# Cardiac Function and Sudden Cardiac Death in Heart Failure With Preserved Ejection Fraction (from the TOPCAT Trial)

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**Patients with heart failure with preserved ejection fraction (HFpEF) have a significantly elevated risk of sudden cardiac death (SCD). However, few imaging data have been correlated to this risk. We evaluated the value of multiple echocardiographic markers of left ventricular (LV) function to predict SCD in HFpEF patients. The Treatment of Heart Failure with Preserved Ejection Fraction with Aldosterone Trial (TOPCAT)-Americas cohort was used to evaluate the echocardiographic predictors of SCD and/or aborted cardiac arrest (SCD/ACA). A retrospective cohort design was used. Cox proportional hazards and Poisson regression models were used to determine the associations between the risk of SCD/ACA and echocardiographic parameters: diastolic dysfunction grade, left ventricle ejection fraction, and LV global longitudinal strain (GLS) during follow-up. Impaired left ventricle ejection fraction and GLS were associated with SCD/ACA in univariate models ($p = 0.007$ and 0.002, respectively), but not diastolic function grade. After multivariate adjustment, only GLS remained a significant predictor of the incidence rate of SCD/ACA ($p = 0.006$). There was a 58% increase in the hazard of incident SCD/ACA for every 1 unit increase in GLS (1.58, 95% CI: 1.12 to 2.22, $p = 0.009$). These findings remained robust in the competing risk analyses. In conclusion, amongst the multiple echocardiographic parameters of LV function, GLS may help prognosticate the risk of SCD/ACA in HFpEF patients. Published by Elsevier Inc. (Am J Cardiol 2020;129:46−52)**

Heart failure with preserved ejection fraction (HFpEF) carries a significant morbidity and mortality burden.[1] Most deaths in HFpEF patients are due to cardiovascular (CV) causes.[2] A significant number of these deaths in HFpEF are attributed to sudden cardiac death (SCD).[3] Prior data from major randomized controlled trials suggest that ∼40% of CV deaths and 25% to 30% of all deaths in HFpEF patients are attributable to SCD.[4,5] Despite this knowledge, prior attempts to prognosticate the risk of SCD in HFpEF have yielded few powerful biomarkers or prognostication tools.[6] Other data have evaluated the use of echocardiographic parameters of left ventricular (LV) systolic and diastolic dysfunction to prognosticate the composite risk of incident heart failure hospitalization, CV death, or aborted cardiac arrest (ACA) in HFpEF.[7,8] However, there is a dearth of focused data to evaluate how the echocardiographic parameters of LV function specifically predict the risk of SCD in HFpEF. We evaluated the association between key echocardiographic markers of LV systolic/diastolic function and SCD and/or ACA. We hypothesized that impairment in the echocardiographic indices of LV function would have differing relative predictive values for the risk of SCD/ACA in patients with HFpEF. We present an investigation that evaluates these hypotheses in the Treatment of Heart Failure with Preserved Ejection Fraction with Aldosterone (TOPCAT) trial.

## Methods

The TOPCAT study was a multicenter double-blinded placebo-controlled randomized trial that evaluated the utility of spironolactone for preventing adverse clinical outcomes in patients with HFpEF (LV ejection fraction [LVEF] ≥45 %).[9−11]

The patients in this analyses were limited to patients that were enrolled from the United States of America,

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See page 51 for disclosure information.

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Canada, Argentina, and Brazil ("TOPCAT-Americas") due to prior concerns regarding the validation of the HFpEF diagnosis[12] and treatment adherence[13] for patients outside of these regions.

The study protocol was approved by the University of Alabama Institutional Review Board and National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center (NHLBI-BioLINCC) and does not necessarily reflect the opinions or views of TOPCAT or the NHLBI. No specific informed consent was needed for this current investigation. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

The demographic and clinical data used in this investigation were obtained at the time of the subject's enrollment into TOPCAT.[9] The demographic and clinical data were presented for the overall Americas-cohort. The echocardiographic parameters except baseline LVEF used in this investigation were derived in a subset of patients at the time of enrollment for a preplanned TOPCAT echocardiographic substudy. The design, methods, and the baseline findings of this substudy have been published previously.[7] The details of strain imaging are given in S1 Supplementary Appendix and have been published previously.[8] The echocardiographic parameters collected for this analysis are listed in Table 1. Diastolic dysfunction was reported in 4 grades from 0 to 3, with an increasing number suggestive of increasing severity of diastolic dysfunction.[14] Global longitudinal strain (GLS) is a negative value and more negative strain implies better myocardial function. For ease of interpretation, GLS is described as an absolute value and a pre-specified threshold of <15.8% was used to define abnormal left ventricle peak GLS.[8,15] None of the authors were involved in the echocardiographic measurements or data acquisition.

The outcome for this investigation was incident SCD/ACA. SCD was defined as an unexpected death in an otherwise stable patient and was classified as either witnessed (if death was observed or if last seen within 24 hours) or presumed (if last seen ≥24 hours with the clinical context suggestive of SCD).[16] ACA, a prespecified component of the primary composite endpoint for the overall TOPCAT trial, was defined as successful resuscitation after cardiac arrest (with or without antecedent myocardial infarction or heart failure) with meaningful recovery. This definition is consistent with prior TOPCAT data.[5] All clinical outcomes in TOPCAT were adjudicated by a blinded clinical events committee. The adjudication process has been described previously.[9,10]

Continuous variables were represented as medians with interquartile range and categorical variables were represented as counts with proportions. Using Poisson regression models associations between diastolic dysfunction grade, GLS and LVEF and incident SCD/ACA were explored in adjusted and unadjusted models. Nonlinearity was also accounted for where needed using restricted cubic splines. We then used Cox proportional hazard models to evaluate the association between measures of diastolic and systolic dysfunction and SCD/ACA. To further test these hypotheses, we evaluated the independent prognostic value of diastolic dysfunction grade, LVEF and GLS in a multivariable Cox model consisting of the following covariates: age,

Table 1
Baseline characteristics in TOPCAT Americas

| Baseline characteristic | TOPCAT Americas (n = 1767) |
|---|---|
| Age at randomization (years) | 72 (64, 79) |
| Female | 882 (49.9%) |
| Black race | 302 (17.1%) |
| Enrollment strata: Previous Hospitalization | 975 (55.2%) |
| Height (m) | 1.7 (1.6, 1.8) |
| Weight | 90.7 (76, 108.9) |
| Body mass index (kg/m$^2$) | 32.9 (27.9, 38.4) |
| Hypertension | 1,588 (90) |
| Systolic blood pressure (mm Hg) | 129 (118, 138) |
| Diastolic blood pressure (mm Hg) | 70 (62, 80) |
| Diabetes mellitus | 788 (44.6%) |
| Dyslipidemia | 1,250 (70.8%) |
| Obesity | 1,144 (64.7%) |
| Smoking (current) | 117 (6.6%) |
| Stroke | 158 (9%) |
| Atrial fibrillation | 743 (42.1%) |
| Chronic obstructive pulmonary disease | 291 (16.5%) |
| Coronary artery disease | 815 (46.1%) |
| Angina pectoris | 486 (27.5%) |
| Prior MI | 359 (20.3%) |
| Prior CABG | 336 (19%) |
| Prior PCI | 344 (19.5%) |
| Peripheral arterial disease | 207 (11.7%) |
| Treatment with spironolactone | 886 (49.9%) |
| Echocardiographic Parameters | |
| E/E' ratio, average | |
| E/e' ratio, lateral | 11.1 (8.2, 15.3) |
| E/e' ratio, medial | 15.3 (11.2, 19.9) |
| Global longitudinal strain, % | −15.6 (−18.2, −13.2) |
| Left atrial volume | 58.3 (45, 75.3) |
| Left ventricular ejection fraction | 58 (53, 64) |
| Left ventricular end diastolic volume | 89.5 (73, 114) |
| Left ventricular end systolic volume | 35 (26.2, 46.7) |
| Mitral inflow (E/A) ratio | 1.1 (0.9, 1.6) |
| Tricuspid regurgitant velocity, m/s | 2.7 (2.5, 3.1) |
| Hematocrit (%) | 38.5 (35.3, 41.8) |
| Estimated GFR (ml/min/1.73m$^2$) | 61.2 (49, 76.6) |
| Serum albumin (g/dl) | 3.9 (3.6, 4.2) |
| Serum creatinine (mg/dl) | 1.1 (0.9, 1.4) |
| Diuretic | 1,573 (89.1%) |
| Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker | 1,395 (79%) |
| $\beta$ blocker | 1,387 (78.6%) |
| Calcium channel blocker | 682 (38.6%) |
| Aspirin | 1,027 (58.2%) |
| Statin | 1,148 (65%) |
| Long-acting nitrate | 305 (17.3%) |
| Warfarin | 592 (33.5%) |

BMI = body mass index; CABG = coronary artery bypass grafting; g/dl = grams per deciliter; GFR = glomerular filtration rate; mEq = milliequivalents per liter; mg/dl = milligrams per deciliter; MI = myocardial infarction; ml/min = milliliters per minute; mm Hg = per millimeters of mercury; mmol/L = millimoles per liter; PCI = percutaneous coronary intervention; $\mu$l = microliter.

GFR was estimated by the Modification of Diet in Renal Disease (MDRD) 4-component study equation. Coronary artery disease was defined as a composite of angina pectoris, previous MI, PCI, or CABG. Data are represented as median (25th to 75th percentile), number (percentage).

Dyslipidemia was self-reported.

Obesity was defined as BMI ≥30 kg/m$^2$.

gender, race, presence of atrial fibrillation at baseline, New York Heart Association class, randomization strata, randomized treatment assignment, history of stroke, heart rate, baseline hematocrit, and creatinine. We first evaluated the univariate associations of echocardiographic parameters and incident SCD/ACA. We also performed competing risk analyses with aforementioned covaraites where all nonsudden deaths that were considered competing events. All statistical analyses were conducted in Stata version 14.2 (StataCorp, College Station, TX).

## Results

Within the overall TOPCAT cohort of 3,445 patients, 1,767 patients were in the TOPCAT-Americas cohort (Figure 1). All the TOPCAT-Americas patients had site reported LVEF available at baseline (Table 1 and Figure 1). The baseline characteristics of the overall cohort are outlined in Table 1. The median age at the time of randomization was 72 years (64, 79 years). There were almost equal proportions of males and females enrolled and 17.1% of patients self-identified as being of the black race. A high proportion of patients had hypertension and obesity. The prevalence of diabetes mellitus, atrial fibrillation, and history of coronary artery disease were also moderately high in the overall cohort. Approximately 90% of the cohort was on diuretic therapy at baseline and 80% of the cohort were on angiotensin-converting enzyme therapy and beta-blockade (Table 1).

The median GLS in the overall cohort was −15.6% (−18.2, −13.2%). The median LVEF was 58% (53, 64%) (Table 1). The median mitral inflow (E/A) ratio was 1.1 (0.9, 1.6). Most subjects had normal renal function with a median estimated GFR of 61.2 ml/min/1.73m$^2$ (49.0, 76.6 ml/min/1.73m$^2$) and a median creatinine of 1.1 mg/dl (0.9, 1.6 mg/dl).

A total of 77 SCD/ACA occurred events over a median follow-up of 2.9 years at an incident rate of 1.47 per-100-person-years in the TOPCAT-Americas cohort. Of these, 376 had diastolic dysfunction grade assessment and 340 patients had GLS data available from the echocardiography substudy. Among the patients where LVEF, GLS, and diastolic function (n = 225) were all available, 14 SCD/ACA events occurred over a median follow-up of 2.9 years at an incidence rate of SCD/ACA was 1.47 per-100-person-years.

In the univariate analyses, both LVEF and GLS significantly predicted the incidence rate of SCD/ACA (p = 0.007 and 0.002, respectively; Table 2 and Figure 2). The inflection points for the incidence rate of SCD/ACA occurred at approximately 58% for LVEF and −15% for GLS. The incident rate of SCD/ACA among those with abnormal GLS (greater than −15.8%) was ~6 times higher compared with those with normal GLS (less than −15.8%); 2.4% vs. 0.4% (p=0.020). In the univariate analyses, diastolic dysfunction grade, E/e' septal, E/E' lateral, left atrial volume, and tricuspid regurgitant velocity were not associated with the incidence rate of SCD/ACA. The association between incident SCD/ACA and LV end-diastolic volume (HR: 1.01, 95%CI: 1.00 to 1.02, p = 0.158) and LV end-systolic volume (HR: 1.01, 95%CI: 1.00 to 1.03, p = 0.165) trended towards significance (Table 2).

In the fully adjusted nonlinear model, the trend for LVEF reached borderline significance (p = 0.054) (Figure 2, panel B), whereas GLS remained a significant predictor of the incidence rate of SCD/ACA (p = 0.006; Figure 3 panel D). Once again, diastolic dysfunction grade was not a significant predictor of the incidence rate of SCD/ACA (p = 0.933).

We then evaluated the relative value of the echocardiographic parameters of the LV function to predict the hazard of incident SCD/ACA in HFpEF in the Cox and competing risk models (Table 3). We found that the hazard of SCD/ACA increased by 58% to 60% ([$HR_{Cox}$: 1.58, 95%CI: 1.12 to 2.22], sub distributional [$HR_{competing\ risk}$: 1.60, 95%CI: 1.03 to 2.49]) for every 1 unit increase in GLS. The trend was significant in both the fully adjusted and the competing risk models ($p_{cox}$ = 0.009 and $p_{competing\ risk}$=0.036). Changes in diastolic dysfunction and LVEF were not predictive of the hazard of incident SCD/ACA in the fully adjusted Cox and the competing risk models (Table 3).

## Discussion

In summary, we assessed the relative value of multiple echocardiographic indices of cardiac function in predicting SCD/ACA in patients with HFpEF. We found that GLS

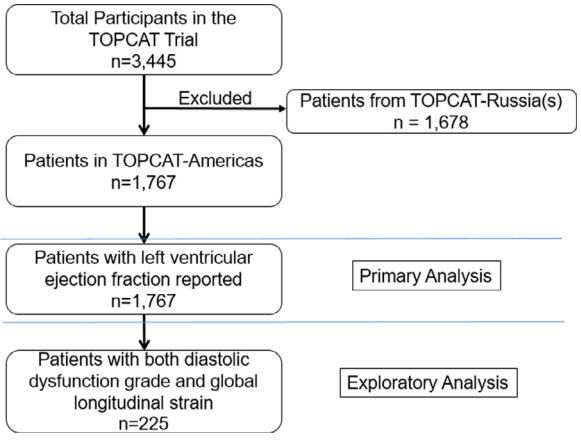


Figure 1. Study flow diagram for patient inclusion in the TOPCAT Americas cohort.

Table 2
Univariate association of echocardiographic parameters with sudden cardiac death in TOPCAT-Americas

| Echocardiographic parameter (for every 1-unit increase) | Unadjusted hazard ratio (95%confidence interval) |
|---|---|
| Diastolic dysfunction grade | 1.06 (0.66−1.69) |
| E/e' septal | 1.04 (0.97−1.11) |
| E/e' lateral | 1.01 (0.93−1.09) |
| Global longitudinal strain* | 1.29 (1.10−1.50) |
| Left atrial volume | 1.00 (0.99−1.02) |
| Left ventricular ejection fraction* | 0.96 (0.93−0.99) |
| Left ventricular end-diastolic volume | 1.01 (1.00−1.02) |
| Left ventricular end-systolic volume | 1.01 (1.00−1.03) |
| Tricuspid regurgitant velocity | 1.00 (0.99−1.01) |

Diastolic dysfunction reported in 4 grades from 0 to 3, with an increasing number suggestive of increasing severity of diastolic dysfunction.
* p <0.05.

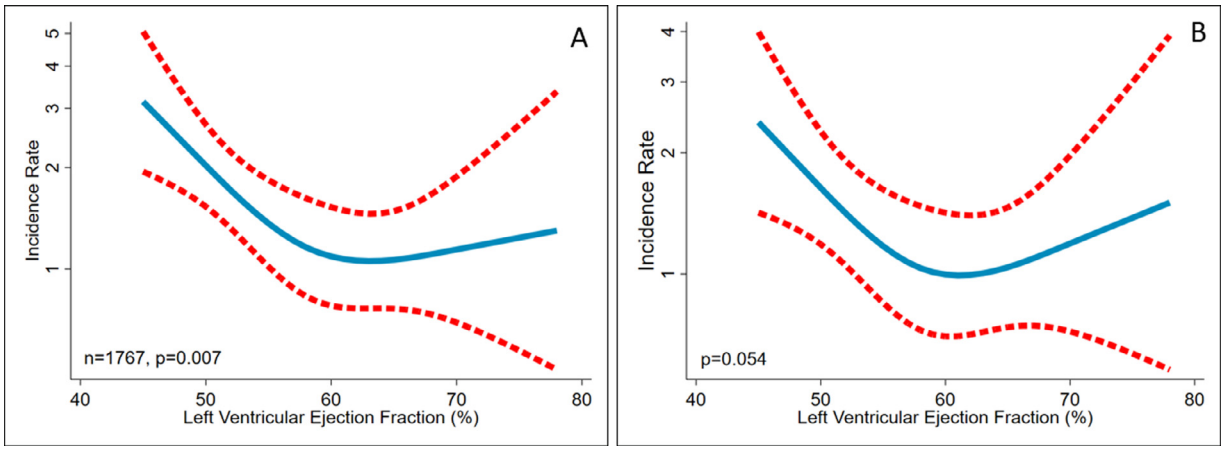


Figure 2. Relationship of the incidence rate of sudden cardiac death with left ventricular ejection fraction in unadjusted (Panel A) and adjusted (Panel B) analyses. The adjusted model includes age, gender, race, randomization strata, atrial fibrillation, heart rate, treatment with spironolactone, New York Heart Association class, stroke, serum creatinine (mg/dl), and hematocrit in the TOPCAT Americas. Restricted Cubic spline Poisson regression models(3 knots) with incidence rate (solid blue) with 95% confidence intervals (dashed red). (Color version of figure is available online.)

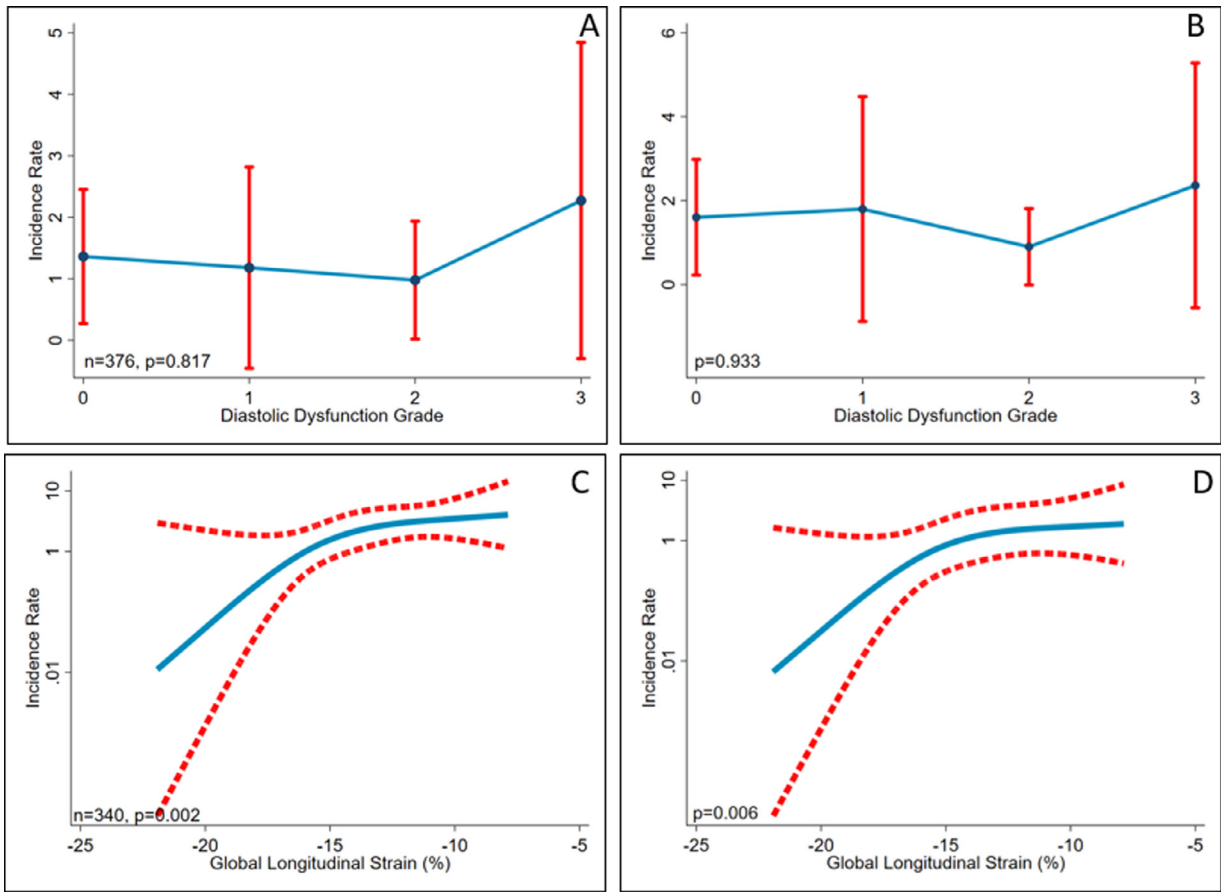


Figure 3. Relationship of the incidence rate of sudden cardiac death with diastolic dysfunction grade and global longitudinal strain in unadjusted (Panel A and C) and adjusted (Panel B and D) analyses. The adjusted model includes age, gender, race, randomization strata, atrial fibrillation, heart rate, treatment with spironolactone, New York Heart Association class, stroke, serum creatinine (mg/dl), and hematocrit in the TOPCAT Americas. Poisson regression models (restricted cubic spline with 3 knots for GLS) with incidence rate (solid blue) with 95% confidence intervals (dashed red). (Color version of figure is available online.)

was independently predictive of incident SCD/ACA in these patients in aggregate with other demographic,clinical, and echocardiographic parameters, such as diastolic dysfunction and LVEF. Our findings remained valid in extensively adjusted proportional hazard modeling and in competing risk analyses.

Prior findings regarding the myocardial and clinical substrate of patients with HFpEF may offer mechanistic

Table 3
Multivariable adjusted association of left ventricular ejection fraction and global longitudinal strain with sudden cardiac death in the TOPCAT-Americas

| For every 1 grade worsening in DD grade hazard ratio (95%CI) | p value | For every 1% increase in LVEF hazard ratio (95%CI) | p value | For every 1 % increase in GLS hazard ratio (95%CI) | p value |
|---|---|---|---|---|---|
| Fully Adjusted Model | | | | | |
| 0.53 (0.19−1.46) | 0.219 | 1.01 (0.91−1.11) | 0.901 | 1.58 (1.12−2.22) | 0.009 |
| Fully Adjusted Competing Risk Regression Model | | | | | |
| 0.60 (0.27−1.33) | 0.210 | 1.00 (0.93−1.06) | 0.886 | 1.60 (1.03−2.49) | 0.036 |

CI = confidence interval; DD = diastolic dysfunction; GLS = global longitudinal strain; LVEF = left ventricular ejection fraction.

Fully adjusted model included age, gender and race, atrial fibrillation, creatinine, heart rate, hematocrit, NYHA class, randomization strata, randomized treatment assignment, stroke at baseline, diastolic dysfunction grade, LVEF and GLS.

explanations for our findings. Cho et al previously described the occurrence of delayed repolarization as a key feature of incident arrhythmic SCD in HFpEF.[17] In their HFpEF murine model, they described that a prolonged QT interval and potassium current downregulation may contribute to this delayed repolarization, thus leading to ventricular arrhythmias and SCD. Skampardoni et al later linked repolarization abnormalities to abnormal GLS in 178 patients on hemodialysis with a mean LVEF of 62 ± 13%.[18] They demonstrated that abnormal GLS and repolarization abnormalities were strongly linked and that subjects with abnormal repolarization and GLS had a higher incidence of cardiac mortality. Thus, abnormal GLS may correlate with abnormal repolarization, arrhythmogenesis, and increased SCD/ACA in the HFpEF population.

Abnormal GLS may also indicate a greater cardiac fibrosis burden in HFpEF patients. A greater burden of cardiac fibrosis has been associated with increased cardiac mortality in HFpEF patients.[19] This fibrosis burden may itself develop due to the greater prevalence of cardiac comorbidities such as coronary artery disease and hypertension in patients with HFpEF. This was seen in our investigation with a high prevalence of hypertension and a moderately high prevalence of coronary artery disease. These fibrotic areas may be associated with abnormal myocyte repolarization,[20] greater diastolic dysfunction,[21] and impaired GLS.[22] These fibrotic areas may ultimately serve as important substrates for arrhythmogenesis. We speculate that the echocardiographic markers of impaired diastolic dysfunction, LVEF, and GLS may be markers of these abnormalities in repolarization and cardiac fibrosis burden.

Our data also offer important comparisons to the existing literature on SCD and, separately, SCD in HFpEF. Multiple prior investigations have highlighted that SCD is an important cause of death amongst patients with HFpEF.[2,3,5] Our echocardiographic data provide a mechanistic explanation for the basis of these findings. Prior data has also focused on the prognostic utility of GLS in HFpEF. Stampehl et al found that impaired GLS was a univariate predictor of lower event-free survival in a population of patients with HFpEF.[23] Pellicori et al also used GLS to predict CV death or heart failure hospitalization in a small cohort of HFpEF patients with weak predictive value.[24] However, both Stampehl et al and Pellicori et al found that GLS had greater predictive value than LVEF in predicting hospitalization and CV death. A post-hoc analysis of TOPCAT by Shah et al also found that GLS <15.8% predicted CV death, heart failure hospitalization, and ACA.[8] We also suggest that impaired GLS is also a predictor for incident SCD/ACA in HFpEF. We build upon the aforementioned findings by demonstrating the relative predictive value of multiple metrics of LV function in predicting incident SCD/ACA. We also quantify the hazard of SCD/ACA according to the degree of change in GLS and LVEF. Finally, our supposition that a greater burden of cardiac fibrosis may be a key effect measure modifier in the causal pathway of SCD/ACA in HFpEF patients is also supported by other imaging literature. Data derived from cardiac magnetic resonance imaging correlated a greater degree of cardiac fibrosis in HFpEF patients to disease severity and clinical outcomes.[19,25] Thus, our data support these findings by delineating the relative utility of the echocardiographic predictors of cardiac fibrosis and SCD in patients with HFpEF.

Our work has important implications. Prior investigations have attempted to predict the risk of SCD in HFpEF using clinical variables.[6] Our findings suggest that the inclusion of echocardiographic markers, such as GLS, may improve existing risk prediction indices for SCD prognostiation in HFpEF. To the best of our knowledge, no study has specifically evaluated the utility of GLS in predicting incident SCD/ACA in HFpEF. Our data and other's[25] support aggressive control CV risk factors in patients at high risk for HFpEF and those diagnosed with HFpEF to limit cardiac fibrosis. The potential benefits of spironolactone in TOPCAT-Americas also support the development of antifibrotic therapies in CV disease.[12] Where possible, cardiac magnetic resonance imaging may also offer additional utility by quantifying myocardial fibrosis in HFpEF patients.[21,25] Finally, our findings again raise the question of the optimal strategy for prophylaxis against SCD amongst HFpEF patients. Our findings also lend credence to these efforts given that the incidence of SCD in HFpEF in some series[26] is comparable to the rate of SCD in the placebo arms of trials examining the utility of implantable cardioverter-defibrillator usage in HFrEF.[27−29]

We acknowledge that our investigation also has important limitations. Our investigation was limited to events in the TOPCAT-Americas due to prior concerns about the data validity for the Russia and Georgia cohort in the TOPCAT trial.[12] However, our findings remained valid in the proportional hazards and competing risk analyses, suggesting robustness. In our investigation, we assume that all SCD/ACA is arrhythmic. There is acknowledged heterogeneity in the definition of SCD in the HFpEF literature. SCD in HFpEF may be due to a multitude of other causes, such as myocardial infarction, ventricular failure, or a competing

non-CV cause.[2,4,5] In assuming that all SCD/ACA is arrhythmic, we acknowledge that there is limited data to identify the type of rhythm at the time of the event. We also note that there was a low incidence of SCD events and a low number of absolute events in the overall cohort. Therefore, this investigation should be considered hypothesis-generating. However, the TOPCAT trial remains, to the best of our knowledge, the largest cohort of HFpEF patients who experienced SCD/ACA. Additionally, all outcomes were rigorously adjudicated in the TOPCAT trial.

In conclusion, SCD is an important cause of mortality in HFpEF. Amongst multiple echocardiographic parameters evaluated in TOPCAT, GLS maybe the most useful to prognosticate the risk of SCD/ACA in HFpEF.

## Author contributions

All authors made substantial contributions to the conception or design of the work and/or acquisition, analysis, or interpretation of data for the work; drafted the work and/or revised it critically for important intellectual content and gave final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## Disclosures

None of the authors had any conflicts of interest or financial disclosures to declare.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.04.038.

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