

ORIGINAL RESEARCH

# Prognostic Value of Echocardiographic Calcium Score in Patients With a Clinical Indication for Stress Echocardiography



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## ABSTRACT

**OBJECTIVES** The value of the echocardiographic calcium score (eCS) was evaluated to predict cardiac events in a multicenter cohort of subjects without known coronary disease, who underwent stress echocardiography (SE) for suspected coronary artery disease (CAD).

**BACKGROUND** Several studies have established that aortic valve sclerosis and/or calcification and mitral calcification, as detected by echocardiography, predict cardiovascular morbidity and mortality. The use of a semiquantitative total cardiac calcium score (eCS) to assess aortic and mitral valves, papillary muscles, and the ascending aorta has never been tested in multicenter studies; the inherent subjectivity and clinical applicability of such a parameter remains a concern.

**METHODS** We identified 1,303 patients from 5 Italian institutions and 1 U.S. institution, who had no known CAD and who underwent clinically-indicated pharmacological or exercise SE. They were followed up for myocardial infarction (MI) and all-cause death. eCS was assessed from archived images, and its discrimination and reclassification prognostic potential was determined.

**RESULTS** Fifty-eight patients met the combined endpoint of all-cause death ( $n = 37$ ; 2.8%) or MI ( $n = 21$ ; 1.6%) during a median follow-up of 808 days. Age, diabetes mellitus, eCS  $>0$ , and ischemic SE were multivariate predictors of hard events. Kaplan-Meier curves demonstrated that patients with ischemic SE or eCS  $>0$  had worse outcomes. When both variables were abnormal, the prognosis was worse ( $p < 0.001$ ). The multivariate model demonstrated that both eCS and ischemic SE independently contributed to risk prediction more than clinical variables. Both wall motion during SE and eCS were able to significantly reclassify the risk of events, but only stress wall motion demonstrated an incremental discrimination value.

**CONCLUSIONS** eCS demonstrated significant prognostic value in predicting hard cardiac events in a multicenter population of patients who required noninvasive evaluation. Its value was independent from clinical assessment and wall motion during SE, although it did not show incremental value over these factors for discrimination of patients with and without events. (J Am Coll Cardiol Img 2015;8:389-96) © 2015 by the American College of Cardiology Foundation.

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**ABBREVIATIONS  
AND ACRONYMS****AVC** = aortic valve  
sclerosis/calcification**CAD** = coronary artery disease**eCS** = echocardiographic  
calcium score**MAC** = mitral annular  
calcification**MI** = myocardial infarction**NRI** = net reclassification  
improvement**SE** = stress echocardiography

**C**alcified plaques in the coronary arteries are markers of atheromatous-plaque burden, which, in turn, is highly predictive of future cardiovascular events and mortality (1). The coronary calcium score (2), as assessed by cardiac computed or electron-beam tomography, has unequivocally demonstrated prognostic superiority (added to clinical risk scores) to screen asymptomatic subjects, compared with biomarkers (e.g., C-reactive protein) or established imaging parameters such as carotid intima-media thickness (3,4). Conse-

quently, European guidelines on cardiovascular disease prevention (5) support the use of the coronary calcium score in asymptomatic adults at moderate cardiovascular risk. A number of studies have established that both aortic valve sclerosis/calcification (AVC) and mitral annular calcification (MAC), as detected by echocardiography, independently predict cardiovascular morbidity and mortality (6-9).

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The use of echocardiographic semiquantitative calcium scores (eCS), which comprehensively assess aortic and mitral valves, papillary muscle, and the ascending aorta—and range from no visible calcium to severe and diffused calcium deposits—have also been associated with: 1) coronary and total cardiac calcium by computed tomography; 2) angiographically obstructive coronary artery disease (CAD); 3) worse prognosis in several patient subgroups; and 4) very recently, to ischemic stress echocardiography (SE) results (10-18).

We aimed to evaluate the prognostic stratification value of a simple semiquantitative eCS to predict future hard cardiac events in a large and multicenter cohort of subjects without previously known coronary disease, who underwent SE for clinical purposes.

**METHODS**

**PATIENT POPULATION.** We retrospectively identified 1,303 patients from 5 European institutions and 1 U.S. institution who underwent clinically-indicated SE during a previous 6-month period (the patients were independently chosen in each center, based on local availability of digitally archived SE images for retrospective eCS assessment) for suspected CAD. Exclusion criteria were: 1) known CAD and/or previous acute coronary syndrome or revascularization; 2) significant valvular heart disease or previous heart surgery; and 3) chronic renal insufficiency. All patients provided written informed consent to

research participation and collection of follow-up data at the time of SE.

Patients' age, sex, and presence of other CAD risk factors (hypertension, diabetes mellitus, family history of premature CAD, and cigarette smoking) were recorded in a prospectively collected database at the time of SE, as is the current practice in each of the 6 study centers. Hypertension was defined as systolic blood pressure >140 mm Hg and diastolic blood pressure >90 mm Hg, or current use of antihypertensive medications. Diabetes mellitus was defined as a history of oral hypoglycemic drugs or insulin use, or fasting blood glucose levels >126 mg/dl. Tobacco use was defined as currently smoking cigarettes. Family history was defined as CAD in first-degree relatives, in men <55 years of age, and in women <65 years of age. Hypercholesterolemia was defined as history of total cholesterol >200 mg/dl or use of cholesterol-lowering drugs. Obesity was defined as a body mass index  $\geq 30$  kg/m<sup>2</sup>.

**STRESS ECHOCARDIOGRAPHY.** SE was performed using pharmacological stressors in 782 patients (60%) (486 received dipyridamole 0.84 mg/kg/6 min and 296 received dobutamine up to 40  $\mu$ g/kg + atropine up to 1 mg), whereas exercise echocardiography (treadmill Bruce Protocol or semisupine cycloergometer) was used in 521 (40%) patients, depending on patients' contraindications and center preferences. SE, either pharmacological or with exercise, was defined as abnormal if new or worsening wall motion abnormalities developed in at least 1 segment during the stress phase, whereas it was defined as normal if wall motion did not change or improved. Depending on the specific institution, Philips ie33 (Philips, Amsterdam, the Netherlands) or GE vivid 7 equipment (GE Healthcare, Little Chalfont, United Kingdom) were used for the echocardiographic examinations.

**CALCIUM ASSESSMENT.** All patients underwent standard transthoracic echocardiography at rest as part of their baseline examination before starting their SE. Both baseline images acquired before starting SE and the at rest clips of the SE protocol (parasternal long-axis and short-axis views at mid-ventricular and aortic levels, apical 4 chamber and 2-chamber views) were selected for the retrospective assessment of semiquantitative eCS. Criteria for judging AVC, MAC, ascending aorta, and papillary muscle calcium were similar to grading systems used in previous studies (10,11,14) and are detailed in **Table 1**. Aortic valve sclerosis was defined as focal areas of increased echogenicity and thickening of the aortic valve leaflets in the absence of aortic stenosis

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