Coronary computed tomography angiography and calcium scoring in routine clinical practice for identification of patients who require revascularization

Coronaroscanner et score calcique en routine clinique pour identifier les patients ayant une indication à la revascularisation coronaire

Grazina Urbonaviciene\textsuperscript{a,b,*}, Christin Isaksen\textsuperscript{a}, Sigitas Urbonavicius\textsuperscript{b,c}, Jørgen Selmer Buhl\textsuperscript{a}, Jane Kirk Johansen\textsuperscript{a}, Ånette Hedemann Nielsen\textsuperscript{a}, Kirsten Schou Nørgaard\textsuperscript{a}, Aage Nørgaard\textsuperscript{a}, Lars Frost\textsuperscript{a,b}

\textsuperscript{a} University Clinic for Development of Innovative Patient Pathways, Silkeborg Hospital, Diagnostic Centre, Silkeborg, Denmark
\textsuperscript{b} Aarhus University, Institute for Clinical Medicine, Aarhus, Denmark
\textsuperscript{c} Viborg Hospital, Department of Vascular Surgery, Viborg, Denmark

Received 25 May 2015; received in revised form 25 October 2015; accepted 20 January 2016
Available online 20 May 2016

KEYWORDS
Coronary computed tomography angiography;

Summary
Background. — The predictive value of CCTA to predict coronary artery disease is high in particular in the absence of coronary calcification. However, the consideration of both CCTA and the calcium score, in addition to the risk factors to determine the indication for coronary revascularization, has not been yet studied.

Abbreviations: AUC, area under the ROC curve; CACS, coronary artery calcium score; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CI, confidence interval; HR, hazard ratio; ICA, invasive coronary angiography; MACE, major adverse cardiac events; NRI, net reclassification improvement; OR, odds ratio; ROC, receiver operating characteristic.

* Corresponding author. Falkevej 3, DK-8600 Silkeborg, Denmark.
E-mail address: graurb@rm.dk (G. Urbonaviciene).

http://dx.doi.org/10.1016/j.acvd.2016.01.013
1875-2136/© 2016 Elsevier Masson SAS. All rights reserved.
Materials and methods. — This study included 2302 patients (mean age: 60 ± 9.8 years, 46% men), without known coronary artery disease (CAD), who underwent 320-row CCTA. Logistic regression, c-statistic and net reclassification improvement (NRI) were used to assess the role of coronary artery calcium score (CACS) in predicting revascularization after CCTA.

Results. — The revascularization rates were 0.75% in patients with a CACS of 0, and there were no adverse events during the follow-up period. The revascularization rates were 3.3% in patients with a CACS of 1–99, 15.4% in patients with a CACS of 100–399, 25.6% in patients with a CACS of 400–999, and 42.4% in patients with a CACS ≥ 1000. The crude and adjusted odds ratios (95% confidence interval) for revascularization per CACS group category were 2.89 (2.53–2.3) and 2.71 (2.33–2.15), respectively; the area under the ROC curve (AUC) was 0.85 (0.83–0.88). The addition of CACS to conventional risk factors improved the accuracy of risk prediction model for revascularization (AUC 0.74 vs 0.63, \( P = 0.001 \)), but it did not reclassify a substantial proportion of patients with positive CACS to risk categories (NRI = −0.023, \( P = 0.66 \)).

Conclusions. — The 320-row CCTA might rule out CAD in low- to intermediate-risk patients. However, its accuracy in identifying patients who require revascularization is limited. The CACS added to the conventional risk factors did not improve the identification of patients who require revascularization.

© 2016 Elsevier Masson SAS. All rights reserved.

MOTS CLÉS
Coronaroscanner ; Score calcique ; Sténose hémodynamiquement significative ; Revascularisation coronaire

Résumé

Justification. — La valeur prédictive du coronaroscanner pour éliminer une coronaropathie est élevée en particulier en l’absence de calcification coronaire. Cependant, la prise en compte simultanée des résultats du coronaroscanner, et de l’évaluation du score calcique en sus de la prise en compte des facteurs de risque pour déterminer l’indication à une revascularisation, n’a pas été étudiée à ce jour.

Méthodes. — Cette étude a inclus 2302 patients, d’âge moyen 60 ± 9,8 ans, 46 % de sexe masculin, sans coronaropathie connue qui ont bénéficié d’un coronaroscanner. La régression logistique, le score C-statistic et l’amélioration nette de la reclassification (NRI) ont été utilisés pour évaluer le rôle du score calcique dans la prédiction de l’indication à une revascularisation au décours d’un coronaroscanner.

Résultats. — Le taux de revascularisation était de 0,75 % chez les patients ayant un score calcique = 0 et il n’y avait pas d’événement indésirable colligé pendant la période de suivi. Le taux de revascularisation était de 3,3 % chez les patients ayant un score calcique entre 0 et 99, 15,4 % lorsque ce score était entre 100 et 399, 25,6 % lorsque ce score était entre 400 et 999 et 42,4 % chez les patients ayant un score ≥ 1000. Les odds ratios brut et ajusté avec IC 95 % pour l’indication à la revascularisation par catégorie de score calcique étaient de 2,89 (IC 95 % = 2,3–2,53) et de 2,71 (IC 95 % = 2,33–2,15), respectivement. La surface sous la courbe ROC était à 0,85 (IC 95 % = 0,83–0,88). Le fait de prendre en considération les facteurs de risque en sus du score calcique améliore la précision du modèle pour prédire l’indication à une revascularisation puisque la surface sur la courbe ROC passe de 0,63 à 0,74, \( P = 0,001 \). En revanche, il n’y a pas d’amélioration de la classification correcte des patients en utilisant le résultat du score calcique par catégorie, puisque le NRI est égal à −0,023, \( P = 0,66 \).

Conclusion. — Le coronaroscanner peut éliminer une coronaropathie chez les patients à faible risque où à risque intermédiaire. Cependant, sa capacité à identifier les patients ayant une indication à une revascularisation est limitée. Le score calcique améliore la prédiction d’un geste de revascularisation, en sus de la prise en compte des facteurs de risque cardiovasculaire mais n’améliore pas l’identification des patients ayant une indication à revascularisation.

© 2016 Elsevier Masson SAS. Tous droits réservés.

Background

320-detector row coronary computed tomography angiography (CCTA) has become a valuable imaging method for patients with suspected coronary artery disease (CAD), to avoid unnecessary invasive coronary angiography (ICA) [1–3]. However, one of the major limitations of CCTA is the discrepancy between angiographic and functional stenosis
Coronary artery calcification is a marker of atherosclerosis that can be assessed using non-contrast CTA. While the coronary artery calcium score (CACS) can assist the clinician in effectively ruling out angiographically significant CAD [5], the absence of coronary calcium does not preclude the presence of significant CAD with non-calcified plaques [6–10]. Therefore, all patients with a CACS of 0 might benefit from further evaluation with contrast-enhanced CTA [11]. Previous studies showed that the CACS and CCTA had high sensitivity, but a much lower specificity for obstructive CAD in symptomatic patients with no prior diagnosis of CAD [12,13]. Limited data exist on the assessment of ICA rates and revascularization in relation to CCTA results. Accordingly, we aimed to investigate the use of ICA and revascularization after CCTA in symptomatic patients at low to intermediate risk of CAD; and the relationship between the CACS with obstructive CAD and major adverse cardiac events (MACE) in patients with a positive CACS.

Methods

Study population

The present single-center study included consecutive symptomatic patients with a low to intermediate likelihood of CAD who underwent 320-detector row CCTA as a first-choice non-invasive test at the Silkeborg Diagnostic Centre, Denmark, from January 2011 to June 2013. Patients with a history of chest pain or other symptoms suggestive of CAD were included. The exclusion criteria were known CAD and CCTA scans with non-diagnostic image quality (n = 108). Clinical characteristics, including age, sex, body mass index, cardiovascular risk factors (diabetes mellitus, use of antihypertensive and cholesterol-lowering drugs, smoking status, renal function), ICA and revascularization information were obtained from the Western Denmark Heart Registry, to which all patients were reported at the time of the CCTA. Follow-up data regarding MACE and all-cause deaths were obtained from the Danish National Patient Registry and patients’ health records. The study was approved by the Danish Data Protection Agency.

Computed tomography scan protocol and investigation reporting

All CACS and CCTA scans were performed using a 320-slice multislice computed tomography scanner (Aquilion One; Toshiba Medical Systems, Tokyo, Japan). Before imaging, patients with a heart rate > 65 beats/min were given metoprolol tartrate (Seloken® 2.5–20 mg, single dose, intravenously; AstraZeneca) in the scanner room. Scanning for CACS was performed with a tube voltage of 120 kV, a tube current of 80 mA and a slice thickness of 0.5 mm. Patients were given a sublingual nitroglycerine spray (800 μg) 2 minutes before the CCTA scan, for coronary artery vasodilation. A contrast bolus of 60–90 mL non-ionic contrast material (iomepron® 350 mg/mL; Bracco Imaging Scandinavia AB, Hisingen Backa, Sweden) was administered at a flow rate of 5–6 mL/s, followed by a 40–50 mL saline chaser. Automated detection of peak enhancement in the aortic root was used to time the scan. A prospective electrocardiogram-triggered scan was performed at tube voltages between 100 and 135 kV, adapted to body mass index and thoracic anatomy, with an effective tube current of 100–580 mA, 0.5 mm slice thickness reconstruction and a gantry rotation time of 350 ms. All images were acquired during tidal inspiration, with patients holding their breath for approximately 10 seconds, and with simultaneous registration of the patient’s electrocardiogram. Before acquisition, breath-holding and heart rate tests were performed. The radiation dose was quantified with a dose-length product conversion factor of 0.014 mSv/(mGy × cm).

Images were initially reconstructed at 75%, and the best phase of the R–R interval using a soft-tissue kernel algorithm was optimized for cardiac imaging. In the case of motion artefacts and heart arrhythmia, a representative single slice was reconstructed throughout the cardiac cycle in steps of 10–20 ms, to determine the most optimal additional reconstruction phases. Subsequently, datasets were reconstructed and transferred to a remote Vitrea Workstation (Vitrea software, version 6.5.1, Vital images) for further diagnostic workup.

Image analysis

Independent observers with level 2 experience in CCTA performed the CCTA image analysis. The CACS was assessed with the Vitrea Workstation, using CACS analysis software. Coronary calcium was defined as an area of at least three “face-connected” voxels of peak density ≥ 130 HU within a coronary artery, corresponding to a minimum lesion area > 1 mm², which was used as the reference value for the calcium scores. All lesions were added to calculate the Agatston calcium score. The total CACS was used in the analysis, and was determined by adding all lesions from each of the four main coronary arteries: left main coronary artery; left anterior descending coronary artery; left circumflex coronary artery; and right coronary artery. Patients with a high CACS (≥ 1000) did not undergo contrast CCTA, and were referred for ICA.

For all coronary artery segments, axial and multiplanar reformatted reconstruction images were created. Coronary anatomy was assessed in a standardized manner, by dividing the coronary artery tree into 17 segments based on the modified American Heart Association classification [14]. A significant lesion was defined as a stenosis of ≥ 50% in the luminal diameter of the left main coronary artery or of ≥ 50–70% in the major epicardial coronary artery. The presence of significant lesions was determined based on visual estimation.

A three-point scoring system was used for image quality evaluation for each coronary artery. Scores defined as 1 had good image quality with no motion artefacts; scores defined as 2 had moderate image quality, acceptable for clinical diagnosis; and scores defined as 3 had poor image quality, with diagnosis being impossible because of severe artefacts. Only CCTA scans with scores of 1 or 2 were included in the study.

Outcomes

Referral for ICA and revascularization within 90 days after CCTA was considered to be an endpoint. The secondary
Endpoints were the incidences of MACE, defined as non-ST-segment elevation myocardial infarction, unstable angina requiring revascularization and cardiovascular death, and all-cause death during follow-up to a medium of 27 months (interquartile range 21–34 months).

Statistical analysis

Continuous variables are presented as means ± standard deviations; categorical variables are presented as percentages. The Kruskal–Wallis test was used to examine the mean differences within groups. Frequencies were compared using the \( \chi^2 \) test for categorical variables. Total CACS values were classified into five categories: 0 (calcium absent); 1–99; 100–399; 400–999; and ≥1000. Spearman’s \( r \) was used to assess the relationship between obstructive CAD on CCTA and revascularization. Logistic regression was used to identify the role of CACS in predicting revascularization within 90 days after CCTA. Adjustments were made for conventional risk factors: age, sex, family history of CAD, diabetes mellitus, current smoking and use of cholesterol-lowering and antihypertensive drugs. Multivariable regression models with and without CACS were composed to predict revascularization. Receiver operating characteristic (ROC) curves were used to assess the accuracy of the models for predicting revascularization. Significant differences in the areas under the ROC curves (AUCs) were compared using MedCalc statistical software. Net reclassification improvement (NRI) was based on the reclassification tables, and was calculated from the sum of the differences between the “upward” movement in categories for event subjects and the “downward” movement of non-event subjects [15]. Cox regression was used to examine an association between CACS and MACE, and all-cause death. Ninety-five percent confidence intervals (CIs) were calculated for each comparison. A \( P \)-value < 0.05 was considered statistically significant. All tests were two-tailed. The Statistics Package for Social Sciences (SPSS) for Windows, version 17.0 (IBM, Armonk, NY, USA) was used for the analysis.

Results

Patient characteristics

The study population consisted of 2302 patients who underwent CCTA and matched the inclusion criteria. The mean age of the study cohort was 60 ± 9.8 years; 46% were men. During CCTA image acquisition, a mean heart rate of 56 ± 8 beats per minute was recorded. The estimated average radiation dose for the CCTA protocol was 3.5 ± 2.8 mSv (0.47 ± 0.02 mSv for CACS scans), using a conversion coefficient \( k \) of 0.014 for the chest; the mean contrast dose was 71 ± 12 mL. Of our 2302 study patients, 1064 patients had a CACS of 0, and 1238 patients had positive CACS values. The prevalence of a positive CACS was 64.5% (673/1042) for men, which was significantly higher \(( P < 0.001)\) than that for women (44.8%; 565/1260). After CCTA, obstructive CAD was excluded in 1804 patients (78%). The remaining 498 patients (22%) with obstructive CAD on CCTA \(( n = 393)\) and CACS ≥1000 \(( n = 105)\) were referred for ICA, but only 187 (8.1%) underwent revascularization within 90 days after CCTA (a total of 137 percutaneous coronary intervention and 55 coronary artery bypass graft procedures). Nine patients underwent both percutaneous coronary intervention and coronary artery bypass graft surgery, and the remaining patients were recommended for conservative medical treatment.

Patient characteristics according to the CACS

Table 1 presents the baseline characteristics of the study population, distributed according to the CACS groups. The patients with higher CACS values were significantly older and were men. There was a significantly higher prevalence of diabetes mellitus, current smoking and use of antihypertensive and cholesterol-lowering treatments in patients with higher CACS values (Table 1). We found no significant differences between these groups concerning family history of CAD, blood pressure, creatinine concentrations or body mass index.

ICA and revascularization rates based on the CACS

A CACS of 0 was detected in 1064 patients (369 men and 695 women). Twenty-nine patients (2.7%; 9 men and 20 women) with obstructive non-calcified lesions on CCTA were referred for ICA. CCTA-guided revascularization was performed in eight patients (0.75%; three men and five women) (Fig. 1). Seven patients underwent percutaneous coronary intervention with stents (Fig. 2); one patient underwent coronary artery bypass graft surgery. Conservative medical treatment was recommended for the remaining patients. During the follow-up period there were no MACE among patients with a CACS of 0; one patient died from severe pulmonary insufficiency caused by infection.

A positive CACS was detected in 1238 patients (673 men and 565 women). All patients with obstructive CAD identified from the CCTA underwent ICA. There was a moderate correlation between obstructive CAD on CCTA and coronary revascularization (\( \rho = 0.57; P < 0.0001 \)). Of the 541 patients

![Coronary Artery Calcium Score Categories](Image)

**Figure 1.** The frequency of invasive coronary angiography (ICA) and revascularization therapy (REV) after coronary computed tomography angiography, divided into five coronary artery calcium score categories.
<table>
<thead>
<tr>
<th></th>
<th>CACS groups</th>
<th>0 (n = 1064)</th>
<th>1–99 (n = 541)</th>
<th>100–399 (n = 364)</th>
<th>400–999 (n = 215)</th>
<th>≥ 1000 (n = 118)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td>54 ± 9.1</td>
<td>61 ± 9.5</td>
<td>64 ± 8.4</td>
<td>66 ± 7.3</td>
<td>67 ± 7.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td>35</td>
<td>51</td>
<td>52</td>
<td>64</td>
<td>61</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td>48</td>
<td>46</td>
<td>56</td>
<td>50</td>
<td>47</td>
<td>0.051</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>7.1</td>
<td>8.6</td>
<td>15.5</td>
<td>12.6</td>
<td>19.5</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Current smoking</td>
<td></td>
<td>17</td>
<td>18</td>
<td>23</td>
<td>22</td>
<td>29</td>
<td>0.008</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>(mmHg)</td>
<td>135 ± 18</td>
<td>140 ± 19</td>
<td>140 ± 17</td>
<td>141 ± 17</td>
<td>144 ± 22</td>
<td>0.125</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>(mmHg)</td>
<td>82 ± 910</td>
<td>82 ± 9.5</td>
<td>82.5 ± 10</td>
<td>82.5 ± 10</td>
<td>82 ± 10</td>
<td>0.807</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td>26.5 ± 4.6</td>
<td>26.7 ± 4.3</td>
<td>26.7 ± 4.3</td>
<td>26.9 ± 4.2</td>
<td>26.9 ± 4.8</td>
<td>0.84</td>
</tr>
<tr>
<td>Creatinine concentration</td>
<td>(µm/L)</td>
<td>72 ± 14</td>
<td>75 ± 14</td>
<td>76 ± 16</td>
<td>78 ± 16</td>
<td>78 ± 18</td>
<td>0.404</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td></td>
<td>59.5 ± 5.3</td>
<td>60.5 ± 5.4</td>
<td>59.8 ± 4.6</td>
<td>59.6 ± 5.6</td>
<td>58.5 ± 6.6</td>
<td>0.004</td>
</tr>
<tr>
<td>Antihypertensive drug use</td>
<td></td>
<td>30</td>
<td>42</td>
<td>48</td>
<td>56</td>
<td>60</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Cholesterol-lowering drug use</td>
<td></td>
<td>25</td>
<td>38</td>
<td>42</td>
<td>49</td>
<td>58</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation or number (%). CACS: coronary artery calcium score.
with a low CACS (1–99), obstructive CAD was found in 56 (10.3%), and revascularization was performed in 18 (3.3%). A moderate CACS (100–399) was detected in 364 patients, and there was obstructive CAD in 158 patients (43.4%); revascularization was performed in 56 of these patients (15.4%). A high CACS (400–999) was found in 215 patients, and 150 (69.7%) with obstructive coronary lesions on CCTA were referred for ICA; revascularization was performed in only 55 (25.6%) of these patients (Fig. 3). An extremely high CACS (≥1000) was identified in 118 patients; these patients did not undergo contrast-enhanced CCTA, but instead were referred for ICA. One hundred and five patients (89%) underwent ICA, but early revascularization was performed in only 50 (42.4%). The remaining patients were recommended for conservative medical treatment. Seven patients refused to undergo ICA. Six patients underwent myocardial perfusion imaging, which was found to be negative. Thus, obstructive CAD and the rate of revascularization therapy increased according to the CACS group (Fig. 1).

During follow-up, 14 MACE (1.1%) and 30 all-cause deaths (2.4%) were recorded in patients with a positive CACS. Eight MACE (1.05%) were found in patients who were discharged after CCTA with no need for further examination (two non-ST-segment myocardial infarctions, two non-ST-segment myocardial infarctions with revascularization and four cardiovascular deaths). Five patients underwent re-evaluation with ICA, with no need for revascularization.

The CACS was significantly associated with MACE (hazard ratio [HR] 1.97, 95% CI 1.36–2.86) and with all-cause death (HR 2.13, 95% CI 1.64–2.76), even after adjusting for age and sex (HR 1.65, 95% CI 1.09–2.50 and HR 1.83, 95% CI 1.37–2.44, respectively) in patients with a positive CACS.

**Relationship between the CACS and revascularization**

The CACS was found to be an independent predictor of revascularization within 90 days after CCTA. An increase in the CACS per CACS group category was significantly associated with an increased risk of revascularization, with crude and adjusted odds ratios (ORs) of 2.89 (2.53–2.3) and 2.71 (2.33–3.15), respectively; the AUC was 0.85 (95% CI 0.83–0.88). Considering high CACS, the most reliable cut-off value was found to be ≥400, and a CACS ≥400 was significantly associated with an increased risk of ICA and revascularization (Table 2). A CACS ≥400 yielded an AUC of 0.73 (95% CI 0.71–0.76) for ICA and of 0.73 (95% CI 0.68–0.77) for revascularization.

Diagnostic accuracy for prediction revascularization by CCTA was 86%, and it decreased with increasing CACS: the AUC was 0.96 (95% CI 0.94–0.98) in patients with a CACS of 1–99, 0.83 (95% CI 0.79–0.87) in patients with a CACS of 100–399 and 0.70 (95% CI 0.63–0.77) in patients with a CACS of 400–999.

To assess the clinical usefulness of CACS in predicting CCTA-guided revascularization in patients with a positive CACS, we created two multivariable regression models, with and without CACS. Higher calcium scores lead to increasing specificity, so we used the CACS as a continuous variable in the regression models. The CACS was associated with coronary revascularization, with crude and adjusted ORs of 8.86 (95% CI 5.36–14.6) and 7.96 (95% CI 4.71–13.4), respectively. Age, male sex, family history, diabetes mellitus, current smoking and use of cholesterol-lowering and antihypertensive drugs were included in the
G. Urbonaviciene et al.

Figure 3. A. Coronary artery calcium scans showing high calcification (592) in the left anterior descending artery (LAD) territory. B. Coronary computed tomography angiography demonstrating a calcified plaque (arrow) in the LAD. C. Invasive coronary angiography confirmed the obstructive LAD stenosis (arrow), but the results were not haemodynamically significant, and it was suggested that the patient be treated medically.

Table 2 The results of univariate and multivariable logistic regression analyses for invasive coronary angiography and revascularization in patients at low to intermediate risk of coronary artery disease.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis (ICA)</th>
<th>Multivariable analysis (ICA)</th>
<th>Univariate analysis (REV)</th>
<th>Multivariable analysis (REV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.04 (1.03–1.0)</td>
<td>1.04 (1.03–1.06)</td>
<td>1.07 (1.05–1.08)</td>
<td>1.05 (1.03–1.07)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.81 (1.48–2.21)</td>
<td>1.59 (1.22–2.06)</td>
<td>2.26 (1.66–3.08)</td>
<td>1.92 (1.33–2.76)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>1.17 (0.95–1.43)</td>
<td>1.41 (1.09–1.83)</td>
<td>1.08 (0.79–1.48)</td>
<td>1.26 (0.88–1.79)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.39 (1.09–1.77)</td>
<td>1.49 (1.09–2.04)</td>
<td>1.19 (0.83–1.72)</td>
<td>1.19 (0.78–1.83)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.87 (1.34–2.51)</td>
<td>1.49 (0.96–2.29)</td>
<td>1.67 (1.09–2.57)</td>
<td>1.01 (0.57–1.77)</td>
</tr>
<tr>
<td>Antihypertensive drug use</td>
<td>1.83 (1.49–2.24)</td>
<td>1.11 (0.84–1.46)</td>
<td>1.89 (1.39–2.55)</td>
<td>1.09 (0.75–1.59)</td>
</tr>
<tr>
<td>Cholesterol-lowering drug use</td>
<td>1.87 (1.52–2.29)</td>
<td>1.13 (0.86–1.49)</td>
<td>1.87 (1.38–2.53)</td>
<td>1.17 (0.80–1.71)</td>
</tr>
<tr>
<td>CACS ≥ 400</td>
<td>23.2 (17.4–30.9)</td>
<td>15.3 (11.1–21.6)</td>
<td>10.6 (7.69–14.5)</td>
<td>6.45 (4.40–9.3)</td>
</tr>
</tbody>
</table>

Data are expressed as odds ratio (95% confidence interval). CAD: coronary artery disease; CACS: coronary artery calcium score; ICA: invasive coronary angiography; REV: revascularization.

model of conventional cardiovascular risk factors. Based on c-statistics, the model included conventional risk factors, and adding the CACS revealed a significant improvement in the accuracy of predicting revascularization compared with the model that used conventional cardiovascular risk factors (AUC 0.74 [95% CI 0.69–0.78] vs AUC 0.63 [95% CI 0.59–0.68]; P = 0.001) (Fig. 4).

In the reclassification analyses, the patients were classified across tertiles of estimated risk of revascularization categories, as having a low risk (4.1%), an intermediate
risk (6.9%) or a high risk (18.5%). The majority of patients remained at the same level of risk after the CACS was included as an additional variable in the prediction model; some were reclassified “upward” and some were reclassified “downward”. Of the patients who underwent revascularization, 17.5% were reclassified “upward” into a risk category and 1.8% were reclassified “downward” when the CACS was added to the model, yielding an overall change of 15.7%; this finding indicated that the classification improved. For patients who did not undergo revascularization, 1.1% were reclassified downward and 19.1% were reclassified upward, resulting in a classification worsening of 18% and an NRI of −0.023 for revascularization (P = 0.66).

Discussion

The present single-center study has demonstrated that CCTA may be a good non-invasive imaging method that could potentially prevent patients at low to intermediate risk of CAD from receiving unnecessary ICA. In our study, significant CAD based on using CCTA as the initial test was ruled out in 78% of patients. The remaining 22% of patients with obstructive CAD were referred for ICA after CCTA, but only 8.1% received revascularization. The ICA and revascularization rates increased as the CACS increased, and the CACS was found to be an independent predictor of CCTA-guided revascularization. However, the addition of the CACS to conventional risk factors did not improve the classification of patients in risk prediction models.

The prevalence of obstructive CAD has been reported to range from 1% to 3% in symptomatic patients with a CACS of 0. The authors investigated patients with a CACS of 0 to assess obstructive CAD, and reported that the absence of coronary calcification in stable patients at low to intermediate risk helps to exclude flow-limiting CAD [16]. However, other studies have shown that the absence of a CACS does not exclude obstructive CAD [7,8]. In the present study, obstructive CAD was found in 2.7% of patients who had a CACS of 0, and revascularization was performed for 0.75% of these patients (Fig. 2). We maintain, along with previous researchers, that the prevalence of non-calcified coronary plaques and obstructive CAD in CCTA imaging is too great to be ignored [6,9].

New-generation CCTA has high sensitivity and specificity, resulting in excellent accuracy in patients with suspected CAD. However, in clinical practice, 320-row CCTA still has limited value in detecting the vessels that require revascularization, especially for patients with a high CACS. Our results showed that the prevalence of obstructive CAD increased according to the CACS groups. At the threshold of 400, the CACS predicted the patients with a more than 6-fold higher risk of ICA and CCTA-guided revascularization. In a previous multicenter study that examined patterns of ICA and revascularization, follow-up CCTA similarly demonstrated that rates of ICA and revascularization increased in patients with the extent of CAD [17]. But the degree of calcification might affect image quality, and could be the main cause of false-positive findings, resulting in an overestimation of the calcified plaque (Fig. 3). Our results are consistent with those of previous studies, in which the tendency to overestimate CAD severity was reported [18–20]. Although numerous studies have shown good agreement between CCTA and ICA in detecting CAD, a major limitation of CCTA is the discrepancy between angiographic and flow-limiting stenoses [21,22]. Using a 320-row CT scanner, we identified 215 patients with a high CACS (400–999), and 69.7% of these patients were referred for ICA; however, only 25.6% underwent revascularization. Moreover, all patients with an extremely high CACS (≥1000) on CCTA were referred for ICA after non-enhanced CCTA, but revascularization was only performed in 42.3%. Hence, for a large proportion of patients with a high CACS, ICA was still performed only for diagnostic purposes.

Similarly, a study of high-risk patients showed that the correct therapeutic decision regarding conservative therapy versus revascularization based on CCTA was made in 62% of patients who were scheduled for ICA [20]. Moreover, a recently published study demonstrated that the subsequent CCTA-guided ICA rate was 76%, but the revascularization rate was only 47% [23]. In line with previous research, we found that in a population at low to intermediate risk of CAD, the correct decision regarding revascularization was made for about 38% of patients after CCTA. Therefore, we agree with the authors who suggest that a high CACS (≥400, ≥1000) is a logical threshold for initiating follow-up myocardial perfusion testing [24], to avoid overestimating the calcified plaques on CCTA. CCTA is an ideal non-invasive method for ruling out obstructive CAD, but the combination of CCTA and functional non-invasive imaging techniques might play an important role in clinical practice in selecting patients who require ICA and revascularization. Finally, referral for revascularization in patients with a high CACS should rely on the patient’s symptoms and reversible ischemia demonstrated during a functional assessment [25,26]. Consequently, we support the conclusion that was reached in the articles discussed above that, although imaging quality has improved considerably, CCTA alone should not be used to identify patients who require revascularization. Additionally, we
found that the CACS was significantly associated with CCTA-guided revascularization; however, it did not reclassify a substantial proportion of patients with a positive CACS to risk categories.

Study limitations
A number of limitations of the present study should be mentioned. First, the study data are from a single center, with only regional patients, who were subject to referral bias. Thus, our study may not reflect general low- to intermediate-risk symptomatic CAD patients. Second, some observational bias from interobserver variation might have occurred. The high proportion of patients referred for ICA had a high prevalence of different stages of calcifications that influenced image quality. Third, revascularization was indicated based on the detection of significant stenosis (≥75%) in ICA, and was independently called for by an examiner who did not verify existing ischemia.

Conclusions
The results of our single-center study support the concept that 320-row CCTA might rule out significant CAD and may restrict ICA referrals in patients with low to intermediate pretestes for CAD. Nevertheless, a higher CACS causes false-positive CCTA findings, and in clinical practice, a large proportion of patients still underwent ICA after 320-row CCTA for only diagnostic purposes. The CACS was significantly associated with revascularization within 90 days after CCTA, but adding the CACS to conventional risk factors did not improve the classification of patients who required revascularization. Further clinical research is necessary to evaluate the role of the combination of CCTA and functional testing in identifying potential revascularization candidates.

Disclosure of interest
The authors declare that they have no competing interest.

References


