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Clinical Exacerbations as a Surrogate End Point in Heart Failure Research

Abstract

Background

We examined the utility of an index of clinical exacerbations of heart failure (HF) as a surrogate measure of outcome for use in modestly sized clinical trials and observational studies.

Methods

Electronic records of 189 outpatients with HF in a US Veterans Affairs Medical Center were examined over a 2- to 3-year period. Data collected included patient characteristics, clinical exacerbations of HF, hospitalizations, and deaths. Subsets of patient were also assessed for HF-related level of functioning.

Results

Episodes of clinical exacerbation could be detected reliably ($\kappa = .83$). An index of episodes (number of episodes divided by the time in years) was associated with lower quality of life, higher functional class, increased rate of HF hospitalization, poorer exercise tolerance, and up to 30% increased risk of mortality across 2 years.

Conclusions

The index of HF exacerbations is potentially a useful surrogate end point for use in clinical HF research.

Disciplines

Analytical, Diagnostic and Therapeutic Techniques and Equipment | Cardiology | Cardiovascular Diseases | Circulatory and Respiratory Physiology | Critical Care | Critical Care Nursing | Medical Humanities | Medicine and Health Sciences | Nursing

Chart-extracted Clinical Exacerbations as a Surrogate Endpoint in Heart Failure Outcome

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ABSTRACT

Purpose: An index of a patients' rate of clinical exacerbations of heart failure (HF) was examined as a surrogate endpoint in clinical outcome.

Method: One hundred ninety-one patients with HF were followed subsequent to their entry into a clinical screening database when being considered for study of treatment adherence. The patients' electronic records were examined retrospectively over a 2 – 3 year period regarding their demographic and clinical characteristics, clinical exacerbations of heart failure, hospitalizations, and deaths. Some these patients were also assessed using measures of depression (N = 40), HF-specific quality of life (HF-QOL), and exercise tolerance (6-minute walk test).

Results: Two trained research assistants were able to reliably code patients' clinical visits with regard to the existence of clinical exacerbations of HF (kappa = .83). An index of the chart-extracted exacerbations (CEEs) of HF was associated with lower HF-QOL, relatively higher New York Heart Association (NYHA) Class, and poorer exercise tolerance. The index of CEEs was also associated with the risk of mortality; 54% of the patients with greater than 2 CEEs per year died within a 2-year follow-up period, whereas only 27% of patients with 2 or fewer CEEs per died within the same follow-up period.

Conclusions: This index of CEEs is potentially a useful surrogate endpoint for use in clinical HF research. Future research should examine the patterns of clinical exacerbations over time and the utility of this index in predicting mortality risk on a prospective basis.

Heart failure (HF) is a highly prevalent clinical syndrome that represents a great burden to the patient and family members, and is associated with a 50% mortality risk over 5 years.[1] Consistent with the high mortality risk of HF, the reduction of this risk has been the gold standard clinical endpoint used in most investigations of interventional medications [2]. However, as treatments have lengthened survival of patients with CHF, increasingly larger samples are required to show improved survival risk for newer treatments [2]. Thus, there has been recent increase in the consideration of surrogate end points (e.g., exercise capacity, left ventricle ejection fraction), potentially as a way to lower the demands in a clinical trial for sample size and reduce the time needed to evaluate the potential usefulness of a medication or treatment strategy. Disease-related quality of life (QOL) has also been considered an important “true” end point, in that specific interventions may prolong life but not contribute significantly to improved functioning or well-being from the patient’s point of view. Most investigators would consider reduced symptoms and improved functioning important to the overall management of HF, although some treatments that improve QOL also appear to adversely affect survival. [3-5] Thus, QOL is considered an important and separate dimension of health status[6], and potentially an important component of a surrogate end point in studies of CHF treatment.

The purpose of the current study is to propose an index of chart-extracted clinical exacerbations or decompensations of HF as a useful surrogate end point, and present data support the reliability and validity of this end point. Exacerbations of heart failure as extracted from chart information over time may have a number of practical applications, including epidemiological studies not allowing extensive examinations of disease related quality of life, studies of health care systems of the process and quality of care, as well as a refinement of hospitalization as a near term surrogate end point of studies that also use the gold standard of mortality as an end point. Because a chart-extracted clinical exacerbation of HF also represents a significant worsening of symptoms, it is likely that HF-related QOL is reflected in this surrogate end point. Patients who spend a significant amount of time in a clinically decompensated state will likely have worse QOL.

Anand and colleagues [2] described several types of surrogate end points, including a *strong surrogate*, which refer to antecedent outcomes that have been definitively established as directly related

to a gold standard outcome (eg., strong surrogate: lowered hypertension—gold standard: cardiovascular events such as stroke). Chart-extracted clinical exacerbations are closer to two other types of surrogate end points, namely, *developmental* and *supportive surrogates*. A developmental surrogate refers to an outcome that has preliminary evidence indicating it is closely related to an important end point, and a supportive surrogate refers to an outcome that appears to be closely related and predictive of a beneficial outcome. Patients who are volume-overloaded with accompanying symptoms of increased weight, edema, shortness of breath, and reduced exercise tolerance are at greater risk of ventricular arrhythmias and sudden death due to cardiac arrest (**ref**). Patients who spend relatively greater time in this clinically decompensated state are at greater risk for permanent worsening of their clinical status (**ref**), and thus, increasing the risk of mortality in the near term.

Validation of a surrogate endpoint is never fully complete [2] although important criteria that support a surrogate's validity has been discussed in the literature. Practically speaking, a surrogate endpoint should have a positive statistical association with the gold-standard outcome, and changes in the surrogate endpoint over time should be associated with the outcome. Furthermore, there must be a plausible explanatory link between the surrogate endpoint and the outcome. In the current study, we examined evidence for the validity of chart-extracted exacerbations as a surrogate endpoint for mortality, as well as disease-related quality of life. We included several other measures as covariates in our empirical evaluation that may also have impact on mortality. These included those that might be confounding factors in examining the utility of chart-extracted exacerbations of heart failure (e.g., comorbid medical), as well as common demographic factors associated with exacerbations for other reasons (e.g., age, race/ethnicity).

METHOD

Subjects: Participants in this study were HF patients initially screened at the Philadelphia Veterans Affairs Medical Center (PVAMC) for the purpose of recruiting them for a pilot study of treatment adherence [7]. During the period of active recruitment for that study, patients who had an appointment in the Congestive Heart Failure (CHF) Clinic of the PVAMC, or had been recently referred to the CHF Clinic and been evaluated by echocardiogram were screened for potential recruitment into the

adherence study. The patients who fit criteria for this database study had a chart diagnosis of heart failure, and their medical record was examined further to confirm the diagnosis. Patients were required to meet the criteria of systolic dysfunction as indicated on an echocardiogram, with left ventricle ejection fraction (LVEF) $\leq 40\%$, or with well-documented diastolic dysfunction, right-side heart failure, or other heart disease documented as responsible for heart failure, and with a New York Heart Association (NYHA) Class I/II or above. We also entered an additional set of patients into the study that were well-compensated (NYHA Class I) due to current management for HF and no current heart failure symptoms upon entry into the study ($N=20$). For entry into the study, these patients were required to have a well-documented history of episodes of heart failure decompensation prior to the period examined in the current study (see below).

Of 277 patients screened, 191 met criteria for inclusion. The patients were primarily older ($M = 64.4$, $SD = 11.7$), male veterans ($N = 2$ females). Most of the patients were Black/African American (62.3%), 30.9% were White, and 1% reported Latino ethnicity; 5.8% were of unknown race or ethnicity. Only 33.5% of these patients had a marital partner, according to medical records. A minority of the patients had diastolic dysfunction only ($N=18$, 9.4%), and on average, patients had a high number of comorbid conditions, $M = 4.4$, $SD = 2.3$. For the patients with systolic dysfunction, the mean of each patients' minimum LVEF was $M = 26.2$, $SD = 11.0$.

A portion of these patients were approached and recruited for the pilot study regarding adherence to treatment ($N = 40$). There was a possibility that the patients participating in the adherence study would have different outcomes due to pre-existing differences in severity of illness from the larger cohort or because the assessment methods of the pilot study had a positive effect on the patient's self-care. Thus, we examined differences in those patients in the pilot study compared to those that did not and found only minor differences. Using a series of two-sample t-tests, we found that participators had a lower mean age, $M = 60.8$, $SD = 11.2$, compared to those that did not, $M = 65.5$, $SD = 11.6$, $t = 2.7$, $p < .01$, $df = 189$. There were no differences between the groups on the mean number of comorbid conditions, $t = -1.42$, $p > .05$, $df = 50.7$, minimum LVEF, $t = 0.45$, $p > .05$, $df = 182$, or number of adjusted clinical exacerbations per year, $t = -0.40$, $p > .05$, $df = 189$. In addition, a 2 X 2 chi-square test of participators vs. non-

participants indicated that participants were not more likely to die within the follow-up period covered in the current study, $\chi^2 = 0.69$, $p > .05$, $df = 1$. A multivariate test of differences for these comparisons between the groups was not used because it would have eliminated too many patients from consideration due to patterns of missing data, resulting in an underpowered test.

Definition of Chart-extracted Exacerbations of HF. The essential feature of coding chart-extracted exacerbations of HF (CEEs) was that the clinician judged that the patient was suffering from the decompensation of the underlying HF, along with supporting evidence in the clinical record to ensure that an exacerbation was being clearly designated. CEEs were defined as the presentation and documentation of at least two of the common following symptoms HF: new/worsened edema, increased weight, worsened dyspnea (at rest or on exertion), worsened orthopnea, worsened paroxysmal nocturnal dyspnea, jugular venous distention, and/or the decision by the physician to increase diuretic medication. If the symptoms present were not specific to HF when considering other conditions that the patients had (i.e., dyspnea attributed to chronic obstructive pulmonary disease), then that particular symptom was discounted. Exacerbations were also designated if the clinician explicitly noted in the electronic record that the patient was “volume overloaded” or “decompensated.”

The total number of exacerbations was divided by the length of time in years that each patient’s electronic record was followed (see coding procedures), yielding an index of the number of adjusted exacerbations per year. An effort was made to define discrete exacerbations so that the index would not be artificially inflated. Patients who were evaluated in the emergency department or in an outpatient visit with their cardiologist and then subsequently hospitalized due to HF exacerbation were not counted for more than one exacerbation for this instance. Similarly, clinical symptoms across consecutive daily evaluations, such as in an inpatient hospitalization, were not counted more than once as an exacerbation.

Coding Procedures: Our goal was to sample a sufficient period of time surrounding the entry of the patient into the clinical database to estimate CEEs and predict mortality risk on a prospective basis from that date of entry. The notes in subjects’ electronic records at the PVAMC were examined for clinical events such as outpatient visits with primary care or cardiology service appointments, hospitalizations, emergency department visits, and were coded for involving CEE of HF. Clinical events

were recorded for each patient beginning one year prior to the patient's entry into the screening database for the pilot study [7] until either 1) the patient died, 2) six months past the termination of recruitment for the adherence pilot study, 3) until the patient was removed from consideration for the pilot study (i.e., due to dementia or another disqualifying condition). Patients were followed an average of 1.5 years, with a range of 1.0 – 2.3 (see Figure 1). Patients needed at least 1 year of data (entry into the database minus 1 year) to be considered for the current study. CEEs were adjusted for most analyses, normalizing the index to the rate of CEEs per year. We also counted hospitalizations and created a similar index of hospitalizations per year for the analyses described below.

Other clinical information was also coded from the patients' electronic records, including the number of conditions noted in the following areas: 1) diabetes, 2) other endocrine disorders, 3) hypertension, 4) stroke, 5) circulatory disorders, 6) autoimmune or joint disease, 7) upper gastrointestinal diseases, 8) lower gastrointestinal diseases, 9) pulmonary disorders, 10) vision problems, 11) auditory problems, 12) skin diseases, 13) cancer, 14) liver diseases, 15) gall bladder disease, 16) kidney disease, 17) broken bones, 18) anemia, 19) nutritional problems, 20) neurological disorders, 21) back or neck problems, 22) bleeding disorders. NYHA Class, as assigned by the patient's cardiologist or nurse practitioner closest to the date of the patient's entry into the tracking database, was recorded for each patient. Forty-five percent of the patients (N=88) did not have NYHA Class designations on the electronic record.

Assessment of mortality. We examined the patients' electronic records for evidence of mortality for the 2-year period following each patient's date of entry into the screening database so that each patient would have a standard follow-up period regarding mortality. Approximately 1 year elapsed between the final closing date of the follow-up period and the final chart examination to determine if each patient died. This ensured that the report of death would appear in the veterans' clinical records (if the patient had indeed died) when death occurred in care settings outside the Veterans Health Administration system.

Additional measures. Patients who entered the adherence pilot study (N = 40) had available additional measures assessed by interview, and 27 patients were assessed at one or more additional interviews in which a 6-minute walk test was administered. [8] Measure relevant to the current study

include the Kansas City Cardiomyopathy Questionnaire [9] the Hamilton Depression Rating Scale [10], the Beck Hopelessness Scale [11], a 25-item version of the Hopkins symptoms Checklist [12, 13], and the 6-minute walk test [8]. The mean of the available distances walked in the latter measure was used in the analyses presented below. These measures have demonstrated reliability and validity for use with this population.

The procedures for screening the patients and including them in the current database study were reviewed and approved by the IRB of the Philadelphia VAMC.

RESULTS

Descriptive data regarding clinical exacerbations. Most of the patients (72.2%) had at least 1 chart extracted exacerbation (CEE) over the 1 – 2.3 year follow-up period. The distribution of the absolute number of CEEs in ascending order was as follows: 0 – 27.8%, 1 – 31.4%, 2 – 15.2%, 3 – 11.0%, ≥ 4 – 14.6%. The mean and range of the CEEs per year, after adjusting for the length of each patient's follow-up period, was $M = 1.23$ ($SD = 1.41$), range, 0 – 8.2.

Reliability. In order to estimate the reliability of judgments regarding the occurrence of CEEs of HF, the judgments of two research assistants were examined on a subset of 15% of the patients ($N = 30$; a total of 270 visits or clinical events). For purposes of coding for the final data and the reliability analyses, the visits examined included outpatient visits to the patient's cardiology provider, primary care provider, emergency department provider, or inpatient provider. The two raters were highly reliable in identifying CEEs (or identifying an event and deciding there was no exacerbation): Cohen's kappa=.83. Errors in date identification of the clinical event (i.e., outpatient visit) had been reconciled prior to the analysis.

Associations of exacerbations with clinical and demographic factors. The index of CEE of HF, adjusted for the length of follow-up period, was associated with factors reflecting poorer cardiac functioning (see Table 2). The CEE index was positively corrected with higher NYHA Class, and negatively correlated with functional status on the KCCQ and distance walked on the 6 MWT. As indicated in the table, the index of HF exacerbations was not associated with the number of comorbid medical conditions, age, or the left ventricle ejection fraction.

We also examined whether the number of exacerbations differed by White vs. non-White race as well as marital status, using t-tests of independent samples. CEE did not differ by race, $t = -1.22$, $p > .05$, $df = 189$, nor marital status, $t = -0.30$, $p > .05$, $df = 180$.

In order to examine evidence that the CEE index reflected increasingly poorer functioning in an ordinal fashion, we examined the mean number of CEE adjusted for follow-up period, within each of the NYHA Classes. As can be see in Table 1, the mean CEEs increased in an ordinal fashion over the NYHA Classes represented by patients in the sample. The 95% confidence intervals suggest, however, that there is some overlap of the CEEs across the NYHA Classes.

Prediction of mortality. A total of 30.4% ($N = 58$) of the patients died over the 2-year mortality follow-up period. We used logistic regression to examine whether CHF exacerbations predicted risk of mortality in this sample of patients, first testing a model with the following demographic and clinical variables as covariates: age, number of comorbid conditions, presence/absence of relationship partner, and White vs. non-White race. The results are presented in Table 3, and suggest that only the number of comorbid conditions was a significant covariate. Including NYHA class and lowest LVEF limited the sample by almost half, and so we did not examine a model including those variables. The second model in the table examined CEEs as a predictor of mortality over the two years considering only the number of comorbid conditions as a covariate.

An index of the number of adjusted hospitalizations per year were included in the final model in Table 3 in order to examine the utility of the CEE index after adjusting for this common surrogate endpoint. The results suggested that CEEs still conferred increased odds of 33% risk of mortality for each additional exacerbation per year, even when all-cause hospitalization rate was taken into account. Thus, the findings suggest that each additional HF exacerbation increased the odds of mortality over the span of the study. The magnitude of the association is noteworthy when compared to the effects of medical comorbidity.

Survival odds associated with clinical exacerbations. We conducted a series of survival analyses in order to test the predictive value of CEE over the course of two years, using the Kaplan-Meier estimates of the survival function, with the time variable being the number of days from the entry of the

patient into the study database and death. The data were right-censored by the end of the follow-up period for examining mortality (i.e., 730 days), for patients who remained alive at the end of the study.

After examining the distribution of the exacerbation data, we tested two different cut-points strategies for defining the strata in the survival models in order to examine evidence for a criterion number of CEEs that confer risk of mortality over a 2-year follow up period. We first defined three strata using the number of CEEs adjusted for the length of the CEE follow-up period in the following way: $CEE = 0$, $0 < CEE \leq 1$, and $CEE > 1$. The number of comorbid medical conditions was entered as a covariate in each analysis because of the demonstrated importance of the variable in previous analyses. The test of heterogeneity of the strata was significant, indicating that the survival curves for the strata did differ, $\chi^2 = 9.53$, $p < .01$, $df = 2$. The comorbidity covariate also was significant, $\chi^2 = 3.95$, $p < .05$, $df = 1$, indicating greater mortality risk associated with greater medical comorbidity. There was little separation between the survival curves for the groups with no exacerbations (77% survived) and those having an adjusted $CEE \leq 1$ (76% survived), compared to those having more than 1 (54% survived).

The second strategy defined two strata using a cut-point of 2 adjusted CEEs in the following way: $0 \leq CEE \leq 2$ and $CEE > 2$. The test of heterogeneity of the strata was significant, indicating that the survival curves for the strata were significantly different, $\chi^2 = 8.47$, $p < .005$, $df = 1$, and the comorbidity covariate was significant, $\chi^2 = 4.09$, $p < .05$, $df = 1$. As shown in Figure 1, patients with greater than 2 adjusted CEEs survived at a lower rate, 46%, compared to those with 2 or fewer adjusted CEEs, of whom 73% survived. The figure indicates that a good portion of mortality occurred within 100 days of the entry into the study, suggesting that patients with relatively higher numbers of clinical exacerbations were at greatest risk of dying in within the short-term (i.e. $< \frac{1}{2}$ year).

DISCUSSION AND CONCLUSIONS

The central theme of the findings is that exacerbations of heart failure can be judged reliably from clinical notes by non-medical personnel and appear to be an early indicator of patients at risk of mortality. The index of HF exacerbations was associated with other indices of poor clinical functioning, NYHA class, HF related quality of life, and a measure of exercise capacity but was not associated with the

patients' mean or lowest LVEF, age or the number of comorbid medical conditions. The index was a significant predictor of risk of mortality over 2-year period, even after adjusting for a variety of covariates. Preliminary evidence supports the role of this index as surrogate endpoint for mortality and disease-related quality of life.

Importantly, our index of exacerbations was associated with increased risk of mortality even after adjusting for the patients' number of hospitalizations per year and medical comorbidity. This suggests that exacerbations carry additional information about mortality risk over and above the overall severity of illness. Combined with the consistent associations with cardiac-related measures of functioning, the findings suggest that exacerbations represent mortality risk associated with poorer cardiac functioning and the progression of cardiac disease. This notion is consistent with evidence that patients with advanced heart failure develop nonresponsiveness to standard treatments such as furosemide. In a study by MacFadyen and colleagues,[14] the primary factor in patients' poorer response to chronic furosemide treatment was intrarenal diuretic resistance, as opposed to non-adherence to the treatment. The authors suggested that increased resistance to diuretic medication and renal deterioration might serve as surrogate endpoints for the progression of the illness.

Other factors than illness progression may result in clinical exacerbations, such as medication nonadherence, leading to the question of the appropriateness of the CEE index as a surrogate endpoint for mortality. Mortality, however, can also be adversely affected by poor treatment adherence. Similarly, poor education in self-care of HF can affect mortality risk, but clearly these factors affect mortality through influence on general illness progression and patients becoming volume-overloaded, which are central to the assessment of clinical exacerbations. Future research examining the escalation of clinical exacerbations in relation to the patient's death may be particularly useful in understanding the predictive role of this index. As noted in the introduction, changes in surrogate endpoints should be proportionally associated with changes in a gold standard endpoint (i.e., death) and research is needed to document this with CEEs.

This index of clinical exacerbations might be especially useful for signs of increased mortality risk for patients in clinical trials, particularly in cases when a patient is not hospitalized for a clinical

exacerbation. The current data suggest that it may be prudent to withdraw patients participating in a medication or care management randomized trial who decompensate repeatedly, when the experimental treatment represents an untested or higher risk approach to therapy. Another advantage to the index is that the cost of obtaining information on the occurrence of an exacerbation is minimal, especially when recorded prospectively. The advent of clinical tests for B-type natriuretic peptide (BNP) [15], may sharpen the identification and proper response to clinical exacerbations of HF. The basic strategy, however, of identification of clinical exacerbations appears to be a useful method of detecting patients who may be at relatively early risk of mortality.

Our current strategy of following patients in an outpatient cardiology clinic in a VA medical center setting led to a number of limitations to the study. As noted above many patients may become nonresponsive to diuretic treatment and maintain a chronic fluid-overloaded state. This status is undoubtedly associated with increased mortality risk, but our method of counting exacerbations did not take into account patients who may have been in this chronic state. Also, our periods of follow-up varied by patient, leading to potential error in identification of exacerbations for patients with relatively shorter follow-up periods for detecting these episodes. Additionally, lack of our coders being blind to death status may have led to bias in recording CEEs. Coders could have been aware of patients who had died when they noted clinical exacerbations when surveying the electronic record. The assessment of clinical exacerbations was partly retrospective, in that we examined the 1-year period prior to the entry of the patient into the screening database. Furthermore, we may have missed some clinical exacerbations in creating the CEE index. A portion of the patients had additional providers outside the VA medical system, and exacerbations that occurred were not necessarily reported on in the patient's electronic record in a reliable manner (i.e., hospitalizations that occurred in non-VA institutions). Finally, as noted above, a number of patients lacked information in the electronic record, such as NYHA Class or LVEF, which was necessary for building comprehensive predictive models of outcome.

Future prospective research is needed to examine fully the potential utility of the index of chart-extracted exacerbations of HF as a surrogate endpoint for mortality or disease-related quality of life.

Preliminary evidence, however, suggests that this index may serve well as a surrogate endpoint for both mortality and HF-related quality of life.

REFERENCES

1. National Heart Lung and Blood Institute, *Congestive Heart Failure in the United States: A New Epidemic*. 1996, US Dept of Health and Human Services: Bethesda, Md.
2. Anand, I.S., V.G. Florea, and L. Fisher, *Surrogate end points in heart failure*. *Journal of the American College of Cardiology*, 2002. **39**(9): p. 1414-21.
3. Cohn, J.N., et al., *A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure*. *Vesnarinone Trial Investigators*. *New England journal of medicine*, 1998. **339**(25): p. 1810-1816.
4. Packer, M., J. Rouleau, and K. Swedberg, *Effect of flosequinan on survival in chronic heart failure: Preliminary results of the PROFILE study (abstr.)*. *Circulation*, 1993. **88**(Suppl 1): p. 301.
5. Rector, T.S. and J.N. Cohn, *Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan*. *Pimobendan Multicenter Research Group.*, in *American heart journal*. 1992. p. 1017-1025.
6. Patrick, D.L. and P. Erickson, *Concepts of Health-Related Quality of Life, Health Status, and Health Policy*. *Quality of Life in Health Care evaluation and Resource Allocation*, 1993. **76**(1): p. 201-206.
7. Sayers, S., et al. *Depression, family environment, and adherence to treatment of heart failure*. in *Annual Meeting of the Society of Behavioral Medicine*. 2003. Salt Lake City, Utah.
8. Guyatt, G.H., et al., *The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure*. *Canadian Medical Association Journal*, 1985. **132**(8): p. 919-923.
9. Green, C.P., et al., *Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure*. *Journal of the American College of Cardiology*, 2000. **35**(5): p. 1245-1255.

10. Hamilton, M., *A rating scale for depression*. Journal of Neurology, Neurosurgery, and Psychiatry, 1960. **23**: p. 56 - 65.
11. Beck, A.T., R.A. Steer, and M.G. Garbin, *Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation*. Clinical Psychology Review, 1988. **8**(1): p. 77-100.
12. Derogatis, L.R., et al., *The Hopkins Symptom Checklist (HSCL): A self-report symptom inventory*. Behavioral Science, 1974. **19**: p. 1-15.
13. Hough, R.L., et al., *Comparison of psychiatric screening questionnaires for primary care patients (Final report for National Institute of Mental Health Contract No. 2778-81-0036 [DB])*.
14. MacFadyen, R.J., et al., *Furosemide responsiveness, non-adherence and resistance during the chronic treatment of heart failure: a longitudinal study*. British journal of clinical pharmacology, 2004. **57**(5): p. 622-631.
15. Dao, Q., et al., *Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting*. Journal of the American College of Cardiology, 2001. **37**(2): p. 379-385.

Table 1 Frequency of Patients in each New York Heart Association Class

NYHA Class	Frequency	percent	Mean Adjusted Exacerbations	95% C.I.
I	20	19.4	0.45	0.20 – 0.70
I/II	9	8.7	0.67	0.09 – 1.25
II	40	38.8	1.41	0.94 – 1.89
II/III	13	12.6	1.49	0.69 – 2.29
III	21	20.4	2.39	1.45 – 3.32
III/IV – IV	0	0	–	–
Total	103	100.0	–	–

Notes: NYHA = New York Heart Association.

95% CI = 95% confidence interval.

N = 88 who were missing any designation of NYHA Class at the time of entry into the screening database.

Table 2 Correlations of Adjusted Exacerbations with Clinical and Demographic Variables

	Comorbidity Conditions	Age	Minimum LVEF	Mean LVEF	NYHA	KCCQ	Mean 6MWT distance
Adjusted Exacerbations Per Year	0.14	0.13	-.03	.02	0.41***	-.37*	-.47**
N	191	191	184	186	103	41	27

Notes: * $p < .05$. ** $p < .01$. *** $p < .001$.

NYHA = New York Heart Association Class (I = 1, I/II = 2, II = 3, etc.)

LVEF = Left Ventricle Ejection Fraction

KCCQ = Kansas City Cardiomyopathy Questionnaire-Functional Status (higher scores = better functioning)

6MWT distance = Distance walked in the 6 Minute Walk Test.

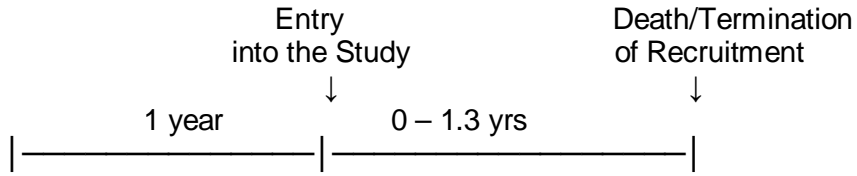
Table 3 Logistic Regression Models of Mortality

	Variable	OR	95% CI	<i>p</i>
Covariates only model				
N = 182, $\chi^2 = 13.97, p < .001$	Age	1.03	1.00 – 1.06	Ns
	Comorbid Conditions	1.24	1.07 – 1.43	< .01
	Partner	0.87	0.43 – 1.76	Ns
	Race	1.47	0.73 – 2.97	Ns
CEE model				
N = 191 $\chi^2 = 20.41, p < .0001$	Comorbid Conditions	1.19	1.04 – 1.37	< .05
	CEEs	1.48	1.17 – 1.87	< .005
CEE and Hospitalization model				
N = 191 $\chi^2 = 28.87, p < .0001$	Comorbid Conditions	1.15	0.99 – 1.33	ns
	Hospitalizations	1.58	1.14 – 2.19	< .01
	CEEs	1.33	1.02 – 1.72	< .05

OR = odds ration. 95% CI = 95% confidence interval. CEE = Chart Extracted Exacerbations.

Figure 1

Follow-up Period For Coding Exacerbations



Follow-up Period for Death Determination

