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Prognostic value of coronary artery disease-reporting and data system (CAD-RADS) score for cardiovascular events in ischemic stroke

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HIGHLIGHTS

- Ischemic stroke patients have a substantial prevalence of coronary artery disease.
- CAD-RADS has prognostic value for future MACEs in stroke patients.
- CAD-RADS provides additional risk-prediction over CACS.

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ABSTRACT

Background and aims: The coronary artery disease-reporting and data system (CAD-RADS) was recently developed to standardize CAD classifications and incorporate clinical management. We aimed to investigate the prognostic value and additional risk stratification benefits of CAD-RADS compared to coronary artery calcium scores (CACS) and CAD extent classifications in ischemic stroke patients without cardiac symptoms.

Methods: From January 2013 to December 2014, 762 ischemic stroke patients with risk factors for CAD and without chest pain underwent coronary computed tomography angiography. CACS, CAD extent classification, and CAD-RADS scores were used to evaluate the computed tomography angiography images. The primary endpoint was major adverse cardiovascular events (MACEs), which were defined as cardiovascular death, nonfatal myocardial infarction, unstable angina requiring hospitalization, and revascularization.

Results: During the mean follow-up period of 3.36 years, 67 MACEs were recorded. Of the 762 patients, 23.5% were classified as CAD-RADS 0, 19.7% as CAD-RADS 1, 18.2% as CAD-RADS 2, 18.6% as CAD-RADS 3, 15.4% as CAD-RADS 4A, 2.2% as CAD-RADS 4B, and 2.4% as CAD-RADS 5. CACS, CAD extent classification, and CAD-RADS scores independently stratified the risk of future MACEs (all $p < 0.05$). The C-statistics revealed that both CAD extent classification and CAD-RADS scores improved risk stratification beyond CACS (C-index: 0.767 *vs.* 0.715; 95% confidence interval [CI] 0.026, 0.105), and 0.781 *vs.* 0.715; 95% CI 0.015, 0.086).

Conclusions: In ischemic stroke patients without chest pain, CAD-RADS had prognostic value for future MACEs and better risk discrimination compared with CACS alone.

1. Introduction

Patients with ischemic stroke have a substantial prevalence of coronary artery disease (CAD). In addition, the presence and severity of CAD affect the risk of future cardiovascular events in patients with ischemic stroke. However, the current American Heart Association (AHA) and American Stroke Association guidelines do not specify how to perform CAD screening in stroke patients [1,2].

The coronary artery calcium score (CACS) is a useful tool for predicting cardiovascular and coronary heart diseases and stroke/transient ischemic attack events [3,4]. Indeed, the 2010 AHA Guidelines recommended the use of CACS for assessing cardiovascular risk in asymptomatic adults [1]. However, risk-benefit assessments of the use of coronary computed tomography (CT) angiography (CCTA) to assess asymptomatic patients are controversial according to the appropriateness criteria of the American College of Radiology [5].

Multiple lines of evidence now support the predictive value of CCTA for adverse cardiac events in high-risk and asymptomatic patients

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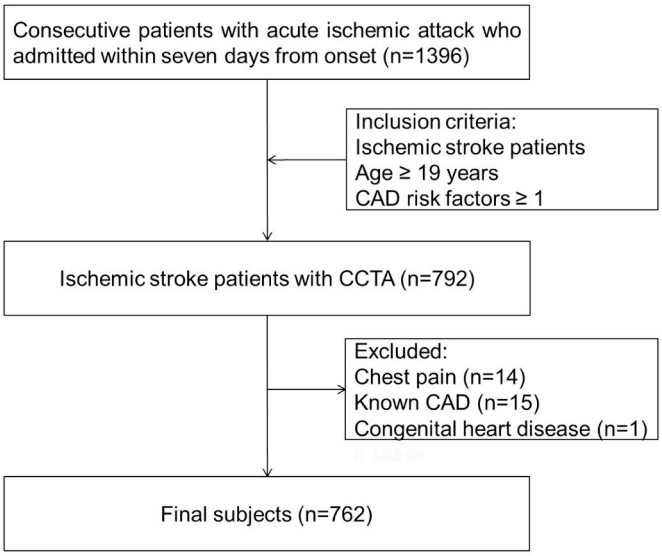
[6–9]. A previous study has reported that CCTA findings of CAD extent and severity can predict the risk of major adverse cardiovascular events (MACEs) in asymptomatic patients with diabetes [8]. According to a follow-up study of over 5 years, CCTA showed prognostic value for MACEs and all-cause mortality in the patients with diabetes without chest symptoms [10,11]. Patients with strokes are presumed to be at high risk of further atherosclerotic coronary events. Several studies have reported the impact of the prognostic value of CCTA for future cardiovascular events in patients with ischemic stroke. In a previous study, the extent of CAD on CCTA showed incremental risk stratification over CACS [12]. Another study suggested that the presence and extent of asymptomatic stenosis on coronary angiography are strong predictors of major vascular events within two years in patients with nonfatal cerebral infarctions [13].

The Coronary Artery Disease-Reporting and Data System (CAD-RADS) is a new standardized method that is used to describe CCTA findings and that can be used to triage patients with stable or acute chest pain [14]. Compared to prior classifications of CAD that were based on the number of affected vessels, the CAD-RADS provides information on stenosis severity as well. One recent study revealed that the CAD-RADS predicted all-cause mortality and myocardial infarctions to a similar degree as the Duke CAD Index and CAD extent classification [15]. Thus, we hypothesized that CAD-RADS scores are useful for predicting cardiovascular events in ischemic stroke patient without known CAD or cardiac symptoms. The purpose of this study was to evaluate the prognostic value of CAD-RADS classifications to predict the risk of MACEs in ischemic stroke patients without cardiac symptoms compared with the CACS and CAD extent classifications.

2. Materials and methods

2.1. Study population

This study, which was a retrospective cohort study, was approved by our institutional review board. From January 2013 to December 2014, 1396 consecutive ischemic stroke patients were admitted for a recent stroke (onset within the previous seven days). Of these patients, 792 with acute ischemic attacks underwent CCTA for the evaluation of concomitant CAD. The inclusion criteria were the following: 1) adult who was 19 years old or older, 2) had an ischemic stroke, and 3) presence of 1 or more CAD risk factors, including hypertension, diabetes mellitus, dyslipidemia, smoking, and/or obesity. Patients were diagnosed with hypertension if they had a systolic blood pressure of 140 mmHg or more, a diastolic blood pressure of 90 mmHg or more, or were taking antihypertensive medications. Patients were diagnosed with diabetes if their fasting plasma glucose level was at least 126 mg/dL or they were currently taking oral hypoglycemic drugs or insulin. Patients had dyslipidemia if their total serum cholesterol was at least 200 mg/dL, their low-density lipoprotein was at least 130 mg/dL, and/or they were taking a lipid lowering agent. Patients who smoked one cigarette in the past month was defined as a current smoker. Patients were considered ex-smokers if they had quit smoking for more than 3 months before the study. Obesity was defined as a body mass index of at least 30 kg/m^2. The following exclusion criteria were used: 1) patients with chest pain or equivalent symptoms related to CAD (n = 14); 2) patients who had known CAD (myocardial infarction, angiographically confirmed CAD, prior coronary angioplasty, stent, or coronary artery bypass graft) (n = 15); and 3) patients with congenital heart disease (n = 1) (Fig. 1). Finally, a total of 762 patients (mean age, 64.1; range, 25–91; 461 men, 301 women) were included in the analysis. The clinical data, including risk factors and stroke history, were reviewed. Patient-level data that support the findings of this study are available from the corresponding author on a reasonable request and after clearance by the ethics committee.



CAD, coronary artery disease; CCTA, coronary computed tomography angiography

Fig. 1. Flow chart of the study.
CAD, coronary artery disease; CCTA, coronary computed tomography angiography.

2.2. CT imaging

CCTA was performed using a second-generation dual-source CT scanner (Somatom Definition Flash; Siemens Healthcare GmbH, Erlangen, Germany) or a 64-row multidetector single-source CT scanner (Discovery CT750 HD; GE Healthcare, Milwaukee, WI, USA) during a single breath hold. To determine the CACS, an unenhanced scan was obtained with prospective electrocardiography (ECG) gating with a tube voltage of 120 kV and tube current of 50 mAs. Next, contrast-enhanced CCTA was performed using prospective ECG gating. An injection of a 70-mL bolus of iopamidol (370 mg of iodine/mL, Iopamiro®; Bracco Imaging S.p.A., Milan, Italy or Pamiray; Dongkook Pharma Co., Ltd., Seoul, Korea) was injected with a 50-mL saline chaser. The parameters for the dual-source CT scanning were as follows: section thickness, 0.6 mm; gantry rotation time, 280 ms; tube voltage, 100–120 kV; tube current, 280–380 mAs; and pitch, 0.2–0.43. The scanning parameters for the single-source CT scanner were as follows: section thickness, 0.625 mm; gantry rotation time, 0.5 s; tube voltage, 140 kV; tube current, 630 mAs; and pitch, 1.375:1.

Prospectively, the ECG-gated scans were triggered at 70% of the R-R interval in patients with heart rates of 75 beats per minute or less. In contrast, for patients with heart rates of over 75 beats per minute, we centered the prospective ECG-triggering at 40% of the R-R interval or used a fixed time delay after a R wave. We estimated the radiation exposure from the dose-length product (DLP). The calculated median radiation dose was 363.5 mGy*cm depending on the scan range and the patient's body weight.

2.3. Data and image analysis

The CACS was quantified using the Agatston methods [16]. We categorized the subjects into 5 groups using CACS: group 0 (0), group 1 (1–10), group 2 (11–100), group 3 (101–400), and group 4 (> 400). All CT images were evaluated by a dedicated clinical workstation (Aquarius; TeraRecon, Foster City, CA, USA) that was unaware of the patients' clinical histories. The presence and degree of stenosis were assessed using a 16-segment coronary artery model modified from the AHA classification [17]. Stenosis was assessed on a per-patient and per-vessel [left main (LM), left anterior descending, left circumflex, and right

Table 1
Baseline characteristics of the study population according to major cardiovascular events.

Variable	All patients (n = 762)	Patients without events (n = 695)	Patients with events (n = 67)	*p* value
Mean age (years)	66 (55, 73)	65 (55, 73)	70 (63.5, 74.5)	0.008
Gender (male)	461(60.4)	417 (60.0)	44 (65.7)	0.364
BMI (kg/m^2)	23.8(22.1, 25.9)	23.9 (22.1, 25.9)	23.3 (21.3, 25.5)	0.168
Diabetes	181(23.7)	157 (22.6)	24 (35.8)	0.015
Hypertension	442(58.0)	398 (57.3)	44 (65.7)	0.183
Current smoking	184(24.1)	172 (24.7)	12 (17.9)	0.116
Dyslipidemia	248(32.5)	223 (32.1)	25 (37.3)	0.383
Old CVA	114(14.9)	102 (14.7)	12 (17.9)	0.478
Total cholesterol	166(139, 194)	166 (141, 194)	159 (123, 189)	0.103
HDL cholesterol	41(35, 49)	41 (35, 49)	39 (32, 44.5)	0.014
LDL cholesterol	103(78, 126)	104 (79, 127)	91 (66, 117)	0.009
Agatston score	32.2(0, 212)	23.5 (0, 175.8)	163.6 (33.5, 465.8)	< 0.001
CACS group				< 0.001
0 (0)	241(36.1)	235 (33.8)	6 (9)	
1 (1–10)	77(10.1)	73 (10.5)	4 (6)	
2 (11–100)	168(22.0)	150 (21.6)	18 (26.9)	
3 (101–400)	155(20.3)	137 (19.7)	18 (26.9)	
4 (> 400)	121(15.8)	100 (14.4)	21 (31.3)	
CAD-RADS				< 0.001
CAD-RADS 0	179(23.5)	172 (24.7)	7 (10.4)	
CAD-RADS 1	150(19.7)	142 (20.4)	8 (11.9)	
CAD-RADS 2	139(18.2)	130 (18.7)	9 (13.4)	
CAD-RADS 3	142(18.6)	130 (18.7)	12 (17.9)	
CAD-RADS 4A	117(15.4)	103 (14.8)	14 (20.9)	
CAD-RADS 4B	17(2.2)	8 (1.2)	9 (13.4)	
CAD-RADS 5	18(2.4)	10 (1.4)	8 (11.9)	
CAD extent				< .0001
No CAD	179(23.5)	172 (24.7)	7 (10.4)	
Minimal CAD	149(19.5)	141 (20.3)	8 (11.9)	
Mild CAD	140(18.3)	131 (18.8)	9 (13.4)	
One-vessel CAD	152(19.9)	135 (19.4)	17 (25.4)	
Two-vessel CAD	75(9.8)	69 (9.9)	6 (9)	
Three-vessel CAD/LM	67(8.7)	47 (6.8)	20 (29.9)	

The values are presented as median value (1st quantile, 3rd quantile) or patient number (%).
BMI, body mass index; CACS, coronary artery calcium scoring; CAD, coronary artery disease; CAD-RADS, Coronary Artery Disease-Reporting and Data System; CVA, cardiovascular accident; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LM; left main.

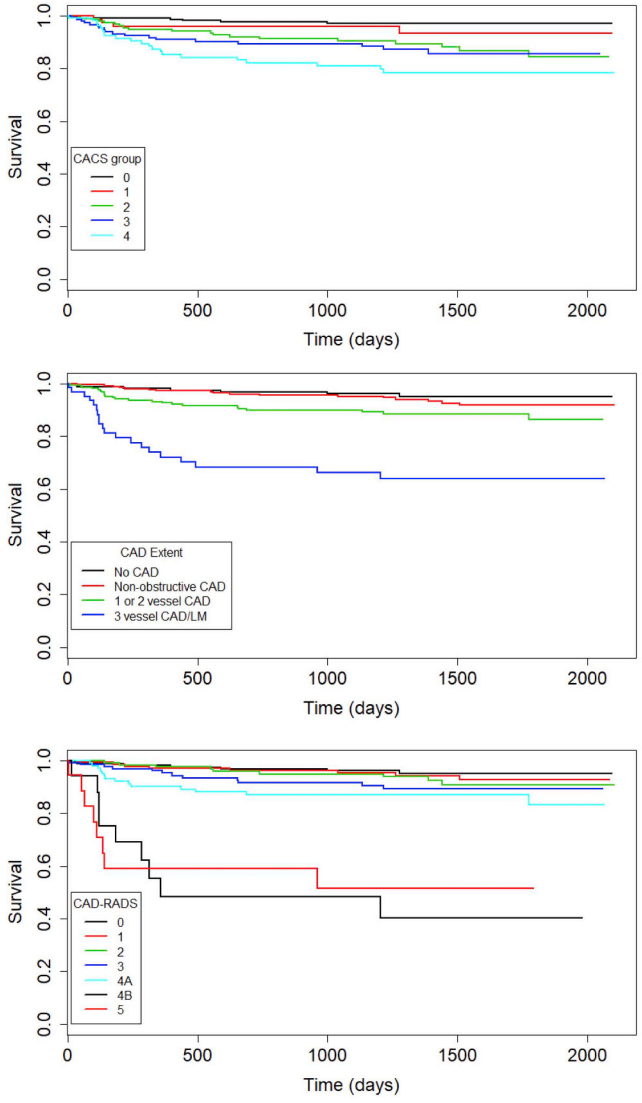
coronary artery] basis. The maximum stenosis severity of CAD was graded as the following: no stenosis, minimal stenosis (< 25% stenosis), mild stenosis (25–49% stenosis), moderate stenosis (50–69% stenosis), or severe stenosis (≥70% stenosis). Moderate and severe stenosis was considered obstructive CAD. The extent of CAD was categorized as the following: one-vessel disease, two-vessel disease, three-vessel disease, or LM disease. We also classified all CCTA data sets according to the CAD-RADS to assess CAD [14]. Based on the stenosis severity, the CAD-RADS categories were as follows: 1) CAD-RADS 0 (0%), 2) CAD-RADS 1 (1–24% stenosis), 3) CAD-RADS 2 (25–49% stenosis), 4) CAD-RADS 3 (50–69% stenosis), 5) CAD-RADS 4A (70–99% stenosis in one or two vessels), 6) CAD-RADS 4B (70–99% stenosis in three vessels or ≥50% stenosis in LM disease), or 7) CAD-RADS 5 (100% stenosis, or total occlusion).

2.4. Follow-up

All patients were regularly followed up at 3 months and 1 year and every year subsequently. The clinical follow-up data were obtained by reviewing the electronic medical records. The primary endpoint was the occurrence of MACEs. A MACE was defined as a cardiovascular death from any cause except for an established noncardiovascular cause, including unobserved sudden death, nonfatal myocardial infarction, and unstable angina requiring hospitalization or revascularization either by percutaneous coronary intervention or coronary artery bypass graft. We excluded elective revascularization within three months after the index CT examination to prevent bias from early treatment. Patient death status was ascertained by querying the National Health Insurance Corporation.

2.5. Statistical analysis

Categorical variables were compared by chi-square or Fisher's exact tests. Continuous variables were compared by Mann-Whitney U tests (nonparametric). Overall survival duration was defined as the interval between the CT exam date and death or the date of the last follow-up visit until December 31, 2017. Cumulative event rates were calculated using Kaplan-Meier survival analysis for CACS and CAD extent and CAD-RADS classification and compared using the log-rank test. Cox regression analyses were used to identify CACS and CCTA predictors of MACEs. From the Cox regression analyses, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Only variables with *p* values less than 0.20 in the univariate analyses were added to the final multivariate models to prevent model over-fitting. For the assessments of the prognostic value of CAD-RADS in the study group, we developed the following models: model 1, clinical risk factors plus CACS grade as five categories (0, 1–10, 11–100, 101–400, > 400); model 2, clinical risk factors plus the CAD-RADS classification; model 3, clinical risk factors plus the CAD extent classification according to the number of affected vessels; model 4, combination of CACS with CAD-RADS; and model 5, combination of CACS with CAD extent classification. The C-index was calculated to predict the prognostic power of each model.



CACS, coronary artery calcium scoring; CAD, coronary artery disease; CAD-RADS, Coronary Artery Disease-Reporting and Data System

Fig. 2. Kaplan-Meier survival curves of MACE as stratified by coronary computed tomography angiography features.
(A) CACS categories stratified into group 0 (CACS 0), 1 (CACS 1–10), 2 (CACS 11–100), 3 (CACS 101–400) and 4 (CACS > 400). (B) CAD categories stratified into extent of CAD as none or non-obstructive CAD, 1 or 2-vessel disease, and 3-vessel disease. (C) CAD categories stratified into CAD-RADS. CACS, coronary artery calcium scoring; CAD, coronary artery disease; CAD-RADS, Coronary Artery Disease-Reporting and Data System.

p values less than 0.05 were considered statistically significant. All analyses were performed with the R statistical package (version 3.4.3, R foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline clinical and CT characteristics

Overall, the study population consisted of 762 ischemic stroke patients without chest pain. Of the 762 patients, 60.5% (461) were men with a mean ± standard deviation age of 64.1 ± 11.8 years. The clinical and CT characteristics of the patient population are summarized according to the clinical events in Table 1. Patients with MACE had older age, higher prevalence of diabetes, lower high-density lipoprotein cholesterol levels and higher Agatston scores ($p < 0.05$). No other baseline clinical characteristics differed significantly between the groups.

The mean ± standard deviation Agatston scores of the patients with and without events were 378.3 ± 533.6 and 166.2 ± 320.3, respectively ($p < 0.001$). Of the 762 patients, 241 (31.6%) had a CACS of zero. The remaining patients were classified into four groups based on the CACS, and the number of patients in each group were as follows: CACS (1–10, n = 77), CACS (11–100, n = 168), CACS (101–400, n = 155), and CACS (> 400, n = 121). Of the 762 patients, 179 (23.5%) had no CAD, 289 (37.9%) had nonobstructive CAD, and 294 (38.6%) had obstructive CAD. Among these 294 patients, 152 (51.7%) had one-vessel disease, 75 (25.5%) had two-vessel disease, and 67 (22.8%) had three-vessel disease or LM disease. When the patients were classified into seven subsets based on CAD-RADS, the number of patients in each group was as follows: 179 (23.5%) were classified as CAD-RADS 0, 150 (19.7%) were classified as CAD-RADS 1, 139 (18.2%) were classified as CAD-RADS 2, 142 (18.6%) were classified as CAD-RADS 3, 117 (15.4%) were classified as CAD-RADS 4A, 17 (2.2%) were classified as CAD-RADS 4B, and 18 (2.4%) were classified as CAD-RADS 5.

Table 2
Univariate Cox regression analysis for major adverse cardiovascular events.

Variable	Univariate analysis			*p* value
	HR	95% CI		
Mean age (years)	1.031	1.008	1.054	0.008
Gender (male)	1.364	0.824	2.259	0.228
BMI (kg/m^2)	0.959	0.887	1.037	0.292
Diabetes	1.915	1.162	3.157	0.011
Hypertension	1.359	0.821	2.251	0.233
Current smoking	0.850	0.44	1.642	0.630
Dyslipidemia	1.324	0.806	2.175	0.268
Old CVA	1.278	0.684	2.386	0.442
Total cholesterol	0.996	0.990	1.002	0.178
HDL cholesterol	0.968	0.944	0.992	0.011
LDL cholesterol	0.992	0.985	0.999	0.026
CACS group				
0 (0)	1 (ref)			
1 (1–10)	2.105	0.594	7.458	0.249
2 (11–100)	4.407	1.749	11.103	0.002
3 (101–400)	5.010	1.988	12.622	0.001
4 (> 400)	8.097	3.268	20.066	< 0.001
CAD-RADS				
CAD-RADS 0	1 (ref)			
CAD-RADS 1	1.358	0.492	3.745	0.554
CAD-RADS 2	1.646	0.613	4.419	0.323
CAD-RADS 3	2.387	0.939	6.064	0.068
CAD-RADS 4A	3.427	1.383	8.493	0.008
CAD-RADS 4B	20.189	7.5	54.347	< .001
CAD-RADS 5	17.236	6.239	47.612	< .001
CAD extent				
No CAD	1 (ref)			
Minimal CAD	1.368	0.496	3.773	0.545
Mild CAD	1.629	0.607	4.375	0.333
One-vessel CAD	3.170	1.314	7.646	0.010
Two-vessel CAD	2.174	0.731	6.471	0.163
Three-vessel CAD/LM	10.532	4.448	24.937	< 0.001

BMI, body mass index; CACS, coronary artery calcium scoring; CAD, coronary artery disease; CAD-RADS, Coronary Artery Disease-Reporting and Data System; CI, confidence interval; CVA, cardiovascular accident; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; LM; left main.

3.2. Clinical and CT variables associated with MACE

During the mean ± standard deviation follow-up period of 3.36 ± 1.71 years, a total of 67 MACEs occurred. The 67 MACEs included 19 cardiovascular death, 6 nonfatal myocardial infarctions, 11

Table 3
Multiple Cox regression analysis for major adverse cardiovascular events.

	Model 1				Model 2				Model 3			
	HR	95% CI		*p* value	HR	95% CI		*p* value	HR	95% CI		*p* value
Mean age (years)	1	0.974	1.027	0.994	1.007	0.983	1.033	0.553	1.012	0.987	1.038	0.347
Diabetes	1.368	0.819	2.285	0.231	1.247	0.734	2.120	0.414	1.329	0.791	2.234	0.283
Current smoking	0.745	0.386	1.436	0.379	0.794	0.404	1.560	0.503	0.897	0.458	1.756	0.751
HDL cholesterol	0.974	0.951	0.998	0.034	0.983	0.958	1.009	0.195	0.978	0.954	1.002	0.076
LDL cholesterol	0.995	0.988	1.002	0.135	0.995	0.987	1.002	0.161	0.995	0.988	1.002	0.164
CACS												
0 (0)	1 (ref)											
1 (1–10)	1.924	0.537	6.891	0.314								
2 (11–100)	4.102	1.574	10.688	0.004								
3 (101–400)	4.480	1.693	11.854	0.003								
4 (> 400)	6.843	2.548	18.379	< .001								
CAD-RADS												
CAD-RADS 0					1 (ref)							
CAD-RADS 1					1.343	0.484	3.729	0.571				
					1.508							
CAD-RADS 2					1.508	0.550	4.131	0.424				
CAD-RADS 3					2.156	0.820	5.669	0.119				
CAD-RADS 4A					2.910	1.136	7.452	0.026				
CAD-RADS 4B					15.418	5.352	44.418	< .001				
CAD-RADS 5					12.896	4.392	37.863	< .001				
CAD extent												
No CAD									1 (ref)			
Non-obstructive CAD									1.379	0.565	3.369	0.480
One- or two-vessel CAD									2.351	0.973	5.678	0.057
Three-vessel CAD/LM									7.766	3.130	19.273	< .001

CACS, coronary artery calcium scoring; CAD, coronary artery disease; CAD-RADS, Coronary Artery Disease-Reporting and Data System; CI, confidence interval; CVA, cardiovascular accident; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; LM; left main.
Model 1, clinical risk factors plus CACS.
Model 2, clinical risk factors plus CAD-RADS classification.
Model 3, clinical risk factors plus CAD extent classification.

events of unstable angina requiring hospitalization, 31 revascularizations after 90 days of the index test during the follow-up period.

Kaplan-Meier survival curves showed that cumulative events increased significantly with the CACS group, CAD extent and CAD-RADS classification (log-rank test, all $p < 0.001$, Fig. 2).

The univariate Cox regression analysis showed that the presence of diabetes was significantly associated with MACE (HR, 1.915; 95% CI, 1.162–3.157; $p = 0.011$). Higher high-density lipoprotein cholesterol levels were negatively associated with MACE (HR, 0.968; 95% CI, 0.944–0.992; $p = 0.011$). Compared to CACS group 0, CACS group 2 (11–100), CACS group 3 (101–400), and CAC group 4 (> 400) were significantly associated with MACE (all $p < 0.05$) (Table 2). In addition, CAD-RADS scores of 4A, 4B, and 5 and the obstructive CAD were significantly associated with MACE (all $p < 0.05$) (Table 2).

In multivariate Cox regressions that were adjusted for gender, age, diabetes mellitus, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol, CACS groups 2–4 were associated with a higher risk of MACEs compared to CACS groups 0 in model 1. In model 2, CAD-RADS scores from 4 to 5 were significantly associated with a higher risk of MACE compared to CAD-RADS score 0. The HRs for MACEs within the CAD-RADS subgroups were 2.910 for CAD-RADS 4A, 15.418 for CAD-RADS 4B, and 12.896 for CAD-RADS 5 (all $p < 0.005$). In model 3, the relative HRs for MACEs increased proportionally with the CAD extents of the nonobstructive CAD group, and one- or two-, and three-vessel CAD groups and LM disease group (Table 3).

The incremental benefit of CCTA was evaluated using C-statistics, as shown in Table 4. The added benefit of CCTA findings, including CAD-RADS (Model 4) and CAD extent (Model 5), was significant compared

Table 4
C-statistics for the prediction of major adverse cardiovascular events.

Model	C-Statistics			Model comparison Difference (95% CI)
	C-index	95% CI		
Model 1: clinical factors + CACS	0.715	0.682	0.790	NA
Model 2: clinical factors + CAD-RADS	0.766	0.728	0.831	0.051 (0.001, 0.093)
Model 3: clinical factors + CAD extent	0.754	0.711	0.813	0.039 (−0.020, 0.071)
Model 4: model 1 + CAD-RADS	0.781	0.745	0.850	0.066 (0.026, 0.105)
Model 5: model 1 + CAD extent	0.767	0.729	0.832	0.052 (0.015, 0.086)

CACS, coronary artery calcium scoring; CAD, coronary artery disease; CAD-RADS, Coronary Artery Disease-Reporting and Data System; CI, confidence interval; NA, not applicable.
Model 1, clinical risk factors plus CACS.
Model 2, clinical risk factors plus CAD-RADS classification.
Model 3, clinical risk factors plus CAD extent classification.
Model 4, combined CACS with CAD-RADS.
Model 5, combined CACS with CAD extent classification.

with the risk factors plus CACS (Model 1) (C-index: 0.781 vs 0.715, Difference 0.066, 95% CI [0.026, 0.105]; and C-index: 0.767 vs 0.715, Difference 0.052, 95% CI [0.015, 0.086]). However, no incremental benefits of the risk predictions with CAD extent alone (Model 3) over CACS (Model 1) for prognostication were observed (C-index: 0.754 vs 0.715, Difference 0.039, 95% CI [-0.020, 0.071], respectively).

4. Discussion

This study was designed to determine if CAD-RADS scores had added risk stratification benefits over CACS and CAD extent classifications in ischemic stroke patients without chest symptoms. The main results of this study were that CAD-RADS scores had additional risk prediction benefits compared to CACS in ischemic stroke patients with CAD risk factors who had no previous CAD or chest symptoms. In addition, the CAD-RADS showed a predictive power that was like that of the CAD extent classification for MACE prediction.

Many ischemic stroke patients have clinical risk factors for CAD. To date, the CACS has been considered a reasonable tool for cardiovascular risk assessments in asymptomatic adults at intermediate risk. However, a major limitation of the CACS is the lack of data for the management of or downstream testing strategies according to CACS [18]. Although it is clear that a zero CACS guarantees a very good prognosis in a long-term follow-up, no consensus exists for the treatment or downstream screening strategies of patients with a CACS above 1 [19]. Compared with CACS, which is a widely used risk prediction tool in asymptomatic individuals, CCTA is able to further detect coronary plaque burdens that are related to location, severity, and characteristics of plaques. The current guidelines do not yet establish whether CAD screening should be performed in stroke patients. Furthermore, screening with CCTA is not recommended in asymptomatic populations [1]. However, several studies have reported the prognostic power of CCTA for cardiovascular events in high-risk patients [8,10,11].

About two-thirds of the patients with nonfatal strokes die from cardiovascular disease [20]. Even in acute stroke patients without a history of symptoms of CAD, CAD detected using CCTA was associated with an increased risk of MACE, which suggested poor long-term outcomes [21]. A study has demonstrated that CCTA findings of CAD also have prognostic value for future MACEs in ischemic stroke patients [12].

Recently, CAD-RADS was developed and based on CAD severity to standardize CAD classifications and incorporate clinical management [14]. Our hypothesis was that CAD-RADS is a more stratified system that subdivides CAD based on its severity compared to the conventional CAD extent classification, therefore, it would be useful for predicting future MACEs. In this study, we developed several models to test this hypothesis and compared the predictive powers of the models. The results of our study showed that CAD-RADS scores derived from CCTA findings were independent predictors of future MACEs like CACS and CAD extent classifications. In addition, when we added CAD-RADS scores (Model 4) or CAD extent (Model 5) to a model with CACS (Model 1), CAD-RADS scores and CAD extents showed improved predictions of future MACEs. Our results suggested that CAD-RADS scores had added prognostic value for predicting future MACEs compared to CACS alone. Our results were in agreement with the results of a recent study that examined long-term prognoses associated with CAD-RADS scores to predict death or myocardial infarctions in patients from the COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter (CONFIRM) registry [15]. In their study, the authors included 5039 patients without known CAD who underwent CCTA, and then classified them according to their CAD-RADS scores. The authors found that CAD-RADS scores had predictive power for death or myocardial infarctions and were not inferior to the Duke index or CAD extent classifications. These results suggested that CAD-RADS scores were useful as predictors of prognosis in patients with suspected CAD. In addition, CAD-RADS scores have the potential to be used as a predictor of prognosis in a high-risk asymptomatic CAD population.

Nevertheless, concerns for unnecessary radiation exposure have limited the use of CCTA for assessing cardiovascular risk in asymptomatic patients. In our study, we only included acute ischemic stroke patients who had clinical risk factors for CAD to minimize the patients who were exposed to radiation. The estimated median dose-length product of the study population was 363.5 mGy*cm. Compared with diagnostic reference levels and the achievable doses of chest CT scans with contrast material in the United States (469 and 353 mGy-cm) [22], the amount of radiation used for CCTA was not concerning. Continued technological advances that require less contrast and ionizing radiation will increase the importance of CCTA in this field in the future.

Despite the important findings and clinical implications for CAD management in ischemic stroke patients without chest pain in the present study, the study had several limitations. First, this study was conducted at a single center with a modest sample size. In addition, the retrospective nature of this study may be associated with selection bias. Second, the dose recommended by the current guidelines is not allowed in the CT screening for CAD in asymptomatic populations. Therefore, we were unable to perform CCTA in all of the ischemic stroke patients. Instead, we performed CCTA on high-risk ischemic patients with CAD risk factors. However, even the patients with CAD risk factors could not participate if they refused to undergo CT. Nevertheless, the results of our present study demonstrated an added prognostic value of CAD-RADS scores in predicting future MACEs in ischemic stroke patients without chest symptoms. However, additional large-scale, multicenter studies are needed to determine how to screen for high-risk ischemic stroke patients who need CAD CT screening in the future and whether CT screening is beneficial in terms of therapeutic decisions for improving patient outcome. Third, the primary endpoint of our study was MACEs because of the low rate of hard events in asymptomatic individuals. In our study, MACEs occurred in 11.3% (67 cases) of the patients, while hard events occurred in only 3.2% (25 cases). Another important limitation to consider is radiation exposure, which should be considered when deciding whether to use CCTA to screen for significant CAD.

In conclusion, CAD-RADS scores had prognostic value for future MACEs in ischemic stroke patients who had risk factors for CAD without chest pain. In addition, CAD-RADS scores derived by CCTA provided additional risk discrimination over CACS.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

The following authors contributed to the preparation of the manuscript as follows:

Kyungsun Nam: Study design, manuscript editing, interpretation of data, literature search.

Jin Hur: Study design and concept, manuscript editing, interpretation of data, literature search.

Kyunghwa Han: Study design, Statistical analysis, manuscript editing, literature search.

Dong Jin Im: interpretation of data, literature search, manuscript editing.

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