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?

Maureen M. Henneman1, Joanne D. Schuijf1,2, Jacob M. van Werkhoven1, Gabija Pundziute1, Ernst E. van der Wall1,2, J. Wouter Jukema1,2, and Jeroen J. Bax1*

1Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, PO 9600, 2300 RC Leiden, The Netherlands; and 2The Interuniversity Cardiology Institute of The Netherlands, Utrecht, The Netherlands

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Aims
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 pre-test likelihood of CAD.

Methods and results
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 pre-test likelihood of CAD. Patients were evaluated for the presence of coronary artery calcium as well as the presence of atherosclerosis. 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 pre-test likelihood, no coronary atherosclerosis was observed when compared with 33 and 17% of the patients with intermediate and high pre-test likelihood, respectively.

Conclusion
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 pre-test likelihood, MSCT may be an attractive modality to exclude coronary atherosclerosis and may prevent unnecessary additional functional testing or invasive angiography.

Keywords
MSCT • Coronary artery disease • Coronary artery calcium score

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 with 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 (ischaemia 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 pre-test 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 or coronary artery bypass graft surgery, as a history of myocardial infarction, or as the presence of one or more significant stenoses on a previous coronary angiogram. Reasons for referral to MSCT angiography were classified as follows: (i) screening (presence of one risk factor and referral for evaluation prior to high-risk cardiac surgery or presence of one risk factor and prior inconclusive treadmill testing or inconclusive nuclear testing or presence of one risk factor and regional wall motion abnormalities on echocardiography), (ii) elevated risk for CAD (presence of two or more risk factors), without chest discomfort, (iii) non-anginal chest pain, (iv) atypical angina,7 and (v) typical angina.7

Risk factors were derived through a structured interview and existing medical record data. Hypertension was defined as a documented blood pressure ≥140/90 mmHg or the use of antihypertensive medication.8 Hypercholesterolaemia 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 hypoglycaemic 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 pre-test 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.

Multi-slice computed tomography, data acquisition
MSCT examinations were performed with a 64-slice scanner (Aquilion 64, Toshiba Medical Systems, Otawara, Japan, or Lightspeed VR 64-MSCT, General Electric, Milwaukee, WI, USA). First, a non-contrast enhanced scan was performed prior to MSCT coronary angiography to assess the total coronary calcium burden. Collimation was 4 × 3.0 mm and gantry rotation time 500 ms. Tube voltage and tube current were 120 kV and 200 mA, respectively.

For the Toshiba scanner, collimation was 64 × 0.5 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 Electric scanner, collimation was 64 × 0.625 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 b.p.m., beta-blocking agents were administered prior to MSCT imaging if no contraindications 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 artefacts, additional reconstructions were explored at different time points of the R–R interval. Thereafter, the axial data sets were transferred to a remote workstation (Vitrea 2, Vital Images, USA, or Advantage, GE Healthcare, USA) for post-processing and subsequent evaluation.

Multi-slice computed tomography, 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 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 one or more coronary artery segments. In case of severe artefacts due to, for example, motion during the scan or dense calcifications, the scan was classified as uninterpretable. Patients with uninterpretable segments and also at least one identified significant stenosis were classified as having obstructive CAD.

Statistical analysis
The results are presented as mean values ± SD or as actual numbers (%). Continuous variables that are not normally distributed are expressed as medians (25–75th percentile range). Continuous data were compared using the unpaired two-sided Student’s t-test. Categorical data were compared with the χ²-test with Yates’ correction. Ordinal data were analysed with Somer’s d-test. All comparisons were performed in pre-defined 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 agreed 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 pre-test likelihood of CAD, whereas 46 (14%) patients presented with a high pre-test likelihood of CAD. The majority of the patients had an intermediate pre-test 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, hypercholesterolaemia and smoking when compared with women.

Coronary artery calcium score
Overall
In one patient, the calcium scan was not available. In the remaining patients, coronary artery calcium was scored according to
the Agatston method. The median (25–75th 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, 58 (17%) had a CS of 11–100, and 51 (15%) had a CS of 101–400. In 51 (15%) patients, CS exceeded 400 (Figure 2).

Absence of coronary artery calcium vs. pre-test likelihood of CAD

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

Absence of coronary artery calcium vs. 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.

Absence of coronary artery calcium vs. 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 the 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 vs. 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, 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).
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 5% of patients, the MSCT examination was classified as uninterpretable due to the presence of motion artefacts or severe calcifications.

Absence of coronary atherosclerosis vs. pre-test likelihood of CAD

As shown in Figure 6, the prevalence of a normal MSCT coronary angiography study decreased from 58% in patients with low pre-test likelihood to 17% of patients with high pre-test likelihood ($P = 0.0000$).

Absence of coronary atherosclerosis vs. 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 the 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.

Absence of coronary atherosclerosis vs. gender and age

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 pre-test likelihood, ruling out obstructive coronary atherosclerosis in patients ≤60 years old and with low pre-test likelihood was 86% for both women and men. In patients ≤60 years old and with intermediate pre-test likelihood, ruling out was 84% in women and 81% in men, whereas in patients with high pre-test likelihood, obstructive atherosclerosis was ruled out in only 50% of women ≤60 years old and in 53% of men ≤60 years old.

Discussion

The main finding of this study was that MSCT permits ruling out coronary atherosclerosis in 40–46% of patients without known obstructive coronary atherosclerosis according to the presence of coronary artery calcium according to gender and age.

<table>
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<tr>
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<th>Men</th>
<th>Women</th>
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<tr>
<td>&lt;50 years</td>
<td>43/60 (72%)</td>
<td>47/53 (89%)</td>
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<tr>
<td>50−60 years</td>
<td>22/70 (31%)</td>
<td>26/46 (57%)</td>
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<tr>
<td>&gt;60 years</td>
<td>5/52 (10%)</td>
<td>14/58 (24%)</td>
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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).

Figure 6: Absence of coronary atherosclerosis according to pre-test likelihood of CAD. Of patients with low pre-test likelihood, 58% had no coronary atherosclerosis on MSCT angiography. For patients with intermediate and high pre-test likelihood these percentages were 33 and 17%, respectively.
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 pre-test likelihood of CAD was evaluated in the present study.

In patients with low or intermediate pre-test 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 and >60 years, respectively) as well as in women (43 vs. 36% in men). In contrast, coronary artery calcium and 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. 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 et al. reported a considerably lower prevalence of coronary artery calcium in women vs. men until the age of 60.
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 pre-test likelihood (71%), whereas only few patients with a high pre-test 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 non-anginal 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., 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 CS 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 CS ≤ 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. 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.

In the current study, absolute coronary CSs were used rather than age- and gender-adjusted percentiles. However, we preferred to use absolute scores as this facilitates comparison with 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%.

**Conclusion**

MSCT ruled out coronary atherosclerosis in 40–46% 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 pre-test likelihood of CAD. Accordingly, in patients with low-to-intermediate pre-test likelihood, MSCT may be an attractive modality to exclude coronary atherosclerosis and may prevent unnecessary additional functional testing or invasive angiography.

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**References**


The above article uses a new reference style being piloted by the EHJ that shall soon be used for all articles.