Published in final edited form as:

Echocardiography. 2019 March ; 36(3): 451–457. doi:10.1111/echo.14256.

The additive role of echocardiography in the screening for sudden death

Leonardo Tamariz, MD, MPH^{2,3}, Jeffrey J. Goldberger, MD⁴, Ana Palacio, MD, MPH^{2,3}, Gordon Chen, MD¹, Elissa Dawkins, MS¹, Emancia Forbes, RDCS¹, Thiago Tajiri¹, Reyan Ghany, MD, FACC, FASE¹

¹Department of Medicine, Miller School of Medicine at the University of Miami, Miami, FL

²Department of Chen Neighborhood Medical Centers Miller School of Medicine at the University of Miami, Miami, FL

³Veterans Affairs Medical Center, Miami, FL

⁴Division of Cardiology, Miami, FL

Abstract

Background: A clinically based sudden cardiac death (SCD) risk score has been shown to have moderate predictive value. Echocardiographic parameters are also known to predict SCD. Our aim was to evaluate the effect of adding echocardiographic parameters to the clinical SCD risk score on prediction of all-cause mortality.

Methods: We conducted a retrospective cohort of all screening echocardiograms performed on consecutive primary care patients. We calculated the SCD risk score and added the left ventricular (LV) mass index, LV hypertrophy, diastolic dysfunction, and LV ejection fraction (EF). We calculated the c-statistic, net reclassification index and Hosmer Lemeshow chi-square for the SCD score and the combined effect of the score and each echocardiographic parameter in predicting all-cause mortality, as cause-specific mortality information was not available.

Results: We included 6,447 primary care patients who underwent a screening echocardiogram and had a SCD score. The c statistic of the SCD score for mortality was 0.61; 95% CI 0.58–0.62 and the c-statistic for the score combined with LV mass index increased to 0.64; 95% CI 0.63–0.65 and for the score combined with LVEF, the c statistic was 0.64; 95% CI 0.63–0.67. When diastolic dysfunction and LV hypertrophy were added to the SCD score, the c statistic did not significantly change ($p > 0.05$). The NRI for the addition of LV mass index and LVEF was 0.52 $\pm$ 0.02 and the Hosmer Lemeshow statistic was non-significant ($p > 0.05$).

Conclusions: Adding LV mass index or ejection fraction to the SCD risk score improves the ability to predict mortality, but in the primary care setting, the improvement is only mild and underscores the challenge of SCD prediction and prevention in the community.

Introduction

A clinically-based risk prediction score to identify patients at risk of sudden cardiac death (SCD) was developed from the Atherosclerosis Risk in Communities study (ARIC) and validated in the Framingham cohort. The score has a c-statistic of 0.82 and uses commonly collected data points from any clinical encounter. (1) This represents a great initial step to screen the general population but, due to the low overall risk, further risk refinement is needed to make this actionable.

Reduced left ventricular ejection fraction (LVEF) of any cause is the strongest known predictor of SCD. (2) However, there is growing evidence that other echocardiographic measures predict SCD. A individual patient meta-analysis of both the ARIC study and Cardiovascular Health Study (CHS) found that left ventricular mass, mitral annulus calcification and diastolic dysfunction were associated with incident SCD. (3)

The ACC/AHA does not recommend screening echocardiograms in patients without heart disease unless there is a genetic predisposition to cardiomyopathy. (4) However, echocardiograms in asymptomatic consecutive primary care patients have been able to identify new cases of heart failure (HF) and grade 3 diastolic dysfunction leading to changes in management. (5, 6) Therefore, the aim of our study is to evaluate if echocardiographic parameters in primary care patients can improve the ability of the SCD risk score to identify patients at risk of death.

Methods

Study setting

We conducted the study at Chen Senior Medical Centers (CSMC), JenCare Senior Medical Center (JCSMC) and Dedicated Senior Medical Centers (DSMC). These are fully capitated group network practices located across seven states. Patients are insured through Medicare Advantage Plans that serve as fiscal intermediaries for processing claims. As part of a system-wide focus on prevention and wellness, patients are seen every month by their primary care providers and undergo an initial screening echocardiogram upon establishing care.

Study design and study population

We conducted a retrospective cohort study of all the patients who had a screening echocardiogram during the study period. We included all consecutive primary care patients who completed the echocardiogram and had all the elements needed to calculate the SCD risk score. We excluded patients with coronary artery disease, HF, atrial fibrillation or cerebrovascular disease using the corresponding ICD-9 codes to evaluate how the score performs in patients without known heart disease at a population level. The rationale for selecting this population is that this group, despite very low risk, accounts for the highest absolute number of SCD deaths.

Sudden death risk score

The SCD score is race based and includes age, gender, cholesterol, lipid lowering medication use, blood pressure medication use, systolic and diastolic blood pressure, smoking, diabetes and body mass index. The score has a c-statistic of 0.82;95% CI 0.79–0.86. (1)

The algorithm uses the following formulas:

SCD score for Whites $1-0.99538 \exp(\beta-8.19637)$ and SCD score for Blacks $1-0.99135 \exp(\beta-6.08333)$

We used electronic health record data to collect all the elements of the SCD score 3 months before the date of the echocardiogram. We divided the score by deciles and classified patients as high risk if they were part of decile 9 and 10, all others were considered low risk (decile 1–8).(1)

Screening echocardiogram protocol

Screening echocardiograms were performed on all patients who attended a clinic visit between January 1, 2014 and September 9, 2017 (n=21,005). Patients signed informed consent forms and had the echocardiogram performed according to American Society of Echocardiography guidelines (ASE).(7) A single board-certified cardiologist blinded to the patient's history interpreted the echocardiograms at each site. This screening protocol did not include additional maneuvers; hence we could not differentiate between stage 3 and 4 diastolic dysfunction. As a consequence, all patients with grade 4 were classified as grade 3 for the purpose of this analysis.

In the echocardiogram we collected left ventricular hypertrophy, left ventricular mass index, diastolic dysfunction and left ventricular ejection fraction (LVEF). We defined left ventricular hypertrophy as any abnormal left ventricular size measurement (posterior or septal thickness >0.9 cm in women or >1.0 cm in males) and calculated left ventricular mass index adjusted for body surface area.(8) We defined left ventricular mass index as a left ventricular mass >162 g in women or >224 g in males.

We also evaluated for diastolic dysfunction. We used the Doppler mitral flow and tissue velocities tracings (septal and lateral wall) to measure the following diastolic parameters: E-wave velocity, A-wave velocity, E/A, E-wave deceleration time. Diastolic function was classified according to recommendations of ASE on diastolic functional evaluation. The grading scheme was mild or grade I (impaired relaxation pattern), moderate or grade II (pseudonormalized filling), and severe (restrictive pattern) or grade III.(9) LVEF was measured using the modified biplane Simpson's rule as a mean of three cardiac cycles. We defined an abnormal LVEF defined as <50%.

Primary outcome

Our primary outcome was all cause mortality. We ascertained all-cause mortality as self-report from the patient's family during monthly calls conducted to all patients by social workers. We also calculated the Charlson score as a measure of disease burden. This is a

validated method to assess co-morbidity status to adjust mortality. (10) We could not ascertain sudden death within all causes of death since this is an outpatient setting and did not have access to inpatient records.

Statistical analysis

We evaluated the distribution of the continuous variables using measures of central tendency and skewedness. We compared baseline characteristics by SCD risk using chi square and t-test or Wilcoxon rank sum test.

We evaluated both the discrimination and calibration of the score and the addition of echocardiographic parameters to the score. We reported the c-statistic and the net reclassification index (NRI) as measures of discrimination and the Hosmer-Lemeshow statistic as a measure of calibration. We calculated the c-statistic using the method described by Pencian and D'Agostino (11) adjusting for the Charlson score. To compare the additive effects of the echocardiographic parameters we defined high risk if patients belonged to the SCD high score risk and had an abnormal echocardiographic parameter, all others were labelled as low risk. We calculated the area under the curve (AUC) for the SCD score and the AUC for both the score and the echocardiographic parameter and compared the two areas under the curve using the DeLong method. (12) We also calculated the mean predicted probability within each decile of the SCD score and compared the observed and expected event rates by decile using the Hosmer-Lemeshow chi-square test (Appendix figures 1–5). Because of missing data we imputed continuous variables (cholesterol and BMI) using the mean of the variable and for categorical data (race) we used the probability of being white or Black (Appendix table 1 and 2). Because the results were similar we elected to report the unimputed data.

Analyses were performed using STATA version 14 (College Station, Texas), and all significance tests were two-tailed.

Results

Baseline characteristics

We identified 21,005 screening echocardiograms and included 6,447 patients who met our inclusion criteria (figure 1). Table 1 shows the baseline characteristics stratified by risk of SCD; 1,734 were considered high risk for SCD while 4,713 were considered low risk. Those in the highest risk group were older, more likely to be Black males, have a higher Charlson score and have more prevalent cardiovascular risk factors when compared to those in the low risk group ($p<0.01$).

Sudden death risk score prediction and addition of echocardiographic parameters

Four hundred and ninety-nine patients died during the follow-up and the c-statistic of the SCD risk score was 0.61; 95% CI 0.58–0.62.

Table 2 shows the c-statistics, NRI and Hosmer-Lemeshow chi square of the addition of each echocardiographic parameter to the SCD risk score. All echocardiographic parameters when added to the SCD score increased the predictive value of the score, except for LVH.

The addition of LV mass index and LVEF to the SCD risk improved the predictive value of the SCD score and this change was statistically significant ($p<0.01$) while adding diastolic dysfunction was not ($p>0.05$). When all of the measured echocardiographic parameters were added at the same time to the SCD score the c statistic was 0.63; 95% CI 0.62–0.64.

A statistically significant NRI was seen by adding the SCD score and the LV mass index (0.52 ± 0.02) and LVEF (0.52 ± 0.02) ($p<0.01$) while diastolic dysfunction and LV hypertrophy did not have a statistical significant NRI ($p>0.05$). Table 2 shows the reclassification of low and high risk by score and echocardiographic parameter. LV mass index combined with the SCD score reclassified patients to the highest risk category in 22% compared to 16% using LV ejection fraction in the event group while in the non-event group 50% were reclassified to the higher risk group by ejection fraction while 15% were reclassified to the higher group by LV mass index. The Hosmer-Lemeshow statistic was non-significant for all models (Appendix figures 1–5).

Discussion

Our study found that adding echocardiographic parameters to a clinically based SCD risk score improves its ability to predict mortality. The specific echocardiographic parameters that most improved the score were LV mass index and LVEF and this improvement was independent of the Charlson score. The novelty of this finding is that it was found in patients with no known heart disease.

There are several limitations that deserve mention. First, our retrospective design opens the study to information bias. Second, the SCD risk score was developed to predict SCD, but our outcome was all-cause mortality and we most likely included deaths not related to heart disease. Third, we measured mortality using self-report and could have misclassified subjects who were not reached as alive. Fourth, our sample size decreased due to missing data and our results could have been impacted, particularly when calculating the SCD score. However, an imputed analysis showed similar results to the unimputed analysis.

Screening populations for SCD remains a significant challenge. (13, 14) Our study shows that echocardiographic parameters improve the ability of the SCD score to detect patients at risk of dying in patients without known heart disease. However, neither the American College of Cardiology nor the American Heart Association recommend screening echocardiograms for asymptomatic at-risk patients. We have previously shown that screening echocardiograms identify patients with previously unknown asymptomatic heart failure (6) and patients with unknown diastolic heart failure (5). We also showed that identifying patients at higher risk leads to better cardiovascular risk factor control and better outcomes.

There are some studies reporting on echocardiographic measures and how they predict SCD in patients with known heart disease. However, the literature on echocardiographic parameters in patients with no known heart disease is scant. One study by Konety et al reported their results regarding the association between multiple echocardiographic predictors and risk of SCD in a meta-analysis performed from the ARIC (Atherosclerosis

Risk in Communities) and CHS (Cardiovascular Health Study) cohorts. Presence of mitral annular calcification was associated with a two-fold increased risk of SCD, and LV diastolic function (assessed as mitral E/A >1.5 or <0.7) with a one-and-a-half fold increased risk. Increased LV mass and left atrial diameter, were also associated with elevated SCD risk.

There is a growing literature in support of increased LV mass calculated from the echocardiogram as a significant predictor of increased SCD risk. The Oregon Sudden Unexpected Death Study (15) and the Kuopio longitudinal study both found that LV mass was independent of, and equivalent to LVEF <35%. (16)

Two studies have reported the combination of a risk score with echocardiographic parameters. The first, Konety et al. found that all echocardiographic parameters when added to the Framingham risk score improved the predictive value of the score alone. (3). The second, Laukkanen et al. found that LV mass added to a non-validated SCD score did not change the ability of the score to predict SCD among participants of the Kuopio Ischaemic Heart Disease Risk Factor Study. (16)

This study does not advocate doing mass echocardiographic screenings to all patients at risk of heart disease. The main clinical implication of our study is that the SCD score can identify the patients at risk and echocardiogram can further stratify the risk identified by the score. With the echocardiogram rapidly evolving as a hand-held, widely available point-of-care diagnostic tool, the potential enhancement of SCD risk stratification by simultaneous evaluation of multiple risk markers, holds significant promise. This is particularly true for asymptomatic population with no known heart disease, a group that reports the majority of cases of SCD at a population level.

In conclusion, this study provides evidence that in primary care patients with no known heart disease combining the SCD risk score with echocardiographic parameters, particularly LV mass and LVEF is able to identify more patients at risk for SCD. Future studies should evaluate the cost-effectiveness of this strategy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Disclosures: Research reported in this publication was supported by NIMHD and NHGRI of the National Institutes of Health under award number U54MD010722.

References

1. Bogle BM, Ning H, Mehrotra S, Goldberger JJ, Lloyd-Jones DM: Lifetime Risk for Sudden Cardiac Death in the Community. *J.Am.Heart Assoc.* 2016; 5:10.1161/JAHA.115.002398.
2. Chugh SS: Disrupting the Approach to Sudden Cardiac Death: From Vulnerable Ejection Fraction to Vulnerable Patient. *Circulation.* 2018; 137:7–9. [PubMed: 29279335]
3. Konety SH, Koene RJ, Norby FL, Wilsdon T, Alonso A, Siscovick D, Sotoodehnia N, Gottdiener J, Fox ER, Chen LY, Adabag S, Folsom AR: Echocardiographic Predictors of Sudden Cardiac Death:

The Atherosclerosis Risk in Communities Study and Cardiovascular Health Study. *Circ.Cardiovasc.Imaging*. 2016; 9:10.1161/CIRCIMAGING.115.004431.

4. American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, et al.: ACCF/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 Appropriate Use Criteria for Echocardiography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance American College of Chest Physicians. *J.Am.Soc.Echocardiogr*. 2011; 24:229–267. [PubMed: 21338862]
5. Ghany R, Palacio A, Chen G, Dawkins E, Ghany A, Forbes E, Tajiri T, Tamariz L: A screening echocardiogram to identify diastolic dysfunction leads to better outcomes. *Echocardiography*. 2017; 34:1152–1158. [PubMed: 28670777]
6. Ghany R, Tamariz L, Chen G, Ghany A, Forbes E, Tajiri T, Palacio A: Screening echocardiograms in a senior focused value based primary care improves systolic heart failure detection and clinical management. *Cardiovasc.Diagn.Ther*. 2017; 7:236–243. [PubMed: 28567349]
7. Gottdiener JS, Bednarz J, Devereux R, et al.: American Society of Echocardiography recommendations for use of echocardiography in clinical trials. *J.Am.Soc.Echocardiogr*. 2004; 17:1086–1119. [PubMed: 15452478]
8. Ferrara LA, Vaccaro O, Cardoni O, Laurenzi M, Mancini M, Zanchetti A: Indexation criteria of ventricular mass and predictive role of blood pressure and body composition. *Am.J.Hypertens*. 2005; 18:1282–1287. [PubMed: 16202849]
9. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ: Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA*. 2003; 289:194–202. [PubMed: 12517230]
10. Sharabiani MT, Aylin P, Bottle A: Systematic review of comorbidity indices for administrative data. *Med.Care*. 2012; 50:1109–1118. [PubMed: 22929993]
11. Cook NR: Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation*. 2007; 115:928–935. [PubMed: 17309939]
12. DeLong ER, DeLong DM, Clarke-Pearson DL: Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988; 44:837–845. [PubMed: 3203132]
13. Goldberger JJ, Basu A, Boineau R, et al.: Risk stratification for sudden cardiac death: a plan for the future. *Circulation*. 2014; 129:516–526. [PubMed: 24470473]
14. Myerburg RJ, Goldberger JJ: Sudden Cardiac Arrest Risk Assessment: Population Science and the Individual Risk Mandate. *JAMA Cardiol*. 2017.
15. Aro AL, Reinier K, Phan D, Teodorescu C, Uy-Evanado A, Nichols GA, Gunson K, Jui J, Chugh SS: Left-ventricular geometry and risk of sudden cardiac arrest in patients with preserved or moderately reduced left-ventricular ejection fraction. *Europace*. 2017; 19:1146–1152. [PubMed: 27256423]
16. Laukkanen JA, Khan H, Kurl S, Willeit P, Karppi J, Ronkainen K, Di Angelantonio E: Left ventricular mass and the risk of sudden cardiac death: a population-based study. *J.Am.Heart Assoc*. 2014; 3:e001285.

Figure 1:
Flow chart of included patients

Table 1:

Baseline characteristics by SCD risk

Characteristic	Low SCD risk (Decile 1–8)	High SCD risk (Decile 9–10)	p-value
Number	4,713	1,382	
Mean age	66.9+/-9.9	73.2+/-8.5	<0.01
Female gender, %	93	49	<0.01
Black, %	60	76	<0.01
Hypertension	60	80	<0.01
Diabetes	19	55	<0.01
Mean systolic blood pressure	135.2+/-22.9	155.5+/-22.2	<0.01
Mean body mass index	30.3+/-7.2	37.2+/-9.4	<0.01
Mean Charlson score	2.4+/-1.8	3.2+/-1.9	<0.01
Mean HbA1c	6.4+/-1.8	7.0+/-1.7	<0.01

Table 2:

Additive effects of echocardiographic parameters to the SCD score

Parameter	c-statistic (95% CI) p-value	NRI+/-SE p-value	Hosmer-Lemeshow chi square p-value
SCD score alone	0.61 (0.58–0.62)	NA	0.09
SCD score + LV mass index	0.64 (0.62–0.65) <0.01	0.52+/-0.02 <0.01	0.58
SCD score + diastolic dysfunction	0.62 (0.61–0.64) 0.06	0.13+/-0.02 0.10	0.01
SCD score + ejection fraction	0.64 (0.63–0.67) <0.01	0.52+/-0.02 <0.01	0.32
SCD score + LV hypertrophy	0.61(0.59–0.63) 0.61	0.02+/-0.02 0.54	0.32
SCD score + all echocardiographic parameters	0.63 (0.62–0.64) <0.01	NA	0.15

Table 3:

Category dependent NRI by adding echocardiographic parameters to the SCD risk score

Echocardiographic parameter	Group	High SCD risk	Low SCD risk	Risk reclassification high	Risk reclassification low
SCD score	Number in events Number in non-events	122 1612	377 4336	NA	NA
SCD score + LV mass index	Number in events Number in non-events	168 1428	331 4520	113 883	67 1067
SCD score + diastolic dysfunction	Number in events Number in non-events	244 2860	25 595	188 1994	4 52
SCD score + ejection fraction	Number in events Number in non-events	151 1112	341 4798	79 294	49 782
SCD score + LV hypertrophy	Number in events Number in non-events	348 4281	348 4281	238 2812	8 117
SCD score + all parameters	Number in events Number in non-events	253 3140	253 3140	195 2242	0 0