Contemporary economic burden in a real-world heart failure population with Commercial and Medicare supplemental plans

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Abstract

Background: Limited real-world data exist on healthcare resource utilization (HCRU) and associated costs of patients with heart failure (HF) with reduced ejection fraction (HFrEF) and preserved EF (HFpEF), including urgent HF visits, which are assumed to be less burdensome than HF hospitalizations (hHFs).

Hypothesis: This study aimed to quantify the economic burden of HFrEF and HFpEF, via a retrospective, longitudinal cohort study, using IBM® linked claims/electronic health records (Commercial and Medicare Supplemental data only).

Methods: Adult patients, indexed on HF diagnosis (ICD-10-CM: I50.x) from July 2012 through June 2018, with 6-month minimum baseline period and varying follow-up, were classified as HFrEF (I50.2x) or HFpEF (I50.3x) according to last-observed EF-specific diagnosis. HCRU/costs were assessed during follow-up.

Results: About 109,721 HF patients (22% HFrEF, 31% HFpEF, 47% unclassified EF; median 18 months’ follow-up) were identified. There were 3.2 all-cause outpatient visits per patient-month (HFrEF, 3.3; HFpEF, 3.6); 69% of patients required inpatient stays (HFrEF, 80%; HFpEF, 78%). Overall, 11% of patients experienced hHFs (HFrEF, 23%; HFpEF, 16%), 9% experienced urgent HF visits (HFrEF, 15%; HFpEF, 12%); 26% were hospitalized less than 30 days after first urgent HF visit versus 11% after first hHF. Mean monthly total direct healthcare cost per patient was $9290 (HFrEF, $11,053; HFpEF, $7482).

Conclusions: HF-related HCRU is substantial among contemporary real-world HF patients in US Commercial or Medicare supplemental health plans. Patients managed in urgent HF settings were over twice as likely to be hospitalized within 30 days versus those initially hospitalized, suggesting urgent HF visits are important clinical events and quality improvement targets.

KEYWORDS
cost, ejection fraction, healthcare resource utilization, heart failure, real world

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INTRODUCTION

Heart failure (HF) is an important cause of mortality and morbidity, yet has broader health implications, including substantial economic burden on healthcare systems. In the context of shifting HF epidemiology with rising projected disease burden, safely curbing HF-related costs has emerged as a common goal for patients and healthcare systems. Patients may seek acute HF care in non-hospitalization settings, including emergency departments, HF clinics, observation units, urgent-care centers, and ambulatory infusion sites. Increasing HF including emergency departments, HF clinics, observation units, and urgent-care centers. Even less information exists on cost and HCRU variation across care settings. These data exist estimating the impact on healthcare resource utilization (HCRU) and direct medical costs of HF management across care settings. Even less information exists on cost and HCRU variation according to left ventricular ejection fraction (LVEF), specifically patients with HF with preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF), despite increasing awareness of the burden of HFpEF. The primary study aim was to estimate HCRU and associated direct medical costs, including HF hospitalizations (hHFs) and urgent HF visits, in a contemporary HF-patient cohort. Secondary aims were estimation of HCRU/costs by LVEF-specific diagnosis, and comparison of HCRU/cost outcomes by age and prior/recent inpatient stay.

METHODS

This was a retrospective, longitudinal cohort study of a prevalent HF population using linked US claims and electronic healthcare records (EHRs) data between 2012 and 2018. Adult patients were indexed on date of first/earliest claim with an HF diagnosis code (ICD-9/10-CM 428.x/I50.x) from July 2012 through June 2018. Continuous medical and pharmacy eligibility for ≥6 months before indexing (baseline period) was required to capture baseline demographics and clinical characteristics. Variable follow-up extended from indexing until the earliest of loss of medical/pharmacy eligibility or end of study period, that is, ranging from 0 to 71 months (Figure 1).
### TABLE 1  Baseline patient demographics and clinical characteristics

| Characteristic                                      | All (n = 109 721) | Left ventricular ejection fraction |                   |                   |
|----------------------------------------------------|-------------------|-----------------------------------|-------------------|-------------------|
|                                                    |                   | rEF(n = 23 956) | pEF(n = 33 781) | uEF(n = 51 984) |
| Mean age (SD), years                              | 72.8 (14)         | 72.6 (13)    | 74.9 (12)      | 71.5 (15)        |
| Sex                                                |                   |                   |                   |                   |
| Male                                               | 54 312 (50%)      | 14 554 (61%)  | 14 320 (42%)    | 25 438 (49%)     |
| Female                                            | 55 409 (50%)      | 9402 (39%)    | 19 461 (58%)    | 26 546 (51%)     |
| Healthcare plan type                               |                   |                   |                   |                   |
| Comprehensive                                     | 40 325 (37%)      | 9207 (38%)    | 13 331 (39%)    | 17 787 (34%)     |
| Health maintenance organization                    | 29 211 (27%)      | 5905 (25%)    | 9202 (27%)      | 14 104 (27%)     |
| Preferred provider organization                     | 34 719 (32%)      | 7663 (32%)    | 10 158 (30%)    | 16 898 (33%)     |
| Other plan type                                    | 10 964 (10%)      | 2439 (10%)    | 2725 (8%)       | 5800 (11%)       |
| Median length of follow-up (IQR), months           | 17.9 (6.7–35.8)   | 21.0 (8.8–39.7) | 20.4 (8.5–38.6) | 15.3 (5.2–31.8) |
| Comorbidity                                        |                   |                   |                   |                   |
| Hypertension                                       | 89 540 (82%)      | 18 863 (79%)  | 29 188 (86%)    | 41 489 (80%)     |
| T2DM                                               | 44 947 (41%)      | 10 137 (42%)  | 14 730 (44%)    | 20 080 (39%)     |
| Depression, anxiety, and cognitive disorders       | 37 671 (34%)      | 6656 (28%)    | 12 030 (36%)    | 18 985 (37%)     |
| Atrial fibrillation                                | 31 121 (28%)      | 7386 (31%)    | 10 534 (31%)    | 13 201 (25%)     |
| Peripheral artery/vascular disease                 | 30 044 (27%)      | 6354 (27%)    | 10 073 (30%)    | 13 617 (26%)     |
| CKD                                                | 23 764 (22%)      | 5198 (22%)    | 8364 (25%)      | 10 202 (20%)     |
| Anemia (iron deficiency)                           | 20 770 (19%)      | 3983 (17%)    | 7145 (21%)      | 9642 (19%)       |
| Obesity                                            | 20 086 (18%)      | 3523 (15%)    | 7319 (22%)      | 9244 (18%)       |
| Cancer                                             | 19 827 (18%)      | 4124 (17%)    | 6110 (18%)      | 9593 (19%)       |
| Sleep apnea                                        | 19 369 (18%)      | 3616 (15%)    | 6938 (21%)      | 8815 (17%)       |
| Cerebrovascular disease/stroke                     | 17 244 (16%)      | 3284 (14%)    | 5756 (17%)      | 8204 (16%)       |
| Acute coronary syndrome/myocardial infarction      | 14 906 (14%)      | 4187 (17%)    | 4161 (12%)      | 6558 (13%)       |
| Hyperkalemia/hypokalemia                           | 14 421 (13%)      | 2598 (11%)    | 4966 (15%)      | 6857 (13%)       |
| Pulmonary hypertension                             | 2376 (2%)         | 417 (2%)      | 970 (3%)        | 989 (2%)         |
| Mean (SD) baseline Charlson Comorbidity Index      | 2.0 (2.2)         | 1.9 (2.1)     | 2.1 (2.1)       | 1.9 (2.3)        |
| BMI                                                | n = 46 407        | n = 9613      | n = 15 216      | n = 21 578       |
| Mean (SD)                                          | 30.4 (7.9)        | 29.8 (7.3)    | 31.2 (8.2)      | 30.1 (7.8)       |
| Baseline systolic BP, mm Hg                        | n = 47 330        | n = 9800      | n = 15 441      | n = 22 089       |
| Mean (SD)                                          | 134 (21)          | 133 (21)      | 136 (21)        | 133 (21)         |
| Baseline diastolic BP, mm Hg                       | n = 47 303        | n = 9793      | n = 15 433      | n = 22 077       |
| Mean (SD)                                          | 73 (12)           | 74 (12)       | 73 (12)         | 73 (12)          |
| Baseline eGFR, mL/min/1.73 m²                       | n = 28 507        | n = 5855      | n = 9650        | n = 13 002       |
| Mean (SD)                                          | 55.5 (26.3)       | 55.1 (25.2)   | 54.5 (24.4)     | 56.5 (27.9)      |
| Baseline HbA1c, %                                  | n = 19 400        | n = 4091      | n = 6651        | n = 8658         |
| Mean (SD)                                          | 6.8 (1.5)         | 6.9 (1.6)     | 6.8 (1.5)       | 6.7 (1.5)        |
| Baseline BNP, pg/mL                                | n = 10 012        | n = 2067      | n = 3776        | n = 4169         |
| Mean (SD)                                          | 325 (823)         | 444 (1029)    | 303 (890)       | 285 (611)        |
| Baseline N-terminal proBNP, pg/mL                  | n = 3183          | n = 636       | n = 1204        | n = 1343         |
| Mean (SD)                                          | 2160 (4737)       | 2895 (5273)   | 2040 (4713)     | 1918 (4451)      |

Notes: The P < .0001 for all comparisons across LVEF subgroups.
Abbreviations: BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; IQR, interquartile range; pEF, preserved ejection fraction; proBNP, pro-brain natriuretic peptide; rEF, reduced ejection fraction; SD, standard deviation; T2DM, type 2 diabetes mellitus; uEF, unclassified ejection fraction.
| Resource* | All (n = 109 721) | Left ventricular ejection fraction |
|-----------|-------------------|----------------------------------|
|           |                   | rEF(n = 23 956) | pEF(n = 33 781) | uEF(n = 51 984) |
|           |                   |                   |                   |
| All-cause resource use |                   |                   |
| Outpatient |                   |                   |
| No. of outpatient visits, mean (SD) | 71.8 (91.6) | 83.0 (98.3) | 88.2 (105.4) | 56.0 (74.5) |
| Incidence rate (95% CI) | 3.176(3.165–3.187) | 3.312(3.308–3.317) | 3.597(3.593–3.601) | 2.766(2.763–2.769) |
| Most commonly used outpatient resources, visits (% responses) |                   |                   |
| Total frequency of events | 7 020 026 | 2 672 350 | 4 020 627 | 327 049 |
| Acute-care hospital | 1 246 236 (18%) | 485 627 (18%) | 614 788 (17%) | 48 381 (15%) |
| Family practice | 1 089 894 (16%) | 426 725 (18%) | 614 788 (17%) | 48 381 (15%) |
| Internal medicine (NEC) | 520 997 (7%) | 194 912 (7%) | 301 967 (8%) | 24 117 (7%) |
| Supply center | 428 275 (6%) | 151 159 (6%) | 258 718 (6%) | 18 398 (6%) |
| Cardiovascular disease/cardiology | 372 439 (5%) | 174 327 (7%) | 182 421 (5%) | 17 744 (5%) |
| Radiology | 312 863 (4%) | 116 000 (4%) | 180 368 (4%) | 14 442 (4%) |
| Treatment center | 284 280 (4%) | 114 748 (4%) | 156 899 (4%) | 12 633 (4%) |
| Home help agency | 197 596 (3%) | 70 170 (3%) | 119 446 (3%) | 79 800 (3%) |
| Unknown | 188 580 (3%) | 66 991 (3%) | 114 133 (3%) | 74 566 (2%) |
| Laboratory | 171 284 (2%) | 68 310 (3%) | 95 074 (2%) | 79 000 (2%) |
| Inpatient |                   |                   |
| n = 75 705 | n = 19 276 | n = 26 207 | n = 30 222 |
| No. of hospital admissions, mean (SD) | 1.6 (2.0) | 2.0 (2.3) | 2.0 (2.3) | 1.1 (1.5) |
| Incidence rate (95% CI) | 0.070(0.069–0.070) | 0.081(0.081–0.082) | 0.083(0.082–0.083) | 0.053(0.052–0.053) |
| Mean (SD) LoS/hospitalization | 6 (6.3) | 5.9 (5.8) | 5.8 (5.1) | 6.3 (7.4) |
| Mean (SD) cumulative LoS | 14.3 (21.9) | 15.7 (23.0) | 16.0 (22.9) | 12.1 (20.0) |
| Reasons for admission |                   |                   |
| n = 124 654 | n = 49 267 | n = 69 804 | n = 5583 |
| HF | 15 673 (13%) | 7583 (15%) | 7419 (11%) | 671 (12%) |
| Other sepsis | 8042 (6%) | 2857 (6%) | 4773 (7%) | 412 (7%) |
| Acute myocardial infarction | 5381 (4%) | 3170 (6%) | 1851 (3%) | 360 (6%) |
| Atrial fibrillation and flutter | 5233 (4%) | 2285 (5%) | 2727 (4%) | 221 (4%) |
| Other chronic obstructive pulmonary disease | 4568 (4%) | 1366 (3%) | 3050 (4%) | 152 (3%) |
| Respiratory failure (NEC) | 4225 (3%) | 1367 (3%) | 2654 (4%) | 204 (4%) |
| Acute kidney failure | 3986 (3%) | 1468 (3%) | 2357 (3%) | 161 (3%) |
| Pneumonia, unspecified organism | 3723 (3%) | 1332 (3%) | 2257 (3%) | 134 (3%) |
| Hypertensive heart and chronic kidney disease | 2811 (2%) | 1197 (2%) | 1492 (2%) | 122 (2%) |
| Chronic ischemic heart disease | 2701 (2%) | 1431 (3%) | 1129 (2%) | 141 (3%) |
| Cerebral infarction | 2297 (2%) | 935 (2%) | 1235 (2%) | 127 (2%) |
| Other | 66 014 (53%) | 24 726 (49%) | 38 860 (56%) | 2878 (52%) |
| HF-related resource use |                   |                   |
| Urgent visits (all patients) |                   |                   |
| Mean no. (SD) | 0.1 (0.6) | 0.3 (0.8) | 0.2 (0.7) | 0 (0.3) |
| Incidence rate (95% CI) | 0.006(0.006–0.006) | 0.010(0.010–0.010) | 0.008(0.008–0.008) | 0.002(0.002–0.003) |
| Urgent visits (resource users) | n = 10 000 | n = 3583 | n = 4214 | n = 2203 |
| Mean no. (SD) | 1.5 (1.2) | 1.7 (1.3) | 1.6 (1.2) | 1.2 (0.5) |
| Incidence rate (95% CI) | 0.056(0.055–0.057) | 0.057(0.055–0.058) | 0.053(0.052–0.054) | 0.062(0.060–0.065) |
| hHFs (all patients)* |                   |                   |
| Mean no. (SD) | 0.1 (0.5) | 0.3 (0.7) | 0.2 (0.6) | 0 (0.2) |
| Incidence rate (95% CI) | 0.006(0.006–0.006) | 0.012(0.012–0.013) | 0.009(0.009–0.009) | 0.001(0.001–0.001) |

(Continues)
models for dichotomous outcomes. The p-values < .05 were considered statistically significant.

Statistical analyses were conducted in Stata 16 (StataCorp LP, College Station, Texas).

3 | RESULTS

The study cohort consisted of 109,721 eligible patients with HF (HFrEF, 22%; HFpEF, 31%; HfUEF, 47%) (Figure S1). Among the HfUEF subgroup (n = 51,984), 92% did not receive an LVEF-specific diagnosis during follow-up and 8% received a combined HFrEF/HFpEF diagnosis. This article focuses on the HFrEF and HFpEF subgroups because of the ambiguity of HfUEF diagnoses. The mean age at index was 73 years and 50% were men (Table 1). Median follow-up was 18 months (HFrEF, 21 months; HFpEF, 20 months). The most frequently reported comorbidities were hypertension (82%), type 2 diabetes (41%), and depression/anxiety/cognitive disorders (34%).

Baseline characteristics were numerically similar between HFrEF and HFpEF, except for age (HFrEF, 73 years; HFpEF, 75 years), sex (HFrEF, 61% men; HFpEF, 42% men), and comorbidities (generally more prevalent in HFpEF).

Beta-blockers (58%; HFrEF 74%, HFpEF 61%) and angiotensin-converting enzyme inhibitor/angiotensin receptor blockers (45%; HFrEF 56%, HFpEF 47%) were the most frequently dispensed guideline-directed medical therapy (GDMT); sodium-glucose cotransporter-2 inhibitors (SGLT2is) and angiotensin receptor-neprilysin inhibitors (ARNIs) were dispensed to 1.0% (93% with prior diabetes diagnosis) and 0.5% of the study cohort, respectively; 39% (HFrEF 56%, HFpEF 41%) received ≥ 2 GDMT classes (Figure S2). GDMT use was higher in patients with HFrEF versus HFpEF for all therapy classes. Other frequently dispensed classes included diuretics and statins (both 52%). Notable significant differences were observed between HFrEF and HFpEF in dispensing of calcium channel blockers (23% vs. 35%) and mineralocorticoid receptor antagonists (24% vs. 14%). Diuretic use was similar between HFrEF (63%) and HFpEF (62%).

The rate of outpatient visits was 3.2 per patient-month in the study cohort (HFrEF 3.3, HFpEF 3.6; Table 2). The mostvisited outpatient service providers were acute-care hospitals (18% of single-day visits) and family practitioners (16%). Two-thirds (69%) of the study cohort required an inpatient stay; the rate of inpatient stays was 0.07 per patient-month and was comparable between HFrEF and HFpEF (both 0.08). HF was the most frequently recorded primary diagnosis across all inpatient stays (13% of stays); other diagnoses were "other sepsis" (6%), "acute myocardial infarction" (4%), and "atrial fibrillation and flutter" (4%). The mean (SD) length of stay (LoS) was 6.0 (6.3) days and mean (SD) inpatient LoS across entire follow-up was 14.3 (21.9) days; LoS did not differ substantially between HFrEF and HFpEF.

In total, 9% of patients had an urgent HF visit (HFrEF, 15%; HFpEF, 12%; Table 2). The rate of urgent HF visits among

### Table 2 (Continued)

| Resource* | All (n = 109,721) | Left ventricular ejection fraction |
|-----------|------------------|----------------------------------|
|           | rEF(n = 23,956)  | pEF(n = 33,781)                  | uEF(n = 51,984) |
| hHFs (resource users) | n = 12,252 | n = 5,544 | n = 5,549 | n = 11,594 |
| Mean no. (SD) | 1.3 (0.7) | 1.3 (0.7) | 1.3 (0.8) | 1.1 (0.3) |
| Incidence rate (95% CI) | 0.048 (0.047–0.049) | 0.048 (0.047–0.049) | 0.046 (0.045–0.047) | 0.059 (0.056–0.062) |
| Mean (SD) LoS (all hHF events) | 5.2 (6.0) | 5.3 (5.5) | 5.1 (6.3) | 5.1 (7.2) |
| Mean (SD) cumulative LoS | 6.8 (8.5) | 7.1 (8.4) | 6.8 (7.7) | 5.6 (8.1) |
| Direct medical costs, mean (SD)* |  |  |  |  |
| Medication, all | 10,723 (31,256) | 11,363 (30,082) | 12,537 (34,960) | 9,249 (29,091) |
| HF medication |  |  |  |  |
| All | 1,577 (5,555) | 2,009 (4,112) | 1,886 (1,886) | 1,176 (2,957) |
| Resource users | 1,941 (6,106) | 2,327 (4,341) | 2,214 (9,301) | 1,541 (3,301) |
| Outpatient visits, all | 39,730 (105,902) | 48,909 (114,597) | 45,427 (114,075) | 31,799 (95,185) |
| Urgent visits |  |  |  |  |
| All | 104 (881) | 201 (1,219) | 141 (1,109) | 35 (382) |
| Resource users | 1,141 (2,709) | 1,346 (2,897) | 1,130 (2,958) | 828 (1,667) |
| Inpatient stays, all | 40,317 | 54,386 | 44,292 | 31,250 |
| hHFs |  |  |  |  |
| All | 2578 | 6536 | 3171 | 368 |
| Resource users | 23,084 | 28,243 | 19,304 | 16,505 |

Notes: The *P < .0001 for all comparisons across LVEF subgroups.

Abbreviations: CI, confidence interval; HF, heart failure; hHF, heart failure hospitalization; LoS, length of stay; NEC, not elsewhere classified; pEF, preserved ejection fraction; rEF, reduced ejection fraction; SD, standard deviation; uEF, unclassified ejection fraction.
resource-users was 0.06 per patient-month (HFrEF 0.06, HFpEF 0.05). One-quarter (26%) of patients were hospitalized (all-cause) within 30 days of initial urgent HF visit (HFrEF, 29%; HFpEF, 27%), with 65% of patients hospitalized any time following the urgent HF visit (HFrEF, 69%; HFpEF, 71%; Figure 2). Furthermore, 11% of all patients had an hHF during follow-up (HFrEF, 23%; HFpEF, 16%; Figure 2). The rate of hHFs among resource users was 0.05 per patient-month, with a mean LoS of 5.2 days (numerically similar for HFrEF and HFpEF). Among all resource users, the rate of hospitalizations requiring ≥1 overnight stay with secondary diagnosis of HF (i.e., not an hHF) was 0.07 per patient-month, with a mean LoS of 7.0 days. In total, 11% of all patients were readmitted (all-cause) within 30 days of their first hHF (HFrEF, 12%; HFpEF, 10%); 61% were subsequently readmitted at some time during follow-up (HFrEF, 62%; HFpEF, 65%).

All-cause costs associated with HF management by LVEF are shown in Table 2 and Figure 3(A). The mean total healthcare cost per patient (monthly cost per patient) was $90 770 ($9290); $114 658 ($11 053) for HFrEF, and $102 256 ($7482) for HFpEF. The total medication cost per patient was $10 723 ($457); ≈12% of total healthcare costs (5% of total monthly costs). Although total medication costs were higher for HFpEF versus HFrEF ($12 537 [$495] and $11 363 [$429]), HF-related medication costs were higher for HFrEF compared with HFpEF ($2009 [$4112] and $1886 [$1886]).

The total cost of outpatient visits per patient (all cause) was $39 730 ($2395); 44% of total healthcare costs (26% of total monthly costs). Outpatient costs were $48 909 ($2603) for HFrEF and $45 427 ($2318) for HFpEF. The cost of inpatient stays per patient was $40 317 ($6438); 44% of total healthcare costs (69% of total monthly costs). Inpatient stays cost $54 386 (monthly $8021) for HFrEF and $44 292 ($4668) for HFpEF.

HF costs, reported per resource-using patient, included HF medication costs of $1941 ($82) (Figure 3(B)); $2327 ($90) for HFrEF and
produced similar results for cost data as primary study analyses (Figure S3). Results were directionally consistent (i.e., higher for HFrEF vs. HFpEF), and numerically similar. The proportions of costs attributed to each setting were also consistent with primary analyses.

4 | DISCUSSION

This longitudinal cohort study of linked claims/EHRs data highlights substantial economic burden related to contemporary HF care. The average per-patient monthly cost for healthcare was estimated at $9290, driven by high rates of inpatient and outpatient visits. Estimated costs (and most HCRU measures) were generally higher for HFrEF compared with HFpEF. Higher costs were observed among those recently hospitalized. Urgent HF visits were frequent for both HFrEF and HFpEF. Patients managed via urgent-care settings were over twice as likely to be hospitalized for any reason within 30 days versus those managed via hHFs. Young patients with HF spent the most time in hospital and experienced shorter readmission times.

The economic cost of HF management is considerable. Hospitalizations contribute substantially to direct medical costs of HF, but other significant direct costs should be considered, including medications, procedures, nursing-home costs, and physician appointments. Although the economic cost of HF has been widely studied, few studies examined burden of HFpEF and HFrEF. HCRU and costs have been reported to be significantly greater in patients with chronic HFrEF after a worsening HF event versus patients who remain stable. This study, undertaken to quantify the real-world economic burden of these subgroups in the US, adds to those findings and provides a more comprehensive insight into clinical profiles, HCRU, and direct medical costs of patients with HFrEF and HFpEF.

Observed HCRU was high: during follow-up patients experienced a rate of 3.2 all-cause outpatient visits per month: patients with HFpEF had a higher incidence rate of all-cause outpatient visits versus HFrEF (3.6 vs. 3.3 visits per month). One in 10 patients had ≥1 urgent HF visit during follow-up. Our study included a high proportion of patients with HFrEF, many of whom had not yet received an LVEF-specific diagnosis, suggesting these patients may be recently diagnosed and awaiting further testing. Such patients may have had a milder or even transient disease state compared with the HFpEF and HFrEF subgroups, thereby diluting the rate of worsening HF events during follow-up. These patients likely also contributed to underestimation of other resources and corresponding costs in the study cohort. Alternatively, these patients may simply reflect less specific diagnostic classification by the treating physician.

Two-thirds of the study cohort were hospitalized (all-cause) and 10% experienced ≥1 hHF. Patients with HF are frequently multimorbid and HF was not always the primary diagnosis; other diagnoses included sepsis, acute myocardial infarction, and atrial fibrillation/flutter. Total healthcare costs were high, particularly for HFrEF, driven almost equally by inpatient and outpatient costs, a finding misaligned with traditional focus on reducing financial costs for inpatient
settings. Nonetheless, we found that patients with a recent hospitalization had higher HCRU than those without. Overall, these data provide support for measures to reduce costs in both care settings.

Urgent HF visits are important clinical events and our real-world data highlight the related, substantial HCRU. A key finding was that patients managed in urgent-care settings were more than twice as likely to be hospitalized (all-cause) within 30 days versus those managed via an hHF (26% vs. 11%, respectively). This likely reflects that patients presenting at urgent HF visits represent a high-risk cohort with substantial longitudinal care needs. The 30-day readmission rate after an hHF in our study is lower than the 25% of readmissions reported for Medicare beneficiaries, although differences in study designs, patient populations, and study definitions may account for this disparity.

The importance of urgent HF visits is increasingly being recognized. Inclusion of urgent HF visits in a sensitivity analysis of the PARAGON-HF trial resulted in statistically significant differences in the primary outcome for a study that otherwise failed to show differences between arms. In that study, sacubitril–valsartan did not significantly lower rates of total hHF deaths and death from cardiovascular disease versus valsartan, although the inclusion of confirmed urgent HF visits in a composite endpoint resulted in a risk ratio of 0.861 (95% confidence interval 0.747–0.993). Notably, the DAPA-HF study included urgent HF visits in the primary endpoint and demonstrated a reduced risk of worsening HF or death from cardiovascular causes in patients who received dapagliflozin versus placebo plus standard therapy. Urgent HF visits also represent important targets for quality improvement, which may require focused attention and resource allocation similar to investments in post-discharge transitional care.

This real-world US study also highlights the substantial economic burden across a broad age range, including younger patients (<65 years). Use of the LCED, primarily covering a commercial health plan including younger patients, allowed detailed description of HCRU/costs in this cohort. Total costs were highest among patients aged less than 60 years, primarily driven by longer inpatient stays, despite lower medication costs; findings supported by another US-based study. Younger patients also experienced shorter times to readmission. Total, all-cause monthly costs per patient were almost twice as high for patients aged less than 65 years compared with patients aged 65+ ($14,386 vs. $7,335), primarily driven by inpatient costs ($10,700 vs. $4,804). Monthly costs per patient for outpatient visits, medications, and all HF-related events were higher in patients aged less than 65 years, apart from HF-related medication costs. Others have shown that young patients with HFpEF have lower quality of life compared with older patients and are more likely to die of cardiovascular-related causes, emphasizing the importance of improving outcomes in these patients. Total healthcare costs were significantly higher for patients diagnosed with T2DM or CKD versus those with no T2DM or CKD, in line with findings from prior work.

Utilization of GDMT was low overall, which is particularly concerning in patients with HFrEF given the strong evidentiary base supporting their clinical benefits in this patient population. Dedicated HF registries encompassing broad real-world HF populations in the United States and worldwide have shown suboptimal use of established and newer therapies targeting HFrEF. In the present study, the proportion of patients on triple therapy (three evidence-based HF therapies) remained less than 20% and use of ARNI and SGLT2i remained less than 2%. Various patient-level (affordability, willingness to take multidrug regimens), clinician-level (comfort with newer agents, knowledge gaps, treatment inertia), and health system-level (local treatment availability, access to healthcare) issues may contribute to observed gaps in evidence-based therapies. Multilevel quality improvement initiatives are needed to promote equitable and widespread care practices to optimize GDMT.

Some study limitations should be considered. Diagnoses were identified using ICD-9/10-CM codes, which are subject to miscoding. Low diuretic use may indicate incomplete reporting of prescriptions, and in some cases, accuracy of HF diagnoses. Recently, LVEF thresholds for HFrEF and HFpEF have evolved, potentially causing confusion in patient classification. Claims-based models aiming to better identify LVEF-specific subgroups are being developed, which may improve characterization of HCRU in these populations. Observed statistically significant differences may be driven, in part, by large sample sizes; comparisons should emphasize absolute differences. Only US Commercial and Medicare supplemental data were evaluated, which may limit the generalizability of these findings to other healthcare systems or other covered patient populations in the United States. Finally, the large proportion of patients classified as HFuEF may have impacted study findings. This subgroup likely comprises a combination of patients with a definitive clinically valid mid-range or borderline LVEF diagnosis, patients with misdiagnosed LVEF status, and patients without a recorded LVEF. This subgroup therefore represents a heterogenous group without an interpretable shared characteristic.

Accurate coding and LVEF-specific diagnosis of patients may represent an opportunity for improvement in care quality. All outcomes during follow-up were attributed to HFrEF, HFpEF, or HFuEF based upon last-observed LVEF-specific diagnosis; this may have resulted in misclassification of patients with multiple or borderline LVEF diagnoses and/or overestimation of HCRU/costs for these patient subgroups. Nonetheless, sensitivity analyses (based on index LVEF only, and excluding patients with conflicting LVEF-specific diagnoses) yielded similar findings to the main analysis.

Study strengths included linkage of claims and EHRs data, which facilitated comprehensive capture of patients’ healthcare interactions. A minimum follow-up for inclusion was not specified, mitigating risk of introducing immortal person-time bias. Code lists were developed with clinical input to ensure they accurately represented disease types and health-related events. The 6-month baseline period was ultimately used as a best effort to balance sample size and certainty that patient characteristics captured were accurate. Finally, the long follow-up allowed assessment of HCRU/costs over a substantial time.

This study, one of the first to assess real-world HCRU specific to HFrEF and HFpEF in the United States, demonstrates the substantial
HCRU of patients with HFrEF and HfP EF, and quantifies HCRU related to urgent HF visits, showing that these are important clinical events representing a target for quality improvement. Future efforts are needed to understand if coordinated multidisciplinary HF clinics or other initiatives may help diffuse and/or reduce healthcare system costs. Overall, our results identify key drivers of costs among patients with HF and highlight the need for their effective management in real-world settings.

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REFERENCES
1. Jackson SL, Tong X, King RJ, Loustalot F, Hong Y, Ritchey MD. National burden of heart failure events in the United States, 2006 to 2014. Circ Heart Fail. 2018;11(12):e004873.
2. Lesyuk W, Kriza C, Kolominsky-Rabas P. Cost-of-illness studies in heart failure: a systematic review 2004-2016. BMC Cardiovasc Disord. 2018;18(1):74.
3. Greene SJ, Wilson LE, Abbasi SA, Yusuf AA, Hammill BG. Outpatient intravenous diuretic therapy for heart failure in the United States. J Am Coll Cardiol. 2019;73(9):1101-1103.
4. Benjamin EJ, Munter P, Alonso A, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. Circulation. 2019;139(10):e56-e528.
5. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013;6(3):606-619.
6. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. Circ Res. 2019;124(11):1598-1617.
7. Centers for Disease Control and Prevention. (2019) International Statistical Classification of Diseases and Related Health Problems, 9th/10th Revision, Clinical Modification [ICD-9/10-CM] 428.x/I50.x; https://icd10cmtool.cdc.gov/. Accessed February 13, 2020.
8. Bidwell JT, Lyons KS, Lee CS. Caregiver well-being and patient outcomes in heart failure: a meta-analysis. J Cardiovasc Nurs. 2017;32(4):372-382.
9. Endrighi R, Waters AJ, Gottlieb SS, et al. Psychological stress and short-term hospitalisations or death in patients with heart failure. Heart. 2016;102(22):1820-1825.
10. Butler J, Djatche LM, Sawhney B, et al. Clinical and economic burden of chronic heart failure and reduced ejection fraction following a worsening heart failure event. Adv Ther. 2020;37(9):4015-4032.
11. Dharmarajan K, Hsieh AF, Lin Z, et al. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. JAMA. 2013;309(4):355-363.
12. Bueno H, Ross JS, Wang Y, et al. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993-2006. JAMA. 2010;303(21):2141-2147.
13. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med. 2019;381(17):1609-1620.
14. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995-2008.
15. Zacharias M, Joffe S, Konadu E, et al. Clinical epidemiology of heart failure with preserved ejection fraction (HFpEF) in comparatively young hospitalized patients. Int J Cardiol. 2016;202:918-921.
16. Tromp J, MacDonald MR, Tay WT, et al. Heart failure with preserved ejection fraction in the young. Circulation. 2018;138(24):2763-2773.
17. Tromp J, Shen L, Jhund PS, et al. Age-related characteristics and outcomes of patients with heart failure with preserved ejection fraction. J Am Coll Cardiol. 2019;74(5):601-612.
18. Olchanski N, Vest AR, Cohen JT, DeNofrio D. Comparing inpatient costs of heart failure admissions for patients with reduced and preserved ejection fraction with or without type 2 diabetes. Cardiovasc Endocervin Metab. 2020;9(1):17-23.
19. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF Registry. J Am Coll Cardiol. 2018;72(4):351-366.
20. Brunner-La Rocca HP, Linssen GC, Smeele FJ, et al. Contemporary drug treatment of chronic heart failure with reduced ejection fraction: the CHECK-HF registry. JACC Heart Fail. 2019;7(1):13-21.
21. Tromp J, Bamadhaj S, Cleland JGF, et al. Post-discharge prognosis of patients admitted to hospital for heart failure by world region, and national level of income and income disparity (REPORT-HF): a cohort study. Lancet Glob Health. 2020 Mar;8(3):e411-e422.
22. Teng TK, Tromp J, Tay WT, et al. Prescribing patterns of evidence-based heart failure pharmacotherapy and outcomes in the ASIAN-HF registry: a cohort study. Lancet Glob Health. 2018;6(9):e1008-e1018.

23. Ouwerkerk W, Voors AA, Anker SD, et al. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. Eur Heart J. 2017;38(24):1883-1890.

24. Samarendra P. GDMT for heart failure and the clinician’s conundrum. Clin Cardiol. 2019;42:1155-1161.

25. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147-e239.

26. Desai RJ, Lin KJ, Patorno E, et al. Development and preliminary validation of a Medicare claims-based model to predict left ventricular ejection fraction class in patients with heart failure. Circ Cardiovasc Qual Outcomes. 2018;11(12):e004700.

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

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