Incremental predictive value for obstructive coronary artery disease by combination of Duke Clinical Score and Agatston score

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Aims
Recent study suggests that algorithms such as the Duke Clinical score (DCS) may overestimate the pretest probability. The Agatston score representing the grade of coronary artery calcification can be simply calculated from low-radiation exposure ECG-gated plain CT. In this study, we investigated whether or not more superior diagnostic performance for obstructive coronary artery disease (CAD) can be obtained by combining DCS with the Agatston score.

Methods and results
Of 3939 consecutive patients suspected of having stable angina without known CAD who underwent Coronary Computed Tomography Angiography (CCTA) as well as calculation of the DCS and Agatston score at our hospital, 3688 patients were selected as subjects. Obstructive CAD was defined as >50% diameter stenosis on CCTA; we investigated the diagnostic performance based on the area under the curve (AUC) of a receiver operating characteristic (ROC) curve, Net Reclassification Improvement (NRI), and Integrated Discrimination Improvement (IDI). The AUCs of ROCs prepared using the DCS alone and combination of the DCS and Agatston score were 0.7137 and 0.8057, respectively, showing that the diagnostic performance of the combination was significantly superior to DCS alone (P < 0.001). NRI was 0.8132 and IDI was 0.1374, showing that the diagnostic performance was improved by the combination of the DCS and Agatston score compared with DCS alone (P < 0.001). NRI (0.3522) and IDI (0.0287) were improved compared with those of the Agatston score alone (P < 0.001).

Conclusion
The combination of the DCS and Agatston score improved the diagnostic performance for obstructive CAD compared with DCS alone and Agatston score.

Keywords
coronary artery disease • prognosis • obstructive coronary artery disease • pretest probability • coronary CT angiography

Introduction
It is necessary to determine the pretest probability based on the Duke Clinical score (DCS) and Diamond-Forrester (DF) to select an appropriate examination and stratify risks for patients suspected of having stable angina.1–4 Although some studies reported that the pretest probability can be more accurately calculated from the DCS than from the DF,5 overestimation of the pretest probability based on either DF or DCS has recently been pointed out6–9 for diagnosing obstructive coronary artery disease (CAD) on Coronary Computed Tomography Angiography (CCTA), and it is considered that selection of the population is biased, because coronary artery angiography findings in high-risk patients are regarded as reference in their algorithms.6–9 Since the cause of coronary artery calcification is arteriosclerosis in many cases and the presence or absence and amount of
calcification are associated with the severity of coronary artery sclerosis, the grade of coronary artery calcification may be useful to predict the presence of obstructive CAD. Use of the coronary artery calcium score (CACS) is a method to evaluate calcification of the coronary artery quantitatively, and it can be simply calculated using low-radiation exposure ECG-gated plain CT. Of CACS, the Agatston score is mainly used, and it has been reported to be a predictor of obstructive coronary artery disease and cardiovascular events in symptomatic patients.

Thus, we retrospectively investigated the ability of the combination of the DCS and Agatston score to calculate the pretest probability of patients suspected of having stable angina accurately, regarding CCTA findings applied for patients including those at low/intermediate risks as reference.

Methods

Study population

Of 3939 consecutive patients suspected of having stable angina without known CAD in whom both the Agatston score and CCTA could be applied using 64-row Multi-Detector Computed Tomography (MDCT) or 320-row Area-Detector Computed Tomography (ADCT) at our institution between 30 September 2008 and 28 February 2014, 3688 patients (male/female: 1845/1843, age: 65.8 ± 11.7 years old) were selected as subjects, excluding those with arteritis syndrome (n = 6), Kawasaki disease (n = 15), severe calcification (n = 128), motion artifact (n = 88), pacemaker lead (n = 11), wire for the sternum (n = 1), poor contrast enhancement (n = 1), and missing data (n = 1) (Figure 1).

Anonymous use of the test data for the study was orally explained to all subjects, and written consent was obtained. This retrospective observational study was approved by the Ethics Committee of our institution.

Definition of risk factors

Hypertensive patients were defined as those with blood pressure of 140/90 mmHg or higher or receiving treatment with oral antihypertensive drugs. Dyslipidaemia patients were defined as those with total cholesterol (T-cho) of 220 mg/dL or higher, low-density lipoprotein cholesterol (LDL-C) of 140 mg/dL or higher, fasting triglycerides of 150 mg/dL or higher, high-density lipoprotein cholesterol of 40 mg/dL or higher, or receiving treatment with oral lipid-lowering agents. Diabetic patients were defined as those with a fasting blood glucose level of 126 mg/dL or higher, casual blood glucose level of 200 mg/dL or higher, HgbA1c of 6.5% (NGSP) or higher, or receiving treatment for diabetes. Patients with a history of cigarette smoking were defined as those who had a smoking habit within 1 year before CT. Patients with brain infarction were defined as those with typical neurological findings or previously diagnosed with it on imaging.

Calculation of the DCS

Chest symptoms were evaluated with regard to the following 6 items based on the Duke Clinical classification: (i) precipitated by exercise, (ii) brief duration (2–15 min), (iii) relieved promptly by rest or nitroglycerin, (iv) retrosternal, (v) radiating jaw, neck, or left arm, and (vi) the absence of another cause. The following 5 items were also evaluated: (i) the presence or absence of smoking (within the past 5 years), (ii) total cholesterol, and the presence or absence of (iii) diabetes, (iv) previous MI and ECG Q wave, and (v) changes in resting ECG. The pretest probability was calculated based on these. Patients with DCS ≤ 30%, 30 < DCS ≤ 70%, and DCS > 70% were classified as low-, intermediate-, and high-risk groups, respectively.
CT image acquisition

Devices and pre-treatment
For 64-row MDCT, Aquilion 64 Super Heart (Toshiba, Medical System) was used. For 320-row ADCT, Aquilion ONE V4.51 and Aquilion ONE VISION Edition (Toshiba, Medical System) were used. The automatic contrast medium injection system used was Stellant Dual Flow (Nihon Medrad K.K.), and the image analysis system used was ZIOSTATION ver. 1.3.1 (Ziosoft Inc.). For an ECG monitor, IVY3000 (Chronos Medical Device Co.) was used for 320-row ADCT. For pre-treatment, when the heart rate was 60 bpm or higher, 25 mg of atenolol was orally administered the day before the test as long as no contraindication was present (past medical history of anaphylaxis to contrast medium, severe aortic valve stenosis, systolic blood pressure < 90, severe atrioventricular block, heart failure, and renal dysfunction). When the effect was insufficient at the time of imaging, propranolol was additionally administered intravenously. On the test day, 2–10 mg of propranolol and/or 12.5 mg of landiolol were intravenously administered immediately before image acquisition to control the heart rate, as needed.

Measurement of Agatston score
The Agatston score was calculated with this image before CCTA, following the method reported by Agatston et al.11 On 64-row MDCT, ECG-gated conventional (non-helical) plain CT images were acquired at 120 kV tube voltage and 150 mA tube current during a single breath holding targeting mid-diastole or end-systole within an acquisition range including the aortic root over the apex, and a half-reconstructed image was prepared at a 3-mm slice thickness and 3-mm slice interval. On 320-row ADCT, plain cardiac CT images targeting mid-diastole or end-systole were acquired using 280 rows to include the aortic root over the apex at 120 kV tube voltage and 50 mA tube current, employing the prospective ECG-gated method, and an image was reconstructed at 120 kV tube voltage and 150 mA tube current during a single breath holding targeting mid-diastole or end-systole within an acquisition range including the aortic root over the apex, and a half-reconstructed image was prepared at a 3-mm slice thickness and 3-mm slice interval. Using the software ZIOSTATION ver. 1.3.1, a calcified lesion was defined as ≥ 3 contiguous pixels with peak attenuation ≥ 130 HU. The total CACS (Agatston score) was calculated as per the recommendations of Agatston et al.11

CCTA acquisition protocol
CCTA images were acquired following the protocol of our institution reported previously.14

64-row MDCT protocol
The contrast medium injection time was fixed, and contrast medium was injected into the cubital vein employing the three-step injection method: injection of contrast medium for 12 s, a mixture (contrast medium: saline = 50:50%) for 6 s, and saline for 2 s. The contrast medium injection rate (2.5–4.5 mL/s) and volume (38–62 mL) were determined based on the body weight.

The acquisition conditions were as follows: acquisition slice thickness, 0.5 mm × 64-row; image slice thickness, 0.5 mm; and reconstruction interval, 0.3 mm. The acquisition tube voltage was set at 120 kV in all subjects, and the gantry rotation speed was 0.35 s/rot. The tube current was basically 440 mA for 60 kg body weight, but it was decided taking the body mass index (BMI) into consideration.

320-row ADCT protocol
The contrast medium injection time was fixed; the contrast medium injection rate was body weight × 0.06 mL/s; and contrast medium was injected into the cubital vein employing the two-step injection method: injection of contrast medium for 10 s followed by saline injection for 8 s.

The acquisition conditions were as follows: acquisition slice thickness, 0.5 mm × 320-row; and image slice thickness, 0.5 mm. The acquisition range was referred to the registration image for plain CT, setting the minimum range covering the entire coronary artery. The acquisition tube voltage was set at 120 kV as a rule, and the tube current was set at the mean tube current calculated so as to set the standard deviation (SD) to 20 using the automatic exposure control (AEC) function. When the tube current reached the maximum, 580 mA, the tube voltage was set at 135 kV. The gantry rotation speed varies depending on the heart rate, but 0.35 or 0.275 s/rot was used. The prospective CTA mode was used as much as possible, and the X-ray exposure range was single heartbeat acquisition at 75% phase of RR.

Image reconstruction
Full-image reconstruction or half-image reconstruction or segmental image reconstruction was performed in the slow filling phase and end-systolic phase using the absolute time delay method to generate images, and the image with the lowest level of motion artifacts was selected on the four-chamber cardiac cine CT.

Evaluation of coronary artery stenosis on CCTA
CCTA findings were evaluated in each segment based on agreement among two cardiologists and one radiological technologist without clinical information of the patients following the modified AHA classification.15 The percentage ratio of the stenotic lumen to the original vessel diameter of the lesion analogized by a presumed-to-be-healthy site distal and proximal to the stenosis was obtained, and the degree of stenosis was expressed by subtracting this from 100.

Obstructive CAD was defined as those with >50% diameter stenosis on CCTA in ≥1 vessel.

Statistical analysis
Statistical analyses were performed using SPSS Version 19 (IBM Corporation, Armonk, NY, USA). R version 3.1.0 (The R Foundation for Statistical Computing). Numerical data are presented as the mean ± SD.

Stratification was applied based on the combination of the DCS and Agatston score, and the prevalence of obstructive CAD was calculated regarding CT-verified stenosis as reference.

In addition, pretest probability (low ≤ 30%, 30% < intermediate ≤ 70%, 70% < high) was calculated from the combination of the DCS and Agatston score to investigate how the DCS-based classified patients were re-stratified.

To investigate the diagnostic performances of the DCS alone and in combination with the Agatston score and those of Agatston score alone and in combination with the DCS, regarding obstructive CAD, logistic analysis of each performance was performed, and the area under the curve (AUC) of the receiver operating characteristic (ROC) curve was compared. Improvement of diagnostic performance by the addition of the Agatston score to DCS and the DCS to Agatston score was calculated using the Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI), regarding P < 0.005 as significant.

Results

Patient characteristics
The patient background is presented in Table 1.

The patients were classified into those with DCS ≤ 30%, 30 < DCS ≤ 70%, and DCS > 70% as low-, intermediate-, and high-risk groups. The Agatston score, DCS, and prevalence of obstructive CAD were 48.1 ± 183.8, 19.0 ± 7.3, and 6.6% (63/961) in the low-risk group (n = 961), 122.3 ± 299.5, 49.7 ± 11.8, and 17.8% (244/
in the intermediate-risk group, and 264.4 ± 600.4, 85.8 ± 8.2, and 34.6% (468/1353) in the high-risk group, respectively.

**Re-stratification by combination of DCS and Agatston score**

The patients were classified into three groups as low-, intermediate-, and high-risk groups, respectively, and each group was further divided into five groups based on the Agatston score into those with 0, 1–99, 100–399, 400–999, and 1000 or higher, being stratified into 15 groups in total. The prevalence of obstructive CAD rose with an increase in the Agatston score, being stratified. It was lower in the low-risk group with an Agatston score of 0 and intermediate- and high-risk groups with an Agatston score of 1–99 or lower than in the groups evaluated using DCS alone (Figure 2).

**Re-stratification with pretest probability calculated from the combination of the DCS and Agatston score**

Based on the pretest probability calculated from the combination of the DCS and Agatston score, 0.6 (6/961) and 0.5% (5/961) of patients in the DCS-based low-risk group (n = 961) were included in the intermediate- and high-risk groups, respectively, 92.1% (1265/1374) and 2.1% (29/1374) in the DCS-based intermediate-risk (n = 1374) group were included in the low- and high-risk groups, respectively, and 64.7% (876/1353) and 26.8% (363/1353) in the DCS-based high-risk group (n = 1353) were included in the low- and intermediate-risk groups, respectively (Table 2).

**Comparison of diagnostic performance for obstructive CAD between DCS alone and combination of DCS and Agatston score**

For the presence of obstructive CAD, AUC determined from the ROC curve prepared using DCS alone was 0.7137 (95% CI 0.6942–0.7331), and that using the combination of the DCS and Agatston score was 0.8057 (95% CI 0.7877–0.8237). AUC was significantly greater when the combination was used (P < 0.0001) (Figure 3A). However, there were no significant difference in the AUC for the Agatston score (0.8185) and the combination of the DCS and Agatston score (0.8057) (P = 0.0873) (Figure 3B).

**Net Reclassification Improvement and Integrated Discrimination Improvement**

The combination of DCS with CACS increased NRI to 0.8132 (95% CI 0.7388–0.8875) and IDI to 0.1374 (95% CI 0.1137–0.1472), showing that the diagnostic performance for obstructive CAD was improved (Table 3).

In addition, NRI and IDI were 0.3522 (95% CI 0.2979–0.4317) and 0.0287 (95% CI 0.0216–0.0358), respectively, being improved compared with those of the Agatston score alone, showing that combining the DCS with the Agatston score improved the diagnostic performance (Table 3).

**Discussion**

To perform appropriate examinations to diagnose stable angina appropriately, it is important to calculate the pretest probability, but overestimation by DF and DCS, which are currently used widely, has been reported.1–4,6–9 One reason for this may be the inclusion of many high-risk cases in the population of DF and DCS, because the presence of obstructive CAD was confirmed by conventional coronary angiography in the subjects of both score systems.6–9 Accordingly, the pretest probability is likely to be calculated higher than that in an actual real-world population. Secondly, with the recent development of drug therapy for coronary risk factors and an increase in patients’ consciousness, the incidence of obstructive CAD may have changed in the population with the same characteristics (age, gender, and coronary risk factors). The risk may be different depending on the presence or absence of drug therapy, even though the test value is the same. In addition, the diagnosis of coronary risk factors and their treatment have become performed...
earlier than before. These conditions make defining coronary risk factors more difficult. In the present study, when CT-verified stenosis including low-/intermediate-risk patients was regarded as reference, the prevalence of obstructive CAD as the pretest probability determined using DCS was about three times overestimated in each of the low-, intermediate-, and high-risk groups.

The Agatston score is a low-radiation exposure test to evaluate coronary artery calcification on plain CT using no contrast medium, and it is applicable for a broad patient population. In addition, it is reported that the combination of electron beam tomographic calcium scanning and pretest probability of disease shows incremental an independent power in predicting the severity and extent of angiographically significant CAD.

We performed re-stratification based on the Agatston score after DCS-based classification and calculated the prevalence of obstructive CAD. The prevalence of obstructive CAD rose with an increase in the Agatston score in each of the low-, intermediate-, and high-risk groups, and more detailed re-stratification than that based on DCS alone was possible. Moreover, we investigated how patients classified based on DCS were re-stratified by calculating pretest probabilities.

Table 2  Re-stratification with pretest probability calculated from the combination of the DCS and Agatston score

<table>
<thead>
<tr>
<th>Prediction by combination of DCS and Agatston score</th>
<th>Total</th>
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<tbody>
<tr>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Low</td>
<td>950</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1265</td>
</tr>
<tr>
<td>High</td>
<td>876</td>
</tr>
<tr>
<td>Total</td>
<td>3091 (83.8%)</td>
</tr>
</tbody>
</table>

DCS, Duke Clinical Score.
probability from the combination of the DCS and Agatston score. As contrasted to DCS, in 96% of all patients were reclassified into low- and intermediate risk.

Thus, AUC was compared between the ROC curves prepared using the DCS alone and combination of the DCS and Agatston score. The diagnostic performance was significantly improved by the combination compared with that using DCS alone or Agatston score. It has been reported that the Agatston score itself represents the expansion and severity of arteriosclerosis of the coronary artery,\(^{19,20}\) the combination with the Agatston score added information on the advancement of coronary artery arteriosclerosis to DCS, predicting the presence of obstructive CAD, which may have improved the diagnostic performance. However, the presence of obstructive CAD and CT-verified high risk plaque cannot be ruled out even though Agatston score \(=0.21\). Furthermore, in previous study, CCTA should not be selected as the next step in the diagnostic workup of patients with a high Agatston score,\(^{22}\) suggesting that investigation employing other modalities is necessary depending on the Agatston score value, regardless of the DCS.

To stratify the risks of patients accurately, it is necessary to determine the pretest probability more accurately, and the method employing the combination of the DCS and Agatston score was useful.

### Limitation

There are several limitations to this study. Firstly, it was a single-centre retrospective study. The patient selection may have been biased because the indication of CCTA is entrusted to individual physicians at the outpatient clinic. It is necessary to perform a multicentre study. Secondly, patients who could not be evaluated due to severe calcification were excluded from the population for calculation of the prevalence. Because not Coronary Angiography but CCTA findings were regarded as reference, calcified regions lead to overestimation of luminal obstruction, which may have

### Table 3  Investigation using NRI and IDI

<table>
<thead>
<tr>
<th>Comparison</th>
<th>NRI (95% CI)</th>
<th>P-value</th>
<th>IDI (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
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<tr>
<td>1. Comparison of DCS alone and combination of the DCS and Agatston score</td>
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<tr>
<td>2. Comparison of Agatston score alone and combination of the DCS and Agatston score</td>
<td>0.3522 (0.2979–0.4317)</td>
<td>0.001</td>
<td>0.0287 (0.0216–0.0358)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

NRI, Net Reclassification Improvement; IDI, Integrated Discrimination Improvement; 95% CI, confidence interval.
influenced the prevalence. Thirdly, since whether or not the addition of the Agatston score to DCS shows an incremental diagnostic value, all patients were examined by CCTA, not based on the values of the DCS and Agatston score. Furthermore, the influence of the Agatston score on the presence of prognostically relevant CAD, myocardial ischaemia, and adverse outcome was not investigated.

Finally, in Japan, DCS is mainly used to determine pretest probability in clinical practice; however, the ESC currently recommends Genders score which diagnosis performance improved. It may be important to investigate the addition of the Agatston score to Genders score.

Conclusion

DCS overestimated the pretest probability. The combination of DCS with the Agatston score improved the diagnostic performance for obstructive CAD compared with that using DCS alone and Agatston score, leading to more appropriate risk stratification for diagnosing stable angina.

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References
