International Journal of Cardiology 167 (2013) 121–125

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Combined use of exercise electrocardiography, coronary calcium score and cardiac CT angiography for the prediction of major cardiovascular events in patients presenting with stable chest pain ☆

Mathijs O. Versteylen [a,*], Ivo A. Joosen [a], Mark H. Winkens [a], Eduard M. Laufer [a], Roel J. Snijder [a], Joachim E. Wildberger [b], Harry J. Crijns [a], Jagat Narula [c], Leonard Hofstra [d]

[a] Department of Cardiology, Maastricht University Medic|al Center, Maastricht, The Netherlands
[b] Department of Radiology, Maastricht University Medical Center, Maastricht, The Netherlands
[c] Cardiovascular Imaging Program, Mount Sinai School of Medicine, New York, USA
[d] Cardiology Center Netherlands, The Netherlands

ARTICLE INFO

Article history:
Received 7 June 2011
Received in revised form 2 December 2011
Accepted 3 December 2011
Available online 5 January 2012

Keywords:
Exercise-ECG
Cardiac CT angiography
Calcium score
ACS
PCI
CABG

ABSTRACT

Background: The usual diagnostic work-up of chest pain patients includes clinical risk profiling and exercise-ECG, possibly followed by additional tests. Recently cardiac computed tomographic angiography (CCTA) has been employed. We evaluated the prognostic value of the combined use of exercise-ECG and CCTA for the development of cardiovascular endpoints.

Methods: In 283 patients (143 male, mean age 54 ± 10 years) with intermediate pre-test probability for coronary artery disease presenting with stable chest pain, exercise-ECG, CCTA and calcium score were performed. Patients were followed-up for combined endpoint of acute coronary syndrome (ACS) and revascularization.

Results: After a median follow-up of 769 days (interquartile range 644–1007), 6 ACS and 9 revascularizations were recorded. A positive exercise-ECG predicted for the combined endpoint, [hazard ratio (HR) 5.14 (95% confidence interval (CI) 1.64–16.13), p = 0.005], as well as a positive calcium score [HR 4.59 (95% CI 1.30–16.28), p = 0.02] and a ≥50% stenosis on CCTA [HR 45.82 (95% CI 6.02–348.54), p < 0.001]. ROC-analysis showed an area under the curve (AUC) of 0.79 (95% CI 0.67–0.90) for exercise-ECG, which increased significantly when CCTA was added: 0.91 (95% CI; 0.86–0.97; p = 0.006). Multivariable Cox regression showed exercise-ECG predicted independently [HR 3.6, (95% CI 1.1–11.2), p = 0.03], as well as CCTA [HR 31.4 (95% CI 4.0–246.6), p = 0.001], but not calcium score [HR 0.6 (95% CI 0.2–2.3), p = 0.5].

Conclusions: The combined subsequent use of exercise-ECG for functional information and CCTA for anatomical information provides a high diagnostic yield in stable chest pain patients with an intermediate pre-test probability for coronary artery disease.

1. Introduction

The clinical work-up of patients presenting with stable chest pain symptoms remains a challenge, especially in patients with an intermediate pre-test probability of coronary artery disease (CAD). Usually, traditional risk factors provide initial risk assessment, and in addition exercise-ECG has been widely used in evaluating patients presenting with chest pain despite only fair diagnostic accuracy. The proportion of inconclusive tests is relatively high and the sensitivity, negative predictive value and prognostic abilities low [1]. Depending on the initial clinical assessment and exercise-ECG results, a combination of stress testing with echocardiography or nuclear perfusion imaging is traditionally recommended [2–4]. Although these imaging tests provide excellent information about the functional significance of the coronary lesions, they are neither ideal for the geographical location of the lesion nor for the assessment of plaque characteristics. Recently, cardiac CT-angiography (CCTA) has gained prominence for the assessment of patients with suspected CAD and has offered valuable information about the severity of stenotic lesions and plaque characteristics [5,6]. However, even though some studies have suggested the simultaneous registration of contrast passage through myocardium as an indicator of perfusion [7], the functional relevance of the anatomical lesions remains unsubstantiated [8]. The aim of this study was to investigate exercise-ECG as a low-cost supplementation to CCTA for a combined possible yield of anatomic and functional significance of coronary artery lesions.

☆ Conflict of interest: none declared.

* Corresponding author at: Universiteitssingel 50, room 4.220, 6229 ER Maastricht, The Netherlands. Tel.: +31 438781232; fax: +31 433875104.
E-mail address: mathijs.versteylen@mumc.nl (M.O. Versteylen).

0167-5273/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2011.12.016

2. Methods

2.1. Study population

We retrospectively analyzed stable chest pain patients who were referred for exercise-ECG and subsequent CCTA by their cardiologist. In all patients referred for CCTA, pre-test probability for CAD was calculated using Diamond–Forrester classification [9]. Patients with a high pre-test probability were not referred for CCTA, consequently our population consisted of patients with a low to intermediate pre-test probability for CAD, which is according to the 2010 appropriateness criteria on CCTA [10]. Excluded were patients with unstable angina, hemodynamic instability, previous CAD, pregnancy, renal insufficiency, iodine allergy, inconclusive exercise-ECG and/or non-diagnostic CCTA. From July 2007 until November 2009, 407 patients were included, 14(3) had a history of CAD, 91(22) had an inconclusive exercise-ECG and 36(9) an inconclusive CCTA (17 patients had both an inconclusive exercise-ECG as an inconclusive CCTA). Eventually 283 subjects were studied. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The Institutional Review Board and ethics committee approved the study and all patients signed informed consent. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [11].

2.2. Risk assessment and diagnostics

In all patients historic details were recorded. Framingham risk score (FRS) was calculated to estimate the 10-year risk of cardiovascular disease, and patients were classified as low risk, intermediate risk or high risk, when FRS was <5%, between 5 and 20% or >20%, respectively [12].

Exercise-ECG tests were performed per standardized Bruce-protocol, with continuous blood pressure, heart rate and ECG monitoring up to at least 5 min into recovery. Tests were classified as inconclusive in patients who did not reach their predicted exercise tolerance (<85% of the age- and sex-predicted heart rate or a heart rate pressure product <18,000). A test was considered positive in case of ≥1.0 mm horizontal or downsloping ST-deviation at 80 ms after the J-point compared to baseline ECG (≥1.5 mm was used for upsloping ST-deviation) and/or typical angina and/or ventricular arrhythmia and/or a decrease in systolic blood pressure >10 mm Hg. Conclusive tests that did not meet any of these criteria were regarded as negative [13].

CCTA was performed using a 64-slice multi detector computed tomography scanner (Brilliance 64; Philips Healthcare) with a 64×0.625 mm slice collimation, a gantry rotation time of 420 ms, a tube voltage of 80–120 kV, depending on the patient's height and weight. In patients with heart rates <65 bpm, a prospective-gated "Step and shoot" protocol was used, and in those with heart rates >65 bpm, a retrospective-gated "Helical" protocol with dose modulation was used to obtain the best image quality at minimal radiation dose [14,15]. Tube current varied from 150 to 210 mAs and from 600 to 1000 mAs, for "Step and shoot" and "Helical" protocol, respectively, again depending on patient weight and height. Patients received 5–20 mg of Metoprolol intravenously to lower the heart rate <65 bpm as well as 0.8 mg sublingual nitroglycerin spray. A native scan was performed to determine the calcium score using the Agatston method [16]. This was followed by CCTA using contrast agent as described before [17]. Using the American Heart Association (AHA) in 16 coronary segments model, CT angiograms were independently analyzed by two experienced cardiologists who were blinded to clinical information [18]. In case of disagreement, consensus was reached by discussion. The coronary artery tree was assessed using the source images on the provided software (Philips Healthcare), and the degree of stenosis was visually defined as insignificant (no lesions, or one or more lesions with diameter stenosis of <50%), or significant (one or more lesions with diameter stenosis ≥50%) [19]. In addition, a segment score was calculated as follows: mild diameter stenosis (<50%, score 1), moderate (50–70%, score 2) and severe diameter stenosis (>70%, score 3); the total score was calculated as the sum of all score points divided by the number of assessable segments, resulting in a score ranging 0–3. An involvement score was calculated by counting all diseased vessel segments (irrespective of the degree of stenosis), and the total score ranged from 0 to 16 [20]. Plaques were categorized as calcified (exclusively content with density >130 Hounsfield units), non-calcified (exclusively content with density <130 Hounsfield units), or mixed (characteristics of both calcified and non-calcified plaques).

2.3. Follow-up

Electronic patient records were monitored for cardiovascular death and acute coronary syndrome (ACS), including myocardial infarction and unstable angina. Additionally, the national mortality records were checked. ACS was defined as typical angina pectoris and troponin T elevation (>0.01 μg/L) and ST-segment elevation/depression of ≥1 mm, or at least two of these symptoms together with invasive angiographic conformation of a culprit lesion [21]. Secondary endpoints included elective percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery. Revascularization procedures <60 days after CCTA were excluded as event, as these would be predominantly CCTA driven. Further, we censored follow-up after the first endpoint, so that the recorded ACS was not a complication of revascularization therapy. Patients were seen by their cardiologist on a regular basis, and all visits were recorded in the electronic patient records.

2.4. Statistics

Data were analyzed using SPSS 17.0. Continuous variables were reported as means and SDs and proportions (%) were used for categorical values. Time to events was presented as mean and interquartile range. All relevant clinical parameters including exercise-ECG, CCTA and calcium score were evaluated for their individual prognostic value using univariable Cox regression analysis. Kaplan–Meier analyses with log-rank testing was used to assess individual predictive value of calcium score, exercise-ECG and CCTA for all endpoints (ACS, PCI and CABG). Additionally, this was followed by multivariable Cox regression analysis, to assess the independent prognostic value of the different methods. Receiver-operating-characteristic (ROC) curves were plotted for four incremental models; FRS, FRS plus exercise-ECG, FRS plus exercise-ECG plus CCTA and FRS plus exercise-ECG plus CCTA plus calcium score. Area under the curve (AUC) for prediction of all endpoints by the four models was produced to evaluate incremental value of the combined approach. The same was done for every individual test. All p-values were 2-sided, and a value below 0.05 was considered significant.

3. Results

3.1. Study population

Of the 283 patients, 143(51) were male, mean age was 54±10 years. The prevalence of a positive exercise-ECG was 102(36). Similarly, the prevalence of a positive CCTA (≥50%) was 71(25). There were 149(53) patients with a zero calcium score, of which 9(6) had a significant stenosis on CCTA. There were no cases of cardiac death. CCTA was performed using 'Step and shoot' protocol in 192(68) patients, corresponding radiation dose was 3.4±1.1 mSv (for 'Helical' protocol 9.7±3.7 mSv).

3.2. Follow-up analysis

During a median total follow-up of 769 days (interquartile range 644–1007), occurrence of ACS, PCI and CABG was recorded. ACS occurred in 6 patients at the median interim interval of 79 days (interquartile range 31–288) after CCTA. Three patients met criteria for myocardial infarction (1 STEMI, 2 NSTEMI), and underwent conventional coronary angiography. Unexpectedly, in one STEMI patient no coronary lesions were identified, also previous CCTA showed no lesions.

An additional 68 patients received invasive angiography, median time interval from CCTA was 64 days (interquartile range 39–106). Of this group, 31(48) underwent invasive angiography within 60 days after CCTA, which was followed by a revascularization procedure in 12 patients. These cases of early revascularization were censored and not analyzed as an event. Uncensored revascularization procedures were 8 PCIs and 1 CABG and occurred after a median interim interval of 83 days (interquartile range 73–87) after CCTA. Thus, total endpoints consisted of 15 events.

3.3. Univariable analysis

Several clinical parameters predicted for the occurrence of an event during follow-up, Table 1. Smoking, typical chest pain symptoms and Framingham risk score were significantly associated with the occurrence of an event. In addition, a positive exercise-ECG significantly predicted for the combined endpoint [hazard ratio (HR) 5.14 (95% confidence interval (CI) 1.64–16.13), p=0.005], as well as a positive calcium score [HR 4.59 (95% CI 1.30–16.28), p=0.02]. A significant stenosis on CCTA was a very strong predictor for events [HR 45.82 (95% CI 6.02–348.54), p<0.001], which was higher than the involvement score [HR 1.24 (95% CI 1.08–1.41), p=0.002] and segment score [HR 9.66 (95% CI 3.26–28.60), p<0.001].

Further, Kaplan–Meier analysis revealed that patients with a positive exercise-ECG showed significantly worse event-free survival when compared to patients with a negative exercise-ECG (Fig. 1). The annual event rate for a positive exercise-ECG was 5.3%, compared to 1.0% for a negative exercise-ECG, p<0.01. Patients with calcium score