ORIGINAL ARTICLE

Diagnostic Performance of Coronary Angiography by 64-Row CT

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ABSTRACT

BACKGROUND

The accuracy of multidetector computed tomographic (CT) angiography involving 64 detectors has not been well established.

METHODS

We conducted a multicenter study to examine the accuracy of 64-row, 0.5-mm multidetector CT angiography as compared with conventional coronary angiography in patients with suspected coronary artery disease. Nine centers enrolled patients who underwent calcium scoring and multidetector CT angiography before conventional coronary angiography. In 291 patients with calcium scores of 600 or less, segments 1.5 mm or more in diameter were analyzed by means of CT and conventional angiography at independent core laboratories. Stenoses of 50% or more were considered obstructive. The area under the receiver-operating-characteristic curve (AUC) was used to evaluate diagnostic accuracy relative to that of conventional angiography and subsequent revascularization status, whereas disease severity was assessed with the use of the modified Duke Coronary Artery Disease Index.

RESULTS

A total of 56% of patients had obstructive coronary artery disease. The patient-based diagnostic accuracy of quantitative CT angiography for detecting or ruling out stenoses of 50% or more according to conventional angiography revealed an AUC of 0.93 (95% confidence interval [CI], 0.90 to 0.96), with a sensitivity of 85% (95% CI, 79 to 90), a specificity of 90% (95% CI, 83 to 94), a positive predictive value of 91% (95% CI, 86 to 95), and a negative predictive value of 83% (95% CI, 75 to 89). CT angiography was similar to conventional angiography in its ability to identify patients who subsequently underwent revascularization: the AUC was 0.84 (95% CI, 0.79 to 0.88) for multidetector CT angiography and 0.82 (95% CI, 0.77 to 0.86) for conventional angiography. A per-vessel analysis of 866 vessels yielded an AUC of 0.91 (95% CI, 0.88 to 0.93). Disease severity ascertained by CT and conventional angiography was well correlated (r=0.81; 95% CI, 0.76 to 0.84). Two patients had important reactions to contrast medium after CT angiography.

CONCLUSIONS

Multidetector CT angiography accurately identifies the presence and severity of obstructive coronary artery disease and subsequent revascularization in symptomatic patients. The negative and positive predictive values indicate that multidetector CT angiography cannot replace conventional coronary angiography at present. (ClinicalTrials.gov number, NCT00738218.)

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Coronary artery disease is the leading cause of death in the United States.[1] In symptomatic patients, diagnosis of the presence and severity of coronary artery disease is critical for determining appropriate clinical management.[2,3] Indirect evaluation of coronary stenosis, such as through stress testing, has limited diagnostic ability as compared with direct conventional coronary angiography.[4,5] Conventional coronary angiography reveals the extent, location, and severity of coronary obstructive lesions, which are potent predictors of outcome,[2,3,6,7] and identifies high-risk patients who may benefit from revascularization.[3,6,8-11] Thus, invasive coronary angiography, despite the associated risks, remains the standard for the diagnosis of obstructive coronary artery disease.

Multidetector computed tomographic (CT) angiography has been proposed as a noninvasive test to determine the presence of coronary obstruction.[12-14] However, systematic analysis of published studies to date has shown marked variation in results, which can probably be explained by the limitations of the selection and number of patients, single-center study design, and CT technology.[15] In addition, the ability of multidetector CT angiography to predict the need for revascularization in symptomatic patients with suspected coronary artery disease has not been investigated. These inconsistencies and gaps in knowledge reinforce the need for large multicenter studies performed with rigorous control of bias, in which data are analyzed in central core laboratories and standardized protocols are applied in diverse institutions around the world.

We conducted a multicenter, international study using centralized, blinded analysis to determine the diagnostic accuracy of multidetector CT angiography involving 64 detectors and a slice thickness of 0.5 mm for the purpose of identifying symptomatic patients with suspected coronary artery disease who should be referred for conventional coronary angiography. Therefore, the study was designed to determine the presence or absence of obstructive disease in patients already at substantial risk for coronary artery disease who may require coronary revascularization.

METHODS

STUDY DESIGN

The Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography (CORE 64) study is a prospective, multicenter diagnostic study performed at nine hospitals in seven countries (three in the United States and one each in Germany, Japan, Brazil, Canada, Singapore, and the Netherlands). All centers received study approval from their local institutional review boards, and all patients gave written informed consent. The study was designed by the CORE 64 Steering Committee; the sponsors had no role in study design, data accrual, data analysis, or manuscript preparation.

POPULATION OF PATIENTS

Eligible patients were at least 40 years of age, had suspected symptomatic coronary artery disease, and were referred for conventional coronary angiography. Patients were not eligible if they had history of cardiac surgery, allergy to iodinated contrast dye or contrast dye–induced nephropathy, multiple myeloma, organ transplantation, elevated serum creatinine level (>1.5 mg per deciliter [133 μmol per liter]) or creatinine clearance less than 60 ml per minute, atrial fibrillation, New York Heart Association 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 (the weight in kilograms divided by the square of the height in meters) of more than 40. Women of childbearing potential had a negative pregnancy test within 24 hours before undergoing multidetector CT angiography. Patients with Agatston calcium scores over 600 were prespecified to be excluded from the primary analysis and entered into a registry.

Investigators, physicians, and patients were unaware of the results of coronary multidetector CT angiography. Patients were followed for the interim occurrence of death, myocardial infarction, stroke, revascularization (percutaneous or surgical), hospitalization for angina or heart failure, and other serious adverse events at 7 and 30 days after conventional coronary angiography. Multidetector CT images were reviewed locally for noncardiac abnormalities, and abnormal findings were communicated to the patient's physician.

ACQUISITION AND ANALYSIS OF DATA FROM MULTIDETECTOR CT ANGIOGRAPHY

Patients underwent two multidetector CT tests (coronary calcium scoring and angiography), before conventional coronary angiography was performed, using 64-row scanners with a slice thickness of 0.5 mm (Aquilion, Toshiba Medical Systems). Tech-

Table 1. Modified Duke Coronary Artery Disease Index.*

Extent of Coronary Artery Disease	Prognostic Weight
Stenosis <50%	0
Stenosis ≥50%	
1 Vessel	23
2 Vessels	37
3 Vessels	56
Stenosis ≥50% and proximal LAD with stenosis ≥50%	
1 Vessel	48
2 Vessels	56
3 Vessels	74
Stenosis in left main coronary artery	
≥50%	80
≥70%	100

* The Duke Coronary Artery Disease Index (described in Mark et al.[2]) is hierarchical, and patients are assigned to the most severe category that applies to them. LAD denotes left anterior descending coronary artery.

Figure 1 (facing page). Enrollment of Study Patients and Data Analyses.
All conventional coronary angiography (CCA) analyses were performed with quantitative coronary angiography. LAD denotes left anterior descending coronary artery, LCX left circumflex coronary artery, LM left main coronary artery, MDCTA multidetector computed tomographic angiography, QCA quantitative coronary angiography, and RCA right coronary artery.

nologists completed centralized training to ensure uniform calcium scoring and compliance with the multidetector CT angiography protocol, as monitored throughout the study. Calcium scoring was performed with the use of prospective electrocardiographic (ECG) gating with 400-msec gantry rotation, 120-kV tube voltage, and 300-mA tube current. For multidetector CT angiography, retrospective ECG gating was used, with heart rate–adjusted gantry rotations of 350 to 500 msec to enable adaptive multisegmented reconstruction. 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 multidetector CT angiography, along with intravenous iopamidol (Isovue 370, Bracco Diagnostics). Beta-blockers were given if the resting heart rate was above 70 beats per minute. If heart rate during acquisition was more than 80 beats per minute, the patient's data were excluded from analysis.

Raw image data sets from all acquisitions were analyzed by an independent core laboratory. Multisegment reconstruction was performed with 0.5-mm slice thickness, 0.3-mm overlap, multiple phases, and ECG editing.[16] Images were reconstructed using both standard (FC43) and sharper (FC05) kernels. Two independent observers, using a modified coronary model,[17,18] visually graded each of 19 nonstented segments that were 1.5 mm or more 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 one visible stenosis of 30% or more were manually quantified with the use of commercially available software (Vitrea2 version 3.9.0.1, Vital Images), and results for the two readers were averaged. Interreader visual and quantitative differences exceeding 50% were resolved by a third observer. Vessel-based data sets were constructed from the final segment data to create the patient-based data sets used in the primary analysis. In the visual analysis, consensus was required for the determination of segments that could not be evaluated. In the quantitative analysis, only segments that could not be measured by any of the three observers were considered not able to be evaluated and therefore negative in patient-based and vessel-based analyses (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

DATA ACQUISITION AND ANALYSIS OF DATA FROM CONVENTIONAL CORONARY ANGIOGRAPHY

Conventional coronary angiography was performed within 30 days after multidetector CT angiography using standard techniques made uniform across all centers for quantitative coronary angiography. Intracoronary nitroglycerin was administered (150 to 200 μg), and angiograms in Digital Imaging in Communications in Medicine (DICOM) format were transferred to the angiographic core laboratory. All coronary segments 1.5 mm or more in diameter were analyzed visually and quantitatively using the 29-segment standard model[9,18] condensed to 19 segments for comparison with data

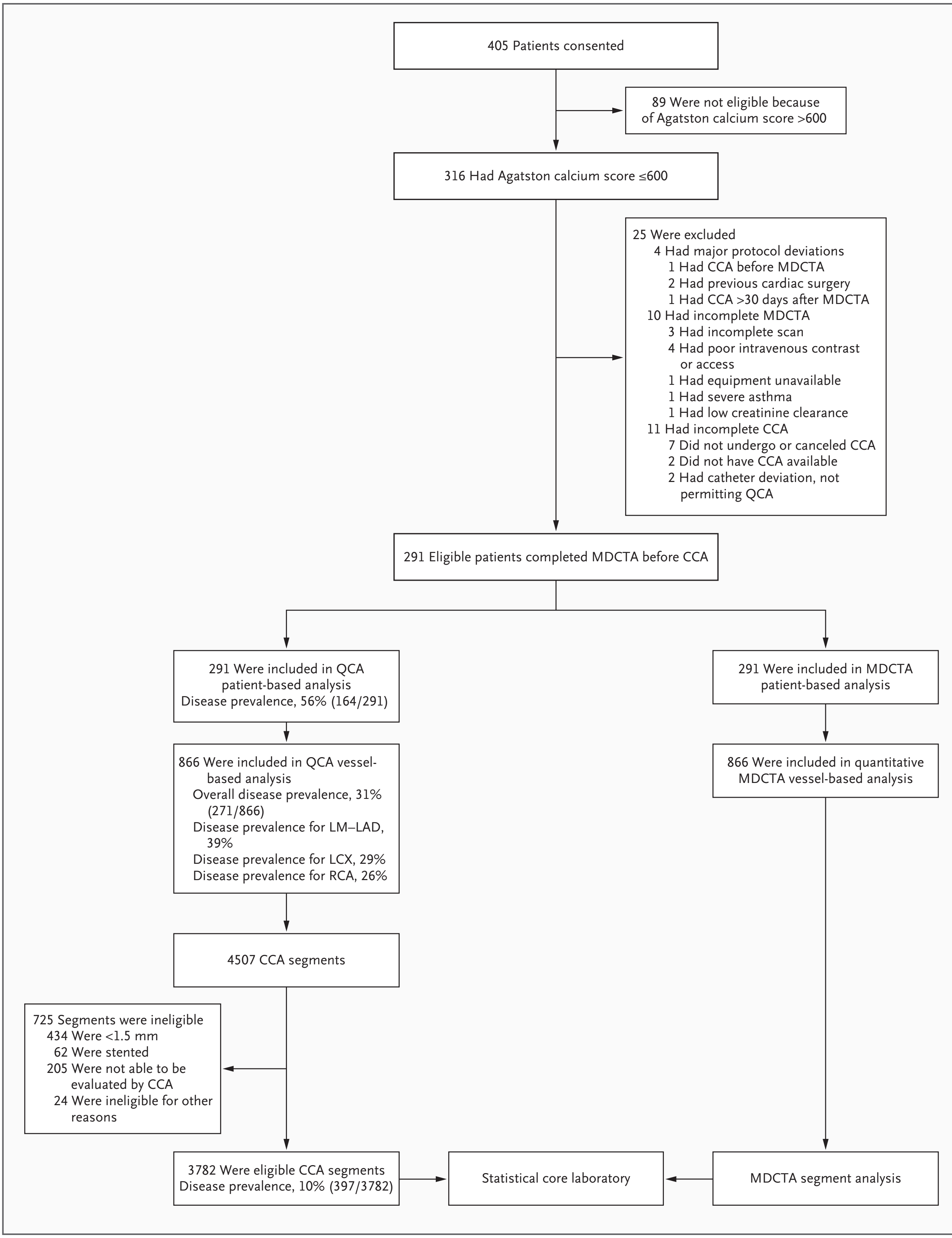
405 Patients consented
89 Were not eligible because of Agatston calcium score >600
316 Had Agatston calcium score ≤600
25 Were excluded
4 Had major protocol deviations
1 Had CCA before MDCTA
2 Had previous cardiac surgery
1 Had CCA >30 days after MDCTA
10 Had incomplete MDCTA
3 Had incomplete scan
4 Had poor intravenous contrast or access
1 Had equipment unavailable
1 Had severe asthma
1 Had low creatinine clearance
11 Had incomplete CCA
7 Did not undergo or canceled CCA
2 Did not have CCA available
2 Had catheter deviation, not permitting QCA
291 Eligible patients completed MDCTA before CCA
291 Were included in QCA patient-based analysis
Disease prevalence, 56% (164/291)
291 Were included in MDCTA patient-based analysis
866 Were included in QCA vessel-based analysis
Overall disease prevalence, 31% (271/866)
Disease prevalence for LM–LAD, 39%
Disease prevalence for LCX, 29%
Disease prevalence for RCA, 26%
866 Were included in quantitative MDCTA vessel-based analysis
4507 CCA segments
725 Segments were ineligible
434 Were <1.5 mm
62 Were stented
205 Were not able to be evaluated by CCA
24 Were ineligible for other reasons
3782 Were eligible CCA segments
Disease prevalence, 10% (397/3782)
Statistical core laboratory
MDCTA segment analysis

Table 2. Baseline Characteristics of the 291 Patients.*

Characteristic	Value
Age — yr	
Median	59
Interquartile range	52–66
Male sex — no. (%)	214 (74)
Race — no. (%)†	
White	196 (67)
Black	18 (6)
Asian	66 (22.7)
Other	11 (4)
Body-mass index‡	
Median	27
Interquartile range	25–30
<19 — no. (%)	6 (2)
19–30 — no. (%)	221 (76)
>30 — no. (%)	64 (22)
Hypertension — no. (%)	192 (66)
Diabetes — no. (%)	68 (23)
Hypercholesterolemia — no. (%)	175 (60)
Smoking — no. (%)	
Current	56 (19)
Past	119 (41)
Never	116 (40)
Family history of CAD — no. (%)	74 (25)
Previous myocardial infarction — no. (%)	58 (20)
Prior percutaneous coronary intervention — no. (%)	28 (10)
History of unstable angina — no. (%)	62 (21)
Creatinine — mg/dl§	
Median	0.9
Interquartile range	0.8–1.1
Cardiac device — no. (%)	5 (2)
Pacemaker	3
Implantable cardioverter–defibrillator	2
Previous congestive heart failure — no. (%)	34 (12)
NYHA class I	2
NYHA class II	25
NYHA class III	4
NYHA class IV	3
Previous cerebrovascular accident — no. (%)	10 (3)
Previous transient ischemic attack — no. (%)	3 (1)

Table 2. (Continued.)

Characteristic	Value
Angina at presentation — no. (%)¶	168 (58)
Class 0	6
Class 1	29
Class 2	103
Class 3	18
Class 4	12
Unstable angina at presentation — no. (%)	62 (21)
Agatston calcium score	
Median	80
Interquartile range	1–244
Mean ±SD	140±159
Distribution of disease by conventional coronary angiography — no. (%)	
None	128 (44)
1 Vessel	79 (27)
2 Vessels	60 (21)
3 Vessels	24 (8)
Heart rate on MDCTA — beats/min	
Initial	
Median	62
Interquartile range	55–70
During breath hold before scan	
Median	59
Interquartile range	53–64
During scan acquisition	
Median	60
Interquartile range	54–65
Characteristics of MDCTA	
Contrast medium — ml	
Median	76
Interquartile range	73–80
Beta-blocker administered before scan — no. (%)	134 (46)
Nitroglycerin administered — no. (%)	263 (90)
Milliamperes	
Median	360
Interquartile range	270–400
Time from MDCTA to CCA — hr	
Median	10
Interquartile range	4–72
<24 hr — no. (%)	145 (50)
24–48 hr — no. (%)	54 (19)
>48 hr — no. (%)	92 (32)

Table 2. (Continued.)

Characteristic	Value
Characteristics of CCA	
Contrast medium — ml	
Median	100
Interquartile range	80–140
Nitroglycerin administered — no. (%)	267 (92)

* Plus–minus values are means ±SD. CAD denotes coronary artery disease, CCA conventional coronary angiography, MDCTA multidetector computed tomographic angiography, and NYHA New York Heart Association.
† Race was determined by on-site investigators at the time of enrollment.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ To convert values for creatinine to micromoles per liter, multiply by 88.4.
¶ Angina classes were assigned according to the classification system of the Canadian Cardiovascular Society.

from multidetector CT angiography.[17] Quantitative coronary angiography of the most severe stenosis was performed (CAAS II QCA Research version 2.0.1 software, Pie Medical Imaging) in all nonstented segments. After all measurements from multidetector CT angiography and conventional coronary angiography were finalized, 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).

Analysis of Severity of Obstructive Coronary Artery Disease

The ability of multidetector CT angiography, as compared with conventional coronary angiography, to assess disease severity was evaluated using a modified Duke Coronary Artery Disease Index,[2] with 50% or more stenosis classified as clinically significant. The number of vessels involved and the location of obstructive lesions (left main and proximal left anterior descending coronary artery) were weighted according to Duke Coronary Artery Disease Index criteria (Table 1).

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, Stata software version 9, and S-PLUS software version 8.0. We estimated that a sample of 350 patients would be needed to determine an accuracy of multidetector CT angiography (measured as the area under the receiver-operating-characteristic [ROC] curve [AUC]) of at least 0.85 with a 95% confidence interval of at most ±5%, assuming a 35% disease prevalence and 10% dropout rate.[19] Computation of confidence limits for vessel-level data took account of within-patient clustering, through either logistic regression with generalized estimating equations or bootstrap resampling[20] for AUC values. Confidence intervals were calculated according to the percentile method, with a beta value of 2000 replicate samples. P values of less than 0.05 were considered to indicate statistical significance. All P values are two-sided, and the 95% confidence intervals are also presented.

Results

Among the 405 patients enrolled in the study from September 2005 through January 2007, 316 were eligible for analysis since they had an Agatston calcium score of 600 or less. Of the 316 patients, 4 were excluded because of major protocol deviations, 11 because conventional coronary angiography was canceled or the results were inappropriate for analysis by quantitative coronary angiography, and 10 due to technical failure of the multidetector CT angiography (Fig. 1). Thus, 291 patients were included in the analysis.

Demographic and clinical characteristics of the patients are shown in Table 2. The median age was 59 years (interquartile range, 52 to 66) and 74% were male. A majority of patients had a history of hypertension or hypercholesterolemia and were past or current cigarette smokers. On quantitative coronary angiography, 163 patients (56%) had at least one obstructive stenosis of 50% or more, with disease in three vessels, two vessels, and one vessel in 8%, 21%, and 27% of patients, respectively. The median interval between multidetector CT angiography and conventional coronary angiography was 10 hours (interquartile range, 4 to 72). The median time to multidetector CT angiography acquisition was 8.5 seconds, using a median contrast-medium volume of 76 ml (interquartile range, 73 to 80). Radiation doses for multidetector CT angiography were 13.8±1.2 mSv for men and 15.2±2.4 mSv for women. Within 30 days after conventional coronary angiography, 98 patients underwent percutaneous revascularization (85 patients) or surgical revascularization (13 patients). Two patients had a myocardial infarction, one had a transient ischemic attack, and one died after coronary angioplasty. Two patients had reactions to contrast dye after multidetector CT angiography (Table 3).

Table 3. Serious Adverse Events and Adverse Events.*

MDCTA-Related Event	No. of Patients
Serious adverse event	
Reaction to contrast dye†	2
Renal failure	0
Cardiovascular event	
Acute stent thrombosis resulting in myocardial infarction and congestive heart failure leading to death	1
Myocardial infarction	2
After coronary-artery bypass grafting	1
After percutaneous coronary intervention	1
Transient ischemic attack after catheterization	1
Hospitalization for cardiovascular event	2
Unstable angina	1
Congestive heart failure	1
Hospitalization for other reason	3
Hematoma after catheterization	1
Pseudoaneurysm after catheterization	1
Thrombosis of vena femoralis	1
Procedure	
Percutaneous coronary intervention	85
Coronary-artery bypass grafting	13
Placement of implantable cardioverter–defibrillator or pacemaker	2
Noncardiac procedure	1

* Hierarchical events occurring within 30 days after conventional coronary angiography (performed after multidetector computed tomographic angiography [MDCTA]) in the 291 patients.

† The two contrast-dye reactions were as follows. A 62-year-old man had a mild allergic reaction related to contrast dye after MDCTA, and a 65-year-old man had a mild anaphylactic reaction after conventional coronary angiography. Both reactions resulted in inpatient hospitalization, were treated medically, and resolved without sequelae.

PATIENT-BASED ANALYSIS

The AUC for quantitative multidetector CT angiography was 0.93 (95% confidence interval [CI], 0.90 to 0.96) for the diagnosis of a patient with at least one coronary stenosis of 50% or more as assessed by quantitative coronary angiography (Fig. 2A). The sensitivity for obstructive stenosis of 50% or more was 85% (95% CI, 79 to 90), and the specificity was 90% (95% CI, 83 to 94) (Table 4). The positive and negative predictive values were 91% (95% CI, 86 to 95) and 83% (95% CI, 75 to 89), respectively, for a disease prevalence of 56%. Quantitatively, 3773 of 3782 segments (almost 100%), 864 of 866 vessels (almost 100%), and 290 of 291 patients (almost 100%) could be evaluated by means of multidetector CT angiography, whereas visually, 3763 of 3782 segments (99%), 855 of 868 vessels (99%), and 286 of 291 patients (98%) could be evaluated.

Visual and quantitative assessments by multidetector CT angiography of stenosis severity were similar. For both methods, the AUC was 0.93 (P=0.69) (Table 4). Moreover, when the reference standard for obstructive stenosis was chosen within 50 to 75% stenosis on quantitative coronary angiography, the performance of multidetector CT angiography, as measured with the use of AUC, was above 0.90; it declined to 0.88 to 0.89 only at a reference standard of 80 to 90% stenosis on quantitative coronary angiography (Fig. 2B). In addition, the number and location of coronary artery disease stenoses were integrated into a modified Duke Coronary Artery Disease Index (Table 1) used to compare the ability to assess the severity of obstructive coronary artery disease with that of conventional coronary angiography. The ratio of the standard deviations from multidetector CT angiography and quantitative coronary angiography was 1.05 (P=0.16), the bias between the two methods was −0.71 Duke Index unit (P=0.90), and the correlation was good (r=0.81; 95% CI, 0.76 to 0.84), suggesting that the extent of obstructive coronary artery disease can be accurately assessed by means of 64-row multidetector CT angiography. Finally, the AUCs for predicting the rate of revascularization at 30 days on the basis of obstructive stenoses revealed by multidetector CT angiography and quantitative

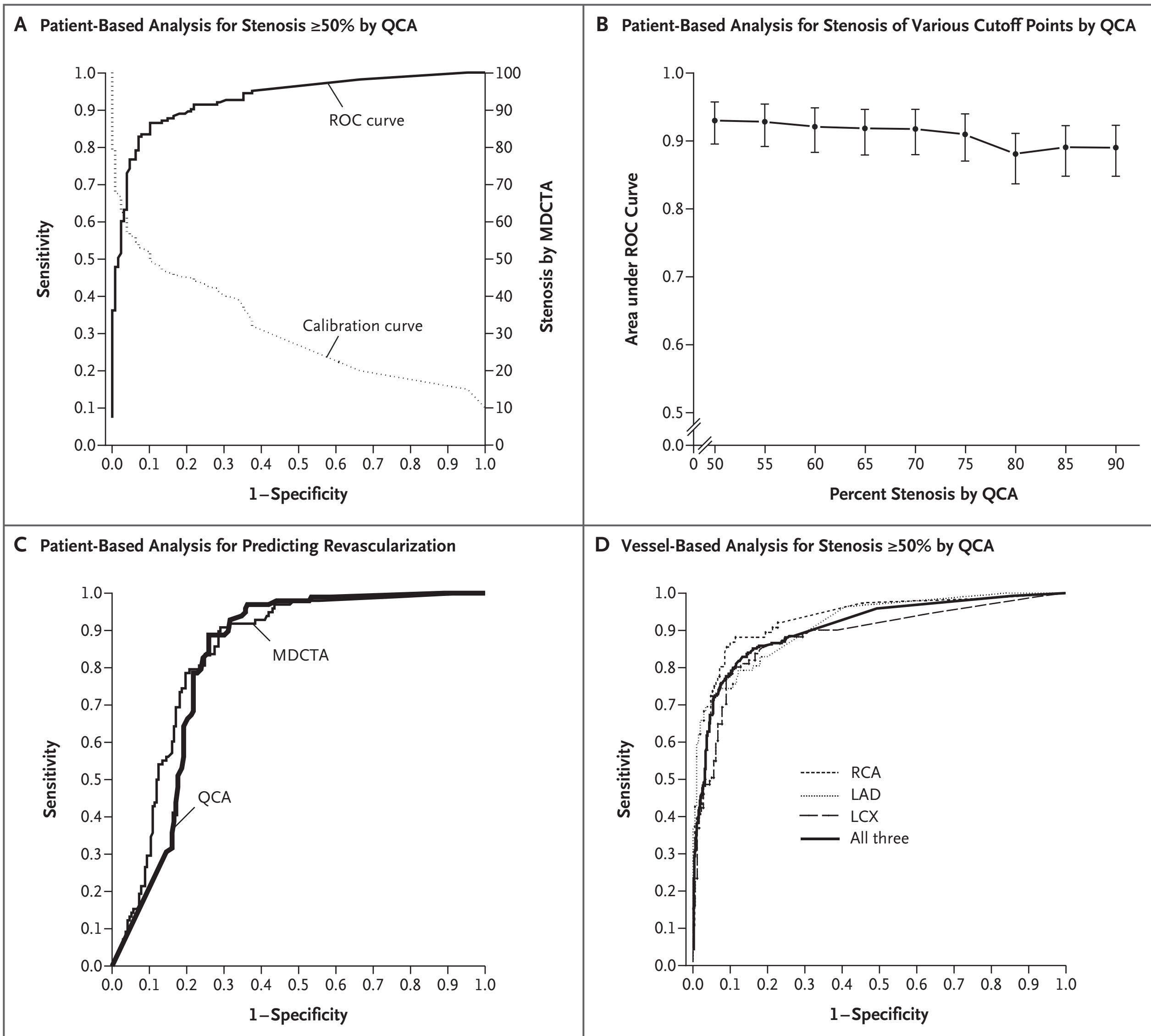

Figure 2. Diagnostic Performance of 64-Row Multidetector Computed Tomographic Angiography (MDCTA).

Panel A shows the receiver-operating-characteristic (ROC) curve (solid line) describing the diagnostic performance of MDCTA to identify coronary stenosis of 50% or more in at least one vessel, as compared with the reference standard of invasive quantitative coronary angiography (QCA), at the level of the patient. The area under the curve (AUC) was 0.93 (95% CI, 0.90 to 0.96). The dotted line is a calibration curve; to identify the corresponding MDCTA cutoff 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 cutoff point. For example, a sensitivity of 85% and a false positive rate (1 – specificity) of 10% correspond to a cutoff point of 50% stenosis detected by MDCTA. Panel B shows estimates of the AUC, with the 95% confidence intervals (I bars), for patients with and those without coronary stenosis at various cutoff points (from 50 to 90%) as measured by QCA. Panel C shows the ROC curves for MDCTA (AUC, 0.84; 95% CI, 0.79 to 0.88) and QCA (AUC, 0.82; 95% CI, 0.77 to 0.86) to predict which patients would undergo surgical or catheter-based coronary revascularization within 30 days after conventional coronary angiography. Both curves were compared with the reference standard: patients who underwent subsequent revascularization and those who did not. Panel D shows the ROC curves describing the capability of MDCTA to identify coronary stenosis of 50% or more in each of three vessels and in all three vessels combined. The AUC for all three vessels was 0.91 (95% CI, 0.88 to 0.93); for the left anterior descending (LAD) coronary artery (including the left main coronary artery), 0.88 (95% CI, 0.84 to 0.92); for the left circumflex (LCX) coronary artery (including the ramus intermedius), 0.92 (95% CI, 0.88 to 0.95); and for the right coronary artery (RCA), 0.93 (95% CI, 0.89 to 0.95).

Table 4. Diagnostic Accuracy of 64-Row Multidetector CT Angiography (MDCTA) for Patient- and Vessel-Based Detection of Coronary Stenosis of ≥50%.*

Measure of Accuracy	Patient-Based Detection				
	Quantitative MDCTA (N=291)	Visual MDCTA (N=291)			
AUC — median (95% CI)	0.93 (0.90–0.96)	0.93 (0.89–0.95)			
Stenosis by CCA — no.	163	163			
Stenosis by MDCTA — no.	152	146			
False positive — no.	13	11			
False negative — no.	24	28			
Sensitivity — % (95% CI)	85 (79–90)	83 (76–88)			
Specificity — % (95% CI)	90 (83–94)	91 (85–96)			
Positive predictive value — % (95% CI)	91 (86–95)	92 (87–96)			
Negative predictive value — % (95% CI)	83 (75–89)	81 (73–87)			
	Vessel-Based Detection†				
	Three-Vessel Quantitative MDCTA (N=866)	Three-Vessel Visual MDCTA (N=868)	LM–LAD (N=291)	LCX (N=288)	RCA (N=287)
AUC — median (95% CI)	0.91 (0.89–0.93)	0.90 (0.88–0.93)	0.88 (0.84–0.92)	0.92 (0.88–0.95)	0.93 (0.89–0.95)
Stenosis by CCA — no.	269	271	111	82	76
Stenosis by MDCTA — no.	247	243	110	73	64
False positive — no.	44	41	21	13	10
False negative — no.	66	69	22	22	22
Sensitivity — % (95% CI)	75 (69–81)	75 (68–80)	80 (72–87)	73 (63–82)	71 (60–80)
Specificity — % (95% CI)	93 (90–94)	93 (91–95)	88 (83–92)	94 (89–96)	95 (91–97)
Positive predictive value — % (95% CI)	82 (77–86)	83 (78–87)	81 (72–87)	82 (72–89)	84 (73–91)
Negative predictive value — % (95% CI)	89 (86–92)	89 (86–91)	88 (82–92)	90 (85–93)	90 (85–93)

* AUC denotes area under the receiver-operator-characteristic curve, CCA conventional coronary angiography, LCX left circumflex artery, LM–LAD left main and left anterior descending coronary arteries, and RCA right coronary artery.

† Of the 868 vessels analyzed visually, 866 could be analyzed with the use of quantitative conventional coronary angiography (defined here as quantitative coronary angiography).

coronary angiography were 0.84 (95% CI, 0.79 to 0.88) and 0.82 (95% CI, 0.77 to 0.86), respectively (P=0.36) (Fig. 2C), indicating similar abilities of the two methods to identify, on the basis of obstructive coronary stenoses, patients who underwent revascularization.

VESSEL-BASED ANALYSIS

The diagnostic performance of quantitative multidetector CT angiography on a per-vessel basis, expressed as an AUC, was 0.91 (95% CI, 0.88 to 0.93), with no significant differences among individual AUCs for the right, left anterior descending, and left circumflex coronary arteries (Fig. 2D) or between the visual and quantitative methods (Table 4). However, when comparing vessel-based and patient-based analyses, there was a small difference in the respective AUCs (0.02; 95% CI, 0.00 to 0.04). The sensitivity and specificity for the overall vessel-based analysis were 75% (95% CI, 69 to 81) and 93% (95% CI, 90 to 94), respectively, with positive and negative predictive values of 82% (95% CI, 77 to 86) and 89% (95% CI, 86 to 92), respectively (Table 4). Overall vessel disease prevalence (≥50% stenosis) was 31% (Table 4). The AUC associated with vessel-specific revascularization was 0.89 (95% CI, 0.86 to 0.91) for quantitative coronary angiography and 0.84 (95% CI, 0.80 to

0.88) for multidetector CT angiography, with a small difference favoring quantitative coronary angiography (0.05; 95% CI, 0.01 to 0.08).

DISCUSSION

In this multicenter, international study of symptomatic patients with suspected coronary artery disease comparing 64-row multidetector CT angiography with conventional coronary angiography, we found that multidetector CT angiography has a reliable accuracy for the diagnosis of obstructive coronary disease. The area under the ROC curve of 0.93 is consistent with robust diagnostic performance and indicates that 64-row multidetector CT angiography has powerful discriminative ability to identify, among symptomatic patients, those with and those without coronary obstruction. However, given the positive predictive value of 91% and the negative predictive value of 83%, multidetector CT angiography cannot replace conventional coronary angiography in this population of patients at present.

Previous studies comparing multidetector CT angiography and conventional coronary angiography have yielded variable results. Underlying these conflicting findings are limitations inherent to single-center designs and the degree of rigor used in controlling for bias in a small study. Although some studies have reported high sensitivity and high negative predictive values, these values were often obtained in selected patients after elimination or imputation of lesions in a substantial number of segments that could not be evaluated. Indeed, in a meta-analysis of primarily single-center studies, Hamon et al.[15] found significant statistical heterogeneity among published studies, with smaller studies reporting higher diagnostic accuracy of multidetector CT angiography, which the authors concluded represented indirect evidence of small-study bias.[15] However, the only available multicenter study performed with the use of 16-detector technology[21] yielded divergent results when segments that could not be evaluated (26%) were taken into account.[15,22]

Moreover, previous studies performed in populations with a low prevalence of disease[21] led to the assumption that multidetector CT angiography should be reserved for use in symptomatic patients with low risk for coronary artery disease.[23] In contrast, the CORE 64 results indicate that the test performs well in symptomatic patients with a calcium score of 600 or less and a high prevalence of obstructive coronary artery disease (56% for ≥50% stenosis on conventional coronary angiography). Patients with calcium scores of more than 600 (22% of our initial cohort) were excluded from the primary analysis because we hypothesized a priori that in these patients multidetector CT angiography would have limited diagnostic utility. The technology as tested in our study population had a positive predictive value of 91% (95% CI, 86 to 95) and a negative predictive value of 83% (95% CI, 75 to 89). These predictive values were not unexpected, given the high prevalence of disease. On the other hand, it is important to highlight that the results of this study should not be used to support the screening of asymptomatic individuals for the presence or absence of coronary artery disease.

Our results for the diagnostic performance of 64-row multidetector CT angiography should be considered in the context of commonly used noninvasive stress tests, coupled with imaging techniques or not. We show that 64-row multidetector CT angiography yields robust diagnostic performance among symptomatic patients with suspected coronary artery disease and calcium scores of 600 or less. However, despite its ability to describe coronary anatomy, multidetector CT angiography misclassified 13% of patients, as compared with quantitative conventional coronary angiography, when the threshold for obstructive stenosis as measured by both techniques was set at 50%. On the other hand, although the concept of severity of coronary artery disease spans the spectrum of disease — from atherosclerotic plaque accumulation to coronary obstruction to ischemic burden and consequent myocardial damage — this work focused on the severity of coronary obstruction (Table 1). For this purpose, 64-row multidetector CT angiography correlates well with conventional coronary angiography. Moreover, because the patient's coronary anatomy as determined by conventional coronary angiography is particularly important for deciding the indication for myocardial revascularization,[3,6,7,10] we also compared the ability of multidetector CT angiography and quantitative conventional coronary angiography to predict the need for coronary revascularization. Multidetector CT angiography and quantitative coronary angiography had a similar ability to identify patients who required coronary revascularization procedures (within 30 days after conventional coronary angiography) on the basis of the identification of coronary obstruction.

Exposure to radiation is a major concern in methods involving radiography or nuclear isotopes. The mean effective doses used in the CORE 64 study were 14 mSv for men and 15 mSv for women, which are consistent with those used in previously published trials of 64-row scanners.[15] These doses, which included the calcium score and multidetector CT angiography, also compare favorably to those used in stress perfusion imaging involving radioisotopes[24] and conventional coronary angiography.[25] It has been estimated that the individual risk of radiation can be clinically significant and depends on the patient's age, sex, and expected life span, with younger female patients at increased risk for radiation-induced complications.[26-28] Thus, 64-row multidetector CT angiography, like radioisotope tests and conventional coronary angiography, should be used with caution in patients with suspected coronary artery disease.

The strengths of our study also include its large number of patients, multicenter design, broad spectrum of clinical characteristics of the patients, and use of centralized core laboratories for data analysis. Moreover, we enrolled a population of patients representative of those with a clinical indication for anatomical coronary imaging.

It has been well established that multidetector CT angiography in highly calcified vessels has historically been difficult because of artifacts caused by high-density calcified lesions. Therefore, most previous studies have limited CT angiography to patients with lesser degrees of coronary calcification. In our study, 22% of patients (89 of 405) with calcium scores of more than 600 were placed in a separate registry and excluded from the primary analysis on the premise that they would be more adequately evaluated through alternative diagnostic strategies. The decision to approach all patients, regardless of the calcium score, was made to limit bias in the selection of patients. In addition, our results do not apply to screening of asymptomatic patients, who were systematically excluded in our study design. We studied patients presenting with a clinical indication for conventional coronary angiography, and therefore our study population had a higher prevalence of disease than is seen in the general outpatient population.

In this international, multicenter study, we have demonstrated that coronary 64-row multidetector CT angiography is accurate in identifying coronary stenoses and characterizing disease severity in symptomatic patients who have coronary calcium scores of 600 or less. However, multidetector CT angiography cannot be used as a simple replacement for conventional coronary angiography, given its negative predictive value of 83% and positive predictive value of 91% in this population of patients. Further studies are needed to define the method's precise role in the diagnostic algorithm for the evaluation of patients with suspected coronary artery disease.

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