Usefulness of the Echocardiographic Calcium Score to Refine Risk of Major Adverse Cardiovascular Events Beyond the Traditional Framingham Risk Score

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Echocardiographic calcifications are associated with major adverse cardiovascular events (MACE). A recently described semiquantitative Global Cardiac Calcium Score (GCCS) has been associated with mortality and stroke, with increasing scores associated with increasing risk. This score assigns points for calcium in the aortic root and valve, mitral valve and annulus, and submitral apparatus, with additional points for restricted leaflet mobility. We tested the hypothesis that the GCCS could improve prediction of MACE beyond traditional risk scores. This was a retrospective study of 216 subjects from a general echocardiography database (mean age 59 ± 15; 51% male). Follow-up was 3.8 ± 1.7 years. The Framingham Risk Score (FRS) and Pooled Cohort Equations (PCE) were applied to each patient. Mean GCCS was 3.2 ± 2. In the total cohort, GCCS predicted MACE (myocardial infarction, stroke, all-cause mortality), even after adjusting for FRS (odd ratio 1.19, p = 0.03). There were 106 subjects (49%) in the low-risk FRS group, 71 (33%) in the intermediate-risk group, and 39 (18%) in the high-risk group. GCCS ≥3 was associated with increased MACE (vs <3) in the low-risk group (p = 0.03), while GCCS <3 was associated with decreased MACE (vs ≥3) in the high-risk group (p = 0.04). When applied to the PCE risk estimate (dichotomized at <7.5% vs ≥7.5%) the GCCS similarly refined risk prediction. In conclusion, the semiquantitative GCCS appears to be a marker of additional unaccounted risk factors; it is easily applied and can further stratify risk of MACE beyond traditional FRS or PCE estimates. **(Am J Cardiol 2019;123:392−395)**

Cardiovascular disease (CVD) is the leading cause of mortality worldwide accounting for 31% of global deaths in 2016.[1] Various instruments for estimating CVD risk are in use, particularly the Framingham Risk Score (FRS)[2] and the ACC/AHA Pooled Cohort Equations (PCE).[3] FRS is a gender-specific multivariable risk factor algorithm, which estimates 10-year risk of CVD events. It classifies patients as low risk (≤10% 10-year risk); intermediate risk (10% to 20% risk); and high risk (≥20% risk) based on age, blood pressure, lipid levels, smoking status, and presence of diabetes mellitus.[2] The race- and gender-specific Pooled Cohort Equations were developed by a joint ACC/AHA task force. Current guidelines recommend various treatments (particularly statin therapy) based on 10-year CVD risk as assessed by the PCE.[4] There are, however, substantial limitations to these models[5−7] and various strategies have been proposed to improve risk prediction. Echocardiographic calcifications share risk factors with atherosclerosis and form through similar inflammatory processes. A semiquantitative echocardiographic Global Cardiac Calcium Score (GCCS) has shown good association with a CT defined coronary artery calcium score (CACS).[8] The echo score also predicts all-cause mortality and stroke in a graded fashion.[9] In this study, we examined the ability of the GCCS to refine risk prediction by traditional FRS and PCE.

Methods

The study sample was retrospectively selected from a cohort of consecutive patients who had transthoracic echocardiography performed for any clinical indication from January 1, 2007 to January 31, 2011 at Einstein Medical Center Philadelphia. The design and patient selection criteria for the original GCCS study have been detailed previously.[9] After exclusion of patients missing data needed to calculate the FRS, a total of 216 patients were included in the present study.

Gender-specific FRS was calculated for each patient. Patients were grouped according to their 10-year risk of cardiovascular disease (<10% as low-risk, 10% to 20% as intermediate-risk, and >20% as high-risk). Risk estimates through PCE were also obtained for each subject. Echocardiograms were evaluated by a single expert reader (SG) who was blinded to clinical data. Standard measurements of various echocardiographic and Doppler parameters were made in accordance with American Society of Echocardiography guidelines. A GCCS was applied which assigned points for calcium in the aortic root and valve, mitral annulus and valve, and submitral apparatus, with additional points for restricted leaflet mobility (Table 1). Intraobserver

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Table 1
Components of the global cardiac calcium score

Components	Score
Posterior annulus	(by thirds, score 0-3)
Posterior mitral leaflet restriction	(0, 1)
Anterior annulus	(0, 1)
Anterior mitral leaflet restriction	(0, 1) [valve opening on long-axis view ≤10 mm]
Mitral valve calcium	(0, 1 [mild], 2 [>mild])
Subvalvular apparatus calcium	(0, 1)
Aortic valve calcium	0 1 [nodule(s) in <3 leaflets] 2 [nodules in 3 leaflets but nonrestrictive] 3 [restrictive]
Aortic root calcium	(0, 1)

and interobserver variability have been reported previously.[9]

Baseline demographics, risk factors for coronary artery disease, and other co-morbidities 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. Hyperlipidemia was defined as a documented history of dyslipidemia or treatment with lipid lowering drugs. Chronic kidney disease was defined as a documented history of chronic kidney disease or an estimated glomerular filtration rate of <60 ml/min per 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 less than a year before the index echocardiogram. Body mass index was defined as weight (kg)/height (m).[2] Previous history of atrial fibrillation and CVA were defined as having a documented history of atrial fibrillation or CVA.

The primary endpoint was major adverse cardiovascular events (MACE) defined as a composite of myocardial infarction, stroke, and total mortality. Vital status was determined at study end (May 31, 2014) through query of the social security death index and review of hospital records. This project was approved by the Institutional Review Board at our institution.

Continuous variables were presented as medians with first and third quartiles and compared using the Kruskal-Wallis rank sum test. Categorical variables were expressed as frequency (%) and compared with chi-square statistics. Patients were divided into subgroups based on FRS risk prediction as well as GCCS (using median of 3). MACE was calculated in each group of FRS and GCCS. p values were calculated to examine any significant differences in prevalence of MACE in patients with low and high GCCS across different Framingham risk groups (low, intermediate, and high). Logistic regression analysis was performed to determine if GCCS remains an independent predictor of MACE after accounting for FRS. Low (<7.5% 10-year risk) and high (≥7.5%) risk groups were also defined using the PCE. MACE rates were also examined within these 2 groups according to low (<3) and high (≥3) GCCS score. A p value <0.05 was considered statistically significant. All statistical analysis was performed using STATA SE 14.0. (College Station, Texas: StataCorp LP).

Results

Baseline demographic and clincal characteristics of the patient population are listed in Table 2. Mean age of the population was 59 ± 15 years and 51% were men. Mean follow-up time was 3.8 ± 1.7 years. The mean GCCS score was 3.2 ± 2 and the median was 3. The mean 10-year FRS in the entire population was 12.3 ± 8% with 49% (n = 106) in the low risk group, 33% (n = 71) in the intermediate risk, and 18% (n = 39) in the high risk group.

The prevalence of MACE in the entire population was 18% through the study period. Using the GCCS score as a binary variable we observed increased MACE in patients with a GCCS ≥ 3 compared with < 3 (20% vs 14%; p = 0.03). The GCCS predicted MACE in the entire population, both in unadjusted analysis (odds ratio [OR] 1.18 [1.01 to 1.38]; p = 0.03) and after adjusting for FRS (OR 1.19 [1.02 to 1.4]; p = 0.03). There was a trend toward increased MACE with increasing FRS risk (12% vs 23% vs 23%; low vs intermediate vs high, respectively; p = 0.09). When adding the GCCS to the FRS groups, GCCS ≥3 was associated with increased MACE in the low- (20% vs 6.5%; p = 0.03) and high- (36.8% vs 10%; p = 0.04) risk groups but not in the intermediate-risk group (24% vs 23.9%; p = 0.99; Table 3 and Figure 1).

Using the ACC/AHA Pooled Cohort Equations median 10-year risk was 13.2% (IQR 6.5 to 24.0); mean 10-year risk was 17.2 ± 14.7%. In those with a predicted risk <7.5% (the cutoff for high-intensity statin treatment) MACE occurred less often in those with a GCCS < 3 versus ≥ 3 (3.6% vs 10.8%, p = 0.03). When predicted risk was

Table 2
Baseline demographic and clinical characteristics

Variable	n = 216
Demographic factors	
Age (median and IQR)	59 (50-70)
Male (%)	51
Traditional risk factors	
Diabetes mellitus (%)	20
Hypertension (%)	60
Hyperlipidemia (%)	18
Smoking (%)	28
Body mass index (median and IQR)	28 (25-32)
Chronic kidney disease (%)	4
Prior history of stroke (%)	25
Prior history of atrial fibrillation (%)	19
Clinical outcome and risk scores	
Major adverse cardiac events (%)	18
Global Cardiac Calcium Score (median and IQR)	3 (2-4.5)
FRS 10-year risk (%; median and IQR)	11 (6-18)
PCE 10-year risk,(%; median and IQR)	13.2 (6.5-24)

FRS = Framingham Risk Score; IQR = Interquartile range; PCE = Pooled Cohort Equations.

Table 3
Prevalence of MACE after adding the echocardiographic global cardiac calcium score to traditional risk scores

Risk groups	MACE %			p value
	Total	GCCS <3	GCCS ≥3	
PCE risk <7.5%	7.7	3.6	10.8	0.03
PCE risk ≥7.5%	22.5	19.6	24.0	0.04
FRS low risk (<10%)	13	6.5	20	0.03
FRS intermediate risk (10-20%)	23	23.9	24	0.99
FRS high risk (>20%)	23	10	36.8	0.04

FRS = Framingham Risk Score; GCCS = Global Cardiac Calcium Score; MACE = major adverse cardiovascular events; PCE = Pooled Cohort Equations.

≥7.5% MACE again occurred less often in those with a GCCS < 3 versus ≥ 3 (19.6% vs 24.0%, p = 0.04).

Discussion

The major findings of this study are: (1) a semiquantitative GCCS predicts MACE independently of standard risk score calculations. This is likely due to the presence of active inflammation which promotes both atherosclerosis and calcification of cardiac structures. (2) The GCCS can refine risk as defined by FRS or PCE. It appears to be particularly useful in low risk groups where it can identify those at increased risk who might otherwise be missed by the traditional risk models. Conversely, absence of cardiac calcium indicates true low risk.

Because of the prevalence and importance of atherosclerotic cardiovascular disease, widespread screening of the public has been recommended. This screening is based on the presence of risk factors and typically employs the Framingham Risk Score or Pooled Cohort Equations. Although useful, these tools have significant limitations. Addition of the CACS, as a direct measure of disease presence, can better define those in "low risk" patients who have early disease and might benefit from aggressive treatment, while certain "high risk" patients who have no evidence of atherosclerosis might not.[10,11] The CACS, however, is not currently recommended for screening due to issues of expense, radiation exposure, and the problem of incidental findings.

Echocardiography is frequently performed in patients with known or suspected heart disease. As opposed to the CACS, it is widely available and does not involve ionizing radiation. Many patients in whom we are interested in assessing CVD risk have already had an echocardiogram performed. Applying the GCCS takes a minimum of time (1 to 2 minutes) and can meaningfully refine risk assessment for the development of CVD events.

This study has several potential limitations. It was a retrospective study and hence causal association cannot be established. In addition, the number of patients was relatively small and there is the possibility of selection bias. The sample was predominantly African-American and thus results may not be generalizable to other groups.

Conclusions

In conclusion, an easily applied semiquantitative echocardiographic calcium score can further stratify risk of MACE beyond traditional measures. The presence of calcium appears to be a marker of additional unaccounted risk factors. Our results need to be reproduced in larger populations but suggest that echocardiography, routinely performed in the clinical setting, can meaningfully refine risk assessment of CVD.

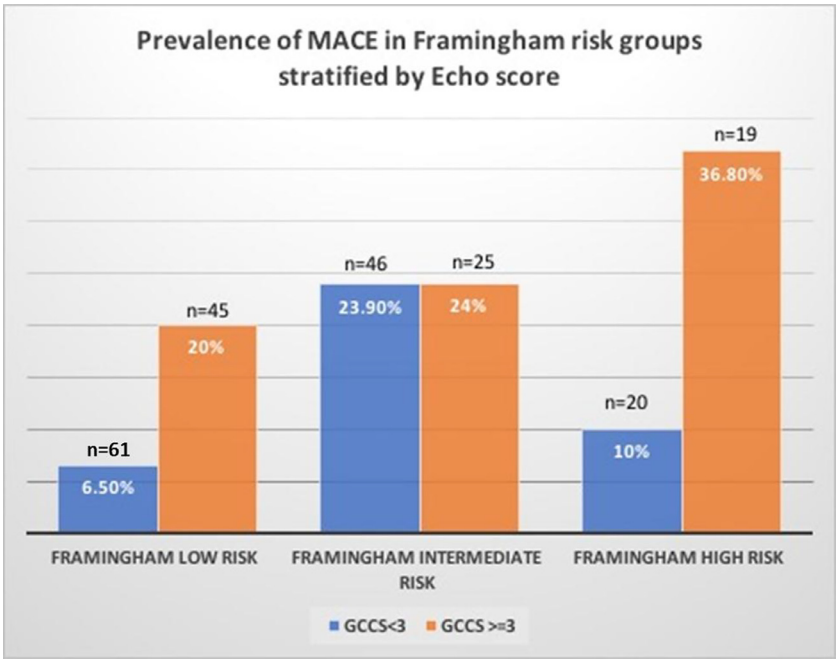

Figure 1. Prevalence of MACE in Framingham risk groups stratified by Echo score.

Disclosure

The authors have no conflicts of interest to disclose.

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