Impact of the Coronary Artery Calcium Score on Mid- to Long-Term Cardiovascular Mortality and Morbidity Measured With Coronary Computed Tomography Angiography

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Background: Although the coronary artery calcium score (CACS) is a prognostic measurement in asymptomatic individuals, it is measured in symptomatic patients using coronary computed tomography angiography (CCTA). We aimed to examine the predictive value of the CACS for mid- to long-term cardiovascular mortality and morbidity in patients who underwent CCTA.

Methods and Results: We studied 736 patients with suspected coronary artery disease (CAD) who underwent CCTA. During a median follow-up period of 6.5 years, there were 39 primary outcomes (composite of cardiovascular disease death, non-fatal myocardial infarction, and non-fatal stroke). The estimated 10-year cumulative rates of the primary outcome were significantly increased across CACS classes (3.9%, 9.2%, 11.8%, and 18.2% in CACS of 0, 1–99, 100–399, and ≥400, respectively, P<0.001). These rates of cardiovascular disease death and stroke were also significantly increased across CACS classes. Multivariate Cox proportional hazard analysis showed that a CACS ≥100 was independently predictive for the primary outcome (hazard ratio [HR] 2.82, 95% confidence interval [CI] 1.40–6.00, P=0.003), as well as the presence of ≥50% stenosis on CCTA (HR 2.27, 95% CI 1.13–4.46, P=0.022).

Conclusions: An elevated CACS with the use of CCTA is an independent predictor of mid- to long-term cardiovascular mortality and morbidity in patients suspected of having CAD.

Key Words: Cardiovascular morbidity; Coronary artery calcium score; Coronary computed tomography angiography; Mortality

The coronary artery calcium score (CACS) is associated with overall atherosclerotic plaque burden and the development of subsequent cardiovascular events and all-cause death. Contrast-enhanced coronary computed tomography angiography (CCTA) provides a high degree of accuracy in identifying obstructive coronary artery disease (CAD), and has high diagnostic accuracy and prognostic values. A previous report demonstrated that CCTA added incremental discriminatory power over CACS for identifying symptomatic subjects at risk of death or myocardial infarction (MI). The CACS as measured using CCTA examinations provides information of diagnostic performance to detect obstructive lesions in CCTA. A high CACS (>400 or >600) has decreased diagnostic accuracy. We also reported that a high CACS had clinically useful predictive value for discriminating high-risk Japanese patients for coronary morbidities. However, the usefulness of the CACS as a predictive indicator in the use of CCTA has not been fully determined.

The CACS is also associated with indicators of systemic atherosclerosis, such as carotid intima-media thickness, increased pulse wave velocity, and the incidence of cerebrovascular disease. Therefore, this study aimed to examine whether the CACS is an indicator for cardiovascular mortality and morbidity, including coronary and cerebral artery diseases, or for all-cause death during mid- to long-term follow-up. We investigated patients who were suspected of having CAD and who underwent CCTA.

Study Population
We recruited 897 consecutive patients with suspected CAD who underwent CACS measurement and CCTA between 2004 and 2010, after excluding known CAD (history of MI, prior coronary revascularization, or status of acute coronary syndrome). Patients were excluded from the analysis for the following reasons: inadequate image quality.
ity (n=19), lack of blood biochemical information or information on clinical risk factors (n=13), history of stroke (hemorrhage or infarcts) requiring hospitalization (n=30), follow-up for less than 1 year (n=9), and elective coronary revascularization performed within 1 year after CCTA (n=100).

Finally, 736 patients were enrolled with long-term follow-up. The subjects constituted patients with chest symptom (n=346), asymptomatic patients with abnormal findings on electrocardiography, echocardiography, or scintigraphy (n=255), those with aortic or peripheral artery disease (n=18), and those with accumulated coronary risk factors (n=117). The study was approved by the hospital’s ethics committee.

Coronary Risk Factors and Blood Examinations
Hypertension was defined as blood pressure ≥140/90 mmHg or use of antihypertensive drugs. Hypercholesterolemia was characterized by fasting serum low-density-lipoprotein cholesterol levels ≥140 mg/dL on direct measurement or the patient was using lipid-lowering agents. Diabetes mellitus was diagnosed as hemoglobin A1c level ≥6.5% and/or use of hypoglycemic agents. Current smokers were considered as subjects who smoked regularly at the time of CCTA. Serum C-reactive protein (CRP) levels were measured by nephelometry using a latex particle-enhanced immunoassay (Dade Behring Inc., Tokyo, Japan). The estimated glomerular filtration rate was calculated according to the Modification of Diet in Renal Disease study equation.

We obtained information on management of risk factors at 3 months after CCTA, including administration of statins, hypertensive drugs, antiplatelet drugs, and treatment for diabetes.

CCTA and the CACS
We used a 16-slice computed tomography (CT) scanner (LightSpeed Ultrafast16; GE Healthcare, Waukesha, WI, USA) before 2005 (n=30) and a 64-slice CT scanner (LightSpeed VCT; GE Healthcare) after 2006 (n=706) for coronary evaluation. Before contrast-enhanced CCTA, 48 contiguous images that were 2.5-mm thick were obtained and the CACS was calculated by Agatston method with dedicated software (SmartScore, version 3.5; GE Healthcare) as previously described. A retrospective ECG-gated CCTA protocol with dose modulation was performed. Details of the CCTA protocol and acquisition have been described previously. Briefly, patients with a heart rate ≥60 beats/min received an oral β-blocker (metoprolol 40 mg) 60 min before the examination. Sublingual nitroglycerin was administered to all patients just before scanning. A body weight-adjusted volume (0.6–0.7 mL/kg) of iodine contrast (Iopamiron 370; Bayer Healthcare, Berlin, Germany) was administered via an antecubital vein. Reconstructed CT image data were transferred to an offline workstation (Advantage Workstation Ver. 4.2; GE Healthcare) for post-processing and subsequent image analysis.

Evaluation of CCTA Results
All images were evaluated using curved multplanar reconstructions by 2 blinded readers in accordance with the Society of Cardiovascular Computed Tomography. All coronary segments >2 mm in diameter were evaluated. The severity of obstructive coronary lesions was visually graded as 0%, 1–49%, and ≥50%. If ≥50% lumen stenosis was not ruled out because of a beam-hardening effect caused by calcification, it was defined as a non-assessable result. Patients with ≥50% stenosis or a non-assessable result because of calcification were considered to have obstructive CAD.

Follow-up and Outcomes
Follow-up information was obtained from medical records, telephone interviews with patients or their families, or
from the patients’ primary care physicians. All end points were determined by consensus of 2 blinded reviewers. The primary outcome was a composite of cardiovascular disease death, non-fatal MI, and non-fatal stroke. Cardiac death was defined as death caused by acute MI, ventricular arrhythmias, or cardiogenic shock. Patients with acute MI had 2 of the 3 following criteria: chest pain lasting >30 min, increased serum creatine kinase levels with an MB fraction, and new pathological Q waves of 0.04 s in duration. Cerebrovascular disease events were defined as fatal or non-fatal strokes requiring hospitalization because of hemorrhage, infarct, or transient ischemic attack. The secondary endpoints were all-cause death and coronary events, including cardiac death, non-fatal MI, and late coronary revascularization beyond 1 year after the index CCTA, which were based on chest symptoms and/or positive myocardial ischemic findings in stress tests.

Statistical Analysis
Values with a skewed distribution, such as the CACS, are expressed as the median (interquartile range). Other measurements are expressed as mean±SD. Coronary events were compared among the following 4 groups stratified by the CACS score: 0, 1–99, 100–399, and ≥400, according to previous studies. Cumulative event rates at 10 years were estimated by Kaplan-Meier curves and compared using the log-rank test. Cox proportional hazard regression models were used to determine predictors of future events. Unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. Variables with P<0.10 in univariate models were entered into a multivariate model. Using receiver-operating characteristic analysis, c-statistics were determined to evaluate the prognostic discriminatory capacity. Incremental improvements were compared after the addition of the 4 CACS grades or the presence of ≥50% stenosis on CCTA over basal clinical risks (age, sex, hypertension, diabetes, hypercholesterolemia, and current smoking status). All statistical analyses were performed using JMP for Windows version 13.1 (SAS Institute, Inc., Cary, NC, USA). A P value of <0.05 was considered statistically significant.

Results
Baseline Clinical Characteristics
Table 1 shows the baseline clinical characteristics overall. The mean age was 65.0±11.0 years and 61.5% of the patients were men. The median CACS was 20 (interquartile range, 0–162). The rates of the CACS classes of 0, 1–99, 100–399, and ≥400 were 36.1%, 31.0%, 22.0%, and 10.9%, respectively. The severity of stenosis rates of 0%, 1–49%, and ≥50% on CCTA were 46.2%, 39.5%, and 14.3%, respectively. For management of coronary risk factors, administration rates of statins, hypoglycemic drugs, anti-hypertensive drugs, and antiplatelet drugs after the index CCTA were 35.6%, 18.5%, 64.0%, and 21.7%, respectively.

Long-Term Cardiovascular Outcomes and Survival
During a median follow-up period of 6.5 years (range, 1–12 years), 68 (9.2%) patients died of cardiovascular
CACS and Long-Term Prognosis by CCTA

Multivariate Analysis for Primary Outcomes, Coronary Events, and All-Cause Death

All of the patients were divided into high and low groups according to a CACS of 100 for the primary outcome, cardiovascular death, and coronary events. For all-cause death, the CACS categories were divided into ≥1 and 0 because the mortality rates were increased in groups with CACS ≥1. For the primary outcome, multivariate Cox proportional hazard analysis showed that a CACS ≥100 was independently predictive for the primary outcome (HR 2.82, 95% CI 1.40–6.00, P=0.003), as well as the presence of ≥50% stenosis on CCTA (HR 2.27, 95% CI 1.13–4.46, P=0.022) (Table 3).

For cardiovascular death, Cox proportional hazard analysis showed that a CACS ≥100 remained as an independent predictor for the primary outcome (HR 5.47, 95% CI 1.68–24.51, P=0.004), but the presence of ≥50% stenosis on CCTA was not an independent predictor (P=0.253).

Figure 2. Kaplan-Meier curves of freedom from the primary outcome (composite of cardiovascular disease death, non-fatal MI, and non-fatal stroke) stratified by CACS grade (A) and stenotic severity on CCTA (0%, 1–49%, and ≥50%) (B). Kaplan-Meier curves of freedom from coronary events (composite of cardiac death, non-fatal MI, and coronary revascularization more than 1 year after CCTA) stratified by CACS grade (C) and by CCTA (D). Abbreviations as in Figure 1.
≥1.4 mg/L, 4th quartile range; HR 2.35, 95% CI 1.43–3.82, P<0.001), and decreased estimated glomerular filtration rate (<60 mL/min/1.73 m²; HR 1.84, 95% CI 1.09–3.04, P=0.022). However, the presence of ≥50% stenosis on CCTA was not an independent predictor (P=0.378) (Table S3).

Incremental Value of the CACS and CCTA for Predicting the Primary Outcome

For the primary outcome, the CACS significantly improved the c-statistics beyond the clinical risk (from 0.665 to 0.749, P=0.023), but obstruction (≥50% stenosis) on CCTA did not significantly improve the c-statistics beyond the clinical risk (P=0.378) (Table S3).

**Table 3. Predictors of the Primary Outcome**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate HR (95% CI)</th>
<th>P value</th>
<th>Multivariate HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥66 years (median)</td>
<td>5.30 (2.15–14.70)</td>
<td>&lt;0.001</td>
<td>3.68 (1.56–10.84)</td>
<td>0.002</td>
</tr>
<tr>
<td>Male</td>
<td>1.19 (0.63–2.36)</td>
<td>0.463</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Chest symptoms, yes</td>
<td>0.99 (0.52–1.88)</td>
<td>0.980</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>2.39 (1.11–5.91)</td>
<td>0.024</td>
<td>1.55 (0.72–3.89)</td>
<td>0.283</td>
</tr>
<tr>
<td>Statin treatment</td>
<td>1.09 (0.55–2.06)</td>
<td>0.807</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hypoglycemic drugs</td>
<td>1.41 (0.65–2.82)</td>
<td>0.363</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Smoking</td>
<td>1.29 (0.65–2.47)</td>
<td>0.450</td>
<td>–</td>
<td>–</td>
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<tr>
<td>CRP ≥1.4 mg/L*</td>
<td>1.44 (0.70–2.81)</td>
<td>0.309</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>eGFR &lt;60 (mL/min/1.73 m²)</td>
<td>0.94 (0.40–1.94)</td>
<td>0.866</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CACS ≥100</td>
<td>4.45 (2.29–9.13)</td>
<td>&lt;0.001</td>
<td>2.82 (1.40–6.00)</td>
<td>0.003</td>
</tr>
<tr>
<td>≥50% stenosis on CCTA</td>
<td>4.09 (2.09–7.77)</td>
<td>0.001</td>
<td>2.27 (1.13–4.46)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

*4th quartile range. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

For coronary events, multivariate Cox proportional hazard analysis showed that a CACS ≥100 (HR 2.16, 95% CI 1.08–4.43, P=0.030) and the presence of ≥50% stenosis on CCTA (HR 4.55, 95% CI 2.30–9.00, P<0.001) were independently predictive for the primary outcome (Table S2).

For all-cause death, multivariate Cox proportional hazard analysis showed that a CACS ≥1 remained as an independent predictor for the primary outcome (HR 2.67, 95% CI 1.32–6.18, P=0.005), as well as older age (≥66 years, median; HR 2.55, 95% CI 1.36–5.15, P=0.003), male sex (HR 1.91, 95% CI 1.12–3.40, P=0.017), elevated CRP level (≥1.4 mg/L, 4th quartile range; HR 2.35, 95% CI 1.43–3.82, P<0.001), and decreased estimated glomerular filtration rate (<60 mL/min/1.73 m²; HR 1.84, 95% CI 1.09–3.04, P=0.022). However, the presence of ≥50% stenosis on CCTA was not an independent predictor (P=0.378) (Table S3).

Incremental Value of the CACS and CCTA for Predicting the Primary Outcome

For the primary outcome, the CACS significantly improved the c-statistics beyond the clinical risk (from 0.665 to 0.749, P=0.023), but obstruction (≥50% stenosis) on CCTA did not significantly improve the c-statistics beyond the clinical risk (P=0.378) (Table S3).
we showed that an elevated CACS was an independent predictor of the composite of cardiovascular mortality and morbidity in patients suspected of having CAD who underwent CCTA. Therefore, assessment of the CACS provides clinically useful information for cardiovascular risk stratification, and not only for coronary events, in the current era of using CCTA.

CACS and CCTA

The CACS is widely used. Multiple population-based studies have shown that it provides powerful prognostic information across different age categories, sex, and ethnicities. Additionally, measuring the CACS is technically convenient, and requires only low-dose additional radiation exposure. The CACS is obtained from non-contrast scans with high reproducibility, which is useful for comparing serial changes.

Several previous studies have shown that obstruction verified by CCTA is independently predictive for all-cause mortality and coronary morbidity. However, the usefulness of the CACS in patients suspected of having CAD as assessed by CCTA is not well understood. A previous study showed that obstruction verified by CCTA added incremental prognostic value over the CACS in symptomatic individuals. In contrast, another previous study showed the long-term prognostic value of the CACS and stress myocardial perfusion imaging in patients with suspected CAD, but not with CCTA. Therefore, our data supported the notion that measuring the CACS still has
clinical usefulness.

CACS and Non-Coronary Diseases

Our study showed that an elevated CACS was an independent predictor of cardiovascular disease mortality and morbidity. The CACS is an important prognostic factor, particularly for cardiovascular disease mortality and stroke. The presence of obstruction on CCTA was independently and incrementally predictive for coronary events, particularly coronary revascularization. An increase in the CACS may be associated with an increase in plaque volume in systemic vascular atherosclerosis. Previous reports showed a positive association between the CACS and carotid intima-media thickness or increased pulse wave velocity. Previous studies have also shown that atherosclerosis in the coronal bed suggests the presence of atherosclerosis in the cerebral circulation and that the CACS improves prediction over known risk factors for cerebrovascular events.

In the subgroup analysis by age in our study, a higher CACS was significantly associated with the composite of cardiovascular mortality and morbidity in older patients (≥66 years). However, a significant association between a high CACS and coronary events was observed in the younger and older subgroups. Most of the coronary events appeared to be coronary revascularization, but the major events of cardiovascular mortality and morbidity were low in the younger subgroup.

For all-cause death, we found that even a small increase in the CACS (≥1) remained as an independent predictor, and several clinical factors, including age, male sex, inflammation, and decreased renal function, also contributed to prediction. Recent studies have shown that the CACS and exercise capacity are important determinants for all-cause death. Aronson et al showed that all-cause death progressively increased with increasing CACs and decreasing exercise. von Bonsdorff et al identified a positive synergistic interaction between the extent of the CACS and gait speed in non-cardiovascular disease death. However, the diagnostic ability of CCTA has a limitation in patients with a high CACS.

Study Limitations

First, this study was retrospectively conducted and the sample size was small. The incidence of fatal or non-fatal MI was low. A large number of studies in a multicenter setting are required to determine the clinical implications of our findings. Significant differences in either the CACS or CCTA stenosis grade were not found. A previous Japanese epidemiological study showed a lower incidence of coronary death compared with Western populations. Second, recent intensive management of coronary risk factors and/or early coronary revascularization appeared to prevent incident MI during the mid- to long-term follow-up. Our study did not evaluate precise management for coronary risk factors or serum lipid levels throughout the follow-up period. We could only evaluate medications at the time point after the index CCTA. Third, possible mechanisms of the association between an increased CACS and increased mortality and morbidity from non-coronary causes were not evaluated. We hypothesize that systemic or vascular inflammation or renal insufficiency is associated with coronary artery calcification. We found that elevated serum CRP level remained as an independent predictor of all-cause death. Finally, we found a positive association between a high CACS and incident stroke, but we could not evaluate detailed causes of stroke.

Conclusions

Our results from a median of 6.5 years of follow-up showed that an elevated CACS was an independent predictor of the mid- to long-term composite of cardiovascular mortality and morbidity when using CCTA examinations. Additionally, a small increase in the CACS elevated the all-cause mortality rate. The CACS is still clinically useful for risk stratification for mid- to long-term cardiovascular prognosis and may provide important information on therapeutic strategies in combination with CCTA examinations.

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Conflicts of Interest

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