European Heart Journal (2007) **28**, 3034–3041
doi:10.1093/eurheartj/ehm150

EUROPEAN SOCIETY OF CARDIOLOGY®

Clinical research
Imaging

Non-invasive coronary computed tomographic angiography for patients with suspected coronary artery disease: the Coronary Angiography by Computed Tomography with the Use of a Submillimeter resolution (CACTUS) trial

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Received 10 July 2006; revised 27 February 2007; accepted 5 April 2007; online publish-ahead-of-print 31 May 2007

KEYWORDS
Coronary artery disease;
Computed tomography;
Sensitivity and specificity

Background Non-invasive coronary angiography by multislice spiral computed tomography (MSCT) is a promising method for the diagnosis of coronary artery disease (CAD). However, the clinical role of this method has not been established for specific patient cohorts. Therefore, the objective of the current prospective, blinded study was to investigate the diagnostic value of coronary MSCT angiography in patients with an intermediate pre-test probability for having CAD when compared with invasive angiography.
Methods and results A total of 243 patients with an intermediate pre-test probability for having CAD were asked to undergo coronary 16- or 64-slice CT angiography before planned invasive angiography from 12 September 2003 to 13 July 2005. The primary end point was defined as the diagnostic accuracy in the detection of significant coronary stenosis ($\geq$50% lumen diameter reduction) on a per-patient and an 'intention-to-diagnose'-based analysis. Secondary end points comprised per-artery and per segment-based analyses as well as the comparison of diagnostic accuracy of 16- vs. 64-slice MSCT angiography. Of 243 enrolled patients, 129 and 114 patients were studied by 16- and 64-slice CT angiography, respectively. The overall sensitivity, negative predictive value, and specificity for CAD detection by MSCT were 99% (95% CI, 94–99%), 99% (95% CI, 94–99%), and 75% (95% CI, 67–82%), respectively. On a per-segment basis, the use of 64-slice CT was associated with significantly less inconclusive segments (7.4 vs. 11.3%, $P < 0.01$), resulting in a trend to an improved specificity (92 vs. 88%, $P = 0.09$).
Conclusion In patients with an intermediate pre-test probability for having CAD this large, prospective trial demonstrates that non-invasive coronary CT angiography is a very sensitive method for CAD detection. Furthermore, this method allows ruling out CAD very reliably and safely. Finally, 64-slice CT appears to be superior for CAD detection when compared with 16-slice CT.

Introduction

Cardiovascular disease has long been the leading cause of death in developed countries, and it is rapidly becoming the number one killer in the developing countries.[1] Currently, invasive coronary angiography provides the standard of reference for definitive diagnosis.[2] Thus, in many patients with an intermediate pre-test probability for coronary artery disease (CAD), significant coronary artery stenosis is being ruled out by invasive angiography. To prevent 'unnecessary' invasive tests, a reliable and reproducible non-invasive diagnostic method for the detection and grading of coronary artery stenosis is highly desirable.

Non-invasive coronary multislice spiral computed tomography (MSCT) is a promising diagnostic methodology for the identification of significant coronary artery stenosis in vessels >1.5–2 mm in size.[3–8] However, in most studies comparing non-invasive MSCT with invasive coronary angiography, the presented sensitivities and specificities to detect significant coronary stenosis were calculated after the exclusion of coronary segments with inadequate image quality. Furthermore, these studies did not address

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the clinical usefulness of coronary MSCT in a well-defined patient population in which the diagnostic value is expected to be greatest. According to the Bayesian theory, coronary MSCT angiography is anticipated to have the greatest impact in increasing or lowering the likelihood of significant CAD in patients with an intermediate probability for CAD. Finally, the diagnostic impact of the recent advances in MSCT technology with 64-slice scanners has not been compared with the earlier 16-slice systems. Therefore, the rationale of the current prospective, blinded study was to assess the clinical usefulness of coronary MSCT angiography for the detection of significant CAD in a patient population with an intermediate pre-test probability for having CAD on an 'intention-to-diagnose'-based analysis.

Methods

Study population

This prospective study included patients with an intermediate pre-test probability for having CAD and who were scheduled to have elective invasive coronary angiography. The intermediate pre-test probability for having CAD was defined as (i) patients with chest pain, dyspnea or with intermittent arrhythmias in the absence of a positive stress test or with an equivocal stress test for myocardial ischemia and (ii) asymptomatic patients with a positive stress test. Patients with intermittent arrhythmias were defined by stable sinus rhythm at the time of study inclusion, but either exercise-induced premature ventricular beats during stress testing or short runs of non-sustained ventricular tachycardias during holter ECG monitoring (e.g. $\geq$3 consecutive beats) or intermittent atrial arrhythmias with increasing frequency within the last year. Exclusion criteria included absence of sinus rhythm, patients with known CAD or with previous myocardial infarction, patients with previous revascularization procedures, patients at risk for iodinated contrast agents (dye allergy, elevated serum creatinine $>$1.8 mg/dL or reduced thyroid stimulating hormone $<$0.36 mU/L), patients $<$40 years, and pregnancy. The study was approved by the local Ethics Committee as well as the Federal Office for Radiation Protection (Bundesamt für Strahlenschutz, Munich and Braunschweig, Germany), and all patients gave written informed consent for participation in this trial.

Patient preparation and computed tomographic angiography

From 12 September 2003 to 13 July 2005, a total of 243 patients were enrolled to undergo non-invasive coronary CT angiography prior to scheduled invasive catheterization. Between September 2003 and September 2004, patients were scanned on a 16-slice CT scanner, whereas a 64-slice CT scanner was used in the subsequent time period (Somatom Sensation 16 and 64 Cardiac, Siemens Medical Systems, Forchheim, Germany).

In patients with a heart rate of $>$60 b.p.m. up to four doses of 5 mg of metoprolol were administered intravenously to lower heart rate at the time of the CT study. In addition, coronary vasodilatation was achieved by the administration of nitroglycerin 0.8 mg sublingually in all patients with a systolic blood pressure of at least 100 mmHg. An initial non-enhanced ECG-gated scan was performed for calcium scoring. After an initial bolus-timing, single-slice scan using 20 cc of contrast (Iomeprol, Imeron 350, Bracco Altana Pharma GmbH, Konstanz, Germany, iodine content 350 mg/cc) followed by a 50 cc saline chaser, a contrast-enhanced scan was obtained using an average of 100 $\pm$ 8 cc (range, 80–140 cc) of contrast injected through an antecubital vein at 4–5 cc/s followed by a 50 cc saline chaser. The contrast volume was individually adapted to the selected table feed, scan range, and contrast dye injection rate. The scan parameters were 16 $\times$ 0.75 mm collimation with 16-slice CT and 32 $\times$ 0.6 mm collimation employing an oscillating electron beam to produce two parallel X-ray beams with 64-slice CT. The oscillating electron beam (z-flying focal spot) results in an improved spatial resolution that corresponds to that of a 64 $\times$ 0.3 mm detector.[9] Using an ECG-gated half-scan reconstruction algorithm, the temporal resolution was 210 and 164 ms for 16- and 64-slice CT, respectively. In patients with higher heart rates ($>$72 b.p.m. with 16-slice CT, $>$65 b.p.m. for 64-slice CT), a bi-segmental reconstruction algorithm was applied, which uses data obtained from two consecutive heartbeats reducing the effective reconstruction interval per heart cycle down to 105 and 83 ms for 16- and 64-slice CT, respectively. In patients with stable sinus rhythm, the tube current was modulated according to the ECG, with a maximum current during a time period of $\sim$330 ms centred at 675 ms after the R-wave and reduction by 80% during the remaining cardiac cycle (maximum current of 500–600 mAs and of 850–950 mAs for 16- and 64-slice CT, respectively).[10] Images were reconstructed in mid-diastole; additional image reconstructions were performed in end-systole if required. The position of the reconstruction window within the cardiac cycle was individually optimized to minimize motion artefacts. The effective dose of CT angiography was estimated by a method proposed by the European Working Group for Guidelines on Quality Criteria in CT.[11] In this method, the effective dose is derived from the dose–length product and a conversion coefficient for the chest ($k = 0.017$ mSv/mGy per cm averaged between male and female models).

Multislice spiral computed tomography image interpretation

After image acquisition, all patient relevant data were removed from the image data sets by a technician to allow for an absolutely anonymous data analysis. Vessel wall calcifications were quantified on a separate workstation (Wizard, Siemens Medical Systems), based on the standard built-in algorithm using an Agatston score equivalent (ASE) adapted for MSCT. An experienced investigator, blinded to the invasive angiography results, evaluated the contrast-enhanced CT scans by the assessment of the axial slices, of multiplanar reformations and of three thin-slab maximum intensity projections (MIPs). Orientated along the heart axis, the thin-slab (5 mm thickness, 1 mm increment) MIPs were reconstructed perpendicular to each other, resulting in a traditional cardiac short- and long-axis view as well as a 'four-chamber' view. The coronary artery tree was segmented according to the modified American Heart Association classification,[12] and the segments were investigated for the presence or absence of lumen narrowings. A second, experienced investigator evaluated a subgroup of 25 randomly selected patients for the interobserver variation in the detection of significant coronary stenoses on a per-artery and on a per-segment basis.

Conventional invasive angiography

Arterial catheterization and selective conventional angiography of the coronary arteries were performed according to standard techniques. The angiograms were evaluated by two invasive cardiologists blinded to the MSCT results. Lumen narrowings were analysed using the same segmental model employed for MSCT analysis. Lumen narrowings were classified according to the maximal lumen diameter stenosis, and a $\geq$50% luminal decrease was considered significant stenosis. Segments with a diameter of $<$2.0 mm at their origin were excluded. In lesions with borderline significance, an automated edge detection system (CMS, Medis Medical Imaging Systems, Nuenen, The Netherlands) was applied to determine lesion severity. The effective dose for invasive cardiac catheterization was estimated from the product of the measured dose–area product and a conversion coefficient k. This conversion coefficient ($k = 0.0022$ mSv/cGy per cm^2, averaged between male and female models) was evaluated from organ–dose conversion coefficients given for an average of typical projections in cardiac angiography,[13] and interpolated for radiation qualities applied in the present study. This value is in reasonable agreement with respective conversion coefficients for various chest postero-anterior (PA) projections.[14]

Study end points and statistical analysis

The analysis of the study was performed on an 'intention-to-diagnose'-based analysis including all enrolled patients. Coronary segments determined as inconclusive by MSCT angiography because of extensive coronary calcifications or severe motion artefacts were considered significantly diseased by MSCT (lumen narrowing ≥50%). Therefore, every patient with at least one inconclusive coronary segment by MSCT angiography was considered as having significant CAD. The primary end point of the study was the accuracy in the detection of patients with significant CAD by MSCT angiography. Patients were classified as positive for the presence of CAD if there was a lumen narrowing ≥50% in any coronary artery segment by invasive angiography, which was regarded as the standard of reference. Assuming a sensitivity and specificity of 97 and 75% in a per-patient-based analysis and a prevalence of significant stenosis of 33%, the sample size calculations indicated that 240 patients needed to be enrolled to obtain a lower confidence interval of 90% for sensitivity and of 67% for specificity. Secondary end point analyses encompassed the accuracy of CAD detection on a 'per-artery' and 'per-segment' level, the accuracy with 16- vs. 64-slice CT angiography, the impact of coronary calcifications and higher heart rates on the accuracy as well as the comparison of radiation dose estimates and contrast dye volumes for MSCT and invasive coronary angiography.

Results are expressed as counts (or proportions in %), as mean ± standard deviation or as median [interquartile range, (IQR)]. Categorical variables were compared with χ^2 analysis. Continuous variables were compared using Student's *t*-test. Precision of the diagnostic parameters (sensitivity, specificity, and positive and negative predictive value) was expressed using 95% CI. Possible correlations between arteries and segments within patients were considered using the generalized estimation equation (GEE) model for binomial data.[15] The sensitivity, specificity, and positive and negative predictive values of two groups were compared by the GEE model which included the grouping variable as a binary covariate. The concordance between observers 1 and 2 for the detection of coronary lesions by MSCT was calculated by the Cohen kappa (κ) value. $P < 0.05$ was considered statistically significant. All study-related data including patient history, current medication, laboratory results, as well as MSCT-related data and results were collected prospectively in a dedicated coronary MSCT angiography reporting system with the use of an Oracle database.

Results

A total of 243 patients were enrolled in this trial. The clinical characteristics of the patients studied are summarized in *Table 1*. The main inclusion criterion was chest pain in the absence of a positive stress testing in 168 (69.1%) patients. Coronary MSCT angiography was performed successfully in all but one patient, in whom an allergic contrast dye reaction with severe hypotension occurred after the test bolus for the determination of the contrast appearing time (*Figure 1*). The characteristics of the MSCT studies are summarized in *Table 2*. For heart rate reduction and coronary vasodilatation, β-blockers and nitrates were administered in 167 (68.7%) and in 239 (98.4%) patients, respectively. In all patients, invasive coronary angiography was performed after MSCT angiography, usually on the same or next day after MSCT angiography. In 102 patients, at least one significant lesion was detected by invasive angiography, resulting in prevalence of CAD of 42%.

Table 1 Characteristics of patients

	243 Patients
Age, years	62.0 ± 9.9
Male sex, *n* (%)	158 (65.0)
Body mass index, kg/m^2	26.9 ± 4.3
Total cholesterol, mg/dL	219.3 ± 43.4
LDL cholesterol, mg/dL	134.0 ± 38.0
HDL cholesterol, mg/dL	55.3 ± 15.9
Triglycerides, mg/dL	159.1 ± 108.3
Arterial hypertension, *n* (%)	108 (44.4)
Diabetes mellitus, *n* (%)	37 (15.2)
Active smoker, *n* (%)	38 (15.6)
Positive family history, *n* (%)	91 (37.4)
Framingham score	14.6 ± 10.9
Non-invasive stress testing for ischemia	
Treadmill, *n* (%)	129 (53.1)
Myocardial scintigraphy, *n* (%)	10 (4.1)
Stress echocardiography, *n* (%)	4 (1.6)
Indication for invasive angiography	
Chest pain, *n* (%)	168 (69.1)
Dyspnea, *n* (%)	8 (3.3)
Intermitt. arrhythmia, *n* (%)	21 (8.7)
Positive stress test, *n* (%)	46 (18.9)
Current medication	
Aspirin or thienopyridine, *n* (%)	91 (37.4)
β-Blocker, *n* (%)	126 (51.9)
ACE inhibitor/AT1-blocker, *n* (%)	100 (41.2)
Diuretics, *n* (%)	37 (15.2)
Ca^{2+}-antagonists, *n* (%)	25 (10.3)
Nitrates, *n* (%)	9 (3.7)
Statins, *n* (%)	64 (26.3)

Data are *n* (%) or mean ± standard deviation.

Multislice spiral computed tomography compared with invasive angiography on per-patient basis

Multislice CT was accurate in the detection of significant lumen narrowings (*Figure 2*). From the 102 patients with CAD detected with invasive angiography, 101 were correctly recognized with coronary MSCT angiography. One stenosis in the origin of posterior descending branch of the right coronary artery with a stenosis grade of 55% by quantitative analysis of the invasive angiogram was underestimated by non-invasive MSCT. The sensitivity was 99% (101/102 patients; 95% CI, 94–99%), the specificity was 75% (106/141 patients; 95% CI, 67–81%), and the negative predictive value was 99% (106/107 patients; 95% CI, 94–99%; *Table 3*). On the basis of these values, CT angiography would have indicated not to perform invasive angiography in 44% (107/243) of patients. On the other hand, CT angiography indicated the need for an 'unnecessary' invasive testing in 14% (35/243) of patients without CAD as a result of an overestimation of lumen narrowings (19/35 patients, 54%) or inconclusive results (16/35 patients, 46%). In the 16 patients with inconclusive results, severe coronary calcifications (9/16 patients, 56%) and motion artefacts (7/16 patients, 44%) in at least one coronary segment were the main reasons for the inconclusive MSCT results.

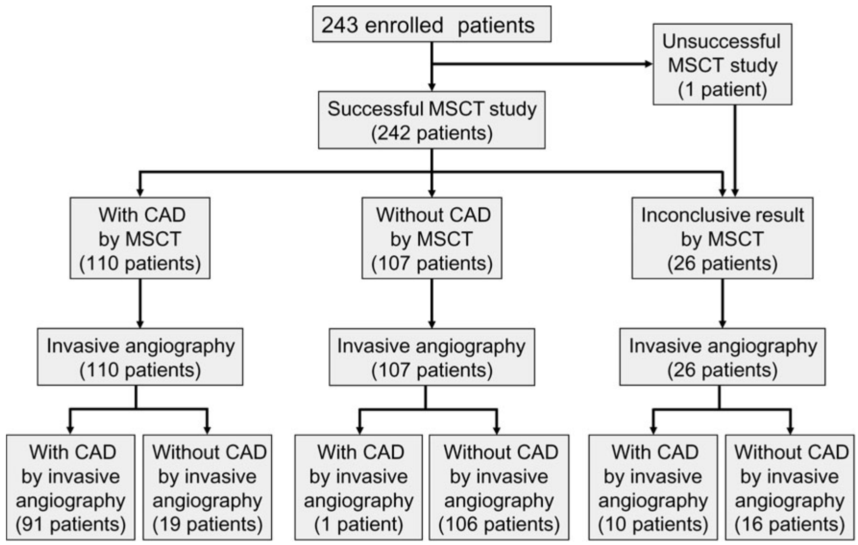

Figure 1 Flow of study participants.

Table 2 Characteristics of MSCT studies

	243 Patients
16-slice CT, *n* (%)	129 (53.1)
64-slice CT, *n* (%)	114 (46.9)
Metoprolol i.v., mg	10 ± 5.5
Nitrates p.o., *n* (%)	239 (98.4)
Heart rate, b.p.m.	56.6 ± 6.5
Scan length, mm	125.4 ± 17.2
Agatston score equivalent (ASE)	96 [4, 398]
ASE = 0, *n* (%)	49 (20.2)
ASE > 1000, *n* (%)	24 (9.9)
MSCT radiation dose estimates	
Non-enhanced scan for calcium scoring, mSv	0.7 ± 0.4
MSCT angiography, mSv	7.4 ± 3.0
Total radiation dose, mSv	8.1 ± 3.2
Total radiation dose for 16-slice CT, mSv	5.9 ± 1.6
Total radiation dose for 64-slice CT, mSv	10.5 ± 2.8

Data are *n* (%) or mean ± standard deviation or median [interquartile range].

Multislice spiral computed tomography compared with invasive angiography on per-artery and per-segment basis

In this study, a total of 967 coronary arteries with 2683 segments were analysed. The prevalence of significant stenosis was 18.2 and 9.6% on a per-artery and on a per-segment basis, respectively. *Table 3* summarizes the accuracy values for CAD detection on a per-artery and per-segment basis. The *k*-value for interobserver variation in the detection of significant coronary stenoses was 0.84 and 0.76 on a per-artery and on a per-segment basis, respectively.

A significant stenosis could neither be demonstrated nor be ruled out in 254 (9.5%) of 2683 coronary segments, which were considered inconclusive due to coronary calcifications (165/254 segments, 65%), motion artefacts (85/254 segments, 33%), or insufficient contrast (4/254 segments, 2%). These inconclusive coronary segments were maintained in the analysis and were considered as significantly diseased by MSCT, resulting in low positive predictive values. The prevalence of significant stenoses by invasive angiography in these segments with inconclusive CT readings was 15.3% (13/85) in segments with motion artefacts and 37.0% (61/165) in segments with extensive coronary calcifications.

Diagnostic accuracy with low vs. high Framingham risk scores

The median Framingham risk score was 12.0 (IQR, 6.7–19.4). When the patient population was divided according to the median Framingham risk score in a low-risk (median, <12.0) and high-risk (median, ≥12.0) patient population, the prevalence of significant stenosis increased from 30 to 53% in the low- and high-risk groups ($P < 0.01$). Similarly, significantly higher ASE values were seen in higher risk patients (ASE, 289 ± 507 vs. 510 ± 706 units for low- vs. high-risk patients; $P < 0.01$). In a per-patient-based analysis, the sensitivity, specificity, as well as the positive and negative predictive values did not differ between the low- and high-risk patient populations (sensitivity, 97 vs. 100%; specificity, 77 vs. 70%; positive predictive value, 65 vs. 79%; negative predictive value, 99 vs. 100% for low- vs. high-risk groups, respectively).

Diagnostic accuracy with 16- vs. 64-slice computed tomography angiography

One hundred and twenty-nine and 114 patients with 1417 and 1266 coronary segments were scanned with 16- and 64-slice CT systems, respectively. *Table 4* summarizes the results for the diagnostic accuracy for both MSCT systems. With 64-slice CT angiography, significantly fewer segments were determined inconclusive, resulting in a trend for an improved specificity on a per-segment basis. The reduction in inconclusive segments was mainly because of a reduction in motion artefacts (4.9 vs. 1.3% of coronary segments with 16- and 64-slice CT, $P < 0.01$), whereas the frequency of inconclusive segments due to coronary calcifications were comparable between 16- and 64-slice CT (6.2% of segments with both CT systems, $P = 0.93$).

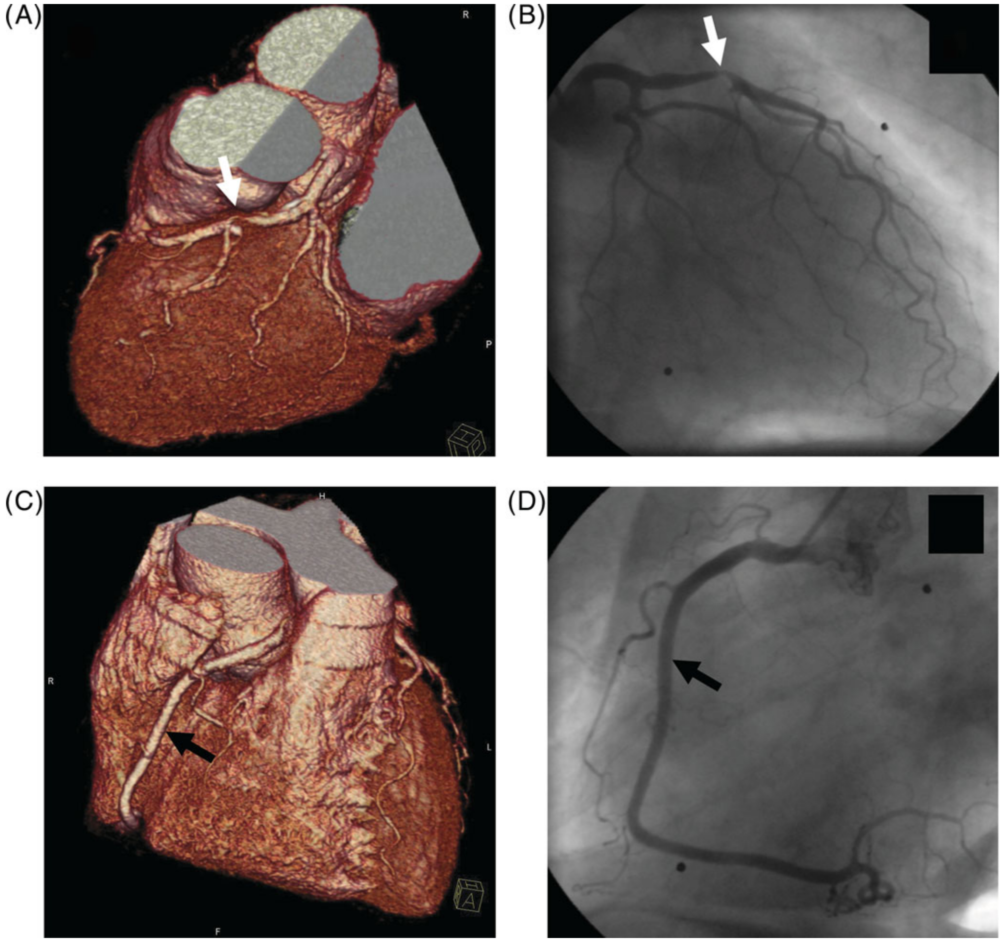

Figure 2 A 63-year-old male patient who presented with atypical chest pain. The MSCT angiogram revealed a stenosis in the proximal segment of the left anterior descending coronary artery [white arrow, (*A*), three-dimensional reconstruction]. Invasive coronary angiography confirmed the stenosis [white arrow, (*B*)]. The circumflex and the right coronary arteries were without significant disease. (*C*) and (*D*) The right coronary artery in MSCT and invasive coronary angiography, respectively (black arrows).

Table 3 Diagnostic accuracy of coronary multislice spiral computed tomography compared with invasive angiography for detection of lesions ≥50%

	Patients ($n = 243$)	Arteries ($n = 967$)	Segments ($n = 2653$)
Prevalence of lesions	41.6	18.2	9.6
Sensitivity	99 (94–99)	96 (92–98)	95 (88–95)
Specificity	75 (67–82)	87 (83–90)	90 (87–92)
Positive predictive value	74 (66–81)	62 (56–69)	50 (42–57)
Negative predictive value	99 (94–99)	99 (98–100)	99 (99–100)

Values are percentages (95% confidence intervals).

Influence of coronary calcifications on multislice spiral computed tomography accuracy

Twenty-four patients with 275 coronary segments presented with an ASE over 1000. In these patients, significantly more segments were considered inconclusive, resulting in a significantly lower specificity on a per-segment basis (*Table 4*). On a per-patient basis, CT angiography could not rule out significant CAD in any of these patients; thus, all 24 patients had an indication for invasive angiography by MSCT. Invasive angiography demonstrated significant coronary artery stenosis in 20 (83%) of these 24 patients.

The MSCT study demonstrated a total of 49/243 (20.2%) patients with an absence of coronary calcifications (ASE of 0). Of these 49 patients, six (12.2%) patients presented with a significant stenosis by invasive angiography, and all of these non-calcified lesions were correctly detected by CT angiography.

Influence of heart rate on multislice spiral computed tomography accuracy

A heart rate of ≥65 b.p.m. was present in 20 (8.2%) of 243 patients during scanning despite the administration of β-blockers. In these patients, significantly more segments were considered inconclusive on a per-segment basis, resulting in significantly lower specificity and a trend for a lower positive predictive value (*Table 4*).

Comparison of radiation dose estimates and contrast dye volumes

Radiation dose estimates for MSCT studies are summarized in *Table 2*. After the exclusion of patients in whom cardiac

Table 4 Subgroup analysis for the diagnostic accuracy of coronary multislice spiral computed tomography compared with invasive angiography

	MSCT technology			Calcification (ASE)			Heart rate		
	16-Slice ($n = 1417$)	64-Slice ($n = 1266$)	*P*-value	<1000 ($n = 2408$)	≥1000 ($n = 275$)	*P*-value	<65 b.p.m. ($n = 2449$)	≥65 b.p.m. ($n = 234$)	*P*-value
Lesion prevalence (%)	10.0	8.8		7.7	25.1		9.5	9.0	
Inconclusive results (%)	11.3	7.6	<0.001	5.5	44.4	<0.001	6.7	38.0	<0.001
Sensitivity (%)	93 (87–97)	92 (87–95)	0.98	93 (88–96)	97 (88–99)	0.32	89 (84–92)	95 (59–100)	0.91
Specificity (%)	87 (83–91)	92 (89–94)	0.09	93 (90–94)	60 (49–71)	<0.001	91 (89–93)	78 (62–89)	0.022
Positive predictive value (%)	46 (36–57)	54 (46–63)	0.22	52 (43–60)	45 (33–57)	0.33	52 (44–59)	30 (13–55)	0.09
Negative predictive value (%)	99 (98–100)	99 (99–100)	0.64	99 (99–100)	98 (94–100)	0.13	99 (99–100)	99 (95–100)	0.97

Values are percentages (95% confidence intervals). MSCT, multi-slice computed tomography; ASE, Agatston score equivalent. All coronary segments determined as inconclusive were considered significantly diseased by MSCT angiography (lumen narrowing ≥50%) for the calculation of sensitivitiy, specificity, and positive and negative predictive values.

catheterization was accompanied by aortic root or renal artery angiography or by percutaneous coronary intervention, a comparison of radiation dose estimates and contrast dye volumes for CT and invasive angiography was possible in 119 patients. In these patients, the radiation dose of CT angiography was significantly higher than that of invasive angiography (7.7 ± 2.8 vs. 4.6 ± 2.4 mSv for CT vs. invasive angiography, $P < 0.001$). The volume of contrast dye was significantly lower with CT angiography than with invasive angiography (100 ± 7 vs. 135 ± 36 mL for CT vs. invasive angiography, $P < 0.001$).

Discussion

Several previous studies have compared non-invasive MSCT with invasive coronary angiography for the detection of significant coronary artery lesions. With the recent advances in MSCT imaging technology, these studies demonstrated that significant coronary artery lesions (>50% stenosis) could be identified with high accuracy.[3–8] However, all of them present with significant limitations for transferring these results into clinical practice. First, patients with a wide range of pre-test probabilities for having CAD were included in these studies.[3–8] In addition to patients with suspected CAD, other studies included patients with known CAD, with previous percutaneous coronary intervention, or patients before a planned aorto-coronary bypass procedure. Accordingly, the prevalence of patients with at least one significant stenosis ranged from 31 to almost 80% with a majority of studies presenting with a disease prevalence of >50%.[3–8] Therefore, the investigated patients do not resemble patients in whom non-invasive coronary CT angiography is most likely being used.[16] Second, a significant proportion of coronary segments remain inconclusive despite the advances in spatial and temporal resolution.[3,4,7] In most studies, these inconclusive segments were excluded from the statistical analysis favouring high sensitivity and specificity values. However, with an inconclusive reading of e.g. a proximal coronary segment significant CAD cannot be ruled out in a patient in clinical practice. Finally, the small sample sizes of studied patients result in large confidence intervals for the diagnostic accuracy of CT angiography on a per-patient basis. Therefore, we assessed in the current prospective and adequately powered study the clinical usefulness of coronary MSCT angiography for the detection of significant CAD in a patient population with an intermediate pre-test probability for having CAD on an 'intention-to-diagnose'-based analysis. In contrast to previous studies, our study focuses on a patient population in which the application of this new imaging method appears to be most attractive. The main finding was that the use of this non-invasive diagnostic tool is associated with a high diagnostic accuracy for the detection as well as the exclusion of CAD in a clinically relevant setting. Coronary CT angiography identified all but one patient with at least one significant coronary stenosis in whom invasive angiography would have been correctly recommended on the basis of the CT results. Similarly, CAD was ruled out by CT angiography with a negative predictive value of 99%, demonstrating that 44% of enrolled patients (107/243 patients) would not have been sent for further invasive testing. On the basis of this analysis, coronary CT angiography may be used as a sensitive and safe 'gate-keeper' for invasive angiography in a large proportion of patients with an intermediate probability for having CAD.

In previous studies, inconclusive segments were usually excluded from the analysis. In contrast, an 'intention-to-diagnose'-based analysis without the exclusion of inconclusive coronary segments was used in the current study, and all patients with inconclusive segments were considered as having significant CAD. Therefore, this conservative assessment of CT angiographies resulted in lower specificities and positive predictive values than in previous trials comparing both methodologies.

Extensive coronary calcifications have been identified as a substantial problem for the interpretation of CT angiograms and the detection of coronary stenosis, because of the blooming effect and beam hardening of these.[4] Although the smaller voxel sizes of newer 16- and 64-slice CT systems ameliorate these imaging difficulties, our study demonstrates that the frequency of inconclusive segments increased substantially with a significant reduction in specificity, when stratified according to an ASE of 1000. Interestingly, significant coronary stenoses could not be ruled out in any of the patients with an ASE of >1000. Therefore, the diagnostic yield of CT angiography in these patients is small, if CT angiography is used with a 'gate-keeping' function for invasive angiography.

The susceptibility to motion artefacts that increases in patients with higher heart rates, constitute another important limitation of coronary CT angiography. Although β-blockers were administered routinely, the heart rate remained >65 b.p.m. in 8.2% of patients, in whom the diagnostic accuracy was significantly lower. Besides the consequent application of β-blockers, several techniques are being used to improve the temporal resolution for image acquisition. With the reduction in gantry rotation time from 420 to 330 ms in the latest CT scanner generation, an improvement in temporal resolution (210–165 ms) can be achieved with half-scan reconstruction methods. Recently, a new concept for CT, which combines two arrays of X-ray tube with detectors in one acquisition gantry, has been introduced, which may eliminate the occurrence of motion artefacts even in patients with high heart rates.[17]

With current CT scanner systems, the value of the 'gate-keeping' function is affected by the need for 'unnecessary' invasive testing in a small subgroup of patients. In the current study, ~7% of the patient population would have undergone invasive testing because of inconclusive MSCT readings. It remains speculative if the future improvements in the MSCT technologies may help to reduce the frequency of inconclusive MSCT readings. On the basis of the current analysis, at least two diagnostic work-up strategies are conceivable to improve the 'gate-keeping' function of coronary CT angiography: (i) patients with extensive coronary calcifications in the low-dose calcium scoring scan should not undergo subsequent CT angiography, because the diagnostic yield appears to be low and (ii) patients with inconclusive CT angiography results may undergo other non-invasive functional tests before invasive angiography, e.g. magnetic resonance perfusion imaging or myocardial scintigraphy, to rule out haemodynamically relevant CAD.

General limitations of coronary MSCT angiography include the pre-requisite of sinus rhythm, the application of potentially nephrotoxic contrast dyes, and the associated radiation exposure. To decrease radiation exposure, we consequently used dose-saving algorithms including prospective ECG-gated tube current modulation and 100 kV acquisition protocols, whenever possible. The application of these algorithms has been shown to decrease radiation dose estimates up to 64% in coronary MSCT angiography.[18] Despite the consequent use of dose-saving algorithms, the radiation dose estimates are almost doubled with 64-slice CT angiography when compared with 16-slice systems. This increase in dose was associated with a significant reduction in inconclusive CT readings, which resulted in a trend for an improved specificity to detect coronary artery stenosis. However, these findings also underline the importance to carefully select patients in whom this method could be useful, and they support the need for additional studies investigating the trade-offs between improvements in CT technologies with raising dose estimates and their impact on the diagnostic results.

Limitations

The definition of patient inclusion criteria is crucial for investigating new diagnostic techniques. Previous definitions of 'intermediate CAD risk' are mainly based on age, gender, and quality of chest pain. Although some of our patients may have been classified as having a low probability for CAD with the use of these previous definitions, addition of myocardial stress test results as additional inclusion factor in the current study may have allowed for a better discrimination of pre-test probabilities for CAD. Indeed, the prevalence of 41.6% of patients with CAD as well as a mean 10 year coronary heart disease risk prediction of 14.6 by the Framingham score indicate that a patient population with a true intermediate probability for CAD was investigated in this study.

Significant coronary stenosis was defined by the reduction in lumen diameter exceeding 50%; a threshold that has been used in almost all other studies comparing MSCT with invasive coronary angiography.[3–8] Owing to the spatial resolution of current CT technologies, previous studies have shown that coronary MSCT is insensitive for the discrimination of lesions exceeding 50% and e.g. >70% in diameter reduction.[19] Small coronary segments (diameter, <2.0 mm) were excluded from the analysis, which may have led to a selection bias and to a possible overestimation of sensitivity because it is likely that stenoses in those small segments would have been missed owing to the limited spatial resolution of MSCT. However, stenoses in coronary segments with a diameter of <2.0 mm do usually not represent a target for revascularization procedures. Thus, the limitation of the current analysis to coronary segments ≥2.0 mm is clinically justified.

Clinical implications

The present study may have important clinical implications. Coronary MSCT angiography seems to be able to reliably detect those patients who have at least one coronary stenosis with very high sensitivity values (99% by patient-, 96% by artery-, and 95% by segment-based analysis). Furthermore, the very high negative predictive value observed in this study (99% by patient-, artery-, and segment-based analysis) suggests that CT angiography with high-resolution scanners could be a suitable means for the management of patients with an intermediate pre-test likelihood of significant CAD. Invasive angiography would not be necessary if coronary MSCT angiography demonstrates normal coronary arteries. Although MSCT angiography only allows for a morphological detection of coronary stenoses without the ability to assess their functional relevance on the myocardium, MSCT angiography appears to be superior to detect suspected CAD, when the current sensitivity and specificity values are compared with the previous results on the performance of other non-invasive diagnostic modalities including stress echocardiography, magnetic resonance imaging and nuclear medicine.[20,21] However, direct comparisons between coronary CT angiography and other non-invasive diagnostic modalities are warranted to prove the superiority of one method over the others.

In conclusion, the observations from this large, prospective study demonstrate that MSCT angiography consistently provides high-quality non-invasive coronary angiographies that allow the accurate delineation of the presence or absence of coronary stenosis in patients with an intermediate risk for having significant CAD.

Acknowledgements

We are indebted to the medical and technical staff members of the computed tomography and the catheterization laboratories for their invaluable contribution and in particular to Mrs C. Schwarzer, U. Lang, and B. Child (all radiographers) for their expert technical assistance. This trial was supported by grants from Deutsches Herzzentrum, Munich, Germany (KKF 37–02). The funding source had no role in the study design, data collection and analysis, data interpretation, writing of the report, or decision to publish the findings.

Conflict of interest: none declared.

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