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Progression of Coronary Artery Calcification According to Changes in Risk Factors in Asymptomatic Individuals

Jin Young Yoo [1,†], Se Ri Kang [2,†] and Eun Ju Chun [3,*]

[1] Department of Radiology, Chungbuk National University College of Medicine and Hospital, South Korea; immdjy@gmail.com
[2] Department of Radiology, Wonkwang University College of Medicine and Hospital, South Korea; kangseli21@naver.com
[3] Department of Radiology, Seoul National University Bundang Hospital, South Korea
* Correspondence: happyejchun@naver.com; Tel.: +82-31-787-7618
† These authors contributed equally to this work.

Abstract: This retrospective study aimed to assess coronary artery calcium (CAC) progression in serial computed tomography measurements according to risk factor changes. In 448 asymptomatic adults who underwent CAC measurements with more than one-year intervals, CAC progression was assessed according to age, sex, variable traditional risk factors (diabetes mellitus, hypertension, hyperlipidemia, and smoking), and initial CAC score (0, 0.1–100, and >100). Univariate and multivariate logistic regression analyses were assessed for independent predictors of rapid CAC progression (△CAC/year>20). During the 3.5-year follow-up, coronary artery calcifications occurred in 43 (12.8%) of 336 individuals with an initial CAC score of zero. Of 112 individuals with initial CAC presence, 60 (53.6%) had △CAC/year>20. Age, male sex, body mass index, and all risk factors were significantly associated with △CAC/year>20, but recently diagnosed hypertension (odds ratio [OR], 11.3) and initial CAC score (OR, 1.05) were significant independent predictors in multivariate regression analyses. CAC progression was affected by demographic and traditional risk factors, but adjusting for these factors, recently diagnosed hypertension and initial CAC score were the most influential factors for rapid CAC progression. These findings suggest that patients with higher initial CAC scores may benefit from more frequent follow-up scans and checks regarding risk factor changes.

Keywords: coronary artery calcium; computed tomography; clinical risk factors

1. Introduction

Coronary artery calcium (CAC) scoring assessed by computed tomography (CT) is a widely used and reproducible tool to guide risk stratification, as well as a powerful surrogate marker for cardiovascular disease (CVD) [1,2]. The CAC score has been extensively validated as a strong predictor of coronary events, and its superiority to risk factor-based paradigms such as the Framingham Risk Score, and individual risk factors has been demonstrated [3–5]. Therefore, the CAC score is recommended for the assessment of asymptomatic middle-aged populations, particularly of intermediate-risk cohorts, by various cardiovascular society guidelines across the world [6,7].

In addition to using a single CAC score for assessments, several studies have suggested the clinical significance of CAC progression determined using serial CT scans, as CAC progression is significantly more associated with a worse prognosis than CAC non-progression [8,9]. Moreover, CAC progression has been associated with several traditional risk factors [10,11]. Some of these risk factors, such as smoking or hyperlipidemia, are modifiable, so changes in these risk factors may affect CAC changes. Currently, little evidence exists for CAC progression related to changes in risk factors;

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thus, current guidelines do not specify the optimal timing for follow-up CAC scanning. Therefore, we aimed to assess CAC progression according to changes in risk factors through serial CT measurements in asymptomatic individuals.

2. Materials and Methods

2.1. Study Design and Participants

Based on the health screening data registry of the Seoul National University Bundang Hospital (SNUBH) between January 2006 and December 2012, patients who underwent serial CAC scoring at least two times with more than one-year intervals were assessed. All individuals were asked whether they had chest pain or equivalent symptoms according to the WHO Rose angina questionnaire [12]. Physicians subsequently determined asymptomatic individuals who were free of coronary artery disease based on the patients' history including the answers from the questionnaire. We excluded participants who had a history of myocardial infarction, stroke, percutaneous coronary intervention, or coronary artery bypass graft. Finally, we enrolled 448 self-referred asymptomatic individuals who had undergone serial CAC scoring at least two times with more than one-year intervals.

2.2. Risk Factor Assessment

Basic demographic data were acquired from a database maintained by the SNUBH Health Promotion Center. Medical history of myocardial infarction, angina, hypertension, stroke, diabetes mellitus (DM), family history of CVD (myocardial infarction or stroke history in first-degree relatives), current medication profile, and smoking status were systematically determined by personal interviews during the patients' hospital visits for initial and follow-up CAC scans.

Body weight and height were also recorded during their visits, and blood samples were collected and analyzed. We recorded the mean blood pressure (BP) after the measurement of the resting BP three times with the participant in a seated position. Hypertension was defined as a systolic/diastolic BP≥140/90 mmHg, respectively, or the current use of antihypertensive medication. Lipid profiles, including total cholesterol and triglycerides, and fasting plasma glucose were measured with blood sampling obtained after a 12-h fast. DM was defined as a fasting blood glucose level ≥126 mg/dL or current antidiabetic treatment. Hyperlipidemia was defined as a total cholesterol concentration of ≥240 mg/dL or current treatment with lipid-lowering drugs. Current smoking was considered if the participant had smoked regularly during the previous 3 months.

2.3. Data Acquisition

CT data were acquired using 64-multidetector cardiac CT (Brilliance 64; Philips Medical Systems, Best, The Netherlands) with collimation of 64 × 0.625 mm and rotation time of 420 ms. CT scans used 120 kVp with variable mA according to the patient's body weight and non-overlapping sections with 2.5 mm slice thickness [13].

Calcium scoring was calculated using the Agatson score with a threshold of 130 Hounsfield Units (HU), with only contiguous voxels totaling ≥1 mm^2 in the area on pre-contrast CT images [14]. The score for an individual lesion was obtained by multiplying the lesion area with the density weighting factor determined by the maximum CT attenuation in the specified lesion. The density weighting factor was determined as follows: lesions with a peak attenuation of 130–199 HU were assigned a value of 1, those with a peak attenuation of 200–299 HU were assigned a value of 2, those with a peak attenuation of 300–399 HU were assigned a value of 3, and those with a peak attenuation value >400 HU were assigned a value of 4 [15]. The total Agatston score was the summed score of all coronary lesions. According to the initial CAC score, patients were categorized into three groups as follows: zero-CAC (CAC=0), low-CAC (0.1≤CAC score≤100), and high-CAC (CAC score>100) groups.

2.4. Statistical Analysis

Continuous parameters are presented as mean±SD, and nominal or ordinal parameters are given as n (%). Continuous parameters among the three groups classified according to the initial CAC score

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were compared using one-way analysis of variance (ANOVA) with Scheffe's post hoc test, whereas nominal data were evaluated using the chi-square or Fisher's exact test.

Annualized progression of the CAC score (ΔCAC/year) was calculated as the last CAC score minus the initial CAC score divided by the time between the initial and last CAC scan. The group with an initial CAC score of zero was divided into two groups by examining the changes in the follow-up CAC scan: a group with continuous zero CAC scores (zero-CAC_{last}) and a group with new calcium (new-CAC_{last}). Those with calcium present on the initial CT scan were divided into two groups based on an annual CAC increase of more than 20 (ΔCAC/year>20). Differences between two groups were analyzed using Student's t-test for continuous data and the chi-square test for nominal or ordinal data.

Finally, univariate and multivariate logistic regression analyses were assessed for independent predictors of ΔCAC/year>20. SPSS 17.0 package (SPSS Inc., Chicago, Illinois) was used for all statistical analyses, and a p-value <0.05 was regarded as statistical significance.

3. Results

3.1. Basic Demographics of Enrolled Asymptomatic Individuals

A total of 448 asymptomatic individuals underwent serial CAC scans two times with an interval of more than one year. The initial CAC scores ranged from 0 to 758.3. Among them, the initial CAC score was zero in 336 patients (75.0%). The low-CAC group comprised 70 individuals (15.6%) with a CAC score of 31.6±26.7, whereas 42 individuals (9.4%) with a mean CAC score of 250.6±190.3 belonged to the high-CAC group. Table 1 summarizes the baseline demographic characteristics and risk factors of the study population in the three groups classified according to the initial CAC score. The mean age was higher and male sex more prevalent in the low-CAC and high-CAC groups compared to the zero-CAC group (all p<0.05). Hypertension prevalence significantly increased according to the initial CAC score: the high-CAC group had the highest percentage, followed by the low-CAC and then zero-CAC groups (all p<0.05). Other demographic parameters, including the presence of DM and hyperlipidemia, as well as statin and aspirin medication use, were significantly higher in the low- and high-CAC groups than in the zero-CAC group (all p<0.05). However, these parameters were not significantly different between the low-CAC and high-CAC groups. Overall, the number of risk factors was higher in groups with CAC presence (low-CAC and high-CAC group) than in that with CAC absence (zero-CAC group).

Table 1. Patient characteristics.

Parameter	Total (n=448)	Zero-CAC (CAC=0) (n=336)	Low-CAC (0.1≤CAC≤100) (n=70)	High-CAC (CAC>100) (n=42)
Initial CAC score	28.4±93.2	0	31.6±26.7*	250.6±190.3*†
Age (years)	53.4±8.1	51.9±7.2	56.9±9.4*	57.4±8.6*
Male sex	329 (73.4%)	228 (67.9%)	62 (88.6%)*	39 (92.9%)*
BMI (kg/m^2)	24.6±2.9	24.4±2.9	25.6±2.6	24.7±2.9
Risk factors				
Hypertension	90 (20.1%)	40 (11.9%)	21 (30.0%)*	22 (52.4%)*†
DM	29 (6.5%)	7 (2.1%)	11 (15.7%)*	11 (26.2%)*
Current smoker	159 (35.5%)	111 (33.0%)	30 (42.9%)	18 (42.9%)
Hyperlipidemia	77 (17.2%)	48 (14.3%)	19 (27.1%)*	12 (28.6%)*
Family history of CVD	111 (24.8%)	77 (22.9%)	24 (34.3%)	10 (23.8%)
Medication				
Statin	32 (7.1%)	12 (3.6%)	10 (14.3%)*	10 (23.8%)*
Aspirin	38 (8.5%)	14 (4.2%)	13 (18.6%)*	11 (26.2%)*
Number of risk factors				
None	154 (34.4%)	137 (40.8%)	11 (15.7%)*	6 (14.3%)*

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1	174 (38.8%)	135 (42.0%)	23 (32.9%)	16 (38.1%)
≥2	120 (26.8%)	64 (19.0%)	35 (50.0%)*	21 (50.0%)*

Note – BMI, body mass index; CAC, coronary artery calcium; CVD, cardiovascular disease; DM, diabetes mellitus. *p-value<0.05 between the zero-CAC group vs. low-CAC group, or zero-CAC group vs. high-CAC group, from a pairwise comparison that used the zero-CAC group as a control. †p-value<0.05 between low-CAC group vs. high-CAC group.

3.2. CAC Progression and Changes in Risk Factors During Follow-Up

During the mean 3.5±1.3 years of follow-up (range 1.0–7.5 years), the mean annual progression in CAC score was 10.0±29.6. The △CAC/year was >10 in 87 patients (19.4%), whereas △CAC/year was >20 in 61 patients (13.6%). The degree of annual CAC progression was significantly higher in the group with a higher initial CAC score (p<0.001).

During the follow-up period, hypertension, DM, and hyperlipidemia were newly diagnosed in 14 individuals (3.1%), 7 individuals (1.6%), and 31 individuals (6.9%), respectively. In the smoking status survey, 22 individuals (4.9%) quit smoking, whereas 6 individuals (1.3%) started smoking. These new risk factors were more frequently recorded in the group with CAC presence than in that with CAC absence in the initial CAC scan. Table 2 presents CAC progression and changes in risk factors during the follow-up period among the three groups classified according to the initial CAC score.

Table 2. Comparison of CAC progression and changes in risk factors according to the initial CAC score.

Parameter	**Total (n=448)**	**Zero-CAC (CAC=0) (n=336)**	**Low-CAC (0.1≤CAC≤100) (n=70)**	**High-CAC (CAC>100) (n=42)**
Follow-up CAC				
△CAC/year	10.0±29.6	0.6±2.7	19.7±22.4*	69.5±64.3*†
△CAC/year>10	87 (19.4%)	6 (1.8%)	42 (60.0%)*	39 (92.9%)*†
△CAC/year>20	61 (13.6%)	1 (0.3%)	26 (37.1%)*	34 (81.0%)*†
Follow-up risk factors				
Hypertension	103 (23.0%)	48 (14.3%)	29 (41.4%)*	25 (59.5%)*
New hypertension	14 (3.1%)	8 (2.4%)	8 (11.4%)*	3 (7.1%)*
DM	36 (8.0%)	8 (2.4%)	18 (25.7%)*	13 (31.0%)*
New DM	7 (1.6%)	1 (0.3%)	7 (10.0%)*	2 (4.8%)
Current smoker	137 (30.6%)	102 (30.4%)	23 (32.9%)	12 (28.6%)
New smoking	6 (1.3%)	0	4 (5.7%)*	2 (4.8%)*
Stop smoking	22 (4.9%)	9 (2.7%)	7 (10.0%)*	6 (14.3%)*
Hyperlipidemia	106 (23.7%)	65 (19.3%)	28 (40.0%)*	16 (38.1%)*
New hyperlipidemia	31 (6.9%)	17 (5.1%)	9 (12.9%)*	6 (14.3%)*

*p-value<0.05 between the zero-CAC group vs. low-CAC group, or zero-CAC group vs. high-CAC group, from a pairwise comparison that used the zero-CAC group as a control. †p-value<0.05 between low-CAC group vs. high-CAC group.

3.3. Comparison of Changes in CAC Scores and Risk Factors in the Initial Zero-CAC Group: Zero-CAC$_{last}$ vs. New-CAC$_{last}$

Of the 336 individuals with an initial CAC score of zero, 43 individuals (12.8%) developed coronary artery calcifications during follow-up (new-CAC$_{last}$ group), whereas the remaining 293 individuals (87.2%) did not develop coronary artery calcifications (zero-CAC$_{last}$ group).

Table 3 compares the changes in CAC scores and risk factors between these two groups. Age, body mass index (BMI), and hyperlipidemia prevalence were significantly higher in the new-CAC$_{last}$

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group than in the zero-CAC$_{last}$ group (all p<0.05). During follow-up, hypertension developed significantly more frequently in the new-CAC$_{last}$ group; therefore, the prevalence rates of hypertension and hyperlipidemia at the time of the final CAC scan were higher in the new-CAC$_{last}$ group than in the zero-CAC$_{last}$ group (all p<0.05).

Table 3. Changes in CAC score and risk factors in the initial zero-CAC group.

Follow-up CAC	zero-CAC$_{last}$ (n=293)	new-CAC$_{last}$ (n=43)	p-value
Age (years)	51.5±6.9	54.6±8.3	0.009*
Male	194 (66.2%)	34 (79.1%)	0.115
BMI (kg/m^2)	24.2±2.9	25.3±2.8	0.024*
Initial risk factors			
Hypertension	31 (10.6%)	9 (20.9%)	0.073
DM	5 (1.7%)	2 (4.7%)	0.222
Current smoker	92 (31.4%)	19 (44.2%)	0.118
Hyperlipidemia	37 (12.6%)	11 (25.6%)	0.034*
Family history of CVD	65 (22.2%)	12 (27.9%)	0.440
Medication statin	10 (3.4%)	2 (4.7%)	0.657
Medication aspirin	12 (4.1%)	2 (4.7%)	0.697
Follow-up risk factors			
Hypertension	35 (11.9%)	13 (30.2%)	0.004*
New hypertension	4 (1.4%)	4 (9.3%)	0.011*
DM	5 (1.7%)	3 (7.0%)	0.069
New DM	0	1 (2.3%)	0.128
Hyperlipidemia	49 (16.7%)	16 (37.2%)	0.003*
New hyperlipidemia	12 (4.1%)	5 (11.6%)	0.052
Current smoker	86 (29.4%)	16 (37.2%)	0.292
New smoking	0	0	-
Stop smoking	6 (2.0%)	3 (7.0%)	0.095
Follow-up CAC score	0	16.7±27.9	<0.001*

*p-value<0.05.

3.4. Comparison of Changes in CAC Scores and Risk Factors in the Group with Initial CAC Presence: Rapidly vs. Slowly Progressing-CAC Groups

Among the 112 patients with CAC presence in the initial scan, 60 patients had rapid progression in CAC changes with △CAC/year>20, and 52 patients had slow progression with △CAC/year≤20. Table 4 compares the changes in CAC scores and risk factors between these two groups. BMI and prevalence of statin medication were higher in the rapidly progressing-CAC group than in the slowly progressing-CAC group (both p<0.05). Likewise, the prevalence rates of newly developed hypertension and current smoking were higher in the rapidly progressing-CAC group than in the slowly progressing-CAC group (both p<0.05). The initial CAC score was also higher in the rapidly progressing-CAC group than in the slowly progressing-CAC group (178.9±190.5 vs. 38.5±44.2, respectively; p<0.001).

Table 4. Changes in CAC scores and risk factors in the group with initial CAC presence.

Follow-up CAC score	Slowly progressing-CAC: △CAC/year≤20 (n=52)	Rapidly progressing-CAC: △CAC/year>20 (n=60)	p-value
Age (years)	59.3±9.5	56.4±8.5	0.091

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Male sex	46 (88.5%)	55 (91.7%)	0.752
BMI (kg/m²)	24.5±2.6	25.9±2.8	0.010*
Initial risk factors			
Hypertension	15 (28.8%)	28 (46.7%)	0.079
DM	9 (17.3%)	13 (21.7%)	0.638
Current smoker	19 (36.5%)	29 (48.3%)	0.252
Hyperlipidemia	12 (23.1%)	22 (36.7%)	0.398
Family history of CVD	65 (22.2%)	12 (27.9%)	0.150
Medication statin	5 (9.6%)	15 (25.0%)	0.047*
Medication aspirin	10 (19.2%)	14 (23.3%)	0.650
Follow-up risk factors			
Hypertension	35 (30.8%)	38 (63.3%)	0.001*
New hypertension	1 (1.9%)	10 (16.7%)	0.010*
DM	11 (21.2%)	20 (33.3%)	0.204
New DM	2 (3.8%)	7 (11.7%)	0.172
Hyperlipidemia	18 (34.6%)	26 (43.3%)	0.438
New hyperlipidemia	6 (11.5%)	9 (15.0%)	0.782
Current smoker	13 (25.0%)	22 (36.7%)	0.222
New smoking	0	6 (10.0%)	0.029*
Stop smoking	6 (11.5%)	7 (11.7%)	>0.99
CAC score			
Initial CAC score	38.5±44.2	178.9±190.5	<0.001*
Follow-up CAC score	66.7±57.3	434.8±408.6	<0.001*
△CAC/year	7.7±7.0	64.9±54.6	<0.001*

*p-value<0.05.

3.5. Predictors of Rapid CAC Progression

Table 5 shows the results of univariate and multivariate logistic regression analyses for the predictors of rapid CAC progression in asymptomatic adults. Based on univariate analysis, the parameters age, male sex, BMI, and all risk factors including hypertension, DM, hyperlipidemia, current smoking, and family history of CVD were significantly associated with rapid CAC progression defined as △CAC/year>20 (all p<0.05). Using multivariate analysis, strong predictors for rapid CAC progression were the presence of hypertension at the time of the last CAC scan (odds ratio [OR] 11.3; 95% confidence interval [CI] 1.33, 95.42) and the initial CAC score (OR 1.05; 95% CI 1.04, 1.07).

Table 5. Predictors for an annual CAC progression of more than 20.

Parameter	**Rapid CAC progression (△CAC/year>20)**			
	Univariate OR (95% CI)	**p-value**	**Multivariate OR (95% CI)**	**p-value**
Age	1.05 (1.02, 1.08)	0.003*	0.96 (0.89, 1.03)	0.206
Male sex	4.67 (1.83, 11.98)	0.001*	1.15 (0.19, 6.86)	0.876

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BMI	1.18 (1.08, 1.30)	<0.001*	1.30 (1.04, 1.63)	0.051
Initial risk factors				
Hypertension	5.12 (2.87, 9.14)	<0.001*	0.22 (0.02, 1.97)	0.174
DM	6.28 (2.85, 13.85)	<0.001*	0.20 (0.02, 1.87)	0.157
Hyperlipidemia	2.71 (1.49, 4.95)	0.001*	1.77 (0.28, 11.20)	0.545
Current smoking	1.94 (1.12, 3.34)	0.017*	0.66 (0.14, 3.18)	0.606
Family history of CVD	1.89 (1.06, 3.35)	0.03*	1.74 (0.55, 5.46)	0.344
Medication				
Statin	7.09 (3.32, 15.16)	<0.001*	1.61 (0.34, 7.50)	0.546
Aspirin	4.50 (2.18, 9.31)	<0.001*	0.56 (0.16, 2.01)	0.376
Follow-up risk factors				
Hypertension	8.34 (4.65, 14.94)	<0.001*	11.30 (1.33, 95.42)	0.026*
New hypertension	8.24 (3.20, 21.23)	<0.001*		
DM	9.45 (4.66, 19.14)	<0.001*	5.95 (0.79, 44.93)	0.084
New DM	16.59 (4.16, 66.10)	<0.001*	-	
Hyperlipidemia	2.95 (1.69, 5.18)	<0.001*	0.99 (0.19, 5.13)	0.995
New hyperlipidemia	2.74 (1.20, 6.24)	0.016*		
Smoking	1.45 (0.83, 2.54)	0.196	4.18 (0.78, 22.54)	0.096
New smoking	0	-		
Initial CAC score	1.04 (1.03, 1.05)	<0.001*	1.05 (1.04, 1.07)	<0.001*
0	1	(ref)	1	(ref)
0.1–100	0.001 (0, 0.01)	<0.001*	0 (0, 0.01)	<0.001*
>100	0.14 (0.06, 0.35)	<0.001*	0.06 (0.02, 0.19)	<0.001*

Note – BMI, body mass index; CAC, coronary artery calcium; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; OR, odds ratio. *p-value<0.05.

4. Discussion

This study evaluated CAC progression according to changes in risk factors based on serial CTs to calculate the Agatston score in asymptomatic individuals. The main findings of the study were as follows: 1) At the time of the initial CAC scan, the parameters age, prevalence of male sex, and all risk factors were significantly higher in the group with CAC presence than in the no-CAC group; 2) During the mean 3.5±1.3 years of follow-up, 43 (12.8%) of 336 individuals with an initial CAC score of zero developed coronary artery calcifications, and 60 (53.6%) of the 112 individuals with initial CAC presence showed rapid annual CAC progression of more than 20; 3) Age, male sex, BMI, and all risk factors were significantly associated with ΔCAC/year>20, but recently diagnosed hypertension (OR, 11.3) and initial CAC score (OR, 1.05) were significant independent predictors in multivariate regression analyses. This suggests that patients with higher initial CAC scores may benefit from more frequent follow-up scans compared to patients with lower initial scores. This also suggests that continuously checking the changes in risk factors is important because most risk factors are modifiable and dynamic in response to treatment.

Our study was motivated by the lack of guideline-supported recommendations for repeat CAC scans, although an increase in CAC score on serial scans is a well-known and strong predictor of CVD and worse survival rates [16]. Regarding the natural progression of CAC in asymptomatic populations with an initial CAC score of zero, limited prior studies have suggested not to repeat scans for at least 4–5 years because asymptomatic populations have a low incidence of CAC

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progression within 5 years [16–19]. Similarly, we observed a minimal increase (0.6±2.7) in CAC score in the initial zero-CAC group during a mean follow-up of 3.5 years.

However, few studies have examined the natural progression of CAC in populations with an initial CAC score above zero, and no information exists on the optimal timing for follow-up scans in this population [20–22]. Based on several studies [23,24], it is evident that individuals with higher initial CAC scores tend to exhibit more rapid CAC progression over time. This finding is supported by the fact that persons with higher initial CAC scores have a higher risk of developing atherosclerosis and, hence, experience more pronounced CAC progression over time. Our study also demonstrated that the initial CAC score is one of the independent predictors for CAC progression, even after adjusting for traditional risk factors. Accordingly, the optimal timing and frequency of follow-up scans for this population should be decided based on their initial CAC score.

Previous studies have demonstrated that traditional risk factors, such as age, male sex, BMI, hypertension, DM, hyperlipidemia, current smoking, and family history of CVD, are associated with the presence and degree of CAC progression [10,11], which is consistent with our results. Furthermore, Lehmann et al. [25] reported that recent risk factors assessed at the last follow-up, rather than initial risk factors, are the more influential predictors for coronary and cardiovascular event rates. Our study also demonstrates that recently diagnosed hypertension was one of the most powerful predictors of CAC progression. This means that recent health conditions have the greatest impact on CAC progression because most clinical risk factors improve or worsen depending on lifestyle changes or medical treatment. Therefore, regular health checkups and risk factor control may be helpful for slowing down CAC progression.

Regarding medications, the effectiveness of lipid-lowering drugs, such as statins, in slowing the CAC progression rate has been a topic of considerable interest. While initial studies showed CAC regression with statin therapy, more recent data showed the opposite [26]. That is, recent studies have reported persistent CAC progression despite intensive lipid-lowering therapy [27,28]. Our study also identified statin medication as one of the independent predictors for CAC progression. This can be explained by the 'calcium paradox' concept of improved clinical outcome despite plaque progression when plaque progression is characterized by a predominant increase in dense calcium and plaque stabilization [29].

Our study has several limitations. First, our study has no information on cardiovascular events as we aimed to assess CAC progression in relation to changes in risk factors. Second, we assessed major traditional risk factors such as hypertension and DM but did not include novel risk factors such as C-reactive protein or lipid profiles. Although there are no conclusive findings regarding their specific value for CAC progression, a prospective study would be needed to analyze more risk factors. Finally, as this is a single-center retrospective study using a single type of scanner, the generalizability of our findings to other populations and imaging settings may be limited. Hence, large-scale, multicenter, multivendor studies are needed to validate our results.

In conclusion, our study showed that CAC progression was affected by demographic and traditional risk factors, but adjusting for these factors, recently diagnosed risk factors and the initial CAC score were the most influential factors for rapid CAC progression. This suggests that patients with higher initial CAC scores may benefit from more frequent follow-up scans and need continuous checks regarding changes in risk factors. Based on this study, we recommend that the appropriate follow-up time for CAC measurements should be individually determined based on each patient's initial CAC score and changes in risk factors. This personalized approach to follow-up could help optimize the timing of repeat scans and facilitate early detection and management of CVD.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Table S1 in Supplemental Digital Content 1: Predictors for an annual CAC progression of more than 20.

Author Contributions: Conceptualization and design of the work, E.J.C.; methodology, E.J.C.; formal analysis, J.Y.Y. and E.J.C.; data curation, J.Y.Y. and S.R.K.; manuscript drafting, J.Y.Y., S.R.K., and E.J.C.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and the institutional review board of Seoul National University Bundang Hospital approved the study protocol (SNUBH IRB No. 1507-308-105).

Informed Consent Statement: All participants of this study waived informed consent due to retrospective study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author, Eun Ju Chun, upon reasonable request.

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Conflicts of Interest: The authors declare no conflicts of interest.

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