Coronary Artery Calcium Score Improves the Prediction of Occult Coronary Artery Stenosis in Ischemic Stroke Patients

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Background—Coronary heart disease is a significant cause of morbidity and mortality in stroke patients. The coronary artery calcium score (CACS) has emerged as a robust and noninvasive predictor of coronary events. We assessed the predictive ability of CACS to identify stroke patients with severe (≥50%) occult coronary artery stenosis in a stroke/transient ischemic attack population, in addition to the PRECORIS score, based on Framingham Risk Score and presence of cervicocephalic artery stenosis, which was derived and validated for that purpose.

Methods and Results—We enrolled consecutive patients aged 45 to 75 years referred to our stroke unit with noncardioembolic ischemic stroke or transient ischemic attack, and no prior history of coronary disease. The presence of coronary stenosis was assessed with 64-section computed tomography coronary angiography, and all patients had a detailed etiological work-up. CACS was determined from computed tomography measurement using the Agatson score. The predictive value of CACS was assessed by logistic regression and reclassification method. Among 300 patients included in the study, 274 had computed tomography coronary angiography. Fifty patients (18%) had at least 1 coronary artery stenosis ≥50%. In multivariable analysis, after adjustment for the PRECORIS score, CACS was strongly associated with the presence of occult coronary artery stenosis (odds ratio=14.8 [1.8–120.3] for CACS [1–100] and 70.9 [8.9–562.0] for CACS >100). When CACS was added to the standard model, model fit was improved (*P*<0.001), Net Reclassification Improvement was 28.2% (*P*<0.001), and Integrated Discrimination Index was 18.2% (*P*<0.001).

Conclusions—In stroke/transient ischemic attack patients, CACS improves the prediction of occult coronary stenosis beyond classical risk factors. (***J Am Heart Assoc***. 2016;5:e003770 doi: 10.1161/JAHA.116.003770)

Key Words: coronary artery calcium • coronary artery disease • coronary computed tomography angiography • predictors

Coronary heart disease is usually considered a significant cause of morbidity and mortality in patients who have had a stroke or a transient ischemic attack (TIA).[1] Although recurrent strokes occur more commonly than cardiac events over the long term after stroke, cardiac events still account for a greater proportion of mortality.[2] The identification of severe occult coronary artery stenosis may help to improve prevention of cardiac events in stroke/TIA patients. The prevalence of severe (≥50% reduction in diameter) occult

coronary artery stenosis has been reported to be significantly high, between 18% and 38% in patients with stroke or TIA and no previous history of coronary heart disease and predictable.[3–8]

We previously showed in a population with stroke/TIA that in addition to traditional risk factors, the severity of cervicocephalic artery stenosis was strongly associated with severe occult coronary stenosis. Using these simple predictive factors, we derived and validated the 5-point PRECORIS score that was found to have a good predictive ability to identify stroke patients with severe (≥50%) occult coronary artery stenosis in a stroke/TIA population. However, despite its good predictive ability, 50% of patients with a high PRECORIS score (≥4) have no severe occult coronary stenosis.[7] Thus, identification of such patients at high risk of occult coronary artery stenosis still needs to be improved. In large prospective studies, coronary artery calcium score (CACS), a fast and simple computed tomography (CT) measurement of the amount of calcium in the walls of coronary arteries, was shown to be associated with the risk of future cardiovascular events.[9–11] We considered the use of CACS in patients with ischemic stroke or TIA to refine identification of patients with

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occult stenosis who might benefit from a CT coronary angiography but also and most importantly to better identify those without severe coronary artery stenosis who do not justify exposure to unnecessary radiation and contrast load. Therefore, the objective of our study was to assess the additional value of CACS to predict the presence of severe occult coronary artery stenosis in stroke/TIA patients.

Methods

The study was conducted prospectively in consecutive patients aged 45 to 75 years with noncardioembolic ischemic stroke/TIA, and no prior history of coronary artery disease admitted to our stroke unit as previously reported.[3] Patients were referred to our stroke unit by emergency departments from hospitals located in the south part of Paris (France) and emergency ambulance services in the same area. The study was approved by the local ethics committee, and all patients provided informed consent. Among the 368 eligible patients, 58 refused to participate, and 10 could not be enrolled because of participation in another study (Figure 1).[3] Of the 300 included patients, 21 patients eventually refused to undergo CT coronary angiography, 3 could not have CT coronary angiography because of a subsequent medical event, and 2 patients had CT coronary angiography that could not be interpreted. The remaining 274 patients were included in the analysis. All patients had a detailed standardized diagnostic and causal work-up.[3] The presence of coronary artery stenosis was assessed with 64-section CT coronary angiography. All CT coronary angiographies were reviewed and analyzed by a single experienced radiologist (J.L.S.) blinded to clinical data as previously reported.[3] Patients were categorized as having normal coronary arteries (no plaque), mild to moderate coronary artery stenosis (≥1 lesion <50% and no stenosis ≥50%), and severe coronary artery stenosis (≥1 stenosis ≥50%).
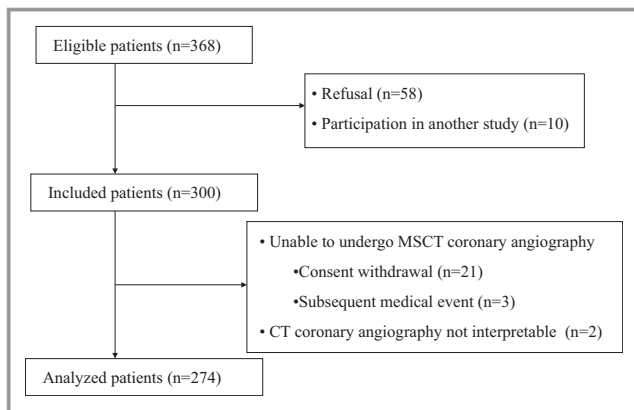

Figure 1. Flow chart. MSCT indicates multislice computed tomography. Reproduced with permission from *Circulation.*[3]

CACS was assessed by 64-section CT, with ECG gating in a prospective mode. The scan parameters were 120 kV, 60 mA. A total of 64 overlapping 3-mm slices per rotation were acquired. CACS was determined from CT measurement of the amount of calcium in the walls of the coronary arteries using the Agatson score on a commercially available external workstation and CAC scoring software. A threshold of 130 Hounsfield units was used during the procedure.

Statistical Analysis

The 5-point PRECORIS score was calculated for each patient from Framingham Risk Score (≥20%=3, 10–19%=1, <10%=0) and the presence of cervicocephalic artery stenosis (≥50%=2, <50%=1, None=0) as previously described.[7] CACS was dichotomized into 3 strata (0, 1–100, >100) as previously proposed.[12] In order to assess the predictive value of CACS with regard to the presence of occult severe coronary artery stenosis, we built 2 separate logistic models. The first model included the Framingham Risk Score and the presence of cervicocephalic artery stenosis (PRECORIS score). In the second model, CACS was added to model 1. The comparison of predictive values of the models was assessed by using the likelihood ratio test and by comparing the C statistics (area under the curve [AUC]). Finally, we computed the net reclassification improvement and the integrated discrimination improvement. We used predefined cutoff values for the reclassification analysis (0–25%, 25–50%, and 50–100%). We also assessed AUC with regard to the presence of left main trunk or 3-vessel disease.

Results

Mean (SD) age was 62.5 years (8.0 years), and 192 patients (70%) were male. Two hundred thirty-five patients (86%) had ischemic stroke, and 39 (14%) had TIA. One hundred forty-one patients (52%) had no coronary artery stenosis, 83 (30%) at least 1 stenosis <50%, and 50 (18%) at least 1 stenosis ≥50 of whom 11 had 3-vessel disease and/or left main trunk disease.

Median (interquartile range) CACS was 24 (0–146). One hundred three (37.6%) patients had a CACS=0, 85 (31.0%) between 1 and 100, and 86 (31.4%) a CACS >100. Patients with ≥50% occult coronary artery stenosis had a higher CACS compared with patients without ≥50% occult stenosis, whether CACS was assessed as a continuous variable (212.5 versus 11.5; *P*<0.001) or dichotomized into 3 strata (*P* for trend <0.001). Among the 103 patients with CACS=0, only 1 patient had a ≥50% occult coronary artery stenosis (negative predictive value of 0.99). In the multivariable model including the Framingham Risk Score and the presence of cervicocephalic artery stenosis (PRECORIS score) (Table 1) as well as CACS (Model 2, Table 2), CACS was strongly

Table 1. Model 1 Predicting the Presence of ≥50% Occult Coronary Artery Stenosis With PRECORIS Score Alone (Logistic Regression With Categorical Predictors)

	n (%)*	Adjusted OR (95% CI)	P Value
PRECORIS score			
0	45 (16.4)	1	
1	75 (27.4)	3.1 (0.4–27.8)	0.303
2	63 (23.0)	9.3 (1.2–75.0)	0.036
3	39 (14.2)	15.1 (1.8–125.0)	0.011
4	26 (9.5)	27.5 (3.3–232.3)	0.002
5	26 (9.5)	44.0 (5.3–368.8)	<0.001

OR indicates odds ratio.
*Percentage of the total population (n=274) in each category.

Figure 2. ROC curve plots for Model 1 including FRS and presence of cervicocephalic artery stenosis (PRECORIS score), CACS and Model 2 (CACS added to Model 1). CACS indicates coronary artery calcium score; FRS, Framingham risk score; ROC, receiver operating characteristic.

associated with the presence of ≥50% occult coronary artery stenosis. In patients with CACS between 1 and 100, odds ratio was 14.8 ([1.8–120.3], *P*=0.011) and in those with CACS >100, odds ratio was 70.9 ([8.9–562.0], *P*<0.001), compared with those with CACS=0 (Table 2). The model fit was improved when CACS was added (Model 2) to the standard model (Model 1), as shown by reduction in log likelihood (likelihood ratio=48.6, *P*<0.001). The predictive value assessed by AUC was improved (Model 1: AUC=0.77 [0.70–0.84], Model 2: AUC=0.88 [0.83–0.92], *P*<0.001) and was also better than that of CACS alone (AUC=0.81 [0.76–0.87], *P*=0.012) (Figure 2). The addition of CACS to Model 1 resulted in an upward reclassification of 58% patients with ≥50% occult coronary artery stenosis, as well as a downward reclassification of 20% of patients without ≥50% occult coronary artery stenosis, yielding an overall net reclassification improvement of 28.2% (*P*=0.001). The addition of CACS also led to a significant integrated discrimination improvement of 18.2% (*P*=0.001).

With regard to identification of patients with left main trunk or 3-vessel disease, the predictive value of the model, as assessed by AUC, was also improved by adding CACS in the model (AUC=0.88 with CACS versus 0.83 without, *P*=0.010).

Discussion

This study shows that in patients with ischemic stroke/TIA and no prior history of coronary artery disease, measurement of CACS improves the prediction of ≥50% occult coronary artery stenosis beyond classical risk factors and the presence of cervicocephalic stenosis.

In particular, our study points out that the use of CACS in these stroke patients allows not only a better identification of patients with severe occult coronary artery stenosis who could benefit from CT coronary angiography but also a better identification of those without severe coronary artery stenosis who do not justify exposure to unnecessary radiation and contrast load.

Our findings are consistent with the recent Euro–Calcific Coronary Artery Disease (CCAD) study, which showed in a cohort of patients with angina symptoms at intermediate risk for coronary heart disease that CACS was the most powerful predictor of ≥50% coronary artery stenosis compared to conventional risk factors. In this study, combination of CACS and conventional risk factors significantly improved the prediction of ≥50% coronary artery stenosis irrespective of

Table 2. Model 2 Predicting the Presence of ≥50% Occult Coronary Artery Stenosis With PRECORIS Score and CACS Dichotomized Into 3 Strata (Logistic Regression With Categorical Predictors)

	n (%)*	Adjusted OR (95% CI)	P Value
PRECORIS score			
0	45 (16.4)	1	
1	75 (27.4)	1.4 (0.1–13.5)	0.774
2	63 (23.0)	2.9 (0.3–25.9)	0.334
3	39 (14.2)	3.9 (0.4–36.2)	0.227
4	26 (9.5)	12.6 (1.3–120.8)	0.028
5	26 (9.5)	20.1 (2.1–189.8)	0.010
CACS			
0	103 (37.6)	1	
1 to 100	86 (31.4)	14.8 (1.8–120.3)	0.011
>100	85 (31.0)	70.9 (8.9–562.0)	<0.001

CACS indicates coronary artery calcium score; OR, odds ratio.
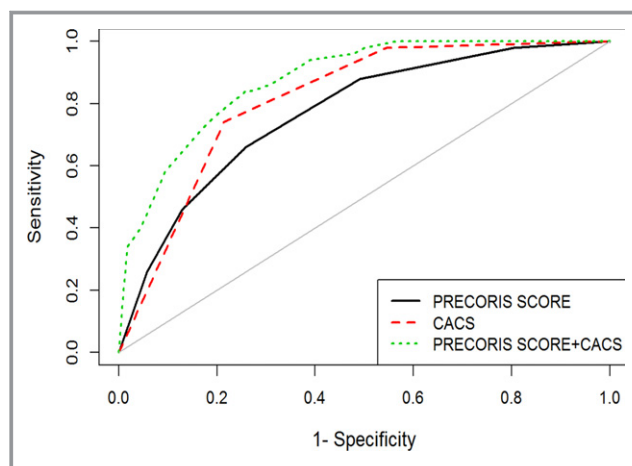*Percentage of the total population (n=274) in each category.

the method used for diagnosis of stenosis (conventional angiography or CT coronary angiography).[13]

Moreover, CACS is also a strong predictor of cardiovascular events.[10] CACS was shown to be the best novel risk factor of a first cardiovascular event in patients at intermediate risk of cardiovascular events based on the Framingham Risk Score.[10] In addition, CACS has also been shown to have a good negative predictive value for cardiovascular events. In a population of 3146 adults aged between 45 and 84 with CACS=0, only 4% had a cardiovascular event during a mean follow-up of 10.3 years.[14]

It is now well accepted that the risk of subsequent cardiac events in stroke patient is high enough to designate stroke a coronary heart disease risk equivalent according to definitions in current guidelines.[1] However, the benefit of screening stroke patients for occult coronary artery stenosis remains to be specifically assessed through a randomized clinical trial comparing standard secondary prevention with a more aggressive approach that would include screening for occult coronary artery stenosis and specific treatments such as coronary revascularization, in particular for patients with left main trunk or 3-vessel disease. Our study provides useful data for conception of such a trial. Pending the results from a randomized trial, the decision to screen for occult coronary stenosis in stroke patients should be individualized, and be based on predictive factors and the feasibility of specific coronary artery disease preventive strategies. In that respect, the use of CACS measurement, which is already recommended to assess cardiovascular risk in asymptomatic adults at intermediate risk according to American College of Cardiology Foundation/American Heart Association Practice Guideline of 2010,[15] appears to be of particular interest in stroke patients.

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Disclosures

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