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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

Calcified 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). Consequently, 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 ≥30 kg/m^2.

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 μg/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

(velocity across the valve <2.5 m/s). Each aortic valve leaflet was graded on a scale of 0 (normal) to 3 (severe) according to leaflet thickening and calcific deposits; the highest score for a given cusp was assigned as the overall degree of aortic valve sclerosis. MAC was defined as an intense and bright echo-producing structure located at the junction of the atrioventricular groove and posterior mitral valve leaflet, and was measured from the leading anterior to the trailing posterior edge and judged on a scale of 0 (normal) to 3 (severe). Papillary muscle calcium was defined as a bright echo involving the head of 1 or both papillary muscles. Ascending aorta calcium was defined as a focal or diffuse area of increased echo-reflectance and thickening in the aortic root on the parasternal long-axis view. Accordingly, a final score was derived by the consensus of 2 readers in each study site, as the sum of all identified cardiac calcific deposits; this score was in the range of 0 (no calcium visible) to 8 (extensive cardiac and ascending aorta calcific deposits).

FOLLOW-UP. Outcome was determined from patients' interviews at outpatient clinics, hospital chart reviews, and telephone interviews with the patient, relatives, or referring physician. Primary outcome variables were death and nonfatal myocardial infarction (MI). To avoid misclassification of the cause of death, we considered overall mortality (19). MI was defined by typical symptoms, and electrocardiographic and serial cardiac enzyme changes. Follow-up time was considered starting from SE date until the first event or the last contact date. Follow-up data were analyzed to evaluate event-free survival according to classical risk factors, the left ventricular ejection fraction at rest, eCS, and SE wall motion response.

STATISTICAL ANALYSIS. Continuous variables were expressed as mean ± SD and categorical variables were described as absolute number and percent. Event-free survival time was estimated using Kaplan-Meier curves, and the log-rank test was used to compare curves. Univariate and multivariate Cox proportional hazard models were used to estimate the incidence of hard events. Variables with $p < 0.1$ at univariate analysis or deemed to be clinically meaningful, such as sex, were considered for the inclusion in multivariate models. A model including only clinical variables was first developed, and then wall motion and eCS were added. The clinical utility of the addition of wall motion and eCS on clinical variables was evaluated in terms of discrimination and reclassification ability. Harrell's C index was used to evaluate discrimination, and continuous net reclassification improvement (NRI) was used for risk reclassification (20). Because of the inclusion of data from different centers, the study center was used as a strata variable, and pooled models over strata were adapted. Analyses were also repeated by using center as a covariate to check consistency of the results. Multicollinearity was examined in all models, and proportional hazard assumption was verified using the Schoenfeld test. In all, the analysis of a dummy variable was used for eCS, dichotomizing the continuous variable according to the best cutoff identified using receiver-operating characteristic curve analysis and the highest Youden index. A p value <0.05 was considered statistically significant. A total of

TABLE 1 Grading System of Cardiac and Ascending Aortic Calcium

Grade	Papillary Muscle Calcium	Mitral Annular Calcium (mm)	Aortic Valve Sclerosis	Ascending Aorta Calcium
0	Absent	Absent	Absent	Absent
1	Present	Mild <5	Mild	Present
2		Moderate 5–10	Moderate	
3		Severe >10	Severe	

Aortic valve sclerosis graded as follows: absent = normal thickness <2 mm, and normal reflectivity; mild = thickness >2 mm and/or increased reflectivity; moderate = thickness >4 mm and/or diffuse or focal cusp hyper-reflectivity; severe = thickness >6 mm and/or marked echoreflectivity.

TABLE 2 Baseline Characteristics of the Study Population (N = 1,303) and Echocardiographic Results

Mean age, yrs	63 ± 12
Age ≥70 yrs	402 (31)
Male	740 (57)
Family history of CAD	328 (25)
Current cigarette smoking	253 (19)
Hypercholesterolemia	644 (49)
Diabetes mellitus	285 (22)
Hypertension	816 (63)
Obesity	216 (17)
Revascularization	125 (6)
Pharmacological stress test	766 (59)
Echocardiography at rest	
Reduced LVEF at rest (<50%)	117 (9)
Total cardiac Ca score >0	542 (42)
MAC >0	318 (24)
AVC >0	330 (27)
SE result	
Inducible wall motion abnormalities	162 (12)
Follow-up data and events	
Revascularization within 3 mo of SE	96 (7.4)
All-cause death	37 (3)
Myocardial infarction	21 (2)

Values are mean ± SD or n (%).

AVC = aortic valve sclerosis/calcification; Ca = calcium; CAD = coronary artery disease; eCS = cardiac calcium score; LVEF = left ventricular ejection fraction; MAC = mitral annular calcification; SE = stress echocardiography.

30 patients were randomly selected and analyzed again 1 month later in the coordinating center by consensus of the same 2 readers to assess eCS intracenter agreement, according to a weighted Cohen's k test and intraclass correlation coefficient. The same 30 examinations were also shared with the remaining 5 participating centers for intercenter agreement, according to the intraclass correlation coefficient. Statistical analyses were performed using standard software (Stata release 10 and R 2.11, StataCorp, College Station, Texas).

RESULTS

BASELINE CLINICAL CHARACTERISTICS AND ECHOCARDIOGRAPHY RESULTS. Baseline characteristics of the study group (n = 1,303) are shown in Table 2; mean age was 63 ± 12 years of age, and there was slight male prevalence (57%). Total eCS was higher than 0 in 542 patients (42%), and 98% of patients had scores 0 to 4. Figure 1 shows the distribution of eCS in the study population according to the occurrence of events; it also shows the absolute number of patients in each eCS category. Reversible wall motion abnormalities during SE were present in 162 patients (12%).

Patients with eCS >0 tested positive at SE more frequently (17.3%; 94 of 542) than patients with eCS = 0 (8.9%, 68 of 761; $p < 0.001$), which indicated a clear association between the presence of cardiac calcium seen at echocardiography at rest (eCS >0) and an ischemic result at SE.

REPRODUCIBILITY DATA. Reassessment of eCS at 30 random examinations, as previously described, resulted in a weighted Cohen's K = 0.765 and intraclass correlation coefficient = 0.91 for intracenter variability, and an intraclass correlation coefficient = 0.80 with regard to intercenter variability.

CLINICAL FOLLOW-UP RESULTS. Median follow-up of the 1,303 enrolled patients was 808 days (lower quartile 483 days, upper quartile 1,447 days). Fifty-eight patients met the hard events combined endpoint of all-cause death (n = 37; 2.8%) or MI (n = 21; 1.6%) during the study follow-up.

The best cutoff for eCS to predict hard events from the receiver-operating curve was eCS >0, using the maximal Youden index method, with a sensitivity and specificity of 74% and 60%, respectively, and an area under the curve of 0.67 (SE 0.03).

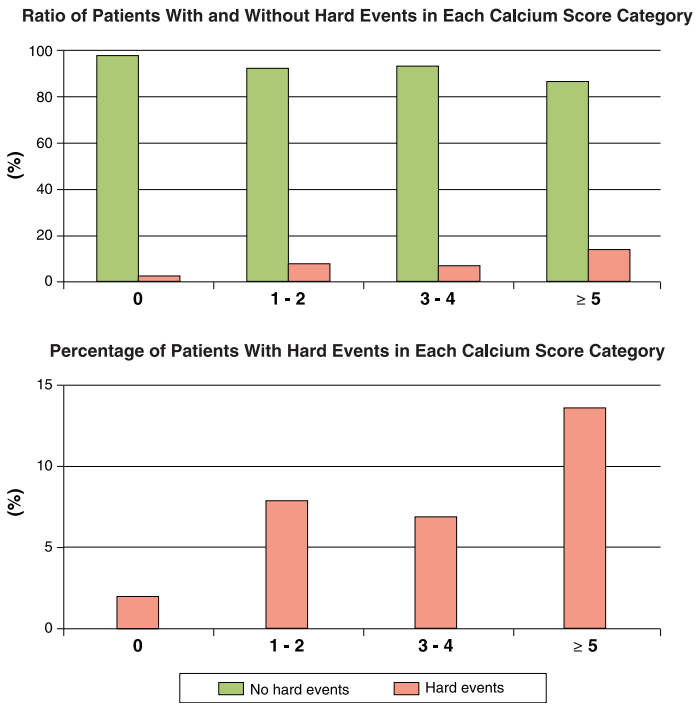
PREDICTION OF HARD EVENTS BY CLINICAL AND ECHOCARDIOGRAPHIC VARIABLES. Increasing age and diabetes mellitus were the clinical variables that were significantly associated with the risk of hard events at univariate analysis (Table 3), and their independent contribution to the stratification of prognosis was demonstrated at multivariate analysis (Table 4).

The 3-year event rate for patients with eCS >0 was significantly less favorable compared with subjects with eCS = 0 (9.8% vs 2.3%; $p < 0.001$).

Figure 2 demonstrates Kaplan-Meier survival curves for either normal (0) or abnormal (>0) eCS and stress wall motion assessment. Data from both eCS and wall motion assessment are shown in Figure 3, which also shows the Kaplan-Meier survival curves for the 4 subgroups corresponding to the possible combinations of the 2 variables. Patients with both wall motion abnormalities at SE and cardiac calcifications had the worst prognosis, with a 3-year event rate of 24%, whereas patients with eCS = 0 and no wall motion abnormalities at SE had the best outcome (2%) at the 3-year event rate ($p < 0.001$).

The multivariate model including eCS and wall motion revealed that both variables independently contributed to risk prediction. Findings were similar when analyses were repeated using the study center as a covariate.

FIGURE 1 Calcium Score Distribution in the Study Population



Calcium score distribution in the study population on the basis of the occurrence of the primary endpoint (all-cause death or myocardial infarction), either based on the percentage ratio of patients with and without events in each calcium score category **(top)** or the percent of patients with hard events in each calcium score category **(bottom)**.

INCREMENTAL PROGNOSTIC VALUE OF WALL MOTION AND eCS TO PREDICT HARD EVENTS. Discrimination. Compared with the baseline multivariate clinical model, the addition of stress wall motion data showed significantly better discrimination ability (Harrell's C index: 0.784; 95% confidence interval [CI]: 0.717 to 0.852 vs. Harrell's C index: 0.739; 95% CI: 0.669 to 0.810; p = 0.028), whereas the further addition of eCS to the clinical + stress wall motion model did not improve the discrimination ability of the model (Harrell's C index: 0.79; 95% CI: 0.727 to 0.856 vs. Harrell's C index: 0.784; 95% CI: 0.717 to 0.852; p = 0.609) (Table 4).

Reclassification. Results from continuous NRI analysis demonstrated the significant and relevant incremental reclassification value of the addition of either stress wall motion data (continuous NRI: 0.28; 95% CI: 0.04 to 0.52; p = 0.021) or eCS (NRI: 0.58; 95% CI: 0.34 to 0.83; p < 0.001) compared with clinical data and also of eCS over clinical and stress wall motion data (NRI: 0.57; 95% CI: 0.32 to 0.82; p < 0.001).

TABLE 3 Univariate Stratified Models and Cox Analysis for Myocardial Infarction or Death Endpoint

	HR (95% CI)	SE	Z	p Value
Sex	0.820 (0.486–1.385)	0.219	−0.740	0.458
Age	1.067 (1.040–1.095)	0.014	4.950	0.000
Family history of CAD	1.268 (0.719–2.239)	0.368	0.820	0.412
Smoking history	1.224 (0.686–2.186)	0.362	0.680	0.494
Hypercholesterolemia	0.862 (0.510–1.457)	0.231	−0.560	0.579
Diabetes	2.045 (1.181–3.539)	0.572	2.550	0.011
Hypertension	1.078 (0.613–1.893)	0.310	0.260	0.795
Obesity	1.286 (0.657–2.516)	0.440	0.730	0.463
Revascularization after 3 mo	5.128 (2.404–10.938)	1.982	4.230	0.000
LVEF <50%	1.652 (0.852–3.204)	0.558	1.490	0.137
Inducible wall motion abnormalities	4.265 (2.346–7.754)	1.301	4.760	0.000
eCS >0	3.685 (2.024–6.709)	1.127	4.270	0.000

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 2.

DISCUSSION

The main finding of our multicenter study was that for the first time we found a significant independent prognostic value of a semiquantitative eCS to predict hard cardiac events in a population of subjects with symptoms that required noninvasive evaluation for suspected CAD.

The prognostic yield of eCS was independent from clinical variables and stress wall motion data, but it was not able to discriminate them incrementally by comparison to the Harrell's C index of the models without and with eCS. In contrast, the addition of eCS was able to reclassify the risk of events, again compared with the model that included clinical and stress wall motion data, but this NRI method has recently been heavily criticized for its risk of frequent false positive results (21,22).

In contrast, the low sensitivity of C statistics for improvement in discrimination, in particular when the baseline comparison model has high C values (as the clinical + stress wall motion model in our study), is well known (23,24).

In conclusion, in the absence of an associated significant difference in the Harrell's C index of the models for discrimination, with an isolated continuous NRI suggesting the significant incremental prognostic value of eCS, we should conservatively and cautiously conclude that eCS in our study failed to demonstrate an incremental value on top of clinical and stress wall motion data. This was the first study that reported intracenter and intercenter variability data for eCS assessment. The variability was key to evaluate its clinical usefulness when testing partially subjective and semiquantitative variables, such as eCS. Repeatability of eCS among the involved centers was good (intraclass correlation coefficient = 0.8) and sufficiently robust to be reliably applied in clinical practice.

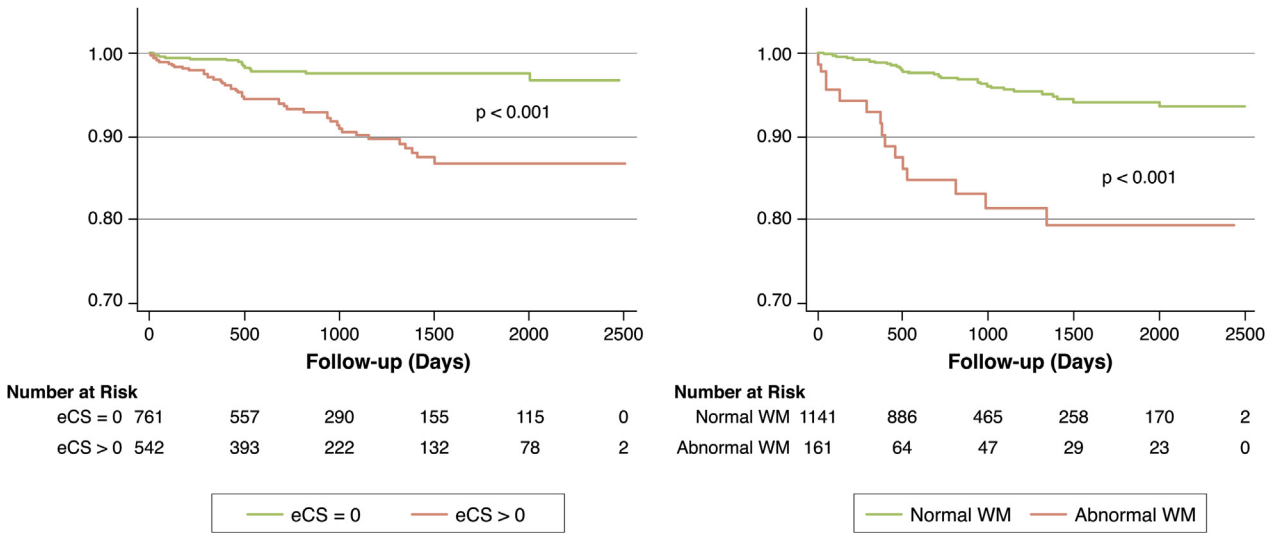
Noninvasive modalities for the diagnosis of CAD are key for risk stratification of symptomatic patients, and to identify higher risk subjects who could benefit more from invasive coronary angiography and possible subsequent revascularization (or in alternative maximal medical therapy). Transthoracic

TABLE 4 Multivariate Models for Prediction of Myocardial Infarction or Death Endpoint

	HR (95% CI)	p Value	Harrell's C Index (95% CI)	p Value Compared With Previous Model
Clinical model				
Female	0.70 (0.41–1.19)	0.192	0.739 (0.669–0.810)	–
Age	1.07 (1.04–1.09)	<0.001		
Diabetes	1.83 (1.52–3.20)	0.032		
Revascularization	3.33 (1.54–7.19)	0.002		
Clinical model + reversible wall motion				
Female	0.68 (0.40–1.15)	0.151	0.784 (0.717–0.852)	0.028
Age	1.06 (1.03–1.09)	<0.001		
Diabetes	1.95 (1.12–3.40)	0.019		
Revascularization	2.45 (1.11–5.39)	0.026		
Inducible WM abnormalities	2.95 (1.58–5.53)	0.001		
Clinical model + reversible wall motion + eCS				
Female	0.65 (0.38–1.10)	0.105	0.792 (0.727–0.856)	0.609
Age	1.05 (1.02–1.08)	<0.001		
Diabetes	1.80 (1.03–3.15)	0.040		
Revascularization	2.54 (1.15–5.64)	0.021		
Inducible WM abnormalities	2.71 (1.44–5.11)	0.002		
eCS >0	2.61 (1.40–4.86)	0.002		

WM = wall motion; other abbreviations as in Tables 2 and 3.

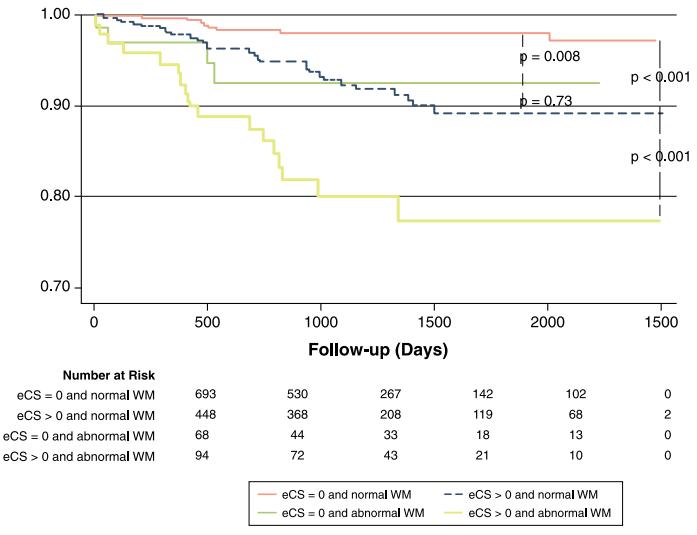
FIGURE 2 Kaplan-Meier Event-Free Survival Curves



Kaplan-Meier event-free survival curves, divided on the basis of echocardiographic calcium score (eCS) >0 at rest, echocardiography **(left)** or reversible wall motion (WM) abnormalities at stress-echocardiography **(right)**. Log-rank p values are superimposed.

echocardiography has the advantage of being a simple, low-cost, radiation-free technique, which is widely available in clinical practice. Although our study patients represented a mixed cohort of patients who underwent SE for clinical purposes, they were generally symptomatic and considered at intermediate-risk, and their all-cause mortality rate (2.9% at 3 years) was lower than expected. Therefore, we speculate the value of eCS for risk stratification might eventually be extended to lower risk subjects, although this hypothesis needs prospective testing in an asymptomatic population. Interestingly, the best eCS cutoff to predict cardiac events was >0, which is probably the easiest score to apply clinically, because accordingly, eCS is "abnormal" whatever amount of calcium is present, in at least 1 of the pre-determined cardiac sites.

FIGURE 3 Kaplan-Meier Event-Free Survival Curves

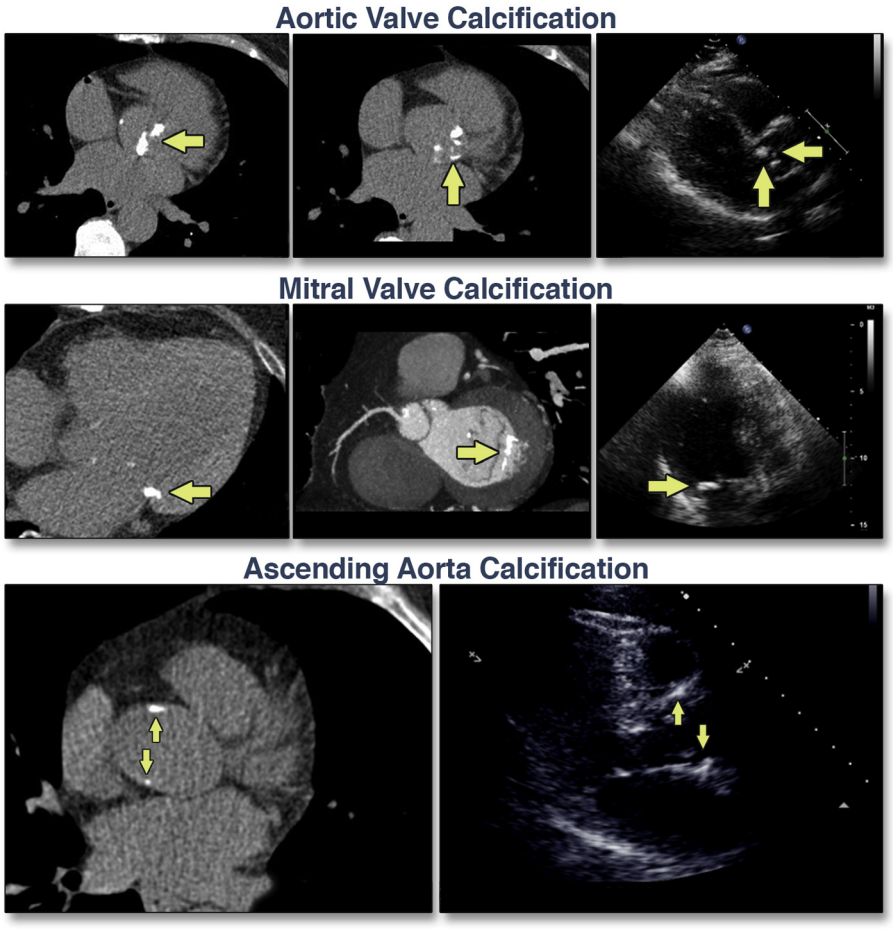


Kaplan-Meier event-free survival curves according to the presence and/or absence of echocardiographic graphic calcium score (eCS) >0 at rest, echocardiography, and/or reversible wall motion (WM) abnormalities. Log-rank p values are superimposed.

Although the present study proved the significant prognostic value of a eCS >0 in a population of patients who underwent SE, it did not clarify how this parameter should be used clinically. Patients with both abnormal eCS and stress wall motion abnormalities had the worst prognoses in our study and might be the patients who benefit more from intensive medical and/or interventional therapies.

STUDY LIMITATIONS. Different institutions with very different case mix and investigator's preferences towards exercise or pharmacologic SE were involved in our multicenter study, so that the study population was very heterogeneous among centers. Furthermore, it was a lower risk population than expected for patients who underwent SE; this is in line with current overuse of provocative testing in western societies. Thus, we could not assess the incremental prognostic value of increasing eCS values due to the

FIGURE 4 Example of Calcifications Imaged in Parallel by Echocardiography and Cardiac Computed Tomography



An example of calcifications imaged by echocardiography **(right)** and cardiac computed tomography **(left/middle)** obtained from patients who underwent cardiac computed tomography following stress-echocardiography. **Arrows** indicate calcifications.

low percent of cases with scores >4. This was also a retrospective study, and clinical data collection was consequently limited to a minimal common data set prospectively collected by all involved centers. The echocardiographic detection of calcium relies on the ability of ultrasound to identify even a minimal quantity of calcium. In contrast, increased echolucency caused by fibrosis might be misinterpreted as calcification, and in addition, there might have been difficulty in ensuring independence of the eCS and SE reads, although this was probably only a minor problem because eCS was assessed (retrospectively) on archived images taken at rest.

Figure 4 shows examples of calcifications imaged in parallel by echocardiography and cardiac computed tomography, obtained from patients who clinically underwent cardiac computed tomography following SE.

CONCLUSIONS

The assessment of an eCS at the time of SE has a significant and independent prognostic value, although it appears that it does not add incrementally to the combination of clinical and stress wall motion data. Because such an assessment appears reproducible and adds virtually no additional cost to the patient, it should be considered as a recommended additional diagnostic assessment at the time of SE. Further prospective evaluation is needed to determine the role of eCS in altering patient management or in specific subsets of patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The use of a simple semiquantitative eCS, which is obtained by visually assessing the aortic and mitral valves, papillary muscles, and the ascending aorta, has been now tested in a multicenter study involving patients who underwent SE. eCS proved robust, reproducible, and was able to stratify future cardiovascular prognoses independently from wall motion behavior during SE.

TRANSLATIONAL OUTLOOK: The inherent subjectivity of such a visually assessed parameter as eCS remains a limitation, and future studies should address objective quantitative measures of cardiac calcium. Additional clinical studies, such as those typical of primary prevention studies, are still needed to confirm the prognostic value of eCS in lower risk patients.

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