Multimodality imaging in chronic coronary artery disease

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Chapter 7

Multi-slice computed tomography coronary angiography for ruling out suspected coronary artery disease: what is the prevalence of a normal study in a general clinical population?

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Abstract

Introduction: The aim of the study was to assess the prevalence of a normal multi-slice computed tomography (MSCT) in patients with suspected coronary artery disease (CAD) and to relate these observations to clinical presentation and pretest likelihood of CAD.

Methods: In total, 340 consecutive patients (182 men, 55±12 years) without a history of CAD who were referred for MSCT angiography, were included in the study. Based on patient characteristics and the referral reason for MSCT angiography, patients were classified as having a low, intermediate, or high pretest likelihood of CAD. Patients were evaluated for the presence of coronary artery calcium as well as the presence of atherosclerosis.

Results: Overall, 157 (46%) patients did not have coronary artery calcium and 133 (40%) patients had a completely normal MSCT angiogram. In 58% of the patients with low pretest likelihood, no coronary atherosclerosis was observed as compared to 33% and 17% of the patients with intermediate and high pretest likelihood, respectively.

Conclusions: MSCT ruled out coronary atherosclerosis in 40-46% of patients without known CAD who were referred for MSCT. Accordingly, in patients with low to intermediate pretest likelihood, MSCT may be an attractive modality to exclude coronary atherosclerosis, and may prevent unnecessary additional functional testing or invasive angiography.

Introduction

Multi-slice computed tomography (MSCT) is a rapidly developing technique and allows reliable evaluation of the coronary arteries in a non-invasive manner. Consistently high sensitivity and specificity for the detection of significant stenosis when compared to invasive coronary angiography have been reported.[1-4] In general, the high negative predictive value is considered to be the major strength of the technique and a normal MSCT virtually excludes coronary artery disease (CAD) on conventional coronary angiography.[5 6] As a result, MSCT is increasingly used as a technique to rule out CAD. However, it is likely that coronary atherosclerosis may be encountered in a considerable number of patients, resulting in ruling out of the disease in only a minor proportion of patients, and referral to additional tests (ischemia testing, invasive angiography) in a large percentage of patients undergoing MSCT. Accordingly, a major concern is that MSCT imaging will potentially lead to an increased "ruling in" rather than "ruling out" coronary atherosclerosis. Currently, no data exist on the percentage of patients in whom coronary atherosclerosis can be ruled out with MSCT in a general clinical population with different levels of cardiovascular risk. Accordingly, the aim of the present study was to determine the prevalence of a normal MSCT study in patients with suspected CAD and relate the observations to clinical presentation and pretest likelihood of CAD.

Methods

Study population

In total, 340 consecutive patients who had been clinically referred for MSCT angiography because of suspected CAD were retrospectively included in the study. Patients with a history of CAD were excluded. A history of CAD was defined as prior percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG), as a history of myocardial infarction or as the presence of ≥1 significant stenosis on a previous coronary angiogram. Reasons for referral to MSCT angiography were classified as follows: 1. screening (presence of 1 risk factor and referred for evaluation prior to high-risk cardiac surgery, or presence of 1 risk factor and prior inconclusive treadmill testing or inconclusive nuclear testing, or presence of one risk factor and regional wall motion abnormalities on echocardiography), 2. elevated risk for CAD (presence of ≥2 risk factors), without chest discomfort, 3. non-anginal chest pain, 4. atypical angina [7], and 5. typical angina[7].

Risk factors were derived through a structured interview and existing medical record data. Hypertension was defined as a documented history of high blood pressure ≥140/90 mmHg or the use of antihypertensive medication.[8] Hypercholesterolemia was defined as a total cholesterol level ≥5 mmol/l or treatment with lipid-lowering medication.[9] Patients were classified as having diabetes if fasting glucose levels were ≥7 mmol/l or receiving treatment with oral hypoglycemic drugs or insulin.[10] A positive family history of CAD was defined as the presence of CAD in first-degree relatives younger than 55 (men) or 65 (women) years of age.[11] According to the patient characteristics and referral reason for MSCT angiography, patients were classified as having low, intermediate, or high

pretest likelihood of CAD using the method described by Diamond and Forrester.[12] The current study was a retrospective study based on previously obtained clinical data.

MSCT

Data acquisition

MSCT examinations were performed with a 64-slice scanner (Aquilion 64, Toshiba Medical Systems, Otawara, Japan or Lightspeed VR 64-MSCT, General Electrics, Milwaukee, WI, US). First, a non-contrast enhanced scan was performed prior to MSCT coronary angiography to assess the total coronary calcium burden. Collimation was 4x3.0 mm and gantry rotation time 500 ms. Tube voltage and tube current 120 kV and 200 mA, respectively.

For the Toshiba scanner, collimation was 64x0.5 mm and rotation time was 400 or 450 ms, depending on heart rate. Tube current and voltage were 300 mA and 120 kV, respectively. For the General Electrics scanner, collimation was 64x0.625 mm, scan rotation 350 ms, tube voltage 120 kV and tube current 600 mA. Total amount of contrast (Iomeron 400, Altana, Konstanz, Germany) was 90-110 ml, followed by a saline flush of 50 ml, both injected at 5 ml/s. Automated detection of peak enhancement in the aortic root was used to time the scan. In all patients, imaging was performed during an inspiratory breath hold and electrocardiographic gating. In patients with a heart rate >65 beats/min, beta blocking agents were administered prior to MSCT imaging if no contra-indications for beta blockade were present. To assess the presence of coronary artery plaques, reconstructions were generated in diastole (typically 75% of the cardiac cycle). Slice thickness was 0.5 mm with an increment of 0.3 mm. In case of motion artifacts, additional reconstructions were explored at different time points of the R-R interval. Thereafter, the axial datasets were transferred to a remote workstation (Vitrea 2, Vital Images, USA or Advantage, GE healthcare, USA) for post-processing and subsequent evaluation.

Data analysis

Coronary artery calcium score

All data were evaluated on a remote workstation using dedicated software. In each patient coronary artery calcium was identified as a dense area in the coronary artery exceeding the threshold of 130 HU, and the total coronary artery calcium score (CS) was calculated based on Agatston.[13] The absence of coronary artery calcium was defined as a CS=0. In addition, the use of a higher coronary artery calcium threshold (CS >100) was explored to define a positive coronary artery calcium study.

Coronary angiography

In all patients, the coronary tree was assessed for the presence of coronary plaques (regardless of their severity) by consensus of two experienced observers who were blinded to all other clinical data. The MSCT angiogram was classified normal if no atherosclerosis or coronary artery calcium could be identified. If coronary atherosclerosis was present, the scan was further classified as significant or non-significant according to the presence or absence of ≥50% luminal narrowing in ≥1 coronary artery segments. In case of severe artifacts due to e.g. motion during the scan or dense calcifications, the scan was classified as uninterpretable. Patients with uninterpretable segments but also at least 1 identified significant stenosis were classified as having obstructive CAD.

Statistical analysis

Results are presented as mean values±SD, or as actual numbers (%). Continuous variables that are not normally distributed are expressed as medians (25^{th} to 75^{th} percentile range). Continuous data were compared using the unpaired two-sided Student t test. Categorical data were compared with the χ^2 test with Yates' correction. Ordinal data were analyzed with Somer's d test. All comparisons were performed in predefined groups. A P-value <0.05 was considered as statistically significant. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Study population

In total, 340 consecutive patients (182 men, 55±12 years) were included in this study. The baseline characteristics of the patients are summarized in **Table 1**. In total, 114 (34%) patients had a low pretest likelihood of CAD, whereas 46 (14%) patients presented with a high pretest likelihood of CAD. The majority of the patients had an intermediate pretest likelihood of CAD (180 patients (52%) (**Figure 1**) . The baseline characteristics according to gender are provided in **Table 2**. Men presented more often with diabetes, hypercholesterolemia and smoking when compared to women.

Table 1. Baseline characteristics of the study population.

Characteristic	
Nr. Patients	340
Gender (M/F)	182/158
Age (years)	55±12
Risk factors for CAD	
Average body mass index (kg/m^2)	27±4
Diabetes mellitus	135 (40%)
Hypertension	163 (48%)
Hypercholesterolemia	119 (35%)
Family history of CAD	150 (44%)
Smoking	83 (24%)
Reason of referral	
Screening	63 (19%)
High risk, no chest discomfort	102 (30%)
Nonanginal chest pain	21 (6%)
Atypical angina	94 (28%)
Typical angina	60 (18%)
Pretest likelihood of CAD	
Low	114 (34%)
Intermediate	180 (52%)
High	46 (14%)

CAD=coronary artery disease

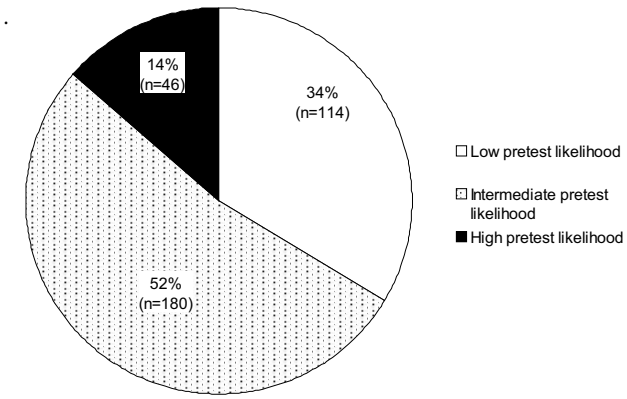

Figure 1. Distribution of pretest likelihood of CAD, evaluated according to complaints, age and gender. In total, 114 (34%) patients had a low pretest likelihood of CAD (white segment), whereas in 46 (14%) patients the pretest likelihood of CAD was evaluated as high (black segment). The majority of patients (n=180, 52%) had an intermediate pretest likelihood of CAD (dotted segment)

Table 2. Baseline characteristics of the study population according to gender.

Characteristic	Men (n=182)	Women (n=158)	P-value
Age (years)	54±12	56±12	0.27
Risk factors for CAD			
Average body mass index (kg/m^2)	27±4	27±5	0.58
Diabetes mellitus	88 (48%)	47 (30%)	0.0007
Hypertension	83 (46%)	80 (51%)	0.41
Hypercholesterolemia	73 (40%)	46 (29%)	0.04
Family history of CAD	73 (40%)	77 (49%)	0.14
Smoking	53 (29%)	30 (19%)	0.04
Reason of referral			
Screening	32 (18%)	31 (20%)	0.73
Elevated risk, no chest discomfort	70 (38%)	32 (20%)	0.0004
Nonanginal chest pain	9 (5%)	12 (8%)	0.43
Atypical angina	40 (22%)	54 (34%)	0.017
Typical angina	31 (17%)	29 (18%)	0.86
Pretest likelihood of CAD			
Low	41 (23%)	73 (46%)	0.0001
Intermediate	110 (60%)	70 (44%)	0.004
High	31 (17%)	15 (10%)	0.06

CAD=coronary artery disease

Coronary artery calcium score

Overall

In 1 patient, the calcium scan was not available. In the remaining patients, coronary artery calcium was scored according to the Agatston method.[13] The median (25th to 75th percentile) CS was 6 (0–134). No coronary artery calcium was detected in 157 (46%) patients. Twenty-two (7%) patients had

a CS of 1-10, in 58 (17%) patients CS was 11-100, and a CS of 101-400 was found in 51 (15%) patients. In 51 (15%) patients CS exceeded 400 (**Figure 2**).

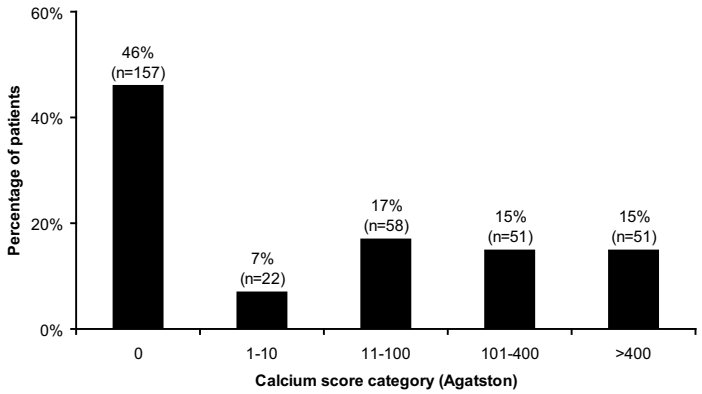

Figure 2. Distribution of coronary artery calcium score (CS) categories. In 157 (46%) patients no calcium was present, whereas in 22 (7%) patients CS was 1-10. In 58 (17%) patients CS was 11-100, and in 51 (15%) patients CS was 101-400. In 51 (15%) patients CS exceeded 400.

Absence of coronary artery calcium

Pretest likelihood of CAD: In **Figure 3** the prevalence of a normal coronary artery calcium scan after the classification of patients according to pretest likelihood is illustrated. As expected, coronary artery calcium was absent in the majority of patients (n=81, 71%) with low pretest likelihood. For patients with intermediate and high pretest likelihood these percentages were 37% and 20%, respectively (P=0.0000).

Versus referral reason: In **Figure 4A**, the absence of coronary artery calcium according to the reason of referral, is shown. In symptomatic patients, the prevalence of coronary artery calcium paralleled the increasing severity of symptoms (P=0.03). Nevertheless, still in 33% of the patients referred for MSCT because of typical angina no coronary artery calcium was observed.

Versus gender and age: In 38% of males and 55% of females, coronary artery calcium was absent (P=0.003, **Figure 4B**). As expected, the absence of coronary artery calcium decreased with age. In patients <50 years, coronary artery calcium was absent in 80% (<50 years), whereas this percentage decreased to 41% (50-60 years) to 17% (>60 years) (P=0.0000, **Figure 4C**).

Stratifying patients according to both age and gender showed a delay in development of coronary artery calcium in women, as described in **Table 3**.

In patients younger than 50 years old, coronary artery calcium was absent in 89% of women vs. 72% of men (P=0.04). Also for patients between 50 and 60 years old, coronary artery calcium was absent in a significantly higher percentage of women (57% versus 31% in men, P=0.01). However, no significant difference was noted between males and females >60 years old, although the percentage of patients without coronary artery calcium was still slightly higher in women.

For practical purposes also, the use of a higher coronary artery calcium threshold (CS <100) was explored to identify the prevalence of clinically relevant coronary artery calcium. Using this

threshold, 70% of patients showed no or only mild coronary artery calcium (62% of men, 78% of women). After stratifying patients according to gender and age, CS <100 was observed in 87% of men <50 years, and in 98% of women <50 years. In patients aged 50-60 years, CS <100 was present in 63% of men, and in 80% of women. Considering patients >60 years old, CS <100 was obtained in 33% of men and in 59% of women (P=0.01).

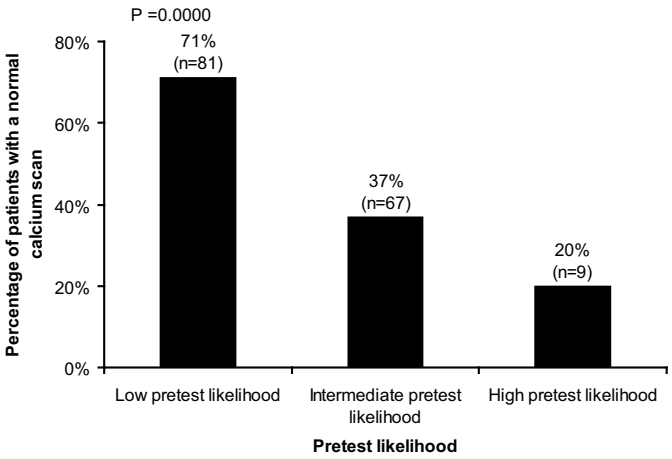

Figure 3. Absence of coronary artery calcium according to pretest likelihood of CAD. In patients with low pretest likelihood, no coronary artery calcium was observed in 71%. For patients with intermediate and high pretest likelihood these percentages were 37% and 20%, respectively.

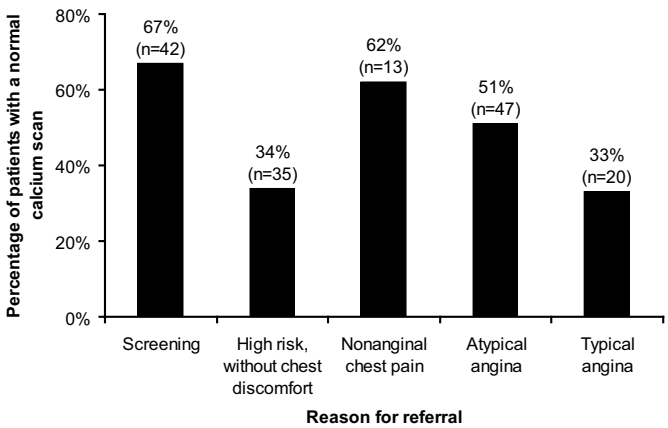

Figure 4A. Absence of coronary artery calcium according to referral reason. Of patients referred to MSCT for screening, 67% had no coronary artery calcium when compared with 34% of patients with elevated risk but without chest discomfort. In symptomatic patients, the prevalence of a normal study decreased with increasing severity of complaints.

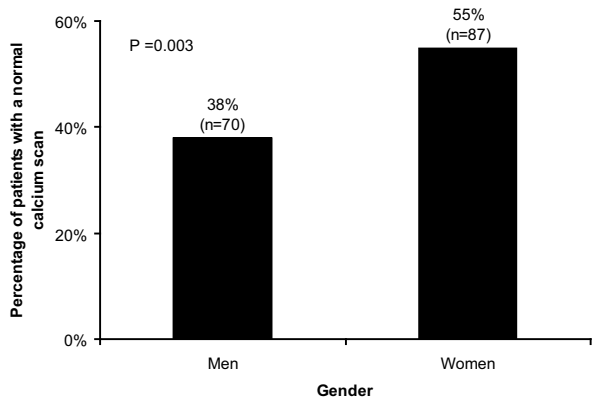

Figure 4B. Absence of coronary artery calcium in relation to gender. In 38% of men, no coronary artery calcium was detected as compared to 55% of women.

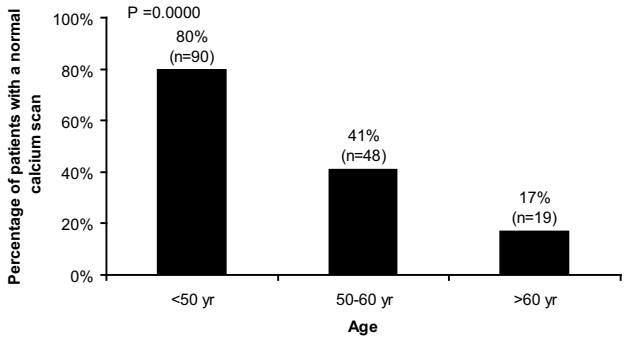

Figure 4C. Absence of coronary artery calcium in relation to age. In 80% of patients <50 years, coronary artery calcium was absent when compared with 41% of patients aged 50-60 years and 17% of patients >60 years.

Table 3. Absence of coronary artery calcium according to gender and age.

	Men	Women
<50 years	43/60 (72%)	47/53 (89%)
50 - 60 years	22/70 (31%)	26/46 (57%)
>60 years	5/52 (10%)	14/58 (24%)

MSCT angiography

Overall

Of the 340 patients included, the presence of coronary atherosclerosis could be ruled out with MSCT angiography in 133 (40%) patients, as illustrated in **Figure 5**.

One hundred and sixteen (34%) patients were diagnosed as having non-obstructive coronary atherosclerosis, whereas in 73 (21%) patients CAD was present. Finally, in 18 (5%), the MSCT examination was classified as uninterpretable due to the presence of motion artifacts or severe calcifications.

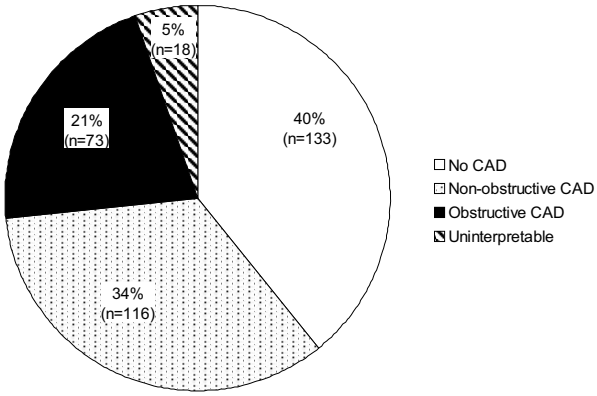

Figure 5. MSCT angiography findings. In 40% of patients, absence of coronary atherosclerosis was observed (white segment). In 34% of patients non-obstructive coronary atherosclerosis was observed (dotted segment), whereas CAD was detected (black segment) in 21% of patients. Finally, in 5% of patients the MSCT scan was uninterpretable (hatched segment).

Absence of coronary atherosclerosis

Versus pretest likelihood of CAD: As shown in **Figure 6**, the prevalence of a normal MSCT coronary angiography study decreased from 58% in patients with low pretest likelihood to 17% of patients with high pretest likelihood (P=0.0000).

Versus referral reason: In **Figure 7A**, the absence of coronary atherosclerosis according to the reason of referral, is shown. CAD was absent in approximately half of patients referred for screening, whereas in symptomatic patients, the absence of coronary atherosclerosis decreased with increasing severity of symptoms with 28% of patients with typical angina having no coronary atherosclerosis.

Versus gender and age: No coronary atherosclerosis was observed in 36% of the men and 43% of the women (P=0.20, **Figure 7B**). As expected, the absence of coronary atherosclerosis decreased with age, from 65% for patients <50 years to 38% and 14% for patients between 50 and 60 years and >60 years old, respectively (P=0.0000, **Figure 7C**). Similar to the CS, a delay in the development of CAD was observed in women when compared with men. In patients between 50 and 60 years old, coronary atherosclerosis was absent in 30% of men vs. 50% of women (P=0.03). These percentages decreased to 10% and 17% for men and women older than 60 years old, respectively (P=0.40, **Table 4**).

In addition, a cutoff value of 50% luminal narrowing was applied, resulting in the rule-out of obstructive coronary atherosclerosis in 73% of patients (71% of men, 76% of women). After stratifying patients according to gender and age, it was demonstrated that in the majority of patients <50 years old (90% men and 89% of women) obstructive coronary atherosclerosis was absent. In patients aged 50-60 years, obstructive coronary atherosclerosis was absent in 69% of men, and in 80% of women. In 52% of the men >60 years old and in 61% of the women >60 years old, obstructive coronary atherosclerosis was absent (P=0.44). Finally, with regard to pretest likelihood, ruling out of obstructive coronary atherosclerosis in patients ≤60 years old and with low pretest likelihood was 86% for both women and men. In patients ≤60 years old and with intermediate pretest likelihood,

ruling out was 84% in women and 81% in men, whereas in patients with high pretest likelihood, obstructive atherosclerosis was ruled out in only 50% of women ≤60 years old and 53% of men ≤60 years old.

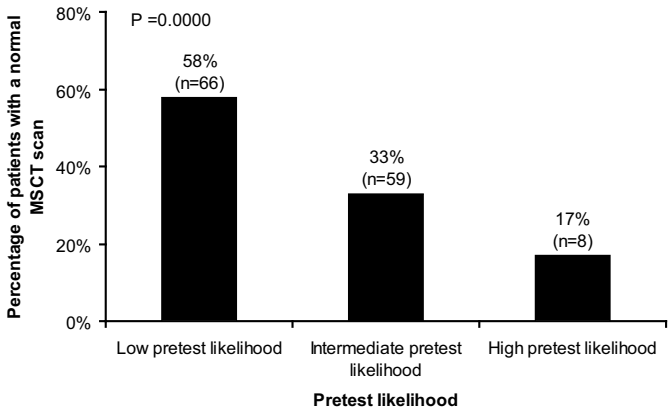

Figure 6. Absence of coronary atherosclerosis according to pretest likelihood of CAD. Of patients with low pretest likelihood, 58% had no coronary atherosclerosis on MSCT angiography. For patients with intermediate and high pretest likelihood these percentages were 33% and 17%, respectively.

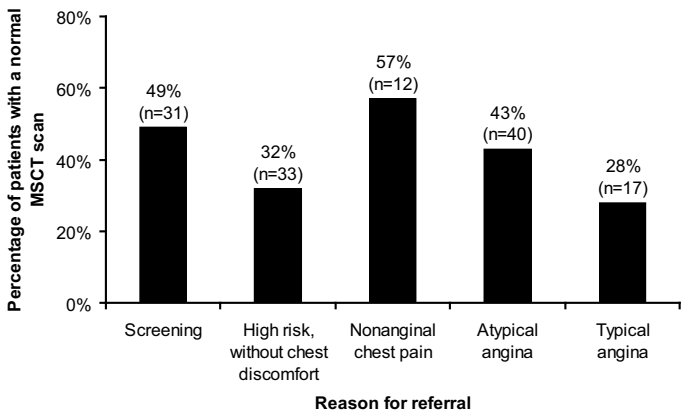

Figure 7A. Absence of coronary atherosclerosis according to reason of referral. Of patients referred to MSCT for screening, 49% had no coronary atherosclerosis when compared with 32% of the patients with high risk but without chest discomfort. The yield of a normal MSCT angiogram was inversely related with the severity of complaints.

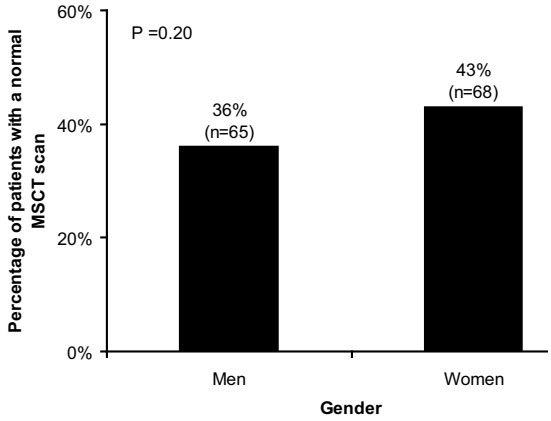

Figure 7B. Absence of coronary atherosclerosis in relation to gender. In 36% of men, no coronary atherosclerosis was detected when compared with 43% of women.

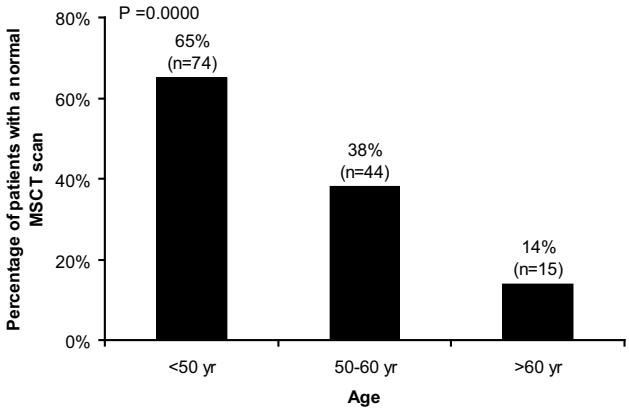

Figure 7C. Absence of coronary atherosclerosis in relation to age. In 65% of patients <50 years, coronary atherosclerosis was absent when compared with 38% of patients aged 50-60 years and 14% of patients >60 years.

Table 4. Absence of coronary atherosclerosis on MSCT according to gender and age.

	Men	Women
<50 years	39/60 (65%)	35/53 (66%)
50 - 60 years	21/70 (30%)	23/46 (50%)
>60 years	5/52 (10%)	10/59 (17%)

Discussion

The main finding of this study was that MSCT permits ruling out coronary atherosclerosis in 40-46% of patients without known CAD. The prevalence of a normal study decreased with age, severity of complaints and higher pretest likelihood, indicating that use of MSCT may be most beneficial in younger patients, with low to intermediate pretest likelihood of CAD.

Ruling out coronary atherosclerosis is an important goal of non-invasive testing. However, with regard to conventionally used tests, such as exercise ECG testing or myocardial perfusion imaging, characteristics inherent to the technique limit definite exclusion of coronary atherosclerosis, since non-obstructive atherosclerosis cannot be excluded. MSCT angiography therefore presents an attractive alternative, since it allows accurate non-invasive evaluation of the coronary arteries within a single breath hold. When compared with invasive coronary angiography, the technique has been shown to have a high negative predictive value: a normal MSCT virtually excludes CAD on conventional angiography. Accordingly, accurate ruling out of coronary atherosclerosis is currently considered to be the major strength of MSCT angiography. The use of MSCT in this setting could potentially avoid invasive angiography in some patients. However, it has been feared that the majority of patients will present with some extent of coronary atherosclerosis on MSCT. As a consequence, anatomical testing with MSCT may in fact more often result in ruling in rather than ruling out coronary atherosclerosis, and will result in an increase in additional testing, including invasive angiography. Accordingly, the prevalence of a normal study in relation to clinical characteristics, clinical presentation and pretest likelihood of CAD was evaluated in the present study.

In patients with low or intermediate pretest likelihood of CAD, the presence of coronary artery calcium or non-calcified plaques was ruled out in 46% and 40% of patients, respectively. These data indicate that the prevalence of a completely normal study is sufficiently high to support MSCT as a technique to rule out coronary atherosclerosis prior to other imaging modalities.

As expected, the prevalence of a normal study was higher in young patients (65% in patients <50 years vs. 38% and 14% in patients aged 50-60 years and >60 years respectively) as well as in women (43% vs. 36% in men). In contrast, coronary artery calcium or non-calcified plaques were absent in only 17% and 14% of patients older than 60 years, respectively. Combining age and gender showed a delay in the development of coronary artery calcium in women. Absence of calcium was observed in the majority of women between 50 and 60 years of age. In contrast, calcium was absent in only 31% of men between 50 and 60 years of age. This observation is consistent with previous studies. [14] This discrepancy appeared to resolve in patients older than 60 years. These observations are in line with previous studies; using ultra-fast CT for calcium scoring in asymptomatic patients, Janowitz and colleagues[14] reported a considerably lower prevalence of coronary artery calcium in women vs. men until the age of 60 years. In patients older than 60 years, the difference diminished. Accordingly the yield of a normal scan appears to be highest in men <50 years and women <60 years. In contrast, the yield may be limited in men >60 years due to the high prevalence of calcifications, as previously suggested. In line with these observations, coronary atherosclerosis could be ruled

out in the majority of patients with low pretest likelihood (71%), whereas only few patients with high pretest likelihood presented without evidence of coronary atherosclerosis on MSCT (17%). Also, the prevalence of a normal study was shown to be inversely related to the severity of clinical presentation, decreasing from 62% for patients with nonanginal chest pain to 33% of patients with typical angina. In asymptomatic patients, the prevalence of coronary atherosclerosis was related to the presence of multiple risk factors.

Observations using MSCT coronary angiography were comparable to coronary calcium scoring, although the percentage of a normal MSCT angiogram was somewhat lower when compared with a normal calcium scan (46% vs. 40%), due to the presence of non-calcified atherosclerosis. A similar percentage was recently reported by Hausleiter et al.[15], who investigated the prevalence of non-calcified coronary plaques using MSCT in patients at intermediate risk for CAD who had absolutely no coronary artery calcium. Particularly in younger patients, non-calcified plaques may be the only manifestation of coronary atherosclerosis. Indeed, in the current study, the most pronounced difference between the calcium score and the MSCT angiogram to rule out coronary atherosclerosis was observed in patients <50 years. In this subgroup, a normal calcium scan was observed in 80%, but a normal MSCT angiogram was observed in 65% of patients.

However, complete absence of calcium or atherosclerosis may be a too stringent threshold to define a normal study. Indeed, the clinical relevance of minor calcifications or minor wall irregularities may be negligible and immediate intervention is in general not required in these patients. In daily practice, therefore less rigid thresholds may be considered. When a normal coronary artery calcium study was defined as a calcium score <100 (no or mild to moderate calcium) the prevalence of a normal study increased to 70%. Moreover, defining a normal coronary angiogram as showing <50% stenosis, CAD was ruled out in 73%.

Several limitations need to be addressed. The radiation burden of initial standard 64-slice MSCT angiography protocols has been substantial (15-20 mSv), but experience with dose reduction strategies such as tube modulation or prospectively ECG-triggered acquisition is being accumulated rapidly.[16]
Also, imaging is at present limited to patients with stable and preferably lower heart rates, resulting in a frequent need for administration of beta-blocking agents prior to MSCT.[17]
In the current study, absolute coronary calcium scores were used rather than age and gender adjusted percentiles. However, we preferred to use absolute scores as this facilitates comparison to previously published data. Furthermore, no systematic comparison between MSCT and invasive coronary angiography was performed in the current study. Moreover, precise quantification of the degree of stenosis is considered to be difficult with MSCT. However, the accuracy of visual evaluation of 50% luminal narrowing or more on MSCT angiography has been extensively validated against invasive angiography previously. Pooled analysis based on 11 studies including 669 patients showed an average weighted sensitivity and specificity of 92% and 96%, respectively, for 64-slice MSCT. Importantly, the average negative predictive value was as high as 99%. [18]

Conclusion

MSCT ruled out coronary atherosclerosis in 40% to 46% of patients without known CAD who were referred for MSCT. The yield of a normal scan was highest in younger patients and patients with low or intermediate pretest likelihood of CAD. Accordingly, in patients with low to intermediate pretest likelihood, MSCT may be an attractive modality to exclude coronary atherosclerosis, and may prevent unnecessary additional functional testing or invasive angiography.

References

1. Ropers D, Baum U, Pohle K, *et al*. Detection of coronary artery stenoses with thin-slice multi-detector row spiral computed tomography and multiplanar reconstruction. *Circulation* 2003;107:664-6.
2. Achenbach S, Giesler T, Ropers D, *et al*. Detection of coronary artery stenoses by contrast-enhanced, retrospectively electrocardiographically-gated, multislice spiral computed tomography. *Circulation* 2001;103:2535-8.
3. Schroeder S, Kopp AF, Baumbach A, *et al*. Noninvasive detection and evaluation of atherosclerotic coronary plaques with multislice computed tomography. *J Am Coll Cardiol* 2001;37:1430-5.
4. Schuijf JD, Pundziute G, Jukema JW, *et al*. Diagnostic accuracy of 64-slice multislice computed tomography in the noninvasive evaluation of significant coronary artery disease. *Am J Cardiol* 2006;98:145-8.
5. Shabestari AA, Abdi S, Akhlaghpoor S, *et al*. Diagnostic performance of 64-channel multislice computed tomography in assessment of significant coronary artery disease in symptomatic subjects. *Am J Cardiol* 2007;99:1656-61.
6. Hausleiter J, Meyer T, Hadamitzky M, *et al*. 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. *Eur Heart J* 2007;28:3034-41.
7. Gibbons RJ, Chatterjee K, Daley J, *et al*. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). *J Am Coll Cardiol* 1999;33:2092-197.
8. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;21:1011-53.
9. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.
10. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;20:1183-97.
11. Taylor AJ, Bindeman J, Feuerstein I, *et al*. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project. *J Am Coll Cardiol* 2005;46:807-14.
12. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979;300:1350-8.
13. Agatston AS, Janowitz WR, Hildner FJ, *et al*. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827-32.
14. Janowitz WR, Agatston AS, Kaplan G, Viamonte M, Jr. Differences in prevalence and extent of coronary artery calcium detected by ultrafast computed tomography in asymptomatic men and women. *Am J Cardiol* 1993;72:247-54.
15. Hausleiter J, Meyer T, Hadamitzky M, *et al*. Prevalence of noncalcified coronary plaques by 64-slice computed tomography in patients with an intermediate risk for significant coronary artery disease. *J Am Coll Cardiol* 2006;48:312-8.
16. Hsieh J, Londt J, Vass M, *et al*. Step-and-shoot data acquisition and reconstruction for cardiac x-ray computed tomography. *Med Phys* 2007;33:4236-48.
17. Cademartiri F, Mollet NR, Runza G, *et al*. Diagnostic accuracy of multislice computed tomography coronary angiography is improved at low heart rates. *Int J Cardiovasc Imaging* 2006;22:101-5.
18. Schuijf JD, Jukema JW, van der Wall EE, Bax JJ. The current status of multislice computed tomography in the diagnosis and prognosis of coronary artery disease. *J Nucl Cardiol* 2007;14:604-12.