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Sudden Death Following Hospitalization for Heart Failure with Reduced Ejection Fraction (From the EVEREST Trial)

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Abstract

Patients with chronic heart failure with reduced ejection fraction (HFrEF) benefit from medical and device therapies targeting sudden cardiac death (SCD). Contemporary estimates of SCD risk after hospitalization for HF are limited. We describe the incidence, timing, and clinical predictors of SCD following hospitalization for HFrEF (≤40%) in the EVEREST trial. Multiple logistic regression analyses tested >30 baseline covariates (including treatment randomization, demographics, comorbid conditions, natriuretic peptides, EF, medical and device therapies) to identify predictors of 1-year SCD. Of the 4,024 (97%) trial patients discharged alive, there were 268 (7%) SCD and 703 (17%) non-SCD deaths during median 9.9 months follow-up. Implantable cardioverter-defibrillator use at baseline was 14.5%. Estimates of SCD at 1-, 3-, 6-, and 12-months were 0.8%, 2.3%, 4.1%, and 7.4%, respectively. Most patients were readmitted prior to SCD (n=147, 55%). Male sex, black race, diabetes mellitus, and angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use were potential predictors of 1-year SCD following hospitalization for HFrEF (all P<0.10), however this final model demonstrated poor discrimination (C-statistic 0.57). In conclusion, in EVEREST, patients hospitalized for HFrEF faced risks of 1-year post-discharge SCD of 7%, which accrued gradually over time, and were balanced with high competing risks of non-sudden death (17%). Traditional clinical characteristics fail to adequately predict SCD risk. Further data are needed to identify patients at greatest relative risk for SCD (compared with non-SCD) after hospitalization for HFrEF.

Keywords

acute heart failure trial; hospitalization; risk prediction; sudden cardiac death

Sudden cardiac death (SCD) due to ventricular arrhythmia represents an important mode of death in patients with chronic heart failure with reduced ejection fraction (HFrEF) (1). The overall rates of SCD have substantially decreased over the past 2 decades, related in part to effective implementation of medical and device therapies (2). Despite these advances, contemporary data suggest that nearly 40% of deaths among those with symptomatic chronic HFrEF are attributable to SCD (1). Hospitalization for heart failure (HF) serves as a marker of disease progression and may shift the relative distribution of cause-specific deaths (with greater proportion of worsening HF-related deaths) (3,4). After periods of worsening HF, identification of patients at highest relative risk of SCD and timing of application of SCD preventative strategies have proved challenging (5). Contemporary estimates of SCD risk after hospitalization for HF and in patients with more advanced HF are limited. Accordingly, we aimed to describe the incidence, timing, and clinical predictors of SCD following hospitalization for HFrEF in the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) trial.

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METHODS

The study design and primary results of EVEREST have been previously described (3). Briefly, EVEREST was a multicenter, global, randomized, double-blind, placebo-controlled trial of oral tolvaptan (vasopressin V_2 receptor antagonist) in patients hospitalized for worsening chronic HFrEF (≤40%), New York Heart Association (NYHA) III and IV symptoms, and ≥2 signs of HF at time of randomization. Relevant exclusion criteria included comorbidities with life expectancy <6 months, end-stage HF, significant valvular disease, acute myocardial infarction (MI), serum potassium >5.5 mEq/dL, serum creatinine >3.5 mg/dL, and those requiring hemodialysis or ultrafiltration. Cause-specific events were independently adjudicated by a blinded clinical events committee. SCD was defined as an unexpected death in a previously stable patient with recent human contact. If the patient was out of contact for 24 hours to 1 week, the event was considered a presumed SCD (4). In our analysis, non-SCD encompassed all deaths not classified as SCD.

All patients discharged alive in either treatment arm of EVEREST were included. Continuous variables are expressed as mean ± standard deviation if normally distributed and median (25^{th} – 75^{th} percentiles) if not normally distributed. χ^2 tests and Kruskal-Wallis tests were used to compare categorical and continuous variables, respectively. Incidence rates of SCD at 1-, 3-, 6-, and 12-months post-discharge were estimated using the Kaplan-Meier method and by cumulative incidence function (accounting for non-SCD competing risks). Time from last known medical contact to SCD was also calculated. To identify independent predictors SCD after HF hospitalization, multiple logistic regression analyses tested >30 discharge covariates (to correspond to roughly 1 covariate per 10 events) using stepwise backward selection. The covariate set was consistent with prior EVEREST analyses (6–9) and included treatment randomization, demographic characteristics, medical history (prior HF hospitalization, atrial fibrillation, coronary artery disease, prior MI, diabetes mellitus, ischemic HF etiology, hypertension, chronic obstructive pulmonary disease, chronic kidney disease, NYHA class IV), vital signs and anthropomorphic measures, laboratory and diagnostic testing (QRS duration, ejection fraction [EF], serum sodium, serum potassium, estimated glomerular filtration rate, blood urea nitrogen [BUN], natriuretic peptides), and discharge therapies (including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEi/ARB), β-blockers, mineralocorticoid receptor antagonists, amiodarone, digoxin, and implantable cardioverter defibrillators [ICD]). Model discrimination (ability to discriminate patients who did or did not experience SCD) was assessed using C-statistics and model calibration (agreement between observed and expected SCD events) was tested using the Hosmer-Lemeshow (H–L) goodness-of-fit test (10). All statistical analyses were performed with SAS v9.3 (SAS Institute, Cary, NC).

RESULTS

Of the 4,133 patients enrolled in EVEREST, 109 died in hospital (12 SCD, 97 non-SCD) and were excluded. The remaining 4,024 (97%) were discharged alive and were included in final analysis. Table 1 describes the discharge clinical profiles of patients who experienced SCD (n=268, 7%), non-SCD (n=703, 17%), or remained alive (3,053, 76%) during median follow-up of 9.9 months (5.3 to 16.1 months). Baseline ICD use overall was 14.5%; patients

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who experienced SCD had lower rates of baseline ICD use compared with patients who died of non-SCD (13% vs. 23%; P=0.001). Of the 583 patients with ICDs, 6% died of SCD and 27% died of non-SCD death. Of the 3,439 patients without an ICD, 7% died of SCD and 16% died of non-SCD death. Compared with patients who experienced non-SCD, patients with SCD tended to be younger, male, with higher body mass indexes, enrolled from Eastern Europe, carry lower rates of diabetes mellitus and chronic kidney disease, and have fewer physical exam findings of HF (P<0.05 for all comparisons; Table 1). Ischemic HF etiology (67% vs. 68%), prior MI (53% vs. 54%), and mean left ventricular EF (25.1±7.7% vs. 25.4±8.2%) did not significantly vary in patients who died of SCD or non-SCD, respectively (P≥0.60 for all comparisons).

Kaplan-Meier estimates of SCD at 1-, 3-, 6-, and 12-months were 0.8%, 2.3%, 4.1%, and 7.4%, respectively; estimates using cumulative incidence function yielded similar rates (Figure 1). Kaplan-Meier estimates of 1-year non-SCD was 17%. After 1 year, there were 41 SCD events, the last occurring 26 months post-discharge.

Over half of patients who ultimately experienced SCD were readmitted prior to SCD (n=147, 55%). The majority of rehospitalizations were for HF (n=83, 56% of rehospitalizations), and 42 died during readmission of SCD. Two other patients died on the same day as a planned or unplanned outpatient visit. Of the 224 SCDs that occurred outside a healthcare facility, 172 died suddenly a mean 17 days after scheduled/unscheduled visits, and 52 died suddenly 20 days (exponentiated mean given right skew) after discharge.

The final multiple logistic regression model identified 4 potential predictors of SCD at 1-year post-HF hospitalization: male sex (adjusted odds ratio [aOR]: 1.56, 95% confidence interval [CI]: 1.11–2.21; P= 0.01), black race (aOR: 1.51, 95% CI: 0.96–2.37; P=0.07), discharge prescription of ACEi/ARB (aOR: 1.45, 95% CI 0.95–2.21, P=0.08), and diabetes mellitus (aOR: 1.26, 95% CI: 0.96–1.65; P=0.09). This final prediction model demonstrated acceptable fit (H–L statistic P=0.27), but poor discrimination (C-statistic 0.57).

DISCUSSION

We report the incidence, timing, and clinical predictors of SCD following hospitalization in patients with chronic HFrEF and NYHA class III–IV functional class. Our analysis highlights several key findings: 1) 1-year risk of post-discharge SCD (~7%) is approximately double the annualized rate of SCD observed in trials of chronic HFrEF (1,2); 2) patients with advanced HFrEF experience high competing risks of non-SCD (~17% at 1 year); 3) more than 50% of patients are readmitted prior to ultimately experiencing SCD and many die during this readmission or within a month of last medical contact; 4) baseline utilization of ICD therapy was low in this global HFrEF clinical trial; and 5) traditional clinical characteristics fail to adequately predict SCD risk following hospitalization for HFrEF. Overall, our findings highlight the unmet need to critically evaluate risk of SCD after hospitalization for advanced HFrEF.

Few studies have evaluated risks of SCD in patients hospitalized for HF. It is noteworthy that the EVEREST population was an exceptionally sick cohort with NYHA III–IV symptoms,

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which in part accounts for the high competing risks of non-SCD. However, even in recent trials of patients hospitalized for HF with broader inclusion and with both preserved and reduced EF, trajectory of post-discharge SCD risk was similar: rates of SCD within 1 month <1% (11) and ~2–4% within 6 months (12). Compared with these prior trial-based analyses, EVEREST enrolled only patients with worsening chronic HFrEF patients, captured more than twice the number of SCD events (n=268), and adjudicated events beyond the immediate post-discharge window (median 9.9 months). Prolonged follow-up in EVEREST revealed that SCD risk accumulated gradually, without an initial period of heightened risk after discharge.

Our analysis highlights inherent challenges in identifying at-risk patients for SCD in clinical practice and adjudicating SCD in trials of advanced HF. Most contemporary clinical definitions of SCD require a period of clinical stability prior to unexpected SCD (13). However, over half of the EVEREST population that experienced SCD were readmitted prior to SCD (commonly for HF), many dying during this readmission. Indeed, most patients were evaluated in a healthcare context within a month of SCD. Taken together, these data suggest that patients who ultimately died suddenly were clinically tenuous prior to their death, which may present challenges for distinguishing specific modes of death. Adjudication is subject to some degree of subjectivity related to the relative perceived contribution of progressive, worsening HF to the patient's death. Populations such as those enrolled in EVEREST with more advanced HF may be less likely to have their death declared as sudden and unexpected. Furthermore, adjunctive rhythm information is rarely available to corroborate final adjudication. Indeed, certain events may not be related to ventricular tachyarrhythmias including major systemic events (massive pulmonary embolism, acute aortic syndrome, etc.) or non-shockable rhythms (asystole or pulseless electrical activity) in the early post-discharge time-frame (14). As such, SCD identified in trials of advanced HF may reflect available clinical information (or lack thereof) rather than a specific, targetable pathophysiological process. Classification of arrhythmic SCD remains an important issue to address in upcoming HF trials, regardless of EF (13).

The benefits of ICD therapy are well-established in many settings in HFrEF. However, our study brings attention to the low rates of use of ICDs at baseline (<15%) in this global trial of patients with worsening chronic HF. Although this may partially be related to the high proportion of patients with advanced HF, ICD therapy utilization was especially low in certain geographic regions (namely, Eastern Europe), which correspondingly have higher relative rates of SCD (15), and this low utilization was similar even in trials of chronic HFrEF (1). As such, appropriate application of ICD therapy continues to require attention.

Our data support current guidelines that note uncertainty regarding the appropriateness of *de novo* implantation of ICDs in patients with advanced HF, in whom an ICD may prolong a period of frequent hospitalizations and poor health-related quality of life (16,17). It is plausible that select patients with advanced HF may derive benefit from SCD preventative efforts, while avoiding unnecessary and costly therapy in those who may succumb to competing risks of death. Unfortunately, our models poorly discriminated patients who do or do not experience SCD. Certain parameters such as ischemic HF etiology or left ventricular EF did not differ by cause-specific deaths, which contrasts with studies of chronic HF (18).

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Although natriuretic peptides were elevated in patients who died, these biomarkers did not differ by cause-specific death and may be more specific for non-sudden modes of death (such as worsening HF). Cardiac biomarkers on injury (not collected in our study) may have potential in SCD risk prediction. The limited predictive ability of traditional risk factors may be related to the modest number of SCD events and selection of high-risk patients with advanced HF in EVEREST.

Future efforts are essential to deeply phenotype the group at specific risk for SCD and low competing risks of non-sudden death. Robust and well-calibrated models (19) are required in patients with advanced HFrEF, perhaps incorporating clinical factors such as frequency and recentness of hospitalizations. There is an enduring need to investigate risk-based ICD implantation strategies, beyond reliance on left ventricular EF alone, including leveraging adjunctive imaging and biomarker data (20,21). At present, given limitations of current risk prediction tools and highly dynamic patient trajectories in advanced HF, treatment decisions regarding ICDs should be individualized and aligned with patient and caregiver preferences.

This *post hoc* analysis is subject to several limitations. Despite multivariable modeling, unmeasured confounders likely remain present. We did not have access to adjudication forms, including availability of autopsies or presence and burden of ICD shocks. Our models did not account for time-varying covariates, such as changes in medications or readmissions in follow-up. The modest number of captured SCD events limited the robustness of our prediction models.

Patients hospitalized for worsening chronic HFrEF and NYHA class III–IV functional class face substantial risks of SCD and competing risks of non-sudden deaths at 1 year. SCD rates accrue gradually and there does not appear to be an immediate period of heightened post-discharge vulnerability. Our data support current guidelines regarding the cautious use of ICDs in patients with advanced HF and recurrent hospitalizations. This analysis also brings attention to low use of ICDs (<15%) and challenges with adjudication of SCD even in the context of carefully-conducted global clinical trials. Further data are needed to identify patients at greatest relative risk for SCD (compared with non-SCD) after hospitalization for HFrEF to better target SCD prevention strategies.

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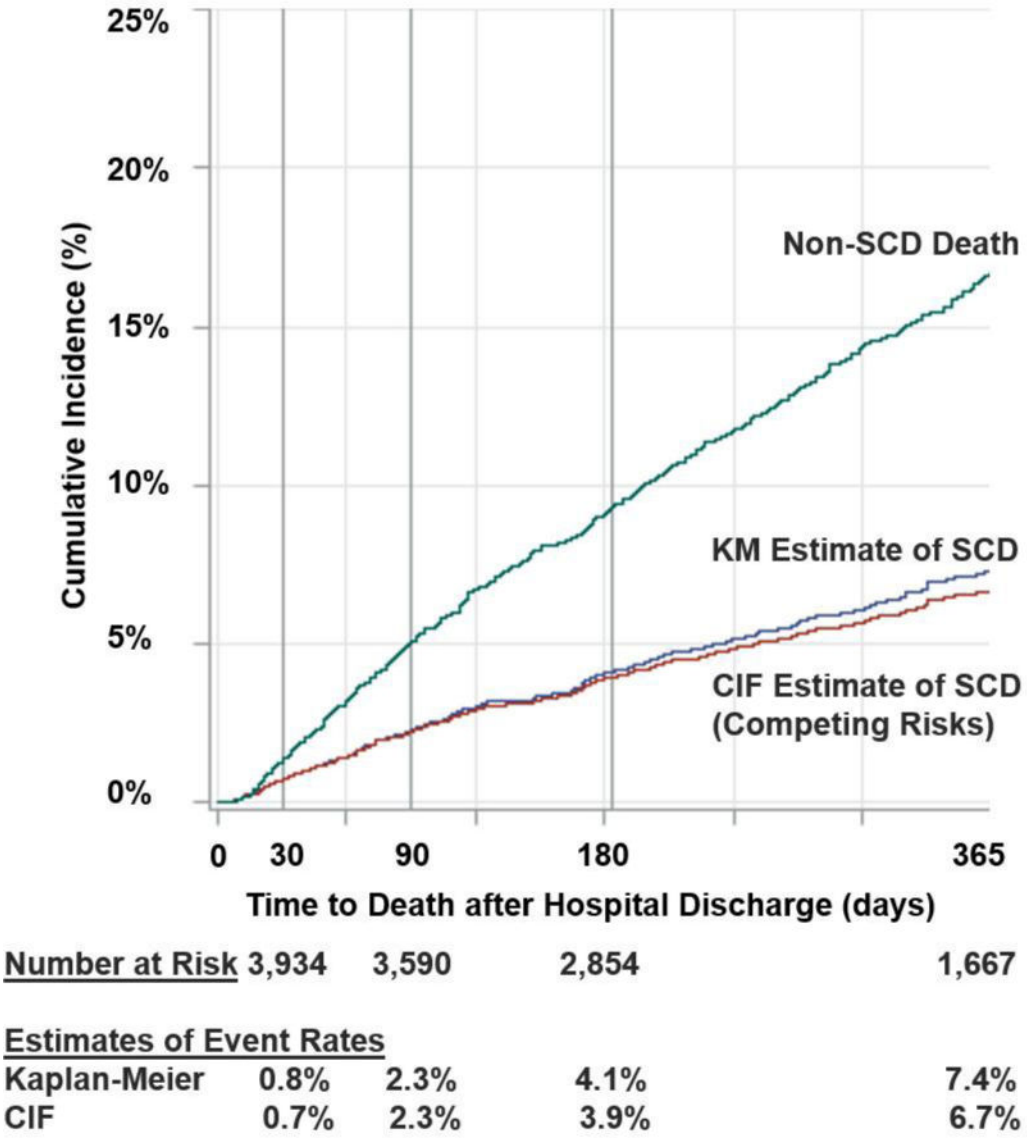

Figure 1.

Estimates of Sudden Cardiac Death (SCD) and Non-Sudden Death at 1-year After Hospitalization for Heart Failure. Kaplan-Meier and cumulative incidence function (CIF, to account for competing risks of non-sudden death) estimates of SCD are shown.

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Table 1

Clinical Profiles of EVEREST Patients by Post-Discharge Cause-Specific Death Status

Characteristic	Sudden Cardiac Death (n=703)	Non-Sudden Cardiac Death (n=703)	P	Alive (n=3,053)	Overall P[a]
Age (years), mean ± SD	65.1±12.6	69±11.8	<0.001	65±11.6	<0.001
Men	221 (82.5%)	535 (76.1%)	0.03	2247 (73.6%)	0.004
Black	28 (10.4%)	58 (8.3%)	0.28	217 (7.1%)	0.10
White	221 (82.5%)	591 (84.1%)	0.55	2624 (85.9%)	0.17
Asian	1 (0.4%)	0 (0%)	0.28	8 (0.3%)	0.36
Hispanic	13 (4.9%)	37 (5.3%)	0.80	149 (4.9%)	0.90
Other race	6 (2.2%)	17 (2.4%)	0.87	62 (2%)	0.80
Eastern Europe	104 (38.8%)	167 (23.8%)	<0.001	1319 (43.2%)	<0.001
Western Europe	31 (11.6%)	111 (15.8%)	0.10	401 (13.1%)	0.11
North America	88 (32.8%)	313 (44.5%)	0.001	818 (26.8%)	<0.001
South America	45 (16.8%)	112 (15.9%)	0.75	515 (16.9%)	0.83
History					
Prior hospitalization for heart failure	218 (82.0%)	602 (85.8%)	0.14	2340 (77.0%)	<0.001
Ischemic etiology of heart failure	178 (66.9%)	468 (67.6%)	0.83	1953 (64.8%)	0.32
New York Heart Association class IV	115 (42.9%)	336 (47.8%)	0.17	1099 (36.1%)	<0.001
Prior myocardial infarction	143 (53.4%)	382 (54.3%)	0.78	1497 (49.1%)	0.03
Coronary artery disease[b]	190 (70.9%)	510 (72.8%)	0.56	2133 (69.9%)	0.33
Hypertension[b]	191 (71.3%)	469 (66.7%)	0.17	2201 (72.1%)	0.02
Hyperlipidemia[b]	131 (48.9%)	355 (50.6%)	0.64	1468 (48.4%)	0.59
Diabetes mellitus	101 (37.7%)	321 (45.7%)	0.03	1133 (37.1%)	<0.001
Chronic kidney disease	82 (30.6%)	311 (44.3%)	<0.001	668 (21.9%)	<0.001
Implantable cardioverter-defibrillator	35 (13.1%)	159 (22.6%)	0.001	389 (12.7%)	<0.001
Chronic obstructive pulmonary disease	30 (11.2%)	108 (15.4%)	0.10	267 (8.8%)	<0.001
Peripheral arterial disease	60 (22.4%)	168 (24%)	0.60	613 (20.1%)	0.06
Discharge Findings					
Dyspnea	65 (24.3%)	188 (27.1%)	0.39	566 (18.7%)	<0.001
Pedal edema	112 (41.9%)	355 (51.1%)	0.01	1115 (36.8%)	<0.001

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Characteristic	Sudden Cardiac Death (n=703)	Non-Sudden Cardiac Death (n=703)	P	Alive (n=3,053)	Overall P[a]
Jugular venous distension ≥10 cm	14 (5.2%)	65 (9.4%)	0.04	118 (3.9%)	<0.001
Rales	69 (25.8%)	219 (31.5%)	0.09	581 (19.2%)	<0.001
Systolic blood pressure (mmHg), mean ± SD	112.6±16.4	110.6±16.9	0.09	117.1±17	<0.001
Body mass index (kg/m^2), median (25th, 75th percentiles)	27.8 (24.4–31.5)	26.7 (23.6–30.8)	0.03	28.3 (25–32.3)	<0.001
Ejection fraction (%), mean ± SD	25.1±7.7	25.4±8.2	0.60	28.3±7.9	<0.001
QRS duration (msec), mean ± SD	132±35.2	137±35.2	0.05	123.7±34.2	<0.001
Serum sodium (mg/dL), mean ± SD	139.7±5.2	139±5.5	0.08	140.5±4.9	<0.001
Estimated glomerular filtration rate (mL/min/1.73 m^2), mean ± SD[c]	53.6±21.2	45.9±20.8	<0.001	56.5±20.6	<0.001
Creatinine (mg/dL), mean ± SD	1.5±0.5	1.6±0.6	<0.001	1.4±0.5	<0.001
Blood urea nitrogen (mg/dL), mean ± SD	33.2±18.1	41.2±22	<0.001	29.9±14.9	<0.001
B-type natriuretic peptide (pg/mL), mean ± SD	1051.6±1268.1	1274.9±1371.1	0.07	791.4±2721.2	0.002
Albumin (mg/dL), mean ± SD	3.8±0.5	3.6±0.5	<0.001	3.9±0.5	<0.001
Discharge Medications					
Angiotensin-converting enzyme inhibitor/Angiotensin II receptor blocker	213 (79.5%)	528 (75.1%)	0.15	2674 (87.8%)	<0.001
Beta-blocker	186 (69.4%)	463 (65.9%)	0.30	2367 (77.7%)	<0.001
Spironolactone	178 (66.4%)	399 (56.8%)	0.006	1879 (61.7%)	0.01
Digoxin	140 (52.2%)	373 (53.1%)	0.82	1400 (45.9%)	0.001
Diuretics	251 (93.7%)	664 (94.5%)	0.63	2832 (92.9%)	0.34
Statins	94 (35.1%)	232 (33%)	0.54	1079 (35.4%)	0.48
Tolvaptan	139 (51.9%)	348 (49.5%)	0.51	1535 (50.3%)	0.80
Amiodarone	57 (21.3%)	179 (25.5%)	0.17	498 (16.3%)	<0.001

[a] Compares across all 3 groups

[b] Patient-reported medical history

[c] Estimated based on the abbreviated Modification of Diet in Renal Disease equation

Abbreviations: SD = standard deviation