

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		Standardized Mean Difference*
	Yes (n=1,551)	No (n=12,679)	
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)	
<u>Vital sign and laboratory data at discharge</u>			
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
<u>Medical history</u>			
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
<u>Device therapy</u>			
CRT-D	332 (21.4)	1,374 (10.8)	29.0
ICD only	361 (23.3)	1,801 (14.2)	23.4
<u>Medical therapy prior to admission†</u>			
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
<u>Medical therapy at discharge</u>			
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
<u>Hospital characteristics</u>			
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
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Data presented as n (%) or median (25th - 75th).

* 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		Standardized Mean Difference*
	Yes (n=1,551)	No (n=12,679)	
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)	
<u>Vital sign and laboratory data at discharge</u>			
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
<u>Medical history</u>			
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
<u>Device therapy</u>			
CRT-D	191 (12.4)	1,525 (12.0)	1.2
ICD only	223 (14.5)	1,929 (15.2)	2.0
<u>Medical therapy at discharge†</u>			
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
<u>Hospital characteristics</u>			
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 (25th - 75th).

*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)			
<u>Vital sign and laboratory data at discharge</u>						
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
<u>Medical history</u>						
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
<u>Device therapy</u>						
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
<u>Medical therapy at discharge</u>						
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
<u>Hospital characteristics</u>						
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 (25th - 75th)

*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		P value
	Yes (n=1,551)	No (n=12,679)	
<u>Effectiveness Endpoints</u>			
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
<u>Falsification (Negative Control) Endpoints</u>			
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
<u>Clinical Endpoints</u>			
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
<u>Falsification (Negative Control) Endpoints</u>			
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; HF_rEF, 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
<u>Effectiveness Endpoints</u>				
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
<u>Falsification (Negative Control) Endpoints</u>				
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
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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).

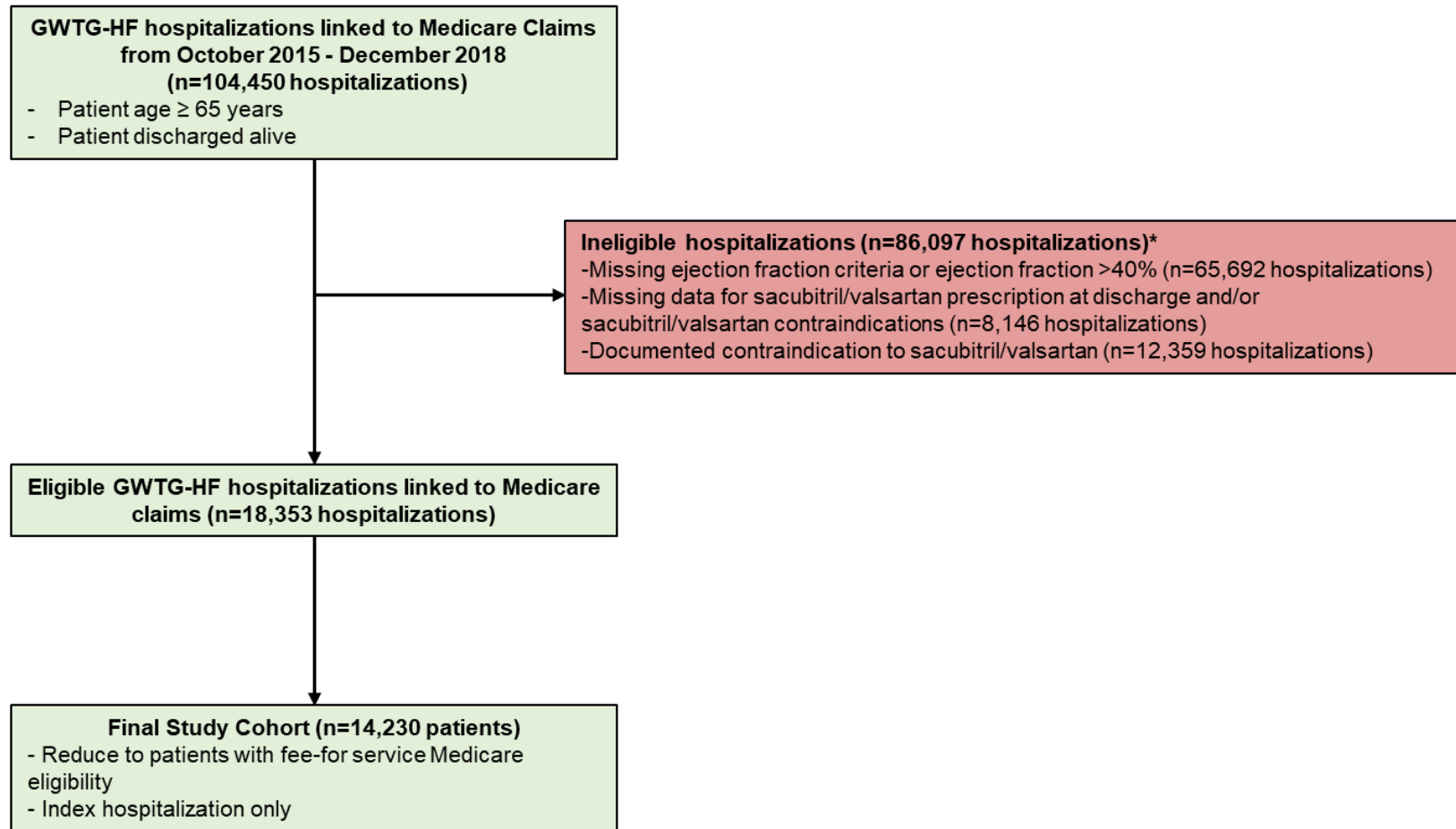


Figure S2. Cumulative Incidence of Mortality and Hospitalization Outcomes for Patients Discharged with and without Sacubitril/Valsartan. Curves reflect adjusted results in the form of directly-adjusted cumulative incidence curves, which were derived from inverse-probability-of-treatment-weighted proportional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

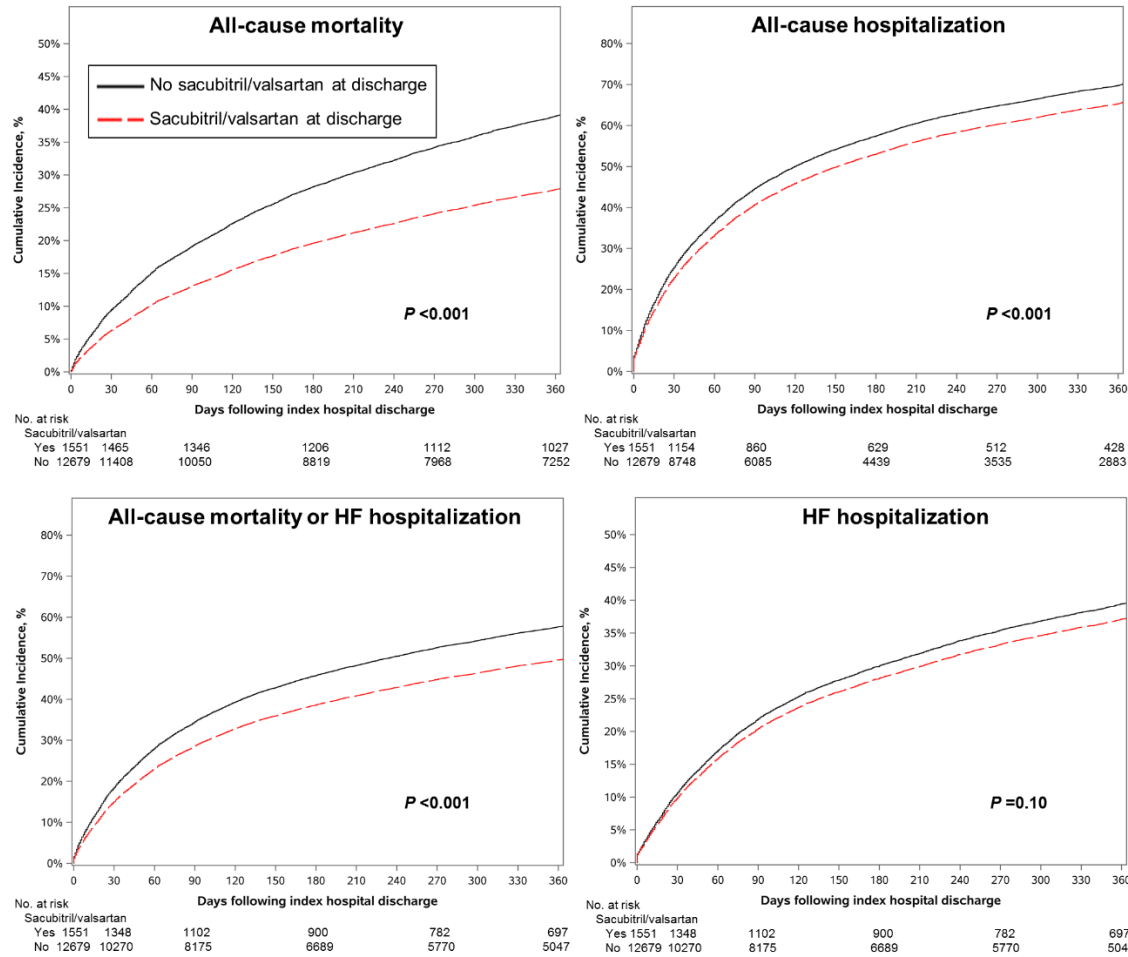


Figure S3. Pre-specified Subgroup Analyses for Mortality and Hospitalization Outcomes for Patients Discharged With and Without Sacubitril/Valsartan. Abbreviations: CI, confidence interval; HF, heart failure

