Impact of Combined Assessment of Coronary Artery Calcium Score, Carotid Artery Plaque Score, and Brachial-Ankle Pulse Wave Velocity for Early Coronary Revascularization in Patients With Suspected Coronary Artery Disease

Ryu Iino, MD, Naoyuki Yokoyama, MD, Kumiko Konno, MD, Kazuya Naito, MD, and Takaaki Isshiki, MD

Summary

Coronary artery calcium score (CACS) measured by multi-detector computed tomography, carotid plaque score (CPS) measured by carotid artery ultrasound, and brachial-ankle pulse wave velocity (baPWV) are noninvasive screening tools for coronary artery disease. The aim of this study was to determine whether the combination of CACS, CPS, and baPWV improves the prognostic value for future cardiac events. CACS, CPS, and baPWV were assessed in 77 patients (mean age, 65 years, 49 males) undergoing invasive coronary angiography. ECG-triggered MSCT was used to assess CACS. CPS was defined as the sum of all plaque heights in bilateral carotid arteries. The highest baPWV was used for analysis. Cardiac events were defined as cardiac death, nonfatal myocardial infarction, or coronary revascularization. Thirty-two cardiac events (41.6%) occurred during follow-up (23.6 ± 20.8 months), consisting of 28 PCIs and 4 CABGs. The best cutoff values of positive CACS, CPS, and baPWV for predicting cardiac events were ≥ 50, ≥ 5, and ≥ 1.6 m/s, respectively. For the combination of the 3 modalities, the positive test was defined as having at least 1 positive result by each method. The negative predictive value of all 3 modalities combined was better than that of CACS alone. The event-free rate was higher in patients with negative results for all 3 parameters compared with those that were positive (100% versus 44.8%, P < 0.0001). The prognostic value of using combined assessment of CACS, CPS, and baPWV is more effective for predicting cardiac events than CACS alone. (Int Heart J 2012; 53: 154-159)

Key words: Coronary artery calcium score, Carotid artery plaque score, Brachial-ankle pulse wave velocity, Coronary artery disease

Coronary artery disease (CAD) is a major cause of morbidity and mortality, particularly in industrialized countries. A noninvasive diagnosis of CAD has an important role in identifying patients at high risk for a future cardiac event. The coronary artery calcium score (CACS) measured by multi-detector computed tomography (MDCT), carotid plaque score (CPS) measured by carotid ultrasound, and pulse wave velocity (PWV) are well-established noninvasive screening tools for the diagnosis and evaluation of CAD. CACS is a measure of calcified atherosclerotic plaques, which are part of the development of atherosclerosis, and correlate with the severity of CAD. Thus, CACS has been used for risk assessment for future cardiovascular events. CPS is a marker of a combination of size and number of carotid plaques. CPS is defined as the sum of the thicknesses of all the plaques for the 3 segments (common carotid artery, bulbus, and internal carotid artery) in the bilateral carotid arteries. CPS has been demonstrated to correlate with severity of atherosclerosis. Thus, CPS has also been used for the risk assessment for cardiovascular events. PWV is an indicator of both arterial stiffness and atherosclerosis.

Methods

Study patients: From October 2005 to April 2007, we studied 77 consecutive patients who underwent elective invasive coronary angiography because of suspected CAD at our institution. Patients with acute coronary syndrome were not included. All
patients underwent MDCT, carotid ultrasound, and baPWV either before or after invasive coronary angiography within 1 month. Patients were excluded if they had cardiac rhythms other than sinus rhythm, internal cardiac pacemakers, and/or defibrillators or history of intervention for a carotid and/or coronary artery. Patients on hemodialysis were also excluded. Informed consent was obtained from all patients and the study was approved by the Institutional Review Board of Teikyo University School of Medicine (Teikyo 08-122).

**Definition of risk factor:** Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of an antihypertensive drug. Diabetes mellitus was defined as HbA1C ≥ 6.5%, or use of oral antidiabetic drugs or insulin. Dyslipidemia was defined as total cholesterol ≥ 220 mg/dL (5.0 mmol/L), LDL cholesterol ≥ 140 mg/dL (3.2 mmol/L), HDL cholesterol < 40 mg/dL, or use of lipid-lowering drugs. Also, a family history of premature coronary disease was defined as a history of angina, myocardial infarction, coronary angioplasty, or coronary artery bypass graft surgery in a first-degree relative at less than 60 years of age.

**CACS:** For CACS assessments, unenhanced ECG-gated cardiac CT was performed by using a 16-MDCT (MX8000IDT, Philips Medical Systems, Cleveland, OH) with the following parameters: 3.0 mm slice thickness, tube voltage of 120 kV, gantry rotation time 420 ms, and effective current 500 mA. CT images were reconstructed from a data acquisition window centered at 75% of the R-R interval of the ECG. Heart beat CS (Philips Medical Systems) was used for CACS analysis to obtain the Agaston Score Equivalent for MDCT acquisition.

**CPS:** B-mode ultrasound examinations were performed with a HDL5000 (ATL, Bothel, WA, USA) with a 5-12 MHz linear array transducer. Plaque was defined as a localized lesion with maximum thickness of > 1.0 mm. Measurements of plaque thickness were made in the observation-possible area of the common, bulbous, and internal carotid arteries on the right and left sides. The plaque score was calculated by summing all plaque thicknesses for the 3 segments (common carotid artery, bulbous, and internal carotid artery) on both sides.

**baPWV:** After the patient was in the supine position for more than 5 minutes, blood pressure and baPWV were measured using an automated waveform analyzer (Colin VP-2000, Colin Medical Instruments Corp., Komaki, Japan). ECG electrodes were placed on both wrists and the cuffs were wrapped around both arms and ankles. Brachial and post-tibial arterial pressure waveforms obtained by the cuff were connected to a plethysmographic sensor that determines volume pulse form and an oscillometric sensor that measures blood pressure. The sampling time was 10 seconds with automatic gain analysis and quality adjustment. The time interval between the wave front of the brachial waveform and that of the ankle waveform was defined as the time interval between the brachium and ankle (Tba). The distance between sampling points of baPWV was calculated automatically according to the height of the subject. The path length from the suprasternal notch to the brachium (La) and from the suprasternal notch to the ankle (Lb) was automatically obtained based on the subject’s height. The following equation was then used to obtain baPWV: baPWV = (La-Lb)/Tba. The highest baPWV measured on both sides was used for analysis.

**Catheter based angiographic analysis:** The angiograms of invasive coronary angiography were used to assess the severity of coronary artery stenosis. An automated edge-detection system, QCA-CMS version 6.0 (Medis, Leiden, The Netherlands), was used for quantitative coronary angiography. Obstructive CAD was defined as ≥ 50% luminal narrowing in at least one major vessel.

**Cardiac events:** The clinical outcomes were collected using telephone questionnaires and/or medical records. Cardiac events were defined as cardiac death, nonfatal myocardial infarction, or coronary revascularization, whichever occurred first.

**Statistical analyses:** Continuous variables were expressed as the mean ± SD, and comparisons between groups were performed using the Student t, chi-square, or Fisher exact test where appropriate. A P < 0.05 was considered statistically significant for all tests. Receiver-operator characteristic (ROC) analysis was used to determine the best cutoff values of positive CACS, CPS, and baPWV for predicting cardiac events. The prognostic value of combination of CACS and CPS (CACS+CPS), CACS and baPWV (CACS+baPWV), and CACS with CPS and baPWV (CACS+CPS+baPWV) for the prediction of cardiac events was determined. For combination of the 3 modalities, a positive test was defined as having at least 1 positive result by each method. A negative test of combination of CACS and other modalities was defined as having all negative results. Sensitivity, specificity, and positive and negative predictive values for the

<table>
<thead>
<tr>
<th>Table I. Patient Characteristics</th>
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<td>Overall (n = 77)</td>
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<td>----------------</td>
</tr>
<tr>
<td>Age</td>
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<tr>
<td>Gender (male)</td>
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<tr>
<td>Hypertension</td>
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<td>Dyslipidemia</td>
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<td>Diabetes mellitus</td>
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<td>Smoking</td>
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<td>Family history</td>
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<tr>
<td>CACS</td>
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<td>CPS</td>
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<td>baPWV (m/second)</td>
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CACS indicates coronary artery calcium score; CPS, carotid plaque score; and baPWV, brachial-ankle pulse wave velocity.
prediction of future cardiac events were determined for CACS, CPS, baPWV, and combination of modalities. Cardiac event-free survival was estimated using the Kaplan-Meier survival methods with log-rank statistics. For the event-free survival analysis, the patients with noncardiac deaths were censored at the time of death but not included as cardiac events. First, the associations of selected variables with outcome were assessed in the univariate Cox proportional hazard models to identify potential predictors. To identify independent predictors, we then performed a forward stepwise multivariable analysis of variables with \( P < 0.20 \) on univariate analysis. Results of Cox proportional hazard analysis are presented as the hazard ratio with 95% confidence intervals. Clinical variables tested in the models included risk factors for coronary artery disease (age, gender, family history of coronary artery disease, smoking, dyslipidemia, hypertension, and diabetes mellitus) and positive results for CACS, CPS, and baPWV. ROC analysis and all other statistical analyses were performed with SPSS statistics 17.0 (SPSS Incorporated, Chicago, Il).

**RESULTS**

**Patient demographics:** The baseline characteristics of the study patients are summarized in Table I. The mean age of the study population was 65.1 ± 18.9 years and the majority were male (63.6%). Of all study patients, 47 patients had typical angina chest pain, 21 had atypical angina chest pain, and 9 had no chest pain. Indications for angiography were typical angina chest pain in 13, an ECG abnormality in 18, abnormal left ventricular wall motion detected by echocardiography in 2, and positive stress test in 44. Invasive coronary angiography revealed that 36 patients (46.8%) had obstructive CAD (1-vessel disease in 17 patients, 2-vessel disease in 7, and 3-vessel disease in 12). The average CACS was 364.2 ± 677.7 (range, 0-3372.0). The CACS increased with severity of CAD. CACSs in 0-, 1-vessel, 2-vessel, and 3-vessel CAD were 158.3 ± 557.9, 257.8 ± 404.6, 696.6 ± 1061.1, and 1024.8 ± 683.9, respectively. The average CPS was 5.8 ± 4.3 (range, 0-18.1). The average baPWV was 15.9 ± 2.9 m/second (range, 1.0-24.7 m/second). CPS and baPWV were not related to severity of CAD.

**Clinical outcomes:** The mean follow-up period was 23.6 ± 20.8 months. During follow-up, cardiac events occurred in 32 patients (41.6%) who had obstructive CAD in coronary angiography. Coronary revascularization was performed in these patients (4 with CABG and 28 with PCI) within approximately 3 months after coronary angiography. There was no cardiac death and no nonfatal myocardial infarction. Thus, we focused on the need for early coronary revascularization.

**Prognostic value of each modality for cardiac events:** ROC analysis revealed that the best cutoff values of positive CACS, CPS, and baPWV for predicting early coronary revascularization were ≥ 50, ≥ 5 and ≥ 16.0 m/second, respectively (Figure 1). The results of each test and prognostic value for early coronary revascularization are shown in Table II. The prognostic value for early coronary revascularization for CACS was better than that of CPS or baPWV. The sensitivity and negative predictive value of all 3 tests combined was better than that of CACS alone. The sensitivity and negative predictive value of combination of each judgment (CACS+CPS+baPWV) for not

![Figure 1. Receiver operator curves for predicting cardiac events for each modality. Receiver-operator characteristic (ROC) curves for 3 noninvasive modalities combined for prediction of cardiac events. CACS indicates coronary artery calcium score; CPS, carotid plaque score; and baPWV, brachial-ankle pulse wave velocity.](Image)

<table>
<thead>
<tr>
<th>Table II. Diagnostic Values of Each Modality for Cardiac Events</th>
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<tr>
<td><strong>Number of positive cases</strong></td>
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<tr>
<td>CACS</td>
</tr>
<tr>
<td>CPS</td>
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<tr>
<td>baPWV</td>
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<tr>
<td>CACS+CPS</td>
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<tr>
<td>CACS+baPWV</td>
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<tr>
<td>CACS+CPS+baPWV</td>
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See Table I for abbreviations.
The present study confirms the previous study. In this study, those with CACS ≥ 100 (relative risk 3.20; 95% CI 1.17-8.71) was significantly higher for patients with CACS < 100 than for those with CACS < 100 in the previous studies. The event rate in the current study was lower than the previous studies with no cardiac death or myocardial infarction. The previous studies included patients with a history of myocardial infarction or coronary revascularization, whereas this study excluded these patients. Moreover, invasive coronary artery angiography was performed for all patients. Thus, appropriate treatments for CAD based on angiographic findings could not result in increased mortality risk.

It is well accepted that carotid ultrasound findings (intima media thickness, CPS, and ultrasound characteristics of carotid plaque) are associated with an increased risk of cardiovascular events. Previous studies demonstrated that presence of carotid plaque was a more powerful predictor of cardiovascular events than intima-media thickness. Carotid plaque score is useful as a means of semiquantitative analysis of degree of atherosclerosis. CPS is obtained by a wider range observation of the carotid arteries than intima-media thickness. Thus, CPS represents more precisely the atherosclerotic condition of the carotid artery than does intima-media thickness. However, the prognostic value of CPS for patients with suspected coronary artery disease has not been reported. Although PWV is also a positive result (100% versus 44.8%, P < 0.0001).

In the Cox proportional hazard model analysis, univariate predictors of cardiac events included a positive result for CACS, followed by a positive result for CPS (Table III). Other variables analyzed, including family history of coronary artery disease, smoking, dyslipidemia, hypertension, diabetes mellitus, and a positive result for baPWV, were not significantly associated with future cardiac events.

Multivariate model revealed that positive CACS was the strongest predictor of early coronary revascularization (Table IV).

### DISCUSSION

This study clearly demonstrated that CACS outperforms both CPS and baPWV as a noninvasive predictor for early coronary revascularization. Moreover, the predictive performance was better for combination of CACS with CPS and baPWV compared with CACS alone. The sensitivity and negative predictive value of combined tests (CACS+CPS+baPWV) conferred a better prognosis than either of the measurements alone.

CACS was the strongest predictor of future cardiac events (relative risk 5.5; 95% CI 2.0-15.3) compared with CPS and baPWV. It is not surprising that CACS reflected coronary artery atherosclerosis directly. However, there are several important differences from the previous studies. In the current study, MDCT was used for assessment of CACS instead of Electron-Beam CT. It has been demonstrated that CACS is generally underestimated when assessed by MDCT compared with Electron-Beam CT. Thus, the threshold of CACS ≥ 50 in our study was substantially lower than the threshold of CACS ≥ 100 in the previous studies. The event rate in the current study was lower than the previous studies with no cardiac death or myocardial infarction. The previous studies included patients with a history of myocardial infarction or coronary revascularization, whereas this study excluded these patients. Moreover, invasive coronary artery angiography was performed for all patients. Thus, appropriate treatments for CAD based on angiographic findings could not result in increased mortality risk.

### Table III. Univariate Predictors of Cardiac Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR (95% CI)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99 (0.96-1.03)</td>
<td>0.660</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.90 (0.85-4.24)</td>
<td>0.116</td>
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<tr>
<td>Diabetes mellitus</td>
<td>1.38 (0.69-2.77)</td>
<td>0.362</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.82 (0.39-1.7)</td>
<td>0.590</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.58 (0.68-3.64)</td>
<td>0.290</td>
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<tr>
<td>Smoking</td>
<td>1.68 (0.82-3.44)</td>
<td>0.156</td>
</tr>
<tr>
<td>Family history</td>
<td>1.45 (0.65-3.23)</td>
<td>0.364</td>
</tr>
<tr>
<td>CACS &gt; 50</td>
<td>8.54 (3.26-22.35)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CPS &gt; 5</td>
<td>5.56 (2.39-12.93)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>baPWV &gt; 1600</td>
<td>1.16 (0.58-2.32)</td>
<td>0.675</td>
</tr>
<tr>
<td>CACS+CPS</td>
<td>13.52 (3.22-56.79)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CACS+baPWV</td>
<td>19.00 (2.59-139.37)</td>
<td>0.004</td>
</tr>
<tr>
<td>CACS+CPS+baPWV</td>
<td>37.53 (1.62-870.30)</td>
<td>0.024</td>
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</table>

See Table I for abbreviations.

### Table IV. Multivariate Predictors of Cardiac Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>CACS &gt; 50</td>
<td>5.52 (2.00-15.32)</td>
<td>0.001</td>
</tr>
<tr>
<td>CPS &gt; 5</td>
<td>2.91 (1.19-7.12)</td>
<td>0.019</td>
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See Table I for abbreviations.
powerful predictor of future cardiovascular events, few studies have been reported using baPWV. This is the first study to evaluate the prognostic value of CPS and baPWV for the same population of patients with suspected coronary artery disease.

Combination of multi-modality: For the need of early coronary revascularization, negative predictive values of CACS+CPS and CACS+baPWV were 93.1% and 95.7%, respectively. Moreover, the negative predictive value of CACS+ CPS+baPWV was 100%. The negative predictive value was higher when all 3 modalities were combined compared with CACS alone. Pathological intimal thickening is the first manifestation of atherosclerosis. Large increases in wall thickness due to atherosclerosis may be seen in carotid and coronary arteries before a decrease in lumen diameter occurs and stenosis develops. Moreover, atherosclerosis of large arteries progresses faster than the small arteries. Since CPS and baPWV reflects the early phase of atherosclerosis, a combination of these 3 noninvasive parameters may thus improve the negative predictive value for future cardiovascular events.

Clinical implication: According to the 2007 ACC/AHA Expert consensus document, CACS in symptomatic patients was comparable to nuclear stress testing in the detection of obstructive CAD and was an effective filter before invasive coronary angiography. Patients with a CACS of < 50 are considered to be low risk population for future cardiac events. From the current study, combined assessment with CACS with CPS and baPWV is potentially a more useful tool for risk stratification of cardiac events than CACS alone. This is the first study to demonstrate better prognostic value of combined assessment with 3 different noninvasive tests.

Limitations: There are several limitations in this study. First, there was a possible selection bias. All study patients were referred for invasive coronary angiography. Early revascularization procedures were performed for most of the patients with obstructive CAD. Thus, the results of this study may not reflect the event rates for cardiac death and nonfatal myocardial infarction. However, coronary revascularization was conducted without knowledge of the value of CACS.

The number of study patients was relatively small in this study. Further studies are needed in a larger population.

Conclusion: CACS can successfully predict the need for early coronary revascularization for patients with suspected CAD. A combination of CACS with other modalities improved the negative predictive value compared with CACS alone. The prognostic value of a negative result for combination of CACS+CPS+baPWV for predicting early coronary revascularization is excellent.

REFERENCES


