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Prognostic Value of Coronary CT Angiography for Predicting Poor Cardiac Outcome in Stroke Patients without Known Cardiac Disease or Chest Pain: The Assessment of Coronary Artery Disease in Stroke Patients Study

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Objective: To assess the incremental prognostic value of coronary computed tomography angiography (CCTA) in comparison to a clinical risk model (Framingham risk score, FRS) and coronary artery calcium score (CACS) for future cardiac events in ischemic stroke patients without chest pain.

Materials and Methods: This retrospective study included 1418 patients with acute stroke who had no previous cardiac disease and underwent CCTA, including CACS. Stenosis degree and plaque types (high-risk, non-calcified, mixed, or calcified plaques) were assessed as CCTA variables. High-risk plaque was defined when at least two of the following characteristics were observed: low-density plaque, positive remodeling, spotty calcification, or napkin-ring sign. We compared the incremental prognostic value of CCTA for major adverse cardiovascular events (MACE) over CACS and FRS.

Results: The prevalence of any plaque and obstructive coronary artery disease (CAD) (stenosis ≥ 50%) were 70.7% and 30.2%, respectively. During the median follow-up period of 48 months, 108 patients (7.6%) experienced MACE. Increasing FRS, CACS, and stenosis degree were positively associated with MACE (all $p < 0.05$). Patients with high-risk plaque type showed the highest incidence of MACE, followed by non-calcified, mixed, and calcified plaque, respectively (log-rank $p < 0.001$). Among the prediction models for MACE, adding stenosis degree to FRS showed better discrimination and risk reclassification compared to FRS or the FRS + CACS model (all $p < 0.05$). Furthermore, incorporating plaque type in the prediction model significantly improved reclassification (integrated discrimination improvement, 0.08; $p = 0.023$) and showed the highest discrimination index (C-statistics, 0.85). However, the addition of CACS on CCTA with FRS did not add to the prediction ability for MACE ($p > 0.05$).

Conclusion: Assessment of stenosis degree and plaque type using CCTA provided additional prognostic value over CACS and FRS to risk stratify stroke patients without prior history of CAD better.

Keywords: *Coronary computed tomography angiography; Coronary artery calcium scoring; Stroke; Plaque, atherosclerotic; Coronary stenosis*

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INTRODUCTION

In stroke survivors, cardiac events are the most common cause of death in long-term survivors after first-ever stroke and the cause of greater medical costs (1-3). Prevalence of asymptomatic coronary artery disease (CAD) is also significant in patients with stroke (4-6). Therefore, the evaluation of occult CAD and the identification of prognostic factors for cardiac events may alter patients' prognosis.

Although the Stroke Council and the Council on Clinical Cardiology of the American Heart Association (AHA) and American Stroke Association recommend noninvasive testing for CAD in patients with significant carotid disease and high CAD risk scores based on Framingham algorithms, there remains the question of how and which of the remaining stroke patients should be screened (7).

With the advancements in non-invasive imaging techniques, coronary artery calcium score (CACS) and coronary computed tomography angiography (CCTA) have been widely adopted for the evaluation of CAD. Recently, several studies have reported that CCTA has incremental prognostic value over CACS because CCTA can evaluate not only the degree of stenosis but also coronary plaque characteristics (8-10). However, there is a paucity of data regarding the potential role of CCTA to screen patients with ischemic stroke. Therefore, our study aimed to evaluate the prevalence of subclinical CAD in acute stroke patients without known cardiac disease or chest pain and assess the incremental prognostic value of CCTA in comparison to clinical risk factors and CACS.

MATERIALS AND METHODS

Study Population

The Assessment of Coronary Artery Disease in Stroke Patients study is a longitudinal retrospective observational cohort study that evaluates CAD in stroke patients without previous cardiac disease or chest pain. From the stroke registry which consists of patients who had ischemic stroke and underwent brain magnetic resonance imaging (MRI) (n = 3130) at Seoul National University Bundang Hospital between July 2006 and December 2012, we retrospectively selected 1657 patients who met the following inclusion criteria: 1) patients who were diagnosed with ischemic stroke using brain MRI when they had an acute focal neurological deficit and 2) patients who underwent CCTA including CACS within 3 months after acute stroke.CCTA was performed if patients presented with at least one of the following: 1) significant stenosis (≥ 50%) in the intracranial or extracranial arteries on imaging such as carotid Doppler, CT angiography, or MR angiography; 2) ≥ 1 risk factors for CAD, such as hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, and central obesity; and 3) older age (men, > 45 years; women, > 55 years) (11, 12). We excluded patients with the following characteristics: 1) patients with history of myocardial infarction (MI) and angina or patients who previously underwent percutaneous coronary intervention (PCI) or bypass grafting (n = 112); 2) patients with intracranial hemorrhage including intracerebral, subdural, or subarachnoid hemorrhage (n = 38); 3) patients with brain tumor (n = 13); or 4) patients with poor CCTA image quality (n = 42) (Fig. 1). Additionally, 34 patients were excluded due to missed follow-up (n = 21) or CT-triggered PCI (n = 13) to prevent CT-related bias. Finally, 1418 patients were enrolled. This study was approved by the local Institutional Review Board, and all patients provided written informed consent for CAD evaluation using cardiac CCTA.

CCTA Data Acquisition

A 64-multidetector row CT scanner (Brilliance 64, Philips Medical Systems) was used with the following parameters: collimation, 64 x 0.625 mm; rotation time, 420 msec; tube voltage, 100 kV or 120 kV; and tube current, 800 mA. Prior to contrast injection, CACS was performed using a prospective electrocardiographically (ECG) triggered acquisition technique with 120-kV tube voltage, 55-mAs tube current, and 2.5-mm scan thickness. Agatston score was calculated using a threshold of 130 Hounsfield units (HU). Patients who had a heart rate > 70 beats per minute received an intravenous injection of 10 mg of esmolol and 0.6 mg of sublingual nitroglycerin as premedications unless contraindicated. To minimize radiation dose, CCTA technique was selected based on heart rate and body mass index (BMI). Based on the BMI, 120 kV was applied in patients with BMI ≥ 25 kg/m^2, and 100 kV was applied in patients with BMI < 25 kg/m^2. Images were acquired using retrospective ECG gating with tube current modulation or prospective ECG triggering based on the heart rate, with 70 beats per minute as the threshold.

Clinical Risk Factors

Basic demographic data were acquired from the electrical

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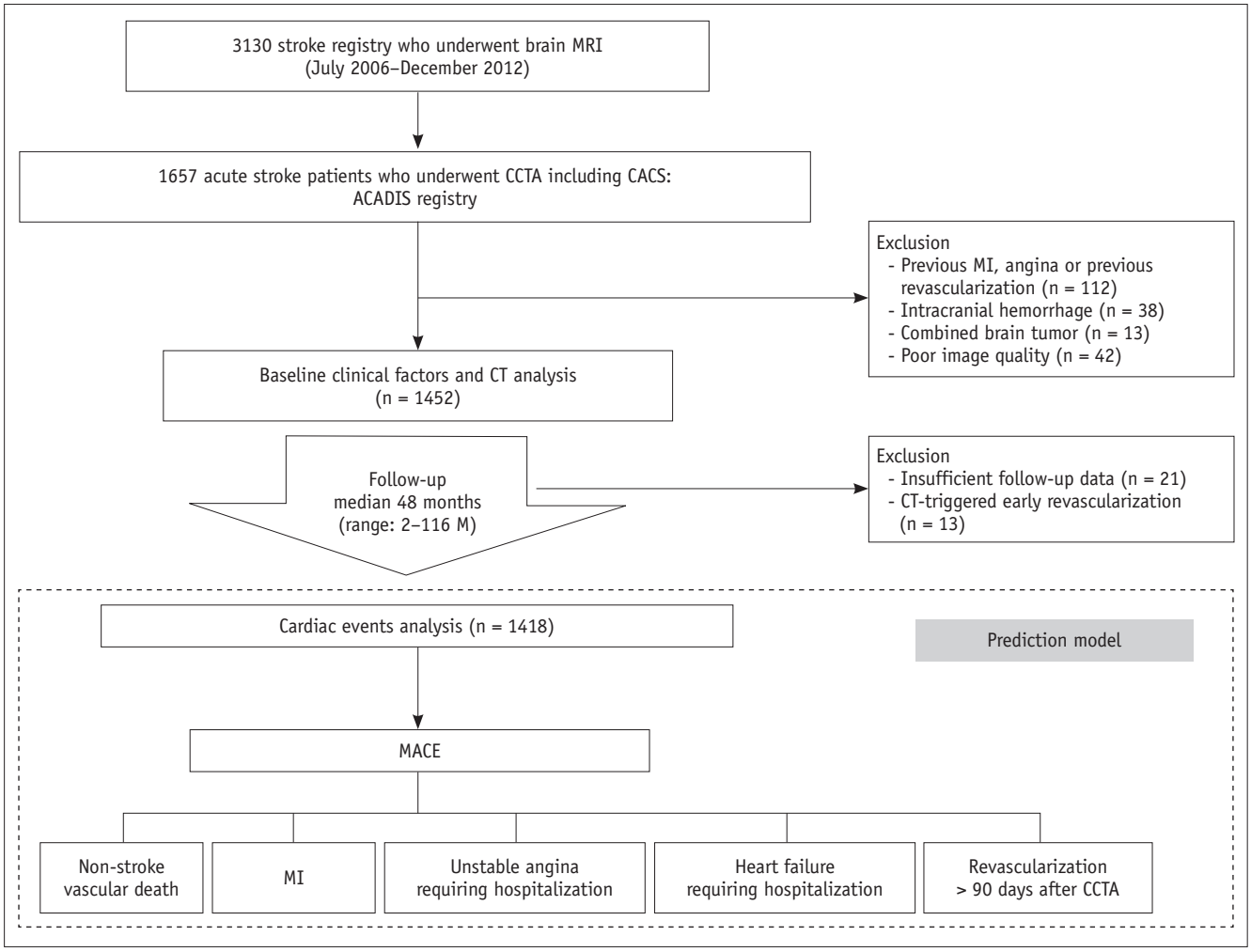

Fig. 1. Flowchart of study design. ACADIS = Assessment of Coronary Artery Disease in Stroke Patients, CACS = coronary artery calcium score, CCTA = coronary computed tomography angiography, MACE = major adverse cardiovascular events, MI = myocardial infarction

medical record. Past medical history of MI, angina, hypertension, stroke, and diabetes mellitus, family history of premature coronary heart disease (CHD) (CHD in male first-degree relatives aged less than 55 years, CHD in female first-degree relatives aged less than 65 years), and smoking were systematically obtained by personal interviews. Body weight, height, and blood pressure were also measured during their visit. Total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, and fasting plasma glucose levels were measured with blood sampling obtained after a 12-hour fast. Framingham risk score (FRS) was calculated to estimate the 10-year risk of CAD (13).

Image Analysis

All scans were evaluated independently by two experienced radiologists (with 12 and 6 years' clinical experience, respectively). After performing an independent evaluation, a consensus interpretation was achieved to establish a final CCTA diagnosis based on the additional reconstruction or review of thin-section data. We analyzed stenosis degree and plaque types according to the 16-segment model based on the AHA classification.

Stenosis degree was evaluated using a 4-point grading scale as follows: none, 1–49%, 50–69%, and ≥ 70%. Each patient was classified into one of the four groups according to the most severe segment. Stenosis more than 50% was defined as obstructive CAD.

Plaque types were classified as follows: 1) calcified plaque, defined as plaque having calcification (≥ 130 HU) in more than 50% of the entire volume; 2) mixed plaque, plaque having calcification in < 50% of the entire volume; 3) non-calcified plaque, plaque having solely soft-tissue density; and 4) high-risk plaque, plaque possessing at least two of the following characteristics: low-density with the

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lowest pixel < 30 HU within each plaque, positive arterial remodeling with remodeling index ≥ 1.1, a napkin-ring sign (characterized by low intraplaque attenuation surrounded by a higher attenuation rim), or spotty calcification < 3 mm in length (14). We hypothesized that the risk of an event would be greatest in high-risk plaque, followed by non-calcified, mixed, and calcified plaques. Patients were stratified into the four plaque types based on highest risk. For example, a patient with both high-risk plaque and non-calcified plaque would be classified in the high-risk plaque group.

Follow-Up and End Point of the Study

During the median follow-up period of 48 months (range, 2–116 months), clinical data were acquired by reviewing patients' medical records or telephone contact with enrolled individuals with trained personnel. The primary end point of this study was non-stroke major adverse cardiovascular events (MACE), which was a composite of the following: 1) non-stroke vascular death; death from a cardiac cause such as acute MI, arrhythmia, or heart failure; and other cardiovascular death, which included any sudden death, including unobserved and unexpected death unless proven otherwise by autopsy (15, 16), 2) MI according to the 4th universal criteria (17), 3) unstable angina (UA) that required hospital stay, 4) revascularization therapy ≥ 90 days after CCTA and referral due to new symptoms or an abnormal functional stress test (late revascularization), and 5) heart failure requiring hospitalization (18). Late revascularization was determined by subsequent diagnostic tests (i.e., single-photon emission computed tomography, stress-induced echocardiography) when subjects were asked regarding the occurrence of new chest pain.

Statistical Analyses

Baseline clinical data and CCTA findings were compared between the group with and without events using a chi-squared test for categorical variables and an independent *t* test for continuous variables.

The Kaplan-Meier survival analysis was used to evaluate the cumulative survival based on stenosis degree and plaque types. Univariate and multivariate Cox proportional hazards regression analysis was used to assess significant associations between baseline FRS, CACS, and CT variables including stenosis degree and plaque types and the risk of MACE.

To determine the incremental prognostic value of CCTA variables compared to the FRS and CACS, we developed six prediction models that assessed the associations between the potential predictors and MACE using a Cox proportional hazards regression as follows: Model A, clinical risk factors (FRS); Model B, FRS + CACS; Model C, FRS + stenosis degree; Model D, FRS + stenosis degree + CACS; Model E, model C + plaque type; and Model F, Model D + plaque type. The Harrell's C-index was determined for each model. Considering that established categories did not exist for the expected rates of MACE in the study population, patient reclassification ability of each model was assessed using the integrated discrimination improvement (IDI) index. The absolute IDI is presented using *p* values.

For all tests, *p* value < 0.05 was considered as statistically significant. All statistical analyses were performed using a statistical package R 2.10.1 (R Foundation for Statistical Computing) and Statistical Analysis System (SAS) version 9.3 (SAS Institute, Inc.).

RESULTS

Study Population and Outcome Results

In 1418 patients, 50 experienced mortality regardless of the cause. Therefore, 16 patients with non-cardiovascular death (6, cancer-related death; 5, respiratory diseases including pneumonia or interstitial lung disease; 4, recurrent stroke-related death; and 1, trauma-related death) were excluded from MACE. Ultimately, MACE was observed in 108 patients (7.6%) (non-stroke vascular death [n = 34], MI [n = 17], UA [n = 12], late revascularization [n = 34], and heart failure requiring hospitalization [n = 11]).

Table 1 summarizes the clinical and CT findings according to the presence or absence of events. Older age, male sex, hypertension, diabetes, family history of premature CHD, and symptomatic carotid artery were more frequently observed in the event group than in the non-event group. The mean FRS and mean CACS were significantly higher in the event group than those in the non-event group (both *p* < 0.001). Among patients with a "zero" CACS (n = 487), 73 patients (15.0%) had non-calcified plaque or high-risk plaque, and ten events (2.1%) (2, non-stroke vascular death; 2, MI; 1, UA; 2, heart failure requiring hospitalization; and 3, revascularization) were observed. Nine of these events were observed in the setting of high-risk plaque (n = 6) and non-calcified plaque (n = 3).

Regarding CCTA analysis, 1002 patients (70.7%) had at least one plaque and 428 patients (30.2%) had obstructive

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CAD. The obstructive CAD was significantly associated with MACE ($p < 0.05$). Regarding plaque analysis, the prevalence of calcified plaque and mixed plaque was not significantly different between the two groups, whereas those of non-calcified plaque and high-risk plaque were significantly higher in the event group than in the non-event group (both

Table 1. Comparison of Baseline Clinical Risk Factors and CT Findings and Major Adverse Cardiovascular Events

Variables	Total (n = 1418)	Event (n = 108)	Non-Event (n = 1310)	*P*
Clinical risk factors				
Age (years)	68.0 ± 12.2	72.4 ± 10.8	67.6 ± 12.2	< 0.001*
Male sex	875 (61.7)	82 (75.9)	793 (60.5)	0.001*
Body mass index (kg/m^2)	23.9 ± 3.4	24.0 ± 3.3	23.3 ± 3.8	0.054
Hypertension	810 (57.1)	73 (67.6)	737 (56.3)	0.033*
Diabetes	345 (24.3)	37 (34.3)	308 (23.5)	0.020*
Hypercholesterolemia	317 (22.4)	26 (24.1)	291 (22.2)	0.720
Current smoker	354 (25.0)	35 (32.4)	319 (24.4)	0.084
Family history of stroke	237 (16.7)	20 (18.5)	217 (16.6)	0.688
Family history of premature CHD	80 (5.6)	15 (13.9)	65 (5.0)	0.001*
Atrial fibrillation	149 (10.5)	17 (15.7)	132 (10.1)	0.075
Symptomatic carotid artery disease	166 (11.7)	21 (19.4)	145 (11.1)	0.019*
Initial NHSS	4.6 ± 5.5	6.7 ± 7.0	4.4 ± 5.4	0.002*
Total cholesterol	127.4 ± 79.0	128.3 ± 79.7	116.9 ± 69.2	0.157
HDL-cholesterol	45.2 ± 10.9	44.6 ± 11.4	45.2 ± 10.9	0.592
LDL-cholesterol	101.2 ± 32.0	101.6 ± 32.1	96.1 ± 29.8	0.096
FRS	14.2 ± 9.1	18.7 ± 7.7	13.8 ± 9.1	< 0.001*
Low	492 (34.7)	12 (11.1)	480 (36.6)	< 0.001*
Intermediate	587 (41.4)	58 (53.7)	529 (40.4)	0.008*
High	339 (23.9)	38 (35.2)	301 (23.0)	0.007*
Medication				
Statin	345 (24.3)	34 (31.5)	311 (23.7)	0.103
ACE-inhibitor or ARB	775 (54.7)	68 (63.0)	707 (54.0)	0.107
β-blocker	192 (13.5)	21 (19.4)	171 (13.1)	0.080
Aspirin	798 (56.3)	71 (65.7)	727 (55.5)	0.055
CACS				
Total score	243.4 ± 546.0	614.6 ± 912.1	212.5 ± 491.6	< 0.001*
0	487 (34.3)	10 (9.3)	477 (36.4)	< 0.001*
0.1–100	421 (29.7)	30 (27.8)	391 (29.8)	0.742
100.1–400	269 (19.0)	25 (23.1)	244 (18.6)	0.253
> 400	241 (17.0)	43 (39.8)	198 (15.1)	< 0.001*
CCTA				
Stenosis degree				
None	416 (29.3)	1 (0.9)	415 (31.7)	< 0.001*
1–49%	574 (40.5)	24 (22.2)	550 (42.0)	< 0.001*
50–69%	227 (16.0)	29 (26.9)	198 (15.1)	0.003*
≥ 70%	201 (14.2)	54 (50.0)	147 (11.2)	< 0.001*
Plaque type				
Calcified plaque	358 (25.2)	18 (16.7)	340 (26.0)	0.805
Mixed plaque	323 (22.8)	30 (27.8)	293 (22.4)	0.232
Non-calcified plaque	237 (16.7)	35 (32.4)	202 (15.4)	< 0.001*
High-risk plaque	84 (5.9)	24 (22.2)	60 (4.6)	< 0.001*

Data are presented as mean ± standard deviation or n (%). *$p < 0.05$. ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blocker, CACS = coronary artery calcium score, CCTA = coronary computed tomography angiography, CHD = coronary heart disease, FRS = Framingham risk score, HDL = high-density lipoprotein, LDL = low density lipoprotein, NIHSS = National Institutes of Health Stroke Scale

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$p < 0.001$). The prevalence of events was highest in patients with high-risk plaque (28.6%, 24/84) and successively decreased for non-calcified plaque (14.8%, 35/237), mixed plaque (9.3%, 30/323), and calcified plaque (5.0%, 18/358). The mean radiation exposures of CCTA at 100 kVp and 120 kVp were 1.7 ± 0.4 mSv and 2.3 ± 0.4 mSv and 6.2 ± 0.7 mSv and 8.2 ± 0.8 mSv by prospective and retrospective ECG gating, respectively.

Clinical and CT Variables associated with Cardiovascular Events

In a univariate Cox regression analysis, FRS, CACS, and CT-related stenosis degree were all positively associated with events (Table 2). The hazard ratios (HRs) of intermediate- and high-risk FRS were 4 and 5 times that of low-risk FRS. After the adjustment of the baseline clinical factors including age, sex, hypertension, diabetes, current smoking, BMI, atrial fibrillation, and family history of premature CHD, the HR of CACS > 400 was the highest (HR = 7.1), followed by the cohort of CACS 100.1–400 (HR = 3.6) and the cohort of CACS 0.1–100 (HR = 3.0) (Table 2). Stenosis degree showed a positive association with event occurrence (all $p <$ 0.05). HRs of stenosis with ≥ 70% and 50–69% were 113.2 and 45.9, respectively (Fig. 2). Regarding plaque types, the risk of events was highest for high-risk plaque (HR = 80.3), followed by non-calcified plaque (HR = 53.8), mixed plaque (HR = 26.2), and calcified plaque (HR = 17.5). The Kaplan-Meier curves showed that cumulative events increased significantly with the extent of stenosis degree and plaque type (all log-rank test, $p < 0.001$) (Fig. 2).

Various Predicting Models and Incremental Prognostic Value of CCTA

Table 3 summarizes the prediction models, which were constructed with covariates of the clinical and CCTA variables, and their comparison. The reclassification ability of the prediction model was significantly better when CACS was added to FRS (Model B: IDI, 0.19; 95% confidence interval [CI], 0.09–0.28; $p < 0.001$) compared with FRS alone (Model A). Adding CCTA-related stenosis degree instead of CACS (Model C) led to better improvement of reclassification ability compared with Model B (IDI, 1.43; 95% CI, 1.24–1.63; $p < 0.001$). However, the addition of CACS into the prediction model (Model D) did not show

Table 2. Univariate and Multivariate Cox Regression Analyses Predicting Coronary Heart Events with FRS, CACS, and CCTA Variables

Variable	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
FRS						
Low	1	(Ref)	< 0.001*			
Intermediate	4.1	2.2–7.7	< 0.001*			
High	4.9	2.5–9.3	< 0.001*			
CACS						
0	1	(Ref)	< 0.001*	1	(Ref)	< 0.001*
0.1–100	3.5	1.7–7.2	0.001*	3.0	1.5–6.3	0.003*
100.1–400	5.0	2.4–10.5	< 0.001*	3.6	1.7–7.7	0.001*
> 400	10.3	5.2–20.6	< 0.001*	7.1	3.4–14.7	< 0.001*
CCTA						
Stenosis degree						
None	1	(Ref)	< 0.001*	1	(Ref)	< 0.001*
1–49%	17.2	2.3–127.4	0.005*	14.9	2.0–110.9	0.008*
50–69%	60.2	8.2–442.0	< 0.001*	45.9	6.2–342.0	< 0.001*
≥ 70%	150.6	20.8–1089.4	< 0.001*	113.2	15.4–834.6	< 0.001*
Plaque type						
No plaque	1	(Ref)	< 0.001*	1	(Ref)	< 0.001*
Calcified plaque	23.3	3.1–174.6	0.002*	17.5	2.3–131.8	0.001*
Mixed plaque	39.1	5.3–286.7	< 0.001*	26.2	3.5–194.2	0.001*
Non-calcified plaque	74.5	10.2–544.1	< 0.001*	53.8	7.3–396.3	< 0.001*
High-risk plaque	125.4	16.9–927.5	< 0.001*	80.3	10.7–601.9	< 0.001*

Multivariate analysis was calculated after adjustment of FRS including baseline clinical risk factors. *$p < 0.05$. CI = confidence interval, HR = hazard ratio, Ref = reference

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better incremental reclassification ability compared with Model C (IDI, 0.01; 95% CI, -0.02–0.04; $p = 0.431$). The incorporation of plaque type into Model C (Model E) showed the highest discrimination index (C-statistics, 0.85) and significantly better reclassification ability compared with Model B (IDI, 1.51; 95% CI, 1.31–1.71; $p < 0.001$) and Model C (IDI, 0.08; 95% CI, 0.01–0.14; $p = 0.023$). However, the addition of CACS into the prediction model (Model F) did not show better reclassification ability for MACE than Model E (IDI, 0.06; 95% CI, -0.01–0.12; $p = 0.067$).

DISCUSSION

The major finding of this study is that the assessment of stenosis degree and plaque type with the use of CCTA provides additional prognostic value over CACS and FRS to

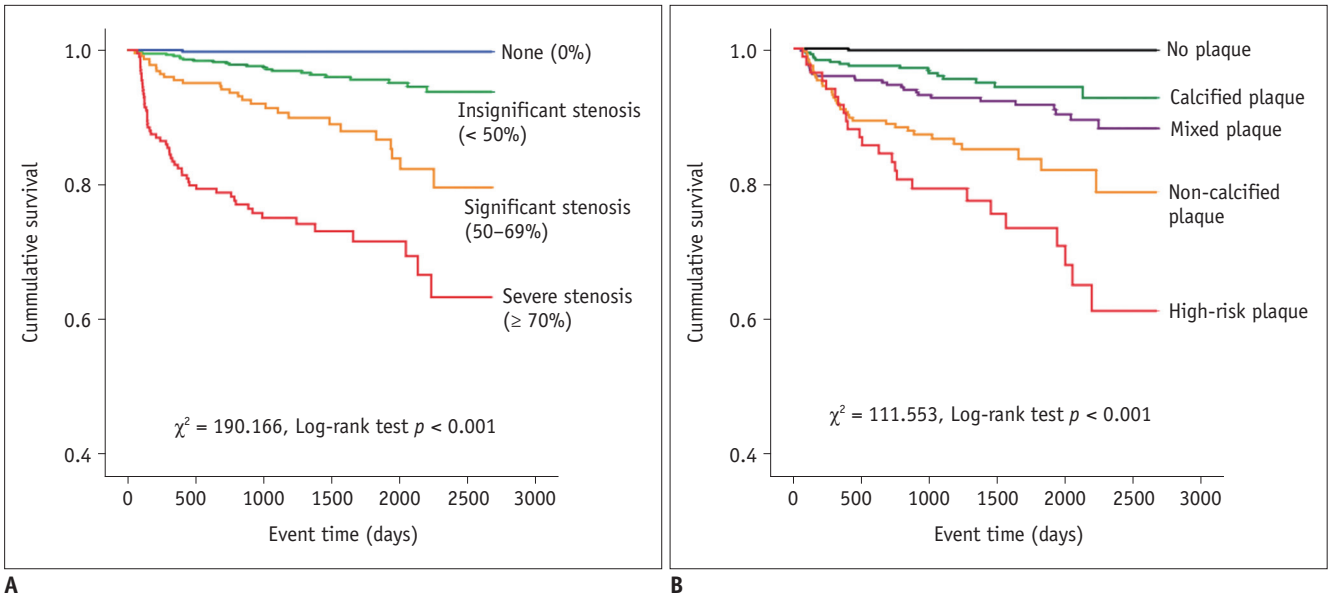

Fig. 2. Kaplan-Meier survival curves of MACE stratified by CCTA features.
A. Segment-based stenosis categories stratified into none, 1–49%, 50–69%, and ≥ 70% luminal stenosis. Of note, half of MACE was observed during first year when stenosis was ≥ 70%. **B.** Plaque type categories stratified into no plaque, calcified plaque, mixed plaque, non-calcified plaque, and high-risk plaque.

Table 3. Effect of Variables on Model Prediction Accuracy and Risk Reclassification

Model	Included Variable	IDI Index (95% CI)	*P*	Model Prediction (C-Index)
Model A	FRS	-	-	0.66
Model B	FRS + CACS	0.19 (0.09–0.28) vs. Model A	< 0.001*	0.72
Model C	FRS + stenosis degree	1.62 (1.42–1.83) vs. Model A	< 0.001*	0.83
		1.43 (1.24–1.63) vs. Model B	< 0.001*	
Model D	FRS + stenosis degree + CACS	1.63 (1.43–1.83) vs. Model A	< 0.001*	0.83
		1.45 (1.26–1.63) vs. Model B	< 0.001*	
		0.01 (-0.02–0.04) vs. Model C	0.431	
Model E	FRS + stenosis degree + plaque type	1.69 (1.50–1.89) vs. Model A	< 0.001*	0.85
		1.51 (1.31–1.71) vs. Model B	< 0.001*	
		0.08 (0.01–0.14) vs. Model C	0.023*	
		0.06 (-0.02–0.14) vs. Model D	0.117	
Model F	FRS + stenosis degree + plaque type + CACS	1.76 (1.56–1.95) vs. Model A	< 0.001*	0.85
		1.57 (1.39–1.75) vs. Model B	< 0.001*	
		0.14 (0.05–0.23) vs. Model C	0.003*	
		0.13 (0.04–0.21) vs. Model D	0.004*	
		0.06 (-0.01–0.12) vs. Model E	0.067	

*$p < 0.05$. IDI = integrated discrimination improvement

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risk stratify stroke patients without prior history of CAD, better.

The prevalence of CAD is substantial in stroke patients, even in the absence of known CHD, because CAD and stroke share similar risk factors. In an autopsy series of fatal stroke, approximately 80% of patients were found to have coronary plaque and 37.5% had obstructive CAD (4). A recent study using invasive coronary angiography has reported an overall CAD prevalence of 61.9% and obstructive CAD prevalence of 25.7% in ischemic stroke patients with no known CHD (6). Studies investigating stroke patients for CAD using CCTA are being reported with the prevalence of obstructive CAD ranging from 18% to 48% (5, 19, 20). These results are similar with the result of our study that the prevalence of obstructive CAD and subclinical atherosclerosis were 30.2% and 70.7%, respectively.

Whether stroke patients should be investigated for asymptomatic CAD remains controversial. Previous studies found that the 10-year risk of non-stroke vascular event is projected to be as close to 20% (16, 21). Therefore, the National Cholesterol Education Program-Adult III recommendation recognizes stroke of carotid origin and carotid atherosclerosis as "CHD risk equivalents" (22). In our study, the 7.6% rate of non-stroke MACE during the median follow-up of 48 months yields a similar annual risk of 2%. This relatively high prevalence suggests the need for the risk stratification to detect and prevent CAD in stroke patients. The FRS is a simple tool used to estimate the 10-year risk for CHD and is considered valuable in stroke patients (23). However, the FRS may inaccurately estimate the risk of MACE because clinical factors underpinning the FRS are variable, are affected by confounding factors, and thus are not easily quantified on a numeric scale (24). CACS predicts CHD independently and provides better prognostic value compared to clinical risk factors (25). However, CACS underestimates the risk of patients with non-calcified plaque because stenosis degree and plaque characteristics are not represented in CACS (26). The prevalence of non-calcified plaque may be higher in high-risk patients than in low-risk patients (26, 27). In our cohort, the prevalence of non-calcified plaque including high-risk plaque were 22.6% in all patients and 15.0% in patients with "zero" CACS. Altogether, 73 patients with plaque showed zero CACS, and 9 developed MACE (12.3%). Therefore, the prevalence of MACE is not negligible even in patients with zero CACS, particularly when non-calcified plaque or high- risk plaque is observed.

Beyond CACS, CCTA-defined severity of CAD has shown improved prognostic value for CHD (8-10). Hur et al. (20) reported that the incremental prognostic value of CCTA-defined stenosis degree in stroke patients, and the incidence rate of cardiac events was 8.2% during a median follow-up period of 409 days. Compared to that study, the present study has the following strengths: it includes a large number of ischemic stroke patients during a relatively long-term observational study (median, 4 years). We believe that intermediate- to long-term follow-up is required for the effective management of CHD because the risk of MI increases continuously in the period beyond 2 years after a stroke (28). Moreover, our study investigates the incremental value of plaque composition in stroke patients. Recently, several studies on plaque features assessed by CCTA associated with cardiac events have been reported, but these studies included only non-stroke patients with suspected CAD (29, 30). Our study shows that plaque component is also important as much as stenosis degree for risk stratification in post-stroke patients.

Furthermore, we suggest that CCTA in the absence of CACS may be a sufficient evaluation, considering that the addition of CACS to the CCTA variables did not improve the reclassification ability in our models and that CACS requires an additional pre-contrast scan. Recently, the introduction of various ultra-low-dose CCTA techniques has reduced radiation dose of CCTA to < 1 mSv (31). In view of the incremental prognostic value of CCTA and comparable radiation dose of CCTA to CACS, our results suggest that CCTA has a potential role for occult CAD screening in asymptomatic stroke patients, although further study assessing its cost-effectiveness, radiation hazard, and requirement of contrast media is needed.

Our study has several limitations. First, it was derived from a single-center study registry performed with a selected group of patients with acute ischemic stroke who underwent CCTA because of vascular risk factors. Furthermore, this study does not reflect on whether CCTA screening improves the outcome of cardiac events. Hence, future large randomized trials should be conducted to evaluate the influence of CCTA screening on treatment and to determine optimal treatment strategies in patients with ischemic stroke. Second, acute ischemic stroke is a heterogeneous disease with different etiologies. Therefore, the prognostic value of CCTA may be different depending on the etiologies of stroke (32). However, these categories were not considered in this study. Third, we considered

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death by unknown cause to be cardiac death because autopsy was not performed in each patient.

In conclusion, our study demonstrated that the assessment of stenosis degree and plaque type using CCTA provides incremental prognostic value over CACS and FRS and is valuable for risk stratification in stroke patients without a prior history of CHD.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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