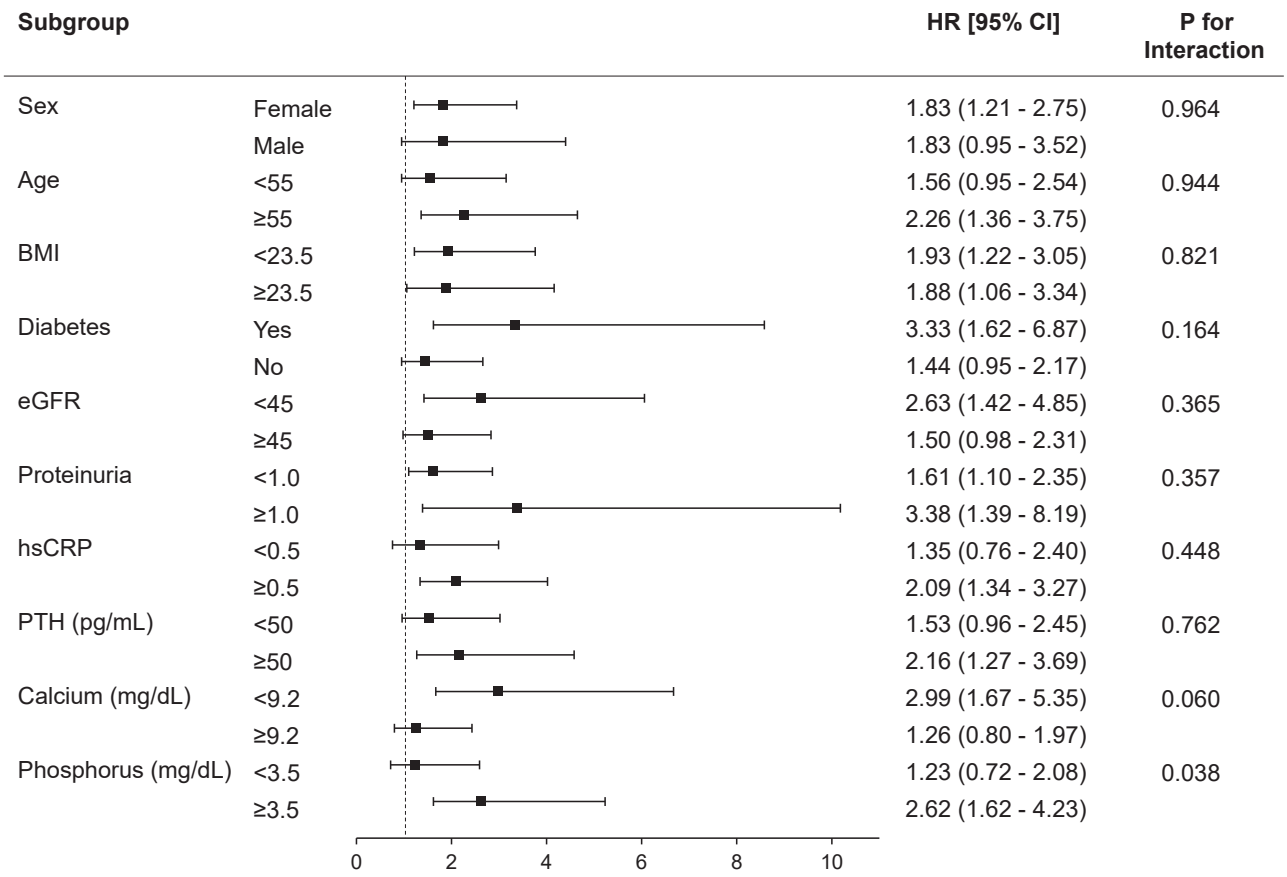

Figure 2. The association between statin use and CAC progression by subgroup. BMI, body mass index; CAC, coronary artery calcification; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; PTH, parathyroid hormone.

associated with denser calcium in plaque, and increased density calcium in coronary plaque was associated with slower plaque progression.[36] Although CAC volume is positively associated with CVD risk, CAC density at certain CAC volume is inversely associated with CVD risk.[37] These changes are associated with intimal calcification, which is characterized by the accumulation of inflammatory cells and lipid deposits. Intimal calcification is known to be the primary contributor to CAC.[38] Therefore, statin-induced CAC progression might be related to intimal calcification rather than medial calcification, which is a chronic systemic vascular disorder and is characterized by precipitation of calcium phosphate in the medial layer.[39] In addition to traditional cardiovascular risk factors, various nontraditional cardiovascular risk factors contribute to the more complex pathophysiology of cardiovascular complications in CKD.[40] Probably due to this complexity, cardiovascular protection by statin is weaker in advanced CKD.[41]

Our findings that statins are related to CAC progression may seem ironic. However, considering the above mechanistic hypothesis, the clinical implications of statin-related CAC progression are not clear. Existing studies suggest that statins are related to CAC progression but may reduce the incidence of CVD by making plaques more stable as described above. A previous large-scale randomized trial has also proven the cardiovascular protective effect of statins in CKD.[6] More information can be provided to patients through further studies on the cardiovascular outcome of patients who showed CAC progression after using statins. Under these circumstances, our findings do not imply any adverse effects of statin use.

Our study has a few limitations. First, this is an observational study, and we could not control all the potential confounders, and therefore could not know the causality of the association between statin use and CAC progression. Second, we only measured CACS and did not measure calcium density or atheroma volume. Therefore, we could not analyze the true nature of atherosclerotic plaque. Third, we did not analyze the cardiovascular risk associated with statin-related CAC progression because the development of cardiovascular events in our cohort was relatively infrequent.[42] Lastly, we defined the treatment group as individuals who took statins for more than 50% of the follow-up period. However, this definition may not fully capture the effect of statin use. Because we only checked statin use status at the time of follow-up every 6

months, we do not have information on the exact statin use status during the intervening period. Factors such as medication adherence or the characteristics of patients who discontinued the statin may have also influenced the outcomes. In patients with CKD, using statins for primary prevention may not yield a significant risk-benefit advantage. In addition, our findings suggest a potential explanation for the lack of mortality benefit observed with statin use in patients with end-stage kidney disease. Therefore, future research should explore the differential effects on mortality associated with primary and secondary preventive strategies in patients with CKD and its pathophysiology. Despite these limitations, we present a well-organized cohort study with consideration of various risk factors and verify the robustness through subgroup and sensitivity analyses, which are the strengths of our study compared with previous studies.

In conclusion, our study revealed that statin use is a risk factor for progression of CAC in CKD. This suggests that caution is needed in the interpretation of CACS in patients with CKD using statins. Further studies are needed to understand the mechanism and clinical significance of statin-related CAC progression.

DISCLOSURE

All the authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared upon reasonable request to the corresponding author.

AUTHOR CONTRIBUTIONS

JY contributed to the design of the study, acquisition, and interpretation of data, and drafting and revising of the work. SWK, YHK, SAS, KBL, HK, and KHO contributed to acquisition of data and revision of the work. JK contributed the analysis of the data and revision of the work.

JYJ and YYH contributed to the design of the study, acquisition/analysis/interpretation of the data, and revision of the work. All the authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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