


Resource utilization and costs among patients with heart failure with reduced ejection fraction following a worsening heart failure event

Michael M. Givertz^{1*} , Mei Yang², Gregory P. Hess³, Bin Zhao², Ashwin Rai⁴ and Javed Butler⁵

¹Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA; ²Merck & Co., Inc., Kenilworth, NJ, USA; ³Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA, USA; ⁴PRA Health Sciences, Kansas City, MO, USA; ⁵Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA

Abstract

Aims The aim of this study is to characterize healthcare resource utilization and costs in patients with heart failure with reduced ejection fraction (HFrEF) following a worsening heart failure event.

Methods and results This was a retrospective observational cohort analysis. Patients with HFrEF were identified from the PINNACLE Registry and linked to a nationwide pharmacy and medical claims database. Worsening heart failure was defined as stable heart failure with a subsequent hospitalization and/or intravenous diuretic therapy. Healthcare resource use and costs in 2015 US dollars were analysed for dispensed prescriptions, outpatient encounters, and hospital encounters. Among 11 064 patients with HFrEF, 3087 (27.9%) experienced a worsening heart failure event during an average follow-up of 973 days. During the first 30 days after the worsening event, 19.8% of patients had hospital readmissions with heart failure as the primary or secondary diagnosis. During that same time period, mean per patient heart failure-related healthcare resource use included 1.3 prescriptions, 0.5 practitioner visits, and 0.5 hospital encounters (admissions, observations, or emergency care), for an average total medical cost of \$8779 per patient including \$5359 in heart failure-related costs. During the first year following worsening heart failure onset, mean per patient total and heart failure-related costs were \$62 615 and \$35 329, respectively.

Conclusions The economic burden following a worsening heart failure event calls for further review of methods to prevent progressive disease, improve adherence to guideline-directed therapy, and develop novel treatments and care strategies to moderate further progression.

Keywords Heart failure/complications; Cost and cost analysis/economics; Health resources; Hospitalization

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*Correspondence to: Michael M. Givertz, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA. Tel: +617-525-7052; Fax: +617-264-5265. Email: mgivertz@bwh.harvard.edu

Introduction

Heart failure-related resource utilization and costs are significant contributors to the national healthcare burden, and heart failure remains one of the most costly chronic diseases.¹ In the United States, approximately 900 000 hospitalizations occur annually for heart failure,² and patients older than 65 years are at particularly high risk for heart failure-related hospitalizations and death.³ Approximately 50% of patients hospitalized for heart failure are readmitted within 6 months of discharge, and almost 30% die within a

year.^{4,5} It has been estimated that direct costs associated with heart failure in the United States will increase to almost \$70 billion by 2030.¹ Estimated indirect costs including lost work and home productivity due to heart failure-related morbidity and premature mortality are estimated at \$9.8 billion.¹

Inpatient costs are often the largest component of total medical costs. In the United States, hospitalizations account for 68% of total heart failure healthcare costs.¹ Multiple studies have found that inpatient costs increase with worsening disease severity and comorbid conditions.^{6–10} Hospital

readmissions following the initial heart failure diagnosis also contribute to inpatient costs. Within 30 days of hospital discharge, up to 25% of patients are readmitted, while readmission rates increase to 65% at 1 year after discharge.^{6,9,11–15}

Approximately half of patients with heart failure have reduced ejection fraction.¹⁶ Substantial evidence suggests that worsening heart failure with reduced ejection fraction (HFrEF), characterized by development of progressively escalating symptoms and signs of heart failure requiring intravenous diuretic treatment in the outpatient, emergency department, or hospitalized setting, is associated with markedly worse prognosis.^{17–20} Outcomes for patients with worsening heart failure are poor, and the survival rate at 5 years is less than 50%.²¹ Patients with HFrEF and worsening heart failure also regularly take multiple medications; however, a high percentage of these patients do not receive guideline-recommended regimens.^{22,23}

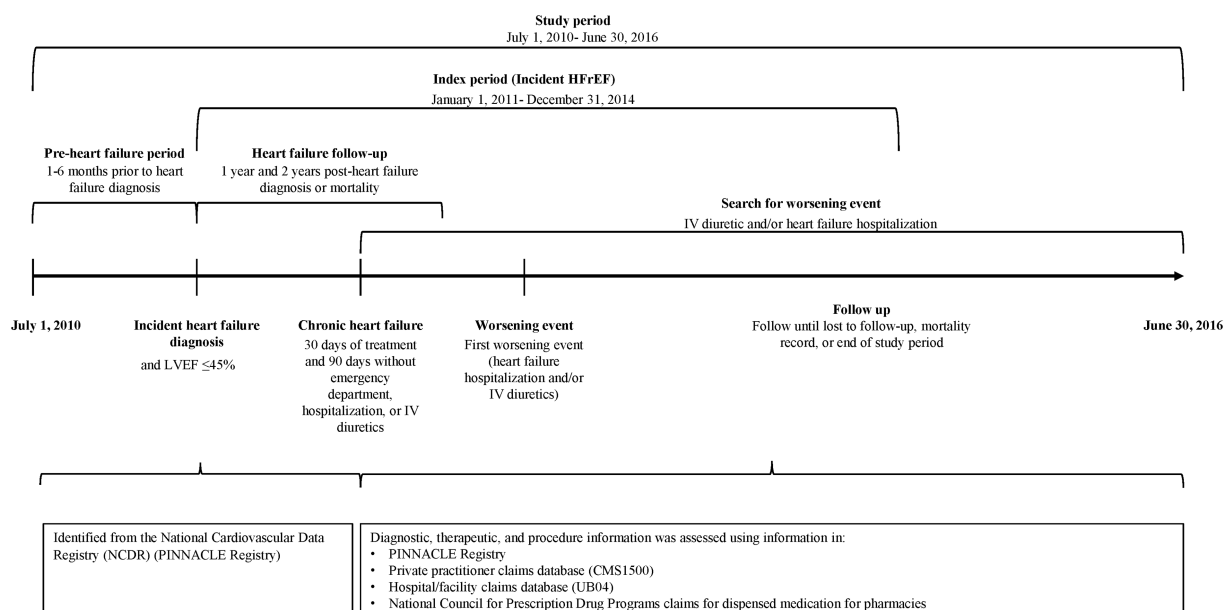
Few studies assessing heart failure resource utilization and costs have focused on the subset of patients following a worsening heart failure event. From these, we know that about half of hospitalizations among patients with HFrEF are for worsening HF¹³ and about half of these patients are rehospitalized within 30 days of the worsening event.²² The objective of this retrospective, observational cohort analysis of registry and claims-based data was to further quantify resource utilization and costs in the subset of patients with HFrEF following a worsening heart failure event.

Methods

Patients diagnosed with HFrEF between January 1, 2011 and December 31, 2014 (the index period) were identified from the National Cardiovascular Data Registry's PINNACLE Registry®, the American College of Cardiology's national, electronic medical record-based outpatient registry capturing data on coronary artery disease, hypertension, heart failure, and atrial fibrillation. Approximately 2500 participating facilities submit data on ambulatory/outpatient care to the PINNACLE Registry. All information comes from data collection forms with International Classification of Diseases 9th and 10th edition codes used to confirm the diagnosis of heart failure. The study design is shown in *Figure 1*.

The PINNACLE Registry and a nationwide claims database were linked at the patient level using unique patient identifiers. The overlap between the PINNACLE Registry population and the claims [private practitioner claims database (CMS1500), hospital/facility claims database (UB04), and National Council for Prescription Drug Programs claims database] master patient population during the study period was 91%. The integrated data utilized in the study were HIPAA certified. Patients were located across all geographical census regions in the United States and had coverage through commercial, Medicare, Medicaid, and other insurers. The American College of Cardiology and analytics group FIGmd (Rockford, IL) evaluate the mapping criteria and search terms used to populate the registry data fields on an ongoing

Figure 1 Study design. ED, emergency department; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LVEF, left ventricular ejection fraction.



basis. Independently, quality assurance and validation were also conducted on the claims data subsets.

Patient population

Patients aged ≥ 18 years with heart failure (defined as having one diagnosis in the index period) and documented ejection fraction of $\leq 45\%$ as a continuous or $< 50\%$ as a categorical value were included in the analysis. The PINNACLE Registry collection form allows for one assessment of ejection fraction. All patients had one or more observed pharmacy and medical claims within 180 days prior to the heart failure diagnosis date and ≥ 365 days after the diagnosis date or a record of mortality. Patients were excluded if they had evidence of clinical trial participation or heart transplantation between January 1, 2011 and December 31, 2014, or left ventricular assist device implantation, adult congenital heart disease, or amyloidosis during the 180 days prior to the heart failure diagnosis.

Worsening heart failure event

Within the cohort of patients with HFrEF, a subcohort of patients with a worsening heart failure event was identified through June 30, 2016 (*Figure 1*). This subcohort was defined as patients who had ≥ 30 days of initial heart failure therapy after their HFrEF diagnosis was identified from the pharmacy database, were stabilized for ≥ 90 days from the date of HFrEF diagnosis (defined as being free from heart failure-related emergency care, hospitalizations, and outpatient intravenous diuretic administrations), and after demonstration of stabilization, subsequently required at least one intravenous diuretic treatment in any healthcare setting (identified from the pharmacy claims database) or had a heart failure-related hospitalization (primary or secondary diagnosis from hospital/facility claims database). Similar definitions of worsening heart failure have been used in previously published studies.^{18,24}

Study measures and analyses

The study objectives were to characterize healthcare resource utilization, costs, and risks for hospitalization over the 24 months following the initial worsening heart failure event in the subcohort of patients with HFrEF. Diagnostic, therapeutic, and procedural information was assessed using data from the PINNACLE Registry, private practitioner claims database (CMS1500), and hospital/facility claims database (UB04) including inpatient stays and observation visits, as well as emergency department care. Data on treatment included National Council for Prescription Drug Programs

claims for dispensed medication from pharmacies contributing to the patient data repository.

Descriptive analyses were used for baseline patient characteristics. Categorical variables were summarized as the number and corresponding percentages of patients. Continuous variables were presented as the mean and standard deviation (SD). Healthcare resource utilization was evaluated from the worsening event through the subsequent 24 months and presented as per person per month utilization in terms of outpatient-dispensed prescriptions, outpatient encounters (e.g., physician office and clinic), and hospital encounters (including admissions, observational visits, and emergency department care). The dispensed medication costs reflect the amounts paid by insurers, and medical costs represent the amount charged to insurers. Costs were from the pre-adjudicated claims submitted to payers, and both costs were adjusted to 2015 US dollars using the Consumer Price Index. Population level data included all healthcare resource utilization and costs, and all patients contributed to the denominator totals whether or not they contributed to the numerator. Both total (all-cause) and heart failure-related (based on primary or secondary diagnosis) resource use and costs were examined for the first 30 days (1 month) and then at 3 month intervals up to the first 24 months after the worsening heart failure event. Costs were presented as cumulative costs. Mortality was not an endpoint of this study, but death was used to define 'alive and observable'. Mortality was determined directly from the PINNACLE Registry or medical/hospital claims based on International Classification of Diseases 9th and 10th edition codes, procedures codes, or discharge status (if available).

Ethics statement

The investigation conforms with the principles outlined in the Declaration of Helsinki.

Results

Among the 11 064 patients with HFrEF that met the selection criteria, 3087 (27.9%) had a worsening heart failure event during an average follow-up of 973 days. The mean (SD) time from heart failure diagnosis to the initial worsening heart failure event was 1.3 (0.9) years.

Patient characteristics

Baseline demographic characteristics are shown in *Table 1*. Mean patient age was 71 years, and 72% of patients were ≥ 65 years of age. The majority were male patients (65%), and 63% of patients were Caucasian. The largest proportion

Table 1 Baseline demographic characteristics of patients with worsening heart failure

Characteristic	Patients (N = 3087)
Age (years), mean (SD)	70.9 (12.5)
Age (years) distribution	
18–44	98 (3.2)
45–54	232 (7.5)
55–64	542 (17.6)
65–74	864 (28.0)
75–79	451 (14.6)
≥80	900 (29.2)
Sex	
Male	1993 (64.6)
Race	
Caucasian	663 (62.8)
African American	367 (11.9)
Other	38 (1.2)
Unknown	744 (24.1)
Geographic region	
South	1275 (41.3)
Midwest	831 (26.9)
West	598 (19.4)
Northeast	383 (12.4)
Payer type	
Medicare	1715 (55.6)
Commercial	598 (19.4)
None	49 (1.6)
Medicaid	38 (1.2)
Other	7 (0.2)
Unknown	680 (22.0)

SD, standard deviation.

Data presented as *n* (%) unless indicated otherwise.

of patients (41%) were from the Southern region, and slightly more than half of patients (56%) were Medicare recipients.

Clinical characteristics in the 6 months prior to the worsening heart failure event are shown in *Table 2*. Among patients with available data, the largest proportion were in New York Heart Association functional class II (23%) or III (14%), and slightly more patients had moderately (34%) or severely (36%) reduced ejection fraction (defined as ejection fractions between 30–39% and <30%, respectively) than mildly (30%) reduced ejection fraction (defined as ejection fraction between 40% and 45%). Body mass indices were above normal (overweight [22%] or obese [30%]) for the majority of patients.

Comorbidities

All patients had at least one cardiac or non-cardiac comorbidity (data not shown). The majority of patients had hypertension (93%), coronary artery disease (79%), abnormal lipid profiles (78%), atrial fibrillation (57%), diabetes mellitus (54%), and myocardial infarction (52%). A smaller proportion of patients had anaemia (43%), chronic obstructive pulmonary disease (42%), chronic kidney disease (29%), peripheral artery disease (33%), sleep apnoea (25%), depression (17%), thromboembolism (10%), or stroke (11%). Patient history of

Table 2 Clinical characteristics of patients with worsening heart failure

Characteristic	Patients (N = 3087)
New York Heart Association functional class	
Class I	299 (9.7)
Class II	701 (22.7)
Class III	438 (14.2)
Class IV	51 (1.7)
Unknown	1598 (51.8)
Left ventricular ejection fraction, mean (SD)	31.5 (9.7)
Mildly reduced (40–45)	934 (30.3)
Moderately reduced (30–39)	1047 (33.9)
Severely reduced (<30)	1106 (35.8)
Systolic blood pressure, mean (SD) mmHg ^a	120.2 (19.5)
Diastolic blood pressure, mean (SD) mmHg ^a	69.2 (11.6)
Heart rate, mean (SD) beats per minute ^a	75.1 (14.9)
Serum creatinine, mean (SD) mg/dL ^a	1.6 (1.4)
Body mass index ^b	
Underweight (<18.5)	47 (1.5)
Normal (18.5–24.9)	505 (16.4)
Overweight (25.0–29.9)	688 (22.3)
Obese (≥30.0)	920 (29.8)
Unknown	927 (30.0)

SD, standard deviation.

Data presented as *n* (%) unless indicated otherwise.

^aAvailable for a subset of the population (*n* = 2152 for systolic blood pressure, *n* = 2148 for diastolic blood pressure, *n* = 2040 for heart rate, and *n* = 496 for serum creatinine).

^bBody mass index is presented as the closest value within 180 days prior.

procedures included implantable cardioverter defibrillator (28%), coronary artery bypass graft (19%), biventricular pacemaker (10%), and cardiac valve surgeries (2%).

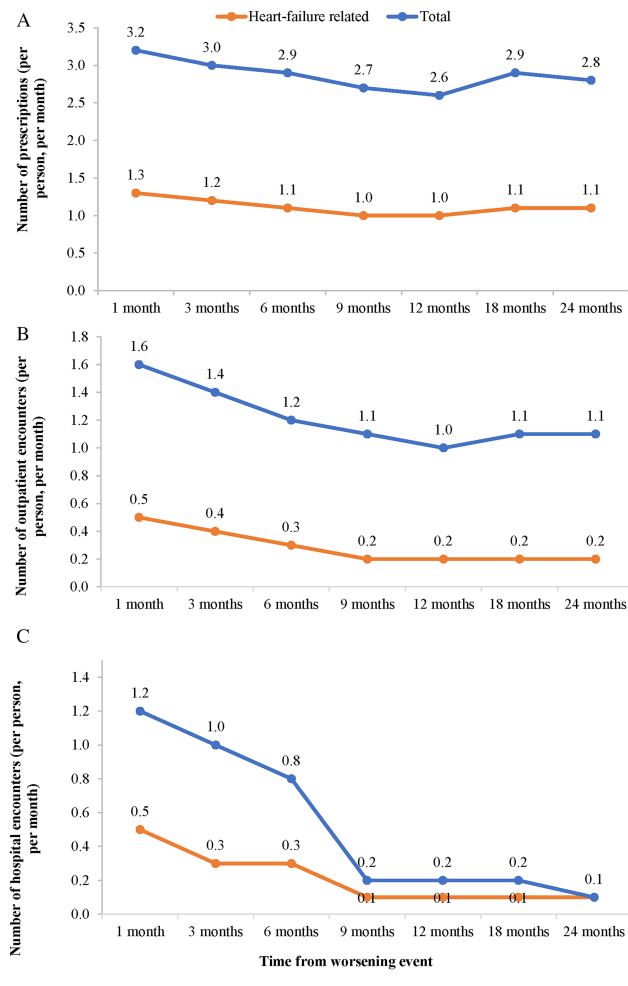
Treatment

Initial therapy reported at the time of the worsening heart failure event included monotherapy or two-class combination therapy (35% and 47% of patients, respectively), with a smaller percentage receiving three-class combination therapy (18%; data not shown). Monotherapy was predominantly beta blockers while two-class combination therapy was predominantly beta blockers plus angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. Three-class combination therapy was predominantly beta blockers plus mineralocorticoid receptor antagonists plus angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

Healthcare resource utilization

Total and heart failure-related resource utilization for the number of prescriptions, outpatient encounters, and hospital encounters during the first 30 days and at 3 month intervals through 24 months after the worsening heart failure event is shown in *Figure 2A–C*. Total utilization per patient

Figure 2 Healthcare resource utilization per person per month following a worsening heart failure event for (A) prescriptions, (B) outpatient encounters, and (C) hospital encounters. The number of patients available at each time point were $n = 3087$ at 1 month, $n = 2984$ at 3 months, $n = 2859$ at 6 months, $n = 2749$ at 9 months, $n = 2672$ at 12 months, $n = 1799$ at 18 months, and $n = 1277$ at 24 months. Outpatient encounters include office and clinic visits. Hospital encounters include admissions, observational visits, and emergency department visits.



per month for all utilization was highest in the first 30 days following the worsening event and then gradually decreased over the next 9–12 months with little or no fluctuation through 24 months.

A similar trend was observed for heart failure-related resource utilization. Specifically, the mean number of heart failure-related prescriptions was 1.3 prescriptions per patient per month during the first 30 days after the initial worsening event and then slightly decreased, with the mean number of prescriptions ranging from 1.0 to 1.2 (Figure 2A). Outpatient heart failure-related medical visits were also highest during the first 30 days (0.5 visits per patient per month), and then

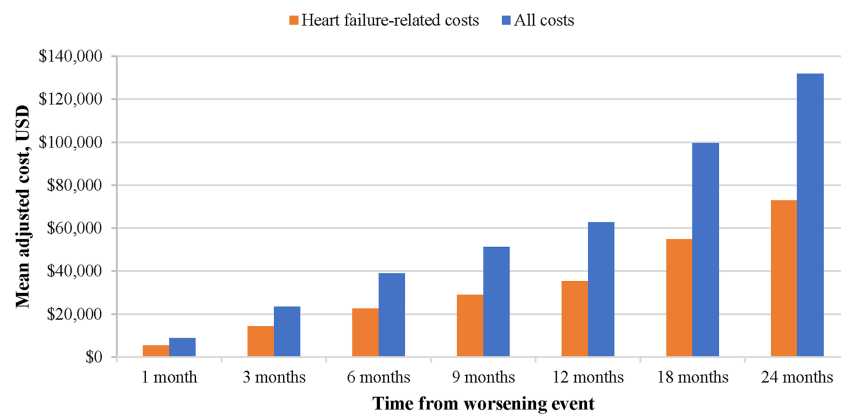
decreased to 0.2 visits per patient per month after 9 months of follow-up (Figure 2B). Similarly, there were 0.5 heart failure-related hospital encounters per patient per month during the first 30 days, decreasing to 0.1 hospital encounters per patient per month over 24 months (Figure 2C).

The percentage of patients with all-cause hospital admissions (inpatient stays) ranged from 31.6% in the first 30 days to 75.5% over the first 24 months (data not shown). A similar trend was observed in the heart failure-related hospital admissions. In the first 30 days, 3, 12, and 24 months from the incident worsening event, 19.8%, 32.1%, 47.4%, and 60.2% of patients had a heart failure-related admission, respectively (data not shown).

Healthcare costs

Costs for prescriptions, outpatient encounters, and hospital encounters during the 30 days following the worsening heart failure event through 24 months are shown in Supporting Information, Table S1 and Figure 3. During the first 30 days, total mean (SD) per patient costs were \$8779 (\$33 720) for all-cause prescriptions, outpatient encounters, and inpatient care and \$5359 (\$29 274) for heart failure-related prescriptions, outpatient encounters, and inpatient care. During the first year following the worsening heart failure event, the mean (SD) per-patient cost for total care was \$62 615 (\$132 771) and the mean cost of heart failure-related care was \$35 329 (\$105 657). Over the 24 months after the worsening event, mean (SD) per-patient costs were \$131 967 (\$235 359) and \$72 947 (\$170 823) for total and heart failure-related resource use, respectively. Costs for heart failure-related prescriptions and outpatient visits accounted for 35% and 33% of total costs in those categories, while the cost of heart failure-related hospital encounters accounted for 64% of the all-cause hospital encounters cost. In general, total heart failure-related costs were driven primarily by heart failure-related hospital encounters, which represented 94% of total costs in the first 30 days following the worsening heart failure event and were maintained at a high level through 24 months. On the other hand, outpatient heart failure-related drug costs only accounted for approximately 2–3% of the total heart failure-related costs and 1% of the total costs from the first 30 days through 24 months of follow-up (Table S1).

Cost data were further stratified by patient characteristics, including geographical region, age, race, and sex. Mean costs within 24 months, stratified by regions of the United States, were lowest for patients in the South (\$123 247), highest in the Northeast (\$146 110) and similar in the Midwest and West (\$133 051 and \$132 455, respectively; data not shown). Costs stratified by patient age were highest for younger patients aged 18–44 years (\$259 090) and decreased with increasing age over 24 months (Figure S1A).

Figure 3 Total cumulative mean adjusted utilization costs following a worsening heart failure event. Costs are in US dollars, inflation-adjusted for 2015.

Furthermore, costs over 24 months for patients age 80 years and older were 28–65% of those in the other age groups. Stratification by race showed that over 24 months, utilization costs were 1.4 times higher for African American patients than Caucasian patients (*Figure S1B*). Costs were similar between sex with the percent difference in female and male participants never exceeding 10% through the 24 month time point (*Figure S1C*).

Discussion

This study provides real-world data on resource utilization and healthcare costs among a cohort of patients with HFrEF following a worsening heart failure event. To our knowledge, this is the first study of patients in a real-world setting that specifically examines resource utilization and costs following a worsening event. A worsening event, characterized by escalating symptoms and signs of congestion requiring intravenous diuretics, is associated with markedly worse prognosis and 5 year survival rates of <50%.^{17–20} In the present study, 28% of patients with HFrEF experienced a worsening event within 24 months of heart failure diagnosis. As we recently showed in the worsening HF population, the use of guideline-recommended therapy is concerning low.²² The extent of economic burden from direct medical costs is substantial in this population and derives primarily from inpatient care.

By focusing on the subset of patients experiencing a worsening heart failure event, our study adds to data published from National Claims History files from the Centers for Medicare and Medicaid Services, the National Inpatient Sample collected by the Agency for Healthcare Research and Quality, and Olmsted County, Minnesota.^{15,25–29} While other studies have identified characteristics and outcomes for patients with chronic HFrEF,^{13,15,25–27} the subset of patients that develop

worsening heart failure has emerged as a distinct group,³⁰ and investigating these individuals presents opportunities to improve outcomes and reduce costs.

In the present study, 20% of patients who experienced a worsening heart failure event had heart failure-related hospital readmissions within 30 days after the worsening event, and 32% had readmissions for any reason. These results are substantially higher than readmission rates reported for all patients (i.e. excluding the subset of patients with a worsening event) after a primary diagnosis of heart failure. Among Medicare beneficiaries, all-cause readmissions within 30 days of heart failure diagnosis were 22–23%.^{6,14,15} Among patients with an inpatient diagnosis of heart failure identified from a large US claims database, the all-cause readmission rate was 15% at 1 month and 40% at 6 months post-discharge.¹² Similarly, all-cause 30 day readmissions for patients with a primary diagnosis of HFrEF identified in the University of Utah Health Care System database were 20%.¹³ These data illustrate the importance of examining the subset of patients following a worsening heart failure event, as they represent a population with increased resource use and higher economic burden.

Total and heart failure-related costs in the first year following a worsening heart failure event (\$62 615 and \$35 329, respectively) reported in the present study were higher than those previously reported for the overall population of patients with HFrEF. In a population study of US adults with heart failure conducted between 2002 and 2011, mean per person direct healthcare costs per year were \$23 854 (2014 US dollars), with inpatient costs representing the most significant contribution (47% of total costs, \$11 318).²⁸ In addition, results from a retrospective study of Medicare patients aged ≥65 years with heart failure reported total annual costs per person of \$22 230 (2009 US dollars).³¹ Similar to these studies of the overall population of patients with HFrEF, our analysis of patients following a

worsening heart failure event also identifies inpatient encounters as the major contributor to overall costs. Furthermore, the results for total and heart failure-related costs following the worsening heart failure event reported here are similar to those previously reported by Obi *et al.*³² for a cohort of patients with heart failure that died within 1 year after the initial heart failure encounter. Decedents incurred \$60 048 (2013 US dollars) in total all-cause costs and \$39 052 (2013 US dollars) in heart failure-related medical costs in 1 year, which was two to three times the costs incurred by a matched cohort of patients that survived 1 year (\$32 394 and \$16 519, respectively, both $P < 0.001$).³²

In a cohort of patients with worsening heart failure similar to those followed in the present study, there was a rapid decline in survival beginning shortly after the worsening event, and ~30% of these patients were not alive within 1 year.²² Most of these patients did not receive recommended heart failure therapy or doses prior to developing worsening heart failure.^{22,32} Previously published data highlight this unmet need to address factors that may improve outcomes for patients after a worsening heart failure event. Addressing these factors would also help reduce the high associated direct medical costs and healthcare utilization identified in the present analysis.

This study is subject to the limitations of registry and claims data. The costs in this study are charges from the pre-adjudicated claims submitted to payers, and not the costs reimbursed by payers. Using charges can lead to an overestimation of costs, which could partially explain why costs reported in the present study were higher than in previously reported studies. In addition, it is possible that random missing data can bias results; however, we would not expect this to alter the principal findings and conclusions of the present study. To strengthen the present study, we linked registry and claims databases in order to access both clinical and pharmacy data for the population of patients with HFREF that would not be available in claims databases alone where some patients are recorded with unspecified heart failure based on International Classification of Diseases 9th and/or 10th edition codes. The study design incorporated a single evaluation of ejection fraction, which is a potential drawback, because the ejection fraction of patients included in the analysis may have normalized over time. However, we focused on the population of patients with an ejection fraction $\leq 45\%$ to capture patients with midrange reduced ejection fraction, and several clinical trials over the last two decades have used an ejection fraction cut-off of 45%.^{20,33}

In summary, more than one in four patients with HFREF will develop worsening heart failure and are at high risk for 30 days of rehospitalization and additional healthcare resource utilization. The extent of economic burden following the development of worsening heart failure calls for further review of interventions to prevent progressive

disease and development of novel treatments to moderate further progression once heart failure has worsened. Further studies are needed to better understand the economic burden following the development of worsening heart failure in different countries. The resource utilization and costs reported here provide a benchmark against which to measure the results of future improvements in the care of patients with worsening heart failure.

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Conflict of interest

M. Givertz has research support from the National Institutes of Health and serves as a consultant to Merck. J. Butler has received research support from the National Institutes of Health, PCORI, and the European Union and serves as a consultant for Amgen, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, G3 Pharmaceutical, Innolife, Janssen, Luitpold, Medtronic, Merck, Novartis, Relypsa, StealthPeptide, SC Pharma, Vifor, and ZS Pharma. G. Hess was previously employed by Symphony Health, which received research support from Merck & Co. for the design and conduct of this study. G. Hess also conducts funded studies with governmental agencies, for example, the NIH, and professional societies, for example, the American College of Cardiology. M. Yang and B. Zhao are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., and are shareholders of Merck & Co., Inc., Kenilworth, NJ, USA.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Mean healthcare costs and heart failure-related costs per-patient following a worsening heart failure event. **Figure S1.** Total mean adjusted costs following a worsening heart failure event by (A) age, (B) race, and (C) sex.

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