Representativeness of the GALACTIC-HF Clinical Trial in Patients Having Heart Failure With Reduced Ejection Fraction

Matthew T. Mefford, PhD; Sandra Y. Koyama, MD; Justine De Jesus, MPH; Rong Wei, MS; Heidi Fischer, PhD; Teresa N. Harrison, SM; Pauline Woo, MD, FACC; Kristi Reynolds, PhD, MPH, FAHA

BACKGROUND: Randomized clinical trials in populations with heart failure with reduced ejection fraction may not be reflective of the general population with heart failure with reduced ejection fraction. Our study assessed the representativeness of the GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure) patient population in Kaiser Permanente Southern California.

METHODS AND RESULTS: We identified 9770 patients with a diagnosis of heart failure with reduced ejection fraction from 2014 to 2018 using electronic health records. Four mutually exclusive cohorts were created, including GALACTIC-HF–ineligible cohorts: (1) not taking guideline-directed medical therapy (GDMT) and (2) taking GDMT; and GALACTIC-HF–eligible cohorts with: (3) ejection fraction (EF) ≤28% and (4) EF 29% to 35%. Patients were followed for 30-day and 1-year mortality and 30-day, 180-day, and 1-year hospitalization. Overall, 3626 (37.1%) met GALACTIC-HF inclusion criteria with EF ≤35%, and 2367 (65.3%) of those individuals had EF ≤28%. The risk of 1-year mortality was lower among all cohorts versus the GALACTIC-HF–ineligible cohort not taking GDMT (hazard ratio, 0.80 [95% CI, 0.70–0.91], 0.84 [95% CI, 0.72–0.98], and 0.62 [95% CI, 0.51–0.75] for the GALACTIC-HF–ineligible cohort taking GDMT and GALACTIC-HF-eligible cohorts with EF ≤28% and 29%–35%, respectively). Compared with the GALACTIC-HF–ineligible cohort not taking GDMT, the short-term hospitalization risk at 30 and 180 days were similar for both GALACTIC-HF–eligible cohorts and the hospitalization risk at 1 year was similar for the GALACTIC-HF–eligible cohort with EF ≤28%.

CONCLUSIONS: A large portion of patients with heart failure with reduced ejection fraction with low EF met inclusion criteria for the GALACTIC-HF trial and, despite being on GDMT, had hospitalization rates similar to those not taking GDMT, suggesting potential benefits from other innovative treatments.

Key Words: cardiovascular disease ■ epidemiology ■ heart failure
Improving Contractility in Heart Failure) RCT aimed to examine improvement of cardiac function at the level of the sarcomere (i.e., contractility unit) in patients with HFrEF with a novel cardiomyosin activator, omecamtiv mecarbil, and found a reduction in the trial’s primary composite end point associated with treatment versus placebo.5

RCTs in HF populations often include stringent selection criteria and may not be reflective of patients with HF seen in clinical practice.6–8 A prior study indicated that only 15% of published RCTs could feasibly be replicated using administrative claims or electronic health records data, and there was potential for studies using real-world data to complement trials.9 Conducting research in a large, integrated health care delivery system such as Kaiser Permanente Southern California (KPSC) provides a unique opportunity to leverage real-world data with more granular clinical details to examine characteristics and outcomes in contemporary HFrEF populations eligible and ineligible for RCTs such as GALACTIC-HF. Assessing clinical characteristics and outcomes in KPSC members similar to RCT populations can provide evidence of the potential impact of improving care in a real-world HF population. The current study examined the representativeness of the GALACTIC-HF RCT population within KPSC.

**METHODS**

Anonymized data that support the findings of this study may be made available from the investigative team in the following conditions: (1) agreement to collaborate with the study team on all publications, (2) provision of external funding for administrative and investigator time necessary for this collaboration, (3) demonstration that the external investigative team is qualified and has documented evidence of training for human subjects protections, and (4) agreement to abide by the terms outlined in data use agreements between institutions.

**Setting**

KPSC is an integrated health care delivery system with ≈4.6 million members within a service area comprising >20% of Southern California’s population.10 KPSC membership is diverse and widely representative of the Southern California region. Members’ receipt of outpatient, inpatient, laboratory, and pharmacy services are tracked in the electronic health record system. Services performed outside of KPSC hospitals are tracked through submitted billing claims. The institutional review board at KPSC reviewed and approved the current study, and a waiver of informed consent was granted given the data-only nature of this study.

**What Is New?**

- In this cohort of 9770 Kaiser Permanente Southern California patients with heart failure with reduced ejection fraction (HFrEF), 74% were taking guideline-directed medical therapy (GDMT) at baseline and 37% met full GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure) inclusion and exclusion criteria.
- Compared with patients with HFrEF not taking GDMT, the risks of 30-day and 1-year mortality were lower for GALACTIC-HF–ineligible patients taking GDMT and GALACTIC-HF–eligible patients.
- Despite GDMT use, hospitalization rates at 30 and 180 days remain high among all GALACTIC-HF–eligible patients, and current GDMT did not reduce the risk of 1-year hospitalization for the GALACTIC-HF–eligible cohort with ejection fraction ≤28% compared with those not taking GDMT.

**What Are the Clinical Implications?**

- A sizable population of patients with HFrEF fall into the eligibility criteria for the GALACTIC-HF study, as indicated by our study cohorts; thus, applicability of the GALACTIC-HF results can have a significant impact on many individuals with HFrEF.
- Similar 30-day, 180-day, and 1-year hospitalization rates among patients with HFrEF not taking GDMT and GALACTIC-HF–eligible patients with low ejection fraction suggests there is potential for benefits from other innovative treatments.
Study Population
In this retrospective cohort study, we identified 9770 patients with an incident or prevalent HF diagnosis between January 1, 2014, and December 31, 2018. HF was identified using a previously validated algorithm based on an inpatient visit with a principal discharge diagnosis of HF or ≥3 outpatient visits coded for HF with ≥1 visits with a cardiologist, using International Classification of Disease, Ninth Revision (ICD-9) codes 398.91, 402.x1, 404.x1, 404.x3, and 428.x; or Tenth Revision (ICD-10) codes I50.x, I11.0, I13.0, I13.2, I97.13, I97.130, I97.131, and I09.81.11,12 All patients were required to have at least 1 year of continuous membership before 30 days after their index date, defined as their inpatient discharge date or third outpatient visit date. We also required documentation of an EF ≤35% within 2 years prior through 30 days after their index date, using the EF value most proximal to the index date. Patients who had an index hospital length of stay >30 days or who died during their index encounter were excluded.

HF Cohorts
Mutually exclusive cohorts of patients with HFrEF who were eligible and ineligible for the GALACTIC-HF RCT were created to compare characteristics and outcomes (Figure 1). Using outpatient prescription medication fills, we first identified patients with HFrEF who were taking and not taking guideline-directed medical therapy (GDMT),13 defined as a fill for an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) or angiotensin receptor neprylisin inhibitor (ARNi), plus a beta blocker (BB) at or within 180 days before the index date. Among patients with HFrEF meeting our definition of GDMT use, we applied additional GALACTIC-HF inclusion and exclusion criteria. Exclusion criteria included having an elevated B-type natriuretic peptide ≥125 pg/mL and, for patients with HFrEF identified in the outpatient setting, having an inpatient or ED visit for HF within 12 months before their index date. Exclusion criteria included age >85 years; history of malignancy; and history of rheumatic heart disease, hypertrophic or obstructive cardiomyopathy, acute myocarditis, constrictive pericarditis, or congenital heart disease. For further convention, the mutually exclusive HFrEF cohorts are described as GALACTIC-HF–ineligible cohorts (1) not taking GDMT; (2) taking GDMT, and GALACTIC-HF–eligible cohorts with (3) EF ≤28% and (4) 29% to 35%—that is, above and below the median EF reported in the GALACTIC-HF RCT.

Outcomes
The primary outcome included 30-day and 1-year all-cause mortality, defined as death from any cause within 30 days and, separately, 31 to 365 days after the index date. Patients were followed for death, administrative censoring, or the end of follow-up occurring on December 31, 2019. KPSC death records were derived by identifying deaths that occurred at KPSC-owned facilities, deaths that occurred at outside facilities that submitted claims to KPSC, or deaths reported to the health plan and supplemented by linking records with California State and Social Security Administration Death Master Files, which has been described previously.14 Secondary outcomes of interest were all-cause hospitalization, defined as an inpatient encounter for any reason after the index date, within 30 days, 31 to 180 days, and 181 to 365 days.

Covariates
Age, sex, race/ethnicity, insurance type, and enrollment status in the health plan were obtained at the index date. Body mass index, smoking status, and clinical variables including heart rate and blood pressure were defined in the 365 days before the index date. Clinical variables were identified in the outpatient setting using the most proximal measure, with the last value used if multiple readings occurred on the same date. Laboratory values including estimated glomerular filtration rate and B-type natriuretic peptide were defined in the outpatient setting using the most proximal measure within 365 days before through 7 days after the index date to account for a potential lag in laboratory reporting, using the last value if multiple measures occurred on the same date. Comorbidities including hypertension, diabetes, dyslipidemia, acute myocardial infarction, stroke/transient ischemic attack, other ischemic history (coronary artery disease, previous percutaneous coronary intervention or coronary artery bypass grafting), chronic obstructive pulmonary disease, and atrial fibrillation were defined using ICD-9/10 diagnosis codes and procedure codes at or in the 365 days before the index date. Additional GDMT including mineralocorticoid receptor antagonists (MRAs), hydralazine, and isosorbide dinitrate were assessed in the 180 days before the index date. Other medications of interest including digoxin, statin and nonstatin lipid-lowering therapy, diabetes medications, diuretics, anticoagulants, and antiarrhythmics were examined in the 365 days before the index date. Medication fills in the 30 days after the index date were also examined. Information on health care use in the 365 days before and 30 days after the index date included the cumulative number of outpatient visits and hospital and ED admissions. For variables with large portions of missing data (eg, estimated glomerular filtration rate and body mass index), missing categories were created.

Statistical Analysis
Baseline sociodemographics, clinical values, comorbidities, medications, health care encounters, 30-day
postdischarge medications, and 30-day postdischarge utilization were described overall, and among mutually exclusive HFrEF cohorts using the analysis of variance F-test for means and the Pearson chi-square test for proportions to test for statistical differences among HFrEF cohorts. The number of events, person-time, and rates per person-month of 30-day all-cause mortality for each mutually exclusive HFrEF cohort were calculated.

Using Cox proportional hazards regression, hazard ratios (HRs) and 95% CIs were calculated for 30-day all-cause mortality using the GALACTIC-HF—ineligible population not taking GDMT as the reference group in unadjusted and progressively adjusted models. The initial model was unadjusted, a second model adjusted for age, sex, and race/ethnicity, and a full multivariable model additionally adjusted for insurance, smoking status (current, former, never), body mass index (≥30, <30 kg/m²), estimated glomerular filtration rate (>60, ≤60 mL/min per 1.73 m², missing), heart rate (>70, ≤70 bpm), hypertension, diabetes, acute myocardial infarction, ischemic stroke, other ischemic heart disease, coronary artery bypass grafting, percutaneous coronary intervention, and lipid-lowering therapy. For the fully adjusted model, covariates were assessed for collinearity using Cramer’s V statistic, and where 2 variables were highly correlated (eg, diabetes/diabetes medications and dyslipidemia/lipid-lowering therapy), one variable was selected for model inclusion. Analyses were then repeated for 1-year all-cause mortality among patients surviving 30 days after the index date. In a secondary analysis, Cox regression was repeated.
as described above for the outcome of 30-day, 31- to 180-day, and 181- to 365-day all-cause hospitalization. Separate time windows between 31 and 365 days were chosen given a violation of the proportionality of hazards assumption for hospitalization-specific models only. Fine-Gray methods were additionally used to examine whether hospitalization outcomes were affected by the competing risk of mortality. Given the minimal impact of mortality on hospitalization results in Fine-Gray models, Cox proportional hazards models, and standard Kaplan-Meier curves were presented for all outcomes to aid in the interpretability of the results. All P values were 2-sided and a P < 0.05 was considered statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Among 9770 patients with HFrEF, 2514 (26%) and 3630 (37%) patients were included in the GALACTIC-HF-eligible cohorts not taking and taking GDMT and 2367 (24%) and 1259 (13%) were included in the GALACTIC-HF-eligible cohorts with EF ≤28% and 29% to 35%, respectively. Overall, the population was on average 70 years of age, a majority male (68%), with a large portion of non-Hispanic White patients (47%). (Table 1) Baseline clinical characteristics including heart rate (mean 78 bpm) and body mass index (mean, 29 kg/m²) varied slightly among all cohorts (P value for differences < 0.001). Baseline hypertension (85%), diabetes (48%), and peripheral vascular disorders (57%) were the most common comorbidities overall, and 11% had a prior acute myocardial infarction. The prevalence of comorbidities varied across HFrEF cohorts, with the highest proportions consistently observed among the GALACTIC-HF-eligible cohort with EF 29% to 35%.

Baseline medication use was low among the GALACTIC-HF-eligible cohort not taking GDMT for most medications including ACEis (15%), ARBs (6%), BBs (52%), MRAs (8%), but GDMT increased in the 30 days after discharge for this group (Table 2). The GALACTIC-HF-eligible cohort taking GDMT and the GALACTIC-HF-eligible cohorts had higher use of GDMT (>70% ACEi use, 30% ARB use, >99% BB use, >15% MRA) as well as other medications including statins and diabetes medications at baseline and 30 days after discharge. Use of ARNis, ivabradine (not shown), and sodium-glucose cotransporter-2 inhibitors (not shown) were low overall (<1%). Usage characteristics are listed in Table 3. Among all patients with HFrEF, 40%, 55%, and 97% had an inpatient hospitalization, an ED encounter, and an outpatient encounter, respectively. The GALACTIC-HF-eligible cohort not taking GDMT had lower percentages of inpatient and outpatient encounters in the year before their index date and a higher percentage of inpatient encounters in the 30 days following their index date compared with all other cohorts (ie, those taking GDMT).

Cumulative incidence curves for mortality are presented in Figure S1. The unadjusted risk of 30-day mortality ranged from 55% to 73% lower among all cohorts versus the GALACTIC-HF-eligible cohort not taking GDMT (Table S1). After multivariable adjustment, the risk of 30-day mortality remained lower for all cohorts versus the GALACTIC-HF-eligible cohort not taking GDMT (HR, 0.44 [95% CI, 0.34–0.58], 0.64 [95% CI, 0.48–0.85], and 0.31 [95% CI, 0.20–0.49] for the GALACTIC-HF-eligible cohort taking GDMT and GALACTIC-HF-eligible cohorts with EF ≤28% and 29%–35%, respectively) (Figure 2). For patients with HFrEF surviving at least 30 days after their index date (n = 9394), the unadjusted risk of 1-year mortality ranged from 33% to 45% lower among all cohorts versus the GALACTIC-HF-eligible cohort not taking GDMT. After multivariable adjustment, the risk of 1-year mortality remained lower among all cohorts versus the GALACTIC-HF-eligible cohort not taking GDMT (HR, 0.67 [95% CI, 0.57–0.78]) but not for the GALACTIC-HF-eligible cohorts with EF ≤28% (HR, 0.86; 95% CI, 0.72–1.00) and EF 29%–35% (HR, 0.88; 95% CI, 0.73–1.07) (Figure 3). For patients with HFrEF surviving at least 30 days and not hospitalized within 30 days after their index date (n = 8344), the unadjusted risk of 180-day hospitalization ranged from 21% to 35% lower among all cohorts versus the GALACTIC-HF-eligible cohort not taking GDMT. After multivariable adjustment, compared with the non-GDMT group, the risk of 31- to 180-day hospitalization was only lower among the GALACTIC-HF-eligible cohort taking GDMT, with estimated HRs of 0.84 (95% CI, 0.74–0.94), 0.99 (95% CI, 0.87–1.13), and 0.98 (95% CI, 0.84–1.14) for the GALACTIC-HF-eligible cohort taking GDMT and GALACTIC-HF-eligible cohorts with EF ≤28% and 29% to 35%, respectively. For patients with HFrEF surviving at least 180 days and not hospitalized within 180 days after their index date (n = 6077), the unadjusted risk of 1-year hospitalization ranged from 8% to 26% lower among all cohorts versus the GALACTIC-HF-eligible cohort not taking GDMT. After
multivariable adjustment, compared with the GALACTIC-HF–ineligible cohort not taking GDMT, the risk of 181- to 365-day hospitalization was lower among the GALACTIC-HF–eligible cohort with EF 29% to 35% (HR, 0.73; 95% CI, 0.58–0.91) but not among the GALACTIC-HF–ineligible cohort taking GDMT (HR, 0.88; 95% CI, 0.75–1.04) or the GALACTIC-HF–eligible cohort with EF ≤28% (HR, 0.99; 95% CI, 0.83–1.18).

### DISCUSSION

In the current study, 74% of all patients with HFrEF were taking GDMT at baseline, and 37% met full GALACTIC-HF clinical trial inclusion criteria. HFrEF cohorts were comparable across sociodemographic, clinical characteristics, and usage, suggesting the advantages of GDMT compared with GDMT in the current study, as well as the importance of the GALACTIC-HF trial in establishing the safety and efficacy of GDMT in HFrEF.

Table 1. Sociodemographic and Clinical Characteristics of Real-World and GALACTIC-HF–Like Cohorts

| Characteristics | Overall | GALACTIC-HF ineligible | GALACTIC-HF eligible | P value |
|-----------------|---------|------------------------|----------------------|---------|
| Guideline directed medical therapy? | … | No | Yes | Yes | Yes |
| Ejection fraction | ≤35% | ≤35% | ≤35% | ≤28% | 29%–35% |
| Sample size, n | 9770 | 2514 | 3630 | 2367 | 1259 |
| Age, y, mean (SD) | 69.6 (13.6) | 72.1 (13.6) | 70.4 (14.1) | 65.9 (12.9) | 69.4 (11.6) | <0.001 |
| Male, n (%) | 6662 (68.2) | 1735 (69.0) | 2431 (67.0) | 1669 (70.5) | 827 (65.7) | 0.005 |
| Race and ethnicity, n (%) | | | | | |
| White | 4615 (47.2) | 1223 (48.6) | 1754 (48.3) | 1005 (42.5) | 633 (50.3) | 0.001 |
| Black | 1859 (19.0) | 457 (18.2) | 664 (18.3) | 526 (22.2) | 212 (16.8) |
| Hispanic | 2449 (25.1) | 632 (25.1) | 907 (25.0) | 610 (25.8) | 300 (23.8) |
| API | 764 (7.8) | 181 (7.2) | 275 (7.6) | 202 (8.5) | 106 (8.4) |
| Other/unknown | 83 (0.8) | 21 (0.8) | 30 (0.8) | 24 (1.0) | 8 (0.6) |
| Insurance type, n (%) | | | | | |
| Commercial | 3191 (32.7) | 701 (27.9) | 1135 (31.3) | 982 (41.5) | 373 (29.6) | <0.001 |
| Private pay | 4002 (41.0) | 1098 (43.7) | 1521 (41.9) | 860 (36.3) | 523 (41.5) |
| Medicare | 2362 (24.2) | 655 (26.1) | 908 (25.0) | 473 (20.0) | 326 (25.9) |
| Medicaid | 205 (2.1) | 56 (2.2) | 64 (1.8) | 49 (2.1) | 36 (2.9) |
| Smoking status, n (%) | | | | | |
| Current | 694 (7.1) | 200 (8.0) | 199 (5.5) | 218 (9.2) | 77 (8.1) | <0.001 |
| Former | 4733 (48.4) | 1239 (49.3) | 1789 (49.3) | 1095 (46.3) | 610 (48.5) |
| Never | 4257 (43.6) | 1026 (40.8) | 1627 (44.8) | 1040 (43.9) | 564 (44.8) |
| Missing | 86 (0.9) | 49 (1.9) | 15 (0.4) | 14 (0.6) | 8 (0.6) |
| BMI, kg/m², mean (SD) | 28.7 (6.8) | 27.8 (6.7) | 28.8 (6.7) | 29.3 (6.8) | 29.3 (7.2) | <0.001 |
| Heart rate, beats per minute, mean (SD) | 78 (17) | 81 (18) | 75 (15) | 79 (17) | 78 (17) | <0.001 |
| eGFR, mL/min per 1.73 m², n (%) | | | | | |
| <15 | 316 (3.2) | 154 (6.1) | 55 (1.5) | 57 (2.4) | 50 (4.0) | <0.001 |
| 15–29 | 590 (6.0) | 236 (9.4) | 175 (4.8) | 101 (4.3) | 78 (6.2) |
| 30–44 | 1325 (13.6) | 384 (15.3) | 486 (13.4) | 286 (12.1) | 169 (13.4) |
| 45–59 | 2100 (21.5) | 478 (19.0) | 827 (22.8) | 509 (21.5) | 266 (22.7) |
| 60–89 | 4485 (45.9) | 911 (36.2) | 1826 (50.3) | 1173 (49.6) | 575 (45.7) |
| ≥90 | 257 (2.6) | 57 (2.3) | 100 (2.8) | 70 (3.0) | 30 (2.4) |
| Hypertension, n (%) | 8258 (84.5) | 2129 (84.7) | 3071 (84.6) | 1951 (82.4) | 1107 (87.9) | <0.001 |
| Diabetes, n (%) | 4660 (47.7) | 1173 (46.7) | 1655 (45.6) | 1149 (48.5) | 683 (54.2) | <0.001 |
| Acute myocardial infarction, n (%) | 1084 (11.1) | 324 (12.9) | 305 (8.4) | 249 (10.5) | 206 (16.4) | <0.001 |
| PCI, n (%) | 314 (3.2) | 97 (3.9) | 80 (2.2) | 79 (3.3) | 58 (4.6) | <0.001 |
| CABG, n (%) | 268 (2.7) | 82 (3.3) | 65 (1.8) | 65 (2.7) | 56 (4.4) | <0.001 |
| Ischemic stroke, n (%) | 332 (3.4) | 81 (3.2) | 122 (3.4) | 81 (3.4) | 48 (3.8) | 0.82 |
| Other ischemic heart disease, n (%) | 5069 (51.9) | 1400 (55.7) | 1789 (49.3) | 1161 (49.0) | 719 (57.1) | <0.001 |
| Atrial fibrillation, n (%) | 2757 (28.2) | 666 (26.5) | 1030 (28.4) | 643 (27.2) | 418 (33.2) | <0.001 |
| Peripheral vascular disorders, n (%) | 5607 (57.4) | 1566 (62.3) | 2081 (57.3) | 1194 (50.4) | 766 (60.8) | <0.001 |

API indicates Asian/Pacific Islander; BMI, body mass index; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; GALACTIC-HF, Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure; and PCI, percutaneous coronary intervention.
Mefford et al GALACTIC-HF Eligible vs Ineligible Patients

GALACTIC-HF RCT population is representative of a real-world HFrEF population. After multivariable adjustment, the GALACTIC-HF–ineligible cohort taking GDMT and the GALACTIC-HF–eligible cohorts had a lower risk of mortality compared with the GALACTIC-HF–ineligible cohort not taking GDMT. Compared with the GALACTIC-HF–ineligible cohort not taking GDMT, the hospitalization risk at 30 and 180 days were similar for both GALACTIC-HF–eligible cohorts and the hospitalization risk at 1 year was similar for the GALACTIC-HF–eligible cohort with EF ≤28%.

GDMT use was higher in the current study compared with what has been reported in prior studies. In an analysis of the National Cardiovascular Data

Table 2. Baseline and 30-Day Postindex Use of Select Medications Among Real-World and GALACTIC-HF–Like Cohorts

| Characteristics | Overall | GALACTIC-HF ineligible | GALACTIC-HF eligible | P value |
|-----------------|---------|-------------------------|----------------------|---------|
| Guideline directed medical therapy? | … | No | Yes | Yes | 0.001 |
| Ejection fraction | ≤35% | ≤35% | ≤35% | ≤28% | 29%–35% |
| Sample size, n | 9770 | 2514 | 3630 | 2367 | 1259 |
| ACEi, n (%) | | | | | |
| Baseline | 5722 (58.8) | 375 (14.9) | 2619 (72.1) | 1803 (76.2) | 925 (73.5) | <0.001 |
| 30-day postindex date | 5422 (55.5) | 709 (28.2) | 2297 (63.3) | 1612 (68.1) | 804 (63.9) | <0.001 |
| ARB, n (%) | | | | | |
| Baseline | 2414 (24.7) | 155 (6.2) | 1175 (32.4) | 674 (28.5) | 410 (32.6) | <0.001 |
| 30-day postindex date | 2322 (23.8) | 237 (9.4) | 1072 (29.5) | 640 (27.0) | 373 (29.6) | <0.001 |
| ARNi, n (%) | | | | | |
| Baseline | 28 (0.3) | 0 (0.0) | 13 (0.4) | 11 (0.5) | 4 (0.3) | 0.01 |
| 30-day post-index date | 55 (0.6) | 7 (0.3) | 20 (0.6) | 21 (0.9) | 7 (0.6) | 0.04 |
| Beta blockers, n (%) | | | | | |
| Baseline | 8518 (87.2) | 1316 (52.3) | 3597 (99.1) | 2351 (99.3) | 1254 (99.6) | <0.001 |
| 30-day post-index date | 8570 (87.7) | 1764 (70.2) | 3395 (93.5) | 2226 (94.0) | 1185 (94.1) | <0.001 |
| MRA, n (%) | | | | | |
| Baseline | 1737 (17.8) | 189 (7.5) | 804 (22.1) | 554 (23.4) | 190 (15.1) | <0.001 |
| 30-day post-index date | 1933 (19.8) | 290 (11.5) | 813 (22.4) | 614 (25.9) | 216 (17.2) | <0.001 |
| Hydralazine, n (%) | | | | | |
| Baseline | 1011 (10.3) | 358 (14.2) | 316 (8.7) | 195 (8.2) | 142 (11.3) | <0.001 |
| 30-day postindex date | 867 (8.9) | 311 (12.4) | 254 (7.0) | 174 (7.4) | 128 (10.2) | <0.001 |
| Nitrates, n (%) | | | | | |
| Baseline | 2392 (24.5) | 589 (23.4) | 908 (25.0) | 543 (22.9) | 352 (28.0) | <0.001 |
| 30-day postindex date | 1890 (19.3) | 549 (21.8) | 643 (17.7) | 415 (17.5) | 283 (22.5) | <0.001 |
| Diuretics, n (%) | | | | | |
| Baseline | 8111 (83.0) | 1752 (69.7) | 3040 (83.7) | 2197 (92.8) | 1122 (91.9) | <0.001 |
| 30-day postindex date | 7762 (79.4) | 1810 (72.0) | 2808 (77.4) | 2096 (88.6) | 1048 (83.2) | <0.001 |
| CCB, n (%) | | | | | |
| Baseline | 2290 (23.4) | 588 (23.4) | 782 (21.5) | 521 (22.0) | 399 (31.7) | <0.001 |
| 30-day postindex date | 1319 (13.5) | 377 (15.0) | 427 (11.8) | 275 (11.8) | 240 (19.1) | <0.001 |
| Statins, n (%) | | | | | |
| Baseline | 7452 (76.3) | 1590 (63.2) | 2949 (81.2) | 1853 (78.3) | 1060 (84.2) | <0.001 |
| 30-day postindex date | 6847 (70.1) | 1518 (60.4) | 2678 (73.8) | 1695 (71.6) | 956 (75.9) | <0.001 |
| Nonstatin LLT, n (%) | | | | | |
| Baseline | 416 (4.3) | 95 (3.8) | 146 (4.0) | 102 (4.3) | 73 (5.8) | 0.03 |
| 30-day postindex date | 252 (2.6) | 54 (2.1) | 86 (2.4) | 62 (2.6) | 50 (4.0) | 0.007 |
| Diabetes medications, n (%) | | | | | |
| Baseline | 3482 (35.6) | 758 (30.2) | 1268 (34.9) | 904 (38.2) | 552 (43.8) | <0.001 |
| 30-day postindex date | 3045 (31.2) | 620 (24.7) | 1129 (31.1) | 801 (33.8) | 496 (39.3) | <0.001 |

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; CCB, calcium channel blocker; GALACTIC-HF, Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure; LLT, lipid-lowering therapy; and MRA, mineralocorticoid receptor antagonist.
Registry from 2007 to 2011, among a random sample of Medicare patients, GDMT use ranged between 51% and 71%. An analysis of the CHAMP-HF (Change the Management of Patients With Heart Failure) registry found that 27%, 33%, and 67% of patients with chronic HFrEF were not prescribed an ACEi/ARB/ARNi, a BB, and MRA therapy, respectively. Characteristics of KPSC patients included in the GALACTIC-HF–eligible cohorts were similar to individuals included in the GALACTIC-HF RCT, suggesting comparability of the RCT population to a real-world HFrEF population. However, the GALACTIC-HF–eligible cohort with EF≤28% in the current study represented a high-risk population with 30-day, 180-day, and 1-year hospitalization rates similar to patients with HFrEF who were not taking GDMT; similarly, 30-day and 180-day hospitalization rates among the GALACTIC-HF–eligible cohort with EF 29% to 35% were not different compared with patients with HFrEF who were not taking GDMT. These differences may be important given the GALACTIC-HF RCT showed an 8% reduction (HR, 0.92; 95% CI, 0.86–0.99) in the composite primary outcome (cardiovascular death, HF hospitalization, or urgent HF visit) with omecamtiv mecarbil treatment, driven primarily by reduced hospitalizations and among patients with low EF.

Prior work has examined the comparability of general HF populations to HF-focused RCTs. A study by Fudim and colleagues found that 71.8% (n=71,633) in the Get With The Guidelines—Heart Failure registry met PIONEER-HF (Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) inclusion criteria and 20.8% (n=20,704) met both inclusion/exclusion criteria. The authors found patient characteristics and clinical outcomes for PIONEER-HF–eligible population were only modestly different from those encountered in routine practice, concluding that sacubitril/valsartan should be routinely considered for patients with acute decompensated HF. In the current study, we observed better outcomes among GALACTIC-HF–eligible cohorts compared with the GALACTIC-HF–ineligible cohort not taking GDMT after adjustment for patient sociodemographics, clinical characteristics, and comorbidities.

GDMT use was high in the current study, but MRA use was low compared with what was reported in the

### Table 3. Health Care Usage Among Real-World and GALACTIC-HF–Like Cohorts

| Characteristics                                      | Overall       | GALACTIC-HF-ineligible | GALACTIC-HF-eligible | P value |
|-------------------------------------------------------|---------------|-------------------------|----------------------|---------|
| Guideline-directed medical therapy?                   | ...           | No                      | Yes                  | Yes     |
| Ejection fraction ≤35%                                 |               | ≤35%                    | ≤35%                 | ≤28%    | 29%–35% |
| Sample size, n                                        | 9770          | 2514                    | 3630                 | 2367    | 1259    |
| Inpatient visits                                      |               |                         |                      |         |
| 1 y before index date, n (%)                          |               |                         |                      |         |
| 0                                                      | 5872 (60.1)   | 1602 (63.7)             | 2265 (62.4)          | 1382 (58.4) | 623 (49.5) | <0.001   |
| ≥1                                                     | 3898 (39.9)   | 912 (36.3)              | 1365 (37.6)          | 985 (41.6) | 636 (50.5) |          |
| 30 d after index date, n (%)                          |               |                         |                      |         |
| 0                                                      | 8613 (88.2)   | 2129 (84.7)             | 3294 (90.7)          | 2091 (88.3) | 1099 (87.3) | <0.001   |
| ≥1                                                     | 1157 (11.8)   | 385 (15.3)              | 336 (9.3)            | 276 (11.7) | 160 (12.7) |          |
| Emergency department visits                           |               |                         |                      |         |
| 1 y before index date, n (%)                          |               |                         |                      |         |
| 0                                                      | 4429 (45.3)   | 1202 (47.8)             | 1496 (41.2)          | 1173 (49.6) | 558 (44.3) | <0.001   |
| ≥1                                                     | 5341 (54.7)   | 1312 (52.2)             | 2134 (58.8)          | 1194 (50.4) | 701 (55.7) |          |
| 30 d after index date, n (%)                          |               |                         |                      |         |
| 0                                                      | 8352 (85.5)   | 2066 (82.2)             | 3197 (88.1)          | 2026 (85.6) | 1063 (84.4) | <0.001   |
| ≥1                                                     | 1418 (14.5)   | 448 (17.8)              | 433 (11.9)           | 341 (14.4) | 196 (15.6) |          |
| Outpatient visits                                     |               |                         |                      |         |
| 1 y before index date, n (%)                          |               |                         |                      |         |
| 0                                                      | 282 (2.9)     | 129 (5.1)               | 33 (0.9)             | 90 (3.8)  | 30 (2.4)  | <0.001   |
| ≥1                                                     | 9488 (97.1)   | 2385 (94.9)             | 3597 (99.1)          | 2277 (86.2) | 1229 (97.6) |          |
| 30 d after index date, n (%)                          |               |                         |                      |         |
| 0                                                      | 1835 (18.8)   | 514 (20.4)              | 805 (22.2)           | 348 (14.7) | 168 (13.3) | <0.001   |
| ≥1                                                     | 7935 (81.2)   | 2000 (79.6)             | 2825 (77.8)          | 2019 (85.3) | 1091 (86.7) |          |

GALACTIC-HF indicates Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure.
GALACTIC-HF RCT (77% versus 18% in the current study). Additionally, certain medications including ARNis, sodium-glucose cotransporter-2 inhibitors, and ivabradine were all used <1% at baseline, with little improvement in the 30 days after the index date. ARNis, first approved by the US Food and Drug Administration (FDA) in 2015, have been recommended for first-line usage by the American College of Cardiology/American Heart Association expert consensus. Sodium-glucose cotransporter-2 inhibitors, initially considered an antidiabetic medication, have shown treatment benefits in HF patients with and without diabetes in multiple HF RCTs. Ivabradine, also approved by the US Food and Drug Administration in 2015, is a rhythm-controlling agent recommended for patients with HF with a resting HR ≥70 bpm, on a maximally tolerated dose of BB, and in sinus rhythm to reduce hospitalizations. The mean HR for patients with HFrEF in the current study was 78 bpm, though this study did not assess patients for heart rhythm or determine if BB treatment was optimized. These medications were not on the KPSC formulary during the study period of 2014 to 2018 (ARNis, ivabradine) or were not indicated for HF treatment during this time (sodium-glucose cotransporter-2 inhibitors). However, additional barriers to uptake in these new medications include cost and prescribing hesitancy, as evidenced in other studies. Increasing the overall use of MRAs and newer agents is an area for improvement given similarities in hospitalization rates among GALACTIC-HF–ineligible patients not taking GDMT and those meeting GALACTIC-HF criteria.

Figure 2. Hazard ratios and 95% CIs for 30-day and 1-year all-cause mortality among real-world and GALACTIC-HF–like cohorts. Squares represent the hazard ratio point estimates and lines/error bars represent the 95% CIs. EF indicates ejection fraction; GALACTIC-HF, Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; and HR, hazard ratio.
Figure 3. Hazard ratios and 95% CIs for 30-day and 1-year all-cause hospitalization among real-world and GALACTIC-HF–like cohorts. Squares represent the hazard ratio point estimates and lines/error bars represent the 95% CIs. EF indicates ejection fraction; GALACTIC-HF, Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; and HR, hazard ratio.
Strengths of the current study include a large, diverse population of adults representative of the Southern California region, with comprehensive health records and near-complete capture of clinically relevant covariates. We also acknowledge limitations. We did not assess appropriateness of dosing, titration, or adherence to GDMT at baseline or during follow-up. MRA use, in addition to ACEis/ARBs/ARNis and BBs, was not a requirement in determining GDMT in our mutually exclusive cohorts given the historic underusage of MRA in patients with HFrEF. However, rates of outcomes remained low in the KPSC population taking GDMT even without this requirement. Time-updated clinical characteristics and comorbidities were not assessed; therefore, we were unable to account for acute changes in health status, which may have affected treatment decisions or outcomes. Although we collected extensive sociodemographic, clinical, and usage characteristics for our population, unmeasured confounding may be possible; however, it is unlikely that unmeasured confounding would be differential across HFrEF cohorts. Finally, these results may not be fully generalizable to patients in less integrated settings often having less robust quality improvement metrics or among uninsured individuals.

In conclusion, a large portion of patients with HFrEF with EF ≤28% met inclusion criteria for the GALACTIC-HF trial and, despite being on GDMT, had hospitalization rates similar to those not taking GDMT, suggesting potential benefits from other innovative treatments.

ARTICLE INFORMATION

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Affiliations

Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA (T.M.T., J.D.J., R.W., H.F., T.N.H., K.R.); Internal Medicine (S.Y.K.) and Department of Cardiology (P.W.), Kaiser Permanente Southern California, Baldwin Park, CA; and Department of Health Systems Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA (K.R.).

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The authors declare no conflicts of interest pertaining to the current study.

Supplemental Material

Tables S1–S2

Figures S1–S2

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SUPPLEMENTAL MATERIAL
Table S1. Number, person time, rates, and unadjusted hazard ratios of 30-day and 1-year mortality among patients having heart failure with reduced ejection fraction

| Characteristics                        | Overall | GALACTIC-HF-ineligible | GALACTIC-HF-eligible |
|----------------------------------------|---------|------------------------|----------------------|
| Guideline directed medical therapy?    | --      | No                     | Yes                  |
| Ejection fraction                      | ≤35%    | ≤35%                   | ≤35%                 |
|                                        | ≥28%    | 29-35%                 |                      |
| 30-day all-cause mortality             | n=9,770 | n=2,514                | n=3,630              |
| Events, n                              | 375     | 177                    | 97                   |
| Person-months                          | 9,557   | 2,408                  | 3,577                |
| Rate per person-month                  | 0.04    | 0.07                   | 0.03                 |
| Unadjusted HR (95% CI)                 | --      | 1 (ref)                | 0.37                 |
|                                        |         |                        | (0.29, 0.47)         |
|                                        |         |                        | 0.45                 |
|                                        |         |                        | (0.34, 0.58)         |
|                                        |         |                        | 0.27                 |
|                                        |         |                        | (0.18, 0.42)         |
| 31-365 day all-cause mortality         | n=9,394 | n=2,337                | n=3,533              |
| Events, n                              | 1,364   | 453                    | 477                  |
| Person-years                           | 7,746   | 1,862                  | 2,932                |
| Rate per person-year                   | 0.18    | 0.24                   | 0.16                 |
| Unadjusted HR (95% CI)                 | --      | 1 (ref)                | 0.67                 |
|                                        |         |                        | (0.59, 0.76)         |
|                                        |         |                        | 0.64                 |
|                                        |         |                        | (0.55, 0.740)        |
|                                        |         |                        | 0.55                 |
|                                        |         |                        | (0.46, 0.67)         |

Abbreviations: CI, confidence interval; HR, hazard ratio
Table S2. Number, person time, rates, and unadjusted hazard ratios of 30-day 31-180-day, and 181-365-day hospitalization among patients having heart failure with reduced ejection fraction

| Characteristics                        | Overall | GALACTIC-HF-ineligible | GALACTIC-HF-eligible |
|----------------------------------------|---------|------------------------|----------------------|
| Guideline directed medical therapy?    | --      | No                     | Yes                  |
| Ejection fraction                      | ≤35%    | ≤35%                   | ≤28%                 |
|                                        |         | 29-35%                |                      |
| 30-day all-cause hospitalization       | n=9,770 | n=2,514                | n=3,630              | n=2,367               | n=1,259               |
| Events, n                              | 1,157   | 385                    | 336                  | 276                   | 160                   |
| Person-months                          | 8,941   | 2,208                  | 3,398                | 2,176                 | 1,159                 |
| Rate per person-month                  | 0.13    | 0.17                   | 0.10                 | 0.13                  | 0.14                  |
| Unadjusted HR (95% CI)                 | --      | 1 (ref)                | 0.57                 | 0.73                  | 0.80                  |
|                                        |         | (0.49, 0.66)           | (0.63, 0.85)         | (0.66, 0.96)          |
| 31-180-day all-cause hospitalization   | n=8,344 | n=2,001                | n=3,217              | n=2,042               | n=1,084               |
| Events, n                              | 1,935   | 508                    | 663                  | 490                   | 274                   |
| Person-years                           | 2,889   | 669                    | 1,140                | 710                   | 370                   |
| Rate per person-year                   | 0.67    | 0.76                   | 0.58                 | 0.69                  | 0.74                  |
| Unadjusted HR (95% CI)                 | --      | 1 (ref)                | 0.77                 | 0.91                  | 0.98                  |
|                                        |         | (0.69, 0.86)           | (0.81, 1.03)         | (0.84, 1.13)          |
| 181-365-day all-cause hospitalization | n=6,077 | n=1,381 | n=2,429 | n=1,490 | n=777 |
|-----------------------------|---------|---------|---------|---------|-------|
| Events, n                   | 1,030   | 261     | 394     | 263     | 112   |
| Person-years                | 2,736   | 612     | 1,099   | 670     | 355   |
| Rate per person-year        | 0.38    | 0.43    | 0.36    | 0.39    | 0.32  |
| Unadjusted HR (95% CI)      | --      | 1 (ref) | 0.84 (0.72, 0.98) | 0.92 (0.78, 1.09) | 0.74 (0.59, 0.93) |

Abbreviations: CI, confidence interval; HR, hazard ratio
Figure S1. Cumulative incidence curves for 30-day and 31-365-day mortality among heart failure with reduced ejection fraction cohorts

30-day Mortality

31-day to 365-day Mortality

Abbreviations: EF, ejection fraction; GALACTIC, Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility; GDMT, guideline-directed medical therapy
Figure S2. Cumulative incidence curves for 30-day and 31-180-day, and 181-365-day hospitalization among heart failure with reduced ejection fraction cohorts

Abbreviations: EF, ejection fraction; GALACTIC, Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility; GDMT, guideline-directed medical therapy