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Cardiac Imaging

Diagnostic Accuracy of Computed Tomography Coronary Angiography According to Pre-Test Probability of Coronary Artery Disease and Severity of Coronary Arterial Calcification

The CORE-64 (Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography) International Multicenter Study

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Objectives The purpose of this study was to assess the impact of patient population characteristics on accuracy by computed tomography angiography (CTA) to detect obstructive coronary artery disease (CAD).

Background The ability of CTA to exclude obstructive CAD in patients of different pre-test probabilities and in presence of coronary calcification remains uncertain.

Methods For the CORE-64 (Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography) study, 371 patients underwent CTA and cardiac catheterization for the detection of obstructive CAD, defined as ≥50% luminal stenosis by quantitative coronary angiography (QCA). This analysis includes 80 initially excluded patients with a calcium score ≥600. Area under the receiver-operating characteristic curve (AUC) was used to evaluate CTA diagnostic accuracy compared to QCA in patients according to calcium score and pre-test probability of CAD.

Results Analysis of patient-based quantitative CTA accuracy revealed an AUC of 0.93 (95% confidence interval [CI]: 0.90 to 0.95). The AUC remained 0.93 (95% CI: 0.90 to 0.96) after excluding patients with known CAD but decreased to 0.81 (95% CI: 0.71 to 0.89) in patients with calcium score ≥600 ($p = 0.077$). While AUCs were similar (0.93, 0.92, and 0.93, respectively) for patients with intermediate, high pre-test probability for CAD, and known CAD, negative predictive values were different: 0.90, 0.83, and 0.50, respectively. Negative predictive values decreased from 0.93 to 0.75 for patients with calcium score <100 or ≥100, respectively ($p = 0.053$).

Conclusions Both pre-test probability for CAD and coronary calcium scoring should be considered before using CTA for excluding obstructive CAD. For that purpose, CTA is less effective in patients with calcium score ≥600 and in patients with a high pre-test probability for obstructive CAD. (J Am Coll Cardiol 2012;59:379–87) © 2012 by the American College of Cardiology Foundation

Computed tomography coronary angiography (CTA) is an emerging tool for the noninvasive assessment of coronary artery disease (CAD). Several expert consensus documents

See page 388

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Abbreviations and Acronyms

AUC = area under the curve

CAD = coronary artery disease

CI = confidence interval

CTA = computed tomography angiography

QCA = quantitative coronary angiography

endorse the use of CTA for excluding CAD in symptomatic patients with reference to numerous studies that have reported high negative predictive values (1,2). However, predictive values heavily depend on disease prevalence within the study population; thus, they cannot be applied outside the context of a defined patient group (3–5). Accordingly, an assessment of pre-test probability of CAD may help predict the value of CTA for excluding or confirming the presence of CAD. In this regard, coronary arterial calcification detected by noncontrast CT correlates well with CAD prevalence, and therefore may help to identify patients in whom ruling out or confirming CAD by CTA is of low yield. Furthermore, coronary arterial calcification may also alter the diagnostic performance of CTA (6–9). Coronary calcium substantially attenuates X-ray penetration, leading to "blooming" artifacts with current CT image reconstruction that may obscure the coronary lumen. Because of the perceived limitation of CTA in patients with severe coronary calcification, many investigators have favored obtaining a coronary calcium score to inform the decision whether to proceed with CTA (10). However, the utilization of a coronary calcium score threshold for deciding to perform or not perform coronary CTA remains controversial (11).

We have previously reported the diagnostic performance of CTA among an international cohort of patients with a calcium score of <600 (12). Including all enrolled patients regardless of the presence and extent of coronary calcification, this investigation tested the following hypotheses: 1) accuracy for CTA to detect obstructive CAD in patients with severe coronary arterial calcification is reduced compared to patients with low or moderate coronary calcification; 2) predictive values for detecting obstructive CAD by CTA are highly variable according to calcium scores and disease prevalence in the study population; and 3) CTA is ineffective for ruling out obstructive CAD in patients with severe coronary arterial calcification and in patients with high pre-test probability of CAD.

Methods

The study design has been described in detail previously (13). In brief, the CORE-64 (Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography) study is a prospective, multicenter diagnostic study performed at 9 hospitals in 7 countries designed to evaluate the diagnostic accuracy of CTA for identifying coronary artery stenosis in patients with suspected or known significant CAD (12). All centers received study approval from their local institutional review boards, and all patients gave written informed consent.

Patient population. Eligible patients were at least 40 years of age, had suspected symptomatic CAD, and were referred for conventional coronary angiography. Patients were not eligible if they had a history of cardiac surgery, allergy to iodinated contrast material or contrast-induced nephropathy, multiple myeloma, organ transplantation, elevated serum creatinine level (>1.5 mg/dl [133 μmol/l]) or creatinine clearance <60 ml/min, atrial fibrillation, New York Heart Association functional class III or IV heart failure, aortic stenosis, percutaneous coronary intervention within the past 6 months, intolerance to beta-blockers, or a body mass index >40. Patients with Agatston calcium scores of ≥600 were pre-specified to be excluded from the primary analysis of the study but were included for secondary analyses performed identically to the main cohort. The rationale by the steering committee for excluding patients with calcium score ≥600 was based on: 1) the precedence of excluding such patients in a prior multicenter study (14); and 2) the concern of futility of CTA imaging in such patients based on the data available at the study design planning. This current investigation includes the results for the primary CORE-64 study patient cohort and for patients with calcium score >600 who were not included in the primary analysis of the CORE-64 study (12).

Acquisition and analysis of data from CT. Patients underwent 2 CT scans (coronary calcium scoring and angiography) before conventional coronary angiography was performed, using 64-row scanners with a slice thickness of 0.5 mm (Aquilion 64, Toshiba Medical Systems, Tochigi-ken, Japan). Calcium scoring was performed with the use of prospective electrocardiographic gating with 400-ms gantry rotation, 120-kV tube voltage, and 300-mA tube current. For CTA, retrospective electrocardiographic gating was used, with heart rate adjusted gantry rotations of 350 ms to 500 ms to enable adaptive multisegmented reconstruction.

mittee of the CORE-320 study, which is sponsored by Toshiba Medical Systems. Drs. Miller, Paul, and Shapiro have received grant support from Toshiba Medical Systems. Dr. Dewey has received grant support from Toshiba Medical Systems, GE Healthcare, Bracco, Guerbet, European Regional Development Fund, German Heart Foundation/German Foundation of Heart Research, and a joint program from the German Science Foundation (DFG) and the German Federal Ministry of Education and Research (BMBF) for meta-analyses; has received speaker fees from Toshiba Medical Systems, Cardiac MR Academy Berlin, Bayer-Schering and Guerbet; is a consultant for Guerbet; is an editor for Cardiac CT from Springer; and is the Cardiac CT Courses Director in Berlin. Dr. Paul has received speaker fees from Toshiba Medical Systems; and advisory fees from Vital Images. Dr. Hoe has served as Director of the Cardiac CT Training Course sponsored by Toshiba Medical Systems, Asia; has received speaker fees from GE Biosciences, Bayer-Schering Pharma, Infinitt Systems, and Toshiba Medical Systems; and has received research grant support from Toshiba Medical Systems. Dr. Lardo reports receiving grant support from CT Core Laboratory and Toshiba Medical Systems; and speaker fees from Toshiba Medical Systems. Dr. Bush has received speaker fees from Bristol-Myers Squibb, Toshiba Medical Systems, and Sanofi-Aventis. Dr. Lima has received grant support from Toshiba Medical Systems, Bracco Diagnostics, and GE Medical Systems; and has received speaker fees from Toshiba Medical Systems. All other authors have reported they have no relationships relevant to the contents of this paper to disclose. Steven E. Nissen, MD, MACC, served as Guest Editor.

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Pitch and tube currents of 240 to 400 mA were determined by patients' weight to ensure a sex-specific radiation dose of 12 to 15 mSv, with a maximum effective dose of 20 mSv, for the combination of multidetector CT calcium scoring and angiographic procedures. This was achieved by instituting a cap of 270 mA for women and 400 mA for men. Sublingual nitrates were given before CTA. Iopamidol (Isovue 370, Bracco Imaging, Milan, Italy) was the intravenous contrast medium used for CTA. Beta-blockers were given if the resting heart rate was >70 beats/min. If the heart rate during acquisition was >80 beats/min, the patient's data were excluded from analysis.

Raw image data sets from all acquisitions were analyzed by an independent core laboratory. Multisegmental reconstruction was performed with 0.5-mm slice thickness, 0.3-mm overlap, multiple phases, and electrocardiogram editing. Images were reconstructed using both standard (FC43) and sharper (FC05) kernels, particularly used to reduce artifacts from high-density structures, such as coronary calcification. Two independent, blinded observers, using a modified coronary model, visually graded each of 19 nonstented segments that were ≥1.5 mm in diameter, according to an ordinal scale (no stenosis, 1% to 29% stenosis, 30% to 49% stenosis, 50% to 69% stenosis, 70% to 99% stenosis, or total occlusion). Then, segments with at least 1 visible stenosis of ≥30% were manually quantified with the use of commercially available software (Vitrea2, version 3.9.0.1, Vital Images, Minnetonka, Minnesota), and results for the 2 readers were averaged. Inter-reader visual and quantitative differences for stenoses >50% were resolved by a third observer.

Data acquisition and analysis of data from conventional coronary angiography. Conventional coronary angiography was performed within 30 days after CTA using standard techniques made uniform across all centers for quantitative coronary angiography (QCA). Intracoronary nitroglycerin was administered (150 to 200 μg), and angiograms in DICOM (Digital Imaging in Communications in Medicine) format were transferred to the angiographic core laboratory. All coronary segments ≥1.5 mm in diameter were analyzed quantitatively and visually by blinded readers using the 29-segment standard model condensed to 19 segments for comparison with data from CTA. Quantitative coronary angiography of the most severe stenosis was performed (CAASII QCA Research, version 2.0.1 software, Pie Medical Imaging, Maastricht, the Netherlands) in all nonstented segments. After all measurements from CTA and conventional coronary angiography were finalized and stored in the database, a detailed adjudication process was performed to ensure the correct cross-modality correspondence of segments (i.e., that the same coronary arterial segments imaged by means of each method were compared).

Statistical analysis. Data management and statistical analyses were performed in the statistical core laboratory (Bloomberg School of Public Health) with the use of SAS software (version 9.1, SAS Institute, Cary, North Carolina), Stata software (version 9, StataCorp, College Station, Texas), and S-PLUS software (version 8.0, Tibco, Palo Alto, California). Computation of confidence limits for AUC values for vessel-level data took account of within-patient clustering through bootstrap resampling, with 2,000 replicate samples. Confidence interval (CI) was calculated according to the percentile method. All p values of < 0.05 were considered to indicate statistical significance. All p values are 2-sided, and 95% CIs are also presented. In addition to the results for the entire cohort, analysis was also performed in subgroups stratified according to pre-test probability of CAD. For this purpose, patients were allocated a probability score according to Morise et al. (15). Because no information was available on chest pain characteristics other than typical angina, all symptomatic patients who did not have typical angina were assumed to have atypical angina. In addition, a secondary analysis was performed for which noncardiac chest pain was assumed in this scenario to assess its effect on reclassification.

Results

Of 405 patients who consented, 34 patients were excluded for technical reasons or because of severe protocol deviations, resulting in a final study population of 371 patients. Demographics and clinical characteristics of study subjects are shown in Table 1. Average age was 61 ± 10 years, and 75% were male. The majority of patients had risk factors for CAD such as arterial hypertension, diabetes mellitus, and hyperlipidemia. Of 371 study patients, only 3 (0.8%) had a low pre-test probability for obstructive CAD (all of whom had a calcium score of <600), whereas 172 (46%) were of intermediate pre-test probability, and 98 (26%) had a high pre-test probability for obstructive CAD. Twenty-six percent of patients (n = 98) had known CAD. Pre-test probability for CAD in the subgroup of patients with calcium score of ≥600 was intermediate in 26% and high in 35%, and known CAD was present in 39% of patients. Pre-test probability was intermediate in 52%, high in 24%, and known CAD was present in 23% of patients with calcium score <600. On QCA, 163 of 291 (56%) patients with calcium score <600 had at least 1 obstructive stenosis of ≥50%, compared to 71 of 80 (89%) patients with calcium score ≥600 and 234 of 371 patients (63%) of the entire cohort. Disease prevalence (≥50% diameter stenosis by QCA) was 48% in patients with intermediate and 70% in patients with high pre-test probability for CAD, and 84% in patients with known CAD.

Patient-based analysis CT angiography. CT DIAGNOSTIC ACCURACY COMPARED TO QCA. The area under the receiver-operating characteristic curve (AUC) for detecting a 50% stenosis by quantitative CTA for the entire cohort was 0.93 (95% CI: 0.90 to 0.95), which is unchanged from the AUC reported in patients with calcium score <600 (0.93, CI: 0.90 to 0.96) (12). In contrast, the AUC was only 0.81 for patients with a calcium score ≥600 (95% CI: 0.71

Table 1 Subject Characteristics

	All Participants (n = 371)	CACS <600 (n = 291)	CACS ≥600 (n = 80)	Intermediate Pre-Test Probability (n = 172)	High Pre-Test Probability (n = 98)	Known CAD (n = 98)
Age, yrs	61 (53–67)	60 (52–66)	63 (58–70)	58 (52–65)	63 (58–71)	63 (55–68)
Men	279 (75.2)	214 (73.5)	65 (81.3)	121 (70.4)	78 (79.6)	80 (81.6)
Race						
White	260 (70.1)	196 (67.4)	64 (80.0)	119 (69.2)	71 (72.5)	68 (69.4)
Black	20 (5.4)	18 (6.2)	2 (2.5)	9 (5.2)	3 (3.1)	7 (7.1)
Asian	78 (21.0)	66 (22.7)	12 (15.0)	37 (21.5)	21 (21.4)	20 (20.4)
Other	13 (3.5)	11 (3.8)	2 (2.5)	7 (4.1)	3 (3.1)	3 (3.1)
BMI,* kg/m^2	27 (25–30)	27 (25–30)	28 (25–32)	27 (25–30)	28 (25–32)	27 (24–31)
<19	6 (1.6)	6 (2.1)	0 (0)	3 (1.7)	1 (1.0)	2 (2.0)
19–30	276 (74.4)	223 (76.6)	53 (66.3)	139 (80.8)	63 (64.3)	71 (72.5)
>30	89 (24.0)	62 (21.3)	27 (33.8)	30 (17.4)	34 (34.7)	25 (25.5)
Hypertension	260 (70.1)	192 (66.0)	68 (85.0)	100 (58.1)	91 (92.9)	67 (68.4)
Diabetes mellitus	97 (26.2)	68 (23.4)	29 (36.3)	17 (9.9)	45 (45.9)	35 (35.7)
Dyslipidemia	236 (63.6)	175 (60.1)	61 (76.3)	82 (47.7)	82 (83.7)	71 (72.5)
Smoking						
Current	67 (18.1)	56 (19.2)	11 (13.8)	28 (16.3)	17 (17.4)	21 (21.4)
Past	154 (41.5)	119 (40.9)	35 (43.8)	63 (36.6)	44 (44.9)	46 (46.9)
Never	150 (40.4)	116 (39.9)	34 (42.5)	81 (47.1)	37 (37.8)	31 (31.6)
FH CAD	111 (29.9)	74 (25.4)	37 (46.3)	39 (22.7)	35 (35.7)	36 (36.7)
Previous MI	83 (22.4)	58 (19.9)	25 (31.3)	n/a	n/a	83 (84.7)
Prior PCI	51 (13.8)	28 (9.6)	23 (28.8)	n/a	n/a	51 (52.0)
Angina	212 (57.1)	169 (58.1)	43 (53.8)	76 (44.2)	86 (87.8)	50 (51.0)
CCS class						
0	7 (1.9)	6 (2.1)	1 (1.3)	4 (2.3)	2 (2.0)	1 (1.0)
1	40 (10.8)	29 (10.0)	11 (13.8)	11 (6.4)	18 (18.4)	11 (11.2)
2	128 (34.5)	103 (35.4)	25 (31.3)	48 (27.9)	52 (53.1)	28 (28.6)
3	24 (6.5)	19 (6.5)	5 (6.3)	9 (5.2)	11 (11.2)	4 (4.1)
4	13 (3.5)	12 (4.1)	1 (1.3)	4 (2.3)	3 (3.1)	6 (6.1)
CACS	148 (8–478)	80 (1–244)	1,066 (786–1,539)	49 (0–337)	251(65–653)	303 (106–764)
Mean ± SD	396 ± 623	60.0 ± 8.6	1,325 ± 781	263 ± 473	515 ± 756	522 ± 669
CTA HR, beats/min	61 (55–69)	62 (55–70)	60 (55–67)	62 (55–68.5)	62 (55–70)	60 (55–67)

Values are median (interquartile range) or n (%). *Calculated as weight in kilograms divided by height in meters squared.
BMI = body mass index; CACS = coronary artery calcium score; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; CTA = computed tomography angiography; FH = family history; HR = heart rate; MI = myocardial infarction; n/a = not available; PCI = percutaneous coronary intervention.

to 0.89, p = 0.077, vs. <600). The AUC curves, including the calibration curve for CTA, are shown in Figure 1. The calibration curve allows assessing CTA performance at different thresholds for determining obstructive CAD. For example, when using a 45% stenosis threshold for determining CAD by CTA, sensitivity for the entire cohort rises to 92% while specificity decreases to 75% (Fig. 1A). The AUC values did not differ significantly in patients with intermediate and high pre-test probability (0.93 [95% CI: 0.89 to 0.97] vs. 0.92 [95% CI: 0.85 to 0.96], p = 0.70). The AUC for patients with known CAD was also similar (0.93 [95% CI: 0.86 to 0.97]) (Fig. 1B). Furthermore, the AUC did not change (0.93 [95% CI: 0.90 to 0.96]) for the remaining 273 patients (disease prevalence 55.7%) after excluding patients with known CAD (sensitivity, specificity, and positive and negative predictive values and their 95% CIs were 91% [85% to 95%], 87% [79% to 92%], 90% [84% to 94%], and 88% [81% to 93%]). The point statistics for CT diagnostic accuracy according to subgroups are listed in Table 2.

VISUAL CT ASSESSMENT. Visual and quantitative assessments by CTA of stenosis severity were similar (Table 2). The AUC for the detection of obstructive CAD by visual assessment for the entire cohort, the initial group with calcium score <600, and patients with calcium score ≥600 were 0.92, 0.93, and 0.86, respectively (p = 0.36, <600 vs. ≥600 calcium score group), which were not statistically significantly different from quantitative assessment (p = 0.135, ≥600 vs. quantitative CTA).

Analysis according to calcium scores and pre-test probability of CAD. Table 3 presents the disease prevalence (≥50% stenosis by QCA) according to calcium score brackets. Whereas only 53 of 151 (35%) patients with calcium score <100 had obstructive disease by QCA, 181 of 220 (82%) patients with calcium score ≥100 had significant disease. For patients with calcium score <100 and intermediate pre-test probability, disease prevalence was only 25% compared to 55% in patients with high pre-test probability or known CAD (data were combined since they are similar in characteristics). For

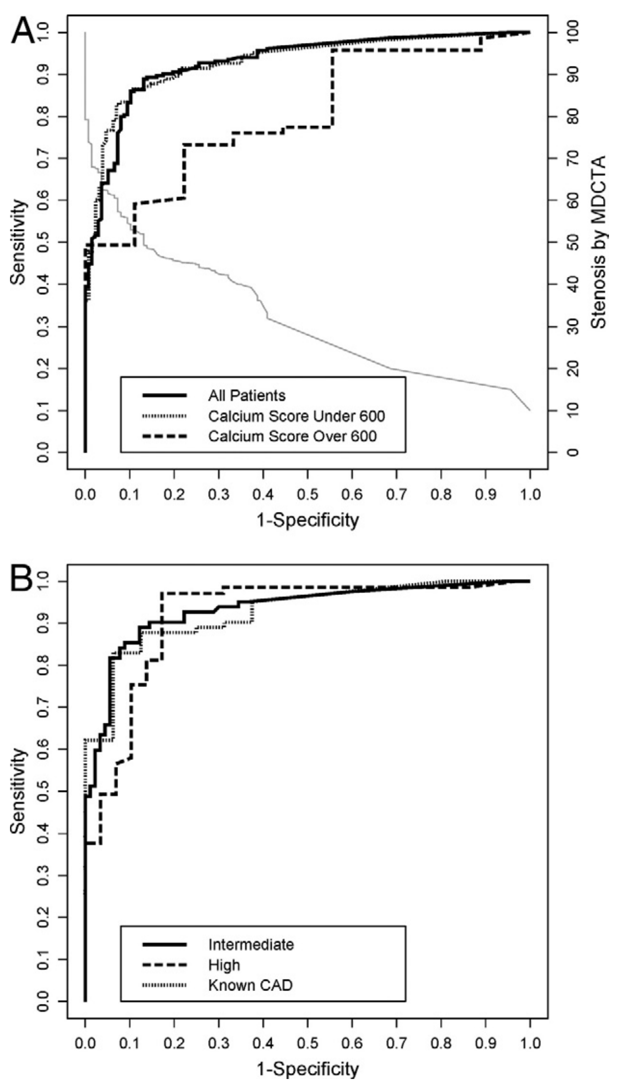

Figure 1 **ROC Curves for CTA Diagnostic Accuracy According to Calcium Scores and Pre-Test Probability**

(A) Receiver-operating characteristic (ROC) curves for all patients **(solid line)**, patients with calcium score <600 **(dotted line)**, and patients with calcium score ≥600 **(dashed line)**, describing the diagnostic performance of quantitative multidetector (MD) computed tomography angiography (CTA) to identify a ≥50% coronary arterial stenosis in a patient when compared to quantitative coronary angiography (QCA). The **light gray line** is a calibration curve; to identify the corresponding CTA threshold point, extend a vertical line from a point on the ROC curve to the calibration curve and then a horizontal line to the right ordinate, which gives the CTA threshold. For example, a sensitivity of 88% and a false positive rate (1-specificity) of 13% correspond to a threshold point of 50% stenosis detected by CTA. The area under the curve (AUC) was 0.93 for all patients, 0.93 for patients with calcium score <600, and 0.80 for patients with calcium score ≥600 (p = 0.063 vs. score <600). **(B)** The ROC curves for patients with intermediate pre-test probability of coronary artery disease **(solid line)**, high pre-test probability **(dashed line)**, and known coronary artery disease **(dotted line)**. The area under the curve (AUC) was 0.93 for patients with intermediate pre-test probability of coronary artery disease, 0.92 for patients with high pre-test probability, and 0.93 for patients with known coronary artery disease.

patients with calcium score ≥100, disease prevalence was similarly high for patients with intermediate and high pre-test probability/known CAD (77% vs. 85%).

To assess the effect of coronary calcification on positive and negative predictive values, we separately analyzed data according to absent, mild, moderate, and severe calcification and pre-test probability (Fig. 2). Positive predictive values were very good (88% to 98%) and negative predictive values were poor (50% to 64%) for patients with high pre-test probability/known CAD and any coronary calcification (calcium score >0). Only 20 of 196 (10%) patients with high pre-test probability/known CAD had no coronary calcification, and both positive and negative predictive values were excellent for these patients (100% and 93%, respectively). Among patients with intermediate pre-test probability, positive predictive values were modest (60% to 80%), and negative predictive values (91% to 96%) were excellent only with low calcium scores (0 to 99) whereas positive predictive values were very good (90% to 93%) and negative predictive values were poor (71% to 78%) with moderate and severe coronary calcification (calcium scores 100 to 399 and ≥400) (Fig. 2). When combining data into 2 groups, negative predictive value in patients with intermediate pre-test probability was 93% for a calcium score of 0 to 99 and 75% for a calcium score ≥100 (p = 0.053). Because we assumed patients with nonanginal chest pain to have atypical rather than noncardiac chest pain, we may have classified some patients into a higher pre-test probability category. If we assumed noncardiac chest pain instead, 10 patients would have been reclassified from high to intermediate, and 17 from intermediate to low pre-test probability. The reclassifications did not result in different diagnostic accuracy for the groups: for 165 patients with intermediate pre-test probability and 50.3% disease prevalence, sensitivity, specificity, positive and negative predictive values, and AUC including their 95% CIs were 89% (80% to 95%), 85% (76% to 92%), 86% (77% to 93%), 89% (79% to 95%), and 0.93 (0.88% to 0.96%). For 88 patients with high pre-test probability and 70.5% disease prevalence sensitivity, specificity, positive and negative predictive values, and AUC including their CIs were 92% (82% to 97%), 85% (65% to 96%), 93% (84% to 98%), 81% (62% to 94%), and 0.92 (0.84% to 0.97%). For 20 patients with low pre-test probability after reclassification (disease prevalence of 35%), sensitivity, specificity, positive and negative predictive values, and AUC including their lower CIs were 100% (59%), 100% (75%), 100% (59%), 100% (75%) and 1.00 (0.83%). Figure 3 illustrates the dependency of predictive values on disease prevalence in the study population.

Discussion

The main results of this investigation can be summarized as follows. 1) Despite poorer performance in patients with severe coronary calcification, inclusion of such patients did not alter the overall test performance of CTA to detect a

Table 2 **Diagnostic Accuracy of CTA for Detecting ≥50% Coronary Arterial Stenosis**

	n	CAD	Sensitivity	Specificity	PPV	NPV	AUC
Quantitative CTA, all	371	63.1%	0.88 (0.83–0.92)	0.87 (0.80–0.92)	0.92 (0.88–0.95)	0.81 (0.74–0.87)	0.93 (0.90–0.95)
Quantitative CTA, <600	291	56.0%	0.85 (0.79–0.90)	0.90 (0.83–0.94)	0.91 (0.86–0.95)	0.83 (0.75–0.89)	0.93 (0.90–0.96)
Quantitative CTA, ≥600	80	88.8%	0.94 (0.86–0.98)	0.44 (0.14–0.79)	0.93 (0.85–0.98)	0.50 (0.16–0.84)	0.81 (0.71–0.89)
Quantitative CTA, without known CAD	273	55.7%	0.91 (0.85–0.95)	0.87 (0.79–0.92)	0.90 (0.84–0.94)	0.88 (0.81–0.93)	0.93 (0.90–0.96)
Visual CTA, all	371	63.1%	0.85 (0.80–0.89)	0.90 (0.83–0.94)	0.93 (0.89–0.96)	0.78 (0.73–0.87)	0.92 (0.89–0.95)
Visual CTA, calcium <600	291	56.0%	0.83 (0.76–0.88)	0.91 (0.85–0.96)	0.92 (0.87–0.96)	0.81 (0.71–0.85)	0.92 (0.89–0.95)
Visual CTA, calcium ≥600	80	88.8%	0.96 (0.88–0.99)	0.56 (0.21–0.86)	0.94 (0.86–0.98)	0.63 (0.24–0.91)	0.86 (0.77–0.93)
Quantitative CTA, intermed PTP	172	47.7%	0.89 (0.80–0.95)	0.88 (0.79–0.94)	0.87 (0.78–0.93)	0.90 (0.81–0.95)	0.93 (0.89–0.97)
Quantitative CTA, high PTP	98	70.4%	0.93 (0.84–0.98)	0.83 (0.64–0.94)	0.93 (0.84–0.98)	0.83 (0.64–0.94)	0.92 (0.85–0.96)
Quantitative CTA, known CAD	98	83.7%	0.83 (0.73–0.90)	0.88 (0.62–0.98)	0.97 (0.90–1.00)	0.50 (0.31–0.69)	0.93 (0.86–0.97)

Values are presented for all patients, patients with calcium score <600, patients with calcium score ≥600, patients with intermediate pre-test probability, high pre-test probability, and known CAD, including the 95% confidence intervals.

AUC = area under the curve; CAD = coronary artery disease; CTA = computed tomography angiography; intermed = intermediate; NPV = negative predictive value; PPV = positive predictive value; PTP = pre-test probability.

≥50% stenosis in the CORE-64 multicenter study. 2) The diagnostic accuracy for CTA to detect obstructive CAD was reduced in patients with severe coronary calcification (calcium score of ≥600) compared to patients with a calcium score <600. 3) Pre-test probability of CAD and coronary calcium score markedly affect negative predictive values for detecting obstructive CAD by CTA. 4) Noninvasive coronary angiography using CT best rules out obstructive CAD in patients with low-intermediate pre-test probability of CAD and mild coronary calcification or in patients with a calcium score of zero.

CTA diagnostic accuracy. Compared to 2 other multicenter studies using 64-slice technology, our results revealed slightly lower sensitivity but higher specificity for detecting obstructive CAD by CTA, suggesting a higher reader threshold to call a given stenosis obstructive (7,16). When combined with a relatively higher prevalence of obstructive CAD, positive predictive values were higher but negative predictive values were lower compared to other multicenter studies (7,16). A unique feature of the CORE-64 study is the use of continuous quantitative CTA data in addition to semiquantitative assessment, which allows assessing CTA performance with greater independence from reader bias. For example, if a more conservative approach was chosen, namely, a lower threshold to call a stenosis significant such as typically employed in clinical practice, sensitivity for the entire cohort would increase from 88% to 94% for a 40% stenosis threshold, at the expense of specificity, which would decrease from 87% to 64% (Fig. 1). These results are almost

Table 3 **Distribution of Calcium Scores and Associated Disease Prevalences**

Calcium Score	All	Intermediate Risk	High Risk or Known CAD
0	72 (14+, 58−)	50 (7+, 43−)	20 (7+, 13−)
1–99	79 (39+, 40−)	47 (17+, 30−)	31 (21+, 10−)
100–199	52 (36+, 16−)	19 (15+, 4−)	33 (21+, 12−)
200–299	29 (25+, 4−)	11 (9+, 2−)	18 (16+, 2−)
300–399	32 (27+, 5−)	9 (5+, 4−)	23 (22+, 1−)
400–499	18 (14+, 4−)	11 (10+, 1−)	7 (4+, 3−)
500–599	9 (8+, 1−)	4 (3+, 1−)	5 (5+, 0−)
600+	80 (71+, 9−)	21 (16+, 5−)	59 (55+, 4−)

Given are the number of patients in each calcium score bracket (+ and − symbols indicate number of positive and negative findings by quantitative coronary angiography defined as ≥50% coronary arterial stenosis).

CAD = coronary artery disease.

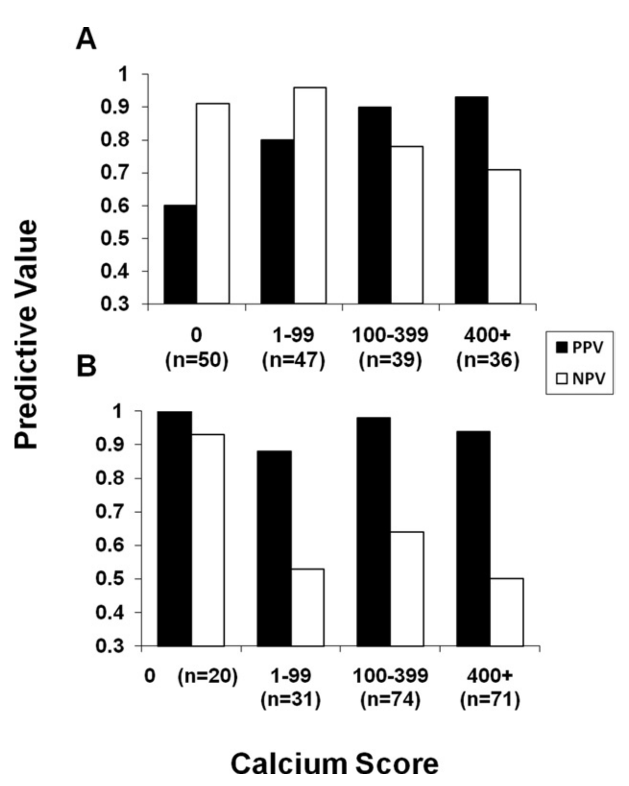

Figure 2 **Predictive Values According to Pre-Test Probability and Presence/Extent of Coronary Calcification**

Shown is a plot of positive predictive values **(solid bars)** and negative predictive values **(open bars)** for **(A)** patients with intermediate pre-test probability of coronary artery disease (n = 172), and **(B)** patients with either high pre-test probability or known coronary artery disease (n = 196 combined), grouped into patients without calcification (calcium score 0) and with mild calcification (score 1 to 99), moderate calcification (score 100 to 399), and severe coronary calcification (score >400).

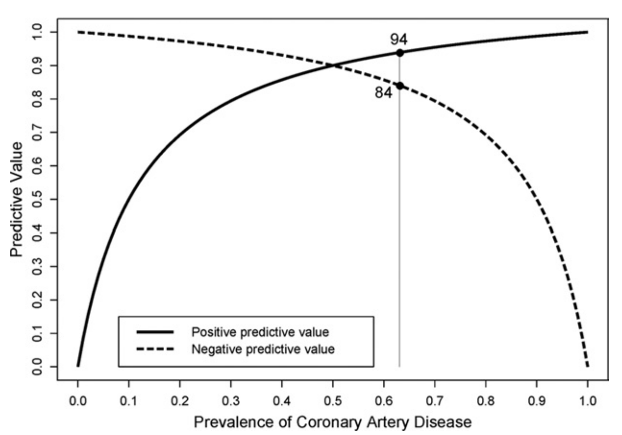

Figure 3 Predictive Values of a Diagnostic Test According to Disease Prevalence

Shown are positive predictive values **(solid line)** and negative predictive values **(dashed line)** as a function of disease prevalence, ranging from 0% to 100% for a diagnostic test with a sensitivity and specificity of 90%, chosen as arbitrary but typical values. The **reference line** indicates the disease prevalence observed in this study (63%). One can appreciate the large shifts in predictive values according to low versus high disease prevalence.

identical to those in reports from another multicenter study in a comparable population (16), demonstrating consistency of CTA accuracy results if methodology and patient characteristics are considered. However, comparison of our results to the ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) multicenter study (7) is difficult because its disease prevalence and patient population were markedly different from ours. Nevertheless, the reported AUC, which depends only on sensitivity and specificity, of 0.96 (95% CI: 0.94 to 0.98) was similar to what we found in our study.

In our study, we demonstrate that predictive values critically depend on the disease prevalence in the study population. With rising disease prevalence, positive predictive values increase while negative predictive values decrease. Thus, general statements regarding the positive or negative predictive value of CTAs or any other tests should be avoided, as even a test with high sensitivity and specificity displays a remarkable variability for predictive values within a clinically applicable range of disease prevalence (Fig. 3). Rather, the predictive value of a diagnostic test has to be seen in the context of the study population and should be applied accordingly. Both pre-test probability and calcium score identify patients of different disease prevalence and may help recognizing the most adequate clinical scenario for the use of CTA.

Impact of severe coronary arterial calcification on CTA performance. Previous investigations have come to different conclusions with regard to whether severe coronary arterial calcification hampers CTA diagnostic performance. Several groups reported the same or better performance in patients with high calcium scores compared to patients with less calcification, whereas others found poorer performance in the former (6–9). Our results revealed reduced CTA accuracy to detect obstructive CAD in patients with severe coronary calcification (≥600 calcium score) that was predominantly the result of markedly poorer specificity while sensitivity actually improved. The poor specificity was driven by the high disease prevalence of 89% in this subgroup—only 9 of 80 patients did not have obstructive CAD by QCA. Accordingly, the negative predictive value was low while the positive predictive value was excellent. Therefore, CTA is ineffective for ruling out coronary arterial stenoses in patients with severe coronary calcification who were referred for invasive angiography because of clinical suspicion of significant CAD.

Impact of pre-test probability on CTA diagnostic accuracy. Because predictive values are substantially influenced by the disease prevalence in the studied population, we separated our population by pre-test probability for obstructive CAD. While overall test accuracy did not vary significantly among patients with intermediate and high pre-test probability and patients with known CAD, which was largely because of balanced shifts in sensitivity and specificity, negative predictive value was higher in patients with intermediate pre-test probability than in other subgroups as disease prevalence was lower. If the purpose of CTA is to exclude obstructive CAD, a high negative predictive value is desired while a less than optimal positive predictive value may be acceptable. In patients with intermediate pre-test probability, remarkably, both positive and negative predictive values were very good in our study, with 87% and 90%, respectively. Our results reveal little about the use of CTA in patients with low pre-test probability as they were poorly represented in our population. As predictive values are a function of a test's sensitivity and specificity for a given disease prevalence, we can confidently state that the negative predictive value would exceed 95% for patients with low pre-test probability (<20%) using CORE-64 study data, confirming results of other studies documenting a high negative predictive value in a population that appears most applicable to the use of CTA at present. Our secondary analysis of 20 patients of low-intermediate pre-test probability and 35% disease prevalence yielding a negative predictive value of 100% supported this notion. Conversely, our results confirm current recommendations to omit CTA for excluding obstructive CAD in patients with high pre-test probability for CAD, with the possible exception of patients with zero calcium score, who were, however, a minority (10%) within this group.

Is there a calcium score threshold beyond which CTA is not effective? Currently, the primary clinical value of CTA is perceived to be its ability to conclusively rule out obstructive CAD in patients of low-intermediate pre-test probability with equivocal test results and atypical symptoms (1,2). Because the probability of obstructive CAD increases with the coronary calcium score, some clinicians withhold

CTA in the setting of severe coronary arterial calcification (11). The coronary calcium score threshold beyond which CTA is deemed unnecessary, however, is controversial. Our analysis reveals that negative predictive values were 90% and greater in patients with intermediate pre-test probability for CAD but not more than mild coronary calcification, as well as in patients with any pre-test probability and a calcium score of zero. Conversely, negative predictive value for CTA was highly variable and on average poor in patients with high pre-test probability and known CAD with any coronary calcification, as well as in patients with intermediate pre-test probability for CAD and more than mild coronary calcification (Fig. 2). A coronary calcium score of ≥100 in patients referred for cardiac catheterization with clinical suspicion of CAD, therefore, identified patients who are very likely to have obstructive CAD and in whom CTA is less effective in ruling out disease. Conversely, the absence of coronary calcification is insufficient to dismiss the possibility of obstructive CAD (17), and CTA is highly effective in excluding significant coronary arterial stenoses in such patients.

Study limitations. Although we attempted to provide a comprehensive characterization of our patient population, our data are incomplete. We attempted to characterize the patient population using an established CAD pre-test probability score, but some factors influencing post-test probability may not have been accounted for. Our results, therefore, may represent a conservative assessment of the utility of CTA in the presence of coronary calcification. Furthermore, we cannot provide data on how many patients were screened but not included in this cohort. Lastly, our patient population is international and not necessarily representative of a North American population per se.

Consistent with current guidelines (1,2), statements with regard to the clinical usefulness of CTA are being made with respect to its ability to detect, and particularly to rule out, obstructive CAD. Moreover, CTA is capable of providing information about lesion location, plaque characteristics, remodeling status, and other features, which may prove to be useful for clinical management of patients in selected situations. Therefore, while the accuracy of CTA to merely detect obstructive disease may be reduced compared to conventional angiography in patients with severe coronary calcification or high pre-test probability, additional CAD assessment may outweigh this "deficiency." This hypothesis is being tested in current investigations.

Although it would be desirable from a clinical standpoint to identify a calcium score "threshold" beyond which CTA is considered not useful, it has to be emphasized that such a threshold does not exist. Rather, there is a continuous shift from what one may consider an effective test to a less effective one, with uncertainty of test performance in the transition zone. Therefore, as with all diagnostic test modalities, clinicians should interpret the calcium score in the greater context for guidance of how to interpret the CTA rather than making binary decisions based on particular score thresholds.

Lastly, some of the secondary analyses contained in this investigation contained relatively small numbers, and results must be interpreted with caution.

Conclusions

The ability of a diagnostic test to predict or to exclude disease is critically dependent not only on its sensitivity and specificity but also on the disease prevalence within the study population. Accordingly, our results demonstrate that pre-test probability for CAD and coronary calcium score, which are both predictive of disease prevalence, are important for the effectiveness of CTA to exclude or confirm the presence of obstructive CAD in patients. Computed tomography angiography accurately rules out obstructive CAD in patients with low or intermediate pre-test probability who have low coronary calcium scores as well as in patients with any pre-test probability and a calcium score of zero. Conversely, CTA is less effective for this purpose in patients with high pre-test probability, known CAD, and patients with extensive coronary calcification. In patients with clinical suspicion of CAD sufficient to consider cardiac catheterization, moderate or severe coronary calcification alone is highly predictive of obstructive CAD.

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