Clinical applications of non-invasive imaging techniques in suspected coronary artery disease and in acute myocardial infarction

Nucifora, G.

Author: Nucifora, Gaetano
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Chapter 4

Relation Between Framingham Risk Categories and the Presence of Functionally Relevant Coronary Lesions as Determined on Multislice Computed Tomography and Stress Testing

Gaetano Nucifora, Joanne D. Schuijf, Jacob M. van Werkhoven, Roxana Djaberi, Ernst E. van der Wall, Albert de Roos, Arthur J.H.A. Scholte, Martin J. Schalij, J. Wouter Jukema, Jeroen J. Bax

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ABSTRACT

Noninvasive assessment of subclinical atherosclerosis by multislice computed tomographic (MSCT) coronary angiography and demonstration of significant, flow-limiting coronary artery disease (CAD) by stress testing may improve patients' risk stratification. However, data relating the complementary information provided by these noninvasive techniques to traditional risk assessment are scarce. In 255 subjects (45% women, mean age 54±12 years) without known CAD, 64-slice MSCT coronary angiography and stress testing (exercise electrocardiographic test or myocardial perfusion imaging) were performed. Framingham risk score (FRS) was calculated from baseline characteristics (50% low, 22% intermediate, 28% high). Angiograms showing atherosclerosis were classified as obstructive (≥50% luminal narrowing) CAD or not. Stress tests were classified as normal or abnormal. Multislice computed tomogram identified 155 patients (61%) with CAD, of whom 78 (31%) showed obstructive CAD. A positive stress test result was observed in 36 patients (46%) with obstructive CAD. In line with increasing FRS categories, a significant increase in the prevalence of functionally relevant obstructive CAD was observed (6% low vs 45% intermediate vs 63% high, $p < 0.001$). In conclusion, a strong positive relation exists between FRS and prevalence of functionally relevant obstructive CAD. Selective use of MSCT coronary angiography and stress testing may refine the traditional risk assessment of CAD events, especially in patients deemed at intermediate and high risk.

INTRODUCTION

Recently, coronary artery calcium score (CACS) and multislice computed tomographic (MSCT) coronary angiography have emerged as useful techniques for the noninvasive direct visualization of coronary atherosclerosis.[1] Their use in selected patients has been suggested to be of potential utility to improve the traditional risk assessment of coronary artery disease (CAD) events.[2-5] However, these imaging techniques, despite providing meaningful information about the presence and extent of coronary atherosclerosis, do not provide information about the functional relevance of the observed coronary lesions.[6-8] This issue appears significant, considering that a large proportion of patients with abnormal CACS or MSCT coronary angiogram has a normal stress test result and thus do not require further invasive imaging.[6,7] Indeed, a better understanding of the complementary information provided by these noninvasive methods (imaging of coronary atherosclerosis vs evidence of inducible ischemia), especially in relation to traditional risk assessment, is needed to define an optimal strategy for patients' risk assessment. The aim of the present study therefore was to evaluate the relation between evidence of coronary atherosclerosis (by CACS and MSCT coronary angiography) and presence of abnormal stress testing result across Framingham risk score (FRS) categories.

METHODS

Two hundred fifty-five consecutive outpatients clinically referred to multislice computed tomography for coronary evaluation were included in the study. In addition, patients underwent stress testing (electrocardiographic exercise test [EET] or myocardial perfusion imaging) within 1 month of MSCT coronary angiography. The patient population is part of an ongoing study protocol addressing the value of multislice computed tomography and other imaging techniques compared to traditional risk assessment. From this prospective registry, results addressing the relation between CACS and MSCT coronary angiographic data across FRS categories have been recently published.[5]

Patients with typical angina, known history of CAD, and/or contraindications to multislice computed tomography were not included in the study, as were patients who were not in sinus rhythm before MSCT examination. History of CAD was defined as the presence of previous acute coronary syndrome, percutaneous or surgical coronary revascularization, and/or ≥1 angiographically documented coronary artery stenosis ≥50% luminal diameter.[7] Contraindications for multislice computed tomography were *(1)* known allergy to iodinated contrast agent, *(2)* renal failure (defined as glomerular filtration rate <30 ml/min), and *(3)* pregnancy.

For each patient, the presence of coronary risk factors (diabetes mellitus, systemic hypertension, hypercholesterolemia, positive family history, cigarette smoking, and obesity) and the presence of chest pain complaints (atypical angina and noncardiac chest pain), defined in accordance to previously published guidelines,[9-13] were recorded. The Framingham 10-year risk of hard CAD events was also calculated as previously described in the National Cholesterol Education Program's Adult Treatment Panel III report.[11] In accordance to the FRS, the study population was then categorized as at low (<10%), intermediate (10% to 20%), and high (>20%) risk.[11]

MSCT coronary angiography was performed with a 64-slice MSCT scanner (Aquilion 64, Toshiba Medical Systems, Tokyo, Japan). Heart rate and blood pressure were monitored before the examination in each patient. In the absence of contraindications, patients with a heart rate ≥65 beats/min were administered oral *β* blockers (metoprolol 50 or 100 mg, single dose, 1 hour before the examination).

First, a prospective coronary calcium scan without contrast was performed, followed by 64-slice MSCT coronary angiography, performed according to protocols previously described.[14] Data were subsequently transferred to dedicated workstations for postprocessing and evaluation (Advantage, GE Healthcare, Milwaukee, Wisconsin; Vitrea 2, Vital Images, Minnetonka, Minnesota).

MSCT data analysis was performed by 2 experienced observers who had no knowledge of a patient's medical history and symptom status; disagreement was solved by consensus or evaluation by a third observer.

CAC was identified as a dense area in the coronary artery >130 HU. A total CACS was recorded for each patient. In accordance to the value of total CACSs, patients were subsequently categorized as having no calcium (total score 0) or a low (total score 1 to 100), moderate (total score 101 to 400), or severe (total score >400) CACS.[15]

MSCT coronary angiograms were evaluated for the presence of obstructive CAD (≥50% luminal narrowing) on a patient and vessel level. For this purpose, the original axial dataset and curved multiplanar reconstructions were used. Each vessel was evaluated for the presence of any atherosclerotic plaque, defined as structures >1 mm2 within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding pericardial tissue, as described previously.[16] Subsequently, the vessels were further classified as *(1)* completely normal, *(2)* having nonobstructive CAD when atherosclerotic lesions <50% of luminal diameter were present, or *(3)* having obstructive CAD when atherosclerotic lesions ≥50% of luminal diameter were present. Prevalences of CAD (including obstructive and nonobstructive CAD) and obstructive CAD were evaluated.

Symptom-limited EET was performed on a bicycle ergometer according to standard protocols.[17] Patients not able to reach ≥85% of age-predicted maximum heart rate in the absence of ischemic changes were not included in the study. Tests were classified as positive or negative for ischemia. The test was considered positive based on the presence of ≥0.1-mV horizontal or downsloping ST-segment depression at 80 ms after the J point in 2 contiguous leads during exercise or recovery. All tests were analyzed by an experienced reader without knowledge of the MSCT results.

Myocardial perfusion imaging during stress and at rest was performed with symptom-limited bicycle exercise or pharmacologic (adenosine or dobutamine) stress using technetium-99m tetrofosmin or technetium-99m sestamibi. Images were acquired on a triple-head (GCA 9300/HG, Toshiba Corp., Tokyo, Japan) single-photon emission computed tomographic camera and reconstructed into long- and short-axis projections perpendicular to the heart axis. Perfusion defects were identified on stress images (segmental tracer activity <75% of maximum) and divided into ischemia (reversible defects, with ≥10% increase in tracer uptake on images at rest) or scar tissue (irreversible defects). Accordingly, examinations were classified as negative or positive. Positive examinations were further divided into those demonstrating reversible defects and those demonstrating fixed defects. Gated images were used to assess regional wall motion to improve differentiation between perfusion abnormalities and attenuation artifacts.[18]

Continuous variables are expressed as mean±SD or median (25th to 75th percentile range), when not normally distributed. Categorical variables are expressed as absolute numbers (percentages). Differences in categorical variables were assessed using chi-square test. A p value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS 15.0 (SPSS, Inc., Chicago, Illinois).

RESULTS

Baseline characteristics of the study population are listed in Table 1. Table 2 presents the results of calcium scoring and MSCT coronary angiography, and Table 3 presents the stress testing results.

Table 1. Baseline characteristics of the study population

Variable	n = 255
Age (years)	54±12
Male/female	140/115
Diabetes mellitus	65 (25%)
Hypertension	131 (51%)
- Systolic blood pressure (mmHg)	135±19
- Diastolic blood pressure (mmHg)	81±12
Hypercholesterolemia	92 (36%)
- Total cholesterol (mg/dl)	205±46
- HDL-cholesterol (mg/dl)	58±19
Family history of coronary artery disease	103 (40%)
Smoke	80 (31%)
Obesity	53 (21%)
- Body mass index (kg/m^2)	27±5
≥ 3 risk factors	78 (31%)
Chest pain complaints	
- Asymptomatic	111 (44%)
- Atypical angina pectoris	75 (29%)
- Non-cardiac chest pain	69 (27%)
Framingham risk score	
- Low	127 (50%)
- Intermediate	56 (22%)
- High	72 (28%)

Data are expressed as means±SD and n (%).

Based on calcium scoring, coronary calcifications were found in 37 patients (29%) with a low FRS, 34 patients (61%) with an intermediate FRS, and 53 patients (74%) with a high FRS. Based on MSCT coronary angiogram, normal coronary arteries were found in 79 patients (62%) with a low FRS, 14 patients (25%) with an intermediate FRS, and 7 patients (10%) with a high FRS. Obstructive CAD was found in 17 patients (13%) with a low FRS, 20 patients (36%) with an intermediate FRS, and 41 patients (57%) with a high FRS. Table 3 lists stress testing results. Positive stress test results were observed in 5 patients (4%) with a low FRS, 16 patients (29%) with an intermediate FRS, and 36 patients (50%) with a high FRS.

Table 2. Results of coronary artery calcium scoring and multi-slice computed tomography coronary angiography in the study population (n = 255)

Coronary artery calcium score	
- Score	0 (0-128)
- Zero	131 (51%)
- Low (total score = 1-100)	50 (20%)
- Moderate (total score = 101-400)	35 (14%)
- Severe (total score >400)	39 (15%)
MSCT coronary angiography	
- Normal coronary arteries	100 (39%)
- Non-obstructive CAD (<50% luminal diameter narrowing)	77 (30%)
- Obstructive CAD (≥50% luminal diameter narrowing)	78 (31%)

Data are expressed as median (25th to 75th percentile range), and n (%).

Table 3. Results of stress testing in the study population (n = 255)

Type of stress test	
- Electrocardiographic exercise test	47 (18%)
- Myocardial perfusion imaging	208 (82%)
Electrocardiographic exercise test	
Mean peak double product	27702±8231
Mean peak workload (Watt)	196±57
Ischemic ST-segment depression	3 (6%)
Myocardial perfusion imaging	
- Symptom-limited bicycle exercise *	80 (38%)
- Pharmacologic stress (adenosine or dobutamine)	128 (62%)
- Stress and rest normal perfusion	154 (74%)
- Reversible perfusion defect	34 (16%)
- Fixed perfusion defect	12 (6%)
- Reversible and fixed perfusion defects	8 (4%)
Overall	
Negative test	198 (78%)
Positive test	57 (22%)

*: In all these patients, ≥85% of maximum age-predicted heart rate was achieved if no stress-induced symptoms or changes in electrocardiogram or blood pressure occurred. Data are expressed as means±SD, and n (%).

Prevalence of positive stress test results in patients with a CACS 0 was low (n = 14, 11%). Conversely, 43 patients (35%) with a CACS >0 had a positive stress test result; as shown in Figure 1, a significant increase in the prevalence of positive stress test results was observed in this group of patients in line with an increasing FRS. Prevalence of positive stress test results in patients with normal coronary arteries or nonobstructive CAD was low (n = 21, 12%). In patients with obstructive CAD, in contrast, a positive stress test result was observed in 36 (46%). As illustrated in Figure 2, a positive relation between prevalence of positive stress test results and FRS was observed in this group of patients and prevalence of positive stress test results increased from 6% in patients with a low FRS and obstructive CAD to 63% in patients with a high FRS and obstructive CAD.

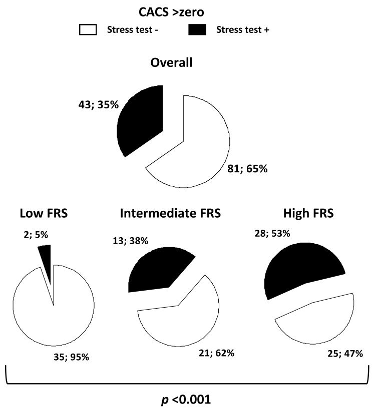

Figure 1. Relation between presence of CAC identified by MSCT calcium scan and stress test results in overall population and across FRS categories.

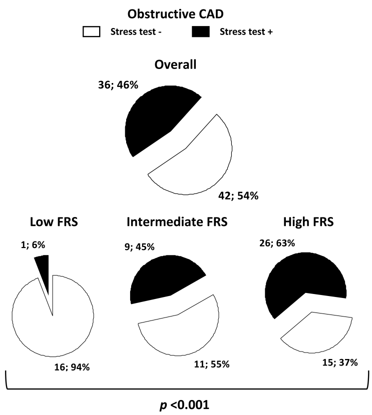

Figure 2. Relation between obstructive CAD identified by MSCT coronary angiography and stress test results in overall population and across FRS categories.

DISCUSSION

The present study describes the prevalence of positive stress testing compared to evidence of coronary atherosclerosis (by CACS and MSCT coronary angiography) across FRS categories. A significant increase in the prevalence of functionally relevant coronary lesions was observed in line with an increasing FRS. In particular, abnormal stress test results were observed in 53% of high-risk patients with abnormal CACSs and 63% of high-risk patients with obstructive CAD on MSCT coronary angiogram.

Previous studies have underlined the potential value of additional risk assessment with stress testing (EET or myocardial perfusion imaging) to improve the identification of patients at risk of CAD events. Gibbons et al,[19] for instance, observed a significant relation between the prognostic information provided by an abnormal EET result in a large cohort of asymptomatic men and the number of coronary risk factors. More recently, Balady et al.[20] showed that different EET variables (including ischemic ST-segment depression) provided incremental prognostic information over the FRS in asymptomatic men. The additional prognostic value of EET has been confirmed by Cournot et al.[21] in men and women with intermediate and high FRSs.

Fewer data are available regarding the prognostic role of myocardial perfusion imaging in asymptomatic subjects.[22] However, it has been suggested that myocardial perfusion imaging may be of incremental value especially in high-risk patients (i.e., diabetic patients or patients with multiple risk factors), taking into account the high prevalence of myocardial perfusion abnormalities despite the absence of symptoms in this group.[23-25]

Direct visualization of subclinical atherosclerosis, by CACS or MSCT coronary angiography, also may possibly refine traditional risk assessment. Greenland et al,[26] in a large cohort of asymptomatic subjects, demonstrated that a high CACS improved the risk stratification provided by FRS alone. More recently, Budoff et al.[27] demonstrated, in a cohort of 25,253 asymptomatic patients, that CACS is an independent predictor of mortality, with significant incremental value over traditional coronary risk factors. A preliminary analysis by Choi et al.[4] suggested also that MSCT coronary angiography may provide prognostic information incremental to baseline risk stratification. The ability of noninvasive coronary imaging techniques to obtain a direct estimate of total atherosclerotic plaque burden in coronary arteries likely explains these findings. Previous studies indeed have demonstrated that a non-negligible proportion of patients with high plaque burden with CACSs or on MSCT coronary angiogram are not identified as at high risk based on FRS categories.[5,28,29]

Stress testing and noninvasive imaging of coronary arteries provide complementary information about CAD (i.e., evidence of myocardial ischemia and evidence of coronary atherosclerosis, respectively).[6-8] The 2 tests may be useful in refining the risk assessment strategy, but data showing how they relate each other in relation to FRS are still missing. Improved knowledge of the different information provided by stress testing and noninvasive coronary imaging is needed to appropriately refine the risk assessment strategy.

In the present study, in patients with a low FRS, the prevalence of an abnormal CACS (29%) and of coronary atherosclerosis on MSCT coronary angiogram (38%) was not negligible. In contrast, prevalence of an abnormal stress testing result (4%) was relatively lower. In addition, an abnormal CACS and obstructive CAD on MSCT coronary angiogram rarely resulted in abnormal findings on stress testing (5% and 6%, respectively). Considering the low prevalence of ischemia, use of stress testing seems to carry limited additional value for risk stratification. Conversely, use of atherosclerosis imaging may possibly provide some benefit, considering the non-negligible prevalence of coronary plaques in this group of patients. However, larger studies with long-term follow-up are needed to demonstrate that identification of atherosclerosis may result in improved treatment and outcome before noninvasive coronary atherosclerosis imaging can be recommended in patients with a low FRS. Currently, use of atherosclerosis imaging may be not justified in this group of patients due to the associated radiation exposure (in particular for MSCT coronary angiography).

In patients with a high FRS, a high burden of coronary atherosclerosis and inducible myocardial ischemia were observed. However, in this group of patients, a high prevalence of coronary atherosclerosis is a priori anticipated and based on the high-risk profile; many patients will already have received medical therapy. Noninvasive coronary atherosclerosis imaging therefore is unlikely to further refine patients' risk assessment. Moreover, taking into account that a large proportion of patients with an abnormal CACS or obstructive CAD on MSCT coronary angiogram also showed an abnormal functional test result (53% and 63%, respectively), it seems reasonable to perform stress testing first, to establish or rule out the presence of flow-limiting stenoses. High-risk patients with evidence of inducible myocardial ischemia should then be referred to invasive coronary angiography and possibly may benefit from revascularization procedures, although supporting data in asymptomatic subjects are scarce.[2]

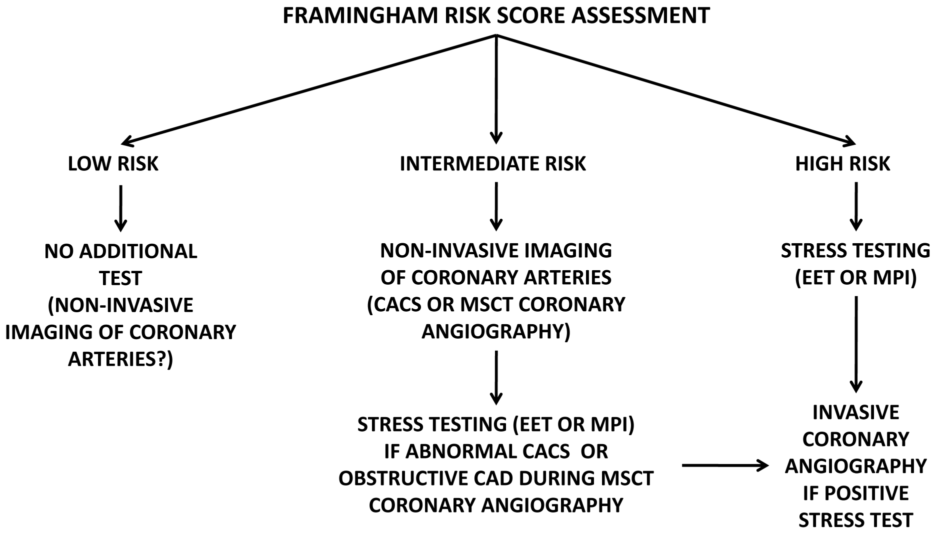

Figure 3. Proposed integration of noninvasive imaging of coronary arteries and stress testing into traditional risk assessment of CAD events. MPI = myocardial perfusion imaging.

In patients with an intermediate-risk profile, however, coronary atherosclerosis imaging may provide valuable information to refine risk stratification and determine further management. A non-negligible prevalence of coronary atherosclerosis (abnormal CACSs in 61% and abnormal MSCT coronary angiographic finding in 75%, including obstructive CAD in 36%) was observed in this population, whereas the prevalence of an abnormal stress test result (29%) was lower. In addition, comparison of coronary imaging data to stress testing data revealed that 38% of patients with an abnormal CACS and 45% of patients with obstructive CAD on MSCT coronary angiogram had an abnormal stress test result. Accordingly, noninvasive imaging of coronary arteries seems to be a reasonable first-line approach to improve risk stratification of

intermediate-risk patients. Patients with an abnormal CACS or obstructive CAD on MSCT coronary angiogram should then be referred to stress testing, to establish or rule out the presence of inducible myocardial ischemia.
A flow chart describing the proposed integration of noninvasive imaging of coronary arteries and stress testing into the traditional risk assessment of CAD events is presented in Figure 3.

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