Cardiac Calcifications on Echocardiography Are Associated with Mortality and Stroke

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Background: Calcium deposits in the aortic valve and mitral annulus have been associated with cardiovascular events and mortality. However, there is no accepted standard method for scoring such cardiac calcifications, and most existing methods are simplistic. The aim of this study was to test the hypothesis that a semiquantitative score, one that accounts for all visible calcium on echocardiography, could predict all-cause mortality and stroke in a graded fashion.

Methods: This was a retrospective study of 443 unselected subjects derived from a general echocardiography database. A global cardiac calcium score (GCCS) was applied that assigned points for calcification in the aortic root and valve, mitral annulus and valve, and submitral apparatus, and points for restricted leaflet mobility. The primary outcome was all-cause mortality, and the secondary outcome was stroke.

Results: Over a mean 3.8 ± 1.7 years of follow-up, there were 116 deaths and 34 strokes. Crude mortality increased in a graded fashion with increasing GCCS. In unadjusted proportional hazard analysis, the GCCS was significantly associated with total mortality (hazard ratio, 1.26; 95% CI, 1.17–1.35; $P < .0001$) and stroke (hazard ratio, 1.23; 95% CI, 1.07–1.40; $P = .003$). After adjusting for demographic and clinical factors (age, gender, body mass index, diabetes, hypertension, dyslipidemia, smoking, family history of coronary disease, chronic kidney disease, history of atrial fibrillation, and history of stroke), these associations remained significant.

Conclusions: The GCCS is easily applied to routinely acquired echocardiograms and has clinically significant associations with total mortality and stroke. (J Am Soc Echocardiogr 2016;■:■-■.)

Keywords: Global cardiac calcium score, Echocardiography

Calcifications of various cardiac structures are frequently encountered on routine echocardiography. They have been associated with an increased risk for cardiovascular events (particularly stroke), cardiovascular death, and even all-cause mortality.[1-6] To date there is no accepted system for scoring such calcifications. Some studies have marked the simple presence or absence of calcium deposits in the mitral annulus or aortic valve.[7] Others have assessed the presence of calcium in different areas and have generally noted an additive risk when calcium is not limited to one location.[8] Mitral annular calcification (MAC) has been graded according to its thickness in millimeters, with greater thickness predicting more events.[2] In the hope of improving on these grading methods, our group developed a global cardiac calcium score (GCCS) that accounts for all visible calcium deposits on echocardiography. Analogizing to coronary calcification, in which greater amounts of calcium deposition predict worse outcomes, we hypothesized that the echocardiographic GCCS could predict mortality and stroke in a graded fashion.

Previous work has found a good correlation between the echocardiographic GCCS and noncoronary cardiac calcification as measured on computed tomography.[9] The GCCS is also associated with the presence of coronary atherosclerosis,[9] conduction abnormalities on electrocardiography,[10] and progression of mitral stenosis when MAC is the underlying cause.[11] In this research we applied the GCCS to a broad clinical sample and tested for associations with all-cause mortality and stroke.

METHODS

Subjects were retrospectively selected from a cohort of consecutive patients who underwent transthoracic echocardiography for any clinical indication between January 1, 2007, and January 31, 2011. Inclusion in the study was based on use of a generic International Classification of Diseases, Ninth Revision (ICD-9), code, 88.72 ("diagnostic ultrasound of the heart") assigned by the hospital's internal coders. The study investigators had no input into the use of this code. Subjects were excluded if they had known cardiomyopathy (ICD-9 codes 428.0–428.9), diagnosed coronary artery disease (ICD-9 codes 414.0–414.9), or significant valvular heart disease

Abbreviations

CKD = Chronic kidney disease

GCCS = Global cardiac calcium score

HR = Hazard ratio

ICD-9 = International Classification of Diseases, Ninth Revision

MAC = Mitral annular calcification

TAPSE = Tricuspid annular plane systolic excursion

(ICD-9 codes 394.0–397.9 and 424.0–424.9). In addition, patients with malignancy (ICD-9 codes 140.0–234.9) or end-stage renal disease on dialysis (ICD-9 code 585.6) were excluded. The second phase of patient selection was done through manual review of individual electronic health records. Cardiomyopathy was defined as a left ventricular ejection fraction < 50%, presence of grade III or IV diastolic dysfunction (per American Society of Echocardiography guidelines), or evidence of infiltrative myocardial disease. Significant valvular heart disease was defined as any degree of stenosis or regurgitation (of the aortic or mitral valves) greater than mild, as reported in the official echocardiographic interpretation (see flowchart in Figure 1).

Echocardiograms were reviewed by a single expert reader (S.G.), who was blinded to clinical data. Standard measurements of various echocardiographic and Doppler parameters were made in accordance with American Society of Echocardiography guidelines. In addition, we recorded tricuspid annular plane systolic excursion (TAPSE) as a measure of right ventricular function.[12] A semiquantitative GCCS (Table 1) was calculated for each patient. The GCCS awards points for calcium deposits in the aortic root and valve, the mitral annulus and valve, and the submittal apparatus. Points are also added for restriction of leaflet mobility (see Figures 2–4 and Videos 1–3 [available at www.onlinejase.com] for examples of scoring). The score is weighted toward the mitral annulus and aortic valve, as these are the areas that calcify most commonly and most extensively. Recognizing that echocardiography cannot precisely differentiate areas of sclerosis (fibrosis) from calcification we used the following guidelines for scoring: to be deemed a calcific deposit, the area in question should be "brighter" than adjacent areas of the same structure and should be nodular or discrete. That area should also be "brighter" than normal myocardium.

Intraobserver and interobserver variability were characterized in a randomly selected sample of 80 subjects.

Baseline demographics, risk factors for coronary artery disease, and other comorbidities were abstracted from electronic medical records. Hypertension was defined as a documented history of hypertension or treatment with antihypertensive medications. Diabetes mellitus was defined as a documented history of diabetes or treatment with antidiabetic medications. Dyslipidemia was defined as a documented history of dyslipidemia or treatment with lipid-lowering drugs. Chronic kidney disease (CKD) was defined as a documented history of CKD or an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease study equation. Smoking was defined as being a current smoker or having stopped smoking <1 year before the index echocardiographic study. Body mass index was defined as weight in kilograms divided by the square of height in meters. A positive family history was defined as having a first-degree relative with a history coronary artery disease or death from myocardial infarction. Atrial fibrillation was defined as having a documented history of atrial fibrillation.
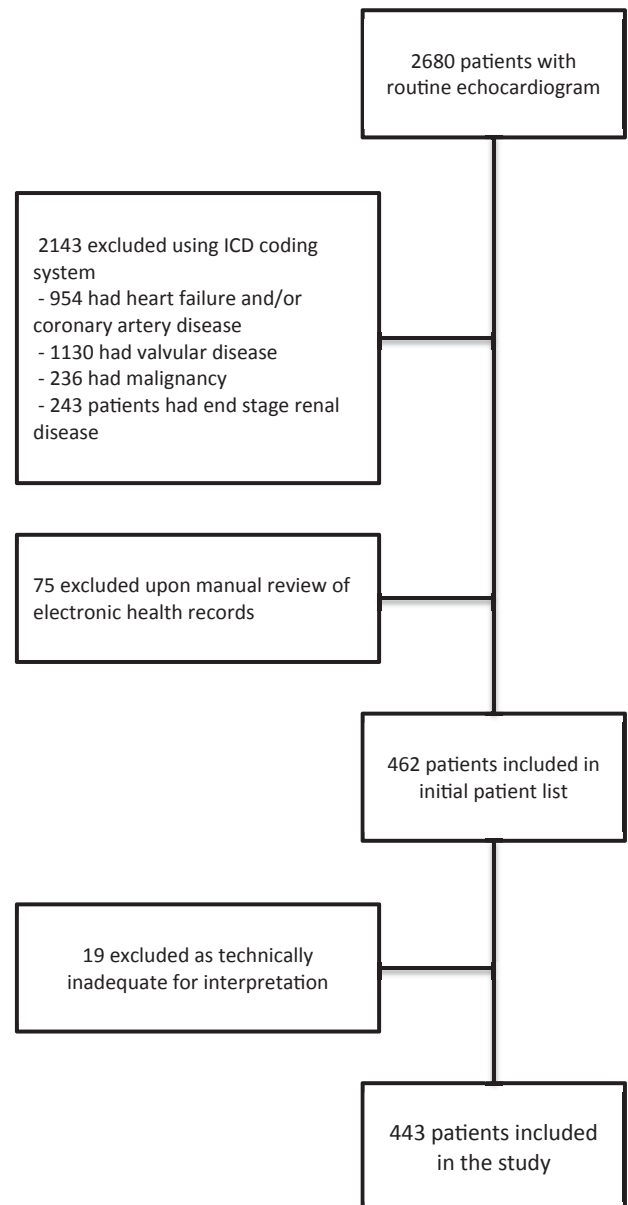

Figure 1 Flowchart of patient selection in the study.

Table 1 Global cardiac calcium scoring system

Posterior annulus (by thirds, score 0–3)

Posterior mitral leaflet restriction (any reduction in mobility) (0, 1)

Anterior mitral leaflet restriction (0, 1 [valve opening on long-axis view ≤ 10 mm])

Mitral valve calcification (either leaflet) (0, 1 [mild], 2 [greater than mild])

Subvalvular apparatus calcification (0, 1)

Aortic valve calcification (0, 1 [nodule(s) in fewer than three leaflets], 2 [nodules in three leaflets but nonrestrictive], 3 [restrictive*])

Aortic root calcification (0, 1)

*Reduced motion of one or more leaflets or a mean gradient ≥ 15 mm Hg.