Replication of the PARADIGM-HF Heart Failure Trial in Healthcare Claims Data

DUPLICATE PARADIGM-HF January 25, 2021

NCT04736433

1. RCT Details

This section provides a high-level overview of an RCT that the described real-world evidence study is trying to replicate as closely as possible given the remaining limitations inherent in the healthcare databases.

1.1 Title

Angiotensin-Neprilysin Inhibition versus Enalapril in Heart Failure (PARADIGM-HF trial)

1.2 Intended aim(s)

The primary objective of the study is to determine LCZ696 200 mg twice daily, a combination of sacubitril/valsartan, is superior to enalapril 10 mg twice daily in reducing the composite endpoint in place of Angiotensin Converting Enzyme inhibitors (ACEi) and Angiotensin II receptor blockers (ARBs)

1.3 Primary endpoint for replication and RCT finding

Composite endpoint of death from cardiovascular (CV) causes or hospitalization for heart failure (HF)

1.4 Required power for primary endpoint and noninferiority margin (if applicable)

After following 8000 patients for 34 months, at an overall two-sided alpha level of 0.05, the primary end point would occur in 2410 patients, which would provide a power of 97% to detect a 15% reduction in the risk of this outcome.

1.5 Trial estimate

HR = 0.80 (95% CI 0.73–0.87) comparing LCZ696 to enalapril (McMurry et al., 2014, NEJM)

2. Person responsible for implementation of replication in Aetion

Helen Tesfaye, Pharm.D, ScM implemented the study design in the Aetion Evidence Platform. She is not responsible for the validity of design and analytic choices. All implementation steps are recorded, and implementation history is archived in the platform.

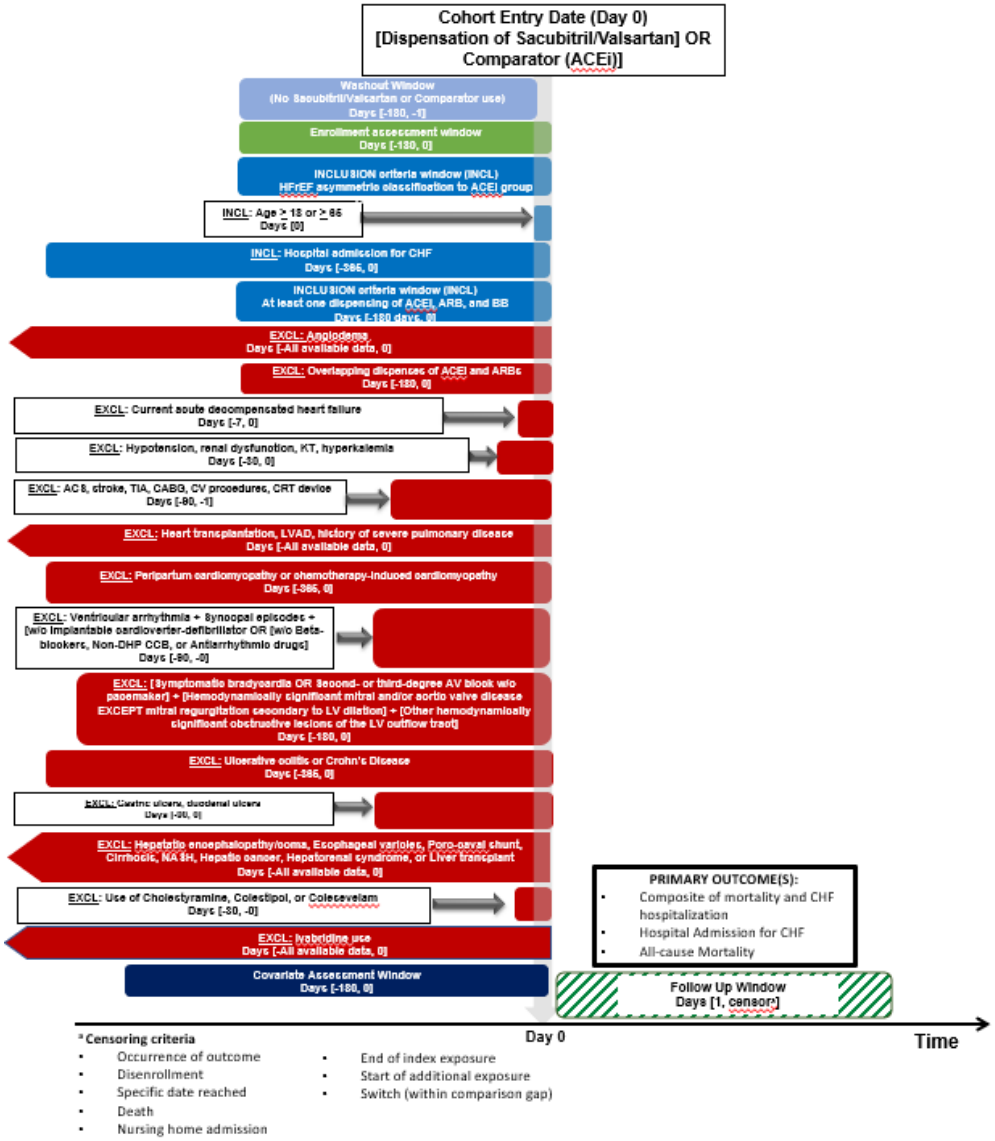
3. Data Source(s)

Optum Cliniformatics Data Mart, IBM MarketScan, Medicare

4. Study Design Diagram

The study design diagram visualizes key aspects of the longitudinal study design for expediated review

Design Diagram – PARADIGM-HF TRIAL REPLICATION



5. Cohort Identification

5.1 Cohort Summary

This study will involve a new user, parallel group retrospective cohort study design comparing sacubitril/valsartan to ACE inhibitors. Although the trial compared sacubitril/valsartan to enalapril, we expanded the definition of the comparator group to include all ACEi therapies to improve power, since all medications within this class of medication are indicated and guideline recommended for use in heart failure with reduced ejection fraction patients and would be expected to have similar effects on the primary outcome of CV death and HF hospitalization.

The patients will be required to have continuous enrollment during the baseline period of 180 days before initiation of sacubitril/valsartan or a ACEi (cohort entry).

5.2 Important steps for cohort formation

New users (defined as no use of sacubitril/valsartan in 180 days prior to index date) of the exposure will be identified. New users of a comparator drug were identified as patients with no ACEi fills during the 60 days prior to the index date to allow for patients who are switching among ACEi drugs or restarting ACEi after a brief lapse.

5.2.1 Eligible cohort entry date

Sacubitril/valsartan was approved by FDA for market availability on July 7, 2015.

- Optum: July 7, 2015 – March 31, 2020 (end of data availability)
- Marketscan: July 7, 2015 – December 31, 2018 (end of data availability)
- Medicare: July 7, 2015 – December 31, 2017 (end of data availability)

5.2.2 Specify inclusion/exclusion criteria for cohort entry and define the index date

Inclusion and exclusion criteria were adapted from the trial as closely as possible. Definitions for all inclusion/exclusion are provided in **Appendix A** and are summarized in the flowcharts below.

5.3 Flowchart of the study cohort assembly

	Optum		Marketscan		Medicare*	
	Less Excluded Patients	**Remaining Patients**	**Less Excluded Patients**	**Remaining Patients**	**Less Excluded Patients**	**Remaining Patients**
All patients		77,673,639		200,203,908		23,466,175
Did not meet cohort entry criteria	-73,445,846	4,227,793	-196,533,760	3,670,148	-18,348,713	5,117,462
Excluded due to insufficient enrollment	-623,954	3,603,839	-340,051	3,330,097	-1,288,867	3,828,595
Excluded due to prior use of referent	-3,168,921	434,918	-2,967,886	362,211	-3,495,789	332,806
Excluded due to prior use of exposure	-29,778	405,140	-12,511	349,700	-33,013	299,793
Excluded because patient qualified in >1 exposure category	-8	405,132	-3	349,697	-9	299,784
Excluded based on Age	0	405,132	-1	349,696	0	299,784
Excluded based on Gender	-39	405,093	0	349,696	0	299,784
Excluded based on Inclusion #1 - Age >=18 years old	-624	404,469	-1,354	348,342	-721	299,063
Inclusion #3 - HFrEF prediction algorithm applied to reference group†	-381,531	22,938	-337,242	11,100	-259,816	39,247
Excluded based on Inclusion #4b - Hospitalization for HF within the last 12 months	-9,321	13,617	-4,618	6,482	-10,685	28,562
Excluded based on Inclusion #5a - ACEis or ARBs	-1,224	12,393	-385	6,097	-1,534	27,028
Excluded based on Inclusion #5b - Beta-blockers	-673	11,720	-248	5,849	-2,128	24,900
Excluded based on Exclusion #3 - Known history of angioedema	-56	11,664	-29	5,820	-200	24,700
Excluded based on Exclusion #4 - Treatment with both ACEis AND ARBs	-15	11,649	-9	5,811	-34	24,666
Excluded based on Exclusion #5 - Acute decompensated HF	-1,060	10,589	-435	5,376	-5,457	19,209
Excluded based on Exclusion #6 - Symptomatic hypotension	-734	9,855	-240	5,136	-1,964	17,245
Excluded based on Exclusion #7 - Low eGFR / renal dysfunction	-1,064	8,791	-403	4,733	-2,833	14,412
Excluded based on Exclusion #8 - Hyperkalemia	-57	8,734	-14	4,719	-116	14,296
Excluded based on Exclusion #9 - ACS, Stroke, TIA, CABG, PCI, Other CV Procedures, Carotid Angioplasty	-765	7,969	-546	4,173	-2,912	11,384
Excluded based on Exclusion #11 - Implantation of CRT device	-41	7,928	-19	4,154	-1,550	9,834
Excluded based on Exclusion #12 - History of heart transplant or LVAD	-56	7,872	-33	4,121	-35	9,799
Excluded based on Exclusion #13 - History of severe pulmonary disease	-463	7,409	-205	3,916	-1,029	8,770
Excluded based on Exclusion #14 - Diagnosis of peripartum- or chemotherapy-induced cardiomyopathy	-38	7,371	-34	3,882	-60	8,710

Excluded based on Exclusion #15 - Documented untreated ventricular arrhythmia with syncopal episodes	-18	7,353	-6	3,876	-25	8,685
Excluded based on Exclusion #16 - Second- and third-degree AV block	-73	7,280	-29	3,847	-73	8,612
Excluded based on Exclusion #17 - Presence of haemodynamically significant mitral and/or aortic valve disease	-124	7,156	-43	3,804	-246	8,366
Excluded based on Exclusion #19a - History of active inflammatory bowel disease (IBD)	-18	7,138	-12	3,792	-37	8,329
Excluded based on Exclusion #19b - Active duodenal/gastric ulcers	-13	7,125	-8	3,784	-25	8,304
Excluded based on Exclusion #19c - Evidence of hepatic disease	-173	6,952	-80	3,704	-265	8,039
Excluded based on Exclusion #19d - Current treatment with cholestyramine or colestipol resins	0	6,952	0	3,704	-4	8,035
Excluded based on Exclusion #21 - Ivabradine use	-6	6,946	-10	3,694	-4	8,031
Final cohort		**6,946**		**3,694**		**8,031**

* The Medicare data cut included all patients with a diagnosis for HF, stroke, or diabetes.

† Algorithm provided in Desai et al. (2018).

6 Variables

6.1 Exposure-related variables:

Study drug:

The study exposure of interest is initiation of sacubitril/valsartan (ARNi) at any dose and frequency. Initiation will be defined by no use of sacubitril/valsartan during the prior 180 days before treatment initiation (washout period). Patients are required to be incident users with respect to their exposure group only, since one of the RCT inclusion criteria was prior treatment with ACEi or ARB.

Comparator agents:

Initiators of ACEi, any dose and frequency.

6.2 Preliminary Covariates:

- Age

- Sex
- Combined Comorbidity Index (CCI), measured over the default baseline covariate assessment period of 180 days prior to and including the index prescription date

Covariates listed above are a small subset of covariates that will ultimately be controlled in the design and analysis phase of the study. They are included in the preliminary assessment to determine the presence of adequate overlap between the two population of patients to proceed to the next phase of the study. Remaining covariates are defined only after the study has passed the initial feasibility analysis and initial power assessment and are listed in Table 1 (**Appendix B**).

6.3 Outcome variables and study follow-up:

6.3.1 Outcome variables

Effectiveness outcome variables of interest (definitions provided in **Appendix A**):

- **Primary outcome:** Composite of hospitalization for heart failure and all-cause mortality
- Secondary outcomes:
  - Heart failure hospitalization
  - All-cause death

Control outcomes of interest (control outcomes only serve to assess aspects of study validity but are not further interpreted, definitions provided in Appendix A):

1. Bleeding (we expect to see a null association, as renin angiotensin aldosterone inhibitors are not expected to have any impact on this outcome)

6.3.2 Study follow-up

Both as-treated (AT) and intention-to-treat (ITT) analysis will be conducted with treatment defined as the index drug on the day of cohort entry. Because adherence in the real-world databases is expected to be much worse than in the trial, the AT analysis is the **primary** analysis, as it targets the relative hazard of outcomes on treatment.

For the AT analysis, the follow-up will start the day after the initiation of sacubitril/valsartan or ACEi and will continue until the earliest date of the following events:

- The first occurrence of the outcome of interest,
- The date of end of continue registration in the database,
- End of the study period,
- Nursing home admission
    - Nursing home admissions are considered a censoring event because the data sources utilized typically provide little to no data on a patient, particularly on drug utilization, after admission. We will utilize this as an exclusion reason for cohorts for the same reason.
- The date of drug discontinuation, defined as the date of the last continuous treatment episode of the index drug (sacubitril/valsartan or ACEi) + a 30-day grace period,
- The date of switching from an exposure to comparator and vice versa,
- The date of switching to or initiation of any angiotensin II receptor blockers (ARBs), including combination medications containing ARBs,
- The date of switching to or initiation of aliskiren, including combination therapies.

For the ITT analyses, the censoring based on the switching and treatment discontinuation will be replaced with a maximum allowed follow-up time of 365 days.

7 Initial Feasibility Analysis

Aetion report name:
Optum- https://bwh-dope.aetion.com/projects/details/1069/results/61863/result/0
Marketscan- https://bwh-dope.aetion.com/projects/details/1072/results/61852/result/0
Medicare - https://bwh-dope.aetion.com/projects/details/1073/results/61854/result/0

Date conducted: 11/24/2020
Complete Aetion feasibility analysis using age, sex, and CCI as the only covariates and the primary endpoint (Section 6.3.1) as the outcome.

- Complete study flowchart from Section 5.3
- Report patient characteristics by treatment group

	Optum	Marketscan	Medicare

Variable	Reference - ACE inhibitors	Exposure - Sacubitril/valsartan	Difference	Reference - ACE inhibitors	Exposure - Sacubitril/valsartan	Difference	Reference - ACE Inhibitors	Exposure - Sacubitril/valsartan Copy	Differ
Number of patients	4,217	2,729	-	2,218	1,476	-	6,293	1,738	-
Age									
...mean (sd)	66.94 (13.39)	68.39 (12.07)	-1.45 (-2.06, -0.84)	60.86 (14.92)	61.21 (13.50)	-0.36 (-1.29, 0.57)	77.16 (8.29)	76.04 (7.56)	1.12 (1.5
...median [IQR]	68.00 [58.00, 77.00]	70.00 [61.00, 77.00]	-	60.00 [52.00, 71.00]	60.00 [53.00, 70.00]	-	76.00 [70.00, 84.00]	75.00 [70.00, 81.00]	-
Gender									
..Males; n (%)	2,829 (67.1%)	1,773 (65.0%)	2.1% (-0.2%, 4.4%)	1,606 (72.4%)	1,018 (69.0%)	3.4% (0.4%, 6.5%)	3,433 (54.6%)	1,003 (57.7%)	-3.2% (- 0.5
...Females; n (%)	1,388 (32.9%)	956 (35.0%)	-2.1% (-4.4%, 0.2%)	612 (27.6%)	458 (31.0%)	-3.4% (-6.5%, -0.4%)	2,860 (45.4%)	735 (42.3%)	3.2% (5.8
CCI (180 days)-ICD9 and ICD10 v2									
...mean (sd)	6.52 (2.50)	6.70 (2.24)	-0.18 (-0.29, -0.06)	5.51 (2.22)	5.70 (2.04)	-0.19 (-0.33, -0.05)	7.53 (2.91)	7.00 (2.51)	0.53 (0.6
...median [IQR]	6.00 [5.00, 8.00]	6.00 [5.00, 8.00]	-	5.00 [4.00, 7.00]	5.00 [4.00, 7.00]	-	7.00 [5.00, 9.00]	7.00 [5.00, 9.00]	-

- Report summary parameters of study population

	Optum	Marketscan	Medicare
Variable	**Value**	**Value**	**Value**
Number of patients in full cohort	6,946	3,694	8,031
Number of patients dropped as incomplete cases	0	0	2
Number of patients that did not begin follow-up	16	5	7
Number of patients in analytic cohort	6,930	3,689	8,022

Number of events	1435	592	1992
Number of person-years	3,277.04	1,877.04	3,093.20
Number of patients in group: ACE Inhibitors - Reference	4,208	2,216	6,286
Number of patients in group: Sacubitril/Valsartan - Exposure	2,722	1,473	1,736
Risk per 1,000 patients	207.07	160.48	248.32
Rate per 1,000 person-years	437.9	315.39	643.99

- Report median follow-up time by treatment group

Patient Group	**Optum Median Follow-Up Time (Days) [IQR]**	**Marketscan Median Follow-Up Time (Days) [IQR]**	**Medicare Median Follow-Up Time (Days) [IQR]**
Overall Patient Population	95 [43, 213]	117 [58, 242]	82 [39, 173]
Referent - ACE Inhibitors	99 [42, 209]	118 [58, 240]	81 [38, 170]
Exposure - Sacubitril/Valsartan	92 [44, 217]	111 [57, 246]	86 [45, 183]

- Report reasons for censoring in the overall study population

	Optum	**Marketscan**	**Medicare**
Overall	6930	3689	8022
Outcome	1,361 (19.6%)	558 (15.1%)	1,933 (24.1%)
Start of an additional exposure	252 (3.6%)	155 (4.2%)	156 (1.9%)
End of Index Exposure	2,445 (35.3%)	1,264 (34.3%)	2,078 (25.9%)
Specified date reached	1,101 (15.9%)	721 (19.5%)	1,964 (24.5%)
End of patient data	0 (0.0%)	0 (0.0%)	0 (0.0%)
End of patient enrollment	645 (9.3%)	713 (19.3%)	691 (8.6%)
Switch to ARBs or Aliskiren + Nursing Home admission Occurred	1,126 (16.2%)	278 (7.5%)	1,200 (15.0%)

8 Initial Power Assessment

Aetion report name:

Optum- https://bwh-dope.aetion.com/projects/details/1069/results/61862/result/0
Marketscan- https://bwh-dope.aetion.com/projects/details/1072/results/61853/result/0
Medicare- https://bwh-dope.aetion.com/projects/details/1073/results/61855/result/0

Date conducted: 11/24/2020

In order to complete the initial power analysis, the dummy outcome of a 90-day gap in database enrollment will be used. Complete a 1:1 PS-matched comparative analysis using this outcome. PS should include only 3 covariates: age, sex, and combined comorbidity index.

- In the appropriate excel sheet below, report number of patients matched in each treatment group. Input the overall risk of outcome from Section 7. Input the desired or assumed HR, alpha level, and non-inferiority margin (if applicable) from the RCT (Section 1.3.1). The number of expected events and corresponding power are then calculated automatically. If the study is to be implemented in more than one database, copy and paste excel sheet to report power for each database separately and for the pooled analysis that uses data from all databases together.

	Optum	Marketscan	Medicare	Pooled
Number of people matched				
Reference	2722.0	1468.0	1736.0	5926.0
Exposure	2722.0	1468.0	1736.0	5926.0
Risk per 1,000 patients	207.1	160.5	248.3	--
Rate per 1,000 person-years	437.9	315.4	644.0	
N of events	1,435	592	1,992	4,019
N of patients (both groups) at Step 1	6,946	3,694	8,031	18,671
Risk per 1,000 patients	206.6	160.3	248.0	215.3

Superiority Analysis (Pooled)	
Number of patients matched	
Reference	5,926
Exposed	5,926
Risk per 1,000 patients	215.25
Desired HR from RCT	0.8
Alpha (2-sided)	0.05
Number of events expected	2551.143
Power	0.99988126

Superiority Analysis (Optum)	
Number of patients matched	
Reference	2,722
Exposed	2,722
Risk per 1,000 patients	207.10
Desired HR from RCT	0.8
Alpha (2-sided)	0.05
Number of events expected	1127.4524
Power	0.9629782

Superiority Analysis (Marketscan)	
Number of patients matched	
Reference	1,468
Exposed	1,468
Risk per 1,000 patients	160.50
Desired HR from RCT	0.8
Alpha (2-sided)	0.05
Number of events expected	471.228
Power	0.677969637

Superiority Analysis (Medicare)	
Number of patients matched	
Reference	1,736
Exposed	1,736
Risk per 1,000 patients	248.30
Desired HR from RCT	0.8
Alpha (2-sided)	0.05
Number of events expected	862.0976
Power	0.905904762

- Stop analyses until feasibility and power are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:	Jessica Franklin	Date reviewed:	12/2/20
Reviewed by FDA:	Ken Quinto	Date reviewed:	12/8/20
Reasons for stopping analysis (if required):			

9. Balance Assessment

Optum- https://bwh-dope.aetion.com/projects/details/1069/results/63131/result/0
Marketscan- https://bwh-dope.aetion.com/projects/details/1072/results/63129/result/0
Medicare- https://bwh-dope.aetion.com/projects/details/1073/results/63128/result/0

Date conducted: 12/22/2020

After review of initial feasibility and power analyses, complete creation of the remaining covariates from Section 6.2. Again, using the

dummy outcome of a 90-day gap in database enrollment, complete a 1:1 PS-matched analysis. The PS should include the complete list of covariates.

- Provide plot of PS distributions stratified by treatment group.

  Note- Please refer to **Appendix B**.

- Report covariate balance after matching.

  Note- For Table 1, please refer to **Appendix B**.

- Report reasons for censoring by treatment group.

	Overall	**Referent**	**Exposure**
Dummy outcome	0 (0%)	0 (0%)	0 (0%)
Death	150 (2.47%)	64 (2.11%)	86 (2.84%)
Start of an additional exposure	309 (5.09%)	106 (3.49%)	203 (6.69%)
End of Index Exposure	2285 (37.67%)	1206 (39.76%)	1079 (35.58%)
Specified date reached	1868 (30.79)	879 (28.98%)	989 (32.61%)
End of patient enrollment	696 (11.47%)	366 (12.07%)	330 (10.88%)
Switch to ARBs or Aliskiren + Nursing Home admission Occurred	758 (12.50%)	412 (13.58%)	346 (11.41%)

- Report follow-up time by treatment group.

Patient Group	Optum Median Follow-Up Time (Days) [IQR]	Marketscan Median Follow-Up Time (Days) [IQR]	Medicare Median Follow-Up Time (Days) [IQR]
Overall Patient Population	118 [58, 286]	139 [59, 296]	102 [46, 189]
Referent - ACE Inhibitors	126 [60, 309]	142 [77, 295]	102 [42, 170]
Exposure - Sacubitril/Valsartan	108 [56, 266]	136 [58, 300]	106 [58, 218]

- Report overall risk of the primary outcome.

	Optum	MarketScan	Medicare	Pooled
Risk per 1,000 patients	206.6	160.3	248.0	215.3

6. Final Power Assessment

Date conducted: 12/22/2020

- Re-calculate power in the appropriate excel table, using the revised number of matched patients from the PS-match in Section 9. All other parameters in the table should be the same as in Section 8.

Superiority Analysis (Pooled)	
Number of patients matched	
Reference	3,033
Exposed	3,033
Risk per 1,000 patients	215.25
Desired HR from RCT	0.8
Alpha (2-sided)	0.05
Number of events expected	1305.7065
Power	0.980850168

Superiority Analysis (Optum)	
Number of patients matched	
Reference	1,279
Exposed	1,279
Risk per 1,000 patients	206.60
Desired HR from RCT	0.8
Alpha (2-sided)	0.05
Number of events expected	528.4828
Power	0.727390963

Superiority Analysis (Marketscan)	
Number of patients matched	
Reference	748
Exposed	748
Risk per 1,000 patients	160.30
Desired HR from RCT	0.8
Alpha (2-sided)	0.05
Number of events expected	239.8088
Power	0.408308308

Superiority Analysis (Medicare)	
Number of patients matched	
Reference	1,006
Exposed	1,006
Risk per 1,000 patients	248.30
Desired HR from RCT	0.8
Alpha (2-sided)	0.05
Number of events expected	499.5796
Power	0.703266933

- Stop analyses until balance and final power assessment are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:	Jessica Franklin	Date reviewed:	12/26/20
Reviewed by FDA:		Date reviewed:	
Reasons for stopping analysis (if required):			

References

Desai RJ, Lin KJ, Patorno E, et al. Development and Preliminary Validation of a Medicare Claims–Based Model to Predict Left Ventricular Ejection Fraction Class in Patients With Heart Failure. Circ: Cardiovascular Quality and Outcomes. 2018;11(12). doi:10.1161/CIRCOUTCOMES.118.004700

McMurray JJV, Packer M, Desai AS, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. New England Journal of Medicine. 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077

Appendix A

#	PARADIGM-HF trial definitions	Implementation in routine care	Please see the following Google Drive for further details or any missing information : https://drive.google.com/drive/folders/1WD618wrywYjEaXzfLTcuK-VCcnb6b-gV	
	Trial details - active comparision - 2 weeks run-in		ICD-10 codes are not listed in this document because of excel cell size limitations and excessive number of ICD-10 codes. Full ICD-10 code lists will be available in the above Google Drive Folder (link above). ICD-9 to ICD-10 code conversions were completed using a SAS macro that implements forward/ backward mapping based on the CMS ICD-9 to ICD-10 mapping: https://www.nber.org/data/icd9-icd-10-cm-and-pcs-crosswalk-general-equivalence-mapping.html	
	EXPOSURE vs. COMPARISON		References/Rationale	Color coding
	LCZ696 (sacubitril/valsartan) 200 mg twice daily vs. enalapril 10 mg twice daily Aim: To determine if LCZ696 is superior to enalapril in reducing the risk of death and of hospitalization for HF	Sacubitril/valsartan vs. enalapril Exposure: new-use of sacubitril/valsartan Reference: enalapril		Criteria
	PRIMARY OUTCOME			Adequate mapping in claims
	The primary outcome is a composite of death from cardiovasclar causes or hositalization for heart failure	**Measured 14 days after drug initiation in diagnosis position specified below and inpatient care setting:** **Hospital admission for CHF (Inpatient only, any position)** ICD-9 diagnosis: 428.x, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93 ICD-10 diagnosis: I50.1, I50.2x, I50.4, I50.814, I09.81, I11.0 (hypertensive heart disease with HF), I13.0 (hypertensive heart and chronic kidney disease with HF and stage 1 through stage 4 CKD), I13.2 (hypertensive heart and CKD with HF and with stage 5 CKD or ESRD) **CV death** Inpatient mortality - heart failure -- Mortality- Dependent on data source. 1. CV mortality Information on CV mortality through data linkage with the National Death Index (NDI) will be available for Medicare and Optum Clinformatics. 2. All-cause inpatient mortality Identified using the discharge status codes- Optum- • 20 = EXPIRED • 21 = EXPIRED TO BE DEFINED AT STATE LEVEL • 22 = EXPIRED TO BE DEFINED AT STATE LEVEL • 23 = EXPIRED TO BE DEFINED AT STATE LEVEL • 24 = EXPIRED TO BE DEFINED AT STATE LEVEL		Intermediate mapping in claims
	INCLUSION CRITERIA			Poor mapping or cannot be measured in claims
1	Age ≥ 18 years	Age 18 years or older **at drug initiation**		Can't be measured in claims but not important for the analysis
2	NYHA functional class II–IV	**Measured 45 days prior to and including the day of oral drug initiation in generic prescription claims requiring 28 days supply of Loop or Thiazide diuretics** **Loop Diuretics:** Bumetanide, Furosemide, Torsemide, Ethacrynic acid **-OR-** **Thiazide and Thiazide-like Diuretics:** Hydrochlorothiazide, Chlorothiazide, Chlorthalidone, Indapamine, Metolazone, Cyclothiazide, Hydroflumethiazide, Bendroflumethiazide, Benzthiazide, Methyclothiazide, Polythiazide		
3	**LVEF ≤ 35%**	**Measured 180 days prior to and including the day of index drug initiation in any diagnosis position and inpatient or outpatient care setting** **Systolic Heart Failure** ICD-9 diagnosis: 428.2x ICD-10 diagnosis: I50.2x **Combined Systolic/Diastolic Heart Failure** ICD-9 diagnosis: 428.4x ICD-10 diagnosis: I50.4x		
4	Plasma BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL at the screening visit and a hospitalization for HF within the last 12 months			
4a	*Plasma BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL at the screening visit*			
	AND the following:			

Appendix A

4b	*Hospitalization for heart failure within the last 12 months*	**Meaured 365 days prior to drug initiation in any diagnosis position and inpatient care setting** **Hospital Admission for CHF** ICD-9 diagnosis: 428.x, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93 ICD-10 diagnosis: I50.1, I50.2x, I50.4, I50.814, I09.81, I11.0, I13.0, I13.2	
5	Treatment with a **stable dose** of an ACE inhibitor **or** an ARB **equivalent to enalapril 10 mg/day** for at least 4 weeks before the screening visit; and treatment with a stable dose of a beta-blocker for at least 4 weeks prior to the screening visit, unless contraindicted or not tolerated		
5a	*Treatment with a **stable dose** of an ACE inhibitor **or** an ARB **equivalent to enalapril 10 mg/day** for at least 4 weeks before the screening visit*	**Measured 47 days to 2 days prior to drug initiation in prescription claims requiring 28 days supply of oral ACEi or ARB -** **ACE inibitors' generic names for prescription claims:** Enalapril, Captopril, Cilazapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolapril, Zofenopril, Benazepril **-OR-** **ARBs generic names for prescription claims:** Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan, Azilsartan	
	AND the following:		
5b	*Treatment with a **stable dose of a beta-blocker for at least 4 weeks** prior to the screening visit, unless contraindicated or not tolerated*	**Measured 45 days prior to index drug initiation in prescription claims (generic names) of an oral beta-blocker for at least 4 weeks (28 days)** **Beta-blocker generic names for prescription claims:** Acebutolol, Atenolol, Betaxolol, Bisoprolol, Carteolol, Carvedilol, Esmolol, Labetalol, Metoprolol, Metiranolol, Nebivolol, Nadolol, Propranolol, Pindolol, Sotalol, Penbutolol, Oxprenolol	
6	Although not required, the protocol specified that an aldosterone antagonist should also be considered in all patients, taking account of renal function, serum potassium, and tolerability. If given, the dose of aldosterone antagonist should be stable for at least 4 weeks prior to the screening visit		
	EXCLUSION CRITERIA		
1	History of hypersensitivity or allergy to any of the study drugs, drugs of similar chemical classes, ACE inhibitors (ACEIs), ARBs, or neprilysin inhibitors, as well as known or suspected contraindications to the study drugs		
2	Previous history of intolerance to recommended target doses of ACEIs or ARBs		
3	Known history of **angioedema**	**Measured from the start of all available data to index drug initiation in any diagnosis position and inpatient or outpatient care setting** ICD-9 diagnosis: 995.1 ICD-10 diagnosis: T78.3x	
4	Requirement for treatment with **both ACEIs and ARBs**	**Measured 180 days prior to and including day of drug initiation in prescription claims (generic names) for any of oral ACEi and ARB for two subsequent dispensings** **ACE inibitors' generic names for prescription claims:** Enalapril, Captopril, Cilazapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolapril, Zofenopril, Benazepril **-AND-** **ARBs generic names for prescription claims:** Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan, Azilsartan	
5	**Current acute decompensated heart failure** (exacerbation of chronic heart failure manifested by signs and symptoms that may require intravenous therapy)	**Measured 7 days prior to and including day of drug initiation in any diagnosis position and inpatient and emergency care setting** ICD-9 diagnosis: 428.41, 428.43 ICD-10 diagnosis: I50.23, I50.41, I50.43	
6	**Symptomatic hypotension** and/or a **systolic blood pressure <100 mmHg** at Visit 1 (screening) or **<95 mmHg** at Visit 3 or at Visit 5 (randomization)	**Measured 30 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting** **Hypotension:** ICD-9 diagnosis: 458.xx, 785.5x ICD-10 diagnosis: I95.xx, R57.xx	

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7	Estimated glomerular filtration rate **(eGFR) <30 mL/min/1.73 m2** at Visit 1 (screening), Visit 3 (end of enalapril run-in), or Visit 5 (end of LCZ696 run-in and randomization) or **>35% decline in eGFR between Visit 1 and Visit 3** or **between Visit 1 and Visit 5**	**Measured 30 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting** **Acute kidney injury (AKI)** ICD-9 diagnosis: 584.xx, 586 ICD-10 diagnosis: N17.x, N19 **Acute glomerulnephritis** ICD-9 diagnosis: 580.xx ICD-10 diagnosis: N00.3, N00.8, N00.9, N01.3 **Chronic Kidney Disease (CKD)** - Stage IV and V ICD-9 diagnosis: 585.4, 585.5 ICD-10 diagnosis: N18.4, N18.5 **ESRD** ICD-9 diagnosis: 403.01, 403.11, 403.91, 404.03, 404.13, 585.6 ICD-10 diagnosis: I12.0, N18.6 **Hemodialysis/Peritoneal Dialysis** ICD-9 diagnosis: V45.1x, V56.xx, 996.56, 996.68, 996.73 ICD-10 diagnosis: Z49.xx, Z91.15, Z99.2, T85.611x, T85.621x, T85.631x, T85.691x, T85.71x ICD-9 procedure: 39.95, 54.98 ICD-10 procedure: 5A1D70Z, 5A1D80Z, 5A1D90Z, 3E1M39Z CPT-4 code: 90935, 90937, 90939	
8	Serum potassium **>5.2 mmol/L** at Visit 1 (screening) **or >5.4 mmol/L** at Visit 3 or Visit 5 (randomization)	**Measured 30 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting** **Hyperkalemia** ICD-9 diagnosis: 276.7 ICD-10 diagnosis: E87.5	
9	Acute coronary syndrome, stroke, transient ischaemic attack, cardiac, carotid, or other major cardiovascular surgery, PCI, or carotid angioplasty within the 3 months prior to Visit 1.	**Measured 90 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting** **Acute Coronary Syndrome: STEMI & NSTEMI** ICD-9 diagnosis: 410.xx (exclude 410.x2), 411.0 ICD-10 diagnosis: I21.xx, I22.xx, I23.xx **Acute Coronary Syndrome: Unstable Angina** ICD-9 diagnosis: 413.xx (exclude 413.1), 411.1, 411.8, 411.81, 411.89 ICD-10 diagnosis: I20.xx (exclude I20.1), I24.xx (exclude 124.1) **Stroke** ICD-9 diagnosis: 430.xx, 431.xx, 433.x1, 434.xx (*excluding* 434.x0), 436.x, 997.02 ICD-10 diagnosis: G97.3x, I60.xx, I61.xx I62.xx, I63.xx, I67.89, I97.81x, I97.82x **TIA** ICD-9 diagnosis: 435.xx ICD-10 diagnosis: G45.xx **CABG/ Transmyocardial Revascularization** ICD-9 diagnosis: V45.81, 996.03 ICD-10 diagnosis: Z95.1 ICD-9 procedure: 36.1x, 36.2, 36.3x ICD-10 procedure: Refer to "CABG & Revascularization" tab within this spreadsheet for complete list of procedure codes	
10	Coronary or carotid artery disease likely to require surgical or **percutaneous intervention within the 6 months after Visit 1**	Included above	
11	Implantation of a **cardiac resynchronization therapy (CRT) device** within **3 months prior Visit 1** or **intent to implant a CRT**	**Measured 90 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting** **Pacemaker and Implantable cardiac Defibillators:** ICD-9 diagnosis: V45.01, V45.02, V45.09, V53.31, V53.32, 996.01, 996.04, 996.61 ICD-10 diagnosis: Z95.0, Z95.810, Z45.010, Z45.018, Z45.02, T82.110A, T82.111A, T82.120A, T82.121A, T82.190A, T82.191A, T82.6XXA, T82.7XXA ICD-9 procedure: 00.50, 00.51, 00.53, 00.54, 37.7x, 37.8x, 37.94 - 37.98 ICD-10 procedure: Refer to "CRT_Implant" tab CPT-4 code: 33200 - 33208, 33220 - 33229, 33230 - 33238, 33240 - 33249, 33262 - 33264, 33270, 33271, 93640 - 93642, 93280 - 93289, 93290 - 93299	

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12	History of heart transplant or on a transplant list or with LV assistance device	**Measured from all available data to and including the day of drug initiation in any diagnosis position and inpatient or outpatient care setting** **Heart Transplantation** ICD-9 diagnosis: V42.1, V49.83, 996.83 ICD-10 diagnosis: Z94.1, Z76.82, T86.20, T86.21, T86.22 ICD-9 procedure: 33.6, 37.51 ICD-10 procedure: 02YA0Z0, 02YA0Z1, 02YA0Z2 CPT-4 code: 33935, 33945 **LVAD/Implantable Heart** ICD-9 diagnosis: V43.2x ICD-10 diagnosis: Z95.811, Z95.812 ICD-9 procedure: 37.60, 37.66 ICD-10 procedure: 02HA0RS, 02HA3RS, 02HA4RS, 5A02116, 5A02216, 02HA0QZ, 02HA3QZ, 02HA4QZ CPT-4 code: 33975, 33976, 33979, 33981 - 33983, 33977, 33978, 33980	
13	History of severe pulmonary disease	**Measured from all available data to and including day of drug initiation in any diagnosis position and in inpatient or outpatient care setting** **Worsening Asthma/Status Asthmaticus** ICD-9 diagnosis: 493.01, 493.02, 493.11, 493.12, 493.2x, 493.91, 493.22 ICD-10 diagnosis: J45.21, J45.22, J45.901, J45.902 **COPD/Chronic Tuberclosis** ICD-9 diagnosis: 491.xx, 492.xx, 494.x, 496, 506.4, 748.61, 011.5x ICD-10 diagnosis: J41.x, J43.x, J47.x, J44.x, J68.4, Q33.4, A15.0 **Pulmonary Firbrosis or Interstitial Lung Disease (ILD)** ICD-9 diagnosis: 515, 516.3x, 516.8, 516.9 ICD-10 diagnosis: J84.10, J84.111, J84.112, J84.113, J84.114, J84.115, J84.116, J84.117, J84.09, J84.2, J84.89, J84.9 **Cystic Fibrosis** ICD-9 diagnosis: 277.0x ICD-10 diagnosis: E84.xx **Pulmonary Hypertension/Other Pulmonary Heart Disease** ICD-9 diagnosis: 416.xx ICD-10 diagnosis: I27.xx **Sarcoidosis**	Pulmonary firbrosis/Interstitial lung disease: Jones N, Schneider G, Kachroo S, et al. A systematic review of validated methods for identifying pulmonary fibrosis and interstitial lung disease using administrative and claims data. Pharmacoepidemiol Drug Saf. 2012;21(1):256-60. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22262614.
14	Diagnosis of peripartum- or chemotherapy-induced cardiomyopathy within the 12 months prior to Visit 1	**Measured from 365 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting** **Peripartum Cardiomyopathy** ICD-9 diagnosis: 674.5x ICD-10 diagnosis: O90.3 **Chemotherapy-Induced Cardiomyopathy** ICD-9 diagnosis: 425.9 ICD-10 diagnosis: I42.7	
15	*Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Visit 1*		
15a	Documented ventricular arrhythmia within the 3 months prior to Visit 1	**Measured 90 days prior to and including day of drug initiation in any diagnosis position and inpatient and outpatient care setting** ICD-9 diagnosis: 427.1, 427.4x, 427.5 ICD-10 diagnosis: I47.2, I49.01, I49.02, I46.9	
	AND the following:		
15b	Syncopal episodes within the 3 months prior to Visit 1	**Measured 90 days prior to and including day of drug initiation in any diagnosis position and inpatient and outpatient care setting** **Syncopal Episodes** ICD-9 diagnosis: 780.2 ICD-10 diagnosis: R55	
	AND the following:		

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15c	Untreated ventricular arrhythmia within the 3 months prior to visit 1	**Measured 90 days prior to and including day of drug initiation WITHOUT any of these non-drug treatments for ventricular tachycardia in any diagnosis position and inpatient and outpatient care setting** **Implantable Cardioverter-Defbrillator** ICD-9 diagnosis: V45.00, V45.02, V45.09, V53.32, 996.04, 996.61 ICD-10 diagnosis: Z95.9, Z95.810, Z95.818, Z45.02, T82.110A, T82.111A, T82.120A, T82.121A, T82.190A, T82.191A ICD-9 procedure: 00.51, 00.54, 37.94 - 37.98 ICD-10 procedure: 02HK0KZ, 02HK3KZ, 02HK4KZ, 02HL0KZ, 02HL3KZ, 02HL4KZ, 0JH609Z, 0JH639Z, 0JH809Z, 0JH839Z CPT-4 code: 33220, 33223, 33230, 33231, 33240 - 33249, 33262 - 33264, 33270, 93640 - 93642, 93280 - 93285, 93287, 93289, 93292, 93295	
	OR the following:		
15d	Untreated ventricular arrhythmia within the 3 months prior to visit 1	**Measured 90 days prior to and including day of drug initiation WITHOUT any of these oral drug treatments for ventricular arrythmia in prescription claims** **Beta-blockers:** Acebutolol, Atenolol, Betaxolol, Bisoprolol, Carteolol, Carvedilol, Labetalol, Metoprolol, Metiranolol, Nebivolol, Nadolol, Propranolol, Pindolol, Sotalol, Penbutolol, Oxprenolol **Non-DHP CCB:** Diltiazem, Verapamil **Antiarrhythmic drugs:** Amiodarone, Procainamide, Mexiletine, Flecainide, Moricizine	
16	Symptomatic bradycardia or second- or third-degree atrioventricular block without a pacemaker	**Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient and outpatient care setting** **Second- and Third-degree AV block** ICD-9 diagnosis: 426.0, 426.1x (except 426.11) ICD-10 diagnosis: I44.2, I44.30, I44.1	
17	Presence of haemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation secondary to LV dilatation	**Measured 180 days prior to and including day of drug initiation in any diagnosis position and in inpatient and outpatient care setting** ICD-9 diagnosis: 394.0, 395.0, 395.2, 396.0, 396.2, V42.2, V43.3 ICD-10 diagnosis: I05.0, I06.0, I06.2, I08.0, Z95.3, Z95.2 ICD-9 procedure: 35.01, 35.02, 35.05, 35.06, 35.11, 35.12, 35.21, 35.22, 35.23, 35.24, 35.97 ICD-10 procedure: 02NF3ZZ, 02NF4ZZ, 02NG3ZZ, 02NG4ZZ, 02RF372, 02RF38Z, 02RF3JZ, 02RF3KZ, X2RF332, 02RF37H, 02RF38H, 02RF3JH, 02RF3KH, 027F04Z, 027F0DZ, 027F0ZZ, 02NF0ZZ, 02QF0ZZ, 027G04Z, 027G0DZ, 027G0ZZ, 02NG0ZZ, 02QG0ZZ, 02VG0ZZ, 02RF07Z, 02RF08Z, 02RF0KZ, 02RF47Z, 02RF48Z, 02RF4KZ, X2RF032, X2RF432, 02RF0JZ, 02RF4JZ, 02RG07Z, 02RG08Z, 02RG0KZ, 02RG37Z, 02RG38Z, 02RG3KZ, 02RG47Z, 02RG48Z, 02RG4KZ, 02RG0JZ, 02RG3JZ, 02RG4JZ 02UG3JZ CPT-4 codes: 33400 - 33403, 33405, 33406, 33420 - 33430, 0257T, 0258T, 0259T	
18	Presence of other haemodynamically significant obstructive lesions of the LV outflow tract, including aortic and subaortic stenosis	Included in the definition of exclusion criterion # 17	
19	*Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs, including, but not limited to, any of the following:*		
19a	History of active inflammatory bowel disease during the 12 months before Visit 1	**Measured 365 days prior to and including day of drug initiation in any diagnosis position in inpatient and outpaient care setting** **Ulcerative Colitis** ICD-9 diagnosis: 556.xx ICD-10 diagnosis: K51.xx **Crohn's Disease** ICD-9 diagnosis: 555.x ICD-10 diagnosis: K50.xx	Thirumurthi S, Chowdhury R, Richardson P, Abraham NS. Validation of ICD-9-CM diagnostic codes for inflammatory bowel disease among veterans. Dig Dis Sci. 2010 Sep;55(9):2592-8. doi: 10.1007/s10620-009-1074-z. Epub 2009 Dec 24. PubMed PMID: 20033847
	OR the following:		
19b	Active duodenal or gastric ulcers during the 3 months prior to Visit 1	**Measured 90 days prior to and including day of drug initiation in any diagnosis position in inpatient and outpaient care setting** **Duodenal Ulcers** ICD-9 diagnosis: 532.0x, 532.1x, 532.2x, 532.3x, 532.9x ICD-10 diagnosis: K25.0 - K25.3, K25.9 **Gastric Ulcers** ICD-9 diagnosis: 531.0x, 531.1x, 531.2x, 531.3x, 531.9x ICD-10 diagnosis: K26.0 - K26.3, K26.9	
	OR the following:		

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19c	Evidence of hepatic disease as determined by any one of the following: aspartate aminotransferase or alanine aminotransferase values exceeding 2× upper limit of normal at Visit 1, history of hepatic encephalopathy, history of oesophageal varices, or history of porto-caval shunt	**Measured from the start of all available data of drug initiation in any diagnosis position in inpatient and outpaient care setting** **Hepatic Encephalopathy/Coma** ICD-9 diagnosis: 070.0, 070.2x, 070.4x, 070.6, 070.71, 572.2 ICD-10 diagnosis: B15.0, B16.0, B16.2, B17.11, B19.0, B19.11, B19.21, K72.90, K72.91 **Esophageal Varicies** ICD-9 diagnosis: 456.0, 456.1, 456.2x, 572.3 ICD-10 diagnosis: I85.xx, K76.6 **Porto-Caval Shunt** ICD-9 procedure: 39.1, 42.91 ICD-10 procedure: Codes are in the sheet 'PCShunt' CPT-4 code: 37182, 37183, 37241 **Cirrohosis/Chronic Hepatic Diseases** ICD-9 diagnosis: 571.0, 571.2, 571.3, 571.4, 571.5, 571.6 ICD-10 diagnosis: K70.0, K70.30, K70.9, K73.0, K73.2, K73.8, K73.9, K75.4, K74.0, K74.60, K74.69, K74.3, K74.4, K74.5, K74.1 **NASH** ICD-9 diagnosis: 571.8, ICD-10 diagnosis: K76.0	
	OR the following:		
19d	Current **treatment with cholestyramine** or **colestipol resins**	**Measured 30 days prior to and including the day of index drug initiation for oral generic prescription claims of** Cholestyramine, Colestipol, Colesevelam	
20	Presence of any other disease with a life expectancy of 5 years	Charlson Comborbidity Index > 10	
21	Any Ivabradine use -- Approved in April 2015 (same year as Entresto)	**Measure since 2015/all available data in drug prescription claims for any dispensings of** Generic name: Ivabradine Brand name: Corlanor	

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	Variable	Codes and Medications (all medical claims, inpatient and outpatient should be used to define the coniditions unless otherwise specified)	Coefficients ("Score")	When Measured for replicating	When Measured (Rishi's algorithm)
1	Intercept	N/A	-1.37219		
2	Cardiomyopathy	ICD-9 diagnosis: 425.x ICD-10 diagnosis: I42.x, I43.x	1.415113	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
3	Diastolic heart failure	ICD-9 diagnosis: 428.3x (*not co-occuring with 428.2x*) ICD-10 diagnosis: I50.3x (*not co-occuring with I50.2x*)	-0.950856	Measured between 180 days prior to and including the date of drug initiation and **pick claim closest to the index initiation**	on index date
4	Left heart failure	ICD-9 diagnosis: 428.1x (*not co-occuring with more specific systolic or diastolic HF codes of 428.2x or 428.3x*) ICD-10 diagnosis: I50.1 (*not co-occuring with more specific systolic or diastolic HF codes of I50.2x or I50.3x*)	0.766415	Measured between 180 days prior to and including the date of drug initiation and **pick claim closest to the index initiation**	on index date
5	Systolic heart failure	ICD-9 diagnosis: 428.2x (*not co-occuring with 428.3x*) ICD-10 diagnosis: I50.2x *(not co-occuring with I50.3x)*	0.754954	Measured between 180 days prior to and including the date of drug initiation and **pick claim closest to the index initiation**	on index date
6	Myocardial infarction	ICD-9 diagnosis: 410.xx ICD-10 diagnosis: I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I22.0, I22.1, I22.2, I22.8, I22.9	0.651778	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
7	Unspecified heart failure	ICD-9 diagnosis: 428.0x, 428.4x, 428.9x, 428.2x PLUS 428.3x ICD-10 diagnosis: I50.4x, I50.8x, I50.9, I50.2x PLUS I50.3x	-0.577221	Measured between 180 days prior to and including the date of drug initiation and **pick claim closest to the index initiation**	on index date
8	Number of hospitalizations for CHF	ICD-9 diagnosis: 428.x, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93 ICD-10 diagnosis: I50.1, I50.2x, I50.4, I50.814, I09.81, I11.0, I13.0, I13.2	0.346289	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date (including index date)
9	Male gender	Male	0.323651	Measured on the date of index drug initiation	on index date
10	Implantable cardioverter defibrillator	ICD-9 diagnosis: V45.02 ICD-10 diagnosis: Z95.810 ICD-9 procedure: 37.94 - 37.98 ICD-10 procedure: Please copy from ICD-10 codes tabs for implantable cardioverter defibrillator	0.275032	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index

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11	ACE inhibitor	Prescription claims for: Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril	0.221748	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
12	Index diagnosis recorded during an outpatient visit	Any diagnosis position in an **outpatient care setting** ICD-9 diagnosis: 428.x, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93 ICD-10 diagnosis: I50.1, I50.2x, I50.4x, I50.814, I09.81, I11.0, I13.0, I13.2	-0.187191	Measured between 180 days prior to and including the date of drug initiation and **pick claim closest to the index initiation**	on index date
13	Mineralocorticoid receptor antagonist	Prescription claims for: Eplerenone, spironolactone	0.166008	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
14	Anemia	ICD-9 diagnosis: 280.xx - 285.xx ICD-10 diagnosis: Please copy from ICD-10 codes tabs for anemia	-0.165353	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
15	Valve disorder	ICD-9 diagnosis: 394.x - 397.x, 398.9x, V42.2, V43.3 ICD-10 diagnosis: Please copy from ICD-10 codes tabs for valve disorder ICD-9 procedure: 35.1x, 35.2x ICD-10 procedure: Please copy from ICD-10 codes tabs for valve disorder CPT code: 33660-33665, 33400-33403, 33420-33430, 33460, 33463-33468, 33475, 33496, 0257T, 0258T, 0259T, 0262T	-0.163684	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
16	Digoxin	Prescription claims for: Digoxin	0.163224	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
17	Thiazide diuretic	Prescription claims for: Bendroflumethiazide, Benzthiazide, Chlorothiazide, Chlorthalidone, Hydrochlorothiazide, Indapamide, Methyclothiazide, Metolazone, Polythiazide, Quinethazone, Trichlormethiazide	-0.160819	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
18	Obesity	ICD-9 diagnosis: 278.00, 278.01, V85.3x, V85.4x ICD-10 diagnosis: E65.x, E66.x, E67.x, E68.x CPT codes: 43842, 43843, 43846, 43847, 43848, G0447 Prescriptions claims for: orlistat, sibutramine, phentermine, benzphetamine, phendimetrazine, diethylpropion	-0.141956	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
19	Nitrate	Prescription claims for: Nitroglycerin, isosorbide dinitrate, isosorbide mononitrate, ranolazine	0.129225	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
20	Other dysrythmias	ICD-9 diagnosis: 427.0x, 427.1x, 427.2x, 427.4x, 427.6x, 427.8x, 427.9x, 785.0x ICD-10 diagnosis: Please copy from ICD-10 tab for other dysrythmias	0.116652	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
21	Hypertension	ICD-9 diagnosis: 401.xx, 402.xx, 405.xx ICD-10 diagnosis: I10, I11.0, I11.9, I12.0, I12.9, I13.0, I13.10, I13.11, I13.2, I15.0, I15.1, I15.2, I15.8, I15.9	-0.098539	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index

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22	Beta blocker	Prescription claims for oral: Acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, labetalol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol	0.087257	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
23	Loop diuretic	Prescription claims for oral: Bumetanide, furosemide, torsemide, ethacrynic acid	0.084251	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
24	Rheumatic heart disease	ICD-9 diagnosis: 393 - 398.x ICD-10 diagnosis: I05.xx - I09.xx	-0.073889	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
25	Psychosis	ICD-9 diagnosis: 290.8x, 290.9x, 295.xx, 297.xx, 298.xx, 299.xx, 780.0x - 780.5x ICD-10 diagnosis: Please copy from ICD-10 tab for Psychosis	-0.068198	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
26	Coronary artery bypass graft	ICD-9 procedure: 36.1x, 36.2x ICD-10 procedure: Please copy from ICD-10 tab for CABG CPT code: 33510 – 33536, 33545, 33572	-0.040175	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
27	COPD	ICD-9 diagnosis: 491.xx, 492.xx, 496.xx, 493.2x ICD-10 diagnosis: J41.x, J42.x, J43.x, J44.x	-0.037023	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
28	Sleep apnea	ICD-9 diagnosis: 327.2x, 780.51, 780.53, 780.57 ICD-10 diagnosis: G47.3x	-0.03556	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
29	Hypertensive nephropathy	ICD-9 diagnosis: 403.xx, 404.xx ICD-10 diagnosis: I12.x, I13.xx	-0.03383	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
30	Depression	ICD-9 diagnosis: 293.83, 296.2x, 296.3x, 296.9x, 298.0x, 300.4x, 309.1x, 309.28, 311.xx ICD-10 diagnosis: F06.3x, F32.x, F33.x, F34.x, F39.x, F43.21, F43.23	-0.033829	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
31	Hypotension	ICD-9 diagnosis: 458.xx ICD-10 diagnosis: I95.x	-0.017282	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
32	Stable angina	ICD-9 diagnosis: 413.xx ICD-10 diagnosis: Please copy from ICD-10 tab for stable angina	-0.015657	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
33	Age	Continous	-0.005747	Measured on the date of index drug initiation	on index date

Appendix A

34	Atrial fibrillation	ICD-9 diagnosis: 427.3x ICD-10 diagnosis: I48.x	-0.002267	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index
35	Hyperlipidemia	ICD-9 diagnosis: 272.xx ICD-10 diagnosis: E78.xx	-0.001805	Measured 180 days prior to and including the date of index drug initiation	6 months prior to index date + index date + 30days post-index

Appendix A

Mortality- Dependent on data source.

1. All-cause mortality / inpatient mortality
Identified using the vital status file-

Medicare
Identified using the discharge status codes-

Optum-
- 20 = EXPIRED
- 21 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 22 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 23 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 24 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 25 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 26 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 27 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 28 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 29 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 40 = EXPIRED AT HOME (HOSPICE)
- 41 = EXPIRED IN A MEDICAL FACILITY (HOSPICE)
- 42 = EXPIRED - PLACE UNKNOWN (HOSPICE)

Truven-
- 20 - Died
- 22 - Died
- 23 - Died
- 24 - Died
- 25 - Died
- 26 - Died
- 27 - Died
- 28 - Died
- 29 - Died
- 40 - Other died status or Expired at home (Hospice claims only) (depends on year)
- 41 - Other died status or Expired in medical facility (Hospice claims only) (depends on year)
- 42 - Other died status or Expired - place unknown (Hospice claims only) (depends on year)
- 21 - Died or Disch./Transf. to court/law enforcement (depends on year)

Appendix A

CPT-4 Code Range
33010 - 33050
33120 - 33130
33140 - 33141
33200 - 33249
33250 - 33275
33300 - 33340
33361 - 33478
33496
33500 - 33507
33600 - 33622
33641 - 33697
33702 - 33722
33724 - 33732
33735 - 33768
33770 - 33783
33786 - 33788
33800 - 33853
33860 - 33877
33880 - 33891
33910 - 33926
33962 - 33993
33999

ICD-9 Procedure Codes	ICD-10 Procedure Codes
36.91, 36.99	02Q00ZZ, 02Q03ZZ, 02Q04ZZ, 02Q40ZZ, 02Q43ZZ, 02Q44ZZ, 02H40YZ, 02H43YZ, 02H44YZ, 02N00ZZ, 02N03ZZ, 02N04ZZ, 02N10ZZ, 02N13ZZ, 02N14ZZ, 02N20ZZ, 02N23ZZ, 02N24ZZ, 02N30ZZ, 02N33ZZ, 02N34ZZ, 02Q00ZZ, 02Q03ZZ, 02Q04ZZ, 02Q40ZZ, 02Q43ZZ, 02Q44ZZ
37.0, 37.1x, 37.3x, 37.4x, 37.5x (exclude 37.51), 37.6x	0W9D30Z, 0W9D30Z, 0W9D3ZX, 0W9D3ZX, 0W9D3ZZ, 0W9D3ZZ, 0W9D40Z, 0W9D40Z, 0W9D4ZX, 0W9D4ZX, 0W9D4ZZ, 0W9D4ZZ, 02N60ZZ, 02N60ZZ, 02N63ZZ, 02N63ZZ, 02N64ZZ, 02N64ZZ, 02N70ZZ, 02N70ZZ, 02N73ZZ, 02N73ZZ,

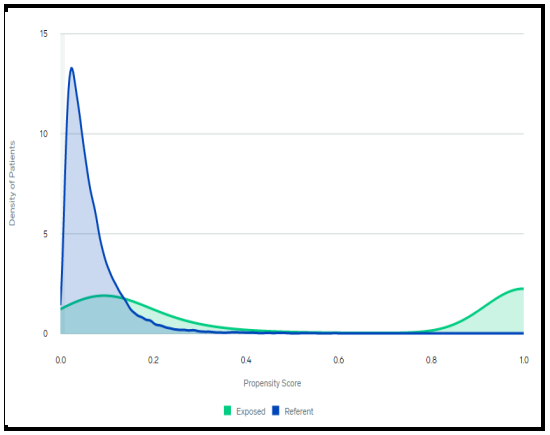
Appendix A

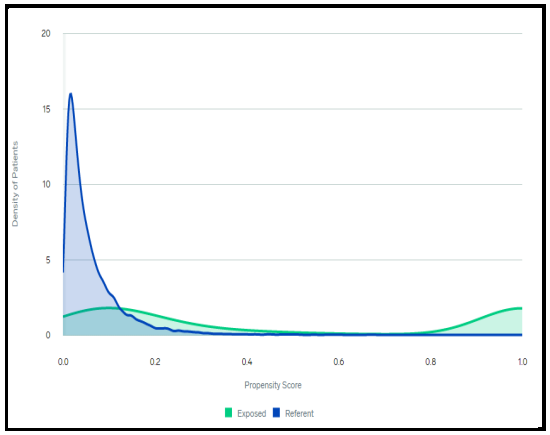
Trial ID	pNDA32
Trial Name (with web links)	PARADIGM-HF
Trial Name (with pdf links)	PARADIGM-HF
NCT	NCT01035255
Trial category	Primary indication
Therapeutic Area	Cardiology/Vascular Diseases
Study batch	Heart failure medications
RCT Category	1a- Intended S with label change
Brand Name	Entresto
Generic Name	Sacubitril/valsartan
Sponsor	Novartis
Year	2015
Measurable endpoint	Composite endpoint including death from cardiovascular causes or and hospitalization for heart failure
Exposure	LCZ696 200 mg
Comparator	Enalapril 10 mg
Population	80% Diuretic, 29% Digitalis, 93% β blocker, 54% Mineralocorticoid antagonists, 15% ICD & 7% CRT users
Trial finding	HR = 0.80 (95% CI 0.73– 0.87)
Notes	
No. of Patients	8442
Non-inferiority margin	-
Assay Sens. Outcome	
Assay Sens. Endpoint (from trial)	
Finding for potential Assay Sens. Outcome from trial-	
Power	
Blinding	Double-blinded
Statistical Method	
Approval indication	To reduce the risk of CV death and hospitalization for heart failure in patient swith chronic heart failure (NYHA class II-IV) and reduced rejection fraction

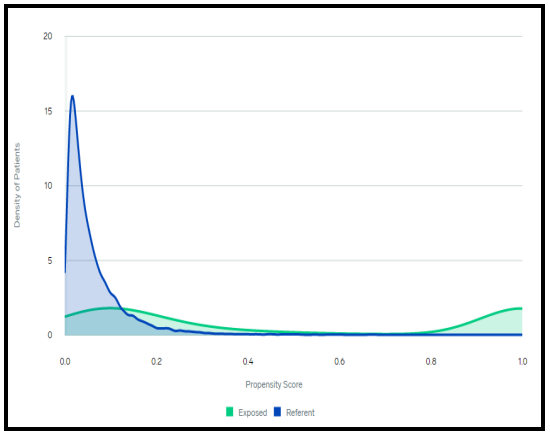
Appendix B: Sacubitril/Valsartan vs. ACE Inhibitors

Optum	MarketScan	Medicare

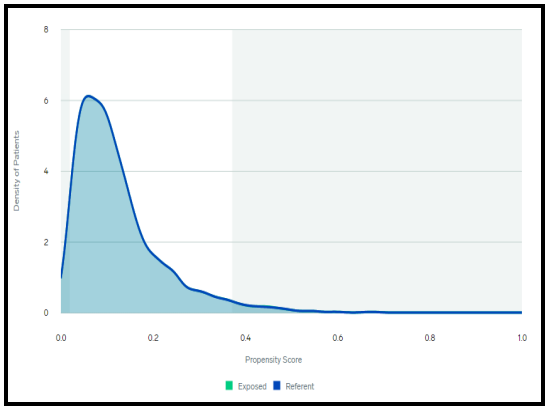
BEFORE PS MATCHING

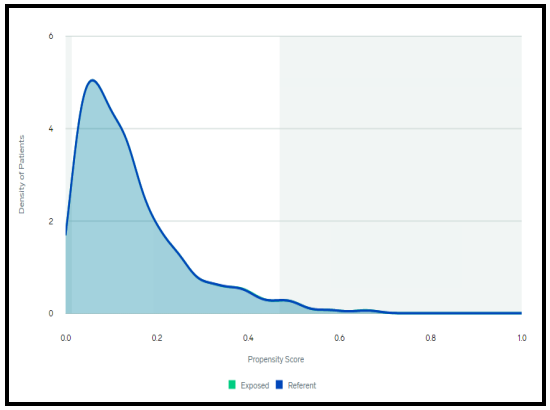


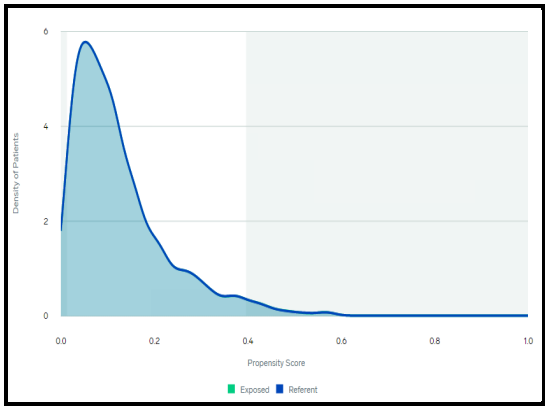




AFTER PS MATCHING







Appendix B: Sacubitril/Valsartan vs. ACE Inhibitors

	BEFORE MATCHING											
	OPTUM			MARKETSCAN			MEDICARE			POOLED		
Variable	Reference - ACE inhibitors	Exposure - Sacubitril/valsartan	St. Diff	Reference - ACE inhibitors	Exposure - Sacubitril/valsartan	St. Diff	Reference - ACE Inhibitors	Exposure - Sacubitril/valsartan Copy	St. Diff	Reference - ACE Inhibitors	Exposure - Sacubitril/valsartan Copy	St. Diff
Number of patients	17,244	2,424		10,721	1,289		18,303	1,658		46,268	5,371	
Age - Continuous												
...mean (sd)	69.53 (11.82)	68.49 (12.18)	0.0867	63.95 (14.26)	60.92 (13.48)	0.2184	76.02 (7.61)	74.09 (8.22)	0.1351	71.23 (11.22)	69.00 (11.33)	0.1978
...median [IQR]	71.00 [63.00, 78.00]	70.00 [61.00, 78.00]	0.0833	63.00 [55.00, 75.00]	60.00 [52.00, 69.00]	0.2162	76.00 [70.00, 83.00]	75.00 [70.00, 81.00]	0.1262	71.12 (11.22)	69.14 (11.33)	0.1756
Age Categories												
...18 - 54; n (%)	1,882 (10.9%)	332 (13.7%)	-0.0853	2,583 (24.1%)	377 (29.2%)	-0.1155	0 (0.0%)	0 (0.0%)	#DIV/0!	4,465 (9.7%)	709 (13.2%)	-0.1101
...55 - 64; n (%)	3,133 (18.2%)	468 (19.3%)	-0.0282	3,626 (33.8%)	504 (39.1%)	-0.1103	0 (0.0%)	0 (0.0%)	#DIV/0!	6,759 (14.6%)	972 (18.1%)	-0.0947
...65 - 74; n (%)	5,925 (34.4%)	807 (33.3%)	0.0232	1,785 (16.6%)	169 (13.1%)	0.0985	7,965 (43.5%)	777 (46.9%)	-0.0684	13,890 (30.0%)	1,584 (29.5%)	0.0109
...>= 75; n (%)	6,304 (36.6%)	817 (33.7%)	0.0608	2,727 (25.4%)	239 (18.5%)	0.1673	10,338 (56.5%)	881 (53.1%)	0.0684	16,642 (36.0%)	1,698 (31.6%)	0.0931
Gender												
...Male; n (%)	11,865 (68.8%)	1,549 (63.9%)	0.1038	7,721 (72.0%)	882 (68.4%)	0.0788	10,308 (56.3%)	951 (57.4%)	-0.0222	22,173 (47.9%)	2,500 (46.5%)	0.0280
...Female; n (%)	5,379 (31.2%)	875 (36.1%)	-0.1038	3,000 (28.0%)	407 (31.6%)	-0.0788	7,995 (43.7%)	707 (42.6%)	0.0222	13,374 (28.9%)	1,582 (29.5%)	-0.0132
Region without zero category Copy												
...Northeast; n (%)	2,101 (12.2%)	273 (11.3%)	0.0280	2,048 (19.1%)	244 (18.9%)	0.0051	3,372 (18.4%)	321 (19.4%)	-0.0255	5,473 (11.8%)	594 (11.1%)	0.0220
...Midwest; n (%)	8,056 (46.7%)	1,390 (57.3%)	-0.2134	3,548 (33.1%)	302 (23.4%)	0.2167	7,376 (40.3%)	771 (46.5%)	-0.1253	15,432 (33.4%)	2,161 (40.2%)	-0.1414
...South; n (%)	3,985 (23.1%)	416 (17.2%)	0.1475	4,096 (38.2%)	636 (49.3%)	-0.2252	4,795 (26.2%)	357 (21.5%)	0.1105	8,780 (19.0%)	773 (14.4%)	0.1236
...West; n (%)	3,086 (17.9%)	342 (14.1%)	0.1038	1,015 (9.5%)	106 (8.2%)	0.0458	2,760 (15.1%)	209 (12.6%)	0.0724	5,846 (12.6%)	551 (10.3%)	0.0723
...Unknown+missing; n (%)	16 (0.1%)	3 (0.1%)	0.0000	14 (0.1%)	1 (0.1%)	0.0000						
Calendar Time - Year of Initiation (2015/16 - 2020)												
...2015-2016; n (%)	4,935 (28.6%)	253 (10.4%)	0.4720	6,045 (56.4%)	380 (29.5%)	0.5647	11,756 (64.2%)	607 (36.6%)	0.5743	16,691 (36.1%)	860 (16.0%)	0.4705
...2017; n (%)	3,881 (22.5%)	500 (20.6%)	0.0462	2,610 (24.3%)	438 (34.0%)	-0.2147	6,547 (35.8%)	1,051 (63.4%)	-0.5743	10,428 (22.5%)	1,551 (28.9%)	-0.1469
...2018; n (%)	3,960 (23.0%)	622 (25.7%)	-0.0629	2,066 (19.3%)	471 (36.5%)	-0.3907	0 (0.0%)	0 (0.0%)	#DIV/0!	3,960 (8.6%)	622 (11.6%)	-0.0997
...2019 - 2020; n (%)	4,468 (25.9%)	1,049 (43.3%)	-0.3721	0 (0.0%)	0 (0.0%)	#DIV/0!	0 (0.0%)	0 (0.0%)	#DIV/0!	4,468 (9.7%)	1,049 (19.5%)	-0.2802
Combined comorbidity score, 180 days												
...mean (sd)	5.30 (2.55)	5.29 (2.40)	0.0040	4.21 (2.23)	4.21 (2.12)	0.0000	5.30 (2.72)	4.75 (2.39)	0.2148	5.05 (2.55)	4.86 (2.33)	0.0778
...median [IQR]	5.00 [3.00, 7.00]	5.00 [3.00, 7.00]	0.0000	4.00 [3.00, 5.00]	4.00 [3.00, 5.00]	0.0000	5.00 [3.00, 7.00]	4.00 [3.00, 6.00]	0.3906	4.77 (2.55)	4.45 (2.33)	0.1310
CV Comorbidity - Pulmonary hypertension/Other pulmonary heart disease ; n (%)	2,893 (16.8%)	506 (20.9%)	-0.1050	1,274 (11.9%)	218 (16.9%)	-0.1428	3,611 (19.7%)	369 (22.3%)	-0.0639	6,504 (14.1%)	875 (16.3%)	-0.0613
CV Comorbidity - Other dysrythmias ; n (%)	9,611 (55.7%)	1,383 (57.1%)	-0.0282	5,648 (52.7%)	685 (53.1%)	-0.0080	9,911 (54.1%)	854 (51.5%)	0.0521	19,522 (42.2%)	2,237 (41.6%)	0.0122
CV Comorbidity - Valve disorder ; n (%)	2,246 (13.0%)	442 (18.2%)	-0.1437	657 (6.1%)	80 (6.2%)	-0.0042	2,921 (16.0%)	323 (19.5%)	-0.0917	5,167 (11.2%)	765 (14.2%)	-0.0902
CV Comorbidity - Hospitalization for heart failure; n (%)	13,310 (77.2%)	1,891 (78.0%)	-0.0192	8,185 (76.3%)	971 (75.3%)	0.0234	15,029 (82.1%)	1,198 (72.3%)	0.2352	28,339 (61.2%)	3,089 (57.5%)	0.0754
CV Comorbidity - Implantable cardioverter defibrillator ; n (%)	4,746 (27.5%)	641 (26.4%)	0.0248	2,170 (20.2%)	319 (24.7%)	-0.1080	2,292 (12.5%)	249 (15.0%)	-0.0726	7,038 (15.2%)	890 (16.6%)	-0.0383
CV Comorbidity - Hypotension; n (%)	2,300 (13.3%)	294 (12.1%)	0.0360	1,109 (10.3%)	112 (8.7%)	0.0546	3,148 (17.2%)	235 (14.2%)	0.0825	5,448 (11.8%)	529 (9.8%)	0.0645
CV Comorbidity - Hypertension; n (%)	15,907 (92.2%)	2,298 (94.8%)	-0.1056	9,139 (85.2%)	1,140 (88.4%)	-0.0946	17,177 (93.8%)	1,591 (96.0%)	-0.1001	33,084 (71.5%)	3,889 (72.4%)	-0.0200
CV Comorbidity - Coronary atherosclerosis and other forms of chronic ischemic heart disease ; n (%)	11,601 (67.3%)	1,788 (73.8%)	-0.1430	6,342 (59.2%)	753 (58.4%)	0.0163	12,704 (69.4%)	1,286 (77.6%)	-0.1866	24,305 (52.5%)	3,074 (57.2%)	-0.0946
CV Comorbidity - Hyperlipidemia ; n (%)	12,847 (74.5%)	1,968 (81.2%)	-0.1619	6,470 (60.3%)	782 (60.7%)	-0.0082	13,795 (75.4%)	1,390 (83.8%)	-0.2096	26,642 (57.6%)	3,358 (62.5%)	-0.1002
CV Comorbidity - Unstable Angina (Inpatient or Outpatient) ; n (%)	2,054 (11.9%)	312 (12.9%)	-0.0303	1,149 (10.7%)	126 (9.8%)	0.0297	1,978 (10.8%)	209 (12.6%)	-0.0560	4,032 (8.7%)	521 (9.7%)	-0.0346
CV Comorbidity - Implantation of CRT device; n (%)	6,249 (36.2%)	845 (34.9%)	0.0272	3,356 (31.3%)	457 (35.5%)	-0.0891	3,595 (19.6%)	357 (21.5%)	-0.0470	9,844 (21.3%)	1,202 (22.4%)	-0.0266
CV Comorbidity - Stable Angina ; n (%)	2,435 (14.1%)	452 (18.6%)	-0.1219	1,114 (10.4%)	143 (11.1%)	-0.0226	2,085 (11.4%)	293 (17.7%)	-0.1794	4,520 (9.8%)	745 (13.9%)	-0.1271
CV Comorbidity - Stroke/TIA; n (%)	1,680 (9.7%)	179 (7.4%)	0.0823	848 (7.9%)	67 (5.2%)	0.1093	2,531 (13.8%)	151 (9.1%)	0.1480	4,211 (9.1%)	330 (6.1%)	0.1134
CV Comorbidity - Peripheral Vascular Disease (PVD) or PVD Surgery; n (%)	2,927 (17.0%)	376 (15.5%)	0.0407	1,096 (10.2%)	119 (9.2%)	0.0338	4,607 (25.2%)	378 (22.8%)	0.0562	7,534 (16.3%)	754 (14.0%)	0.0642
CV Comorbidity - Myocardial Infarction; n (%)	5,921 (34.3%)	817 (33.7%)	0.0127	2,982 (27.8%)	298 (23.1%)	0.1081	6,043 (33.0%)	543 (32.8%)	0.0043	11,964 (25.9%)	1,360 (25.3%)	0.0137
CV Comorbidity - Atrial fibrillation; n (%)	8,728 (50.6%)	1,103 (45.5%)	0.1022	4,718 (44.0%)	476 (36.9%)	0.1450	10,418 (56.9%)	870 (52.5%)	0.0885	19,146 (41.4%)	1,973 (36.7%)	0.0965
CV Comorbidity - CABG/PCI; n (%)	5,216 (30.2%)	865 (35.7%)	-0.1172	1,948 (18.2%)	181 (14.0%)	0.1145	5,049 (27.6%)	586 (35.3%)	-0.1664	10,265 (22.2%)	1,451 (27.0%)	-0.1116
CV Medication - ACE inhibitors; n (%)	17,244 (100.0%)	1,288 (53.1%)	1.3291	10,721 (100.0%)	764 (59.3%)	1.1716	18,303 (100.0%)	1,018 (61.4%)	1.1213	35,547 (76.8%)	2,306 (42.9%)	0.7370
CV Medication - Use of ARBs ; n (%)	570 (3.3%)	1,271 (52.4%)	-1.3091	340 (3.2%)	629 (48.8%)	-1.2169	804 (4.4%)	727 (43.8%)	-1.0379	1,374 (3.0%)	1,998 (37.2%)	-0.9436
CV Medication - Beta blocker ; n (%)	17,106 (99.2%)	2,414 (99.6%)	-0.0518	10,629 (99.1%)	1,284 (99.6%)	-0.0623	18,163 (99.2%)	1,645 (99.2%)	0.0000	35,269 (76.2%)	4,059 (75.6%)	0.0140
CV Medication - Digoxin ; n (%)	2,468 (14.3%)	299 (12.3%)	0.0589	1,512 (14.1%)	187 (14.5%)	-0.0114	3,069 (16.8%)	268 (16.2%)	0.0162	5,537 (12.0%)	567 (10.6%)	0.0442
CV Medication - SGLT-2 Inhibitors ; n (%)	215 (1.2%)	82 (3.4%)	-0.1472	176 (1.6%)	40 (3.1%)	-0.0991	91 (0.5%)	13 (0.8%)	-0.0373	306 (0.7%)	095 (1.8%)	-0.0991
CV Medication - Loop diuretic ; n (%)	13,101 (76.0%)	2,053 (84.7%)	-0.2203	7,601 (70.9%)	1,099 (85.3%)	-0.3536	14,036 (76.7%)	1,424 (85.9%)	-0.2376	27,137 (58.7%)	3,477 (64.7%)	-0.1237
CV Medication - Thiazide diuretics ; n (%)	1,358 (7.9%)	301 (12.4%)	-0.1494	957 (8.9%)	158 (12.3%)	-0.1106	1,716 (9.4%)	204 (12.3%)	-0.0933	3,074 (6.6%)	505 (9.4%)	-0.1033
CV Medication - Mineralocorticoid receptor antagonist ; n (%)	5,642 (32.7%)	1,112 (45.9%)	-0.2728	3,722 (34.7%)	678 (52.6%)	-0.3669	4,839 (26.4%)	707 (42.6%)	-0.3458	10,481 (22.7%)	1,819 (33.9%)	-0.2506
CV Medication - Nitrate; n (%)	3,470 (20.1%)	542 (22.4%)	-0.0562	2,113 (19.7%)	292 (22.7%)	-0.0734	3,868 (21.1%)	405 (24.4%)	-0.0788	7,338 (15.9%)	947 (17.6%)	-0.0455
CV Medication - PCSK9 Inhibitors; n (%)	22 (0.1%)	7 (0.3%)	-0.0448	12 (0.1%)	5 (0.4%)	-0.0601	7 (0.0%)	1 (0.1%)	-0.0447	029 (0.1%)	008 (0.1%)	0.0000
CV Medication - Use of Statins ; n (%)	12,062 (69.9%)	1,780 (73.4%)	-0.0777	6,996 (65.3%)	837 (64.9%)	0.0084	12,124 (66.2%)	1,209 (72.9%)	-0.1460	24,186 (52.3%)	2,989 (55.7%)	-0.0683
CV Medication - Use of other lipid-lowering drugs ; n (%)	904 (5.2%)	141 (5.8%)	-0.0263	600 (5.6%)	90 (7.0%)	-0.0576	946 (5.2%)	117 (7.1%)	-0.0791	1,850 (4.0%)	258 (4.8%)	-0.0390
CV Medication - CCB (non-dihydropyridine) - Non-combo with ACEi; n (%)	962 (5.6%)	116 (4.8%)	0.0360	573 (5.3%)	44 (3.4%)	0.0932	1,397 (7.6%)	92 (5.5%)	0.0850	2,359 (5.1%)	208 (3.9%)	0.0579
CV Medication - CCB (dihydropyridine) - Non-combo with ACEi, ARB; n (%)	2,589 (15.0%)	418 (17.2%)	-0.0599	1,401 (13.1%)	178 (13.8%)	-0.0205	3,085 (16.9%)	263 (15.9%)	0.0270	5,674 (12.3%)	681 (12.7%)	-0.0121
Other Comorbidity - Osteoporosis ; n (%)	919 (5.3%)	135 (5.6%)	-0.0132	283 (2.6%)	33 (2.6%)	0.0000	1,865 (10.2%)	132 (8.0%)	0.0765	2,784 (6.0%)	267 (5.0%)	0.0439
Other Comorbidity - Dementia ; n (%)	1,767 (10.2%)	151 (6.2%)	0.1462	672 (6.3%)	51 (4.0%)	0.1042	4,311 (23.6%)	170 (10.3%)	0.3602	6,078 (13.1%)	321 (6.0%)	0.2434
Other Comorbidity - Hypothyroidism ; n (%)	721 (4.2%)	87 (3.6%)	0.0310	571 (5.3%)	62 (4.8%)	0.0228	1,863 (10.2%)	97 (5.9%)	0.1585	2,584 (5.6%)	184 (3.4%)	0.1063
Other Comorbidity - Hyperthyroidism ; n (%)	229 (1.3%)	40 (1.7%)	-0.0329	148 (1.4%)	18 (1.4%)	0.0000	321 (1.8%)	33 (2.0%)	-0.0146	550 (1.2%)	073 (1.4%)	-0.0177
Other Comorbidity - Hyperkalemia ; n (%)	1,116 (6.5%)	150 (6.2%)	0.0123	445 (4.2%)	48 (3.7%)	0.0257	1,341 (7.3%)	97 (5.9%)	0.0564	2,457 (5.3%)	247 (4.6%)	0.0323
Other Comorbidity - Depression; n (%)	2,995 (17.4%)	418 (17.2%)	0.0053	1,184 (11.0%)	130 (10.1%)	0.0293	4,488 (24.5%)	305 (18.4%)	0.1490	7,483 (16.2%)	723 (13.5%)	0.0760
Other Comorbidity - COPD ; n (%)	4,922 (28.5%)	719 (29.7%)	-0.0264	1,829 (17.1%)	179 (13.9%)	0.0885	5,826 (31.8%)	463 (27.9%)	0.0853	10,748 (23.2%)	1,182 (22.0%)	0.0287
Other Comorbidity - Pneumonia; n (%)	3,145 (18.2%)	488 (20.1%)	-0.0483	1,642 (15.3%)	215 (16.7%)	-0.0382	4,653 (25.4%)	324 (19.5%)	0.1418	7,798 (16.9%)	812 (15.1%)	0.0491
Other Comorbidity - Acute kidney injury (AKI) ; n (%)	4,102 (23.8%)	541 (22.3%)	0.0356	1,922 (17.9%)	247 (19.2%)	-0.0334	5,227 (28.6%)	375 (22.6%)	0.1378	9,329 (20.2%)	916 (17.1%)	0.0797
Other Comorbidity - CKD Stage 1-2; n (%)	1,021 (5.9%)	155 (6.4%)	-0.0208	325 (3.0%)	29 (2.2%)	0.0503	1,072 (5.9%)	125 (7.5%)	-0.0640	2,093 (4.5%)	280 (5.2%)	-0.0326
Other Comorbidity - CKD Stage 3-4; n (%)	4,224 (24.5%)	588 (24.3%)	0.0047	1,389 (13.0%)	159 (12.3%)	0.0211	4,649 (25.4%)	464 (28.0%)	-0.0588	8,873 (19.2%)	1,052 (19.6%)	-0.0101
Other Comorbidity - Any Chronic Kidney Disease; n (%)	5,817 (33.7%)	830 (34.2%)	-0.0106	1,983 (18.5%)	228 (17.7%)	0.0208	6,713 (36.7%)	639 (38.5%)	-0.0372	12,530 (27.1%)	1,469 (27.4%)	-0.0067
Other Comorbidity - Hemodialysis/Peritoneal dialysis ; n (%)	63 (0.4%)	6 (0.2%)	0.0366	39 (0.4%)	1 (0.1%)	0.0601	88 (0.5%)	0 (0.0%)	0.1003	151 (0.3%)	006 (0.1%)	0.0448
Other Comorbidity - DM Related Complications; n (%)	3,822 (22.2%)	592 (24.4%)	-0.0521	1,701 (15.9%)	237 (18.4%)	-0.0664	4,556 (24.9%)	409 (24.7%)	0.0046	8,378 (18.1%)	1,001 (18.6%)	-0.0129
Other Comorbidity - Diabetic/Hypertensive Nephropathy; n (%)	5,349 (31.0%)	792 (32.7%)	-0.0365	1,996 (18.6%)	266 (20.6%)	-0.0504	4,918 (26.9%)	552 (33.3%)	-0.1399	10,267 (22.2%)	1,344 (25.0%)	-0.0660
Other Comorbidity - Sleep apnea; n (%)	3,567 (20.7%)	628 (25.9%)	-0.1232	2,211 (20.6%)	303 (23.5%)	-0.0700	2,859 (15.6%)	332 (20.0%)	-0.1152	6,426 (13.9%)	960 (17.9%)	-0.1096
Other Comorbidity - Cancer ; n (%)	2,002 (11.6%)	281 (11.6%)	0.0000	1,162 (10.8%)	108 (8.4%)	0.0815	2,905 (15.9%)	228 (13.8%)	0.0591	4,907 (10.6%)	509 (9.5%)	0.0366
Other Comorbidity - Type 1 DM ; n (%)	648 (3.8%)	97 (4.0%)	-0.0103	542 (5.1%)	50 (3.9%)	0.0579	991 (5.4%)	72 (4.3%)	0.0512	1,639 (3.5%)	169 (3.1%)	0.0224
Other Comorbidity - Type 2 DM ; n (%)	8,156 (47.3%)	1,313 (54.2%)	-0.1383	4,297 (40.1%)	581 (45.1%)	-0.1012	8,959 (48.9%)	852 (51.4%)	-0.0500	17,115 (37.0%)	2,165 (40.3%)	-0.0678
Other Comorbidity - Anemia ; n (%)	4,612 (26.7%)	663 (27.4%)	-0.0158	2,276 (21.2%)	250 (19.4%)	0.0448	7,712 (42.1%)	578 (34.9%)	0.1484	12,324 (26.6%)	1,241 (23.1%)	0.0811
Lifestyle - Obesity ; n (%)	4,592 (26.6%)	829 (34.2%)	-0.1658	2,387 (22.3%)	387 (30.0%)	-0.1759	3,922 (21.4%)	399 (24.1%)	-0.0644	8,514 (18.4%)	1,228 (22.9%)	-0.1113
Lifestyle - Alcohol/Drug Abuse or Dependence; n (%)	1,823 (10.6%)	202 (8.3%)	0.0787	821 (7.7%)	87 (6.7%)	0.0387	1,365 (7.5%)	83 (5.0%)	0.1034	3,188 (6.9%)	285 (5.3%)	0.0669
Lifestyle - Smoking; n (%)	7,970 (46.2%)	1,118 (46.1%)	0.0020	2,185 (20.4%)	251 (19.5%)	0.0225	8,146 (44.5%)	681 (41.1%)	0.0688	16,116 (34.8%)	1,799 (33.5%)	0.0274
Other Medication - AGI & Meglitinides ; n (%)	77 (0.4%)	13 (0.5%)	-0.0149	57 (0.5%)	3 (0.2%)	0.0508	132 (0.7%)	10 (0.6%)	0.0124	209 (0.5%)	023 (0.4%)	0.0149
Other Medication - Insulin; n (%)	2,459 (14.3%)	402 (16.6%)	-0.0637	1,444 (13.5%)	195 (15.1%)	-0.0457	2,865 (15.7%)	244 (14.7%)	0.0279	5,324 (11.5%)	646 (12.0%)	-0.0155
Other Medication - Glitazones; n (%)	183 (1.1%)	34 (1.4%)	-0.0270	95 (0.9%)	16 (1.2%)	-0.0294	213 (1.2%)	30 (1.8%)	-0.0494	396 (0.9%)	064 (1.2%)	-0.0294
Other Medication - 1st and 2nd Generation SUs; n (%)	2,076 (12.0%)	335 (13.8%)	-0.0537	1,133 (10.6%)	154 (11.9%)	-0.0412	2,165 (11.8%)	242 (14.6%)	-0.0828	4,241 (9.2%)	577 (10.7%)	-0.0501
Other Medication - DPP-4 Inhibitors ; n (%)	761 (4.4%)	158 (6.5%)	-0.0926	598 (5.6%)	97 (7.5%)	-0.0769	935 (5.1%)	147 (8.9%)	-0.1493	1,696 (3.7%)	305 (5.7%)	-0.0946
Other Medication - GLP-1 RA ; n (%)	326 (1.9%)	101 (4.2%)	-0.1341	210 (2.0%)	47 (3.6%)	-0.0971	151 (0.8%)	24 (1.4%)	-0.0575	477 (1.0%)	125 (2.3%)	-0.1022
Other Medication - Metformin ; n (%)	3,558 (20.6%)	643 (26.5%)	-0.1394	2,040 (19.0%)	292 (22.7%)	-0.0912	3,361 (18.4%)	363 (21.9%)	-0.0873	6,919 (15.0%)	1,006 (18.7%)	-0.0990
Other Medication - NSAIDS (COX-2 Selective) ; n (%)	724 (4.2%)	126 (5.2%)	-0.0473	414 (3.9%)	55 (4.3%)	-0.0202	904 (4.9%)	97 (5.9%)	-0.0443	1,628 (3.5%)	223 (4.2%)	-0.0364
Other Medication - NSAIDS (Non-Selective) ; n (%)	1,212 (7.0%)	221 (9.1%)	-0.0772	1,554 (14.5%)	225 (17.5%)	-0.0819	731 (4.0%)	51 (3.1%)	0.0487	1,943 (4.2%)	272 (5.1%)	-0.0428

Appendix B: Sacubitril/Valsartan vs. ACE Inhibitors

Other Medication - Use of antiplatelet agents ; n (%)	4,412 (25.6%)	695 (28.7%)	-0.0697	3,239 (30.2%)	404 (31.3%)	-0.0238	4,061 (22.2%)	466 (28.1%)	-0.1363	8,473 (18.3%)	1,161 (21.6%)	-0.0826
Other Medication - Use of heparin and other low-molecular weight heparins ; n (%)	370 (2.1%)	42 (1.7%)	0.0293	6 (0.1%)	0 (0.0%)	0.0447	472 (2.6%)	18 (1.1%)	0.1115	842 (1.8%)	060 (1.1%)	0.0586
Other Medication - Use of oral anticoagulants ; n (%)	6,844 (39.7%)	935 (38.6%)	0.0225	4,175 (38.9%)	471 (36.5%)	0.0495	7,403 (40.4%)	690 (41.6%)	-0.0244	14,247 (30.8%)	1,625 (30.3%)	0.0109
Other Medication - Use of other hypertension drugs; n (%)	1,923 (11.2%)	300 (12.4%)	-0.0372	1,199 (11.2%)	179 (13.9%)	-0.0816	2,063 (11.3%)	202 (12.2%)	-0.0280	3,986 (8.6%)	502 (9.3%)	-0.0245
Other Medication - Use of antipsychotics ; n (%)	541 (3.1%)	60 (2.5%)	0.0364	233 (2.2%)	22 (1.7%)	0.0362	1,073 (5.9%)	46 (2.8%)	0.1524	1,614 (3.5%)	106 (2.0%)	0.0918
Other Medication - Use of dementia meds ; n (%)	518 (3.0%)	50 (2.1%)	0.0571	216 (2.0%)	21 (1.6%)	0.0301	1,295 (7.1%)	66 (4.0%)	0.1357	1,813 (3.9%)	116 (2.2%)	0.0990
Other Medication - Use of antiparkinsonian meds ; n (%)	435 (2.5%)	74 (3.1%)	-0.0364	189 (1.8%)	28 (2.2%)	-0.0286	741 (4.0%)	45 (2.7%)	0.0723	1,176 (2.5%)	119 (2.2%)	0.0198
Other Medication - Use of anxiolytics/hypnotics ; n (%)	1,014 (5.9%)	159 (6.6%)	-0.0289	671 (6.3%)	85 (6.6%)	-0.0122	1,137 (6.2%)	123 (7.4%)	-0.0477	2,151 (4.6%)	282 (5.3%)	-0.0323
Other Medication - Use of anticonvulsants ; n (%)	3,043 (17.6%)	403 (16.6%)	0.0266	1,319 (12.3%)	137 (10.6%)	0.0534	3,713 (20.3%)	267 (16.1%)	0.1090	6,756 (14.6%)	670 (12.5%)	0.0614
Other Medication - Use of antidepressants ; n (%)	4,418 (25.6%)	618 (25.5%)	0.0023	2,297 (21.4%)	266 (20.6%)	0.0196	5,702 (31.2%)	454 (27.4%)	0.0836	10,120 (21.9%)	1,072 (20.0%)	0.0467
Other Medication - Use of lithium ; n (%)	14 (0.1%)	2 (0.1%)	0.0000	16 (0.1%)	0 (0.0%)	0.0447	16 (0.1%)	0 (0.0%)	0.0447	030 (0.1%)	002 (0.0%)	0.0447
Other Medication - Use of Benzodiazepine; n (%)	2,208 (12.8%)	328 (13.5%)	-0.0207	1,321 (12.3%)	184 (14.3%)	-0.0589	2,763 (15.1%)	257 (15.5%)	-0.0111	4,971 (10.7%)	585 (10.9%)	-0.0064
Other Medication - Use of opioids ; n (%)	5,405 (31.3%)	712 (29.4%)	0.0413	3,310 (30.9%)	336 (26.1%)	0.1065	6,255 (34.2%)	447 (27.0%)	0.1567	11,660 (25.2%)	1,159 (21.6%)	0.0851
Other Medication - Use of COPD/asthma meds ; n (%)	3,139 (18.2%)	549 (22.6%)	-0.1094	1,703 (15.9%)	265 (20.6%)	-0.1219	3,142 (17.2%)	358 (21.6%)	-0.1114	6,281 (13.6%)	907 (16.9%)	-0.0919
HU - Bone mineral density; n (%)	348 (2.0%)	56 (2.3%)	-0.0207	99 (0.9%)	17 (1.3%)	-0.0384	364 (2.0%)	31 (1.9%)	0.0072	712 (1.5%)	087 (1.6%)	-0.0081
HU - Flexible Sigmoidoscopy or colonoscopy or CT virtual colonoscopy; n (%)	646 (3.7%)	86 (3.5%)	0.0107	440 (4.1%)	54 (4.2%)	-0.0050	789 (4.3%)	63 (3.8%)	0.0254	1,435 (3.1%)	149 (2.8%)	0.0177
HU - Flu vaccine; n (%)	2,851 (16.5%)	446 (18.4%)	-0.0501	1,106 (10.3%)	142 (11.0%)	-0.0227	4,410 (24.1%)	491 (29.6%)	-0.1243	7,261 (15.7%)	937 (17.4%)	-0.0458
HU - Mammogram; n (%)	775 (4.5%)	135 (5.6%)	-0.0503	404 (3.8%)	62 (4.8%)	-0.0493	830 (4.5%)	88 (5.3%)	-0.0371	1,605 (3.5%)	223 (4.2%)	-0.0364
HU - Frailty Score: Empirical Version 365 days												
...mean (sd)	0.23 (0.07)	0.22 (0.06)	0.1534	0.20 (0.06)	0.20 (0.05)	0.0000	0.27 (0.09)	0.24 (0.07)	0.3721	0.24 (0.08)	0.22 (0.06)	0.2828
...median [IQR]	0.21 [0.18, 0.26]	0.21 [0.18, 0.25]	0.0000	0.19 [0.16, 0.23]	0.19 [0.16, 0.21]	0.0000	0.25 [0.20, 0.32]	0.23 [0.19, 0.27]	0.2481	0.22 (0.08)	0.21 (0.06)	0.1414
HU - Number of hospitalizations during CAP												
...mean (sd)	1.06 (0.84)	1.03 (0.76)	0.0375	0.96 (0.74)	0.90 (0.68)	0.0844	1.39 (1.10)	1.04 (0.89)	0.3498	1.17 (0.93)	1.00 (0.78)	0.1981
...median [IQR]	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	0.0000	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	0.0000	1.00 [1.00, 2.00]	1.00 [0.00, 1.00]	0.0000	1.00 (0.93)	1.00 (0.78)	0.0000
HU - Number of Emergency Department (ED) visits												
...mean (sd)	1.71 (2.73)	1.79 (2.36)	-0.0314	2.23 (4.68)	2.17 (3.64)	0.0143	2.07 (2.66)	1.59 (2.55)	0.1842	1.97 (3.26)	1.82 (2.77)	0.0496
...median [IQR]	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	0.0000	0.00 [0.00, 3.00]	0.00 [0.00, 3.00]	0.0000	1.00 [0.00, 3.00]	1.00 [0.00, 2.00]	0.0000	0.77 (3.26)	0.76 (2.77)	0.0033
HU - Number of Internal Medicine/Family Medicine Visits												
...mean (sd)	14.57 (17.87)	14.29 (17.89)	0.0157	9.73 (14.69)	9.03 (13.38)	0.0498	12.75 (15.11)	8.88 (11.78)	0.2857	12.73 (16.10)	11.36 (15.17)	0.0876
...median [IQR]	9.00 [4.00, 19.00]	9.00 [4.00, 19.00]	0.0000	5.00 [2.00, 12.00]	5.00 [2.00, 11.00]	0.0000	8.00 [4.00, 16.00]	6.00 [3.00, 11.00]	0.1476	7.68 (16.10)	7.11 (15.17)	0.0364
HU - Number of Distinct Medication Prescriptions (not generalized to generics)												
...mean (sd)	30.67 (20.95)	34.27 (21.45)	-0.1698	25.34 (13.88)	30.86 (15.63)	-0.3735	27.59 (17.12)	33.01 (17.68)	-0.3115	28.22 (18.00)	33.06 (19.05)	-0.2612
...median [IQR]	26.00 [17.00, 38.00]	30.00 [20.00, 42.00]	-0.1887	23.00 [16.00, 32.00]	28.00 [20.00, 38.00]	-0.3383	24.00 [16.00, 35.00]	29.00 [21.00, 40.00]	-0.2873	24.51 (18.00)	29.21 (19.05)	-0.2536
HU - Number of Cardiologist visits												
...mean (sd)	10.80 (10.03)	13.40 (10.60)	-0.2520	5.27 (7.42)	7.15 (7.98)	-0.2440	8.94 (9.61)	11.44 (11.32)	-0.2381	8.78 (9.32)	11.30 (10.27)	-0.2570
...median [IQR]	8.00 [4.00, 15.00]	11.00 [6.00, 18.00]	-0.2907	3.00 [0.00, 8.00]	5.00 [2.00, 10.00]	-0.2596	6.00 [2.00, 12.00]	9.00 [4.00, 15.00]	-0.2857	6.05 (9.32)	8.94 (10.27)	-0.2947
HU - Number of Electrocardiogram												
...mean (sd)	3.68 (3.91)	4.18 (4.12)	-0.1245	2.90 (2.79)	3.12 (2.87)	-0.0777	3.42 (3.25)	3.63 (3.59)	-0.0613	3.40 (3.42)	3.76 (3.69)	-0.1012
...median [IQR]	3.00 [1.00, 5.00]	3.00 [2.00, 6.00]	0.0000	2.00 [1.00, 4.00]	2.00 [1.00, 4.00]	0.0000	3.00 [1.00, 5.00]	3.00 [1.00, 5.00]	0.0000	2.77 (3.42)	2.76 (3.69)	0.0028
HU - Number of Echocardiogram												
...mean (sd)	2.28 (5.02)	2.58 (4.76)	-0.0613	1.52 (1.70)	1.66 (1.59)	-0.0851	1.33 (1.25)	1.60 (1.40)	-0.2034	1.73 (3.27)	2.06 (3.38)	-0.0992
...median [IQR]	1.00 [0.00, 2.00]	1.00 [1.00, 3.00]	0.0000	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	0.0000	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	0.0000	1.00 (3.27)	1.00 (3.38)	0.0000
SES Proxy - Copay for pharmacy cost (charges in U.S. $)												
...mean (sd)	24.10 (34.04)	26.12 (30.50)	-0.0625	14.67 (18.89)	15.10 (17.86)	-0.0234	22.05 (33.42)	26.07 (29.82)	-0.1269	21.10 (30.93)	23.46 (27.77)	-0.0803
...median [IQR]	14.62 [5.79, 30.27]	18.66 [6.73, 34.59]	-0.1250	10.46 [3.57, 19.54]	12.42 [4.76, 20.28]	-0.1066	12.90 [4.04, 28.02]	18.49 [5.40, 34.97]	-0.1765	12.98 (30.93)	17.11 (27.77)	-0.1405
SES Proxy - Low income indicator; n (%)	3,942 (22.9%)	541 (22.3%)	0.0143	0 (0.0%)	0 (0.0%)	#DIV/0!	0 (0.0%)	0 (0.0%)	#DIV/0!	3,942 (8.5%)	541 (10.1%)	-0.0551
SES Proxy - Business type												
...Commercial; n (%)	3,171 (18.4%)	610 (25.2%)	-0.1653	0 (0.0%)	0 (0.0%)	#DIV/0!	0 (0.0%)	0 (0.0%)	#DIV/0!	3,171 (6.9%)	610 (11.4%)	-0.1566
...Medicare; n (%)	14,073 (81.6%)	1,814 (74.8%)	0.1653	0 (0.0%)	0 (0.0%)	#DIV/0!	0 (0.0%)	0 (0.0%)	#DIV/0!	14,073 (30.4%)	1,814 (33.8%)	-0.0729
SES Proxy - Insurance Plan type												
...Comprehensive; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	2,527 (23.6%)	175 (13.6%)	0.2591	0 (0.0%)	0 (0.0%)	#DIV/0!	2,527 (5.5%)	175 (3.3%)	0.1074
...HMO; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	1,060 (9.9%)	112 (8.7%)	0.0413	0 (0.0%)	0 (0.0%)	#DIV/0!	1,060 (2.3%)	112 (2.1%)	0.0136
...PPO; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	4,951 (46.2%)	686 (53.2%)	-0.1403	0 (0.0%)	0 (0.0%)	#DIV/0!	4,951 (10.7%)	686 (12.8%)	-0.0652
...Others; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	2,183 (20.4%)	316 (24.5%)	-0.0984	0 (0.0%)	0 (0.0%)	#DIV/0!	2,183 (4.7%)	316 (5.9%)	-0.0536
SES Proxy - Dual status code (with Medicaid); n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	0 (0.0%)	0 (0.0%)	#DIV/0!	4,785 (26.1%)	343 (20.7%)	0.1278	4,785 (10.3%)	343 (6.4%)	0.1413

Appendix B: Sacubitril/Valsartan vs. ACE Inhibitors

	AFTER MATCHING											
	OPTUM			MARKETSCAN			MEDICARE			POOLED		
Variable	Reference - ACE inhibitors	Exposure - Sacubitril/valsartan	St. Diff	Reference - ACE inhibitors	Exposure - Sacubitril/valsartan	St. Diff	Reference - ACE Inhibitors	Exposure - Sacubitril/valsartan	St. Diff	Reference - ACE Inhibitors	Exposure - Sacubitril/valsartan	St. Diff
Number of patients	1,279	1,279		748	748		1,006	1,006		3,033	3,033	
Age - Continuous												
...mean (sd)	68.68 (11.85)	67.91 (12.31)	0.0637	59.59 (13.80)	60.00 (13.63)	-0.0299	75.41 (7.47)	75.61 (7.51)	-0.0267	68.67 (11.17)	68.51 (11.33)	0.0142
...median [IQR]	69.00 [61.00, 77.00]	69.00 [60.00, 77.00]	0.0000	58.50 [51.00, 68.00]	60.00 [52.00, 68.00]	-0.1094	74.00 [69.00, 81.00]	75.00 [69.00, 81.00]	-0.1335	68.07 (11.17)	68.77 (11.33)	-0.0622
Age Categories*												
...18 - 54; n (%)	137 (10.7%)	196 (15.3%)	-0.1371	263 (35.2%)	236 (31.6%)	0.0764	0 (0.0%)	0 (0.0%)	#DIV/0!	400 (13.2%)	432 (14.2%)	-0.0291
...55 - 64; n (%)	285 (22.3%)	256 (20.0%)	0.0563	265 (35.4%)	284 (38.0%)	-0.0540	0 (0.0%)	0 (0.0%)	#DIV/0!	550 (18.1%)	540 (17.8%)	0.0078
...65 - 74; n (%)	427 (33.4%)	411 (32.1%)	0.0277	111 (14.8%)	103 (13.8%)	0.0286	514 (51.1%)	492 (48.9%)	0.0440	941 (31.0%)	903 (29.8%)	0.0261
...>= 75; n (%)	430 (33.6%)	416 (32.5%)	0.0234	109 (14.6%)	125 (16.7%)	-0.0578	492 (48.9%)	514 (51.1%)	-0.0440			
Gender												
...Male; n (%)	880 (68.8%)	855 (66.8%)	0.0428	541 (72.3%)	535 (71.5%)	0.0178	589 (58.5%)	604 (60.0%)	-0.0305	1,469 (48.4%)	1,459 (48.1%)	0.0060
...Female; n (%)	399 (31.2%)	424 (33.2%)	-0.0428	207 (27.7%)	213 (28.5%)	-0.0178	417 (41.5%)	402 (40.0%)	0.0305	816 (26.9%)	826 (27.2%)	-0.0068
Region without zero category												
...Northeast; n (%)	142 (11.1%)	140 (10.9%)	0.0064	137 (18.3%)	142 (19.0%)	-0.0180	159 (15.8%)	195 (19.4%)	-0.0946	301 (9.9%)	335 (11.0%)	-0.0360
...Midwest; n (%)	722 (56.5%)	715 (55.9%)	0.0121	202 (27.0%)	180 (24.1%)	0.0665	482 (47.9%)	469 (46.6%)	0.0260	1,204 (39.7%)	1,184 (39.0%)	0.0143
...South; n (%)	227 (17.7%)	247 (19.3%)	-0.0412	370 (49.5%)	366 (48.9%)	0.0120	232 (23.1%)	221 (22.0%)	0.0263	459 (15.1%)	468 (15.4%)	-0.0083
...West; n (%)	188 (14.7%)	177 (13.8%)	0.0257	39 (5.2%)	60 (8.0%)	-0.1130	133 (13.2%)	121 (12.0%)	0.0362	321 (10.6%)	298 (9.8%)	0.0264
...Unknown+missing; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	0 (0.0%)	0 (0.0%)	#DIV/0!						
Calendar Time - Year of Initiation (2015/16 - 2020)												
...2015-2016; n (%)	146 (11.4%)	153 (12.0%)	-0.0187	229 (30.6%)	233 (31.1%)	-0.0108	355 (35.3%)	374 (37.2%)	-0.0395	797 (26.3%)	785 (25.9%)	0.0091
...2017; n (%)	293 (22.9%)	280 (21.9%)	0.0240	264 (35.3%)	256 (34.2%)	0.0231	651 (64.7%)	632 (62.8%)	0.0395	293 (9.7%)	280 (9.2%)	0.0171
...2018; n (%)	321 (25.1%)	319 (24.9%)	0.0046	255 (34.1%)	259 (34.6%)	-0.0105	0 (0.0%)	0 (0.0%)	#DIV/0!	321 (10.6%)	319 (10.5%)	0.0033
...2019 - 2020; n (%)	519 (40.6%)	527 (41.2%)	-0.0122	0 (0.0%)	0 (0.0%)	#DIV/0!	0 (0.0%)	0 (0.0%)	#DIV/0!	519 (40.6%)	527 (41.2%)	-0.0122
Combined comorbidity score, 180 days												
...mean (sd)	5.30 (2.47)	5.27 (2.43)	0.0122	4.24 (2.12)	4.19 (2.06)	0.0239	4.77 (2.49)	4.76 (2.40)	0.0041	4.86 (2.40)	4.83 (2.33)	0.0127
...median [IQR]	5.00 [4.00, 7.00]	5.00 [3.00, 7.00]	0.0000	4.00 [3.00, 6.00]	4.00 [3.00, 5.00]	0.0000	4.00 [3.00, 6.00]	4.00 [3.00, 6.00]	0.0000	4.42 (2.40)	4.42 (2.33)	0.0000
CV Comorbidity - Pulmonary hypertension/Other pulmonary heart disease ; n (%)	250 (19.5%)	257 (20.1%)	-0.0151	132 (17.6%)	126 (16.8%)	0.0212	209 (20.8%)	223 (22.2%)	-0.0341	459 (15.1%)	480 (15.8%)	-0.0194
CV Comorbidity - Other dysrythmias ; n (%)	735 (57.5%)	736 (57.5%)	0.0000	424 (56.7%)	409 (54.7%)	0.0403	506 (50.3%)	519 (51.6%)	-0.0260	1,241 (40.9%)	1,255 (41.4%)	-0.0102
CV Comorbidity - Valve disorder ; n (%)	254 (19.9%)	237 (18.5%)	0.0356	46 (6.1%)	49 (6.6%)	-0.0205	202 (20.1%)	203 (20.2%)	-0.0025	456 (15.0%)	440 (14.5%)	0.0141
CV Comorbidity - Hospitalization for heart failure; n (%)	1,041 (81.4%)	1,051 (82.2%)	-0.0207	602 (80.5%)	593 (79.3%)	0.0299	743 (73.9%)	740 (73.6%)	0.0068	1,784 (58.8%)	1,791 (59.1%)	-0.0061
CV Comorbidity - Implantable cardioverter defibrillator ; n (%)	328 (25.6%)	303 (23.7%)	0.0441	170 (22.7%)	170 (22.7%)	0.0000	137 (13.6%)	145 (14.4%)	-0.0231	465 (15.3%)	448 (14.8%)	0.0140
CV Comorbidity - Hypotension; n (%)	167 (13.1%)	169 (13.2%)	-0.0030	67 (9.0%)	73 (9.8%)	-0.0274	160 (15.9%)	150 (14.9%)	0.0277	327 (10.8%)	319 (10.5%)	0.0097
CV Comorbidity - Hypertension; n (%)	1,206 (94.3%)	1,208 (94.4%)	-0.0043	666 (89.0%)	658 (88.0%)	0.0313	972 (96.6%)	960 (95.4%)	0.0613	2,178 (71.8%)	2,168 (71.5%)	0.0067
CV Comorbidity - Coronary atherosclerosis and other forms of chronic ischemic heart disease ; n (%)	959 (75.0%)	946 (74.0%)	0.0229	436 (58.3%)	427 (57.1%)	0.0243	780 (77.5%)	788 (78.3%)	-0.0193	1,739 (57.3%)	1,734 (57.2%)	0.0020
CV Comorbidity - Hyperlipidemia ; n (%)	1,026 (80.2%)	1,020 (79.7%)	0.0125	446 (59.6%)	446 (59.6%)	0.0000	830 (82.5%)	835 (83.0%)	-0.0132	1,856 (61.2%)	1,855 (61.2%)	0.0000
CV Comorbidity - Unstable Angina (Inpatient or Outpatient) ; n (%)	161 (12.6%)	173 (13.5%)	-0.0267	78 (10.4%)	81 (10.8%)	-0.0130	146 (14.5%)	139 (13.8%)	0.0201	307 (10.1%)	312 (10.3%)	-0.0066
CV Comorbidity - Implantation of CRT device; n (%)	428 (33.5%)	409 (32.0%)	0.0320	239 (32.0%)	239 (32.0%)	0.0000	193 (19.2%)	205 (20.4%)	-0.0301	621 (20.5%)	614 (20.2%)	0.0075
CV Comorbidity - Stable Angina ; n (%)	232 (18.1%)	241 (18.8%)	-0.0180	94 (12.6%)	79 (10.6%)	0.0625	203 (20.2%)	184 (18.3%)	0.0482	435 (14.3%)	425 (14.0%)	0.0086
CV Comorbidity - Stroke/TIA; n (%)	81 (6.3%)	101 (7.9%)	-0.0623	44 (5.9%)	45 (6.0%)	-0.0042	83 (8.3%)	90 (8.9%)	-0.0214	164 (5.4%)	191 (6.3%)	-0.0384
CV Comorbidity - Peripheral Vascular Disease (PVD) or PVD Surgery; n (%)	192 (15.0%)	189 (14.8%)	0.0056	69 (9.2%)	68 (9.1%)	0.0035	230 (22.9%)	238 (23.7%)	-0.0189	422 (13.9%)	427 (14.1%)	-0.0058
CV Comorbidity - Myocardial Infarction; n (%)	450 (35.2%)	447 (34.9%)	0.0063	190 (25.4%)	182 (24.3%)	0.0255	363 (36.1%)	362 (36.0%)	0.0021	813 (26.8%)	809 (26.7%)	0.0023
CV Comorbidity - Atrial fibrillation; n (%)	576 (45.0%)	562 (43.9%)	0.0221	258 (34.5%)	275 (36.8%)	-0.0480	537 (53.4%)	524 (52.1%)	0.0260	1,113 (36.7%)	1,086 (35.8%)	0.0187
CV Comorbidity - CABG/PCI; n (%)	478 (37.4%)	478 (37.4%)	0.0000	142 (19.0%)	120 (16.0%)	0.0790	369 (36.7%)	374 (37.2%)	-0.0104	847 (27.9%)	852 (28.1%)	-0.0045
CV Medication - ACE inhibitors; n (%)	1,279 (100.0%)	1,279 (100.0%)	#DIV/0!	748 (100.0%)	748 (100.0%)	#DIV/0!	1,006 (100.0%)	1,006 (100.0%)	#DIV/0!	2,285 (75.3%)	2,285 (75.3%)	0.0000
CV Medication - Use of ARBs ; n (%)	118 (9.2%)	127 (9.9%)	-0.0238	92 (12.3%)	89 (11.9%)	0.0123	75 (7.5%)	81 (8.1%)	-0.0224	193 (6.4%)	208 (6.9%)	-0.0201
CV Medication - Beta blocker ; n (%)	1,273 (99.5%)	1,273 (99.5%)	0.0000	747 (99.9%)	746 (99.7%)	0.0448	998 (99.2%)	999 (99.3%)	-0.0116	2,271 (74.9%)	2,272 (74.9%)	0.0000
CV Medication - Digoxin ; n (%)	162 (12.7%)	158 (12.4%)	0.0091	104 (13.9%)	106 (14.2%)	-0.0086	172 (17.1%)	160 (15.9%)	0.0323	334 (11.0%)	318 (10.5%)	0.0161
CV Medication - SGLT-2 Inhibitors ; n (%)	48 (3.8%)	42 (3.3%)	0.0270	18 (2.4%)	22 (2.9%)	-0.0311	2 (0.2%)	5 (0.5%)	-0.0508	050 (1.6%)	047 (1.5%)	0.0081
CV Medication - Loop diuretic ; n (%)	1,078 (84.3%)	1,081 (84.5%)	-0.0055	645 (86.2%)	637 (85.2%)	0.0286	880 (87.5%)	859 (85.4%)	0.0614	1,958 (64.6%)	1,940 (64.0%)	0.0125
CV Medication - Thiazide diuretics ; n (%)	147 (11.5%)	155 (12.1%)	-0.0186	82 (11.0%)	88 (11.8%)	-0.0252	97 (9.6%)	119 (11.8%)	-0.0712	244 (8.0%)	274 (9.0%)	-0.0359
CV Medication - Mineralocortcoid receptor antagonist ; n (%)	573 (44.8%)	578 (45.2%)	-0.0080	393 (52.5%)	386 (51.6%)	0.0180	443 (44.0%)	427 (42.4%)	0.0323	1,016 (33.5%)	1,005 (33.1%)	0.0085
CV Medication - Nitrate; n (%)	289 (22.6%)	277 (21.7%)	0.0217	172 (23.0%)	160 (21.4%)	0.0385	245 (24.4%)	230 (22.9%)	0.0353	534 (17.6%)	507 (16.7%)	0.0239
CV Medication - PCSK9 Inhibitors; n (%)*	0 (0.0%)	3 (0.2%)	-0.0633	2 (0.3%)	1 (0.1%)	0.0448	3 (0.3%)	0 (0.0%)	0.0776	003 (0.1%)	003 (0.1%)	0.0000
CV Medication - Use of Statins ; n (%)	907 (70.9%)	926 (72.4%)	-0.0333	495 (66.2%)	475 (63.5%)	0.0566	728 (72.4%)	743 (73.9%)	-0.0339	1,635 (53.9%)	1,669 (55.0%)	-0.0221
CV Medication - Use of other lipid-lowering drugs ; n (%)	67 (5.2%)	68 (5.3%)	-0.0045	44 (5.9%)	48 (6.4%)	-0.0208	81 (8.1%)	71 (7.1%)	0.0377	148 (4.9%)	139 (4.6%)	0.0141
CV Medication - CCB (non-dihydropyridine) - Non-combo with ACEi; n (%)	50 (3.9%)	58 (4.5%)	-0.0299	22 (2.9%)	27 (3.6%)	-0.0395	58 (5.8%)	59 (5.9%)	-0.0043	108 (3.6%)	117 (3.9%)	-0.0158
CV Medication - CCB (dihydropyridine) - Non-combo with ACEi, ARB; n (%)	205 (16.0%)	208 (16.3%)	-0.0082	113 (15.1%)	110 (14.7%)	0.0112	133 (13.2%)	143 (14.2%)	-0.0291	338 (11.1%)	351 (11.6%)	-0.0158
Other Comorbidity - Osteoporosis ; n (%)	60 (4.7%)	57 (4.5%)	0.0095	21 (2.8%)	16 (2.1%)	0.0453	74 (7.4%)	74 (7.4%)	0.0000	134 (4.4%)	131 (4.3%)	0.0049
Other Comorbidity - Dementia ; n (%)	102 (8.0%)	91 (7.1%)	0.0341	36 (4.8%)	36 (4.8%)	0.0000	94 (9.3%)	94 (9.3%)	0.0000	196 (6.5%)	185 (6.1%)	0.0165
Other Comorbidity - Hypothyroidism ; n (%)	40 (3.1%)	48 (3.8%)	-0.0384	28 (3.7%)	34 (4.5%)	-0.0404	76 (7.6%)	63 (6.3%)	0.0511	116 (3.8%)	111 (3.7%)	0.0053
Other Comorbidity - Hyperthyroidism ; n (%)	27 (2.1%)	22 (1.7%)	0.0293	9 (1.2%)	10 (1.3%)	-0.0090	25 (2.5%)	21 (2.1%)	0.0267	052 (1.7%)	043 (1.4%)	0.0243
Other Comorbidity - Hyperkalemia ; n (%)	78 (6.1%)	79 (6.2%)	-0.0042	45 (6.0%)	35 (4.7%)	0.0578	70 (7.0%)	68 (6.8%)	0.0079	148 (4.9%)	147 (4.8%)	0.0047
Other Comorbidity - Depression; n (%)	207 (16.2%)	216 (16.9%)	-0.0188	76 (10.2%)	75 (10.0%)	0.0066	187 (18.6%)	182 (18.1%)	0.0129	394 (13.0%)	398 (13.1%)	-0.0030
Other Comorbidity - COPD ; n (%)	378 (29.6%)	380 (29.7%)	-0.0022	108 (14.4%)	104 (13.9%)	0.0143	290 (28.8%)	297 (29.5%)	-0.0154	668 (22.0%)	677 (22.3%)	-0.0072
Other Comorbidity - Pneumonia; n (%)	263 (20.6%)	270 (21.1%)	-0.0123	147 (19.7%)	139 (18.6%)	0.0280	185 (18.4%)	203 (20.2%)	-0.0456	448 (14.8%)	473 (15.6%)	-0.0223
Other Comorbidity - Acute kidney injury (AKI) ; n (%)	284 (22.2%)	321 (25.1%)	-0.0683	158 (21.1%)	150 (20.1%)	0.0247	259 (25.7%)	253 (25.1%)	0.0138	543 (17.9%)	574 (18.9%)	-0.0258
Other Comorbidity - CKD Stage 1-2; n (%)	68 (5.3%)	79 (6.2%)	-0.0387	18 (2.4%)	18 (2.4%)	0.0000	81 (8.1%)	75 (7.5%)	0.0224	149 (4.9%)	154 (5.1%)	-0.0092
Other Comorbidity - CKD Stage 3-4; n (%)	310 (24.2%)	289 (22.6%)	0.0378	90 (12.0%)	84 (11.2%)	0.0250	267 (26.5%)	273 (27.1%)	-0.0135	577 (19.0%)	562 (18.5%)	0.0128
Other Comorbidity - Any Chronic Kidney Disease; n (%)	421 (32.9%)	408 (31.9%)	0.0214	133 (17.8%)	125 (16.7%)	0.0291	381 (37.9%)	371 (36.9%)	0.0207	802 (26.4%)	779 (25.7%)	0.0159
Other Comorbidity - Hemodialysis/Peritoneal dialysis ; n (%)*	7 (0.5%)	4 (0.3%)	0.0317	1 (0.1%)	1 (0.1%)	0.0000	4 (0.4%)	0 (0.0%)	0.0896	011 (0.4%)	004 (0.1%)	0.0601
Other Comorbidity - DM Related Complications; n (%)	289 (22.6%)	304 (23.8%)	-0.0284	118 (15.8%)	115 (15.4%)	0.0110	235 (23.4%)	224 (22.3%)	0.0262	524 (17.3%)	528 (17.4%)	-0.0026
Other Comorbidity - Diabetic/Hypertensive Nephropathy; n (%)	419 (32.8%)	402 (31.4%)	0.0300	143 (19.1%)	141 (18.9%)	0.0051	329 (32.7%)	319 (31.7%)	0.0214	748 (24.7%)	721 (23.8%)	0.0210
Other Comorbidity - Sleep apnea; n (%)	298 (23.3%)	307 (24.0%)	-0.0165	171 (22.9%)	177 (23.7%)	-0.0189	177 (17.6%)	189 (18.8%)	-0.0311	475 (15.7%)	496 (16.4%)	-0.0191
Other Comorbidity - Cancer ; n (%)	150 (11.7%)	150 (11.7%)	0.0000	58 (7.8%)	56 (7.5%)	0.0113	126 (12.5%)	131 (13.0%)	-0.0150	276 (9.1%)	281 (9.3%)	-0.0069
Other Comorbidity - Type 1 DM ; n (%)	40 (3.1%)	47 (3.7%)	-0.0331	24 (3.2%)	22 (2.9%)	0.0174	36 (3.6%)	40 (4.0%)	-0.0209	076 (2.5%)	087 (2.9%)	-0.0247
Other Comorbidity - Type 2 DM ; n (%)	662 (51.8%)	673 (52.6%)	-0.0160	348 (46.5%)	322 (43.0%)	0.0704	531 (52.8%)	504 (50.1%)	0.0540	1,193 (39.3%)	1,177 (38.8%)	0.0102
Other Comorbidity - Anemia ; n (%)	380 (29.7%)	356 (27.8%)	0.0420	155 (20.7%)	144 (19.3%)	0.0350	340 (33.8%)	348 (34.6%)	-0.0169	720 (23.7%)	704 (23.2%)	0.0118
Lifestyle - Obesity ; n (%)	407 (31.8%)	437 (34.2%)	-0.0511	222 (29.7%)	222 (29.7%)	0.0000	236 (23.5%)	239 (23.8%)	-0.0071	643 (21.2%)	676 (22.3%)	-0.0267
Lifestyle - Alcohol/Drug Abuse or Dependence; n (%)	113 (8.8%)	122 (9.5%)	-0.0243	66 (8.8%)	64 (8.6%)	0.0071	60 (6.0%)	56 (5.6%)	0.0171	173 (5.7%)	178 (5.9%)	-0.0086
Lifestyle - Smoking; n (%)	613 (47.9%)	628 (49.1%)	-0.0240	181 (24.2%)	163 (21.8%)	0.0571	440 (43.7%)	436 (43.3%)	0.0081	1,053 (34.7%)	1,064 (35.1%)	-0.0084
Other Medication - AGI & Meglitinides ; n (%)*	5 (0.4%)	4 (0.3%)	0.0169	5 (0.7%)	2 (0.3%)	0.0567	11 (1.1%)	7 (0.7%)	0.0424	016 (0.5%)	011 (0.4%)	0.0149
Other Medication - Insulin; n (%)	192 (15.0%)	210 (16.4%)	-0.0385	129 (17.2%)	108 (14.4%)	0.0768	162 (16.1%)	150 (14.9%)	0.0332	354 (11.7%)	360 (11.9%)	-0.0062
Other Medication - Glitazones; n (%)	17 (1.3%)	20 (1.6%)	-0.0251	15 (2.0%)	11 (1.5%)	0.0381	17 (1.7%)	18 (1.8%)	-0.0076	034 (1.1%)	038 (1.3%)	-0.0184
Other Medication - 1st and 2nd Generation SUs; n (%)	187 (14.6%)	184 (14.4%)	0.0057	87 (11.6%)	84 (11.2%)	0.0126	131 (13.0%)	137 (13.6%)	-0.0177	318 (10.5%)	321 (10.6%)	-0.0033

Appendix B: Sacubitril/Valsartan vs. ACE Inhibitors

Other Medication - DPP-4 Inhibitors ; n (%)	90 (7.0%)	85 (6.6%)	0.0159	56 (7.5%)	46 (6.1%)	0.0556	90 (8.9%)	85 (8.4%)	0.0178	180 (5.9%)	170 (5.6%)	0.0129
Other Medication - GLP-1 RA ; n (%)	51 (4.0%)	51 (4.0%)	0.0000	21 (2.8%)	23 (3.1%)	-0.0177	17 (1.7%)	13 (1.3%)	0.0329	068 (2.2%)	064 (2.1%)	0.0069
Other Medication - Metformin ; n (%)	337 (26.3%)	341 (26.7%)	-0.0091	179 (23.9%)	172 (23.0%)	0.0212	218 (21.7%)	217 (21.6%)	0.0024	555 (18.3%)	558 (18.4%)	-0.0026
Other Medication - NSAIDS (COX-2 Selective) ; n (%)	72 (5.6%)	64 (5.0%)	0.0268	36 (4.8%)	31 (4.1%)	0.0340	43 (4.3%)	43 (4.3%)	0.0000	115 (3.8%)	107 (3.5%)	0.0160
Other Medication - NSAIDS (Non-Selective) ; n (%)	126 (9.9%)	129 (10.1%)	-0.0067	136 (18.2%)	137 (18.3%)	-0.0026	35 (3.5%)	34 (3.4%)	0.0055	161 (5.3%)	163 (5.4%)	-0.0044
Other Medication - Use of antiplatelet agents ; n (%)	355 (27.8%)	377 (29.5%)	-0.0376	249 (33.3%)	237 (31.7%)	0.0342	282 (28.0%)	292 (29.0%)	-0.0222	637 (21.0%)	669 (22.1%)	-0.0268
Other Medication - Use of heparin and other low-molecular weight heparins ; n (%)*	29 (2.3%)	27 (2.1%)	0.0136	1 (0.1%)	0 (0.0%)	0.0447	27 (2.7%)	9 (0.9%)	0.1357	056 (1.8%)	036 (1.2%)	0.0494
Other Medication - Use of oral anticoagulants ; n (%)	478 (37.4%)	470 (36.7%)	0.0145	255 (34.1%)	270 (36.1%)	-0.0419	429 (42.6%)	419 (41.7%)	0.0182	907 (29.9%)	889 (29.3%)	0.0131
Other Medication - Use of other hypertension drugs; n (%)	149 (11.6%)	140 (10.9%)	0.0222	105 (14.0%)	97 (13.0%)	0.0293	105 (10.4%)	108 (10.7%)	-0.0098	254 (8.4%)	248 (8.2%)	0.0072
Other Medication - Use of antipsychotics ; n (%)	33 (2.6%)	36 (2.8%)	-0.0123	10 (1.3%)	11 (1.5%)	-0.0170	32 (3.2%)	27 (2.7%)	0.0296	065 (2.1%)	063 (2.1%)	0.0000
Other Medication - Use of dementia meds ; n (%)	35 (2.7%)	25 (2.0%)	0.0462	15 (2.0%)	14 (1.9%)	0.0072	33 (3.3%)	34 (3.4%)	-0.0056	068 (2.2%)	059 (1.9%)	0.0212
Other Medication - Use of antiparkinsonian meds ; n (%)	34 (2.7%)	38 (3.0%)	-0.0180	13 (1.7%)	13 (1.7%)	0.0000	26 (2.6%)	29 (2.9%)	-0.0183	060 (2.0%)	067 (2.2%)	-0.0139
Other Medication - Use of anxiolytics/hypnotics ; n (%)	78 (6.1%)	81 (6.3%)	-0.0083	39 (5.2%)	54 (7.2%)	-0.0830	54 (5.4%)	62 (6.2%)	-0.0342	132 (4.4%)	143 (4.7%)	-0.0144
Other Medication - Use of anticonvulsants ; n (%)	181 (14.2%)	194 (15.2%)	-0.0282	76 (10.2%)	68 (9.1%)	0.0373	166 (16.5%)	165 (16.4%)	0.0027	347 (11.4%)	359 (11.8%)	-0.0125
Other Medication - Use of antidepressants ; n (%)	306 (23.9%)	317 (24.8%)	-0.0210	159 (21.3%)	159 (21.3%)	0.0000	284 (28.2%)	280 (27.8%)	0.0089	590 (19.5%)	597 (19.7%)	-0.0050
Other Medication - Use of lithium ; n (%)*	0 (0.0%)	0 (0.0%)	#DIV/0!	3 (0.4%)	0 (0.0%)	0.0896	2 (0.2%)	0 (0.0%)	0.0633	002 (0.1%)	000 (0.0%)	0.0447
Other Medication - Use of Benzodiazepine; n (%)	197 (15.4%)	187 (14.6%)	0.0224	92 (12.3%)	104 (13.9%)	-0.0474	131 (13.0%)	141 (14.0%)	-0.0293	328 (10.8%)	328 (10.8%)	0.0000
Other Medication - Use of opioids ; n (%)	385 (30.1%)	386 (30.2%)	-0.0022	213 (28.5%)	206 (27.5%)	0.0223	267 (26.5%)	281 (27.9%)	-0.0315	652 (21.5%)	667 (22.0%)	-0.0121
Other Medication - Use of COPD/asthma meds ; n (%)	296 (23.1%)	269 (21.0%)	0.0507	139 (18.6%)	152 (20.3%)	-0.0430	195 (19.4%)	218 (21.7%)	-0.0569	491 (16.2%)	487 (16.1%)	0.0027
HU - Bone mineral density; n (%)	28 (2.2%)	28 (2.2%)	0.0000	8 (1.1%)	9 (1.2%)	-0.0094	16 (1.6%)	14 (1.4%)	0.0165	044 (1.5%)	042 (1.4%)	0.0084
HU - Flexible Sigmoidoscopy or colonoscopy or CT virtual colonoscopy; n (%)	61 (4.8%)	55 (4.3%)	0.0240	30 (4.0%)	27 (3.6%)	0.0209	36 (3.6%)	41 (4.1%)	-0.0260	097 (3.2%)	096 (3.2%)	0.0000
HU - Flu vaccine; n (%)	235 (18.4%)	238 (18.6%)	-0.0052	76 (10.2%)	83 (11.1%)	-0.0292	306 (30.4%)	304 (30.2%)	0.0044	541 (17.8%)	542 (17.9%)	-0.0026
HU - Mammogram; n (%)	63 (4.9%)	62 (4.8%)	0.0047	36 (4.8%)	30 (4.0%)	0.0390	51 (5.1%)	46 (4.6%)	0.0233	114 (3.8%)	108 (3.6%)	0.0106
HU - Frailty Score: Empirical Version 365 days												
...mean (sd)	0.22 (0.06)	0.22 (0.06)	0.0000	0.20 (0.05)	0.19 (0.05)	0.2000	0.24 (0.07)	0.24 (0.07)	0.0000	0.22 (0.06)	0.22 (0.06)	0.0000
...median [IQR]	0.21 [0.18, 0.25]	0.21 [0.18, 0.25]	0.0000	0.18 [0.16, 0.22]	0.18 [0.16, 0.21]	0.0000	0.22 [0.19, 0.27]	0.22 [0.19, 0.27]	0.0000	0.21 (0.06)	0.21 (0.06)	0.0000
HU - Number of hospitalizations during CAP												
...mean (sd)	1.06 (0.77)	1.08 (0.76)	-0.0261	0.98 (0.65)	0.95 (0.66)	0.0458	1.07 (0.91)	1.07 (0.90)	0.0000	1.04 (0.79)	1.04 (0.79)	0.0000
...median [IQR]	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	0.0000	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	0.0000	1.00 [1.00, 1.00]	1.00 [0.75, 1.00]	0.0000	1.00 (0.79)	1.00 (0.79)	0.0000
HU - Number of Emergency Department (ED) visits												
...mean (sd)	1.81 (2.51)	1.84 (2.32)	-0.0124	2.56 (5.33)	2.40 (3.90)	0.0343	1.73 (2.19)	1.65 (2.78)	0.0320	1.97 (3.35)	1.92 (2.93)	0.0159
...median [IQR]	1.00 [0.00, 3.00]	1.00 [0.00, 3.00]	0.0000	2.00 [0.00, 3.00]	2.00 [0.00, 3.00]	0.0000	1.00 [0.00, 3.00]	1.00 [0.00, 2.00]	0.0000	1.25 (3.35)	1.25 (2.93)	0.0000
HU - Number of Internal Medicine/Family Medicine Visits												
...mean (sd)	14.51 (18.56)	14.34 (19.30)	0.0090	9.77 (15.50)	8.91 (12.31)	0.0614	8.50 (9.54)	8.89 (10.84)	-0.0382	11.35 (15.32)	11.19 (15.28)	0.0105
...median [IQR]	9.00 [4.00, 18.00]	9.00 [4.00, 19.00]	0.0000	5.00 [2.00, 11.75]	5.00 [2.00, 11.00]	0.0000	6.00 [3.00, 11.00]	6.00 [3.00, 11.00]	0.0000	7.02 (15.32)	7.02 (15.28)	0.0000
HU - Number of Distinct Medication Prescriptions (not generalized to generics)												
...mean (sd)	33.63 (25.85)	33.96 (20.50)	-0.0141	30.49 (17.53)	30.50 (15.10)	-0.0006	31.27 (19.20)	32.09 (16.13)	-0.0462	32.07 (21.91)	32.49 (17.88)	-0.0210
...median [IQR]	28.00 [19.00, 41.00]	30.00 [20.00, 43.00]	-0.0857	28.00 [19.00, 38.00]	28.00 [20.00, 38.00]	0.0000	27.00 [19.00, 38.00]	29.00 [21.00, 40.00]	-0.1128	27.67 (21.91)	29.18 (17.88)	-0.0755
HU - Number of Cardiologist visits												
...mean (sd)	13.79 (13.06)	13.37 (10.66)	0.0352	6.17 (8.33)	6.95 (7.55)	-0.0981	11.33 (12.78)	11.70 (11.61)	-0.0303	11.09 (11.97)	11.23 (10.33)	-0.0125
...median [IQR]	11.00 [5.00, 18.00]	11.00 [6.00, 18.00]	0.0000	4.00 [0.00, 9.00]	5.00 [2.00, 10.00]	-0.1258	8.00 [3.00, 15.00]	9.00 [4.00, 15.00]	-0.0819	8.28 (11.97)	8.86 (10.33)	-0.0519
HU - Number of Electrocardiogram												
...mean (sd)	4.47 (4.88)	4.32 (4.33)	0.0325	3.27 (3.08)	3.22 (2.91)	0.0167	3.88 (3.82)	3.73 (3.96)	0.0386	3.98 (4.15)	3.85 (3.90)	0.0323
...median [IQR]	3.00 [1.00, 6.00]	3.00 [2.00, 6.00]	0.0000	2.00 [1.00, 4.00]	2.00 [1.00, 4.00]	0.0000	3.00 [1.00, 5.00]	3.00 [1.00, 5.00]	0.0000	2.75 (4.15)	2.75 (3.90)	0.0000
HU - Number of Echocardiogram												
...mean (sd)	2.86 (5.89)	2.82 (5.27)	0.0072	1.78 (2.00)	1.76 (1.58)	0.0111	1.66 (1.50)	1.62 (1.34)	0.0281	2.20 (4.05)	2.16 (3.60)	0.0104
...median [IQR]	1.00 [1.00, 3.00]	1.00 [1.00, 3.00]	0.0000	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	0.0000	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	0.0000	1.00 (4.05)	1.00 (3.60)	0.0000
SES Proxy - Copay for pharmacy cost (charges in U.S. $)												
...mean (sd)	27.20 (42.97)	25.88 (29.41)	0.0359	14.87 (18.19)	14.75 (14.06)	0.0074	25.85 (36.56)	26.03 (30.53)	-0.0053	23.71 (36.11)	23.18 (26.88)	0.0167
...median [IQR]	15.93 [5.74, 32.88]	18.14 [6.52, 33.73]	-0.0600	10.53 [3.58, 20.38]	12.40 [5.11, 19.94]	-0.1150	16.10 [5.26, 32.03]	18.78 [5.57, 34.95]	-0.0796	14.65 (36.11)	16.94 (26.88)	-0.0719
SES Proxy - Low income indicator; n (%)	275 (21.5%)	299 (23.4%)	-0.0455	0 (0.0%)	0 (0.0%)	#DIV/0!	0 (0.0%)	0 (0.0%)	#DIV/0!	275 (9.1%)	299 (9.9%)	-0.0273
SES Proxy - Business type												
...Commercial; n (%)	325 (25.4%)	340 (26.6%)	-0.0274	0 (0.0%)	0 (0.0%)	#DIV/0!	0 (0.0%)	0 (0.0%)	#DIV/0!	325 (10.7%)	340 (11.2%)	-0.0160
...Medicare; n (%)	954 (74.6%)	939 (73.4%)	0.0274	0 (0.0%)	0 (0.0%)	#DIV/0!	0 (0.0%)	0 (0.0%)	#DIV/0!	954 (31.5%)	939 (31.0%)	0.0108
SES Proxy - Insurance Plan type												
...Comprehensive; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	105 (14.0%)	94 (12.6%)	0.0412	0 (0.0%)	0 (0.0%)	#DIV/0!	105 (3.5%)	094 (3.1%)	0.0224
...HMO; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	62 (8.3%)	71 (9.5%)	-0.0422	0 (0.0%)	0 (0.0%)	#DIV/0!	062 (2.0%)	071 (2.3%)	-0.0207
...PPO; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	403 (53.9%)	400 (53.5%)	0.0080	0 (0.0%)	0 (0.0%)	#DIV/0!	403 (13.3%)	400 (13.2%)	0.0029
...Others; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	178 (23.8%)	183 (24.5%)	-0.0164	0 (0.0%)	0 (0.0%)	#DIV/0!	178 (5.9%)	183 (6.0%)	-0.0042
SES Proxy - Dual status code (with Medicaid); n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	0 (0.0%)	0 (0.0%)	#DIV/0!	202 (20.1%)	203 (20.2%)	-0.0025	202 (6.7%)	203 (6.7%)	0.0000

***Excluded from PS model: Age Cateogries, Use of Lithium, Use of AGI & Meglinitides, PCSK9 Inhibitors, Use of heparin or LMWH, Hemodialysis/Peritoneal dialysis**