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In-Hospital Therapy for Heart Failure With Reduced Ejection Fraction in the United States

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ABSTRACT

OBJECTIVES This study sought to characterize in-hospital treatment patterns and associated patient outcomes among patients hospitalized for heart failure (HF) in U.S. clinical practice.

BACKGROUND Hospitalizations for HF are common and associated with poor patient outcomes. Real-world patterns of in-hospital treatment, including diuretic therapy, in contemporary U.S. practice are unknown.

METHODS Using Optum de-identified Electronic Health Record data from 2007 through 2018, patients hospitalized for a primary diagnosis of HF (ejection fraction ≤40%) and who were hemodynamically stable at admission, without concurrent acute coronary syndrome or end-stage renal disease, and treated with intravenous (IV) diuretic agents within 48 h of admission were identified. Patients were categorized into 1 of 4 mutually exclusive hierarchical treatment groups defined by complexity of treatment during hospitalization (intensified treatment with mechanical support or IV vasoactive therapy, IV diuretic therapy reinitiated after discontinuation for ≥1 day without intensified treatment, IV diuretic dose increase/combination diuretic treatment without intensified treatment or IV diuretic reinitiation, or uncomplicated).

RESULTS Of 22,677 patients hospitalized for HF with reduced ejection fraction (HFrEF), 66% had uncomplicated hospitalizations without escalation of treatment beyond initial IV diuretic therapy. Among 7,809 remaining patients, the highest level of therapy received was IV diuretic dose increase/combination diuretic treatment in 25%, IV diuretic reinitiation in 36%, and intensified therapy in 39%. Overall, 19% of all patients had reinitiation of IV diuretic agents (26% of such patients had multiple instances), 12% were simultaneously treated with multiple diuretics, and 61% were transitioned to oral diuretic agents before discharge. Compared with uncomplicated treatment, IV diuretic reinitiation and intensified treatment were associated with significantly longer median length of stay (uncomplicated: 4 days; IV diuretic reinitiation: 8 days; intensified: 10 days) and higher rates of in-hospital (uncomplicated: 1.6%; IV diuretic reinitiation: 4.2%; intensified: 13.2%) and 30-day post-discharge mortality (uncomplicated: 5.2%; IV diuretic reinitiation: 9.7%; intensified: 12.7%).

CONCLUSIONS In this contemporary real-world population of U.S. patients hospitalized for HFrEF, one-third of patients had in-hospital treatment escalated beyond initial IV diuretic therapy. These more complex treatment patterns were associated with highly variable patterns of diuretic use, longer hospital lengths of stay, and higher mortality. Standardized and evidence-based approaches are needed to improve the efficiency and effectiveness of in-hospital HFrEF care.
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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin II receptor blocker

ARNI = angiotensin receptor-neprilysin inhibitor

EF = ejection fraction

EHR = electronic health record

ESRD = end-stage renal disease

GDMT = guideline-directed medical therapy

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

ICD-9 = International Classification of Diseases-9th Revision

ICD-10 = International Classification of Diseases-10th Revision

IV = intravenous

MRA = mineralocorticoid receptor antagonist

Hospitalizations for heart failure (HF) are exceedingly common, expensive, and a marker of poor prognosis (1,2). Nonetheless, there remain no Class I, Level of Evidence: A guideline recommendations for the in-hospital treatment of HF (3). Based on weak to moderate evidence, a relatively narrow set of therapies are recommended by current guidelines, including intravenous (IV) diuretic agents for patients with volume overload and adjunctive use of vasodilators, inotropes, and mechanical support devices in selected patients (3). However, patients hospitalized for HF represent a heterogeneous population with variable clinical trajectories, and decision making regarding the use, sequencing, and duration of in-hospital therapy remains largely subject to clinician discretion (4).

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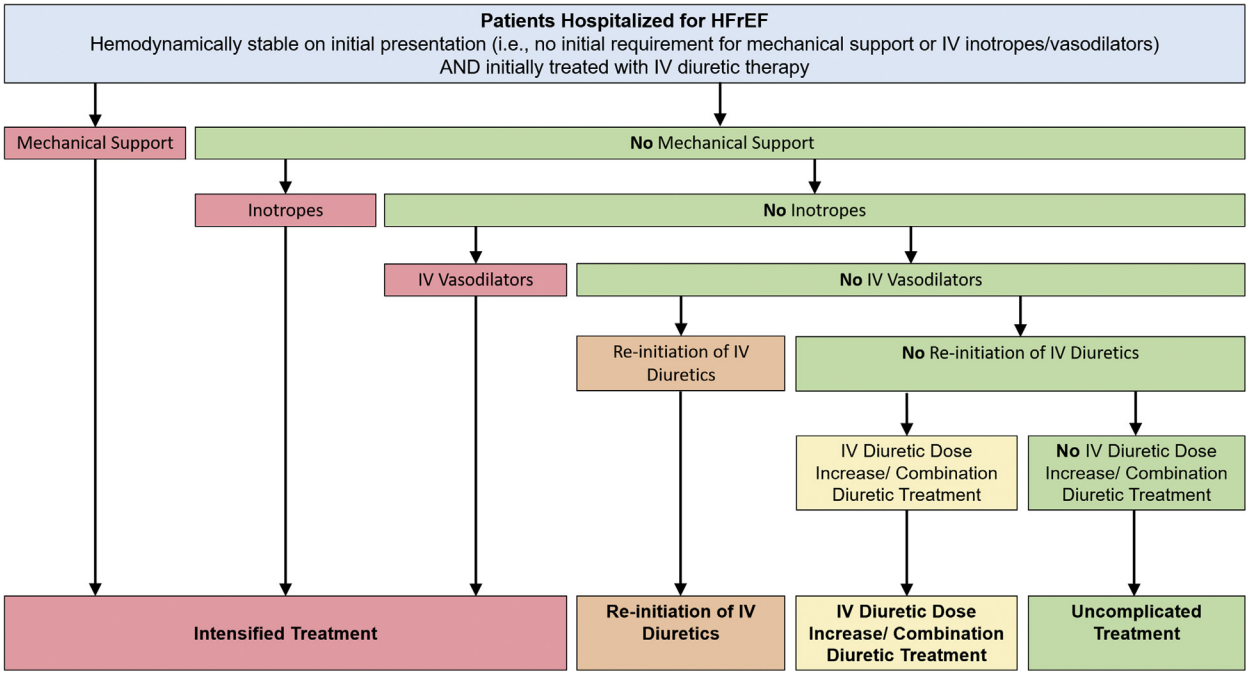
Given the enormous public health and economic burden of hospitalizations for HF, a more standardized, evidence-based approach to in-hospital care would potentially lead to major improvements in health care resource use and patient outcomes. However, the ability to improve in-hospital care is hindered by scarce data from contemporary U.S. clinical practice. Data from clinical trial populations suggest that 5% to 42% of hospitalizations may be complicated by in-hospital worsening of HF requiring intensification of initial therapy, but extrapolation of these findings to real-world settings is complicated by varying definitions of worsening HF, selected trial populations, and generally low proportions of U.S. trial participants (4). Moreover, although the Acute Decompensated Heart Failure National Registry (ADHERE) registry suggested that approximately 90% of U.S. patients receive IV diuretic agents during hospitalization and that 11% have in-hospital worsening of HF, these data reflect care more than a decade ago and may not represent current patterns of in-hospital use of diuretic agents and other therapies (5,6). Likewise, prior and ongoing U.S. registries describe the use of medications before admission and at discharge but generally lack detailed and complete data regarding type of in-hospital treatment or the decision to escalate or de-escalate the intensity of therapy (7). Given these substantial knowledge gaps, an improved understanding of the use and variability of in-hospital therapy would be foundational to future research efforts aimed to inform best practices, optimize resource use, and improve patient outcomes. In this context, the objectives of the current study were to leverage a large, longitudinal, real-world dataset to characterize in-hospital treatment patterns and associated clinical outcomes among patients hospitalized for HF in contemporary U.S. clinical practice.

METHODS

DATA SOURCES. This study used deidentified data within the Optum de-identified Electronic Health Record (EHR) dataset (Eden Prairie, Minnesota). This deidentified clinical dataset aggregates longitudinal outpatient and hospital data from health care systems across the United States, where they are subsequently normalized and restructured. Data include patient demographics, medical diagnoses, vital signs, laboratory test results, procedural data, medications, hospitalizations, and outpatient visits. Patients with a variety of health insurance coverages are included (i.e., private insurance, Medicare, Medicaid, no insurance). Before patient deidentification, deaths are identified from the U.S. Social Security Death Index and supplemented by searches within the medical record. Primary diagnoses for hospitalizations are defined by International Classification of Diseases-9th Revision (ICD-9) and International Classification of Diseases-10th Revision (ICD-10) codes, with a primary diagnosis of HF defined as ICD-9 code 428.xx and ICD-10 code I50xx. Institutional review board approval was not needed because this work involved secondary analysis of deidentified data.

STUDY POPULATION. The current study included patients age ≥18 years with ejection fraction (EF) ≤40% (measured by echocardiogram during index hospitalization or ≤1 year prior) who were hospitalized for a primary diagnosis of HF without concurrent acute coronary syndrome between January 1, 2007, and September 30, 2018. All patients were part of an individual integrated delivery network—a large health care network where patients were likely to receive all of their care. As a result, it is expected that complete information should be available for these patients, both before and after the index hospitalization. For patients with ≥1 inpatient hospitalization meeting inclusion criteria, an index hospitalization was selected at random. To further support HF as the primary medical problem, and consistent with existing clinical trial endpoint definitions of HF hospitalization events, patients were included only if they received IV diuretic agents within 48 h of admission (i.e., on admission day or the day following admission day) (8). Given the intent of this analysis to inform care for the large majority of

FIGURE 1 Composition of Hierarchical and Mutually Exclusive In-Hospital Treatment Groups for Comparison



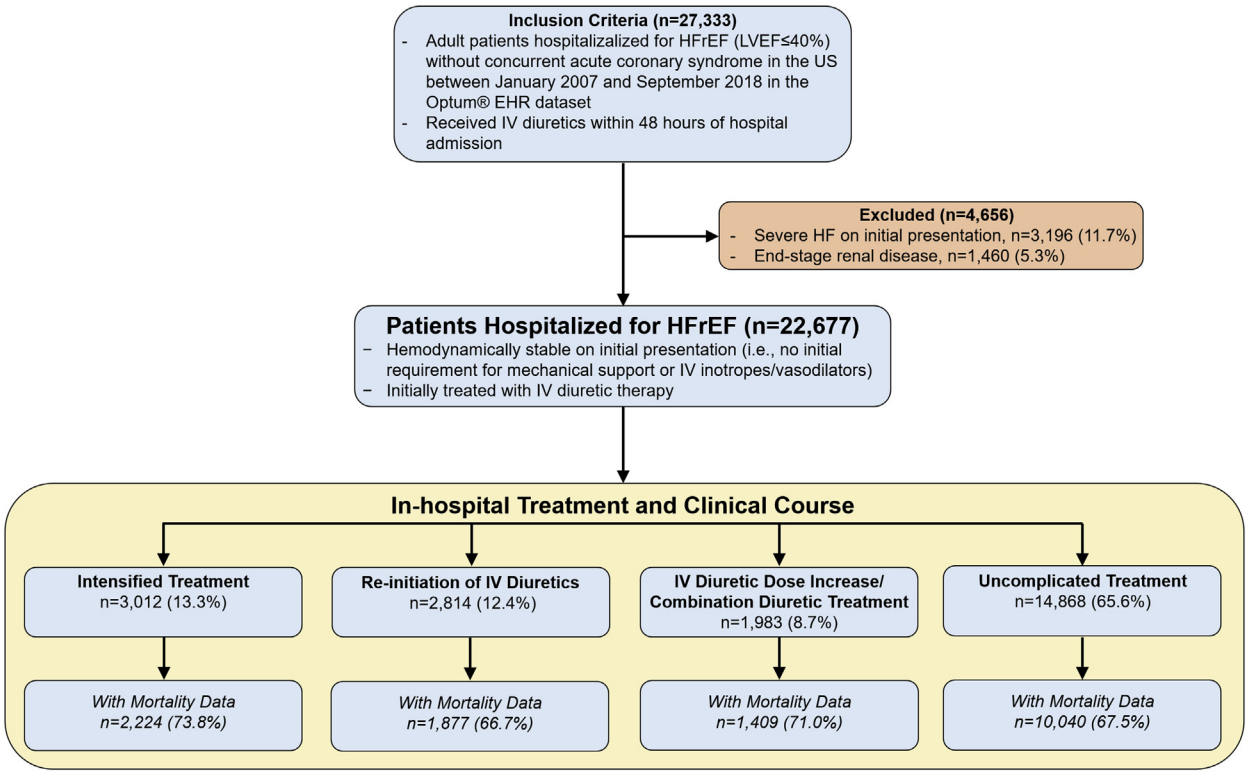
From most complicated to least complicated treatment, 4 treatment groups were defined by the most intense therapy received and termed as follows: intensified, IV diuretic reinitiation, IV diuretic dose increase and/or combination diuretic treatment, and uncomplicated. HFrEF = heart failure with reduced ejection fraction; IV = intravenous.

patients with heart failure with reduced ejection fraction (HFrEF) who are hemodynamically stable at presentation and initially treated with IV diuretic therapy, pre-specified study exclusion criteria included: 1) severe acute HF/cardiogenic shock at initial hospital presentation (defined as use of mechanical support, IV inotropes, or IV vasodilators on the day of index hospital admission); and 2) end-stage renal disease (ESRD) (defined as diagnosis of ESRD any time before the index admission; [ICD-9 code: 585.6x; ICD-10 code: N186x] or estimated glomerular filtration rate of <15 ml/min/1.73^2 at the time of index hospital admission and before the initiation of IV diuretic therapy).

IN-HOSPITAL TREATMENT GROUPS. Eligible patients were categorized into 1 of 4 mutually exclusive, pre-specified hierarchical treatment groups defined by HF treatment complexity during the index hospitalization (Figure 1). From most complicated to least complicated treatment, the 4 groups were defined by the most intense therapy received during the index hospitalization as follows: 1) intensified: initiation of mechanical support, inotropes, or IV vasodilators on hospital day 2 or later; 2) IV diuretic reinitiation: IV diuretic reinitiation after a ≥1-day gap, without intensified treatment; 3) IV diuretic dose increase and/or combination diuretic treatment: increase in daily dose of IV diuretic or administration of ≥2 different diuretic agents (i.e., loop, thiazide, or potassium-sparing) on the same day, at least 1 of which was IV; and 4) uncomplicated: IV diuretic agents without intensified treatment, IV diuretic reinitiation, or IV diuretic increase and/or combination diuretic treatment.

STATISTICAL ANALYSIS. Baseline characteristics were described for the overall population and each in-hospital treatment group. In addition, patterns of IV diuretic treatment (e.g., duration, interruption, reinitiation, transition to oral diuretics) were described among treatment groups, as applicable. Continuous variables are reported as mean and median, and categorical variables are reported as frequencies and percentages. Temporal trends in the distribution of in-hospital HF treatment groups were assessed across the study period from 2007 to 2018.

FIGURE 2 Selection of the Analytic Cohort and In-Hospital HFrEF Treatment Groups



EHR = electronic health record; HF = heart failure; LVEF = left ventricular ejection fraction; other abbreviations as in Figure 1.

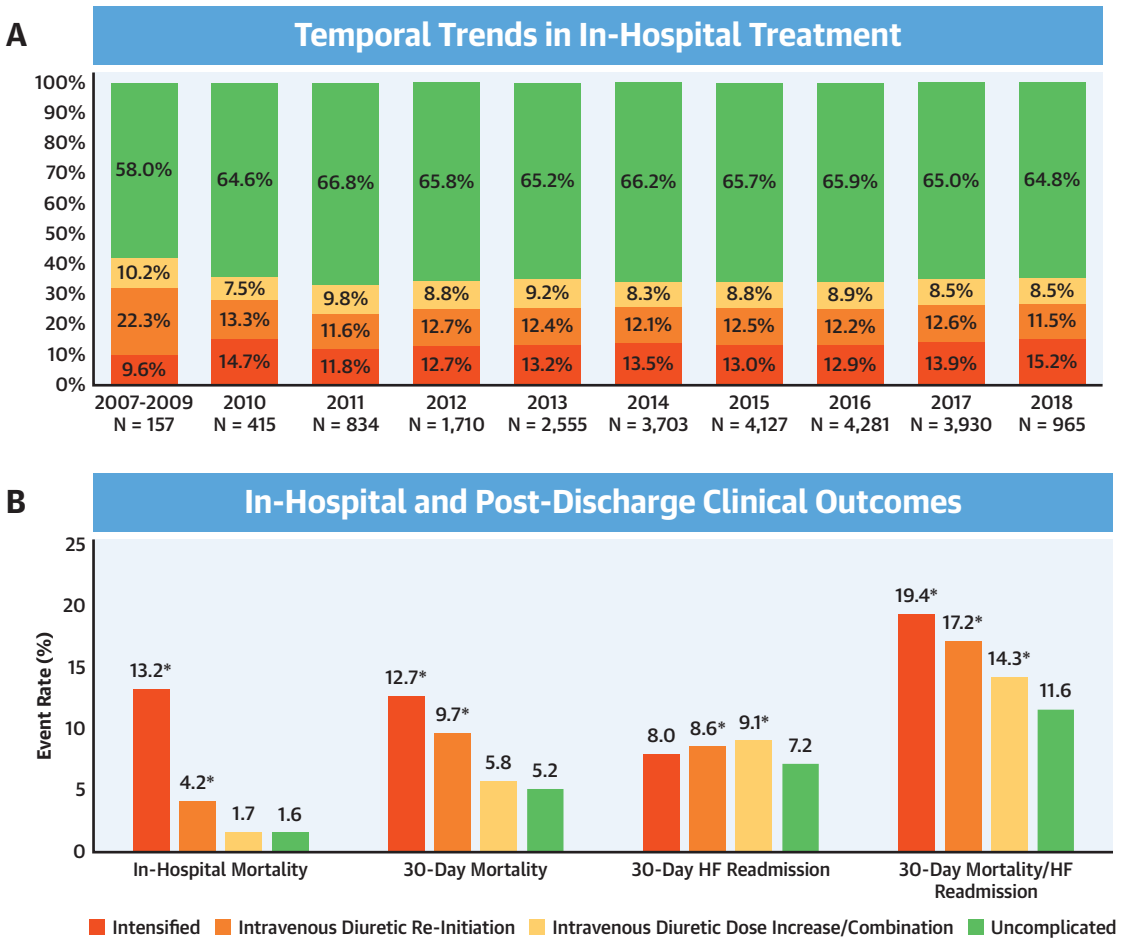
Among the subset of patients with available mortality data, in-hospital and post-discharge outcomes were tabulated for each in-hospital treatment group and compared using the Pearson chi-square test or the Fisher exact test. Logistic regression models were constructed to evaluate the associations between in-hospital treatment group and clinical outcomes. Statistical analyses were performed with SAS, version 9.4, SAS Enterprise Guide 2017 (SAS Institute, Cary, North Carolina) and R, version 3.5.1 (R Core Team, Vienna, Austria). A 2-tailed p value of <0.05 was considered statistically significant.

RESULTS

PATIENT COHORT AND DISTRIBUTION OF IN-HOSPITAL HF TREATMENT. From the total sample of 27,333 patients meeting the inclusion criteria and without concurrent acute coronary syndrome, 3,196 (11.7%) patients were excluded because of severe acute HF on initial presentation, and 1,460 (5.3%) patients were excluded because of presence of ESRD (Figure 2). The present analysis included the remaining 22,677 (74.4%) patients hospitalized for HFrEF. Within this cohort, 3,012 (13.3%) were categorized as intensified treatment, 2,814 (12.4%) as IV diuretic reinitiation after an initial discontinuation, and 1,983 (8.7%) as IV diuretic dose increase and/or combination diuretic treatment. The remaining 14,868 (65.6%) patients received uncomplicated treatment without escalation of initial IV diuretic therapy. With the possible exception of the early study period from 2007 through 2009, the proportions of patients within each treatment group were generally stable over time (Central Illustration). Within the full study sample of 22,677 patients, 15,550 (68.6%) patients had available mortality data and made up the subset of patients within which mortality and hospitalization outcomes were assessed.

PATIENT CHARACTERISTICS. Patient characteristics by in-hospital HF treatment group are presented in Table 1. Overall, the median age was 72 years, and 36% were women, with rates of older patients and

CENTRAL ILLUSTRATION **In-hospital Therapy and Outcomes for Patients Hospitalized for Heart Failure With Reduced Ejection Fraction in the United States**



Greene, S.J. et al. J Am Coll Cardiol HF. 2020;8(11):943–53.

(A) Temporal trends in in-hospital treatment reflect the full sample of 22,677 patients. **(B)** Mortality and hospitalization outcomes reflect 15,550 patients with available mortality data. *$p < 0.05$ compared with uncomplicated treatment. HF = heart failure.

women lowest in the intensified group and highest in the IV diuretic reinitiation group. Patients receiving uncomplicated treatment were least likely to have prior HF hospitalization and tended to have higher systolic blood pressure, better renal function, and lower serum troponin concentrations. Patients with intensified treatment tended to have lower systolic blood pressure and EF and higher natriuretic peptide level, whereas patients receiving IV diuretic dose increase and/or combination diuretic treatment had the highest rates of most comorbidities. In general, troponin and natriuretic peptide concentrations were higher among patients receiving more complicated treatments.

Overall, 45.2% of patients reported use of diuretic agents before admission, and 70.3% of patients were receiving an oral diuretic on the day of discharge. The intensified group had the lowest rate of loop diuretic use at discharge (64.8%). The rate of thiazide diuretic use at discharge was 5.0%, ranging from 1.2% of patients in the uncomplicated group to 32.4% among patients treated with IV diuretic dose increase/combination therapy. At admission, the use rates of angiotensin-converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB), angiotensin-receptor neprilysin inhibitor, evidence-based beta-blocker, and mineralocorticoid receptor antagonist (MRA) were 32.2%, 0.8%, 42.6%, and 13.3%,

TABLE 1 Baseline Characteristics by In-Hospital Heart Failure Treatment Group

	Overall (N = 22,677)	Intensified (n = 3,012)	IV Diuretic Reinitiation (n = 2,814)	IV Diuretic Dose Increase/Combination Therapy (n = 1,983)	Uncomplicated (n = 14,868)
Age, yrs	69.8 [72]	67.2 [69]	72.0 [74]	68.9 [70]	70.1 [73]
Age ≥65 yrs	15,119 (66.7)	1,850 (61.4)	2,062 (73.3)	1,267 (63.9)	9,940 (66.9)
Women	8,255 (36.4)	957 (31.8)	1,088 (38.7)	630 (31.8)	5,580 (37.5)
Race					
White	17,119 (75.5)	2,349 (78.0)	2,213 (78.6)	1,467 (74.0)	11,090 (74.6)
African American	4,467 (19.7)	500 (16.6)	471 (16.7)	433 (21.8)	3,063 (20.6)
Asian	127 (0.6)	15 (0.5)	18 (0.6)	8 (0.4)	86 (0.6)
Other/unknown	964 (4.3)	148 (4.9)	112 (4.0)	75 (3.8)	629 (4.2)
De novo HF	8,621 (38.0)	1,178 (39.1)	1,043 (37.1)	637 (32.1)	5,763 (38.8)
HF hospitalization in prior year (among patients with pre-existing HF)	6,494 (46.2)	908 (49.5)	829 (46.8)	705 (52.4)	4,052 (44.5)
LVEF, %					
0–20	6,936 (30.6)	1,234 (41.0)	783 (27.8)	577 (29.1)	4,342 (29.2)
21–30	7,955 (35.1)	949 (31.5)	1,004 (35.7)	735 (37.1)	5,267 (35.4)
31–40	7,786 (34.3)	829 (27.5)	1,027 (36.5)	671 (33.8)	5,259 (35.4)
Vital signs and laboratory data					
Systolic BP, mm Hg	125.5 [122]	115.3 [112]	125.5 [122]	123.9 [120]	127.8 [124]
Heart rate, beats/min	85.3 [82]	86.3 [84]	87.3 [84]	82.7 [80]	85.1 [82]
BMI ≥30 kg/m^2	8,676 (41.0)	1,194 (41.5)	1,082 (41.0)	956 (51.1)	5,444 (39.5)
Sodium, mmol/l	138 [138]	136 [137]	137 [138]	138 [138]	138 [139]
BUN, mg/dl	28 [23]	33 [28]	30 [26]	33 [27]	26 [22]
eGFR, ml/min/1.73m^2					
≤30	2,458 (11.1)	501 (17.1)	349 (12.8)	316 (16.4)	1,292 (8.9)
30–59	6,763 (30.7)	965 (33.0)	973 (35.8)	662 (34.3)	4,163 (28.7)
≥60	12,833 (58.2)	1,459 (49.9)	1,395 (51.3)	953 (49.4)	9,026 (62.3)
BNP,* pg/ml	2,104 [1,153]	2,610 [1,333]	1,887 [1,201]	2,040 [1,075]	2,073 [1,127]
NT-proBNP,* pg/ml	10,616 [6,415]	12,321 [7,918]	12,242 [7,729]	10,798 [6,196]	9,909 [5,912]
Troponin I,† ng/l	99 [40]	198 [50]	98 [40]	95 [40]	83 [40]
Troponin T,† ng/l	41 [11]	62 [20]	47 [20]	41 [16]	35 [10]
Past medical history					
Coronary artery disease	12,057 (53.2)	1,506 (50.0)	1,518 (53.9)	1,123 (56.6)	7,910 (53.2)
Hypertension	15,388 (67.9)	1,851 (61.5)	1,933 (68.7)	1,444 (72.8)	10,160 (68.3)
Atrial fibrillation/flutter	13,015 (57.4)	1,674 (55.6)	1,624 (57.7)	1,234 (62.2)	8,483 (57.1)
Diabetes	8,521 (37.6)	1,111 (36.9)	1,130 (40.2)	918 (46.3)	5,362 (36.1)
Chronic kidney disease	7,506 (33.1)	1,058 (35.1)	1,028 (36.5)	794 (40.0)	4,626 (31.1)
Peripheral vascular disease	6,604 (29.1)	920 (30.5)	865 (30.7)	665 (33.5)	4,154 (27.9)
Chronic pulmonary disease	8,619 (38.0)	1,122 (37.3)	1,184 (42.1)	817 (41.2)	5,496 (37.0)
Medical therapy before admission‡					
Diuretics	10,257 (45.2)	1,534 (50.9)	1,136 (40.4)	1,046 (52.7)	6,541 (44.0)
Loop	9,811 (43.3)	1,477 (49.0)	1,087 (38.6)	912 (46.0)	6,335 (42.6)
Thiazide	1,394 (6.1)	272 (9.0)	150 (5.3)	484 (24.4)	488 (3.3)
Potassium-sparing	87 (0.4)	11 (0.4)	10 (0.4)	23 (1.2)	43 (0.3)
ACE inhibitor/ARB	7,305 (32.2)	917 (30.4)	750 (26.7)	640 (32.3)	4,998 (33.6)
ARNI	189 (0.8)	29 (1.0)	19 (0.7)	21 (1.1)	120 (0.8)
Evidence-based beta-blocker§	9,662 (42.6)	1,342 (44.6)	1,034 (36.7)	882 (44.5)	6,404 (43.1)
MRA	3,016 (13.3)	523 (17.4)	305 (10.8)	303 (15.3)	1,885 (12.7)

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respectively. Use of all guideline-directed medical therapies (GDMTs) increased at discharge (ACE inhibitor/ARB: 49.8%; angiotensin-receptor neprilysin inhibitor: 1.5%; evidence-based beta-blocker: 71.3%; MRA: 26.5%). In general, use of GDMTs at discharge decreased with progressively more complicated in-hospital treatment group. The characteristics of patients with and without available mortality data were generally similar, with rare exceptions including higher heart rate and systolic blood pressure among patients without mortality data (Supplemental Table 1).

TABLE 1 Continued

	Overall (N = 22,677)	Intensified (n = 3,012)	IV Diuretic Reinitiation (n = 2,814)	IV Diuretic Dose Increase/Combination Therapy (n = 1,983)	Uncomplicated (n = 14,868)
Medical therapy at discharge‖					
Diuretics	10,530 (70.3)	1,273 (66.0)	1,215 (67.6)	1,123 (81.1)	6,919 (70.1)
Loop	10,325 (68.9)	1,251 (64.8)	1,203 (66.9)	979 (70.7)	6,892 (69.8)
Thiazide	752 (5.0)	104 (5.4)	83 (4.6)	449 (32.4)	116 (1.2)
Potassium-sparing	16 (0.1)	1 (0.1)	0 (0.0)	12 (0.9)	3 (0.0)
ACE inhibitor/ARB	7,460 (49.8)	753 (39.0)	704 (39.2)	636 (45.9)	5,367 (54.3)
ARNI	219 (1.5)	25 (1.3)	19 (1.1)	26 (1.9)	149 (1.5)
Evidence-based beta-blocker§	10,693 (71.3)	1,190 (61.7)	1,180 (65.6)	995 (71.8)	7,328 (74.2)
MRA	3,978 (26.5)	502 (26.0)	402 (22.4)	441 (31.8)	2,633 (26.7)

Values are mean [median] or n (%). *BNP was measured in 46% of patients; NT-proBNP was measured in 43% of patients. Overall, 88% of patients had either a BNP or NT-proBNP measurement. †Troponin I was measured in 52% of patients; troponin T was measured in 31% of patients. Overall, 81% of the total population had either a troponin I or troponin T measurement. ‡Based on self-reported medication at admission; 74% of patients self-reported at admission the use of some medication. §Evidence-based beta-blockers were defined as bisoprolol, carvedilol, and metoprolol succinate. ‖Discharge medical therapy data for patients discharged alive with available mortality data.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; HF = heart failure; IV = intravenous; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

PATTERNS OF IN-HOSPITAL DIURETIC TREATMENT. In-hospital patterns of diuretic therapy are displayed in Table 2. The median time between the first and last dose of in-hospital IV diuretic therapy was 3 days, ranging from a median of 7 days among those receiving intensified treatment to a median of 2 days for patients receiving uncomplicated treatment. Overall, 19% of all patients had IV diuretic therapy reinitiated after an initial discontinuation of ≥1 day, with 26% of such patients having multiple reinitiations during the index hospitalization. The median gap of IV diuretic therapy among those reinitiated was 3 days, with such patients receiving a median of 2 additional days of IV diuretic therapy before discharge and 36% of patients receiving oral diuretic agents during the gap. Among patients receiving intensified treatment, 51% also had IV diuretic reinitiation, with 43% of such patients with multiple gaps in treatment.

Overall, 2.5% of patients received an increase in initial IV diuretic dose. Among patients in the intensified and IV diuretic reinitiation groups, IV dose escalation was used as an adjunctive strategy in 3.3% and 3.5% of cases, respectively. In addition, 12% of the overall population was treated with a combination diuretic regimen, with rates of 24% in the intensified treatment group and 13% in the IV diuretic reinitiation group. Across all treatment groups, patients were transitioned to oral diuretic agents before discharge in 59% to 65% of instances, with a median duration of oral diuretic therapy before discharge of 2 days.

CLINICAL OUTCOMES. In the overall cohort, the median length of stay was 4 days (mean: 6.6 days). Patients receiving more complicated therapy had increasingly longer lengths of stay, with intensified treatment associated with the longest stays (median: 10 days; mean: 13.7 days) and uncomplicated treatment with the shortest stays (median: 4 days; mean: 4.5 days).

Patients receiving intensified treatment had the highest rates of in-hospital mortality (13.2%), 30-day post-discharge mortality (12.7%), and the composite of 30-day post-discharge mortality or HF readmission (19.4%) and intermediate rates of 30-day post-discharge HF readmission (8.0%) (Central Illustration). The rate of 30-day HF readmission was highest in the IV diuretic dose increase and/or combination group (9.1%), whereas the rate of composite 30-day mortality or HF readmission was highest in the intensified treatment and the IV diuretic reinitiation groups (19.4% and 17.2%, respectively). Patients with an uncomplicated treatment course had the lowest rates of all post-discharge mortality and readmission events. Compared with uncomplicated therapy, the odds of in-hospital mortality were >9-fold higher among patients in the intensified group and >2.5-fold higher among patients in the IV diuretic reinitiation group (Figure 3). The odds of 30-day mortality and 30-day mortality or HF readmission were highest in the intensified group and IV diuretic reinitiation group and were lower among patients with less complicated in-hospital treatment (reference: uncomplicated group). The odds of 30-day post-discharge HF readmission had minimal variation across treatment groups.

TABLE 2 Patterns of Intravenous Diuretic Therapy by Treatment Group

	Overall (N = 22,677)	Intensified (n = 3,012)	IV Diuretic Reinitiation (n = 2,814)	IV Diuretic Dose Increase/Combination Therapy (n = 1,983)	Uncomplicated (n = 14,868)
Days from first to last IV diuretic dose	4.4 [3]	9.4 [7]	7.6 [6]	4.1 [4]	2.9 [2]
IV diuretic reinitiation (minimum gap: 1 day)	4,350 (19.2)	1,536 (51.0)	2,814 (100.0)	–	–
Patients with multiple gaps in IV diuretics	1,117 (25.7)	663 (43.2)	454 (16.1)	–	–
Number of days on IV diuretic agents before first stop in IV diuretics	2.4 [2]	2.8 [2]	2.1 [1]	–	–
Days from first stop of IV diuretic agents to restart of IV diuretics	3.6 [3]	4.1 [3]	3.3 [2]	–	–
Use of oral diuretic agents between first stop in IV diuretic agents and restart of IV diuretics	1,568 (36.0)	526 (34.2)	1,042 (37.0)	–	–
Number of days on IV diuretic agents after first stop in IV diuretics	3.5 [2]	5.2 [3]	2.5 [2]	–	–
Patients with IV diuretic dose increase	570 (2.5)	100 (3.3)	98 (3.5)	372 (18.8)	–
Patients with IV diuretic agents used in combination	2,797 (12.3)	722 (24.0)	378 (13.4)	1,697 (85.6)	–
Use of oral diuretic agents after last IV diuretic dose					
Patients initiated on oral diuretics	13,881 (61.2)	1,785 (59.3)	1,785 (63.4)	1,283 (64.7)	9,028 (60.7)
Duration of oral diuretics, days	2.3 [2]	3.1 [2]	2.4 [2]	2.3 [2]	2.2 [2]

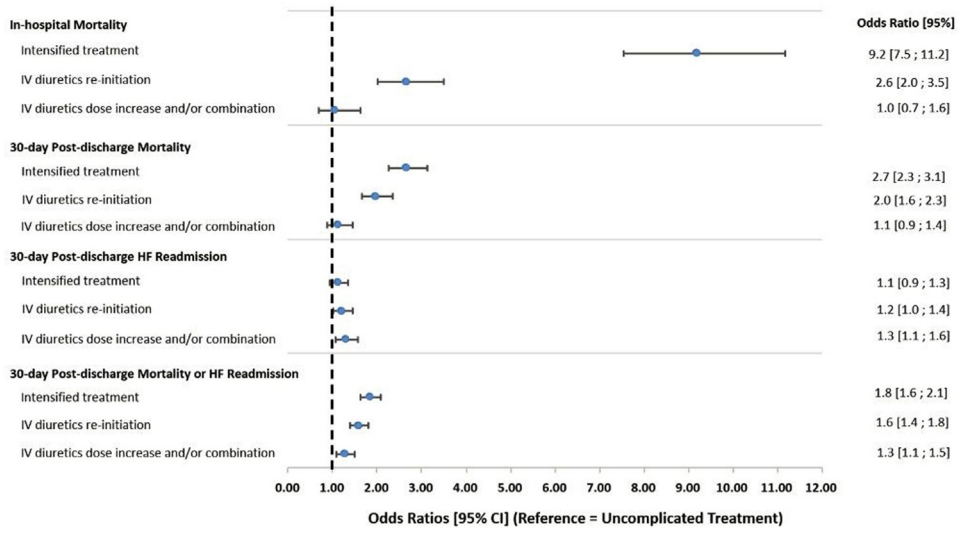
Values are mean [median] or n (%).
IV = intravenous.

DISCUSSION

In this large, contemporary, real-world population of U.S. patients hospitalized for HFrEF, one-third of initially hemodynamically stable patients had a complicated in-hospital treatment course, and this proportion remained generally consistent over time. Complicated hospitalizations were uniformly marked by treatment escalation beyond initial IV diuretic therapy but were subject to wide variation in the treatment provided. The degree of treatment escalation ranged from mechanical support and/or IV vasoactive therapy to multiple diuretic-based approaches, with variable overlap between specific strategies. Among patients receiving the most complicated therapy (i.e., intensified treatment with mechanical support, inotropes, and/or IV vasodilators), the majority had IV diuretic therapy discontinued and subsequently resumed, and nearly one-fourth received simultaneous treatment with multiple types of diuretics. However, these complex patterns of diuretic management also extended to patients with less complex treatment; 12% of the total population had IV diuretic reinitiation without intensified treatment, and 9% received an increase in IV diuretic dose or combination diuretic therapy without more complex treatment. Overall, 61% of patients were transitioned to an oral diuretic regimen before discharge, and the use of this strategy was similar irrespective of treatment complexity. Patient characteristics varied widely by complexity of in-hospital treatment, with patients receiving intensified therapy and IV diuretic reinitiation having exceptionally high-risk clinical profiles and substantially longer hospital lengths of stay. These patient profiles were consistent with observed clinical outcomes, as greater treatment complexity was strongly associated with markedly higher rates of in-hospital and post-discharge mortality.

To our knowledge, we present the first comprehensive analysis of the in-hospital treatment of HFrEF in contemporary U.S. clinical practice. In this regard, several strengths and novel features of this analysis warrant mention. First, these in-hospital data capture all administered medical and device therapy for each day of the index hospitalization. This feature not only allowed characterization of patients by treatment received, but afforded granular description and classification of patients by changes in a specific therapy (i.e., initiation, discontinuation, dose increase, dose decrease) throughout the hospitalization. Second, these data from the Optum EHR database reflect a large, representative, real-world sample of patients and health institutions spanning all geographic regions across the United States. Third, acknowledging possible limitations of using medical record or administrative coding to define HF as the primary reason for hospitalization, the current analysis required patients to receive IV diuretic agents within 48 h of the index hospital admission to confirm HF as a primary medical problem. Fourth, recognizing that the minority of patients with HFrEF presenting with concurrent acute coronary syndrome, cardiogenic shock, and ESRD may not receive in-hospital care

FIGURE 3 Risk of In-Hospital Mortality and 30-Day Post-Discharge Outcomes by In-Hospital Treatment Group



CI = confidence interval; other abbreviations as in Figures 1 and 2.

generalizable to the at-large HFrEF community, the current analysis excluded such patients and informs the clinical experience for the large majority of patients with HFrEF who are hemodynamically stable at presentation and treated with IV diuretics.

Multiple prior analyses from U.S. registries and claims data have focused on therapy at the time of hospital admission and discharge (7,9–11). By comparison, data regarding the use of therapies during the course of an index HF hospitalization in U.S. practice are scarce and generally limited to the ADHERE registry, a program that enrolled patients between 2001 and 2004 (6). Analyses from ADHERE broadly defined in-hospital worsening of HF (i.e., initiation of inotropes or IV vasodilators >12 h after hospital presentation, transfer to the intensive care unit, or receipt of mechanical circulatory support/mechanical ventilation/hemodialysis after the first inpatient day), but descriptions of IV diuretic therapy beyond the first 24 h of care are not available (5,6,12). Thus, despite HF being a leading cause of hospitalization in the United States and IV diuretic therapy being the cornerstone treatment, there are paradoxically few data describing how hospitalized patients are managed with this therapy. The present analysis was designed to fill this knowledge gap, identifying the real-world prevalence and potential implications of various diuretic and other therapeutic approaches to patients hospitalized for HF in current U.S. practice.

Although precise clinical circumstances surrounding individual treatment decisions are not available, the patterns of care documented in the current study suggest major inefficiencies and uncertainties regarding in-hospital use of diuretic therapy. Specifically, nearly 20% of all patients had IV diuretic agents initially discontinued but subsequently restarted, and one-fourth of such patients had this occur multiple times during the index hospitalization. When IV diuretic agents were restarted, it was typically for multiple days, suggesting that initial discontinuation potentially occurred in the setting of significant residual congestion, complications (e.g., worsening renal function), or in the context of switching to grossly inadequate alternative treatment regimens. IV diuretic reinitiations were especially prevalent among patients with greater complexity and risk, potentially suggesting that patients with greatest clinical need elicit the most clinician uncertainty regarding the optimal use of diuretics. Indeed, prior work has highlighted limitations with the in-hospital assessment of congestion whereby clinicians must rely on an assortment of grading methods (e.g., daily weights, clinical examination findings, and natriuretic peptide levels) that are subject to variable interpretation and have potential for conflicting information (13). Alternatively, in the context of IV diuretic reinitiation generally corresponding with high mortality and greater use of mechanical circulatory support and IV vasoactive therapies, IV diuretic reinitiation may be consistent with in-hospital worsening HF and the dynamic clinical status of sicker patients.

Although management of congestive and hemodynamic symptoms are a major focus of hospital-based care, the HF hospitalization has been championed as a key opportunity to improve the use and dosing of evidence-based chronic HFrEF therapy (7,14). In this respect, the current findings regarding the use of GDMTs at the time of hospital discharge are disappointing. Although information regarding contraindications and intolerance is not available, the proportions of patients discharged without MRA, ACE inhibitor/ARB, or evidence-based beta-blocker therapy were substantial at 73%, 50%, and 29%, respectively. The proportions of untreated patients were generally highest among patients with complicated hospitalizations for whom the rates of contraindications/intolerance are potentially higher, but medication use at discharge was only modestly better for those with uncomplicated hospitalizations. These data are consistent with other recent U.S. data supporting major gaps in the use and dosing of HFrEF medical therapy and the existence of a risk-treatment paradox, where patients at highest risk are less likely to receive appropriate therapy (15–18). Likewise, as evidenced by the event rates observed in the current study, the combination of a complicated HFrEF hospitalization and withdrawal/intolerance of GDMTs should be understood as an exceptionally high-risk scenario for which advanced HF therapies or palliative care may be considered. These high-risk patients were also less likely to be prescribed a diuretic at discharge, perhaps suggesting hypoperfusion/shock, rather than congestion, as a more significant factor underlying their hospital course and markedly high rates of post-discharge mortality.

STUDY LIMITATIONS. First, although important for clarifying the current U.S. landscape of inpatient HF care, these observational data cannot determine cause-effect relationships. Second, reasons underlying clinician treatment decisions were not available, and analyses were based on the use of a particular treatment strategy rather than its appropriateness or necessity. Third, the Optum EHR database is not a closed system, and these data do not capture post-discharge hospitalizations occurring within an outside health network. Thus, the reported rates of 30-day HF readmission may be underestimated. However, this analysis included only patients from an integrated delivery network and had a short follow-up period (i.e., 30 days post-discharge), thus minimizing the likelihood of such underestimations. Fourth, because of limitations of the data source and efforts to fully ensure patient confidentiality, the characteristics of treating hospitals are not available. This lack of hospital-level data precludes analyses of hospital-level variation in care patterns and patient outcomes. Fifth, this study was derived from the medical record and is subject to potential limitations related to the quality or completeness of documentation.

CONCLUSIONS

In this contemporary real-world population of U.S. patients hospitalized for HFrEF, one-third of patients had in-hospital treatment escalated beyond the initial IV diuretic regimen. These complicated hospitalizations were subject to wide variation in treatment provided, particularly for diuretic therapy. Specifically, reinitiations of IV diuretic treatment after discontinuation, IV diuretic dose increases, and combination diuretic treatments were common, and transitions to oral diuretic agents before discharge were inconsistent. Compared with patients receiving uncomplicated IV diuretic therapy, complex treatment patterns were associated with substantially longer hospital lengths of stay and markedly higher in-hospital and post-discharge mortality. These findings support major inefficiencies and uncertainties regarding the in-hospital treatment of HFrEF in U.S. practice and highlight potential adverse consequences for health resource use and patient outcomes. Further efforts are needed to develop standardized and evidence-based approaches to in-hospital HFrEF care.

AUTHOR RELATIONSHIP WITH INDUSTRY

Dr. Greene has received a Heart Failure Society of America/Emergency Medicine Foundation Acute Heart Failure Young Investigator Award funded by Novartis; has received research support from Amgen, AstraZeneca, Bristol-Myers Squibb, Merck, and Novartis; serves on Advisory Boards for Amgen and Cytokinetics; and serves as a consultant for Amgen and Merck. Drs. Ionescu-Ittu and Burne and Ms. Guérin are employees of Analysis Group Inc., which has received consultancy fees from Bristol-Myers Squibb for this study. Drs. Borentain, Kessler, Tugcu, and DeSouza are employees of Bristol-Myers Squibb. Dr. Felker has received research funding from Otsuka, Novartis, Roche Diagnostics, Amgen, Merck, the American Heart Association, and the National Heart, Lung, and Blood Institute; and has served as a consultant for Novartis, Roche Diagnostics, Amgen, Trevena, Cytokinetics, Madeleine, MyoKardia, Bristol-Myers Squibb, Stealth Biotherapeutics, and GlaxoSmithKline. Dr. Chen was an employee of Bristol-Myers Squibb at the time the research was conducted. Dr. Triana has reported that she has no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Two thirds of U.S. patients hospitalized for HFrEF who are hemodynamically stable at presentation have an uncomplicated in-hospital treatment course managed with IV diuretic therapy. The remaining one-third of patients go on to receive escalated therapy during the hospital stay, ranging from mechanical support and/or IV vasoactive therapy to intensified diuretic-based treatment.

COMPETENCY IN MEDICAL KNOWLEDGE 2: In current U.S. clinical practice, patients hospitalized for HFrEF frequently experience reinitiation of IV diuretic therapy after initial discontinuation, IV diuretic dosing increases, and combination treatment with multiple diuretics. These treatment patterns have remained stable over time and are associated with longer hospital lengths of stay and higher mortality.

TRANSLATIONAL OUTLOOK: Approximately 20% of patients hospitalized for HFrEF in the United States have IV diuretic agents discontinued but subsequently restarted later in the hospital stay, with one-fourth of such patients experiencing this multiple times. When IV diuretic agents are restarted, it is typically for multiple days, potentially suggesting initial discontinuation in the setting of significant residual congestion or in the context of switching to an inadequate alternative treatment. For patients hospitalized for HFrEF in the United States, there is wide variation in treatment provided, particularly for patients with complicated courses who do not respond to initial IV diuretic therapy. Complex treatment patterns are associated with longer hospital lengths of stay and higher mortality. These data suggest inefficiencies and uncertainties regarding the in-hospital treatment of HFrEF. Standardized and evidence-based approaches are needed to improve the efficiency and effectiveness of in-hospital HFrEF care.

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KEY WORDS diuretic, heart failure, hospitalization, therapy

APPENDIX For a supplemental table, please see the online version of this paper.