Atherosclerosis 233 (2014) 190–195

Contents lists available at ScienceDirect

Atherosclerosis

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

Incremental prognostic value of coronary artery calcium score versus CT angiography among symptomatic patients without known coronary artery disease

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ARTICLE INFO

Article history:
Received 25 October 2013
Received in revised form
28 November 2013
Accepted 4 December 2013
Available online 8 January 2014

Keywords:
Coronary computed tomography angiography
Coronary artery calcium score
Atherosclerosis
Epidemiology

ABSTRACT

Objective: To evaluate the prognostic value and test characteristics of coronary artery calcium (CAC) score for the identification of obstructive coronary artery disease (CAD) in comparison with coronary computed tomography angiography (CCTA) among symptomatic patients.

Methods: Retrospective cohort study at two large hospitals, including all symptomatic patients without prior CAD who underwent both CCTA and CAC. Accuracy of CAC for the identification of ≥50% and ≥70% stenosis by CCTA was evaluated. Prognostic value of CAC and CCTA were compared for prediction of major adverse cardiovascular events (MACE, defined as non-fatal myocardial infarction, cardiovascular death, late coronary revascularization (>90 days), and unstable angina requiring hospitalization).

Results: Among 1145 included patients, the mean age was 55 ± 12 years and median follow up 2.4 (IQR: 1.5–3.5) years. Overall, 406 (35%) CCTA were normal, 454 (40%) had <50% stenosis, and 285 (25%) had ≥50% stenosis. The prevalence of ≥70% stenosis was 16%. Among 483 (42%) patients with CAC zero, 395 (82%) had normal CCTA, 81 (17%) <50% stenosis, and 7 (1.5%) ≥ 50% stenosis. 2 (0.4%) patients had ≥70% stenosis. For diagnosis of ≥50% stenosis, CAC had a sensitivity of 98% and specificity of 55%. The negative predictive value (NPV) for CAC was 99% for ≥50% stenosis and 99.6% for ≥70% stenosis by CCTA. There were no adverse events among the 7 patients with zero calcium and ≥50% CAD. For prediction of MACE, the c-statistic for clinical risk factors of 0.62 increased to 0.73 ($p < 0.001$) with CAC versus 0.77 ($p = 0.02$) with CCTA.

Conclusion: Among symptomatic patients with CAC zero, a 1–2% prevalence of potentially obstructive CAD occurs, although this finding was not associated with future coronary revascularization or adverse prognosis within 2 years.

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Coronary artery disease (CAD) and its complications remain the leading cause of morbidity and mortality in most industrialized nations [1]. For decades, triage has begun with an assessment of pretest probability of obstructive CAD [2], based upon known cardiovascular risk factors such as hypertension, dyslipidemia, family history of CAD, and smoking [3,4]. Additionally, the presence of anginal symptoms increases the clinical likelihood of significant CAD [2]. In spite of the progress made and efforts put into clinical assessment of pretest probability, this remains an imperfect science [5], thus promoting interest in imaging tests as a means of

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0021-9150/$ – see front matter Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.atherosclerosis.2013.12.029

diagnosing CAD and identifying sub-groups of patients who have a favorable prognosis.

Contrast enhanced coronary CT angiography (CCTA) provides high resolution images of the coronary arteries, and due to its high negative predictive value, has an excellent accuracy for excluding the presence of coronary stenosis or ischemia [6]. On the other hand, coronary artery calcium (CAC) scanning is more widely available, simpler to perform (e.g., not heart rate dependent), does not require contrast, less expensive, and offers highly reproducible results. However, this test cannot determine whether stenosis is present or absent and cannot identify the presence or extent of exclusively non-calcified plaque. While the role of CAC has been extensively studied among asymptomatic patients, recently there has been increasing debate [7,8] regarding the potential role of CAC among low risk symptomatic patients. Central to this debate is whether the prevalence and clinical significance of non-calcified plaque and stenosis in the setting of zero calcium is low enough to allow for exclusion of obstructive CAD.

In recognition of recent data regarding CAC testing in symptomatic patients, the United Kingdom National Institute for Health and Clinical Excellence (NICE) guidelines for assessment of possible angina have incorporated the use of CAC as part of the recommended algorithm [9]. Although major American guidelines for unstable angina do not identify CAC as part of any diagnostic algorithm [3], the 2007 expert consensus document on calcium scoring published by the American College of Cardiology and the American Heart Association states that CAC may serve “as a filter prior to invasive coronary angiography or stress nuclear imaging” but acknowledges that the “prognostic studies of CAC in symptomatic patients have generally been limited by biased samples (e.g., patients referred for invasive coronary angiography) and small numbers of hard outcome events. Future studies should include larger numbers of patients and should allow for adequate length of follow-up and assessment of larger numbers of hard endpoint events, especially all-cause mortality and myocardial infarction” [10].

Therefore, our objective was to evaluate the diagnostic accuracy of CAC for excluding coronary stenosis among symptomatic patients also having CCTA and to investigate the prognostic value of each test.

1. Methods

1.1. Study population

We included all consecutive subjects, 18 years or older, who underwent both a non-contrast CAC score and a contrast enhanced CCTA at the Massachusetts General Hospital or the Brigham and Women’s Hospital from 2004 − 2011. We included in and outpatients. All CAC and CTA scans were performed with 64 detector (or newer generation) scanner. We excluded patients without symptoms referred for screening purposes or research protocols and patients with prior known CAD (defined as prior percutaneous coronary intervention (PCI)), coronary artery bypass graft surgery (CABG), or MI. The Partners’ Healthcare Institution Review Board approved the study.

1.2. CCTA exam acquisition and interpretation

CAC and CCTA scans were performed according to established guidelines [11,12] and institutional protocol at the time of the scan. CAC scans were performed and read according to the Agatston method [13]. All CCTA exams were categorized as having no (0%), non-obstructive (<50%), or obstructive (≥50%) coronary artery disease (CAD). Vessels smaller than 2 mm were not evaluated. We used the Society of Cardiovascular Computed Tomography 18 segment coronary model based upon the original American Heart Association model [12], to categorize CAD presence and severity for each segment. Extent of CAD was also assessed by the number of vessels with CAD [left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA)] as 1-vessel, 2-vessel and 3-vessel/left main (LM) disease. More detailed analysis of the extent and severity of CAD were performed using previously validated scores:

- Segment involvement score (SIS): the sum of the number of segments with disease, which ranges from 0 to 16. [14]
- Segment severity score (SSS): each segment receives a value according the amount of disease present in that vessel (0: no CAD, 1: non-obstructive CAD, 2: 50–70% stenosis, 3: >70% stenosis). The final score is the sum of each individual score, and ranges from 0 to 48. [15]

1.3. Baseline risk factors

We defined systemic arterial hypertension as a systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or diagnosis/treatment of hypertension. Dyslipidemia was defined as total cholesterol >240 mg/dL or serum triglycerides >150 mg/dL or high density lipoprotein cholesterol (HDL) < 40 mg/dL (male) or <50 mg/dL (women) or diagnosis/treatment of dyslipidemia. Diabetes was defined by a hemoglobin A1C ≥ 6.5% [16], physician-based diagnosis, or use of anti-diabetic medications. Smoking was defined as current (tobacco products used within the last month), former or never. Family history of premature CAD was defined as any first-degree family member with a history of clinical CAD prior to age 60. The pretest probability of CAD was calculated using the Morise score [17], which includes age, gender, risk factors and symptoms to predict the probability of obstructive CAD.

1.4. Cardiovascular outcomes

All patient medical records were reviewed by two cardiologists who were blinded to CTA results for adjudication of cardiovascular events. A standardized questionnaire was mailed to each patient in order to ensure that events outside of our healthcare network are captured. For patients who did not reply to the questionnaire upon repeated mailings, scripted phone interviews were performed. In addition, patients had the option of completing a web-based version of the questionnaire via the REDCap (Research Electronic Data Capture) system [18], which is encrypted, secure, and HIPAA compliant. All self-reported events were verified via outside medical record review by two cardiologists, blinded to CTA results with discordant events adjudicated by consensus.

Major adverse cardiovascular events (MACE) was defined as a composite of non-fatal myocardial infarction, late coronary revascularization (>90 days), unstable angina, and cardiovascular mortality. We additionally evaluated the outcome of cardiovascular mortality and non-fatal MI to avoid inherent bias of softer outcomes (e.g., angina, coronary revascularization). Diagnosis of MI was confirmed by two of three: chest pain or equivalent symptom complex; positive cardiac biomarkers; ECG changes typical of MI [19]. Time to the first coronary revascularization procedure (PCI or CABG) was evaluated. Early revascularizations (≤90 days post CCTA) were removed from survival analysis to minimize verification bias [20–22]. That is, patients with ≥50% stenosis by CCTA more frequently undergo invasive angiography and revascularization early after the CCTA, whereas late revascularizations are less likely to be associated with the CCTA and more associated with CAD progression and prognosis. Unstable angina without