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ORIGINAL RESEARCH

Clinical Effectiveness of Sacubitril/Valsartan Among Patients Hospitalized for Heart Failure With Reduced Ejection Fraction

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BACKGROUND: Sacubitril/Valsartan has been highly efficacious in randomized trials of heart failure with reduced ejection fraction (HFrEF). However, the effectiveness of sacubitril/valsartan in older patients hospitalized for HFrEF in real-world US practice is unclear.

METHODS AND RESULTS: This study included Medicare beneficiaries age ≥65 years who were hospitalized for HFrEF ≤40% in the Get With The Guidelines–Heart Failure registry between October 2015 and December 2018, and eligible for sacubitril/valsartan. Associations between discharge prescription of sacubitril/valsartan and clinical outcomes were assessed after inverse probability of treatment weighting and adjustment for other HFrEF medications. Overall, 1551 (10.9%) patients were discharged on sacubitril/valsartan. Of those not prescribed sacubitril/valsartan, 7857 (62.0%) were prescribed an angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker. Over 12-month follow-up, compared with a discharge prescription of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, sacubitril/valsartan was independently associated with lower all-cause mortality (adjusted hazard ratio [HR], 0.82; 95% CI, 0.72–0.94; *P*=0.004) but not all-cause hospitalization (adjusted HR, 0.97; 95% CI, 0.89–1.07; *P*=0.55) or heart failure hospitalization (adjusted HR, 1.04; 95% CI, 0.91–1.18; *P*=0.59). Patients prescribed sacubitril/valsartan versus those without a prescription had lower risk of all-cause mortality (adjusted HR, 0.69; 95% CI, 0.60–0.79; *P*<0.001), all-cause hospitalization (adjusted HR, 0.90; 95% CI, 0.82–0.98; *P*=0.02), but not heart failure hospitalization (adjusted HR, 0.94; 95% CI, 0.82–1.08; *P*=0.40).

CONCLUSIONS: Among patients hospitalized for HFrEF, prescription of sacubitril/valsartan at discharge was independently associated with reduced postdischarge mortality compared with angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, and reduced mortality and all-cause hospitalization compared with no sacubitril/valsartan. These findings support the use of sacubitril/valsartan to improve postdischarge outcomes among older patients hospitalized for HFrEF in routine US clinical practice.

Key Words: heart failure ■ reduced ejection fraction ■ registry ■ sacubitril/valsartan

Sacubitril/valsartan is an angiotensin receptor–neprilysin inhibitor indicated for the treatment of heart failure with reduced ejection fraction (HFrEF).[1] In the PARADIGM-HF (Prospective Comparison of Angiotensin II Receptor Blocker Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor [ACEI]

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CLINICAL PERSPECTIVE

What Is New?

- Among older patients hospitalized for heart failure with reduced ejection fraction, prescription of sacubitril/valsartan at time of discharge is independently associated with improved postdischarge outcomes, including improved survival.

What Are the Clinical Implications?

- In aggregate, these findings suggest that significant benefits of sacubitril/valsartan observed in randomized trials extend to older patients hospitalized for heart failure with reduced ejection fraction receiving routine clinical care.
- Combined with data from randomized trials, these data suggest that to improve postdischarge outcomes for patients with heart failure with reduced ejection fraction, every effort should be made to prescribe sacubitril/valsartan to eligible patients at time of hospital discharge.

Nonstandard Abbreviations and Acronyms

CHAMP-HF	Change the Management of Patients with Heart Failure
HFrEF	heart failure with reduced ejection fraction
IPW	inverse probability of treatment weighting
PARADIGM-HF	Prospective Comparison of Angiotensin II Receptor Blocker Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure
PIONEER-HF	Comparison of Sacubitril–Valsartan Versus Enalapril on Effect on NT-proBNP [N-terminal pro-B-type natriuretic peptide] in Patients Stabilized from an Acute Heart Failure Episode

to Determine Impact on Global Mortality and Morbidity in Heart Failure [HF]) randomized trial of patients with chronic HFrEF, treatment with sacubitril/valsartan reduced cardiovascular mortality or HF hospitalization by 20% and all-cause mortality by 16% compared with standard treatment with an ACEI.[2] More recently, safety and efficacy of in-hospital initiation of sacubitril/valsartan were supported by the PIONEER-HF (Comparison of Sacubitril–Valsartan Versus Enalapril on Effect on NT-proBNP [N-terminal pro-B-type natriuretic peptide] in Patients Stabilized from an Acute Heart Failure Episode) trial, where exploratory analysis found patients with HFrEF randomly assigned to sacubitril/valsartan to have a 46% lower risk of serious clinical events over 8-week follow-up as compared with an ACEI.[3]

The results of PARADIGM-HF were published in 2014, and the US Food and Drug Administration approved sacubitril/valsartan for use in July 2015. Nonetheless, despite robust clinical benefits in randomized clinical trials and strong guideline recommendations, use of sacubitril/valsartan in US clinical practice has been low. Data from the CHAMP-HF (Change the Management of Patients with Heart Failure) registry demonstrate that in contemporary US practice, <14% of eligible outpatients with HFrEF are treated with sacubitril/valsartan, and that few patients are initiated on therapy during follow-up.[4,5] Likewise, among US patients hospitalized for HF during the 12 months following sacubitril/valsartan approval, only 2.3% of eligible patients were prescribed the therapy at discharge.[6] Although the slow and varied adoption of sacubitril/valsartan is likely multifactorial, uncertainty regarding the clinical effectiveness of therapy outside the context of a clinical trial may be a key contributor. This uncertainty may be particularly relevant to older patients, women, racial/ethnic minorities, and patients with significant comorbidities, populations comprising a significant proportion of patients seen in routine practice but generally underrepresented in HFrEF clinical trials.[7] In this context, we designed the current study using a US national registry linked to Medicare claims to address an existing evidence gap regarding the clinical effectiveness of sacubitril/valsartan on postdischarge mortality and readmission in a contemporary real-world cohort of older patients hospitalized for HFrEF.[8,9]

METHODS

Data Source

Data, methods, and study materials other than those provided in this manuscript will not be made available to other researchers. This study used the GWTG-HF (Get With The Guidelines-Heart Failure) registry, an ongoing observational, national, HF quality improvement program initiated in 2005 by the American Heart Association.[10,11] Briefly, the registry includes patients hospitalized with a primary diagnosis of new or worsening HF, or patients who develop significant HF symptoms during hospitalization such that HF was the primary diagnosis. Trained personnel at each center use an Internet-based patient management tool (IQVIA, Parsippany, NJ) to collect patient-level

information on consecutive patients with HF admitted to the hospital. Collected data include demographics, medical history, laboratory results, discharge medications, contraindications to medications, and discharge status. All participating centers obtain institutional review board approval and follow local regulatory and privacy guidelines. Because the primary purpose of the registry is for quality improvement, all centers are granted a waiver of patient informed consent under the Common Rule. IQVIA serves as the data collection and coordinating center for American Heart Association Get With The Guidelines programs. The Duke Clinical Research Institute serves as the data analytic center. For our analysis, registry participants aged ≥65 years with fee-for-service Medicare coverage were linked to Medicare inpatient claims using a previously validated technique.[12] The institutional review board of the Duke University Health System approved the study.

Study Population

The study population included GWTG-HF participants aged ≥65 years who were hospitalized between October 2015 and December 2018, discharged alive with complete medical history and laboratory data, and successfully linked to Medicare inpatient claims. October 2015 was used as the study start date to allow a 3-month transition period after Food and Drug Administration approval of sacubitril/valsartan in July 2015. Other inclusion criteria included left ventricular ejection fraction ≤40%, complete information on both contraindications and discharge prescription status for sacubitril/valsartan, and enrollment in Medicare fee-for-service on the date of discharge. We excluded patients who had documented contraindications to sacubitril/valsartan. For patients with multiple eligible hospitalizations during the study period, the first hospitalization was chosen as the index hospitalization.

Exposure

The exposure variable for all analyses was prescription of sacubitril/valsartan at index hospital discharge. We evaluated outcomes relative to 2 separate comparator groups representing distinct clinical questions of interest. We first compared patients prescribed sacubitril/valsartan at discharge to patients prescribed an ACEI/ARB at discharge to evaluate clinical effectiveness of sacubitril/valsartan relative to a comparator similar to that used in the randomized clinical trials. Second, we compared patients prescribed sacubitril/valsartan with patients *not* prescribed sacubitril/valsartan at discharge, a conventional method for evaluating effectiveness of therapy (yes versus no) in real-world settings.

Study Outcomes

The prespecified study outcomes were all-cause mortality, all-cause hospitalization, the composite of all-cause mortality or HF hospitalization, and HF hospitalization. All outcomes were identified using the Medicare Master Beneficiary Summary File and inpatient administrative claims files, including data from 2015 to 2019 (Table S1).

Statistical Analysis

Baseline characteristics were compared (1) between patients prescribed sacubitril/valsartan at hospital discharge versus those not prescribed sacubitril/valsartan, and (2) between patients prescribed sacubitril/valsartan versus patients prescribed ACEI/ARB therapy at discharge. In secondary analysis, this second comparison with patients not prescribed sacubitril/valsartan was further broken down into a 3-way comparison between sacubitril/valsartan versus ACEI/ARB versus neither therapy at discharge. Continuous variables were presented as medians (25th and 75th percentiles) and categorical variables as counts and percentages. Treatment groups were compared using standardized mean differences, with a standardized difference ≥10% reflecting imbalance between groups.

To describe patient outcomes, we compared the cumulative incidence of each outcome at 30 days and 12 months after discharge. For mortality, we estimated cumulative incidence using the Kaplan-Meier method and compared groups using log-rank tests. For hospitalization outcomes, we estimated cumulative incidence using the cumulative incidence function to account for the competing risk of mortality and compared groups using Gray tests. Patients were censored when they no longer had fee-for-service Medicare coverage or at the end of Medicare data availability (December 31, 2019); for readmission outcomes, censoring also occurred on the date of death.

To address potential selection bias among patients discharged with sacubitril/valsartan, we used inverse probability of treatment weighting (IPW) to account for 25 baseline patient characteristics and 6 index hospital characteristics that may affect likelihood of patients being prescribed sacubitril/valsartan and the risk of adverse clinical outcomes (Table S2). For each comparator group, weights were obtained from a treatment selection model and were estimated using logistic regression, with discharge sacubitril/valsartan status as the dependent variable and baseline patient characteristics as independent variables. To confirm adequacy of the treatment selection model, each patient was weighted by the inverse of their predicated probability of treatment, and baseline characteristics were reexamined using standardized differences to evaluate balance after weighting.

Cox proportional hazards models were used to estimate the unadjusted and adjusted associations between sacubitril/valsartan prescription at discharge and each time-to-event outcome. First, unadjusted associations were estimated using proportional hazards models where treatment group was the only independent variable. Second, IPW was applied to obtain adjusted associations. Third, additional adjustment for beta-blocker and mineralocorticoid receptor antagonist therapy at discharge was added to IPW models. Hazard ratios and 95% CIs) were calculated. Directly adjusted cumulative incidence curves for outcome were plotted on the basis of IPW models.

In addition, associations between sacubitril/valsartan prescription and outcomes were assessed across prespecified subgroups of interest (age [65–74 versus ≥75 years], sex, and race [White versus Black or African American versus other race]), and interaction testing was performed. Race was self-reported by patients (if not available, the clinician or institution's assessment was used). To assess risk of residual confounding, adjusted models were used to test the association between sacubitril/valsartan and 2 prespecified falsification end points (ie, negative controls) chosen on the basis of the lack of biologically plausible associations with sacubitril/valsartan: hospitalization for urinary tract infection at 12 months and hospitalization for metabolic/nutritional disorder at 12 months. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC) within the Centers for Medicare & Medicaid Services Virtual Research Data Center secure data environment. Two-tailed $P<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

Between October 2015 and December 2018, 14 230 patients hospitalized for HFrEF within the GWTG-HF linked to a Medicare data set met study eligibility criteria (Figure S1). Of these patients, 1551 (10.9%) were prescribed sacubitril/valsartan at discharge and 12 679 (89.1%) patients were not. Among patients not prescribed sacubitril/valsartan, 7857 (62.0%) were prescribed an ACEI/ARB at discharge.

Baseline characteristics among patients prescribed sacubitril/valsartan and prescribed an ACEI/ARB are displayed in Table 1. The proportion of patients prescribed sacubitril/valsartan relative to ACEI/ARB therapy increased over time. Patients prescribed sacubitril/valsartan tended to be younger with lower left ventricular ejection fraction and systolic blood pressure. After application of IPW, there were no significant differences in reported baseline characteristics between patients prescribed sacubitril/valsartan and patients prescribed ACEI/ARB therapy (Table 2). In both groups, after weighting, median age was 78 years, 41% were women, and median left ventricular ejection fraction was 27% to 28%.

Compared with patients not prescribed sacubitril/valsartan, patients prescribed sacubitril/valsartan tended to be younger with lower left ventricular ejection fraction and systolic blood pressure (Table S3). After application of IPW, there were no significant differences in reported baseline characteristics between patients prescribed versus not prescribed sacubitril/valsartan, with exception of higher rates of beta-blocker and mineralocorticoid receptor antagonist therapy at discharge among sacubitril/valsartan patients (ie, these medications not included in IPW model and subsequently accounted for in full adjusted model) (Table S4). Baseline characteristics of patients prescribed sacubitril/valsartan, ACEI/ARB, and neither therapy at discharge are displayed in Table S5.

Outcomes for Sacubitril/Valsartan Versus ACEI/ARB

Compared with patients prescribed an ACEI/ARB, patients prescribed sacubitril/valsartan had similar cumulative incidence of all-cause mortality, all-cause hospitalization, all-cause mortality or HF hospitalization, and HF hospitalization at 30 days and 12 months, with the exception of higher incidence of 12-month HF hospitalization among patients prescribed sacubitril/valsartan (Table 3).

After IPW and adjustment for discharge medications, sacubitril/valsartan was independently associated with lower risks of all-cause mortality but was not significantly associated with all-cause hospitalization, mortality or HF hospitalization, and HF hospitalization at 12 months, compared with ACEI/ARB therapy (Figure 1; Table 4). Sacubitril/valsartan prescription was not associated with either falsification end point in unadjusted or adjusted analyses.

Outcomes for Sacubitril/Valsartan Versus No Sacubitril/Valsartan

Compared with patients not prescribed sacubitril/valsartan, patients prescribed sacubitril/valsartan had a lower cumulative incidence of all-cause mortality and all-cause mortality or HF hospitalization at 30 days and 12 months. The cumulative incidence of all-cause hospitalization and HF hospitalization were similar, with the exception of higher incidence of HF hospitalization at 12 months among patients prescribed sacubitril/valsartan (Table S6).

After IPW and adjustment for discharge medications, sacubitril/valsartan prescription was associated with significantly lower risks of all-cause

Table 1. Characteristics of Patients Discharged With Sacubitril/Valsartan Versus an ACEI/ARB *Before* Application of Inverse Probability Weights

	Sacubitril/Valsartan (n=1551)	ACEI/ARB (n=7857)	Standardized Mean Difference*
Age, y	77 (71–83)	78 (71–85)	17.4
Women	560 (36.1)	3262 (41.5)	11.1
Race			3.9
White	1259 (81.2)	6302 (80.2)	
Black or African American	191 (12.3)	965 (12.3)	
Other§	101 (6.5)	590 (7.5)	
Medicaid dual eligibility	218 (14.1)	1230 (15.7)	4.5
Ejection fraction (%)	25 (20–32)	28 (22–35)	28.7
Index hospitalization year			51.5
2015/2016	294 (19.0)	3190 (40.6)	
2017	529 (34.1)	2413 (30.7)	
2018	728 (46.9)	2254 (28.7)	
Vital sign and laboratory data at discharge			
Systolic blood pressure, mm Hg	113 (102–126)	118 (107–132)	30.7
Heart rate, beats/min	74 (67–83)	75 (67–84)	4.5
Sodium, mEq/L	139 (136–141)	139 (136–141)	6.0
Creatinine, mg/dL	1.2 (1.0–1.5)	1.2 (0.9–1.5)	3.5
Medical history			
Ischemic HF etiology	1105 (71.2)	4957 (63.1)	17.4
Prior PCI	451 (29.1)	1883 (24.0)	11.6
Prior CABG	460 (29.7)	2007 (25.5)	9.2
Hypertension	1329 (85.7)	6594 (83.9)	4.9
Hyperlipidemia	981 (63.2)	4769 (60.7)	5.3
Valve disease†	292 (18.8)	1364 (17.4)	3.8
Atrial fibrillation/flutter	716 (46.2)	3313 (42.2)	8.1
Diabetes mellitus	667 (43.0)	3237 (41.2)	3.7
Stroke/TIA	256 (16.5)	1304 (16.6)	0.2
Chronic kidney disease	239 (15.4)	993 (12.6)	8.0
Anemia	259 (16.7)	1293 (16.5)	0.7
COPD	451 (29.1)	2328 (29.6)	1.2
Smoking in past 12 mo	168 (10.8)	973 (12.4)	4.8
Device therapy			
CRT-D	332 (21.4)	809 (10.3)	30.8
ICD only	361 (23.3)	1064 (13.5)	25.3
Medical therapy before admission‡			
ACEI/ARB	287 (18.5)	3439 (43.8)	56.9
Sacubitril/Valsartan	297 (19.1)	19 (0.2)	85.1
Beta-blocker	668 (43.1)	3660 (46.6)	32.7
MRA	185 (11.9)	718 (9.1)	32.1
Medical therapy at discharge			
Beta-blocker	1437 (92.6)	7294 (92.8)	0.7
MRA	604 (38.9)	2633 (33.5)	11.3
Hospital characteristics			
Teaching hospital	1202 (77.5)	6415 (81.6)	10.3
Profit status			10.3
Not-for-profit	1225 (79.0)	5863 (74.6)	
Government	222 (14.3)	1356 (17.3)	

(*Continued*)

Table 1. Continued

	Sacubitril/Valsartan (n=1551)	ACEI/ARB (n=7857)	Standardized Mean Difference*
For-profit	104 (6.7)	638 (8.1)	
Region			33.4
Northeast	411 (26.5)	2028 (25.8)	
Midwest	299 (19.3)	1803 (22.9)	
South	716 (46.2)	2677 (34.1)	
West	125 (8.1)	1349 (17.2)	
Hospital bed size	393 (259–564)	376 (253–564)	2.5
Cardiac catheterization lab on site	1416 (91.3)	7348 (93.5)	8.4
Heart transplantation on site	50 (3.2)	474 (6.0)	13.4

Data presented as n (%) or median (25th–75th percentile). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy and defibrillator; HF, heart failure; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

*Standardized mean differences represents differences in means or proportions divided by the standard error and multiplied by 10. Standardized mean differences >10 indicate imbalance between groups.

†Moderately severe or severe regurgitation or stenosis of any valve, with exception of functional (ie, secondary) mitral regurgitation.

‡Data were missing for 718 patients in the sacubitril/valsartan group and 2615 patients in the ACEI/ARB group. Percentages reflect patients receiving medication among total patients in the group.

§Includes American Indian or Alaska Native, Asian, or Native Hawaiian or Pacific Islander.

mortality, all-cause hospitalization, and mortality or HF hospitalization at 12 months, but not HF hospitalization (Figure S2; Table S7). There were no significant associations between sacubitril/valsartan prescription and falsification end points before or after adjustment.

Outcomes for Sacubitril/Valsartan Versus ACEI/ARB Versus Neither Therapy

Comparing patients prescribed sacubitril/valsartan, a ACEI/ARB, and neither therapy, patients prescribed sacubitril/valsartan had the lowest unadjusted incidences of 30-day and 12-month mortality, and those prescribed neither therapy had the highest incidences. Cumulative incidence of all-cause hospitalization and HF hospitalization was lowest among patients prescribed an ACEI/ARB (Table S8).

Subgroup Analyses

In comparisons of sacubitril/valsartan versus ACEI/ARB, findings for all end points were consistent irrespective of age, sex, and race (all *P* for interaction ≥0.12) (Figure 2). In analyses of sacubitril/valsartan prescription versus no prescription, associations between sacubitril/valsartan and clinical end points were consistent across subgroups defined by age and sex (all *P* for interaction ≥0.06). However, a statistically significant interaction by race was observed for the all-cause mortality or HF hospitalization and HF hospitalization end points, whereby associations with improved outcomes were driven by results among White patients (Figure S3).

DISCUSSION

In this contemporary real-world population of US patients hospitalized for HFrEF, despite clinical trial evidence and guideline recommendations that were available during the study period, nearly 90% of eligible patients were not prescribed sacubitril/valsartan at hospital discharge. After adjustment for patient characteristics and other HFrEF medications, prescription of sacubitril/valsartan at hospital discharge was significantly associated with lower risk of mortality compared with ACEI/ARB therapy. Likewise, compared with patients not prescribed sacubitril/valsartan, prescription of sacubitril/valsartan at discharge was independently associated with reduced risk of mortality, all-cause hospitalization, and the composite of mortality or all-cause hospitalization. In aggregate, these findings suggest that significant benefits of sacubitril/valsartan observed in randomized trials extend to older patients hospitalized with HFrEF receiving routine clinical care.

In randomized trials, sacubitril/valsartan has substantially reduced the risk of HF hospitalization compared with an ACEI, an effect that was not observed in the current observational study.[2,3] This lack of significant association in the current study may relate to residual confounding and a tendency for sacubitril/valsartan to be prescribed to patients with higher risk of readmission in real-world practice. Indeed, unadjusted results found patients prescribed sacubitril/valsartan to have the highest incidence of 12-month HF hospitalization (ie, higher than patients prescribed an ACEI/ARB and neither sacubitril/valsartan nor an ACEI/ARB), suggesting that sacubitril/valsartan may be preferentially

Table 2. Characteristics of Patients Discharged With Sacubitril/Valsartan Versus an ACEI/ARB *After* Application of Inverse Probability Weights

	Sacubitril/Valsartan (n=1551)	ACEI/ARB (n=7857)	Standardized Mean Difference*
Age, y	78 (72–84)	78 (71–85)	1.3
Women	630 (40.6)	3187 (40.6)	1.6
Race			2.9
White	1219 (79.6)	6317 (80.3)	
Black or African American	187 (12.2)	968 (12.3)	
Other§	124 (8.1)	578 (7.4)	
Medicaid dual eligibility	255 (16.6)	1212 (15.4)	3.4
Ejection fraction (%)	27 (20–33)	28 (20–35)	6.0
Index hospitalization year			2.0
2015/2016	552 (36.0)	2908 (37.0)	
2017	490 (32.0)	2463 (31.3)	
2018	489 (32.0)	2492 (31.7)	
Vital sign and laboratory data at discharge			
Systolic blood pressure, mm Hg	118 (106–130)	118 (106–131)	3.5
Heart rate, beats/min	75 (68–84)	75 (67–84)	0.1
Sodium, mEq/L	139 (136–141)	138 (136–141)	1.1
Creatinine, mg/dL	1.2 (1.0–1.5)	1.2 (0.9–1.5)	1.1
Medical history			
Ischemic HF etiology	998 (65.2)	5073 (64.5)	1.4
Prior PCI	400 (26.1)	1953 (24.8)	2.9
Prior CABG	427 (27.9)	2070 (26.3)	3.5
Hypertension	1265 (82.6)	6622 (84.2)	4.3
Hyperlipidemia	922 (60.3)	4804 (61.1)	1.7
Valve disease†	263 (17.2)	1382 (17.6)	1.1
Atrial fibrillation/ flutter	638 (41.7)	3365 (42.8)	2.2
Diabetes mellitus	650 (42.5)	3267 (41.5)	1.9
Stroke/TIA	261 (17.0)	1308 (16.6)	1.0
Chronic kidney disease	219 (14.3)	1041 (13.2)	3.1
Anemia	259 (16.9)	1298 (16.5)	1.0
COPD	452 (29.5)	2321 (29.5)	0.1
Smoking in past 12 mo	181 (11.8)	950 (12.1)	0.7
Device therapy			
CRT-D	192 (12.6)	961 (12.2)	1.0
ICD only	229 (14.9)	1197 (15.2)	0.8
Medical therapy at discharge‡			
Beta-blocker	1419 (92.7)	7313 (93.0)	1.2
MRA	558 (36.5)	2669 (33.9)	5.3
Hospital characteristics			
Teaching hospital	1255 (82.0)	6376 (81.1)	2.4
Profit status			1.5
Not-for-profit	115 (7.5)	620 (7.9)	
Government	257 (16.8)	1319 (16.8)	
For-profit	115 (7.5)	620 (7.9)	
Region			0.9
Northeast	404 (26.4)	2044 (26.0)	
Midwest	341 (22.3)	1758 (22.4)	
South	548 (35.8)	2831 (36.0)	

(*Continued*)

Table 2. Continued

	Sacubitril/Valsartan (n=1551)	ACEI/ARB (n=7857)	Standardized Mean Difference*
West	239 (15.6)	1231 (15.7)	
Hospital bed size	393 (286–581)	374 (253–564)	2.0
Cardiac catheterization lab on site	1435 (93.7)	7326 (93.2)	2.3
Heart transplantation on site	88 (5.8)	435 (5.5)	1.0

Data presented as n (%) or median (25th–75th percentile). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy and defibrillator; HF, heart failure; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

*Standardized mean differences represents differences in means or proportions divided by the standard error and multiplied by 100. Standardized mean differences >10 indicate imbalance between groups.

†Moderately severe or severe regurgitation or stenosis of any valve, with exception of functional (ie, secondary) mitral regurgitation.

‡Discharge medications were not included within inverse probability of treatment weighted models. Adjustment for beta-blocker and MRA therapy at discharge was added to inverse probability of treatment weighted models to constitute the fully adjusted model.

§Other includes American Indian or Alaska Native, Asian, or Native Hawaiian or Pacific Islander.

prescribed to those with particularly high risk of HF hospitalization.

To our knowledge, only 2 prior large analyses (ie, >1000 patients) have evaluated the real-world effectiveness of sacubitril/valsartan for HFrEF, and both have limitations.[13,14] Similar to the present study, an analysis from the US Veterans Health Administration found no significant association between sacubitril/valsartan and HF hospitalization, but that study did not assess mortality.[13] A second analysis by Tan et al from OptumLabs, a US administrative database of privately insured patients, found sacubitril/valsartan to be significantly associated with a 20% relative reduction in all-cause mortality compared with ACEI/ARB, and no significant association with HF hospitalization, findings that are both consistent with the current study.[14] However, the OptumLabs study was limited by reliance on diagnostic codes for patient characteristics and the study population was defined using a diagnosis of systolic HF, as compared with precise measurement of EF. By contrast, the present work used patient-level clinical data from the GWTG-HF registry, thus facilitating more accurate selection of patients eligible for treatment, more comprehensive risk adjustment, and

Table 3. Unadjusted Cumulative Incidence of Clinical Outcomes for Patients Discharged With Sacubitril/Valsartan Versus an ACEI/ARB

	Sacubitril/Valsartan (n=1551)	ACEI/ARB (n=7857)	*P* Value
Effectiveness end points			
All-cause mortality			
30 d	75 (4.9)	428 (5.5)	0.32
12 mo	444 (29.5)	2369 (30.9)	0.22
All-cause hospitalization			
30 d	356 (23.0)	1704 (21.7)	0.25
12 mo	984 (64.7)	4835 (62.6)	0.07
All-cause mortality or HF hospitalization			
30 d	195 (12.6)	1035 (13.2)	0.54
12 mo	792 (52.3)	3876 (50.4)	0.18
HF hospitalization			
30 d	142 (9.2)	652 (8.3)	0.26
12 mo	560 (37.0)	2418 (31.4)	<0.001
Falsification (negative control) end points			
Metabolic/Nutritional hospitalization within 12 mo	36 (2.4)	144 (1.9)	0.19
Urinary tract infection hospitalization within 12 mo	17 (1.1)	100 (1.3)	0.58

Data presented as n (%). Cumulative incidence of mortality and mortality or HF hospitalization end points were calculated using the Kaplan-Meier method and group differences were evaluated using log-rank tests. Cumulative incidence for hospitalization outcomes was estimated using the cumulative incidence function to account for the competing risk of mortality, and group differences were evaluated using Gray tests. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; and HF, heart failure.

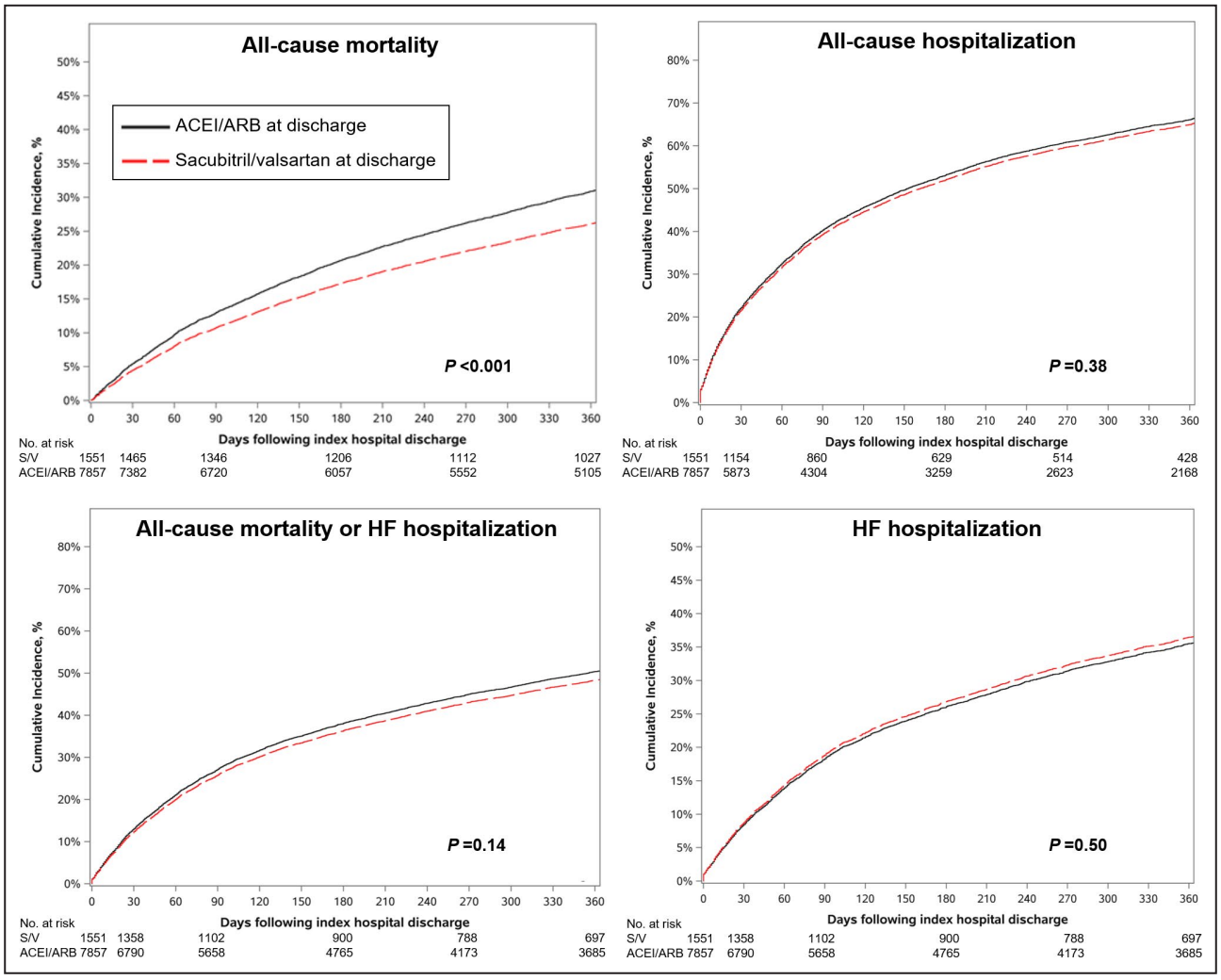

Figure 1. Cumulative incidence of mortality and hospitalization outcomes for patients discharged with sacubitril/valsartan vs an ACEI/ARB.
Curves reflect adjusted results in the form of directly adjusted cumulative incidence curves, which were derived from inverse-probability-of-treatment-weighted proportional hazards models. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; and HF, heart failure.

improved generalizability of findings through a more detailed description of the patient profile. Moreover, patients in the OptumLabs analysis were outpatients with a median age of ≈69 years, whereas the current study informs the use of sacubitril/valsartan in a distinct cohort of patients hospitalized for HFrEF with a median age of 78 years, a population for which large-scale data were previously not available and where concerns over risks and benefits of therapy may be greatest. Finally, the prior analysis by Tan et al[14] reported differing effectiveness of sacubitril/valsartan by race, and generated the hypothesis that sacubitril/valsartan may be less effective among Black patients. This interaction was not seen in the current study in the comparison of sacubitril/valsartan by ACEIs/ARBs. However, significant interactions by race were seen in comparisons between sacubitril/valsartan versus no sacubitril/valsartan, whereby favorable associations between sacubitril/valsartan and the composite of mortality or HF hospitalization and HF hospitalization were confined to White patients. Nevertheless, in the context of randomized trial data from PARADIGM-HF and PIONEER-HF supporting consistent treatment effect in Black patients, the racial differences seen by Tan et al and the present analysis may reflect residual confounding or the play of chance.

Clinical Implications

Despite significant benefits in randomized clinical trials and strong guideline recommendations, there is substantial underuse and underdosing of sacubitril/valsartan and other guideline-directed medical therapies in

Table 4. Associations Between Sacubitril/Valsartan Prescription and Clinical Outcomes at 12 Months

	Unweighted	Inverse-Weighted*	Inverse-Weighted+Adjusted for Discharge Medications†
	HR (95% CI), *P* Value	HR (95% CI), *P* Value	HR (95% CI), *P* Value
Clinical end points			
All-cause mortality	0.94 (0.85–1.04), 0.22	0.82 (0.72–0.93), 0.003	0.82 (0.72–0.94), 0.004
All-cause hospitalization	1.04 (0.96–1.12), 0.32	0.97 (0.88–1.06), 0.51	0.97 (0.89–1.07), 0.55
All-cause mortality or HF hospitalization	1.05 (0.97–1.14), 0.21	0.94 (0.85–1.04), 0.26	0.95 (0.86–1.05), 0.30
HF hospitalization	1.19 (1.07–1.33), 0.001	1.03 (0.90–1.18), 0.63	1.04 (0.91–1.18), 0.59
Falsification (negative control) end points			
Hospitalization for metabolic/nutritional disorder	1.26 (0.87–1.82), 0.23	1.52 (0.96–2.41), 0.08	1.52 (0.96–2.40), 0.08
Hospitalization for urinary tract infection	0.85 (0.52–1.39), 0.52	0.95 (0.54–1.68), 0.86	0.95 (0.54–1.69), 0.87

Referent=ACEI/ARB Prescription. HF indicates heart failure; and HR, hazard ratio.
*Model reflects inverse probability of treatment weighting including 25 demographic and clinical variables and 6 index hospital variables.
†Model reflects inverse probability of treatment weighting and adjustment for discharge prescription for beta-blocker and mineralocorticoid receptor antagonist therapy.

contemporary US clinical practice.[4–6] Prior work has estimated that optimal implementation of evidence-based therapy among undertreated patients with HFrEF could prevent as many as 100 000 deaths in the United States each year.[15,16] Specifically, such analyses estimated that optimal use of sacubitril/valsartan alone would result in >28 000 fewer US deaths.[16] In this context, the present data comparing patients with and without discharge prescription of sacubitril/valsartan further illustrate the magnitude of real-world clinical benefit that could be achieved with improved implementation. As compared with no discharge prescription, sacubitril/valsartan was associated with large magnitudes of risk reduction, including 31% lower risk of all-cause mortality and 10% lower risk of all-cause hospitalization. Future efforts to improve use of sacubitril/valsartan may focus on improved patient and clinician engagement and education regarding efficacy and safety, as well as innovative strategies centered on behavioral economics or technological innovation (eg, mobile applications).[17]

Although the precise reasons for low use of sacubitril/valsartan are unclear, this may reflect, in part, concerns that the findings from randomized clinical trials may not generalize to patients encountered in routine clinical practice, who are often older and with more comorbid conditions.[7,18] Notably, the mean age of patients enrolled in PARADIGM-HF was 64 years, and the median age was 62 years in PIONEER-HF, as compared with 78 years in the present study.[2,3] Likewise, proportions of women in PARADIGM-HF and PIONEER-HF were 22% and 28%, respectively, as compared with ≈40% in the current study.[2,3] Although current results for all-cause and HF hospitalization were not significant, considering the totality of the mortality and hospitalization findings, these data also support the benefit of initiation or continuation of sacubitril/valsartan during the HF hospitalization. These findings extend the results of PIONEER-HF and support hospitalization as a key opportunity for optimizing evidence-based HFrEF therapy (Table 5).[19–21]

Limitations

First, despite adjustment for several variables and rigorous statistical methods, residual confounding, unmeasured confounding, or both, may exist. Second, because of moderate missing data for admission medications, this analysis did not distinguish effectiveness of continued versus new prescription of sacubitril/valsartan, and may be subject to prevalent user bias. Nonetheless, real-world populations comprise a mix of patients who have and have not received a therapy in the past; thus, the current approach examining discharge use may be more reflective of clinical practice. Moreover, available admission medication data suggest that the majority of patients discharged on sacubitril/valsartan in the current analysis were initiated on therapy during the index hospitalization (Table 1). Third, by defining treatment groups by discharge prescription, this study did not account for potential crossover that could occur with postdischarge initiation or discontinuation of sacubitril/valsartan during the follow-up period. Likewise, this study did not assess postdischarge adherence or persistence of discharge therapy, and these factors could contribute to associations with clinical outcomes. Medication dosing data were also not available. Nonetheless, recent data suggest that such changes in sacubitril/valsartan use and dosing during longitudinal US outpatient care are modest.[5] Finally, data on postdischarge patient adherence to sacubitril/valsartan therapy were not available.

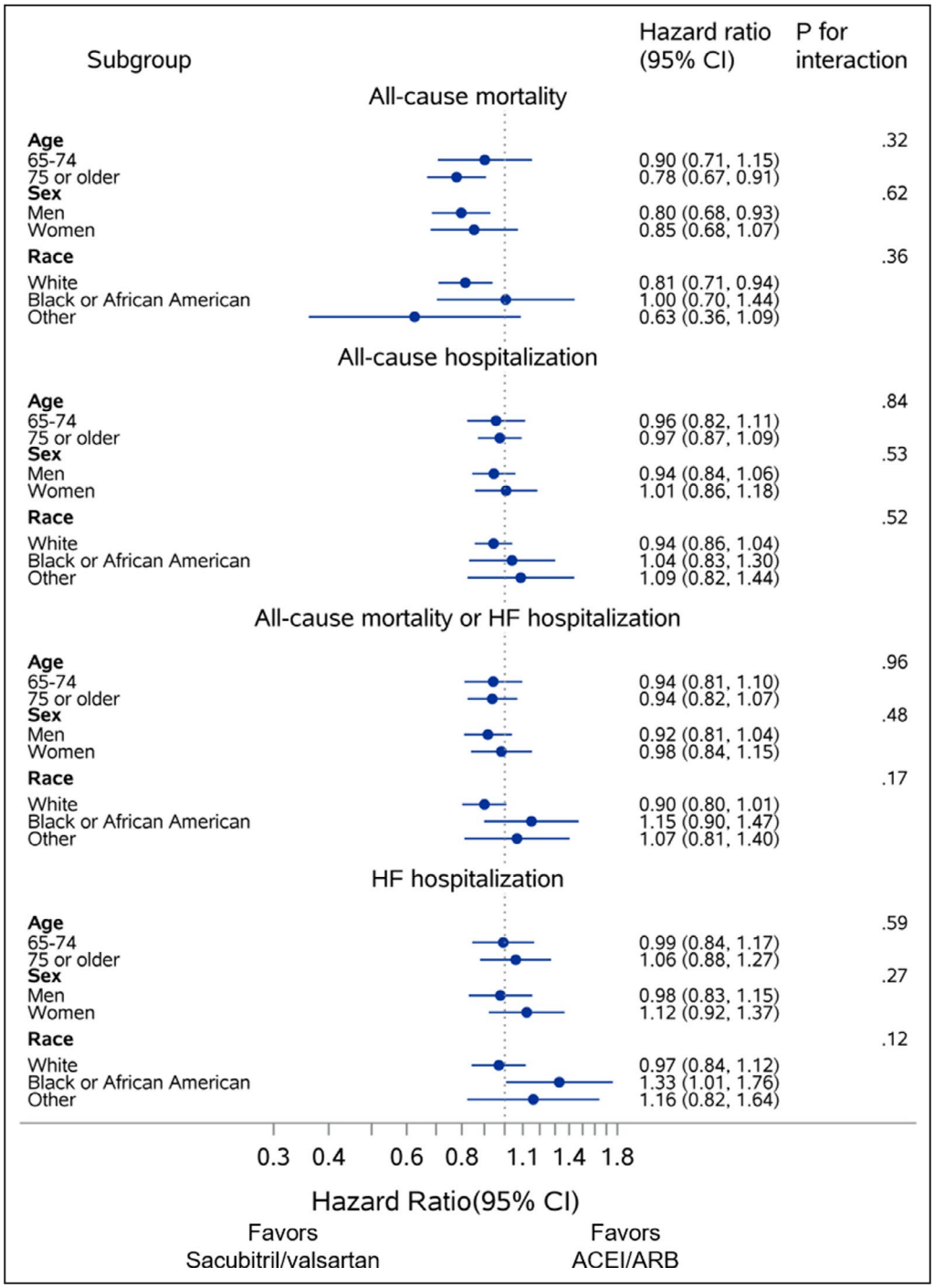

Figure 2. Prespecified subgroup analyses for mortality and hospitalization outcomes for patients discharged with sacubitril/valsartan vs an ACEI/ARB.
ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; and HF, heart failure.

CONCLUSIONS

In this contemporary real-world population of older US patients hospitalized for HFrEF and eligible for sacubitril/valsartan, prescription of sacubitril/valsartan at discharge was significantly associated with reductions in postdischarge mortality and hospitalization. These results complement existing efficacy and safety data from randomized clinical trials, and suggest that clinical benefits of sacubitril/valsartan extend to older patients hospitalized for HFrEF in real-world US clinical practice.

Table 5. Comparison of Current Findings From GWTG-HF With PIONEER-HF

	GWTG-HF		PIONEER-HF[3]	
	9408 Patients From 301 US Sites		887 Patients From 129 US Sites	
Patient Characteristics	Sacubitril/Valsartan (n=1551)	ACEI/ARB (n=7857)	Sacubitril/Valsartan (n=440)	ACEI (n=441)
Age	78 (72–84)	78 (71–85)	61 (51–71)	63 (54–72)
Women	630 (40.6)	3187 (40.6)	113 (25.7)	133 (30.2)
Black race	187 (12.2)	968 (12.3)	158 (35.9)	158 (35.8)
Systolic blood pressure, mm Hg	118 (106–130)	118 (106–131)	118 (110–133)	118 (109–132)
Heart rate, beats/min	75 (68–84)	75 (67–84)	81 (72–92)	80 (72–91)
Creatinine, mg/dL	1.2 (1.0–1.5)	1.2 (0.9–1.5)	1.3 (1.1–1.5)	1.3 (1.1–1.5)
Prior PCI	400 (26.1)	1953 (24.8)	2 (0.5)	6 (1.4)
Prior CABG	427 (27.9)	2070 (26.3)	18 (4.1)	17 (3.9)
Diabetes mellitus	650 (42.5)	3267 (41.5)	79 (18.0)	89 (20.2)
Atrial fibrillation	638 (41.7)	3365 (42.8)	147 (33.4)	165 (37.4)
Relative Risk of Clinical Outcomes—Sacubitril/Valsartan vs RASi—HR (95% CI)				
End Point	12-mo Follow-Up		8-wk Follow-Up	
All-cause mortality	0.82 (0.72–0.94)*		0.66 (0.30–1.48)	
HF hospitalization	1.04 (0.91–1.18)*		0.56 (0.37–0.84)	

Data presented as n (%) or median (25th–75th percentile). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; GWTG-HF, Get With The Guidelines–Heart Failure registry; PCI, percutaneous coronary intervention; PIONEER-HF, Comparison of Sacubitril–Valsartan Versus Enalapril on Effect on NT-proBNP [N-terminal pro-B-type natriuretic peptide] in Patients Stabilized from an Acute Heart Failure Episode; and RASi, renin-angiotensin system inhibitor.

*Reflects full model incorporating inverse probability of treatment weighting for 25 demographic and clinical variables and 6 index hospital variables, as well as adjustment for discharge prescription for beta-blocker and mineralocorticoid receptor antagonist therapy.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S8
Figures S1–S3

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SUPPLEMENTARY MATERIAL

Table S1. Definitions of Study Outcomes	
Outcome	**Definition**
All-cause mortality	Presence of a death date during the follow-up period in the CMS beneficiary summary file.
All-cause hospitalization	Any inpatient claim for post-discharge admission to an acute care hospital.
Heart failure hospitalization	Inpatient claim having a primary diagnosis of heart failure (ICD-10-CM diagnosis codes: I098.1, I50.x, I11.0, I13.0, I13.2).
Composite of all-cause mortality or HF hospitalization	Mortality and heart failure hospitalization definitions above used to form composite outcome.
Hospitalization for metabolic/nutritional disorder	Inpatient claims with Diagnosis-related group (DRG) codes 640, 641
Hospitalization for urinary tract infection	Inpatient claims with primary diagnosis of ICD-10-CM code N39.0

Table S2: List of Variables Included in the Inverse Probability of Treatment Weighting Model
Demographics: age, sex, race, Medicaid dual eligibility, index hospitalization year
Vital signs and laboratory data at discharge: systolic blood pressure, heart rate, creatinine, sodium
Medical history: ejection fraction, ischemic etiology, anemia, atrial fibrillation/flutter, chronic obstructive pulmonary disease, diabetes, hyperlipidemia, hypertension, prior coronary artery bypass grafting surgery, prior percutaneous coronary intervention, chronic kidney disease, smoking in past 12 months, stroke/transient ischemic attack, valvular heart disease
Heart failure device therapy: cardiac resynchronization therapy and defibrillator, implantable cardioverter-defibrillator
Hospital characteristics of site of index hospitalization: teaching hospital, profit status, region, hospital bed size, cardiac catheterization lab on site, heart transplantation on site

Table S3. Characteristics of Patients Discharged With and Without Sacubitril/Valsartan *Before* Application of Inverse Probability Weights

	Sacubitril/Valsartan at Discharge		
	Yes (n=1,551)	**No (n=12,679)**	**Standardized Mean Difference***
Age (years)	77 (71-83)	79 (72-86)	25.8
Women	560 (36.1)	5,012 (39.5)	7.1
Race			3.6
White	1,259 (81.2)	10,272 (81.0)	
Black or African-American	191 (12.3)	1,480 (11.7)	
Other	101 (6.5)	927 (7.3)	
Medicaid dual eligibility	218 (14.1)	1,927 (15.2)	3.2
Ejection fraction (%)	25 (20-32)	28 (23-35)	32.2
Index hospitalization year			49.9
2015/2016	294 (19.0)	5,089 (40.1)	
2017	529 (34.1)	3,824 (30.2)	
2018	728 (46.9)	3,766 (29.7)	
Vital sign and laboratory data at discharge			
Systolic blood pressure (mmHg)	113 (102-126)	118 (107-132)	27.1
Heart rate (beats/min)	74 (67-83)	75 (67-85)	9.5
Sodium (mEq/L)	139 (136-141)	139 (136-141)	5.4
Creatinine (mg/dL)	1.2 (1.0-1.5)	1.3 (1.0-1.7)	3.5
Medical history			
Ischemic HF etiology	1,105 (71.2)	8,268 (65.2)	13.0
Prior PCI	451 (29.1)	3,094 (24.4)	10.6
Prior CABG	460 (29.7)	3,461 (27.3)	5.2
Hypertension	1,329 (85.7)	10,507 (82.9)	7.7
Hyperlipidemia	981 (63.2)	7,778 (61.3)	3.9
Valve disease†	292 (18.8)	2,400 (18.9)	0.3
Atrial fibrillation/ flutter	716 (46.2)	5,733 (45.2)	1.9

Diabetes	667 (43.0)	5,233 (41.3)	3.5
Stroke/TIA	256 (16.5)	2,248 (17.7)	3.3
Chronic kidney disease	239 (15.4)	2,401 (18.9)	9.4
Anemia	259 (16.7)	2,448 (19.3)	6.8
COPD	451 (29.1)	3,867 (30.5)	3.1
Smoking in past 12 months	168 (10.8)	1,415 (11.2)	1.0
Device therapy			
CRT-D	332 (21.4)	1,374 (10.8)	29.0
ICD only	361 (23.3)	1,801 (14.2)	23.4
Medical therapy prior to admission‡			
ACEI/ARB	287 (18.5)	4,081 (32.2)	34.2
Sacubitril/valsartan	297 (19.1)	31 (0.2)	84.5
Beta-blocker	668 (43.1)	5,906 (46.6)	31.5
MRA	185 (11.9)	1,157 (9.1)	31.2
Medical therapy at discharge			
ACEI/ARB	--	7,857 (62.0)	--
Beta-blocker	1,437 (92.6)	11,113 (87.6)	16.8
MRA	604 (38.9)	3,437 (27.1)	25.4
Hospital characteristics			
Teaching hospital	1,202 (77.5)	10,316 (81.4)	9.6
Profit status			9.8
Not-for-profit	1,225 (79.0)	9,501 (74.9)	
Government	222 (14.3)	2,101 (16.6)	
For profit	104 (6.7)	1,077 (8.5)	
Region			32.2
Northeast	411 (26.5)	3,427 (27.0)	
Midwest	299 (19.3)	2,747 (21.7)	
South	716 (46.2)	4,352 (34.3)	
West	125 (8.1)	2,153 (17.0)	
Hospital bed size	393 (259-564)	370 (253-557)	
Cardiac catheterization lab on site	1,416 (91.3)	11,818 (93.2)	7.2

Heart transplantation on site	50 (3.2)	694 (5.5)	11.0

Data presented as n (%) or median (25^{th} - 75^{th}).

* Standardized mean differences represents differences in means or proportions divided by the standard error and multiplied by 100. Standardized mean differences greater than 10 indicate imbalance between groups.

† Moderately severe or severe disease of any valve, with exception of functional (i.e., secondary) mitral regurgitation.

‡ Data were missing for 718 patients in the sacubitril/valsartan group and 4,272 patients in the no sacubitril/valsartan group. Percentages reflect patients receiving medication among total patients in the group.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy and defibrillator; HF, heart failure; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; TIA, transient ischemic attack

Table S4. Characteristics of Patients Discharged With and Without Sacubitril/Valsartan *After* Application of Inverse Probability Weights

	Sacubitril/Valsartan at Discharge		
	Yes (n=1,551)	**No (n=12,679)**	**Standardized Mean Difference***
Age (years)	78 (72-84)	79 (72-86)	0.9
Women	601 (38.7)	4,964 (39.2)	1.9
Race			2.5
White	1,239 (80.5)	10,275 (81.0)	
Black or African-American	179 (11.6)	1,491 (11.8)	
Other	121 (7.9)	915 (7.2)	
Medicaid dual eligibility	248 (16.1)	1,913 (15.1)	2.9
Ejection fraction (%)	28 (20-33)	28 (21-35)	8.0
Index hospitalization year			3.1
2015/2016	559 (36.3)	4,795 (37.8)	
2017	3,881 (30.6)	486 (31.5)	
2018	494 (32.1)	4,006 (31.6)	
Vital sign and laboratory data at discharge			
Systolic blood pressure (mmHg)	117 (106-130)	118 (106-131)	3.3
Heart rate (beats/min)	75 (68-84)	75 (67-85)	0.0
Sodium (mEq/L)	139 (136-141)	139 (136-141)	0.4
Creatinine (mg/dL)	1.3 (1.0-1.6)	1.3 (1.0-1.7)	1.2
Medical history			
Ischemic HF etiology	1,028 (66.8)	8,357 (65.9)	1.9
Prior PCI	403 (26.2)	3,161 (24.9)	2.8
Prior CABG	460 (29.9)	3,499 (27.6)	5.1
Hypertension	1,255 (81.6)	10,547 (83.2)	4.2
Hyperlipidemia	932 (60.5)	7,805 (61.5)	2.1
Valve disease †	284 (18.4)	2,396 (18.9)	1.2
Atrial fibrillation/ flutter	694 (45.1)	5,744 (45.3)	0.4

Diabetes	663 (43.1)	5,261 (41.5)	3.3
Stroke/TIA	281 (18.3)	2,235 (17.6)	1.7
Chronic kidney disease	316 (20.5)	2,358 (18.6)	4.9
Anemia	292 (18.9)	2,411 (19.0)	0.2
COPD	465 (30.2)	3,847 (30.3)	0.3
Smoking in past 12 months	163 (10.6)	1,409 (11.1)	1.7
Device therapy			
CRT-D	191 (12.4)	1,525 (12.0)	1.2
ICD only	223 (14.5)	1,929 (15.2)	2.0
Medical therapy at discharge‡			
ACEI/ARB	--	7,875 (62.1)	--
Beta-blocker	1,420 (92.3)	11,130 (87.8)	15.1
MRA	534 (34.7)	3,494 (27.6)	15.5
Hospital characteristics			
Teaching hospital	1,255 (81.6)	10,270 (81.0)	1.5
Profit status			1.0
Not-for-profit	1,154 (75.0)	9,557 (75.4)	
Government	253 (16.5)	2,071 (16.3)	
For profit	132 (8.5)	1,053 (8.3)	
Region			4.1
Northeast	395 (25.7)	3,418 (27.0)	
Midwest	339 (22.0)	2,716 (21.4)	
South	540 (35.1)	4,516 (35.6)	
West	265 (17.2)	2,031 (16.0)	
Hospital bed size	393 (286-581)	370 (253-557)	
Cardiac catheterization lab on site	1,451 (94.3)	11,795 (93.0)	
Heart transplantation on site	84 (5.5)	662 (5.2)	

Data presented as percentages or median (25^{th} - 75^{th}).

*Standardized mean differences represents differences in means or proportions divided by the standard error and multiplied by 100. Standardized mean differences greater than 10 indicate imbalance between groups.

† Moderately severe or severe regurgitation or stenosis of any valve, with exception of functional (i.e., secondary) mitral regurgitation.

‡ Discharge medications were not included within inverse probability of treatment weighted models and are not expected to be balanced. Adjustment for beta-blocker and mineralocorticoid receptor antagonist (MRA) therapy at discharge was added to inverse probability of treatment weighted models to constitute the fully adjusted model.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy and defibrillator; HF, heart failure; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; TIA, transient ischemic attack

Table S5. Characteristics of Patients Discharged with neither Sacubitril/Valsartan nor ACEI/ARB versus ACEI/ARB versus Sacubitril/Valsartan Without Application of Inverse Probability Weights

				Standardized Mean Differences*		
	Neither ACEI/ARB nor Sacubitril/Valsartan (n=4,822)	**ACEI/ARB (n=7,857)**	**Sacubitril/ Valsartan (n=1,551)**	**Neither ACEI/ARB nor Sacubitril/Valsartan vs. Sacubitril/Valsartan**	**Neither ACEI/ARB nor Sacubitril/Valsartan vs. ACEI/ARB**	**ACEI/ARB vs. Sacubitril/Valsartan**
Age (years)	81 (73-87)	78 (71-85)	77 (71-83)	39.7	21.3	17.4
Women	1,750 (36.3)	3,262 (41.5)	560 (36.1)	0.4	10.7	11.1
Race				5.3	5.6	3.9
White	3,970 (82.3)	6,302 (80.2)	1,259 (81.2)			
Black or African American	515 (10.7)	965 (12.3)	191 (12.3)			
Other	337 (7.0)	590 (7.5)	101 (6.5)			
Medicaid dual eligibility	697 (14.5)	1,230 (15.7)	218 (14.1)	1.1	3.4	4.5
Ejection fraction (%)	30 (23-35)	28 (22-35)	25 (20-32)	37.8	9.5	28.7
Index hospitalization year				47.4	5.9	51.5
2015/2016	1,899 (39.4)	3,190 (40.6)	294 (19.0)			
2017	1,411 (29.3)	2,413 (30.7)	529 (34.1)			
2018	1,512 (31.)	2,254 (28.)	728 (46.9)			
Vital sign and laboratory data at discharge						
Systolic blood pressure (mmHg)	118 (105-130.0)	118 (107-132)	113 (102-126)	21.4	8.8	30.7
Heart rate (beats/min)	76 (68-86)	75 (67-84)	74 (67-83)	17.3	12.5	4.5
Sodium (mEq/L)	138 (136-141)	139 (136-141)	139 (136-141)	4.3	2.6	6.0
Creatinine (mg/dL)	1.6 (1.2-2.1)	1.2 (0.9-1.5)	1.2 (1.0-1.5)	13.0	22.1	3.5
Medical history						
Ischemic HF etiology	3,311 (68.7)	4,957 (63.1)	1,105 (71.2)	5.6	11.8	17.4
Prior PCI	1,211 (25.1)	1,883 (24.0)	451 (29.1)	8.9	2.7	11.6
Prior CABG	1,454 (30.2)	2,007 (25.5)	460 (29.7)	1.1	10.3	9.2

Hypertension	3,913 (81.1)	6,594 (83.9)	1,329 (85.7)	12.2	7.3	4.9
Hyperlipidemia	3,009 (62.4)	4,769 (60.7)	981 (63.2)	1.8	3.5	5.3
Valve disease †	1,036 (21.5)	1,364 (17.4)	292 (18.8)	6.6	10.4	3.8
Atrial fibrillation/ flutter	2,420 (50.2)	3,313 (42.2)	716 (46.2)	8.1	16.1	8.1
Diabetes	1,996 (41.4)	3,237 (41.2)	667 (43.0)	3.3	0.4	3.7
Stroke/TIA	944 (19.6)	1,304 (16.6)	256 (16.5)	8.0	7.7	0.2
Chronic kidney disease	1,408 (29.2)	993 (12.6)	239 (15.4)	33.6	41.6	8.0
Anemia	1,155 (24.0)	1,293 (16.5)	259 (16.7)	18.1	18.8	0.7
COPD	1,539 (31.9)	2,328 (29.6)	451 (29.1)	6.2	5.0	1.2
Smoking in past 12 months	442 (9.2)	973 (12.4)	168 (10.8)	5.6	10.4	4.8
Device therapy						
CRT-D	565 (11.7)	809 (10.3)	332 (21.4)	26.3	4.5	30.8
ICD only	737 (15.3)	1,064 (13.5)	361 (23.3)	20.4	5.0	25.3
Medical therapy at discharge						
Beta-blocker	3,819 (79.2)	7,294 (92.8)	1,437 (92.6)	39.4	40.1	0.7
MRA	804 (16.7)	2,633 (33.5)	604 (38.9)	51.3	39.6	11.3
Hospital characteristics						
Teaching hospital	3,901 (80.9)	6,415 (81.6)	1,202 (77.5)	8.4	1.9	10.3
Profit status				9.9	5.7	10.3
Not-for-profit	3,638 (75.4)	5,863 (74.6)	1,225 (79.0)			
Government	745 (15.5)	1,356 (17.3)	222 (14.3)			
For profit	439 (9.1)	638 (8.1)	104 (6.7)			
Region				31.1	9.7	33.4
Northeast	1,399 (29.0)	2,028 (25.8)	411 (26.5)			
Midwest	944 (19.6)	1,803 (22.9)	299 (19.3)			
South	1,675 (34.7)	2,677 (34.1)	716 (46.2)			
West	804 (16.7)	1,349 (17.2)	125 (8.1)			
Hospital bed size	366 (253-540)	376 (253-564)	393.0 (259-564)	0.4	2.9	2.5

Cardiac catheterization lab on site	4,470 (92.7)	7,348 (93.5)	1,416 (91.3)	5.2	3.2	8.4
Heart transplantation on site	220 (4.6)	474 (6.0)	50 (3.2)	6.9	6.6	13.4

Data presented as percentages or median (25^{th} - 75^{th})

*Standardized mean differences represents differences in means or proportions divided by the standard error and multiplied by 100. Standardized mean differences greater than 10 indicate imbalance between groups.

† Moderately severe or severe regurgitation or stenosis of any valve, with exception of functional (i.e., secondary) mitral regurgitation.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy and defibrillator; HF, heart failure; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; TIA, transient ischemic attack

Table S6. Unadjusted Cumulative Incidence of Clinical Outcomes For Patients Discharged With and Without Sacubitril/Valsartan

	Sacubitril/Valsartan at Discharge		
	Yes (n=1,551)	**No (n=12,679)**	**P value**
Effectiveness Endpoints			
All-cause mortality			
30 days	75 (4.9)	1,218 (9.6)	<0.001
12 months	444 (29.5)	4,870 (39.2)	<0.001
All-cause hospitalization			
30 days	356 (23.0)	3,126 (24.7)	0.16
12 months	984 (64.7)	7,949 (63.6)	0.87
All-cause mortality or HF hospitalization			
30 days	195 (12.6)	2,386 (18.9)	<0.001
12 months	792 (52.3)	7,215 (57.9)	<0.001
HF hospitalization			
30 days	142 (9.2)	1,307 (10.3)	0.16
12 months	560 (37.0)	4,167 (33.4)	0.02
Falsification (Negative Control) Endpoints			
Metabolic/nutritional hospitalization within 12 months	36 (2.4)	236 (1.9)	0.20
Urinary tract infection hospitalization within 12 months	17 (1.1)	183 (1.5)	0.28

Data presented as n (%). Cumulative incidence of mortality and mortality or HF hospitalization endpoints were calculated using the Kaplan-Meier method and group differences were evaluated using log-rank tests. Cumulative incidence for hospitalization outcomes was estimated using the cumulative incidence function to account for the competing risk of mortality, and group differences were evaluated using Gray tests.

Abbreviations: HF, heart failure

Table S7. Associations Between Sacubitril/Valsartan Prescription and Clinical Outcomes at 12 Months (Referent = No Sacubitril/Valsartan Prescription)

	Unweighted	Inverse-Weighted*	Inverse-Weighted + Adjusted for Discharge Medications†
	HR (95% CI), p value	HR (95% CI), p value	HR (95% CI), p value
Clinical Endpoints			
All-cause mortality	0.69 (0.62-0.75), p<0.001	0.66 (0.58-0.75), p<0.001	0.69 (0.60-0.79), p<0.001
All-cause hospitalization	0.92 (0.85-0.99), p=0.03	0.88 (0.81-0.97), p=0.008	0.90 (0.82-0.98), p=0.02
All-cause mortality or HF hospitalization	0.83 (0.77-0.90), p<0.001	0.80 (0.72-0.89), p<0.001	0.83 (0.74-0.92), p<0.001
HF hospitalization	1.02 (0.91-1.13), p=0.76	0.92 (0.80-1.07), p=0.28	0.94 (0.82-1.08), p=0.40
Falsification (Negative Control) Endpoints			
Hospitalization for Metabolic/Nutritional Disorder	1.15 (0.81-1.63), p=0.44	1.49 (0.94-2.36), p=0.09	1.51 (0.95-2.41), p=0.08
Hospitalization for UTI	0.69 (0.43-1.13), p=0.14	0.80 (0.45-1.41), p=0.43	0.81 (0.46-1.43), p=0.47

* Model reflects inverse probability of treatment weighting including 24 demographic and clinical variables and 6 index hospital variables.

† Model reflects inverse probability of treatment weighting and adjustment for discharge prescription for beta-blocker and mineralocorticoid receptor antagonist therapy.

Abbreviations: CI, confidence interval; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; UTI, urinary tract infection

Table S8. Unadjusted Cumulative Incidence of Clinical Outcomes For Patients Discharged with neither Sacubitril/Valsartan nor ACEI/ARB versus ACEI/ARB versus Sacubitril/Valsartan

	Neither Sacubitril/Valsartan nor ACEI/ARB (n=4,822)	ACEI/ARB (n=7,857)	Sacubitril/Valsartan (n=1,551)	p-value
Effectiveness Endpoints				
All-cause mortality				
30 days	790 (16.4)	428 (5.5)	75 (4.9)	< .001
12 months	2501 (52.8)	2369 (30.9)	444 (29.5)	< .001
All-cause hospitalization				
30 days	1422 (29.5)	1704 (21.7)	356 (23.0)	< .001
12 months	3114 (65.3)	4835 (62.6)	984 (64.7)	< .001
All-cause mortality or HF hospitalization				
30 days	1351 (28.1)	1035 (13.2)	195 (12.6)	< .001
12 months	3339 (70.2)	3876 (50.4)	792 (52.3)	< .001
HF hospitalization				
30 days	655 (13.6)	652 (8.3)	142 (9.2)	< .001
12 months	1749 (36.8)	2418 (31.4)	560 (37.0)	< .001
Falsification (Negative Control) Endpoints				
Metabolic/nutritional hospitalization within 12 months	92 (1.9)	144 (1.9)	36 (2.4)	.42

Urinary tract infection hospitalization within 12 months	83 (1.8)	100 (1.3)	17 (1.1)	.06

Data presented as n (%). Cumulative incidence of mortality and mortality or HF hospitalization endpoints were calculated using the Kaplan-Meier method and group differences were evaluated using log-rank tests. Cumulative incidence for hospitalization outcomes was estimated using the cumulative incidence function to account for the competing risk of mortality, and group differences were evaluated using Gray tests.

Abbreviations: HF, heart failure

**Figure S1. Selection of the final study cohort. ***For ineligible hospitalizations, n for each specific exclusion reflect sequential application of each criterion in the order displayed (e.g., ejection fraction criterion applied first).

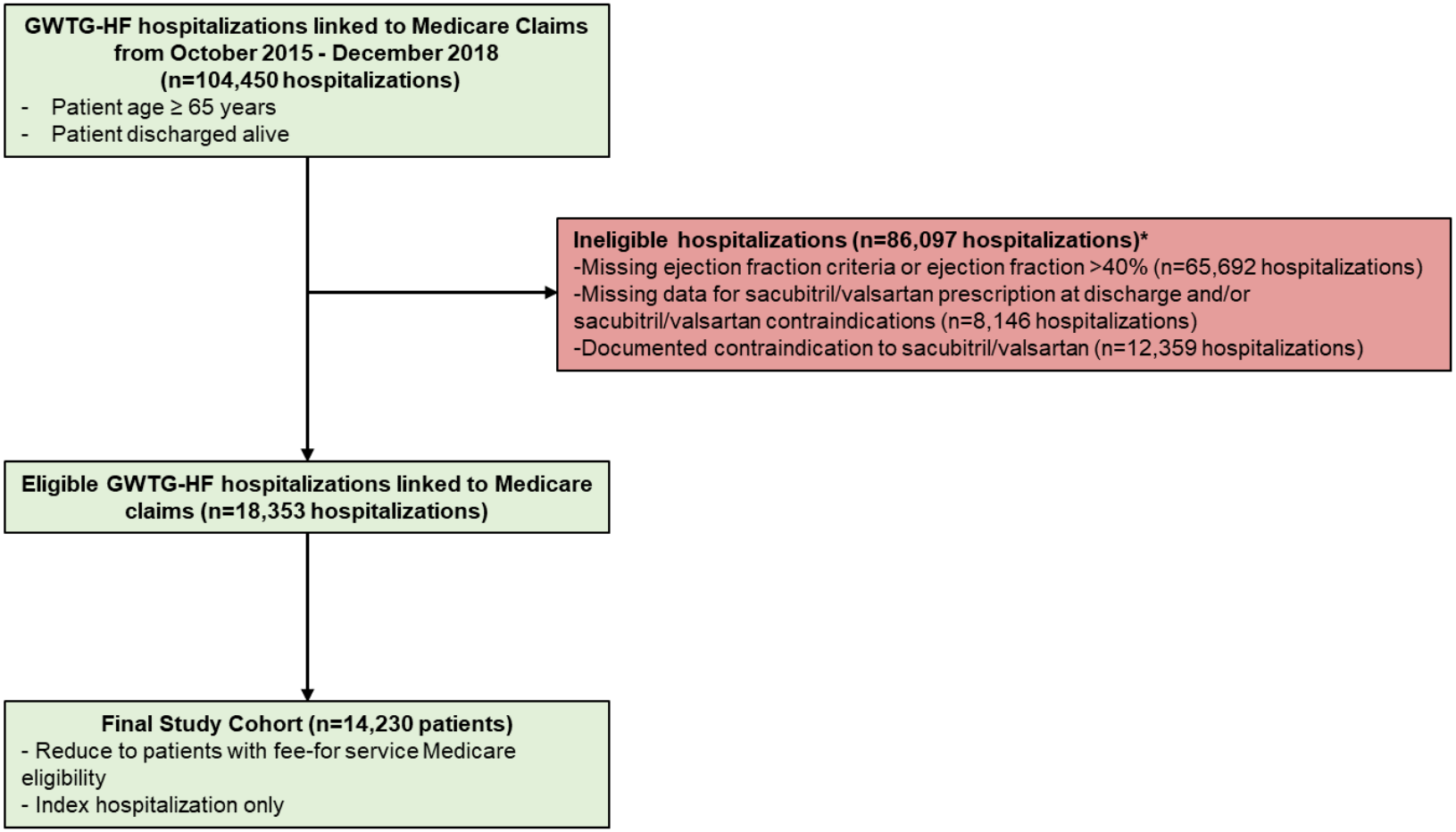

Figure S2. Cumulative Incidence of Mortality and Hospitalization Outcomes for Patients Discharged with and without Sacubitril/Valsartan. Curves reflect adjusted results in the form of directly-adjusted cumulative incidence curves, which were derived from inverse-probability-of-treatment-weighted proportional hazards models. Abbreviations: HF, heart failure

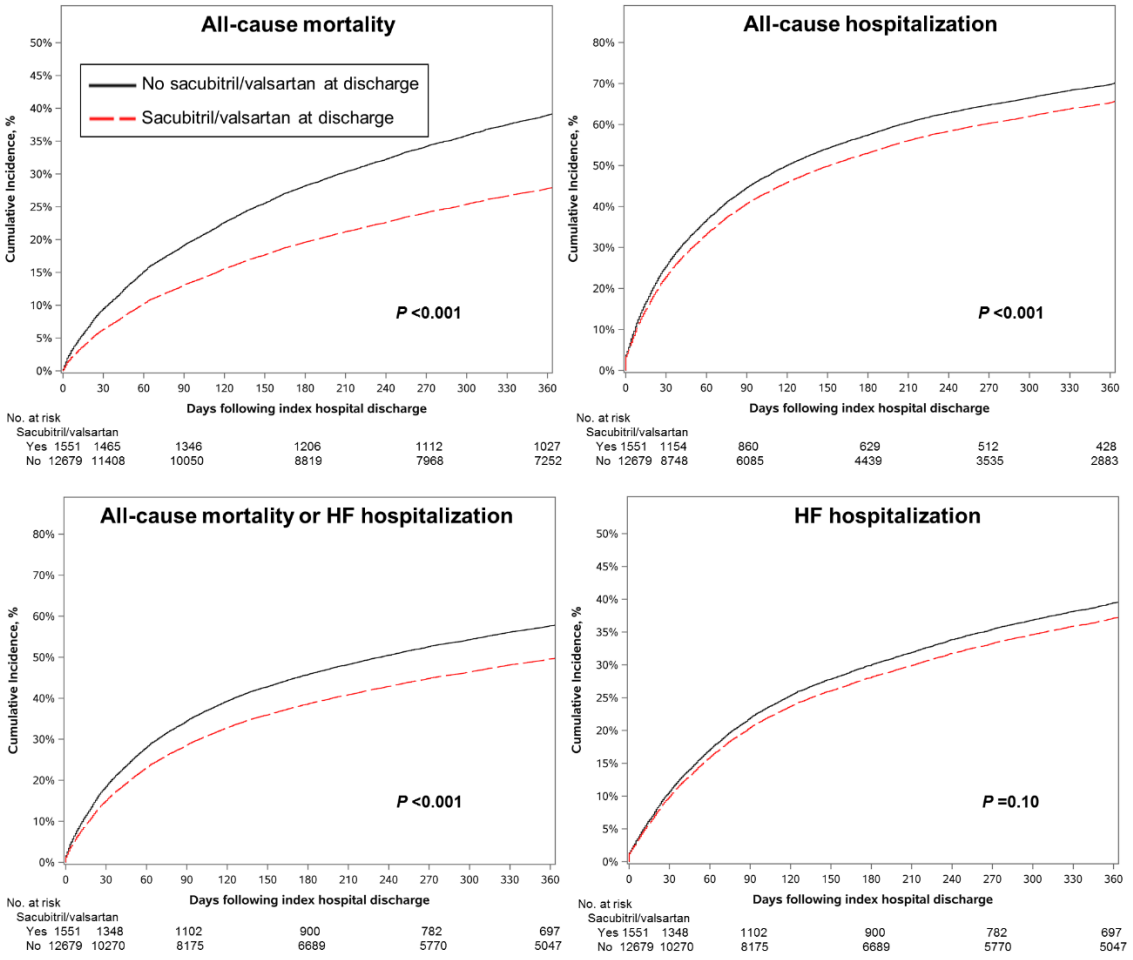

Figure S3. Pre-specified Subgroup Analyses for Mortality and Hospitalization Outcomes for Patients Discharged With and Without Sacubitril/Valsartan. Abbreviations: CI, confidence interval; HF, heart failure