Review

Clinical Implications of the Coronary Artery Calcium Score in Japanese Patients

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Coronary artery calcification (CAC) is a well-established surrogate marker of the total burden of coronary atherosclerosis. The CAC score, as measured on coronary computed tomography (CT), is associated with the prevalence of coronary artery disease (CAD) as well as cardiovascular morbidity and mortality. The CAC score is used to reclassify coronary risks in asymptomatic individuals with intermediate risks. However, there are few clinical data regarding the usefulness of the CAC score for identifying high-risk Japanese patients. In this review article, we describe our previous studies of the prognostic value of the CAC score in patients with proven or suspected CAD. In addition, we reanalyzed our previous data for 723 patients with suspected CAD and found both all-cause and cardiovascular disease mortality to be significantly higher among the patients with a CAC score of ≥ 100 than among those with a CAC score of < 100 . Several studies from Japan have also shown that the CAC score is associated with the prevalence of obstructive CAD, as demonstrated on invasive coronary angiography or stress myocardial perfusion imaging. Furthermore, the CAC score provides useful information for performing coronary CT angiography, as asymptomatic patients without CAC are expected to have favorable outcomes. In contrast, the diagnostic accuracy is decreased in patients with a high CAC score (> 400 or 600). In conclusion, the CAC score may have useful clinical applications in symptomatic and asymptomatic Japanese individuals. However, further studies are required to evaluate the prognostic value of this parameter for predicting cardiovascular morbidity and mortality in population-based analyses of asymptomatic Japanese subjects.

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Key words: Coronary artery calcium score, Mortality, Morbidity

Introduction

Coronary artery calcification (CAC) is a well-established surrogate marker of the total burden of coronary atherosclerosis. A recent histopathological study showed that coronary artery calcium is present in proportion (approximately 20%) to the overall extent of atherosclerosis¹⁾. In contrast, the CAC score is not related to the severity of stenosis²⁾. In 1990,

Agatston and colleagues³⁾ reported that the CAC score, as determined on electron-beam computed tomography (CT), is an indicator of obstructive coronary artery disease (CAD) on invasive coronary angiography. Furthermore, a higher CAC score is associated with an increased risk of CAD-related events, and the addition of the CAC score to traditional risk factors improves risk stratification in intermediate-risk asymptomatic individuals⁴⁻¹⁶⁾, namely in the range of 1.0% to 2.0%, as stratified according to the Framingham Risk Score in Western countries.

Measurement of the CAC Score

CAC is observed on non-contrast cardiac CT scans with low levels of radiation exposure (1-2 mSv).

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Vessel	Volume (mm ³)	Plaque number	Agatston score	Ca mass score	Mean CT-number(HU)	Max CT-number(HU)
LM	0.00	0	0	0	-	-
LAD	240.64	4	319.1	957.2	593.1	2117
LCX	3.93	2	1.3	3.9	188.6	308
RCA	87.76	5	114.2	342.5	443.4	1714
total	332.33	11	434.6	1303.6	548.8	2117

Fig. 1. Measurement of the CAC score.

A 72-year-old man was referred for atypical chest symptoms and underwent a coronary CT examination (320-slice CT, Aquilion One; Toshiba, Ohtahara, Japan). Non-contrast CT images were analyzed to calculate the CAC score using a dedicated software program (Virtual Place; Aze, Tokyo, Japan) on an offline computer.

Several parameters for quantifying the degree of CAC employ measurements of the area and density of all foci of calcification, including the Agatston score³⁾, volumetric score¹⁷⁾ and calcium mass score¹⁸⁾. The Agatston score, the most commonly used tool, is calculated based on the sum of the area and density weightings across the coronary arteries. This score is defined according to regions of interest for vessels and slices, with a threshold option of pixels >130 Hounsfield units (HU) used to measure the area and peak density of plaques. Depending on the peak density of the plaque, an area of at least 1 mm² is multiplied by one of the following cofactors: a factor of 1 for 130-199 HU, a factor of 2 for 200-299 HU, a factor of 3 for 300-399 HU and a factor of 4 for densities greater than 400 HU. The total CAC score is calculated as the sum of the individual lesion scores for all coronary arteries (**Fig. 1**).

Risk Stratification

The CAC score is thought to be associated with the prevalence of CAD as well as cardiovascular morbidity and mortality, especially in asymptomatic intermediate-risk individuals⁶⁻¹⁶⁾. Guideline and consensus documents have shown that the presence and extent of coronary calcium depend on age, sex, ethnicity and standard cardiac risk factors^{4, 5)}. The Multi-Ethnic Study of Atherosclerosis (MESA) was initiated in July 2000 to investigate the prevalence, correlates and progression of subclinical cardiovascular disease in a population-based sample of 6,500 men and women 45-84 years of age¹⁹⁾. The cohort consisted of approximately 38% White, 28% African-American, 23% Hispanic and 11% Asian (of Chinese descent) subjects. In that study, the baseline measurements included the CAC score determined on CT in addition to other clinical markers²⁰⁾.

In the MESA study, the prevalence of coronary

Table 1. CAC score and morbidity and mortality in Japanese patients

Studies	Subjects	numbers	Endpoints	Risk
Itani <i>et al.</i> ²³⁾	Asymptomatic individual	6120	Cardiac mortality	HR 2.66 (95% CI 0.76-9.37) CAC present vs. absent
Abbott <i>et al.</i> ²⁴⁾	Honolulu Heart Program	224	All-cause death	Risk of death 13.2 and 48.6 per 1000 person-years in CAC scores 10-100 and >1000, respectively.
Yamamoto <i>et al.</i> ²⁶⁾	Suspected or proven CAD undergoing coronary angiography	317	Cardiac mortality	HR 2.98 (95% CI 1.15-9.40) CAC score >1000 vs. 0-100
Kunita <i>et al.</i> ²⁷⁾	Suspected CAD	723	Cardiac mortality	HR 17.1 (95%CI 2.9-324.0) CAC score $\geq$ 100 vs. < 100 group

CAC, coronary artery calcium; CAD, coronary artery disease; HR, hazard ratio.

calcification (Agatston score >0) among Whites, African-Americans, Hispanics and Asians was 70.4%, 52.1%, 56.5% and 59.2%, respectively, in men ($p < 0.001$) and 44.6%, 36.5%, 34.9% and 41.9%, respectively, ($p < 0.001$) in women. After adjusting for age, education, lipids, body mass index, smoking, diabetes mellitus, hypertension, treatment for hypercholesterolemia, sex and the scanning center, the relative risk of having coronary calcification was 0.78 (95% confidence interval [CI] 0.74-0.82) in Blacks, 0.85 (95% CI 0.79-0.91) in Hispanics and 0.92 (95% CI 0.85-0.99) in Chinese individuals compared with Whites⁶⁾. The adjusted hazard ratio (HR) (1.25; 95% CI 0.95-1.63, $p = 0.11$) for major coronary events was not significant for the Asian participants, who exhibited only six coronary events¹⁷⁾. In addition, Pacific Asians (particularly Chinese Americans, Japanese Americans and immigrants from Southeast Asia) have lower morbidity and mortality rates than do Whites^{21, 22)}.

CAC Score and Cardiovascular Morbidity and Mortality in the Japanese

The association between all-cause mortality and cardiovascular morbidity with the CAC score has not yet been fully determined in the Japanese population (Table 1). Using a conventional single-slice helical CT scanner, Itani *et al.*²³⁾ investigated CAC and cardiovascular mortality among a total of 6,120 subjects invited to participate in a chest CT examination and follow-up visit. Consequently, 14 of the participants died of cardiac disease and 64 died of other diseases. CAC was detected in 10 patients with death due to cardiac disease and 31 of those with death due to non-cardiac disease. Furthermore, a study of the Honolulu Heart Program compared the prevalence of CAC as well as risk factors and morbidity between Japanese and Japa-

nese Americans²⁴⁾. In that study, the three-year all-cause mortality rate increased in association with an increase in the CAC score (CAC score <10, 13.2 per 1,000 person-years; and CAC score >1,000, 48.6 per 1,000 person-years)²⁵⁾.

We previously studied 317 suspected or proven CAD patients who underwent both invasive coronary angiography and CAC measurements using electron-beam CT or 16-multidetector CT between 1994 and 2005²⁶⁾. During a mean of 6.0 years (range, 1-10 years) of follow-up, the HR for cardiac mortality in the patients with a CAC score of >1,000 was 2.98 (95% CI 1.15-9.40, $p < 0.001$) compared with those with a CAC score of 0-100.

In another of our previous studies, 723 suspected CAD patients who underwent coronary CT for calcium scoring using 16- or 64-slice CT between 2004 and 2009 were followed up²⁷⁾. That study investigated whether a high epicardial adipose tissue volume and/or CAC score are independently and incrementally predictive of future coronary events in patients without proven CAD.

We subsequently undertook a further analysis of the data of Kunita and colleagues in order to reevaluate the all-cause and cardiovascular mortality rates in their study²⁷⁾. Consequently, there were 31 all-cause deaths, including 10 due to cardiovascular disease. In addition, the Kaplan-Meier survival curves showed that all-cause mortality and mortality from cardiovascular disease were significantly higher among the patients with a CAC score of ≥ 100 than among those with a CAC score of <100 ($p < 0.0001$ and $p < 0.001$, respectively). Following adjustment for age, sex, hypertension, hypercholesterolemia, diabetes and cigarette smoking, the all-cause mortality of the patients with a CAC score of ≥ 100 was 4.86-fold (95% CI 2.24-11.4, $p < 0.001$) higher than that for the patients

Fig. 2. Kaplan-Meier survival curves free from all-cause mortality (upper) and cardiovascular mortality (lower) according to CAC scores of ≥ 100 and < 100 .

with a CAC score of < 100 . Moreover, the cardiovascular disease mortality in the CAC score ≥ 100 group was 17.1-fold (95% CI 2.9-324.0, $p < 0.001$) higher than that noted in the CAC score < 100 group (**Fig. 2**).

Furthermore, we evaluated all coronary events, including cardiac death, non-fatal myocardial infarction and late coronary revascularization > 3 months after CT. Such coronary events were observed in 37 patients, with five cardiac deaths, six cases of non-fatal myocardial infarction and 26 cases of late coronary revascularization, during a mean follow-up period of four years. The annual event rate increased across the CAC categories (0.3%, 1.0%, 2.5% and 4.0% in the patients with a CAC score of 0, 1-99, 100-399 and ≥ 400 , respectively, $p < 0.001$)²⁷. Notably, the Kaplan-Meier survival curves showed that future coronary events are almost completely excluded in patients with a CAC score of 0, whereas the estimated event-free rate at six years in patients with a CAC score of ≥ 400 is approximately 75%. Meanwhile, the adjusted HRs indicate 4.74-fold (95% CI 1.80-14.3, $p < 0.001$) and 8.75-fold (95% CI 2.74-31.5, $p < 0.001$) increases in risk among patients with a CAC score of 100-399 and ≥ 400 , respectively, compared with those with a CAC

score of 0 (**Fig. 3**).

CAC scoring is recommended to estimate the risk of coronary events in asymptomatic individuals, particularly those with intermediate risks^{4, 5}. Such scoring is also considered to have prognostic value in symptomatic patients. According to a meta-analysis conducted by Sawar *et al.*²⁸, the event rate is significantly lower in patients with a CAC score of 0 than in those with a positive CAC score (1.8% vs 9.0%). Furthermore, results for Japanese populations, as shown in this review, have shown that the CAC score has a high diagnostic or prognostic value for predicting CAD in intermediate- to high-risk patients. This finding may be influenced by the fact that the incidence of morbidity or mortality of CAD is lower in the Japanese than in Western populations. In the Hisayama studies, the incidence and mortality of CAD in Japanese patients were reported to be approximately 30%^{29, 30}. Taken together, these results suggest that longitudinal studies are needed to evaluate the association between the CAC score and rate of long-term coronary events in both asymptomatic and symptomatic Japanese individuals.

Fig. 3. Kaplan-Meier event-free survival curves stratified by four CAC classes.

CI, confidence interval; HR, hazard ratio. The HRs were adjusted for age, sex, hypertension, hypercholesterolemia, diabetes mellitus and smoking.

Association between the CAC Score and Prevalence of CAD

The CAC score has high diagnostic value for detecting obstructive CAD or inducible ischemia associated with CAD in Japanese patients with suspected or proven CAD (**Table 2**). Our previous study showed that the prevalence of obstructive CAD in subjects with stenosis of $>50\%$ in diameter on coronary angiography increases across increasing CAC categories (CAC score=0, 5%; 1-99, 36%; 100-399, 78%; 400-999, 80%; and $\geq 1,000$, 94%)²⁶. In addition, a previous study using a hybrid single photon emission computed tomography (SPECT)/CT camera showed that the extent of myocardial perfusion defects tends to worsen as the degree of coronary calcification increases³¹. Furthermore, in a study of 92 patients with 819 segments who underwent invasive CT angiography, the accuracy of a CAC score of 0 was excellent (93%) and a higher number of stenosed vessels was found to be associated with a higher CAC score³².

CAC Score and Coronary CTA

Based on a sub-analysis of an international multicenter study, the pretest probability of CAD and coronary calcium score should be considered before using CT angiography to exclude obstructive CAD. CT angiography is less effective for this purpose in

patients with a calcium score ≥ 600 and those with a high pretest probability of obstructive CAD³³. The prevalence of obstructive CAD also increases in association with increases in the CAC score in Japanese patients. In general, a CAC score of ≥ 400 is recommended for performing invasive coronary angiography, while a CAC score of 1-399 is recommended for performing CT angiography or myocardial perfusion imaging. Asymptomatic patients without CAC are considered to be low risk, and coronary CT angiography is not recommended in this group³⁴.

It has also been reported that the CAC score positively correlates with the number of coronary vessels affected by CAD, even in patients with proven CAD³⁵, while an elevated CAC score is associated with higher morbidity and mortality rates³⁶. Nevertheless, the general use of CAC scoring may be limited, as the high prevalence of CAC results in low specificity for obstructive CAD in symptomatic patients³⁷. Furthermore, while the use of CAC scoring to guide decision-making regarding coronary CT is well established, the application of the CAC score for this purpose with respect to contrast-enhanced examinations has not been validated. As previously discussed, CAC scoring is thought to be best suited for estimating the probability of obstructive CAD in patients referred for CT angiography.

Table 2. CAC score and the prevalence of obstructive CAD or inducible ischemia associated with CAD

Studies	CT scanner	number	Definition of CAD	Percentage across CAC classes				
				0	1-99	100-399	400-999	≥ 1000
Yamamoto <i>et al.</i> ²⁶⁾	EBCT or 16-MDCT	317	>50% stenosis on angiography	5%	36%	78%	80%	94%
Kunita <i>et al.</i> ²⁷⁾	16- or 64-MDCT	723	Early coronary revascularization*	0.5%	4.2%	13%		25%
Matsuo <i>et al.</i> ³¹⁾	Hybrid-CT	101	Perfusion defect on SPECT	13%	–	–		48.5%

*coronary revascularization within three months from coronary CT. EBCT, electron beam computed tomography; MDCT, multidetector computed tomography; SPECT, single photon emission computed tomography. Other abbreviations are as in Table 1.

Limitations and Perspectives Beyond the CAC Score

The precise mechanisms underpinning the association between the presence of calcified plaque and the onset of cardiac events are not fully understood. Although the amount of CAC correlates with the overall magnitude of the atherosclerotic plaque burden in the whole heart, histological studies have shown that CAC deposition is not necessarily observed at sites of stenosis and does not correlate with the severity of stenosis²⁾. Sangiorgi and colleagues concluded that the lack of correlation between lumen narrowing and the degree of mural calcification is likely explained by the effects of remodeling and reported that coronary calcium quantification is an excellent means of assessing the presence of atherosclerotic plaque at individual artery sites. Moreover, while calcified plaque is considered to be a stable component of atherosclerosis, a high proportion of lipids within sites of plaque and/or the detection of spotty-type calcification are thought to be associated with a high risk of plaque rupture^{38, 39)}. Beyond the concept of the CAC score, other characteristics of cardiac calcium deposits, such as density and size, are thought to influence the incidence of coronary events. A recent study reported that, despite the positive and independent association between the CAC volume, at any level, and cardiovascular events, the CAC density is also inversely and significantly associated with the risk of such events⁴⁰⁾.

Non-Electrocardiography (ECG)-Triggered CAC Scoring

Recently, non-ECG triggered calcium scoring was attempted⁴¹⁾. Aging and cigarette smoking are major risk factors for cardiovascular disease as well as lung or esophageal cancer. The clinical importance of non-ECG triggered calcium scoring lies in its potential for screening for cardiovascular disease in patients who undergo thoracic CT scans for suspected pulmonary

disease or other thoracic organ disease, without the need for additional radiation exposure. In addition, previous cohort studies by Itani *et al.*²³⁾ and Ikeda *et al.*⁴²⁾ evaluated whether the presence of CAC is associated with cardiac mortality or cerebral atherosclerosis using conventional spiral CT. Although this method does not replace dedicated ECG-triggered CT scanning, calcium scoring in the setting of non-triggered CT has the potential to be used to evaluate evidence for diagnostic and prognostic purposes⁴¹⁾.

Conclusion

The CAC score is associated with the prevalence of obstructive CAD as well as cardiovascular morbidity and mortality in Japanese patients with suspected CAD. We previously reported that, in Japanese patients, a very high CAC score (>1,000) represents a substantially and significantly elevated risk of cardiovascular mortality, whereas a CAC score of 0 excludes possible future cardiovascular events, even in those with proven CAD. The CAC score also provides useful information for guiding decisions as to whether to perform coronary CT angiography in patients with suspected and proven CAD. CAC scoring is recommended in asymptomatic subjects with an intermediate risk (considered to be in the range of 1.0% to 2.0%) in the United States and Europe as well as to discriminate or reclassify a high risk of CAD and reduce future coronary events associated with increased medical costs. However, there are few data for asymptomatic subjects in population-based multicenter studies. Hence, a large nationwide survey in Japan is required.

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Conflicts of Interest

None.

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