HHS Public Access

Author manuscript

Am Heart J. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Am Heart J. 2015 December ; 170(6): 1124–1132. doi:10.1016/j.ahj.2015.09.001.

Differences in Health Care Use and Outcomes by the Timing of In-Hospital Worsening Heart Failure

Lauren B. Cooper, MD[a,b], **Bradley G. Hammill, DrPH**[a], **Puza P. Sharma, MBBS, MPH, PhD**[c], **Adam D. DeVore, MD**[a,b], **Robert J. Mentz, MD**[a,b], **Gregg C. Fonarow, MD**[d], **Peter S. Pang, MD, MSc**[e], **Lesley H. Curtis, PhD**[a,b], and **Adrian F. Hernandez, MD, MHS**[a,b]

[a]Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina

[b]Department of Medicine, Duke University School of Medicine, Durham, North Carolina

[c]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey

[d]Ahmanson-UCLA Cardiomyopathy Center, University of California, Los Angeles

[e]Department of Emergency Medicine, Indiana University School of Medicine, Indianapolis, Indiana.

Abstract

Background—Patients hospitalized with acute heart failure may experience worsening symptoms requiring escalation of therapy. In-hospital worsening heart failure is associated with worse in-hospital and postdischarge outcomes, but associations between the timing of worsening heart failure and outcomes is unknown.

Methods—Using data from a large clinical registry linked to Medicare claims, we examined characteristics, outcomes, and costs of patients hospitalized for acute heart failure. We defined in-hospital worsening heart failure by the use of inotropes or intravenous vasodilators, or initiation of mechanical circulatory support, hemodialysis, or ventilation. The study groups were early worsening heart failure (n = 1990), late worsening heart failure (n = 4223), complicated presentation (n = 15,361), and uncomplicated hospital course (n = 41,334).

Address for correspondence: Lauren B. Cooper, MD, Duke Clinical Research Institute, PO Box 17969, Durham, NC 27715, USA; telephone: 919-684-8111; fax: 919-681-9842; lauren.b.cooper@duke.edu..

Additional Contributions: Damon M. Seils, MA, Duke University, provided editorial assistance and prepared the manuscript. Mr Seils did not receive compensation for his assistance apart from his employment at the institution where the study was conducted.

Disclosures: Dr Pang reported receiving honoraria from Relypsa and Palatin Technologies; and serving as a consultant for Cardioxyl, Intersection Medical, INSYS, Janssen, Medtronic, Novartis, Roche Diagnostics, scPharmaceuticals, Trevena, and Roche Diagnostics. Dr Fonarow reported serving as a consultant for Amgen, Bayer, Gambro, Janssen, Medtronic, and Novartis. Dr Curtis reported receiving research support from Boston Scientific, Bristol-Myers Squibb, GE Healthcare, GlaxoSmithKline, Johnson & Johnson, Medtronic, Merck, and Novartis. Dr Hernandez reported receiving research support from the American Heart Association, Amgen, and Novartis. Dr DeVore reported receiving research support from the American Heart Association, Amgen, Maquet, and Thoratec. Dr Mentz reported receiving research support from Amgen, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Novartis, Otsuka, and ResMed; receiving honoraria from Thoratec; and serving on an advisory board for Luitpold Pharmaceuticals, Inc. No other disclosures were reported.

Results—Among 62,908 patients, those with late in-hospital worsening heart failure had higher in-hospital and postdischarge mortality than patients with early worsening heart failure or complicated presentation. Those with early or late worsening heart failure had more frequent all-cause and heart failure readmissions at 30 days and 1 year, with resultant higher costs, compared with patients with an uncomplicated hospital course.

Conclusion—Although late worsening heart failure was associated with the highest mortality, both early and late worsening heart failure were associated with more frequent readmissions and higher health care costs compared to uncomplicated hospital course. Prevention of worsening heart failure may be an important focus in the care of hospitalized patients with acute heart failure.

Keywords

Disease Progression; Heart Failure; Hospitalization; Outcome Assessment (Health Care)

Introduction

Acute heart failure is a costly public health problem that results in more than 1 million hospitalizations annually in the United States.[1] More patients 65 years and older are hospitalized for a primary diagnosis of heart failure than for any other condition.[2] Some patients admitted with acute heart failure will experience a worsening of their condition during hospitalization. Worsening heart failure is defined as persistent or worsening symptoms requiring escalation of therapy.[3-7] In-hospital worsening heart failure is associated with poorer in-hospital and postdischarge outcomes, including mortality, readmission, and higher costs.[8] Outcomes are similar for patients who experience worsening heart failure in the first few days of hospitalization or later in the hospitalization.[9] However, it is unknown whether there is a difference in outcomes and health care expenditures for patients who experience in-hospital worsening heart failure very early in the hospitalization (ie, during the first day) or later in the hospital course.

We sought to describe the characteristics of patients hospitalized for heart failure by the presence and timing of in-hospital worsening heart failure and examine associations between timing of worsening heart failure and mortality, readmission, and health care costs.

Methods

Data Sources

The Acute Decompensated Heart Failure National Registry (ADHERE) was a multicenter registry of patients hospitalized with acute heart failure in the United States.[10] All adult patients hospitalized with new-onset or decompensated heart failure were eligible for inclusion in the registry.[10] Each participating institution had institutional review board approval for participation in the registry. More than 185,000 patients from more than 300 medical centers were enrolled between January 2001 and March 2006. Data were collected via retrospective chart review.

We obtained Medicare fee-for-service standard analytic claim files from the Centers for Medicare & Medicaid Services (CMS). Medicare claims contain information about inpatient

and outpatient services rendered and procedures performed and associated payment information. In addition, Medicare denominator files contain information about patient demographic characteristics, including information about eligibility and enrollment and death.

We linked the Medicare data and the registry data using a previously described method.[11] The institutional review board of the Duke University Health System approved the study.

Study Population

The study population consisted of Medicare fee-for-service beneficiaries 65 years or older who had a hospitalization recorded in the ADHERE registry between January 1, 2001, and December 31, 2004. Registry data after 2005 did not include information about the timing of inotrope administration and were not included in this study. We required that patients be enrolled in fee-for-service Medicare for at least 6 months before the index hospitalization. We excluded patients with elective admissions. We excluded patients who died in the hospital, left against medical advice, or were discharged or transferred to another short-term hospital or hospice from the measurement of 30-day and 1-year outcomes.[12] The ADHERE registry collected information on individual hospital admissions, not individual patients, some patients had multiple enrollments in the registry. For this analysis, we selected the first admission in the registry for each patient.

Study Groups

Consistent with previously published studies, we defined in-hospital worsening heart failure on the basis of the use of intravenous inotropes or vasodilators; mechanical support including ventilator, dialysis, intra-aortic balloon pump, or left ventricular assist device; or an intensive care unit (ICU) stay during the index hospitalization.[8] We assigned patients to 1 of 4 comparison groups: early in-hospital worsening heart failure, late in-hospital worsening heart failure, complicated presentation, and uncomplicated hospital course. To highlight decompensation that occurs early in the hospital course, we categorized worsening heart failure by whether it occurred during the first hospital day or after the first hospital day. “Early inhospital worsening heart failure” occurred during day 1 of the hospitalization (ie, 12 to 24 hours after presentation). “Late in-hospital worsening heart failure” occurred after the first day of the hospitalization. As in previous analyses, we classified patients who met the worsening heart failure criteria during the first 12 hours after presentation as having a complicated presentation, and classified patients who did not meet the worsening heart failure criteria during the hospitalization as having an uncomplicated hospital course.[8] We used the earliest time point recorded or retrievable in the medical record to determine the baseline time point. We excluded patients who were transferred to an ICU but for whom the timing of transfer was not available.

Outcomes

Postdischarge outcomes of interest were all-cause mortality, all-cause readmission, readmission for heart failure, days alive and out of the hospital, and Medicare payments. We summarized these outcomes at 30 days and 1 year after discharge. We excluded patients from calculations of all postdischarge outcomes if they died in the hospital, left against

medical advice, or were transferred to another short-term hospital or hospice. Moreover, we excluded patients who enrolled in Medicare managed care during the follow-up period from calculations of the payment outcomes and of days alive and out of the hospital. We also measured all-cause mortality, length of stay, and Medicare payments associated with the index hospitalization.

We obtained information about all outcomes from the Medicare data. Death dates were available in the Medicare denominator files. Readmissions were identified from subsequent inpatient claims. Heart failure readmissions were identified by claims having a primary diagnosis of heart failure (International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code 428.×, 402.×1, 404.×1, or 404×3). Days alive and out of the hospital were calculated based on mortality and readmission dates identified above. Medicare payments were obtained from Medicare inpatient, outpatient, and professional claims. Payment information was adjusted for inflation using the Consumer Price Index medical care component and reported in 2010 US dollars.

Patient Characteristics

Patient characteristics were ascertained from ADHERE registry documentation, including demographic characteristics, medical history, findings from the initial evaluation, vital signs, laboratory test results, admission and discharge medications, and the year of the index hospitalization.

Statistical Analysis

We describe the baseline characteristics of the study population using frequencies and percentages for categorical variables and means with SDs or medians with interquartile ranges for continuous variables. We tested for differences between groups using χ^2 tests for categorical variables and Kruskal-Wallis test for continuous variables.

We present the observed outcomes by study group. We summarize in-hospital mortality using frequencies and percentages, and we used χ^2 tests to assess differences between groups. We summarize length of stay, days alive and out of the hospital, and Medicare payments using means with SDs or medians with interquartile ranges, and we used Kruskal-Wallis tests to assess differences between groups. Calculations of the incidence of postdischarge mortality were based on Kaplan-Meier estimates, and we used log-rank tests to assess differences between groups. For both readmission outcomes, we estimated incidence using the cumulative incidence function, which accounts for the competing risk of mortality, and we assessed differences between groups using Gray tests.

We estimated unadjusted and adjusted hazard ratios (HRs) for all pairwise study group comparisons for all-cause mortality, all-cause readmission, and heart failure readmission at 30 days and 1 year using Cox proportional hazards models. We used robust standard errors to account for clustering of patients within hospitals. We used linear mixed models to estimate the unadjusted and adjusted differences between the groups in the number of days alive and out of the hospital. We estimated unadjusted and adjusted cost ratios for average postdischarge Medicare payments between the groups using generalized linear mixed models with a log link and a Poisson error distribution that allowed for overdispersion. In

the mixed models, we allowed for hospital-level random intercepts to account for clustering of patients within hospitals. All unadjusted models included only the study group indicators. Consistent with previous studies, the adjusted models also controlled for patient baseline demographic characteristics, medical history, findings from the initial evaluation, vital signs, laboratory test results, and medications.[8,13]

Because of the number of outcomes in the study, we used $\alpha = .01$ to establish statistical significance and we report 99% CIs. We used SAS version 9.3 (SAS Institute Inc, Cary, North Carolina) for all analyses.

Results

Table 1 shows the baseline characteristics of the study population. The study population included 62,908 patients, of whom 1990 (3.2%) had early in-hospital worsening heart failure, 4223 (6.7%) had late in-hospital worsening heart failure, 15,361 (24.4%) had a complicated presentation, and 41,334 (65.7%) had an uncomplicated hospital course. A small percentage of patients (n = 819 [1.3%]) may have experienced in-hospital worsening heart failure, as indicated only by a transfer to the ICU during the hospitalization, but were not included in the analysis because we did not have information about the timing of the transfers.

Table 2 shows the care received by patients during the index hospitalization. Patients with early in-hospital worsening heart failure were least likely to receive diuretics but most likely to receive dialysis, whereas patients with late in-hospital worsening heart failure were most likely to receive inotropes and mechanical ventilation. Patients with a complicated presentation were most likely to have an ICU stay during the index hospitalization but had the lowest rates of inotropes, dialysis, and mechanical circulatory support.

Table 3 shows the observed outcomes by study group. Patients with late in-hospital worsening heart failure had the longest length of stay (mean, 11.4 days) and highest index hospitalization costs, followed by patients with early in-hospital worsening heart failure (mean length of stay, 7.2 days). Patients with a complicated presentation or an uncomplicated hospital course had shorter hospital stays (mean, 6.3 and 4.8 days, respectively). Mortality rates were highest among patients with late in-hospital worsening heart failure—14.9% during the index hospitalization, 21.5% at 30 days, and at 52.2% at 1 year. All-cause readmission rates at 30 days and 1 year were highest among patients with early in-hospital worsening heart failure (30.4% and 73.7%, respectively), compared with patients with late in-hospital worsening heart failure (28.7% and 69.5%, respectively), complicated presentation group (12.9% and 39.7%, respectively), and uncomplicated hospital course group (7.3% and 32.7%, respectively). The main determinant of postdischarge Medicare payments is readmission; thus, patients who experience early in-hospital worsening heart failure had the highest postdischarge Medicare payments. **Figure 1** shows the Kaplan-Meier estimates of all-cause mortality, all-cause readmission, and heart failure readmission among patients with early and late in-hospital worsening heart failure.

Table 4 shows the unadjusted and adjusted associations between study group and outcomes. Compared with late in-hospital worsening heart failure, early in-hospital worsening heart failure was associated with lower mortality at 30 days (adjusted HR, 0.69; 99% CI, 0.57-0.83) and 1 year (adjusted HR, 0.81; 99% CI, 0.73-0.90). However, both groups had similar rates of all-cause and heart failure readmission. Although both groups had similar postdischarge Medicare payments at 30 days (adjusted cost ratio, 1.01; 99% CI, 0.86-1.17), early in-hospital worsening heart failure was associated with higher Medicare payments at 1 year (adjusted cost ratio, 1.12; 99% CI, 1.03-1.21).

Patients in the early in-hospital worsening heart failure and complicated presentation groups had similar mortality at 30 days (adjusted HR, 1.00; 99% CI, 0.85-1.19) and 1 year (adjusted HR, 1.06; 99% CI, 0.96-1.18) and similar rates of all-cause and heart failure readmission. However, compared with complicated presentation, early in-hospital worsening heart failure was associated with higher postdischarge Medicare payments at 1 year (adjusted cost ratio, 1.09; 99% CI, 1.02-1.17).

For all associations, uncomplicated presentation had more favorable outcomes than early or late in-hospital worsening heart failure (**Supplemental Table**).

Discussion

Using data from a large clinical registry of patients with acute heart failure in the United States, we examined associations between the timing of in-hospital worsening heart failure and patient outcomes. Patients with early and late in-hospital worsening heart failure had similar rates of comorbid conditions, with the exception that patients with early in-hospital worsening heart failure had more renal insufficiency. Patients with a complicated presentation or with inhospital worsening heart failure had more comorbid conditions, higher disease burden, and worse outcomes than patients with an uncomplicated hospital course. Patients with late in-hospital worsening heart failure had the longest and most costly hospitalizations and the highest rates of in-hospital and postdischarge mortality. Whereas late worsening heart failure was associated with higher mortality than early worsening heart failure, rates of all-cause and heart failure readmission were similar between the groups. Patients with a complicated presentation had the highest rates of ICU stay, but the stays were shorter than for those with worsening heart failure. Outcomes of patients with complicated presentation and early worsening heart failure were similar with respect to mortality and readmissions. However, at 1 year, patients with complicated presentation spent an average of 20 more days alive and out of the hospital that those with early in-hospital worsening heart failure.

Our findings are consistent with previous clinical trials and registry studies, which found that in-hospital worsening heart failure is associated with longer hospitalizations, more frequent readmissions, and higher mortality.[8,14-19] Although many of these studies used slightly different definitions of worsening heart failure, the overall message remains consistent. Our findings differ from previous studies that showed that outcomes did not differ according to whether worsening heart failure occurred before or after the fourth hospital day.[9,18] To our knowledge, our study is the first to examine whether worsening

heart failure in the first 24 hours differs from worsening heart failure later in the hospitalization. We selected this time point was on the basis of clinical relevance, because the first hospital day is often when the patient either responds to the initial therapy or worsens. We found that outcomes do vary by this cut point. Early in-hospital worsening heart failure is associated with more hospital readmissions and higher health care costs, whereas late in-hospital worsening heart failure is associated with longer hospitalizations and higher in-hospital and postdischarge mortality.

Our results have important implications for the care of patients with acute heart failure. Treatment strategies that reduce in-hospital worsening heart failure may improve in-hospital and postdischarge outcomes and reduce health care expenditures. Our data suggest that patients with a complicated presentation, compared with those who experience worsening heart failure, differ in important ways. The complicated presentation group and the early worsening heart failure group were similar in terms of baseline characteristics and presentation but received different inhospital care and had different outcomes. We defined early in-hospital worsening heart failure to capture patients who were stable at the time of admission and experience decompensation during the first day of hospitalization. However, our findings show that the groups did not differ at baseline but diverged shortly thereafter, with the complicated presentation group receiving more aggressive therapy initially. The consequences of this variation in treatment were that patients with early in-hospital worsening heart failure spent an average of 20 fewer days alive and out of the hospital than those with a complicated presentation. This finding suggests that prompt identification and management for the prevention of early worsening heart failure may lead to better outcomes. These findings highlight the importance of early recognition and aggressive management of acute heart failure in the emergency department and by admitting physicians.

Different factors may account for the timing of in-hospital worsening heart failure. Patients with complicated presentation were those whose clinical instability was recognized early and treated appropriately. Patients with early in-hospital worsening heart failure, while similar at baseline to patients with complicated presentation, were treated less aggressively on arrival. This finding suggests that early in-hospital worsening heart failure may be driven by initial misdiagnosis, inadequate initial therapy, ineffective therapeutic response, or improper level of care decisions, again highlighting the need for the emergency department and admitting providers to promptly identify and aggressively treat appropriately upon presentation. Patients with late in-hospital worsening heart failure were those who did not respond to standard therapies or whose worsening status was not recognized until later in the hospital course, resulting in longer length of stay and increased risk for complications and poor outcomes.

Our study has several limitations. The study population included only patients 65 years and older enrolled in the ADHERE registry with Medicare data. The results may not be generalizable to other groups of patients with acute heart failure, though a previous study suggests that patients in the ADHERE registry are representative of the Medicare fee-for-service heart failure population.[12] Associations with outcomes may be influenced by residual measured and unmeasured confounders. There are limitations related to the definitions of early and late inhospital worsening heart failure. Our definitions of timing

were selected on the basis of clinical experience rather than on previous studies. To highlight the important difference between patients who have adequate response vs inadequate response to early in-hospital therapy, we defined early in-hospital worsening heart failure as occurring on the first hospital day and late inhospital worsening heart failure as occurring after the first hospital day. Data constraints also limited our study in several ways. First, although the decision to escalate care was based purely on the clinical judgment of the provider, we did not have information regarding the reason for the escalation of care. However, in this registry of acute decompensated heart failure, we considered this escalation to be due to worsening heart failure. The definition of what constitutes in-hospital worsening heart failure in ADHERE was different than the definition used in other studies, including RELAX-AHF. We used a 12-hour window for initiation of inotropes or vasodilators to mitigate the risk of misclassifying patients who had a complicated presentation.[7, 19] Second, we were unable to include the group of patients with in-hospital worsening heart failure indicated only by transfer to an ICU during the hospitalization, because we did not have information about the timing of ICU transfers. Third, we were unable to incorporate information about initiation of ultrafiltration or up-titration of inotropes, vasodilators, or diuretics; or hourly timing of mechanical ventilation. These are variables that have been used in other studies to define worsening heart failure. Although all studies use the concept of worsening clinical course requiring escalation of therapy, there is no consensus about the variables that constitute escalation of therapy. Our definition of worsening heart failure was restricted because of the lack of these variables in our data set. Despite this limitation, our data set provides a unique opportunity to examine worsening heart failure in a real-world, older heart failure population. As a result of these limitations, we were unable to analyze data regarding response or lack of response to initial therapy, further complicating the distinction between complicated presentation and early in-hospital worsening heart failure.

In conclusion, in-hospital worsening heart failure can occur at varying times during the hospital course, either on presentation, early in the hospitalization, or late in the hospitalization. Although late in-hospital worsening heart failure was associated with higher mortality, both early and late in-hospital worsening heart failure were associated with more frequent readmissions and higher health care costs. Prevention of both early and late in-hospital worsening heart failure should be an important focus for payers and providers in the care of hospitalized patients with acute heart failure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support

The ADHERE registry was originally sponsored by Scios, Inc. This project was supported by a research agreement between Novartis Pharmaceuticals Corporation and Duke University. Dr Cooper was supported by grant T32HL069749-11A1 from the National Institutes of Health. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents. The content does not necessarily represent the official views of the Agency for Healthcare Research and Quality, the National Heart, Lung, and Blood Institute, or the National Institutes of Health.

References

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015; 131:e29–322. [PubMed: 25520374]
2. DeFrances CJ, Lucas CA, Buie VC, Golosinskiy A. National Hospital Discharge Survey. Natl Health Stat Report. 2006; 2008; (5):1–20.
3. McMurray JJ, Teerlink JR, Cotter G, et al. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. JAMA. 2007; 298:2009–19. [PubMed: 17986694]
4. Massie BM, O'Connor CM, Metra M, et al. Rolofylline, an adenosine a1-receptor antagonist, in acute heart failure. N Engl J Med. 2010; 363:1419–28. [PubMed: 20925544]
5. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med. 2011; 365:32–43. [PubMed: 21732835]
6. Packer M, Colucci W, Fisher L, et al. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. JACC Heart Fail. 2013; 1:103–11. [PubMed: 24621834]
7. Teerlink JR, Cotter G, Davison BA, et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet. 2013; 381:29–39. [PubMed: 23141816]
8. DeVore AD, Hammill BG, Sharma PP, et al. In-hospital worsening heart failure and associations with mortality, readmission, and healthcare utilization. J Am Heart Assoc. 2014; 3 pii: e001088.
9. Mentz RJ, Metra M, Cotter G, et al. Early vs. late worsening heart failure during acute heart failure hospitalization: insights from the PROTECT trial. Eur J Heart Fail. 2015; 17:697–706. [PubMed: 26083764]
10. Adams KF Jr, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the united states: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005; 149:209–16. [PubMed: 15846257]
11. Hammill BG, Hernandez AF, Peterson ED, Fonarow GC, Schulman KA, Curtis LH. Linking inpatient clinical registry data to medicare claims data using indirect identifiers. Am Heart J. 2009; 157:995–1000. [PubMed: 19464409]
12. Kociol RD, Hammill BG, Fonarow GC, et al. Generalizability and longitudinal outcomes of a national heart failure clinical registry: comparison of Acute Decompensated Heart Failure National Registry (ADHERE) and non-ADHERE Medicare beneficiaries. Am Heart J. 2010; 160:885–92. [PubMed: 21095276]
13. Mentz RJ, Mi X, Sharma PP, et al. Relation of dyspnea severity on admission for acute heart failure with outcomes and costs. Am J Cardiol. 2015; 115:75–81. [PubMed: 25456875]
14. Torre-Amione G, Milo-Cotter O, Kaluski E, et al. Early worsening heart failure in patients admitted for acute heart failure: time course, hemodynamic predictors, and outcome. J Card Fail. 2009; 15:639–44. [PubMed: 19786251]
15. Weatherley BD, Milo-Cotter O, Felker GM, et al. Early worsening heart failure in patients admitted with acute heart failure--a new outcome measure associated with long-term prognosis? Fundam Clin Pharmacol. 2009; 23:633–9. [PubMed: 19656213]
16. Cotter G, Metra M, Weatherley BD, et al. Physician-determined worsening heart failure: a novel definition for early worsening heart failure in patients hospitalized for acute heart failure--association with signs and symptoms, hospitalization duration, and 60-day outcomes. Cardiology. 2010; 115:29–36. [PubMed: 19844102]
17. Cotter G, Metra M, Davison BA, et al. Worsening heart failure, a critical event during hospital admission for acute heart failure: results from the VERITAS study. Eur J Heart Fail. 2014; 16:1362–71. [PubMed: 25371147]
18. Kelly JP, Mentz RJ, Hasselblad V, et al. Worsening heart failure during hospitalization for acute heart failure: insights from the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF). Am Heart J. In press.

19. Ponikowski P, Metra M, Teerlink JR, et al. Design of the RELAXin in acute heart failure study. Am Heart J. 2012; 163:149–55. e141. [PubMed: 22305830]

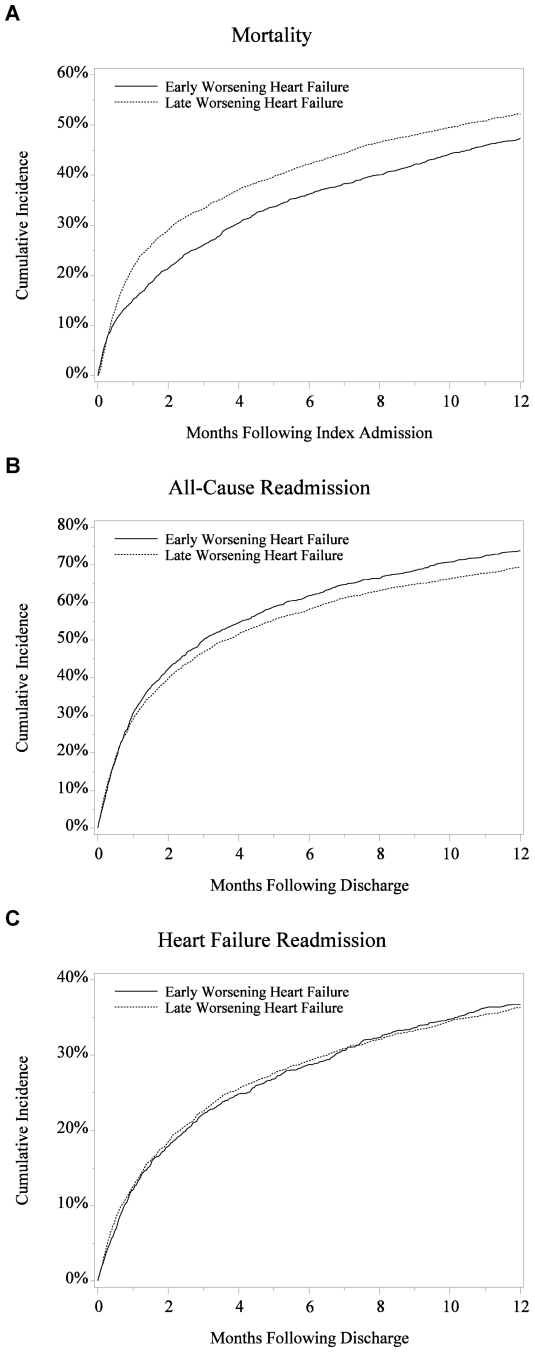

Figure.

Kaplan-Meier Estimates of All-Cause Mortality, All-Cause Readmission, and Heart Failure Readmission Among Patients With Early or Late In-Hospital Worsening Heart Failure

Panel A shows the Kaplan-Meier estimates of all-cause mortality at 1 year after admission from the index hospitalization for patients with early in-hospital worsening heart failure and late in-hospital worsening heart failure ($P < .001$).

Panel B shows the Kaplan-Meier estimates of all-cause readmission at 1 year after discharge from the index hospitalization for patients with early in-hospital worsening heart failure and

late in-hospital worsening heart failure (P = .03 for the unadjusted analysis; P = .60 for the adjusted analysis).

Panel C shows the Kaplan-Meier estimates for heart failure readmission at 1 year after discharge from the index hospitalization for patients with early in-hospital worsening heart failure and late in-hospital worsening heart failure (P = .54 for the unadjusted analysis; P = .30 for the adjusted analysis).

Table 1

Baseline Characteristics of the Study Population

Variable	Early Worsening Heart Failure (n = 1990)	Late Worsening Heart Failure (n = 4223)	Complicated Presentation (n = 15,361)	Uncomplicated Hospital Course (n = 41,334)	*P* Value
Age, mean (SD), y	77.5 (7.3)	78.0 (7.3)	78.3 (7.4)	80.3 (7.8)	< .001
Male, No. (%)	1032 (51.9)	2111 (50.0)	7224 (47.0)	16,678 (40.3)	< .001
Race, No. (%)					< .001
Black	276 (13.9)	457 (10.8)	1947 (12.7)	4802 (11.6)	
White	1622 (81.5)	3623 (85.8)	12,875 (83.8)	35,343 (85.5)	
Other/unknown	92 (4.6)	143 (3.4)	539 (3.5)	1189 (2.9)	
Medical history, No. (%)					
Anemia	1207 (60.7)	2572 (60.9)	7997 (52.1)	22,165 (53.6)	< .001
Atrial fibrillation	665 (33.4)	1505 (35.6)	5117 (33.3)	14,957 (36.2)	< .001
Chronic renal insufficiency	987 (49.6)	1844 (43.7)	5332 (34.7)	9415 (22.8)	< .001
Coronary artery disease	1356 (68.1)	2757 (65.3)	10,123 (65.9)	23,492 (56.8)	< .001
Chronic obstructive pulmonary disease or asthma	582 (29.2)	1323 (31.3)	4606 (30.0)	12,358 (29.9)	.23
Devices					
Pacemaker, any	448 (22.5)	916 (21.7)	3024 (19.7)	7521 (18.2)	< .001
Pacemaker, biventricular	77 (3.9)	142 (3.4)	500 (3.3)	785 (1.9)	< .001
Implantable cardioverter-defibrillator	181 (9.1)	301 (7.1)	1110 (7.2)	1547 (3.7)	< .001
Diabetes mellitus	937 (47.1)	1971 (46.7)	6695 (43.6)	15,921 (38.5)	< .001
Heart failure hospitalization, past 6 months	377 (18.9)	820 (19.4)	2577 (16.8)	5204 (12.6)	< .001
Hyperlipidemia	763 (38.3)	1643 (38.9)	5969 (38.9)	14,031 (33.9)	< .001
Hypertension	1521 (76.4)	3106 (73.5)	11,468 (74.7)	30,343 (73.4)	< .001
Prior myocardial infarction	693 (34.8)	1459 (34.5)	5459 (35.5)	11,765 (28.5)	< .001
Peripheral vascular disease	503 (25.3)	975 (23.1)	3153 (20.5)	7304 (17.7)	< .001
Prior stroke or transient ischemic attack	386 (19.4)	864 (20.5)	2835 (18.5)	7942 (19.2)	.02
Smoking status					< .001
Never smoked	847 (42.6)	1764 (41.8)	6304 (41.0)	18,565 (44.9)	
Former smoker	737 (37.0)	1642 (38.9)	5731 (37.3)	14,459 (35.0)	

Variable	Early Worsening Heart Failure (n = 1990)	Late Worsening Heart Failure (n = 4223)	Complicated Presentation (n = 15,361)	Uncomplicated Hospital Course (n = 41,334)	*P* Value
Current smoker	147 (7.4)	304 (7.2)	1292 (8.4)	2877 (7.0)	
Initial evaluation and test results					
Chronic kidney disease category					< .001
Stage 1 (eGFR 90 mL/min/1.73m^2)	49 (2.5)	126 (3.0)	587 (3.8)	2403 (5.8)	
Stage 2 (eGFR 60-89 mL/min/1.73m^2)	252 (12.7)	728 (17.2)	3173 (20.7)	11,998 (29.0)	
Stage 3 (eGFR 30-59 mL/min/1.73m^2)	805 (40.5)	1950 (46.2)	7443 (48.5)	21,065 (51.0)	
Stage 4 (eGFR 15-29 mL/min/1.73m^2)	445 (22.4)	1032 (24.4)	2729 (17.8)	5128 (12.4)	
Stage 5 (eGFR < 15 mL/min/1.73m^2)	439 (22.1)	387 (9.2)	1429 (9.3)	740 (1.8)	
Dyspnea	1818 (91.4)	3765 (89.2)	14033 (91.4)	36,686 (88.8)	< .001
Ejection fraction					< .001
< 40 %	964 (48.4)	2083 (49.3)	6668 (43.4)	13,045 (31.6)	
≥ 40 %	699 (35.1)	1678 (39.7)	6237 (40.6)	19,955 (48.3)	
Unknown	327 (16.4)	462 (10.9)	2456 (16.0)	8334 (20.2)	
Fatigue	715 (35.9)	1500 (35.5)	4892 (31.8)	12,678 (30.7)	< .001
Pulmonary edema	1764 (88.6)	3649 (86.4)	13805 (89.9)	35,738 (86.5)	< .001
Pulse, mean (SD), bpm	85.9 (21.5)	86.8 (21.6)	90.6 (24.0)	85.7 (21.0)	< .001
Rales	1395 (70.1)	2870 (68.0)	11,363 (74.0)	28,454 (68.8)	< .001
Systolic blood pressure, mean (SD), mm Hg	138.1 (32.1)	136.9 (30.4)	148.2 (37.5)	145.8 (29.6)	< .001
Systolic blood pressure category					< .001
< 140 mm Hg	1107 (55.6)	2407 (57.0)	6817 (44.4)	18,209 (44.1)	
≥ 140 mm Hg	883 (44.4)	1816 (43.0)	8544 (55.6)	23,125 (55.9)	
B-type natriuretic peptide, mean (SD), pcg/mL	1711.9 (1367.1)	1475.3 (1214.5)	1401.7 (1212.9)	991.0 (949.7)	< .001
Missing	932 (46.8)	1982 (46.9)	7646 (49.8)	21,298 (51.5)	< .001
Serum creatinine, mean (SD), mg/dL	2.7 (2.1)	2.0 (1.4)	2.0 (1.6)	1.4 (0.8)	< .001
Serum sodium, mean (SD), mmol/L	137.3 (5.3)	137.6 (5.1)	138.0 (4.8)	138.3 (4.7)	< .001
Admission medications, No. (%)					
ACE inhibitor or ARB	991 (49.8)	1941 (46.0)	7829 (51.0)	20,232 (48.9)	< .001
Aspirin	784 (39.4)	1701 (40.3)	6425 (41.8)	16,125 (39.0)	< .001

Am Heart J. Author manuscript; available in PMC 2016 December 01.

Variable	Early Worsening Heart Failure (n = 1990)	Late Worsening Heart Failure (n = 4223)	Complicated Presentation (n = 15,361)	Uncomplicated Hospital Course (n = 41,334)	*P* Value
β-Blocker	1065 (53.5)	2039 (48.3)	8194 (53.3)	19,753 (47.8)	< .001
Clopidogrel	238 (12.0)	522 (12.4)	2036 (13.3)	4432 (10.7)	< .001
Diuretic	1272 (63.9)	3071 (72.7)	10,181 (66.3)	28,358 (68.6)	< .001
Lipid-lowering agent	708 (35.6)	1446 (34.2)	5572 (36.3)	13,042 (31.6)	< .001
Warfarin	514 (25.8)	1068 (25.3)	3740 (24.3)	10,515 (25.4)	.06
Discharge medications, No. (%)*					
ACE inhibitor or ARB	974 (58.7)	1782 (55.3)	8417 (63.2)	24,506 (63.3)	< .001
Aspirin	822 (49.6)	1585 (49.2)	6961 (52.3)	17,961 (46.4)	< .001
β-Blocker	1074 (64.8)	2015 (62.6)	8542 (64.2)	22,056 (57.0)	< .001
Clopidogrel	246 (14.8)	537 (16.7)	2298 (17.3)	4822 (12.5)	< .001
Diuretic	1149 (69.3)	2508 (77.9)	10,771 (80.9)	34,087 (88.1)	< .001
Lipid-lowering agent	631 (38.1)	1206 (37.5)	5185 (38.9)	12,706 (32.8)	< .001
Warfarin	481 (29.0)	994 (30.9)	3593 (27.0)	10,920 (28.2)	< .001
Year of hospitalization					< .001
2001	47 (2.4)	122 (2.9)	449 (2.9)	1300 (3.1)	
2002	567 (28.5)	1372 (32.5)	4735 (30.8)	13,827 (33.5)	
2003	752 (37.8)	1595 (37.8)	5537 (36.0)	15,387 (37.2)	
2004	624 (31.4)	1134 (26.9)	4640 (30.2)	10,820 (26.2)	

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate.

*Data on discharge medications are presented for patients discharged alive only (early worsening heart failure, n = 1658; late worsening heart failure, n = 3220; complicated presentation, n = 13,314; uncomplicated hospital course, n = 38,708).

Table 2

Care Received During Index Hospitalization by Study Group

Variable	Early Worsening Heart Failure (n = 1990)	Late Worsening Heart Failure (n = 4223)	Complicated Presentation (n = 15,361)	Uncomplicated Hospital Course (n = 41,334)	*P* Value
ICU stay, No. (%)	535 (26.9)	1517 (35.9)	7623 (49.6)	0	< .001
Duration, median (IQR), d*	3.1 (1.9 5.3)	4.0 (2.0 7.0)	2.2 (1.3 4.0)		< .001
Dialysis, No. (%)	528 (26.5)	704 (16.7)	1448 (9.4)	0	< .001
Inotropes, No. (%)	678 (34.1)	2045 (48.4)	3639 (23.7)	0	< .001
Intra-aortic balloon pump, No. (%)	16 (0.8)	61 (1.4)	99 (0.6)	0	< .001
Intravenous diuretics, No. (%)	1604 (80.6)	3884 (92.0)	13665 (88.9)	40962 (91.1)	< .001
Vasodilator, No. (%)	1034 (52.0)	2229 (52.8)	9724 (63.3)	0	< .001
Ventilation, No. (%)	166 (8.3)	717 (17.0)	1937 (12.6)	0	< .001

Abbreviations: ICU, intensive care unit, IQR, interquartile range.

*Among patients with an intensive care unit stay only.

Table 3

Observed Outcomes by Study Group

Outcome	Early Worsening Heart Failure (n = 1990)	Late Worsening Heart Failure (n = 4223)	Complicated Presentation (n = 15,361)	Uncomplicated Hospital Course (n =41,334)	*P* Value
Length of stay, mean (SD), d	7.2 (7.1)	11.4 (9.1)	6.3 (5.4)	4.8 (3.5)	< .001
In-hospital mortality, No. (%)	188 (9.4)	631 (14.9)	1090 (7.1)	951 (2.3)	< .001
Medicare hospital payments, mean (SD) $*	11.242 (17564)	17.027 (23580)	10.279 (13046)	7613 (5906)	< .001
Mortality, No. (cumulative incidence)					
30 days	300 (15.1)	906 (21.5)	1976 (12.9)	3002 (7.3)	< .001
1 year	941 (47.4)	2200 (52.2)	6084 (39.7)	13.446 (32.7)	< .001
Discharged alive, No.†	1658	3220	13.314	38.708	
All-cause readmission, No. (%)‡					
30 days	504 (30.4)	925 (28.7)	3301 (24.8)	8264 (21.4)	< .001
1 year	1221 (73.7)	2231 (69.5)	9305 (70.1)	25.502 (66.1)	< .001
Heart failure readmission, No. (%)‡					
30 days	200 (12.1)	402 (12.5)	1355 (10.2)	2997 (7.7)	< .001
1 year	608 (36.7)	1165 (36.3)	4782 (36.0)	11.585 (30.0)	< .001
Discharged alive, not censored at 30 days, No.§	1658	3218	13.308	38.684	
Days alive and out of hospital, mean (SD)	26.8 (6.4)	26.4 (6.9)	27.4 (5.9)	27.9 (5.3)	< .001
Postdischarge Medicare payments, mean (SD), $*	6993 (15856)	6424 (15226)	5152 (12456)	3830 (10932)	< .001
Discharged alive, not censored at 1 year, No.§	1644	3189	13.173	38.182	
Days alive and out of hospital, mean (SD)	255.8 (132.4)	249.4 (137.6)	275.3 (125.2)	285.7 (120.0)	< .001
Postdischarge Medicare payments, mean (SD), $*	41.688 (48652)	32.966 (42029)	31.524 (41371)	24.456 (33804)	< .001

*Expressed in 2010 US dollars.

†Excludes patients who died in the hospital, left against medical advice, or were discharged or transferred to another short-term hospital or hospice.

‡Presented as the number of patients (cumulative incidence per 100 patients at risk) who were readmitted within 30 days after discharge from the index hospitalization.

§Excludes patients who died in the hospital, left against medical advice, were discharged or transferred to another short-term hospital or hospice, or enrolled in Medicare managed care during the follow-up period.

Am Heart J. Author manuscript; available in PMC 2016 December 01.

Table 4

Unadjusted and Adjusted Associations Between Study Group and Outcomes at 30 Days and 1 Year

Outcome	Unadjusted		Adjusted*	
	Estimate	***P* Value**	**Estimate**	***P* Value**
Mortality, HR (99% CI)†				
30-day				
Early vs late worsening heart failure	0.69 (0.57, 0.83)	< .001	0.69 (0.57, 0.83)	< .001
Early worsening heart failure vs complicated presentation	1.19 (1.00, 1.41)	.009	1.00 (0.85, 1.19)	.97
Late worsening heart failure vs complicated presentation	1.73 (1.55, 1.92)	< .001	1.45 (1.31, 1.61)	< .001
1-year				
Early vs late worsening heart failure	0.84 (0.75, 0.94)	< .001	0.81 (0.73, 0.90)	< .001
Early worsening heart failure vs complicated presentation	1.27 (1.15, 1.41)	< .001	1.06 (0.96, 1.18)	.13
Late worsening heart failure vs complicated presentation	1.51 (1.40, 1.63)	< .001	1.31 (1.22, 1.40)	< .001
All-cause readmission, HR (99% CI)‡				
30-day				
Early vs late worsening heart failure	1.04 (0.91, 1.20)	.44	1.01 (0.88, 1.17)	.83
Early worsening heart failure vs complicated presentation	1.26 (1.10, 1.45)	< .001	1.11 (0.97, 1.27)	.05
Late worsening heart failure vs complicated presentation	1.21 (1.10, 1.33)	< .001	1.10 (1.00, 1.21)	.01
1-year				
Early vs late worsening heart failure	1.08 (0.99, 1.17)	.03	1.02 (0.93, 1.12)	.60
Early worsening heart failure vs complicated presentation	1.16 (1.07, 1.26)	< .001	1.02 (0.94, 1.11)	.55
Late worsening heart failure vs complicated presentation	1.08 (1.01, 1.16)	.003	1.00 (0.93, 1.07)	.98
Heart failure readmission, HR (99% CI)‡				
30-day				
Early vs late worsening heart failure	0.95 (0.75, 1.19)	.54	0.91 (0.72, 1.15)	.30
Early worsening heart failure vs complicated presentation	1.20 (0.98, 1.47)	.02	1.02 (0.83, 1.24)	.82
Late worsening heart failure vs complicated presentation	1.27 (1.09, 1.47)	< .001	1.12 (0.96, 1.30)	.06
1-year				

Outcome	Unadjusted		Adjusted*	
	Estimate	*P* Value	Estimate	*P* Value
Early vs late worsening heart failure	0.99 (0.86, 1.13)	.81	0.94 (0.82, 1.09)	.27
Early worsening heart failure vs complicated presentation	1.08 (0.97, 1.21)	.07	0.95 (0.85, 1.06)	.25
Late worsening heart failure vs complicated presentation	1.10 (1.00, 1.20)	.01	1.01 (0.92, 1.11)	.77
Days alive and out of hospital, difference (99% CI)§				
30-day				
Early vs late worsening heart failure	0.42 (–0.02, 0.85)	.01	0.45 (0.03, 0.88)	.006
Early worsening heart failure vs complicated presentation	–0.57 (–0.94, –0.19)	< .001	–0.16 (–0.52, 0.21)	.28
Late worsening heart failure vs complicated presentation	–0.98 (–1.27, –0.70)	< .001	–0.61 (–0.89, –0.33)	< .001
1-year				
Early vs late worsening heart failure	6.29 (–3.30, 15.88)	.09	8.65 (–0.41, 17.72)	.01
Early worsening heart failure vs complicated presentation	–19.46 (–27.73, –11.19)	< .001	–5.47 (–13.32, 2.37)	.07
Late worsening heart failure vs complicated presentation	–25.75 (–32.00, –19.50)	< .001	–14.12 (–20.05, –8.20)	< .001
Medicare payments, cost ratio (99% CI)§				
30-day				
Early vs late worsening heart failure	1.09 (0.94, 1.28)	.14	1.01 (0.86, 1.17)	.92
Early worsening heart failure vs complicated presentation	1.33 (1.16, 1.52)	< .001	1.13 (0.99, 1.29)	.02
Late worsening heart failure vs complicated presentation	1.21 (1.09, 1.35)	< .001	1.12 (1.01, 1.24)	.005
1-year				
Early vs late worsening heart failure	1.26 (1.16, 1.37)	< .001	1.12 (1.03, 1.21)	< .001
Early worsening heart failure vs complicated presentation	1.28 (1.19, 1.37)	< .001	1.09 (1.02, 1.17)	< .001
Late worsening heart failure vs complicated presentation	1.01 (0.96, 1.08)	.54	0.98 (0.92, 1.03)	.29

Abbreviation: HR, hazard ratio.

*Covariates in the regression models include demographic characteristics (ie, age, sex, race); medical history (ie, anemia, atrial fibrillation, coronary artery disease, chronic renal insufficiency, chronic obstructive pulmonary disease or asthma, diabetes mellitus, heart failure hospitalization in the previous 6 months, hyperlipidemia, hypertension, prior myocardial infarction, peripheral vascular disease, prior stroke or transient ischemic attack, smoking status, pacemaker type, implantable cardioverter-defibrillator); initial evaluation, vital signs, and laboratory test results (ie, fatigue, dyspnea, rales, pulmonary edema, ejection fraction, pulse, systolic blood pressure, serum sodium, hemoglobin, serum creatinine); medications (ie, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, aspirin, β-blocker, diuretic, clopidogrel, lipid-lowering agent, warfarin); and year of the index hospitalization. The mortality models include medication information from admission; the other models include medication information from discharge.

†Includes all patients.

Am Heart J. Author manuscript; available in PMC 2016 December 01.

‡Excludes patients who died in the hospital, left against medical advice, were discharged or transferred to another short-term hospital or hospice.

§Excludes patients who died in the hospital, left against medical advice, were discharged or transferred to another short-term hospital or hospice, or enrolled in Medicare managed care during the follow-up period.