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CARDIAC

Diagnostic performance of computed tomography coronary angiography to detect and exclude left main and/or three-vessel coronary artery disease

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Abstract
Objectives To determine the diagnostic performance of CT coronary angiography (CTCA) in detecting and excluding left main (LM) and/or three-vessel CAD ("high-risk" CAD) in symptomatic patients and to compare its discriminatory value with the Duke risk score and calcium score.
Materials and methods Between 2004 and 2011, a total of 1,159 symptomatic patients (61 ± 11 years, 31 % women) with stable angina, without prior revascularisation underwent both invasive coronary angiography (ICA) and CTCA. All patients gave written informed consent for the additional CTCA. High-risk CAD was defined as LM and/or three-vessel obstructive CAD (≥50 % diameter stenosis).
Results A total of 197 (17 %) patients had high-risk CAD as determined by ICA. The sensitivity, specificity, positive predictive value, negative predictive value, positive and negative likelihood ratios of CTCA were 95 % (95 % CI 91–97 %), 83 % (80–85 %), 53 % (48–58 %), 99 % (98–99 %), 5.47 and 0.06, respectively. CTCA provided incremental value (AUC 0.90, $P<0.001$) in the discrimination of high-risk CAD compared with the Duke risk score and calcium score.
Conclusions CTCA accurately excludes high-risk CAD in symptomatic patients. The detection of high-risk CAD is suboptimal owing to the high percentage (47 %) of overestimation of high-risk CAD. CTCA provides incremental value in the discrimination of high-risk CAD compared with the Duke risk score and calcium score.
Key Points
- *Computed tomography coronary angiography (CTCA) accurately excludes high-risk coronary artery disease.*
- *CTCA overestimates high-risk coronary artery disease in 47%.*
- *CTCA discriminates high-risk CAD better than clinical evaluation and coronary calcification.*

Keywords Computed tomography coronary angiography · Diagnostic performance · Left main and/or three-vessel CAD · "High-risk" CAD · Calcium score, coronary calcification · Duke risk score, clinical evaluation

Abbreviations

1VD	One-vessel CAD
2VD	Two-vessel CAD
3VD	Three-vessel CAD
AUC	Area under the receiver operating characteristic curve
CAD	Coronary artery disease
CTCA	Computed tomography coronary angiography
CX	Circumflex
DSCT	Dual-source CT
ECG	Electrocardiogram
HR	Heart rate
ICA	Invasive coronary angiography
LAD	Left anterior descending artery
LM	Left main

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NS	Not significant
PPV	Positive predictive value
NPV	Negative predictive value
RCA	Right coronary artery
SN	Sensitivity
SP	Specificity
SSCT	Single-source CT
QCA	Quantitative coronary angiography

Introduction

Cardiovascular disease is the leading cause of death in women and men in the western world [1–3]. Identification of symptomatic patients with obstructive coronary artery disease (CAD), in particular those patients with left main (LM) and/or three-vessel CAD (3VD), defined herein as "high-risk" CAD, is important because optimal medical treatment combined with revascularisation not only relieves symptoms but also improves prognosis in this patient group [4–6].

Exercise testing (ET), myocardial perfusion imaging (MPI) or stress echocardiography (SE) are performed for risk stratification of obstructive CAD and high-risk CAD [7–10]. The sensitivity for the diagnosis of LM and/or 3VD by ET is comparable (88 % vs. 92 %) to that of MPI, while the specificity is slightly higher (46 % vs. 34 %) [8]. The sensitivity of SE in detecting high-risk CAD is reported to be approximately 94 % with a specificity of 40 % [10].

Computed tomography coronary angiography (CTCA) has been shown to be an alternative imaging technique for the evaluation of CAD. CTCA excludes obstructive CAD with high accuracy, but has the tendency to overestimate stenosis severity compared with invasive coronary angiography (ICA) [11]. CTCA may be used to detect or exclude high-risk CAD; however, the diagnostic performance of CTCA in detecting or excluding patients with high-risk CAD has not been fully explored. The goal of this study was to determine the diagnostic performance of CTCA in detecting and excluding high-risk CAD in symptomatic patients suspected of having CAD and to compare its discriminatory value, for detecting and excluding high-risk CAD, with clinical risk factors (Duke risk score) and calcium score.

Materials and methods

Study population

Between July 2004 and August 2011 patients referred for ICA on the basis of chest pain symptoms, risk factors, with or without stress testing were invited to undergo a CTCA examination. Exclusion criteria were previous revascularisation, iodine allergy or impaired renal function. Consenting patients were entered into our single-centre cardiac database. The final study population comprised 1,159 patients with stable chest pain complaints who were suspected of having CAD. The pre-test probability of obstructive CAD was determined using the Duke risk score [12] which uses clinical factors such as type of complaints, gender, age, smoking, hypercholesterolaemia, diabetes mellitus, history of myocardial infarction and ECG abnormalities [13]. Parts of this single-centre cardiac database have been used in previous studies [14–18]. The study was approved by the institutional review board of our medical hospital.

Computed tomography imaging protocol and image reconstruction

During the inclusion period three consecutive CT systems were used (Table 1). All patients initially underwent unenhanced CT. Subsequently a bolus tracking technique was used to synchronise the start of image acquisition with the arrival of the iodinated contrast agent [Iomeron, iomeprol (400 mg I/mL), Bracco, Milan, Italy; Ultravist, iopromide (370 mg I/mL), Schering Berlin, Germany] in the coronary arteries followed by a saline chaser. CTCA was performed using a conventional ECG-synchronised low-pitch helical CT protocol between 2004 and 2006. Since 2006 CT protocols have been adjusted to reduce the effective radiation dose, to a low-pitch helical protocol with ECG-triggered tube current modulation (2006–2009) [19], to the "step-and-shoot" sequential CT protocol and in selected patients a high-pitch helical protocol in subsequent years [20]. Data sets were reconstructed retrospectively for the low-pitch and step-and-shoot sequential CT protocols in systolic (31–47 %) and diastolic phases (60–76 %) of the RR interval for high (≥80 beats/min) and low heart rates (≤65 beats/min), respectively, to obtain motion-free images; both systolic and diastolic phases (30–77 %) of the RR interval were used in medium heart rates (66–79 beats/min). CT data sets for the high-pitch helical protocol could only be reconstructed at one diastolic phase. Images were analysed using medium-to-smooth convolution kernels for non-calcified lesions and sharp convolution kernels for calcified lesions.

Computed tomography image evaluation

All data sets were transferred for analyses to an offline workstation (MMWP workstation, Siemens, Erlangen, Germany). The unenhanced CT was used to calculate the total calcium score employing the Agatston method [21] (CaScoring®, MMWP workstation, Siemens, Erlangen, Germany). Two experienced observers with more than 2 years of experience in cardiac CT, who were blinded to the ICA results, independently evaluated all CTCA for the presence of CAD, using

Table 1 CT device generations and respective imaging protocols

	64-slice SSCT[a]	64-slice DSCT 1st generation [b]	128-slice DSCT 2nd generation [c]
β-blocker [d]	Yes	No	Yes
Nitroglycerin [e]	No	Yes	Yes
X-ray tube	1	2	2
Z-FFS	Yes	Yes	
Collimation	32×0.6	32×0.6	64×0.6
Gantry rotation time (ms)	330	330	285
Temporal resolution (ms)	165	83	75
Spatial resolution (mm)	0.4×0.4×0.4	0.4×0.4×0.4	0.4×0.4×0.4
Pitch	0.2	0.2–0.5	0.2–3.4
Unenhanced acquisition			
Tube voltage (kV)	120	120	120
Tube current	200–150 effective mAs	75 mAs/rotation	75 mAs/rotation
ECG-triggered tube current modulation	Yes	Yes	Yes
Imaging protocol			
Low-pitch helical imaging	Yes	Yes	No
High-pitch helical imaging [f]	No	No	Yes
Step and shoot sequential imaging	No	No	Yes
Contrast-enhanced imaging			
Tube voltage (kV)	120	120	80–120
Tube current	850–960 effective mAs	320–412 mAs/rotation	320–412 mAs/rotation
ECG-triggered tube current modulation	No	Yes	Yes
Imaging protocol			
Low-pitch helical imaging	Yes	Yes	Yes
High-pitch helical imaging [f]	No	No	Yes
Step-and-shoot sequential imaging	No	No	Yes
Effective radiation dose (mSv)	13.43	12.26	3.93

SSCT single-source CT, *DSCT* dual-source CT, *Z-FFS* Z-flying focal spot, *ECG* electrocardiogram, mAs/rotation total mA×rotation time; mSv (millisievert) dose–length product×0.014 [50]

[a] Somatom Sensation, Siemens Healthcare, Forchheim, Germany

[b] Somatom Definition, Siemens Healthcare, Forchheim, Germany

[c] Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany

[d] Metoprolol (Seloken, Astra Zeneca, Zoetermeer, Netherlands) administration before imaging when no contraindication was present to achieve better quality images

[e] Nitrolingual (Nitroglycerin Pumpspray, G.Pohl-boskamp, Itohenlockstedt, Germany) was administered before imaging in the absence of contra-indications for better visualisation of the small coronary arteries

[f] Imaging protocol in patients with regular stable heart rate below 65 beats/min

axial source images, multiplanar, curved reformatted reconstructions, and thin-slab maximum intensity projections (Circulation®, MMWP workstation, Siemens, Erlangen, Germany). Inter-observer disagreements were resolved by a joint consensus reading.

The modified 17-segment American Heart Association model was used to classify each segment. Each segment was visually scored as obstructive in the presence of at least 50 % lumen diameter stenosis and non-obstructive when the lumen diameter stenosis was less than 50 % in comparison with the proximal and distal lumen. All anatomically available segments with a diameter of at least 1.5 mm, irrespective of image quality or calcification, were included and scored with the intention to diagnose. Non-evaluable segments of poor quality owing to calcification, stack and motion artefacts or low contrast enhancement were classified as obstructive. Coronary segments distal to a total occlusion were excluded from the analyses.

Invasive coronary angiogram image evaluation

One experienced cardiologist, blinded to the CT results, visually assessed each coronary segment (American Heart Association model) for the presence of luminal stenosis in two orthogonal

planes. Segments scored as more than 20 % stenosis on visual assessment were quantified using a validated quantitative coronary angiography (QCA) algorithm [CAASII (Cardiovascular Angiography Analysis System II); Pie Medical Imaging Maastricht, the Netherlands]. Quantitative at least 50 % lumen diameter stenosis was considered significantly obstructive. Patients were classified as having one- (1VD), two- (2VD) or three-vessel CAD (3VD) (at least 50 % diameter stenosis in one, two or three vessels, respectively) or LM CAD (at least 50 % diameter stenosis). High-risk CAD was defined as LM and/or three-vessel CAD.

Statistical analyses

The statistical analysis was performed using dedicated statistical software programs (IBM SPSS statistics 20.0.0.1 and STATA/SE 12.0). Categorical variables were expressed as percentages and continuous variables were expressed as means±standard deviation. Continuous variables with a skewed distribution were expressed as median with interquartile range. The inter-observer agreement was tested between the two CT readers on a vessel level using the κ statistic. CTCA results were compared with ICA as the reference standard on a patient level to calculate the κ statistic, sensitivity (SN), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) for the detection of at least one obstructive lesion, LM CAD, 3VD and high-risk CAD (LM and/or 3VD). The Wilson score [22] was used to calculate the confidence intervals for small groups. We calculated the positive likelihood ratio (LR+) of CTCA, which is equal to the ratio of the odds of high-risk CAD given a positive CTCA result and the odds of high-risk CAD regardless of the CTCA result (i.e. the pre-test odds of high-risk CAD). Thus, LR+represents the performance of CTCA in detecting high-risk CAD. We also determined the negative likelihood ratio (LR−) of CTCA, which is equal to the odds of absent high-risk CAD given a negative CTCA result and the odds of absent high-risk CAD regardless of the CTCA result (i.e. the pre-test odds of absent high-risk CAD). Thus, LR−represents the performance of CTCA in excluding high-risk CAD. The area under the receiver operating characteristic curve (AUC) was calculated as the ability of a diagnostic test to discriminate patients with and without high-risk CAD. The AUC takes into account the influence of referral bias that may influence the diagnostic performance in our population [23, 24]. The AUC as a value of high-risk CAD discrimination was calculated for univariate and multivariate models that predicted high-risk CAD. Binary logistic regression analysis was used to create these predicting models (see Table 5) using the following variables separate and combined: Duke risk score, calcium score, and CTCA model (LM CAD and 3VD detected by CTCA). The method of Delong et al. [25] was applied to compare the AUC.

Next we also tested whether other variables such as heart rate, calcium score, body mass index and CT generation had an influence on the diagnostic performance of CTCA in ruling in/out high-risk CAD using multivariate logistic regression. A P value of less than 0.05 was considered statistically significant. This study was performed according to the criteria set forth in the Standard for Reporting of Diagnostic Accuracy Initiative [26].

Results

A total of 1,159 patients were included in the study; the mean age was 61±11 years and 31 % (n=360) were women. The patients' clinical and angiographic demographics are detailed in Table 2. High-risk CAD was present in 17 % of the patients (197/1,159; Table 2). The LM coronary artery was absent in 1 patient. ICA identified LM CAD in 48 patients (4 %). In 4 patients with LM CAD there was no additional obstructive CAD (8 %). In 35 % of patients with LM CAD (17/48) there was additional 1VD, in 29 % (14/48) 2VD and in 27 % (13/48) 3VD. 3VD without LM CAD was identified in 149 patients (13 %). The inter-observer agreement for per-vessel detection of obstructive stenosis by the two CT readers showed a good agreement (κ=0.94 [95 % CI 0.93–0.95]).

Diagnostic performance of CTCA

The diagnostic performance of CTCA in detecting CAD is detailed in Table 3. CTCA excluded high-risk CAD in 805 patients out of the 1,159, which was correct in 99 % (795/805) but underestimated the severity of CAD in 10 patients (1 %; Table 3). More specifically, CTCA underestimated 3VD in 13 patients and scored them all as 2VD (Table 4) and correctly detected LM CAD in 3 of these 13 patients (Table 3).

CTCA detected high-risk CAD in 354 patients out of the 1,159, which was correct in 53 % (187/354), but overestimated high-risk CAD in 167 patients (47 %; Table 3). More specifically, CTCA overestimated 3VD in 148 patients, LM CAD in 9 patients, and both LM and 3VD in another 10 patients. These patients with overestimated high-risk CAD by CTCA showed 2VD in 69 % (115/167), 1VD in 27 % (45/167) and obstructive CAD was absent in 4 % (7/167) by ICA (Table 4).

Discrimination of high-risk CAD

All models, univariate and multivariate, significantly contributed to the prediction and discrimination of high-risk CAD (Table 5, Fig. 1). The CTCA outperformed the Duke risk score (P<0.0001) as well as the calcium score (P<0.0001) for the discrimination of high-risk CAD. Calcium score (P=0.23) did not contribute to the prediction and discrimination of high-risk CAD (Table 5) when it was combined with the Duke risk score and CTCA.

Table 2 Patient characteristics

	Mean	Standard deviation
Number patients	1,159	
Women	31 % (360)	
Age (years)	61	[10.8]
Chest pain complaints [a]		
Typical	46 % (538)	[0.50]
Atypical	30 % (353)	[0.46]
Non-anginal	23 % (263)	[0.41]
Current smoker	28 % (319)	[0.45]
Diabetes mellitus [b]	17 % (196)	[0.38]
CAD in family [c]	47 % (546)	[0.50]
Hypercholesterolaemia [d]	57 % (664)	[0.50]
Hypertension [e]	51 % (595)	[0.51]
Body mass index (kg/m^2)	27	[4.3]
ECG pathological Q	15 % (173)	[0.36]
ECG repolarisation disturbances	36 % (423)	[0.48]
Pre-test probability [f]	67 %	[0.30]
Calcium score [g]	250	[42–679]
Prevalence of CAD [h]	74 % (849)	[0.44]
One-vessel CAD	33 % (385)	[0.47]
Two-vessel CAD	27 % (308)	[0.44]
Three-vessel CAD	14 % (162)	[0.35]
Left main CAD	4 % (48)	[0.20]
Left main and/or three-vessel CAD	17 % (197)	[0.38]
Heart rate during CTCA (beats per minute)	65	[12.1]
Effective radiation dose CTCA (mSv)[i]	11	[4.6]

Data are presented as means with the number of patients in parentheses. Data in brackets are the standard deviations and for the calcium score this is the 25th and 75th percentiles

[a] We defined typical angina as substernal discomfort that was precipitated by physical exertion or emotion and relieved by rest or nitroglycerin within 10 min. We classified chest pain with only 1 or 2 of these 3 symptom characteristics as atypical angina pectoris; if none of the characteristics was present, we classified it as non-anginal chest pain [51]

[b] Treatment with oral antidiabetic medication or insulin

[c] Patient had first- or second-degree relatives with premature coronary artery disease

[d] Total cholesterol >180 mg/dL or treatment for hypercholesterolaemia

[e] Blood pressure >120/90 mmHg or treatment for hypertension

[f] Pre-test probability of obstructive CAD using the Duke risk score [13]

[g] Calcium score (Agatston) with median and interquartile range in brackets

[h] Prevalence of having at least one obstructive lesion on a patient level determined by invasive coronary angiography

[i] mSv (millisievert): conversion factor 0.014 [mSv/mGy/cm]×dose–length product

Influence of variables on the diagnostic performance of CTCA

Heart rate during CTCA, calcium score, gender, body mass index, CT imaging protocol, and CT device generation did not have an influence on the sensitivity of CTCA in detecting high-risk CAD (Table 6). The specificity of CTCA in detecting high-risk CAD was influenced by the imaging protocol and calcium score used. When the CTCA was performed using a high-pitch helical imaging protocol or when CTCA was performed in a patient with a calcium score above 400 the specificity decreased significantly. The NPV also significantly decreased with increasing calcium score. The PPV was influenced by the heart rate during the CTCA, but a threshold of 60 beats/min did not result in a significant difference in PPV. The CT device generation showed a significant influence on the PPV. The inter-generation comparison showed no significant differences (Table 6).

Discussion

Numerous studies using ICA in the past [27–30] and more recently using non-invasive CTCA have indicated that higher extent and severity of CAD (LM/3VD) carry a worse prognosis [31–33], which can be improved by revascularisation [4]. In this study we demonstrated the performance of CTCA in detecting and excluding out LM and/or 3VD, defined as high-risk CAD.

The main results of this study are:

1. CTCA accurately excludes high-risk CAD. LM CAD was never missed and 3VD was rarely missed (2 %).
2. CTCA accurately detects high-risk CAD. The high accuracy of CTCA in detecting high-risk CAD was at the expense of the overestimation of high-risk CAD.
3. CTCA provided independent incremental value in the discrimination of high-risk CAD compared with the Duke risk score or calcium score.

Current guidelines indicate that the diagnostic work-up of patients with stable angina and intermediate pre-test probability of CAD requires initial assessment with stress testing with or without imaging [6]. In the presence of ischaemia, stress testing is often followed by anatomical assessment with ICA to assess the appropriateness of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) in addition to optimal medical treatment [6].

However, stress tests such as ET, MPI and SE are limited in detecting and excluding the presence of high-risk CAD anatomy. ET is often used for risk stratification of symptomatic patients as a first-line diagnostic test, because it is widely available, does not use radiation and is inexpensive [8, 34, 35]. In ET the presence of high-risk CAD may be suspected with severe ST segment depression, short exercise duration or blood pressure drop during exercise [7, 35–38] but these parameters are not very sensitive. ET diagnostic performance studies have shown sensitivities ranging from 74 % to 91 % for the detection of LM CAD [8, 36] and from 63 %

Table 3 Diagnostic performance of CT coronary angiography

	Prevalence	TP	TN	FP	FN	κ	SN %	SP %	PPV %	NPV %	LR+	LR−
CAD [a]	74 %	850	227	73	9	0.80*	99 [98–99]	76 [71–80]	92 [90–94]	96 [93–98]	4.07	0.01
LM CAD	4 %	48	1,081	29	0	0.76*	100 [93–100]	97 [96–98]	62 [51–72]	100 [100–100]	38.28	0.000
3VD	14 %	149	827	170	13	0.53*	92 [87–95]	83 [80–85]	47 [41–52]	98 [97–99]	5.39	0.10
LM and/or 3VD	17 %	187	795	167	10	0.59*	95 [91–97]	83 [80–85]	53 [48–58]	99 [98–99]	5.47	0.06

TP true positive, *TN* true negative, *FP* false positive, *FN* false negative, *κ* kappa statistic for the agreement analyses between invasive coronary angiography and CT coronary angiography, *SN* sensitivity, *SP* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *LR+* positive likelihood ratio, *LR−* negative likelihood ratio, *CAD* coronary artery disease, *LM* left main, *3VD* three-vessel CAD

[a] Diagnosis of at least one significant stenosis per patient by ICA

*$P<0.001$

Table 4 The performance of CT coronary angiography in detecting and excluding high-risk CAD compared with invasive coronary angiography

				CTCA			
				LM CAD −		LM CAD +	
				3VD −	3VD +	3VD −	3VD +
ICA	LM CAD −	3VD	−	795	148	9	10
			+	10	129	0	10
	LM CAD +	3VD	−	0	0	23	12
			+	0	0	3	10

				CTCA							
				LM CAD −				LM CAD +			
				Extent vessel CAD				Extent vessel CAD			
				0VD	1VD	2VD	3VD	0VD	1VD	2VD	3VD
ICA	LM CAD −	Extent vessel CAD	0VD	224	56	13	4	1	0	1	1
			1VD	7	212 [a]	104	39	0	2	1	3
			2VD	2	13	164	105	0	0	4	6
			3VD	0	0	10	129	0	0	0	10
	LM CAD +	Extent vessel CAD	0VD	0	0	0	0	2	1	1	0
			1VD	0	0	0	0	0	8	6	3
			2VD	0	0	0	0	0	1	4	9
			3VD	0	0	0	0	0	0	3	10

Correct exclusion of high-risk CAD
Correct detection of high-risk CAD
Overestimation of high-risk CAD
Underestimation of high-risk CAD

CAD coronary artery disease, *CTCA* computed tomography coronary angiography, *ICA* invasive coronary angiography, *0VD* no obstructive CAD, *1VD* 1-vessel CAD, *2VD* two-vessel CAD, *3VD* three-vessel CAD

[a] One patient with 1VD with absent LM

Table 5 Discrimination of high-risk CAD by univariate and multivariate models

Model [a]	AUC [95 % CI]	se AUC	*P*	High-risk CAD discrimination comparison [b]		
				Duke	CaSc	CTCA
Duke	0.68 [0.65–0.72]	0.02	<0.001			
CaSc	0.72 [0.69–0.76]	0.02	<0.001	0.10		
CTCA [c]	0.90 [0.88–0.93]	0.01	<0.001	<0.001	<0.001	
Duke+CaSc+CTCA [c]	0.93 [0.91–0.94]	0.01	<0.001 [d]	<0.001	<0.001	<0.001

Duke Duke risk score, *CaSc* Calcium score, *CTCA* CT coronary angiography, *LM CAD* left main coronary artery disease, *3VD* three-vessel CAD, *AUC* area under the receiver operating characteristic curve, *se* standard error

[a] Logistic regression (univariate and multivariate) analyses were used to calculate the probability of high-risk CAD

[b] Comparison of discrimination of high-risk CAD using the different models with the DeLong method

[c] CTCA model: LM CAD and 3VD were inserted as separate variables into the logistic regression model

[d] CaSc did not contribute (*P*=0.23) to the prediction of high-risk CAD

to 67 % for the detection of 3VD [7, 36]. The specificity of ET for the diagnosis of LM and/or 3VD is around 46 % and for LM CAD this is only 38 % [8].

MPI has a sensitivity of 92 % in detecting high-risk CAD [8]. The specificity of MPI is slightly lower compared with ET (34 % vs. 46 %, *P*<0.01). The under-diagnosis of high-risk CAD by MPI is believed to be a result of a balanced reduction of perfusion [10, 39–41]. The combination with other indirect findings, such as LV function and stress-induced wall motion abnormality (transient ischaemic dilatation), has been shown to improve the prediction of high-risk CAD by MPI [37–40].

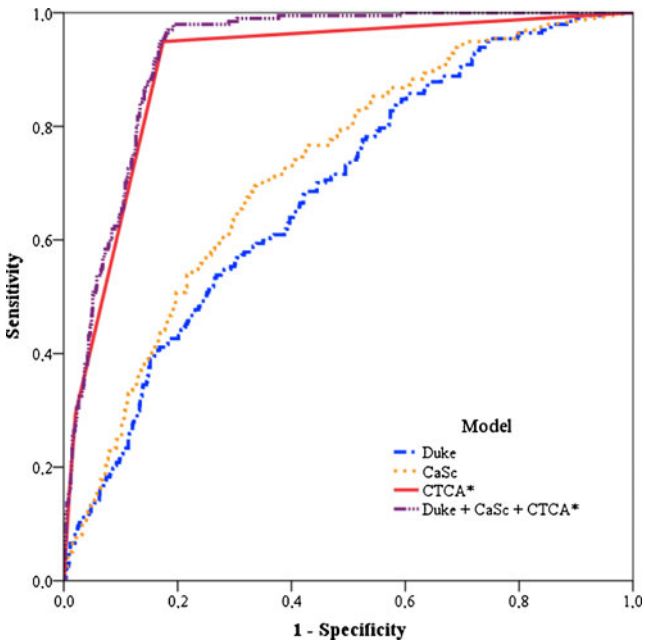

Fig. 1 Receiver operating characteristic curves in the discrimination of high-risk CAD using different models. Logistic regression (univariate and multivariate) analyses were used to calculate the probability of high-risk CAD. *Duke* Duke risk score, *CaSc* calcium score, *CTCA* CT coronary angiography, *LM CAD* left main coronary artery disease, *3VD* three-vessel CAD, *AUC* area under the receiver operating characteristic curve. *CTCA model: LM CAD and 3VD were inserted as separate variables into the logistic regression model

SE has a sensitivity and specificity of 94 % and 40 %, respectively, in detecting high-risk CAD [10]. In a meta-analysis by Mahajan et al., MPI (15 studies with 2,310 patients in total) was compared with SE (14 studies with 1,403 patients in total) for the detection of high-risk CAD; the investigators found a significantly higher sensitivity by SE compared with MPI (94 % vs. 75 %, *P*<0.001), with a similar specificity (40 % vs. 48 %, *P*=0.16) [10]. Although SE discriminates high-risk CAD better than MPI [summary receiver operating characteristic curve (ROC) AUC 0.82 vs. 0.73, *P*=0.01] [10] this technique has its own inherent limitations [42]. Factors such as suboptimal acoustic window can be partly improved by the use of echo-contrast media, but still requires sufficient training and experience for proper evaluation [43].

In our study we used CTCA as an alternative first-line non-invasive diagnostic tool to detect high-risk CAD. CTCA demonstrated a sensitivity of 95 %, which is at least comparable to the conventional non-invasive diagnostic techniques (ET, MPI and SE). Importantly, the specificity of CTCA in excluding LM and/or 3VD appears to be higher (CTCA, 83 %; ET, 46 % [8]; MPI, 48 % [10]; SE, 40 % [10]) with a better negative likelihood ratio of 0.06 compared with SE (0.21) and MPI (0.47) [10]; and CTCA discriminates high-risk CAD better than SE and MPI (AUC CTCA, 0.90; SE, 0.82; MPI, 0.73 [8]). We also assessed the discrimination of high-risk CAD using the Duke risk score and calcium score in addition to CTCA. CTCA was superior to the Duke risk score and calcium score, and showed that the calcium score did not contribute to the prediction of high-risk CAD when the Duke risk score and CTCA were used in symptomatic patients.

The diagnostic performance of CTCA is limited because it overestimates the extent and severity of CAD. Patients in whom CTCA overestimated high-risk CAD (47 %) predominantly had 2VD (69 %) and only 4 % had no obstructive CAD (Table 4). The tendency to overestimate the stenosis

Table 6 Influence of the variables on the diagnostic performance of CTCA in the detection and exclusion of high-risk CAD

Heart rate	SN % *P*=NS	SP % *P*=NS	PPV % *P*=0.007	NPV % *P*=NS
<60 beats/min	97 [91–99]	85 [80–88]	60 [52–68]	99 [97–100]
≥60 beats/min	93 [87–96]	82 [79–85]	49 [43–56]	98 [97–99]
Calcium score	*P*=NS	*P*<0.001	*P*=NS	*P*<0.001
<400	95 [90–97]	90 [87–92]	48 [39–56]	99 [99–100]
≥400	95 [89–97]	68 [63–73]	56 [49–62]	97 [94–98]
Gender	*P*=NS	*P*=NS	*P*=NS	*P*=NS
Women	98 [88–100]	86 [82–90]	48 [38–59]	100 [98–100]
Men	94 [89–97]	81 [78–84]	54 [48–60]	98 [97–99]
BMI	*P*=NS	*P*=NS	*P*=NS	*P*=NS
<30	96 [91–98]	83 [80–85]	52 [46–58]	99 [98–100]
≥30	92 [81–97]	81 [75–86]	54 [44–65]	98 [94–99]
CT imaging protocol [a]	*P*=NS	*P*<0.01 [b]	*P*=NS	*P*=NS
Low-pitch helical	96 [92–98]	84 [81–86]	54 [48–60]	99 [98–100]
Sequential imaging	88 [64–97]	82 [73–89]	48 [31–66]	97 [90–99]
High pitch helical	100 [72–100]	64 [47–78]	45 [27–65]	100 [85–100]
CT device generation [c]	*P*=NS	*P*=NS	*P*<0.001 [d]	*P*=NS
SSCT	95 [83–99]	83 [78–86]	38 [28–47]	99 [97–100]
DSCT 1st generation	96 [90–98]	85 [81–88]	65 [57–71]	99 [97–99]
DSCT 2nd generation	93 [81–97]	78 [72–83]	46 [35–56]	98 [95–99]

P values were determined for heart rate, calcium score and BMI as continuous variables and for gender, CT imaging protocol and CT device generation as categorical variables in the multivariate logistic regression. The diagnostic performance of CTCA is shown at arbitrary thresholds of heart rate, calcium score and BMI

SN sensitivity, *SP* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *NS* not significant ($P \geq 0.05$), *BMI* body mass index, *SSCT* single-source CT, *DSCT* dual-source CT

[a] CT-imaging protocol was inserted as a dummy variable into the multivariate logistic regression. Low-pitch helical imaging protocol was taken as a reference and was compared with a sequential imaging protocol and a high-pitch helical imaging protocol

[b] Sequential imaging protocol ($P=0.007$) and high-pitch helical imaging protocol ($P=0.005$) were significantly different from the low-pitch helical imaging protocol

[c] CT generation was inserted as a dummy variable into the multivariate logistic regression. SSCT was taken as the reference and was compared with 1st and 2nd generation DSCT

[d] 1st generation DSCT ($P=0.56$) and 2nd generation DSCT ($P=0.17$) were not significantly different from the SSCT

severity of a given obstruction is because the CT reader is careful not to "miss" an obstructive stenosis (in the case of breathing, motion or artefacts due to the calcifications), thus to avoid "under-diagnosis" and delay of appropriate treatment, which could negatively affect the prognosis. We found false-positive observations to be associated with a higher heart rate (Table 6). The substantial rate of CAD overestimation and the inability of CTCA to assess the functional significance of lesions [14, 44] require referral of these symptomatic patients with CT-determined high-risk CAD for ICA combined with measurement of the fractional flow reserve (FFR). The FAME study ($n=1{,}005$) demonstrated that FFR-guided revascularisation of multi-vessel CAD by ICA was associated with lower adverse event rates, use of fewer stents and lower healthcare costs [45].

To overcome the high rates of referral to ICA, the integration of anatomical and functional testing is required. Currently this can be achieved by combining PET or SPECT with CT, but more recently by the fusion of CTCA anatomy and CT-derived FFR using computational fluid dynamics during simulated maximal hyperaemia [46]. Another CT-derived method is to compare myocardial enhancement at rest and during adenosine-induced stress CT perfusion to assess the impedance of coronary stenosis on myocardial blood flow [47, 48]. However, these novel approaches are only in their infancy, and further investigation is needed to confirm their applicability in the clinical setting.

The study had a number of limitations. Referral bias was present, because the patients in our population were referred by their treating physician to undergo ICA on the basis of their chest-pain presentation with or without an outcome of stress testing. To account for this referral bias on the diagnostic accuracy of CTCA in detecting high-risk CAD we assessed the ROC AUC [23] for CTCA (0.90) which is comparable to that of stress echocardiography (0.82) [10].

Our study population only consisted of symptomatic patients with stable angina, and our results may not apply to the wider spectrum of patients with suspected CAD, who have unstable symptoms or did not undergo ICA. Of concern was the rather high radiation exposure of CTCA (11 mSv) owing to the most frequently used low-pitch helical imaging protocol, which was standard in the first-generation CT systems [19, 49]. Currently with the newer generation systems and optimal imaging protocols radiation exposure can be kept within much lower levels (<3 mSv) in patients with low heart rates (<65 beats/min) [20].

In conclusion, CTCA accurately excludes high-risk CAD in patients with suggestive symptoms. However, the performance of CTCA in detecting high-risk CAD is suboptimal, owing to the high number of false-positive observations made by overestimating the severity of stenosis. CTCA provides incremental value in the discrimination of high-risk CAD compared with the Duke risk score and the calcium score.

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