CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

"Dose-dependent" Impact of Recurrent Cardiac Events on Mortality in Patients with Heart Failure

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ABSTRACT

BACKGROUND: The mortality impact of recurrent cardiac hospitalizations has not been delineated in community-based heart failure patients. We determined if a "dose-dependent" relationship exists between heart failure events and death, accounting for temporal changes in age, comorbidities, and disease severity.

METHODS: Among heart failure patients in the Enhanced Feedback For Effective Cardiac Treatment Study with onset between April 1999 and March 2001, we compared long-term survival (until March 2006) in those with recurrent heart failure or cardiovascular events, relative to those free of such events.

RESULTS: In 9138 patients, 28,442 person-years of follow-up were examined (mean age: 75.3 years, 49.6% male). Recurrent heart failure events occurred 1, 2, 3, and ≥4 times in 2352 (25.7%), 1020 (11.2%), 505 (5.5%), and 596 (6.5%) patients, respectively. Cardiovascular readmissions occurred 1, 2, 3, and ≥4 times in 2522 (27.6%), 1509 (16.5%), 975 (10.7%), and 1672 (18.3%) patients, respectively. Compared with those without recurrent heart failure events, the adjusted relative mortality rates for 1, 2, 3, and ≥4 heart failure events were 2.41 (95% confidence interval [CI], 2.24-2.60), 3.00 (95% CI 2.72-3.32), 4.00 (95% CI, 3.51-4.56), and 5.16 (95% CI, 4.55-5.85), respectively. Compared with those without cardiovascular events, the adjusted relative mortality rates for 1, 2, 3, and ≥4 cardiovascular events were 3.33 (95% CI, 3.05-3.63), 4.61 (95% CI, 4.16-5.10), 6.29 (95% CI, 5.59-7.07), and 8.95 (95% CI, 8.05-9.95), respectively.

CONCLUSIONS: The risk of death increases progressively and independently with each heart failure or cardiovascular event. The number of prior events predicts mortality and should be ascertained in patients with heart failure.

 • *The American Journal of Medicine (2009) xx, xxx*

KEYWORDS: heart failure; hospitalizations; mortality; outcomes research; prognosis

Heart failure is associated with a high mortality rate and substantial morbidity burden, and there is a need for strategies to improve long-term outcomes.[1] An important and costly dimension of heart failure care is hospitalization, which may recur frequently after the onset of the condition.[2-5] The problems posed on health care by repeated hospitalizations for heart failure are accentuated by the recognition that a large proportion of hospital admissions are preventable.[3,6]

Prior studies in randomized trial settings have suggested an association between the first heart failure hospitalization and mortality but were limited by short follow-up duration, comorbidities that did not reflect "real-world" populations,

Funding: This research was supported by a Canadian Institutes of Health Research (CIHR) grant and a CIHR Team Grant in Cardiovascular Outcomes Research, a clinician-scientist (DSL) and new investigator award (PCA) from the CIHR, career investigator awards from the Heart and Stroke Foundation of Ontario (JVT, DAA), and a Canada Research Chair in health services research (JVT).

Conflict of Interest: The authors have no conflict of interest to disclose.

Authorship: All co-authors had access to the data and contributed to the manuscript.

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doi:10.1016/j.amjmed.2008.08.026

and lack of adjustment for changes in comorbid conditions over time.[7,8] It also has not been determined if putative associations with mortality in heart failure patients extend to other cardiovascular disease events, accounting for time-dependent changes in age and comorbidities. Importantly, new episodes of heart failure can occur at the time of incident hospital presentation or during admission for an unrelated condition as a de novo hospital complication. However, prior studies have not examined the broad range of potential events that could occur in heart failure patients.

In this study, we examined patients who were newly hospitalized for heart failure in the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) Study, a population-based retrospective cohort of patients in Ontario, Canada. We followed the cohort for more than 5 years after the initial index heart failure discharge for all hospitalizations, in-hospital complications, and deaths that occurred over time, and quantified the relationship between each cardiovascular disease event with mortality. We hypothesized that each subsequent heart failure, cardiac ischemic, or cardiovascular disease event after the initial heart failure episode would be associated with a "dose-dependent" increase in risk of death.

CLINICAL SIGNIFICANCE

- In heart failure patients, the occurrence of acute heart failure, ischemic heart and cardiovascular disease events, and hospitalizations are associated with a "dose-dependent" increase in risk of death.
- Prevention of recurrent heart failure and cardiovascular disease events may improve survival in heart failure patients.
- Clinicians should determine the number of prior hospitalizations during which heart failure and cardiovascular events occurred, because it is a simple but powerful predictor of prognosis.

METHODS

Patients

The EFFECT-HF Study cohort consists of 9941 newly admitted patients with clinical heart failure, as defined by the modified Framingham criteria,[9] who were discharged from one of 103 acute care hospitals in Ontario, Canada from April 1, 1999 to March 30, 2001. We determined that the heart failure cohort was newly admitted by examining the time before the index hospitalization, excluding those who had been admitted in the prior 3 years. The 3-year cutoff was determined to be optimal based on the relationship between sample size and number of prior years examined, which followed an exponential decay function of the form:

$$k = k_1 + k_0 \cdot e^{-ct}$$

where k = number of patients remaining, t = number of prior years examined, c = decay constant, and k_0 and k_1 are constants. Detailed clinical data collection was performed from hospital records as previously described.[10,11]

Data Sources

We linked the EFFECT-HF clinical data with administrative databases using each patient's unique, encrypted health card number to determine the occurrence of: subsequent hospitalizations and hospitalizations or new in-hospital complications. The linked administrative databases included the Canadian Institute for Health Information Discharge Abstract Database, an administrative database of all hospitalizations, and the Registered Persons Database, a vital status database of all persons in Ontario. The accuracy of these databases has been described previously.[11-13] Patients with reduced or preserved left ventricular (LV) systolic function were determined from the EFFECT-HF Study using a left ventricular ejection fraction (LVEF) $\leq$50% versus >50% by echocardiography, cardiac catheterization, or radionuclide angiography.

Primary Diagnoses for Hospitalization

We used the *International Classification of Diseases*, 9th edition (ICD-9) or 10th edition (ICD-10-CA) to classify cardiovascular diagnoses. The ICD-9 coding system was used prior to April 1, 2002 and ICD-10-CA was used afterwards.[14,15] All hospitalizations are included in the Canadian Institute for Health Information Discharge Abstract Database, and all in-hospital complications are indicated separately. Heart failure was identified using ICD-9 code 428 and ICD-10 code I50. Ischemic heart disease included acute coronary syndromes and coronary heart disease identified by ICD-9 codes 410-414 and ICD-10 codes I20-I25. Any cardiovascular disease included heart failure, ischemic heart disease, and other cardiovascular conditions including arrhythmias, cerebrovascular, and peripheral vascular disease (Appendix 1, available online).

All hospitalizations and events (eg, hospitalizations or new in-hospital complications) after the EFFECT-HF discharge were counted cumulatively over time. We examined heart failure, ischemic heart disease, and cardiovascular "hospitalizations" (eg, primary reason for rehospitalization) and "events," which additionally included de novo complications occuring in hospital. In each set of analyses, risks were compared relative to those who did not have an event or hospitalization in follow-up. Elective hospital admissions for same-day surgical procedures and those with a length of stay $\leq$1 day were excluded.

Statistical Analysis

Comparisons of continuous covariates were performed using Student's *t* test and categorical variables using the chi-squared statistic.[16] We determined whether increas-

ing number of hospital readmissions and events remained significantly associated with death after adjustment for baseline mortality risk using the previously-validated EFFECT-HF risk score.[10,17-20] The score has been found to stratify risk of death in follow-up extending from 30 days to as long as 6 years.[21]

Time to event was plotted using the Kaplan-Meier method, and comparisons were performed using the log-rank statistic. We examined the cumulative effect of hospitalizations using Cox proportional hazards regression models with time-dependent covariates to determine the relationship between readmissions and events to death, by modeling the number of hospitalizations for heart failure, ischemic heart disease, and cardiovascular disease as time-varying covariates.[22] A patient that died after the index EFFECT hospital discharge but before the first readmission had 0 repeat hospitalizations (referent). Death after the first but before the second readmission was classified as 1 repeat hospitalization, and so on, until a maximum of 4 hospitalizations was reached (Figure 1). The comparator groups, for determination of relative mortality rates (RR) for 1, 2, 3, or ≥4 admissions, were those with no subsequent hospitalizations or events. Both hospitalized and nonhospitalized patients were followed until censored on the date of last follow-up (March 31, 2006) or upon death.

To account for change in age over time, Cox models adjusted for time-varying age, which was updated: a) with each event and, b) deterministically for all patients each calendar year. We also accounted for new EFFECT-HF model comorbidities that developed over time if the condition was not present at baseline (see Appendix 2 [available online] for ICD-9/10 codes used). The proportional hazards assumption was tested for Cox regression analyses. All analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC).

Sensitivity Analyses

In exploratory analyses, we examined the effect of hospitalizations in those with reduced or preserved LVEF, excluding those who did not undergo LV function assessment. We also examined whether the associations were robust after accounting for hospital or discharge medication use.

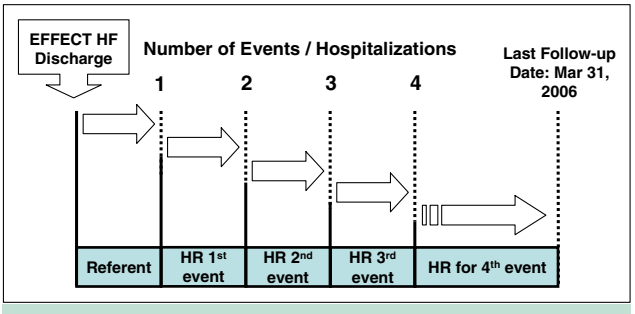

Figure 1 Time sequence of events in analysis. HF = heart failure; HR = hazard ratio.

RESULTS

Study Patients

Among the newly admitted cohort of 9138 patients (mean age 75.3 years, 49.6% male), 3647 patients had at least one hospitalization, and 5491 did not have any hospitalizations for heart failure during a median follow-up duration of 1024 days (interquartile range 306-1974 days). Left ventricular systolic function was evaluated in 4195 patients (45.9%), of which 3008 (71.7%) had reduced and 1187 (28.3%) had preserved LVEF. The baseline characteristics of the study cohort are shown in Table 1. Patients who were readmitted at least once for heart failure had lower LVEF, marginally higher serum urea, and lower sodium concentrations than those who were not (Table 1).

Hospitalizations in Follow-up

Rehospitalization for a primary diagnosis of heart failure occurred 1, 2, 3, and ≥4 times in 2042 (22.3%), 824 (9.0%), 379 (4.1%), and 402 (4.4%) patients, respectively. Ischemic heart disease hospitalizations occurred 1, 2, 3, and ≥4 times in 1271 (13.9%), 357 (3.9%), 123 (1.3%), and 100 (1.1%) patients, respectively. There were 2565 (28.1%), 1304 (14.3%), 695 (7.6%), and 965 (10.6%) patients who were hospitalized 1, 2, 3, and ≥4 times, respectively, for any primary cardiovascular disease diagnosis.

Heart failure events (eg, both primary reasons for hospitalization and de novo in-hospital complications) occurred 1, 2, 3, and ≥4 times in 2352 (25.7%), 1020 (11.2%), 505 (5.5%), and 596 (6.5%) patients, respectively. Ischemic heart disease events (eg, primary reasons for hospitalization and de novo complications) occurred 1, 2, 3, and ≥4 times in 1990 (21.8%), 894 (9.8%), 434 (4.7%), and 495 (5.4%) patients, respectively. Finally, any cardiovascular disease events (eg, any cardiovascular condition most responsible for hospitalization and new in-hospital complications) occurred 1, 2, 3, and ≥4 times in 2522 (27.6%), 1509 (16.5%), 975 (10.7%), and 1672 (18.3%) patients, respectively (Figure 2).

Unadjusted Analyses

Over the entire study duration, crude mortality rates were 67.7%, 75.1%, and 78.6%, respectively, in those admitted for a primary diagnosis of heart failure 0, 1, and ≥2 times. Among those who survived at least 1 year after index hospital discharge, the number of heart failure hospitalizations in the prior year stratified mortality risk as shown in the Kaplan-Meier plots in Figure 3 (log-rank $P < .001$). Similarly, among 2-year and 3-year survivors after index hospital discharge, the number of heart failure hospitalizations in the preceding 2 or 3 years, respectively, also stratified the risk of death in follow-up (log-rank $P < .001$).

Table 1 Baseline Characteristics

Characteristic	No Readmission for HF in Follow-up (n = 5491)	Readmitted Once or More in Follow-up (n = 3647)	*P*-Value
Age, years, mean (SD)	75.2 (12.0)	75.4 (10.9)	.39
Male, n (%)	2730 (49.8%)	1805 (49.6%)	.84
LV ejection fraction, n (%)*			
Reduced	1774 (70.0%)	1234 (74.2%)	.003
Preserved	759 (30.0%)	428 (25.8%)	
EFFECT-HF risk score, mean (SD)†	98.4 (26.8)	98.7 (23.5)	.67
EFFECT-HF risk score category†			
Very low risk	301 (6.4%)	138 (4.4%)	.41
Low risk	1572 (33.4%)	994 (31.5%)	
Intermediate risk	1856 (39.4%)	1456 (46.2%)	
High risk	810 (17.2%)	494 (15.7%)	
Very high risk	166 (3.5%)	69 (2.2%)	
Systolic blood pressure on admission, mm Hg, mean (SD)	149 (33)	150 (34)	.35
Respiratory rate on admission, breaths/min, mean (SD)	26 (7)	26 (7)	.05
Serum urea concentration, mmol/L, mean (SD)	27.6 (17.7)	28.7 (17.7)	.008
Sodium concentration <136 mmol/L, n (%)	1064 (19.7%)	777 (21.6%)	.02
Hemoglobin concentration <100 g/L, n (%)	679 (12.6%)	411 (11.5%)	.12
Prior myocardial infarction, n (%)	1835 (33.4%)	1472 (40.4%)	<.001
Diabetes, n (%)	1735 (31.6%)	1425 (39.1%)	<.001
Stroke or transient ischemic attack, n (%)	838 (15.5%)	586 (16.2%)	.40
Dementia, n (%)	455 (8.4%)	152 (4.2%)	<.001
Chronic obstructive lung disease, n (%)	1181 (21.9%)	787 (21.7%)	.87
Cirrhosis of liver, n (%)	40 (0.7%)	22 (0.6%)	.45
Any cancer, n (%)	629 (11.7%)	356 (9.8%)	.007

HF = heart failure; LV = left ventricular; EFFECT = Enhanced Feedback for Effective Cardiac Treatment study.
*Based on 4195 patients (45.9%) with LV ejection fraction assessed.
†Based on 7856 patients (86.0%) with complete data for calculation of EFFECT-HF risk score.

Effect of Hospitalizations and Cardiac Events on Survival

Compared with patients who were not admitted to the hospital for heart failure after the index discharge (referent group), the risk of death increased progressively with subsequent heart failure readmissions (Table 2). With increasing number of heart failure hospitalizations, the RR for death increased from 2.36 (for the first readmission) to 5.08 (for the fourth readmission), relative to those who were not readmitted (Table 2). Similarly, a progressive increase in

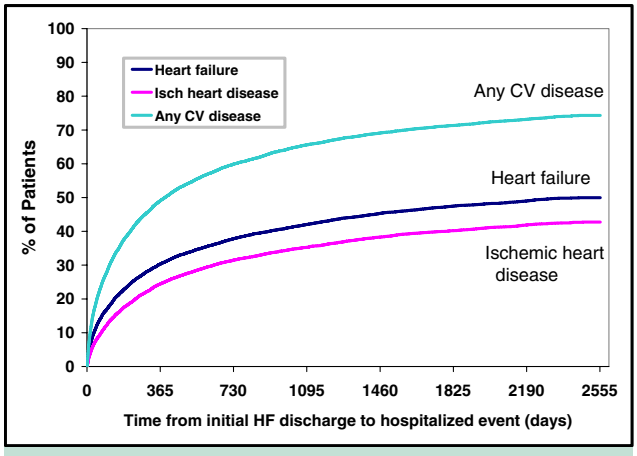

Figure 2 Cumulative number of patients with heart failure, ischemic heart disease, or any cardiovascular disease events, after initial EFFECT-HF hospital discharge (t = 0) CV = cardiovascular; HF = heart failure.

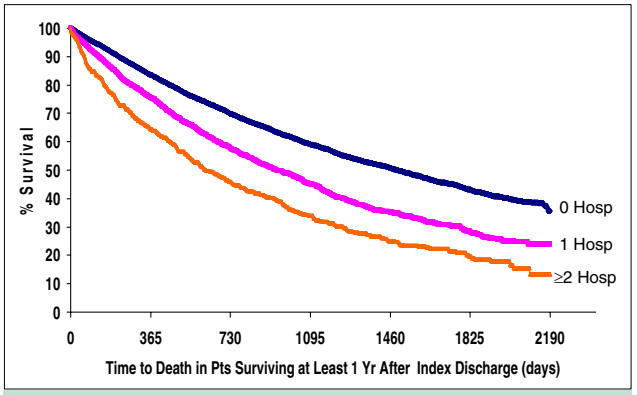

Figure 3 Among 1-year survivors after index EFFECT-HF discharge, the number of heart failure hospitalizations in the preceding year stratified the risk of death in crude analyses.

Table 2 Unadjusted Analyses

Model		Number of Events or Hospitalizations Occurring After the Initial HF Discharge				
		0	1	2	3	≥4
Heart failure						
Any clinical event*	Relative mortality rate	Referent	2.60‡	3.54‡	4.87‡	6.17‡
	95% CI		2.44-2.76	3.26-3.84	4.37-5.42	5.57-6.84
Hospitalization†	Relative mortality rate	Referent	2.36‡	3.40‡	4.19‡	5.08‡
	95% CI		2.22-2.51	3.12-3.71	3.71-4.72	4.52-5.72
Ischemic heart disease						
Any clinical event*	Relative mortality rate	Referent	2.34‡	3.03‡	3.41‡	4.00‡
	95% CI		2.20-2.49	2.78-3.29	3.03-3.83	3.57-4.48
Hospitalization†	Relative mortality rate	Referent	1.96‡	1.96‡	1.99‡	3.10‡
	95% CI		1.82-2.10	1.72-2.24	1.59-2.48	2.45-3.92
Cardiovascular disease						
Any clinical event*	Relative mortality rate	Referent	3.51‡	5.17‡	7.03‡	10.10‡
	95% CI		3.27-3.76	4.76-5.62	6.39-7.74	9.27-11.00
Hospitalization†	Relative mortality rate	Referent	2.55‡	3.67‡	4.41‡	6.20‡
	95% CI		2.39-2.71	3.39-3.97	3.99-4.87	5.66-6.78

HF = heart failure; CI = confidence interval.
*Includes hospitalizations for a primary diagnosis or new in-hospital complications.
†Includes only hospitalizations for a primary diagnosis.
‡P <.001 vs referent group of 0 hospital admissions.

risk was found for heart failure events and cardiovascular disease events (Table 2).

Risk-Adjusted Analysis

EFFECT-HF risk scores were normally distributed with a mean score of 99 ± 26 and median (25^{th}, 75^{th} percentile) score of 97 (81, 115). Adjusting for the EFFECT-HF score, the graded increase in mortality risk remained for both heart failure events and hospitalizations (Figure 4). Similarly, a dose-dependent increase in risk of death was present for cardiovascular disease events and hospitalizations, but was nonlinear for ischemic heart disease events (Figure 4).

Analysis Using Time-Varying Covariates

Adjusting for the EFFECT-HF mortality risk score with updated comorbidities and age, the dose-dependent association between recurrent heart failure and death remained significant (Table 3). The adjusted RR increased progressively from 2.41 to 5.16 and from 2.29 to 4.60 for heart failure events and rehospitalizations, respectively (Table 3). Although the risk of death increased with subsequent readmissions for ischemic heart disease and for any cardiovascular cause, there was a prominent mortality effect for cardiovascular events, with an adjusted RR that increased from 3-fold to 9-fold (Table 3).

Sensitivity Analyses

Analyses of those with reduced or preserved LV ejection fractions were performed using similar approaches to that described for the overall cohort. In patients with reduced LVEF, the unadjusted RR increased from 3-fold after the first to 8-fold after the fourth recurrent heart failure event (Table 4). After adjustment for mortality risk and the time-varying effects of age, the risk of death also increased in those with a recurrent heart failure event or any cardiovascular event, with RR increasing from 2.8-fold for the first and 6.7-fold for the highest readmission category (Table 4). A similar pattern of mortality risk was observed in those with preserved LV systolic function as the number of subsequent heart failure or cardiovascular events increased (Table 4). The rates of use of various heart failure drug therapies are shown in Table 5. After adjustment for the use of all drugs in-hospital or at discharge, the association of heart

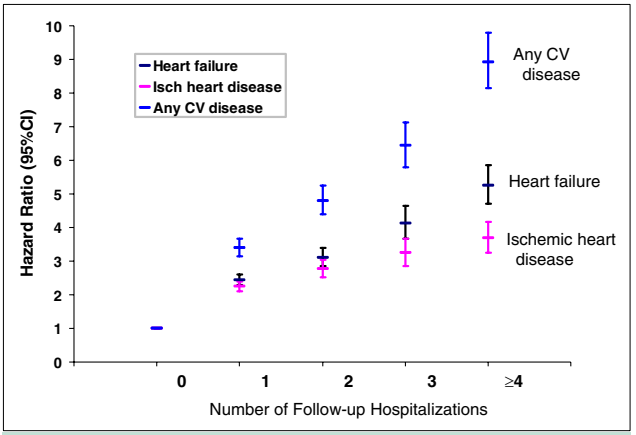

Figure 4 Mortality risk according to the number of subsequent hospitalizations for heart failure, ischemic heart disease, and any cardiovascular disease, adjusted for EFFECT-HF mortality risk score. CV = cardiovascular.

Table 3 Analyses Adjusted for EFFECT Score,* Time-varying Comorbidities, and Time-varying Age

		Number of Events or Hospitalizations Occurring After the Initial HF Discharge				
Model		0	1	2	3	≥4
Heart failure						
Any clinical event†	Relative mortality rate	Referent	2.41§	3.00§	4.00§	5.16§
	95% CI		2.24-2.60	2.72-3.32	3.51-4.56	4.55-5.85
Hospitalization‡	Relative mortality rate	Referent	2.29§	3.04§	3.32§	4.60§
	95% CI		2.12-2.46	2.74-3.37	2.86-3.86	3.99-5.31
Ischemic heart disease						
Any clinical event†	Relative mortality rate	Referent	2.18§	2.57§	3.20§	3.66§
	95% CI		2.02-2.36	2.31-2.86	2.78-3.68	3.18-4.20
Hospitalization‡	Relative mortality rate	Referent	1.97§	2.05§	1.97§	2.62§
	95% CI		1.80-2.15	1.75-2.41	1.49-2.60	1.96-3.51
Cardiovascular disease						
Any clinical event†	Relative mortality rate	Referent	3.33§	4.61§	6.29§	8.95§
	95% CI		3.05-3.63	4.16-5.10	5.59-7.07	8.05-9.95
Hospitalization‡	Relative mortality rate	Referent	2.50§	3.55§	4.09§	5.66§
	95% CI		2.31-2.70	3.22-3.91	3.61-4.62	5.07-6.33

EFFECT = Enhanced Feedback for Effective Cardiac Treatment study; HF = heart failure; CI = confidence interval.
*Analysis includes 7856 of the 9138 patients (86%) with calculated EFFECT-HF risk score.
†Includes hospitalizations for a primary diagnosis or new in-hospital complications.
‡Includes only hospitalizations for a primary diagnosis.
§$P < .001$ vs referent group of 0 hospital admissions.

failure, ischemic heart, and cardiovascular disease with mortality remained robust.

DISCUSSION

Recurrent heart failure hospitalizations have traditionally been considered important because of the quality-of-life implications and the high cost of recurrent hospital care. Although clinicians have recognized that some heart failure patients have repeated episodes of acute decompensation, the prognostic consequences of these events in the community-based setting have not been fully appreciated. In this study, we examined the association between hospitalizations and mortality in heart failure patients, and found that the risk of death increased with each subsequent event in a dose-dependent manner. After adjustment for baseline mortality risk, changing comorbidity profile, and increasing age in both hospitalized and nonhospitalized patients over time, the risk of death increased from 2.4-fold after the first to 5.2-fold after the fourth recurrent heart failure event. Similarly, the adjusted risk of death increased more than 3-fold after the first cardiovascular event and up to 9-fold after the fourth event.

Our study suggests that repeated hospitalizations for heart failure or cardiovascular disease events are strongly associated with mortality. Our findings are novel because we found that a dose-dependent effect exists even after accounting for: baseline mortality risk in a real-world heart failure population, advancing age, and increasing comorbidity profile over time. In addition, we examined all acute heart failure events, including hospitalizations and in-hospital complications. Finally, the dose-dependent relationship was significant in those with reduced or preserved LV ejection fraction.

Our findings extend the literature, which have reported in single-center studies or randomized trials that a prior hospitalization for heart failure may be a marker of adverse prognosis.[23,24] However, few studies have examined the dose-dependent association between heart failure events or hospitalizations and death in a population-based setting. The community-based Cardiovascular Health Study found that prior heart failure history was associated with an increased fatality rate.[25] A population-based evaluation of heart failure patients using administrative data alone, found that median survival worsened progressively with increasing number of hospitalizations.[26] Although consistent with our study, this prior report was limited by absence of clinical information, lack of clinical mortality risk adjustment, and no data on LV systolic function.[26] In our study, repeated heart failure events and hospitalizations were positively associated with death overall, and in those with reduced or preserved LV ejection fraction, adjusting for baseline risk using a validated model for long-term risk adjustment[10] and incident comorbidities over time.

Although the current study did not determine the underlying mechanisms for the association between hospitalizations and death, our findings suggest that the relationship is not due to age, comorbidities, or baseline mortality risk. The mortality effect of recurrent heart failure events also was present in those with preserved or reduced LV systolic function, and therefore this association is not specific to

Table 4 Results for HF, IHD and all CV Events by Reduced Versus Preserved LV Systolic Function

		Number of Events Occurring After the Initial HF Discharge				
Model		0	1	2	3	≥4
Low LVEF - unadjusted analyses						
Heart failure	Relative mortality rate	Referent	3.03*	3.60*	5.83*	7.99*
	95% CI		2.72-3.37	3.10-4.17	4.86-7.00	6.66-9.59
Ischemic heart disease	Relative mortality rate	Referent	2.54*	3.58*	4.22*	4.93*
	95% CI		2.28-2.84	3.10-4.14	3.48-5.12	4.09-5.94
Cardiovascular disease	Relative mortality rate	Referent	3.91*	6.39*	8.81*	13.74*
	95% CI		3.44-4.46	5.51-7.43	7.42-10.45	11.79-16.01
Preserved LVEF - unadjusted analyses						
Heart failure	Relative mortality rate	Referent	2.69*	3.77*	5.00*	7.15*
	95% CI		2.24-3.22	2.99-4.74	3.50-7.13	5.18-9.87
Ischemic heart disease	Relative mortality rate	Referent	2.40*	3.59*	3.46*	3.80*
	95% CI		1.98-2.91	2.79-4.62	2.37-5.04	2.50-5.77
Cardiovascular disease	Relative mortality rate	Referent	4.26*	6.57*	8.77*	12.38*
	95% CI		3.44-5.28	5.13-8.40	6.62-11.63	9.48-16.17
Low LVEF - adjusted analyses†						
Heart failure	Relative mortality rate	Referent	2.75*	3.09*	4.86*	6.73*
	95% CI		2.45-3.08	2.64-3.62	3.99-5.92	5.53-8.18
Ischemic heart disease	Relative mortality rate	Referent	2.33*	3.12*	3.55*	4.72*
	95% CI		2.07-2.62	2.66-3.64	2.88-4.37	3.86-5.77
Cardiovascular disease	Relative mortality rate	Referent	3.75*	5.67*	7.47*	12.62*
	95% CI		3.26-4.31	4.83-6.67	6.19-9.00	10.67-14.91
Preserved LVEF - adjusted analyses†						
Heart failure	Relative mortality rate	Referent	2.37*	3.04*	3.81*	5.28*
	95% CI		1.95-2.88	2.37-3.90	2.58-5.64	3.75-7.44
Ischemic heart disease	Relative mortality rate	Referent	2.00*	2.70*	3.55*	2.62*
	95% CI		1.62-2.46	2.04-3.57	2.42-5.22	1.66-4.15
Cardiovascular disease	Relative mortality rate	Referent	3.74*	5.85*	8.86*	9.74*
	95% CI		2.96-4.73	4.48-7.65	6.57-11.96	7.31-12.98

HF = heart failure; IHD = ischemic heart disease; CV = cardiocascular; LV = left ventricular; LVEF = left ventricular ejection fraction; CI = confidence interval.

*P <.001 vs referent group of 0 hospital admissions.

†Adjusted for EFFECT heart failure risk score and time-varying age.

either LVEF group. Our findings support the concept that recurrent acute heart failure and cardiovascular disease events induce discrete insults in a progressive, stepwise manner with marked prognostic implications. Acute heart failure and cardiovascular disease events should not, therefore, be considered benign episodes in heart failure patients.

The results of this study have significant implications for heart failure research and clinical care. Because mortality is closely linked with the occurrence of heart failure and ischemic cardiac events, prevention of recurrent events is a critically important component in strategies to improve survival. The presence of a "dose-dependent" mortality effect suggests that clinicians should elicit, by history, the number of prior events in the assessment of heart failure patients. Furthermore, enumeration of the number of prior heart failure or cardiovascular disease events may add importantly and cost-effectively to predictive models of heart failure risk. Finally, these findings open a new line of inquiry pertaining to the mechanisms by which recurrent heart failure events lead to a progressive increase in the risk of death.

There are several notable limitations of our study. The primary exposure variable was hospitalizations or events occurring in hospital, and therefore milder forms of acute heart failure that are managed without hospitalization were not included in the analysis. Additionally, we did not determine if medication use, drug adherence, or other therapeutic interventions were associated with decreased proclivity to hospitalization, and therefore decreased mortality risk. However, several drug therapies that are the cornerstones of heart failure therapy because they reduce mortality (eg, angiotensin-converting enzyme inhibitors, beta-adrenoreceptor antagonists) also have been found to reduce morbidity, further supporting the premise of a close association between hospitalizations and death.[27,28] Despite the above, the association with mortality remained robust in analyses that adjusted for heart failure medication use either in-hospital or upon hospital discharge. The analyses stratified

Table 5 Drug Therapies Administered in Hospital or at Discharge

Drug Class	In-hospital Use	At Hospital Discharge
ACE inhibitor, n (%)	6732 (73.8%)	5811 (63.6%)
Angiotensin receptor blocker (ARB), n (%)	616 (6.8%)	525 (5.7%)
ACE inhibitor or ARB, n (%)	7226 (79.2%)	6303 (69.0%)
Aspirin, n (%)	4501 (49.3%)	3630 (39.7%)
β-adrenoreceptor antagonist, n (%)	2831 (31.0%)	2451 (26.8%)
Ca^{2+} channel blocker: amlodipine, n (%)	1293 (14.2%)	1061 (11.6%)
Ca^{2+} channel blocker: others, n (%)	1991 (21.8%)	1567 (17.2%)
Digoxin, n (%)	4063 (44.5%)	3494 (38.3%)
Diuretic: furosemide, n (%)	8379 (91.9%)	7106 (77.8%)
Diuretic: metalozone, n (%)	602 (6.6%)	331 (3.6%)
Diuretic: spironolactone, n (%)	1773 (19.4%)	1508 (16.5%)
Nitrates, topical or oral, n (%)	4506 (49.4%)	3311 (36.2%)
Vasodilator, n (%)	346 (3.8%)	201 (2.2%)

ACE = angiotensin-converting enzyme.

by LVEF were limited to those in whom this test was performed. Finally, we did not subclassify deaths as cardiac or noncardiac, however, our analyses did account for significant noncardiac comorbidities and changes in these conditions over time.

In conclusion, among heart failure patients, each acute heart failure or ischemic cardiac event is associated with an increasing risk of death in a "dose-dependent" relationship. The numbers of prior heart failure, ischemic heart disease, and cardiovascular disease events are critically important predictors of prognosis and should be carefully and routinely ascertained. Because morbid acute cardiovascular events and hospitalizations are strongly linked with death, enhanced efforts are needed to prevent such recurrent events and thus potentially improve survival.

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Appendix 1 ICD-9 and 10 Codes for Heart Failure, Ischemic Heart Disease, and Other Cardiovascular Diseases

Diagnosis	ICD-9 Codes	ICD-10 Codes
Heart failure	428	I50
Ischemic heart disease	410-414	I20-I25
Other cardiovascular disease codes		
Arrhythmia	426, 427	I44-I49
Myo-/peri-/endo-cardial disease	420-423, 425	I30-I33, I40-I43, I51.4
Cerebrovascular disease	430-438	I60-I69
Hypertensive disease	401-405	I10-I13, I15
Pulmonary vascular disease	415-417	I26-I28
Peripheral vascular disease	440-448, 451-453, 785.4	I70-I74, I77-I82, R02
Rheumatic heart disease	390-398	I00-I02, I05-I09
Shock	785.5	R57
Syncope, sudden death	780.2, 798.1	R55, R96.0
Valvular heart disease	424	I34-I39
Other cardiac	429, 458	I51, I52, I95, I97

Appendix 2 Codes for Comorbidity Updates in Time-dependent Analyses

Diagnosis	ICD-9 Codes	ICD-10 Codes
Renal failure	584, 585	N17, N18
Stroke/transient ischemic attack	430-432, 434-436	I60-I64, G45, G46
Dementia	290	F00-F03
Chronic obstructive lung disease	490-493, 496	J20, J40-J45
Hepatic cirrhosis	571.2, 571.5, 571.6	K70.3, K71.7, K74.3-K74.6
Cancer	140-239	C00-C97, D10-D48
Anemia	280-285	D50-D53, D55-D64