

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Sacubitril/Valsartan

Trial Indication(s)

Heart Failure

Protocol Number

CLCZ696B2036

Protocol Title

A cohort study to compare the hospitalization rates between naïve Sacubitril/valsartan and naïve ACEi/ARBs heart failure patients with reduced ejection fraction using secondary US electronic health records data

Clinical Trial Phase

NA

Phase of Drug Development

NA

Study Start/End Dates

Study start date: 03 June 2020

Study Completion date: 19 October 2020

Reason for Termination

NA

Study Design/Methodology

This was a non-interventional retrospective cohort study using the US secondary EHR dataset, Optum EHR, to compare the naive sacubitril/valsartan HFrEF patient population (aged ≥ 18 years) to a matched naive ACEi/ARB HFrEF patient population.

The study comprised of the following periods:

Identification period: 01-Jul-2015 to 31-Mar-2019

Study period

- 01-Jul-2014 to 31-Mar-2020 for primary objective and secondary objective 2 to 7.
- 01-Jul-2008 to 30-Sep-2020 for secondary objective 1.

Follow-up period: Patients were followed up until 31-Mar-2020, death or patient transfer out.

Baseline period: 365 days prior to index

Centers

Novartis Investigative Site

Objectives:**Primary objective(s)**

1. To compare the rate of HF hospitalizations in a Naive HFrEF patient population commencing treatment with sacubitril/valsartan and a Naive HFrEF patient population commencing treatment with ACEi/ARB, both patient populations are naive to both sacubitril/valsartan and ACEi/ARB for 365 days prior to index.

Secondary objective(s)

1. To compare the rate of HF hospitalizations in a Truly naive HFrEF patient population commencing treatment with sacubitril/valsartan and a Truly naive HFrEF patient population commencing treatment with ACEi/ARB, both patient populations are entirely naive to both sacubitril/valsartan and ACEi/ARB.
2. To compare the time to first HF hospitalization for naive sacubitril/valsartan HFrEF patients vs naive ACEi/ARB HFrEF patients.
3. To compare the rate of HF hospitalizations or HF ER encounters for Naive sacubitril/valsartan HFrEF patients vs Naive ACEi/ARB HFrEF patients.
4. To compare the time to first HF hospitalizations or HF ER encounters for Naive sacubitril/valsartan HFrEF patients vs Naive ACEi/ARB HFrEF patients.
5. To compare the rates of all-cause hospitalization for Naive sacubitril/valsartan HFrEF patients vs Naive ACEi/ARB HFrEF patients.
6. To compare the time to first all-cause hospitalization for Naive sacubitril/valsartan HFrEF patients vs Naive ACEi/ARB HFrEF patients.
7. To compare the rates of cardiovascular (CV) hospitalization for Naive sacubitril/valsartan HFrEF patients vs Naive ACEi/ARB HFrEF patients.

Test Product (s), Dose(s), and Mode(s) of Administration

NA

Statistical Methods

All analyses were performed on EVICO. The statistical software used for this study was the latest versions of Statistical Analysis Software (SAS) and/or R.

Descriptive statistics of the cohort demographics were reported as follows:

- Continuous variables were summarized using n, mean, median, standard deviation (SD), minimum, maximum, 95% CI, 25th and 75th percentiles.
- Categorical variables were summarized using frequency counts and percentages.
- Missing data were reported using frequency counts and percentages

Variables were assessed for similarity between the sacubitril/valsartan cohort and ACEi/ARBs cohort. only variables with a standardized mean difference (SMD) ≥ 0.1 (or 10%), age and sex were included in the adjusted negative binomial and sub distribution models, following propensity score matching.

For the primary objective and secondary objectives 1, 3, 5 and 7, negative binomial models were used for the analysis, the rate ratio (RR), total person years, annualized hospitalization rates, 95% CI and p-values were reported. A sensitivity analysis was conducted for the primary objective, where the wash-out period is extended to all available data pre-index (index date included) and reporting the associated RR, 95% CI and p-values. A further sensitivity analysis were conducted on the primary objective, where follow-up is limited to one year post-index, the associated RR, 95% CI and p-values will be reported.

For secondary objectives 2, 4, and 6 a sub distribution model was used, the hazard ratio (HR), total person years, annualized hospitalization rates, 95% CI and p-values were reported. The sub distribution hazards model was chosen, as it allows for an estimation of incidence of the occurrence of an event whilst taking competing risk into account

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

Sacubitril/valsartan incident cohort

Included patients

- Prescribed sacubitril/valsartan within the identification period (01-July-2015 to 31-Mar-2019), that had non-missing gender and year of birth data.
- With at least one ICD-9-CM or ICD-10-CM code for diagnosis of HF within one-year prior to date of first prescription of sacubitril/valsartan (index date), and are treated as part of the integrated delivery network.
- With first month active 365 days prior to index and last date active was greater than or equal to (\geq) index, and the month of provider source data was greater than the final date of patient follow-up.
- That were ≥ 18 years old at index date.
- With a valid LVEF value $\leq 40\%$, prior to index (index date included).

Angiotensin-converting enzyme inhibitors (ACEi) and Angiotensin II receptor antagonist (ARB) incident cohort

Included patient:

- Prescribed ACEi or ARBs within the identification period (01-Jul-2015 to 31-Mar-2019), that had non-missing gender and year of birth data.
- With at least one ICD-9-CM or ICD-10-CM code for diagnosis of HF within one-year prior to date of first prescription of ACEi or ARB (index date), and were treated as part of the integrated delivery network.

- With first month active 365 days prior to index and last date active was \geq index, and the month of provider source data is greater than the final date of patient follow-up.
- That were \geq 18 years old at index date.
- With a valid LVEF value \leq 40%, prior to index (index date included).

Exclusion Criteria:

Sacubitril/valsartan incident cohort

Excluded patients for the primary objective and secondary objective 2 to 7:

- Patients who were prescribed sacubitril/valsartan within one-year prior to index date.
- Patients who were prescribed ACEi or ARBs, within one-year prior to index date (index date included).

Exclude patients for secondary objective 1:

- Patients who were prescribed sacubitril/valsartan prior to index date.
- Patients who were prescribed ACEi or ARBs prior to index date (index date included).

Angiotensin-converting enzyme inhibitors (ACEi) and Angiotensin II receptor antagonist (ARB) incident cohort

Exclude patients for the primary objective and secondary objective 2 to 7:

- Patients who were prescribed ACEi or ARBs within one-year prior to index date.
- Patients who were prescribed sacubitril/valsartan within one-year prior to index date (index date included).
- Which had a valid sacubitril/valsartan prescription that enables inclusion in the sacubitril/valsartan cohort.
- Exclude patients for secondary objective 1:
- Patients who were prescribed ACEi or ARBs prior to index date.
- Patients who were prescribed sacubitril/valsartan prior to index date (index date included).

- Which had a valid sacubitril/valsartan prescription that enables inclusion in the sacubitril/valsartan cohort

Participant Flow

Attrition of patients for Naive cohort and Truly naive cohort are shown below:

| Attrition Table: Naive cohort | | | | | |
|---|---|--------------------|----------|-------------------|----------|
| Criteria Number | Criteria | Patients Remaining | | Patients Excluded | |
| | | n | %* | n | %* |
| Sacubitril/valsartan incident cohort | | | | | |
| 1 | Prescribed sacubitril/valsartan within the identification period (01-July-2015 to 31-March-2019), that have non-missing gender and year of birth data. | 42269 | | | |
| 2 | With at least one ICD-9-CM or ICD-10-CM code for diagnosis of heart failure within one-year prior to date of first prescription of sacubitril/valsartan (index date), and are treated as part of the integrated delivery network. | 25048 | (59.26%) | 17221 | (40.74%) |
| 3 | With first month active 365 days prior to index and last date active is \geq index. | 22273 | (52.69%) | 19996 | (47.31%) |
| 4 | That are \geq 18 years old at index date. | 22267 | (52.68%) | 20002 | (47.32%) |
| 5 | With a valid LVEF value \leq 40%, prior to index (index date included). | 13749 | (32.53%) | 28520 | (67.47%) |
| 6 | That were not prescribed sacubitril/valsartan within one-year prior to index date. | 13749 | (32.53%) | 28520 | (67.47%) |
| 7 | That were not prescribed ACEi or ARBs, within one-year prior to index date (index date included). | 3367 | (7.97%) | 38902 | (92.03%) |
| ACEi and ARB incident cohort | | | | | |
| 1 | Prescribed ACEi or ARBs within the identification period (01-July-2015 to 31-March-2019), that have non-missing gender and year of birth data. | 9344258 | | | |
| 2 | With at least one ICD-9-CM or ICD-10-CM code for diagnosis of heart failure within one-year prior to date of first prescription of ACEi or ARB (index date), and are treated as part of the integrated delivery network. | 361022 | (3.86%) | 8983236 | (96.14%) |
| 3 | With first month active 365 days prior to index and last date active is \geq index. | 319119 | (3.42%) | 9025139 | (96.58%) |
| 4 | That were \geq 18 years old at index date. | 318609 | (3.41%) | 9025649 | (96.59%) |
| 5 | With a valid LVEF value \leq 40%, prior to index (index date included). | 76155 | (0.81%) | 9268103 | (99.19%) |
| 6 | That were not prescribed ACEi or ARBs within one-year prior to index date. | 52057 | (0.56%) | 9292201 | (99.44%) |

| Criteria Number | Criteria | Patients Remaining | | Patients Excluded | |
|-----------------|--|--------------------|---------|-------------------|----------|
| | | n | %* | n | %* |
| 7 | That were not prescribed sacubitril/valsartan within one-year prior to index date (index date included). | 51153 | (0.55%) | 9293105 | (99.45%) |
| 8 | That do not had a valid sacubitril/valsartan prescription that enables inclusion in the sacubitril/valsartan cohort. | 50872 | (0.54%) | 9293386 | (99.46%) |

*Percentages were based on the number of patients who met the first criterion in the database.

Attrition Table: Truly naive cohort

| Criteria Number | Criteria | Patients Remaining | | Patients Excluded | |
|-----------------|--------------------------------------|--------------------|-----|-------------------|----|
| | | n | % * | n | %* |
| | Sacubitril/valsartan incident cohort | | | | |

| Criteria Number | Criteria | Patients Remaining | | Patients Excluded | |
|-------------------------------------|---|--------------------|----------|-------------------|----------|
| | | n | % * | n | %* |
| 1 | Prescribed sacubitril/valsartan within the identification period (01-July-2015 to 31-March-2019), that have non-missing gender and year of birth data. | 42269 | | | |
| 2 | With at least one ICD-9-CM or ICD-10-CM code for diagnosis of heart failure within one-year prior to date of first prescription of sacubitril/valsartan (index date), and are treated as part of the integrated delivery network. | 25048 | (59.26%) | 17221 | (40.74%) |
| 3 | With first month active 365 days prior to index and last date active is \geq index. | 22273 | (52.69%) | 19996 | (47.31%) |
| 4 | That were ≥ 18 years old at index date. | 22267 | (52.68%) | 20002 | (47.32%) |
| 5 | With a valid LVEF value $\leq 40\%$, prior to index (index date included). | 13749 | (32.53%) | 28520 | (67.47%) |
| 6 | That were not prescribed sacubitril/valsartan prior to index date. | 13749 | (32.53%) | 28520 | (67.47%) |
| 7 | That were not prescribed ACEi or ARBs, prior to index date (index date included). | 1230 | (2.91%) | 41039 | (97.09%) |
| ACEi and ARB incident cohort | | | | | |
| 1 | Prescribed ACEi or ARBs within the identification period (01-July-2015 to 31-March-2019), that have non-missing gender and year of birth data. | 9344258 | | | |
| 2 | With at least one ICD-9-CM or ICD-10-CM code for diagnosis of heart failure within one-year prior to date of first prescription of ACEi or ARB (index date), and are treated as part of the integrated delivery network. | 361022 | (3.86%) | 8983236 | (96.14%) |
| 3 | With first month active 365 days prior to index and last date active is \geq index. | 319119 | (3.42%) | 9025139 | (96.58%) |
| 4 | That are ≥ 18 years old at index date. | 318609 | (3.41%) | 9025649 | (96.59%) |
| 5 | With a valid LVEF value $\leq 40\%$, prior to index (index date included). | 76155 | (0.81%) | 9268103 | (99.19%) |
| 6 | That were not prescribed ACEi or ARBs prior to index date. | 26710 | (0.29%) | 9317548 | (99.71%) |
| 7 | That were not prescribed sacubitril/valsartan prior to index date (index date included). | 26197 | (0.28%) | 9318061 | (99.72%) |
| 8 | That do not had a valid sacubitril/valsartan prescription that enables inclusion in the | 26197 | (0.28%) | 9318061 | (99.72%) |

Baseline Characteristics

Propensity score reported pre-and post-matching: Descriptive statistics for Naive sacubitril/valsartan cohort and Naive ACEi/ARB cohort

| | | | Pre-match | | | | | | Post-match | | | | | |
|----------------------|------------------------------|-------|--------------------------|-------|----------|-------|----------|-------|--------------------------|-------|----------|-------|---------|------|
| | | | Sacubitril/ valsartan | | ACEi/ARB | | p value | SMD | Sacubitril/ valsartan | | ACEi/ARB | | p value | SMD |
| | | | N | % | N | % | | | N | % | N | % | | |
| Number of Patients | | N (%) | 3367 | 100 | 50872 | 100 | | | 3060 | 100 | 6120 | 100 | | |
| Socio demographics | | | | | | | | | | | | | | |
| Age (years) at index | N (% non-missing) | | 3367 | 100 | 50872 | 100 | < 0.0001 | | 3060 | 100 | 6120 | 100 | 0.6684 | |
| | Patients with estimated ages | | 173 | 5.14 | 6153 | 12.10 | | | 161 | 5.26 | 567 | 9.26 | | |
| | Mean | | 65.92 | . | 66.94 | . | | | 66.02 | . | 65.93 | . | | |
| | SD. | | 13.08 | . | 13.74 | . | | 7.64 | 13.08 | . | 14.08 | . | | 0.66 |
| | Min | | 21 | . | 18 | . | | | 21 | . | 18 | . | | |
| | Max | | 87 | . | 87 | . | | | 87 | . | 87 | . | | |
| | 25% Percentile | | 58 | . | 58 | . | | | 58 | . | 57 | . | | |
| | Median | | 67 | . | 68 | . | | | 67 | . | 67 | . | | |
| | 75% percentile | | 76 | . | 78 | . | | | 76 | . | 77 | . | | |
| | | | | | | | | | | | | | | |
| Sex | Female | N (%) | 967 | 28.72 | 17927 | 35.24 | < 0.0001 | 14.01 | 907 | 29.64 | 1860 | 30.39 | 0.4594 | 1.64 |
| | Male | N (%) | 2400 | 71.28 | 32945 | 64.76 | | 14.01 | 2153 | 70.36 | 4260 | 69.61 | | 1.64 |



| | | Statistic | Pre-match | | | | | | Post-match | | | | | |
|--------------------------|--------------------|-----------|--------------------------|-------|----------|-------|-------------|-------|--------------------------|-------|----------|-------|---------|------|
| | | | Sacubitril/ valsartan | | ACEi/ARB | | p value | SMD | Sacubitril/ valsartan | | ACEi/ARB | | p value | SMD |
| | | N | % | N | % | N | | | % | N | % | N | | |
| Year of index | 2015 | N (%) | 92 | 2.73 | 8505 | 16.72 | < 0.0001 | 48.57 | 92 | 3.01 | 181 | 2.96 | 0.9694 | 0.29 |
| | 2016 | N (%) | 638 | 18.95 | 18140 | 35.66 | | 38.18 | 636 | 20.78 | 1260 | 20.59 | | 0.48 |
| | 2017 | N (%) | 1040 | 30.89 | 12688 | 24.94 | | 13.29 | 994 | 32.48 | 2019 | 32.99 | | 1.08 |
| | 2018 | N (%) | 1239 | 36.80 | 9377 | 18.43 | | 41.97 | 1054 | 34.44 | 2115 | 34.56 | | 0.24 |
| | 2019 | N (%) | 358 | 10.63 | 2162 | 4.25 | | 24.50 | 284 | 9.28 | 545 | 8.91 | | 1.31 |
| Race | African American | N (%) | 549 | 16.31 | 8409 | 16.53 | 0.0132 | 0.61 | 498 | 16.27 | 1009 | 16.49 | 0.8733 | 0.57 |
| | Asian | N (%) | 36 | 1.07 | 402 | 0.79 | | 2.91 | 30 | 0.98 | 71 | 1.16 | | 1.75 |
| | Caucasian | N (%) | 2669 | 79.27 | 39849 | 78.33 | | 2.29 | 2423 | 79.18 | 4825 | 78.84 | | 0.84 |
| | Other/ Unknown | N (%) | 113 | 3.36 | 2212 | 4.35 | | 5.16 | 109 | 3.56 | 215 | 3.51 | | 0.27 |
| | | | | | | | | | | | | | | |
| Ethnicity | Hispanic | N (%) | 95 | 2.82 | 1810 | 3.56 | 0.0317 | 4.19 | 86 | 2.81 | 190 | 3.10 | 0.7353 | 1.74 |
| | Not Hispanic | N (%) | 3097 | 91.98 | 46696 | 91.79 | | 0.70 | 2823 | 92.25 | 5626 | 91.93 | | 1.21 |
| | Unknown | N (%) | 175 | 5.20 | 2366 | 4.65 | | 2.53 | 151 | 4.93 | 304 | 4.97 | | 0.15 |
| Geographical region | Midwest | N (%) | 1349 | 40.07 | 23556 | 46.30 | < 0.0001 | 12.62 | 1268 | 41.44 | 2590 | 42.32 | 0.8843 | 1.79 |
| | Northeast | N (%) | 512 | 15.21 | 6533 | 12.84 | | 6.81 | 474 | 15.49 | 946 | 15.46 | | 0.09 |
| | South | N (%) | 1326 | 39.38 | 15447 | 30.36 | | 19.01 | 1147 | 37.48 | 2230 | 36.44 | | 2.17 |
| | West | N (%) | 99 | 2.94 | 3917 | 7.70 | | 21.33 | 96 | 3.14 | 202 | 3.30 | | 0.93 |
| | Other/ Unknown | N (%) | 81 | 2.41 | 1419 | 2.79 | | 2.41 | 75 | 2.45 | 152 | 2.48 | | 0.21 |
| Geographical division | East North Central | N (%) | 1006 | 29.88 | 16561 | 32.55 | < 0.0001 | 5.78 | 934 | 30.52 | 1916 | 31.31 | 0.9847 | 1.70 |

| | | | Pre-match | | | | | | Post-match | | | | | |
|--|---------------------------------------|-------|--------------------------|-------|----------|-------|-------------|-------|--------------------------|-------|----------|-------|---------|------|
| | | | Sacubitril/ valsartan | | ACEi/ARB | | p value | SMD | Sacubitril/ valsartan | | ACEi/ARB | | p value | SMD |
| | Statistic | | N | % | N | % | | | N | % | N | % | | |
| | East South Central | N (%) | 255 | 7.57 | 4388 | 8.63 | | 3.86 | 238 | 7.78 | 439 | 7.17 | | 2.30 |
| | Middle Atlantic | N (%) | 326 | 9.68 | 3528 | 6.94 | | 9.97 | 295 | 9.64 | 584 | 9.54 | | 0.33 |
| | Mountain | N (%) | 56 | 1.66 | 2384 | 4.69 | | 17.31 | 53 | 1.73 | 107 | 1.75 | | 0.12 |
| | New England | N (%) | 185 | 5.49 | 3000 | 5.90 | | 1.74 | 178 | 5.82 | 362 | 5.92 | | 0.42 |
| | Pacific | N (%) | 43 | 1.28 | 1522 | 2.99 | | 11.89 | 43 | 1.41 | 95 | 1.55 | | 1.22 |
| | South Atl/West South Crl | N (%) | 1067 | 31.69 | 11019 | 21.66 | | 22.83 | 905 | 29.58 | 1787 | 29.20 | | 0.83 |
| | West North Central | N (%) | 341 | 10.13 | 6933 | 13.63 | | 10.84 | 332 | 10.85 | 667 | 10.90 | | 0.16 |
| | Other/ Unknown | N (%) | 88 | 2.61 | 1537 | 3.02 | | 2.46 | 82 | 2.68 | 163 | 2.66 | | 0.10 |
| Elixhauser Comorbidity Index (ECI) | Low ECI Score < 0 | N (%) | 9 | 0.27 | 205 | 0.40 | | 2.35 | 9 | 0.29 | 29 | 0.47 | | 2.91 |
| | Mild ECI score 0 | N (%) | 7 | 0.21 | 220 | 0.43 | | 3.98 | 5 | 0.16 | 41 | 0.67 | | 7.87 |
| | Moderate ECI Score 1-4 | N (%) | 87 | 2.58 | 1540 | 3.03 | | 2.68 | 83 | 2.71 | 211 | 3.45 | | 4.26 |
| | Severe ECI Score ≥ 5 | N (%) | 3264 | 96.94 | 48907 | 96.14 | | 4.40 | 2963 | 96.83 | 5839 | 95.41 | | 7.37 |
| Comorbidities, signs & symptoms | Altered consciousness | N (%) | 100 | 2.97 | 3699 | 7.27 | < 0.0001 | 19.61 | 99 | 3.24 | 177 | 2.89 | 0.3641 | 1.99 |
| | Anemia (including iron deficiency) | N (%) | 204 | 6.06 | 4319 | 8.49 | < 0.0001 | 9.37 | 199 | 6.50 | 418 | 6.83 | 0.5555 | 1.31 |
| | COPD | N (%) | 630 | 18.71 | 11525 | 22.65 | < 0.0001 | 9.75 | 594 | 19.41 | 1140 | 18.63 | 0.3655 | 2.00 |
| | Dementia | N (%) | 66 | 1.96 | 3115 | 6.12 | < 0.0001 | 21.26 | 65 | 2.12 | 126 | 2.06 | 0.8361 | 0.46 |

| | | | Pre-match | | | | | | Post-match | | | | | |
|--|--|-------|--------------------------|-------|----------|-------|-------------|-------|--------------------------|-------|----------|-------|---------|------|
| | | | Sacubitril/ valsartan | | ACEi/ARB | | p value | SMD | Sacubitril/ valsartan | | ACEi/ARB | | p value | SMD |
| | Statistic | | N | % | N | % | | | N | % | N | % | | |
| | Depression | N (%) | 342 | 10.16 | 6362 | 12.51 | < 0.0001 | 7.41 | 321 | 10.49 | 602 | 9.84 | 0.3263 | 2.16 |
| | Diabetes mellitus | N (%) | 1202 | 35.70 | 18990 | 37.33 | 0.0582 | 3.39 | 1110 | 36.27 | 2193 | 35.83 | 0.6780 | 0.92 |
| | Dyslipidemia (including hypercholesterolemia) | N (%) | 2103 | 62.46 | 31221 | 61.37 | 0.2093 | 2.24 | 1907 | 62.32 | 3812 | 62.29 | 0.9757 | 0.07 |
| | Edema and fluid overload | N (%) | 404 | 12.00 | 6410 | 12.60 | 0.3078 | 1.83 | 373 | 12.19 | 746 | 12.19 | 1.0000 | 0.00 |
| | Hypertension | N (%) | 2339 | 69.47 | 37180 | 73.09 | < 0.0001 | 8.00 | 2158 | 70.52 | 4224 | 69.02 | 0.1402 | 3.27 |
| | Renal Disease | N (%) | 992 | 29.46 | 14921 | 29.33 | 0.8706 | 0.29 | 915 | 29.90 | 1763 | 28.81 | 0.2767 | 2.40 |
| | Renal Failure | N (%) | 581 | 17.26 | 11901 | 23.39 | < 0.0001 | 15.30 | 552 | 18.04 | 1064 | 17.39 | 0.4383 | 1.71 |
| | Shortness of breath (excl. sleep apnea) | N (%) | 1362 | 40.45 | 21056 | 41.39 | 0.2841 | 1.91 | 1248 | 40.78 | 2470 | 40.36 | 0.6959 | 0.87 |
| | Sleep apnea | N (%) | 619 | 18.38 | 7898 | 15.53 | < 0.0001 | 7.62 | 556 | 18.17 | 1032 | 16.86 | 0.1185 | 3.44 |
| Cardiac specific comorbidities, signs, symptoms and devices | Angina Pectoris | N (%) | 264 | 7.84 | 3415 | 6.71 | 0.0117 | 4.34 | 233 | 7.61 | 465 | 7.60 | 0.9778 | 0.06 |
| | Atrial Fibrillation | N (%) | 1398 | 41.52 | 19726 | 38.78 | 0.0016 | 5.60 | 1255 | 41.01 | 2460 | 40.20 | 0.4522 | 1.66 |
| | Cardiac arrhythmia (excluding atrial fibrillation) | N (%) | 1140 | 33.86 | 19196 | 37.73 | < 0.0001 | 8.09 | 1057 | 34.54 | 2103 | 34.36 | 0.8643 | 0.38 |
| | Cardio resynchronization therapy device | N (%) | 1226 | 36.41 | 10333 | 20.31 | < 0.0001 | 36.30 | 1012 | 33.07 | 2008 | 32.81 | 0.8016 | 0.56 |

| | | Statistic | Pre-match | | | | | | Post-match | | | | | |
|----------------|--|-------------------|--------------------------|-------|-------|----------|----------|---------|--------------------------|-------|-------|----------|--------|------|
| | | | Sacubitril/ valsartan | | | ACEi/ARB | | | Sacubitril/ valsartan | | | ACEi/ARB | | |
| | | | N | % | | N | % | p value | SMD | N | % | | N | % |
| | Cerebrovascular disease | N (%) | 349 | 10.37 | 7125 | 14.01 | < 0.0001 | 11.15 | 328 | 10.72 | 652 | 10.65 | 0.9238 | 0.21 |
| | Ischemic heart disease (including myocardial infarction) | N (%) | 2240 | 66.53 | 34331 | 67.49 | 0.2512 | 2.04 | 2047 | 66.90 | 4034 | 65.92 | 0.3491 | 2.08 |
| | Peripheral Artery Disease | N (%) | 190 | 5.64 | 3561 | 7.00 | 0.0027 | 5.58 | 181 | 5.92 | 388 | 6.34 | 0.4262 | 1.77 |
| | Peripheral vascular disease | N (%) | 329 | 9.77 | 5550 | 10.91 | 0.0396 | 3.74 | 307 | 10.03 | 591 | 9.66 | 0.5677 | 1.26 |
| | Tachycardia | N (%) | 824 | 24.47 | 10129 | 19.91 | < 0.0001 | 11.00 | 720 | 23.53 | 1430 | 23.37 | 0.8617 | 0.39 |
| | Valvular heart disease | N (%) | 1475 | 43.81 | 20606 | 40.51 | 0.0002 | 6.69 | 1330 | 43.46 | 2637 | 43.09 | 0.7319 | 0.76 |
| | Left ventricular ejection fraction | N (% non-missing) | 3367 | 100 | 50872 | 100 | < 0.0001 | | 3060 | 100 | 6120 | 100 | 0.4253 | |
| | | Mean | 26.69 | . | 29.21 | . | | | 27.06 | . | 27.15 | . | | |
| | | SD | 8.15 | . | 8.21 | . | | 30.76 | 8.11 | . | 8.48 | . | | 1.06 |
| | | Min | 5 | . | 0 | . | | | 5 | . | 5 | . | | |
| Max | | 40 | . | 40 | . | | | 40 | . | 40 | . | | | |
| 25% Percentile | | 20 | . | 22.50 | . | | | 20 | . | 20 | . | | | |
| Median | | 27 | . | 30 | . | | | 27.50 | . | 27.50 | . | | | |
| 75% Percentile | | 34 | . | 35 | . | | | 35 | . | 35 | . | | | |
| Medications | Antiarrhythmic and digoxin | N (%) | 1792 | 53.22 | 33856 | 66.55 | < 0.0001 | 27.45 | 1703 | 55.65 | 3375 | 55.15 | 0.6454 | 1.02 |

| | | | Pre-match | | | | | | Post-match | | | | | |
|---|-----------------------------|-------|--------------------------|-------|----------|-------|-------------|-------|--------------------------|-------|----------|-------|---------|------|
| | | | Sacubitril/ valsartan | | ACEi/ARB | | p value | SMD | Sacubitril/ valsartan | | ACEi/ARB | | p value | SMD |
| | Statistic | | N | % | N | % | | | N | % | N | % | | |
| | Beta-blockers | N (%) | 995 | 29.55 | 22885 | 44.99 | < 0.0001 | 32.33 | 966 | 31.57 | 1896 | 30.98 | 0.5663 | 1.27 |
| | Calcium channel blockers | N (%) | 400 | 11.88 | 12072 | 23.73 | < 0.0001 | 31.35 | 397 | 12.97 | 782 | 12.78 | 0.7912 | 0.59 |
| | Lipid lowering drugs | N (%) | 1636 | 48.59 | 30346 | 59.65 | < 0.0001 | 22.34 | 1554 | 50.78 | 3142 | 51.34 | 0.6157 | 1.11 |
| | Loop Diuretics | N (%) | 2070 | 61.48 | 33214 | 65.29 | < 0.0001 | 7.92 | 1923 | 62.84 | 3829 | 62.57 | 0.7953 | 0.57 |
| | Nitroglycerin | N (%) | 1700 | 50.49 | 31938 | 62.78 | < 0.0001 | 24.99 | 1616 | 52.81 | 3229 | 52.76 | 0.9646 | 0.10 |
| | Potassium sparing diuretics | N (%) | 1105 | 32.82 | 13388 | 26.32 | < 0.0001 | 14.28 | 966 | 31.57 | 1966 | 32.12 | 0.5904 | 1.19 |
| Previous heart failure (HF) hospitalizations | 0 | N (%) | 2534 | 75.26 | 44243 | 86.97 | < 0.0001 | 30.26 | 2395 | 78.27 | 4843 | 79.13 | 0.6805 | 2.12 |
| | 1 | N (%) | 543 | 16.13 | 4891 | 9.61 | | 19.54 | 455 | 14.87 | 899 | 14.69 | | 0.51 |
| | 2 | N (%) | 153 | 4.54 | 1096 | 2.15 | | 13.31 | 114 | 3.73 | 209 | 3.42 | | 1.67 |
| | 3 | N (%) | 64 | 1.90 | 322 | 0.63 | | 11.35 | 44 | 1.44 | 70 | 1.14 | | 2.61 |
| | ≥ 4 | N (%) | 73 | 2.17 | 320 | 0.63 | | 13.13 | 52 | 1.70 | 99 | 1.62 | | 0.64 |
| Previous all-cause hospitalizations | 0 | N (%) | 1754 | 52.09 | 30097 | 59.16 | < 0.0001 | 14.26 | 1652 | 53.99 | 3329 | 54.40 | 0.9841 | 0.82 |
| | 1 | N (%) | 739 | 21.95 | 11109 | 21.84 | | 0.27 | 680 | 22.22 | 1335 | 21.81 | | 0.99 |
| | 2 | N (%) | 358 | 10.63 | 4392 | 8.63 | | 6.78 | 315 | 10.29 | 641 | 10.47 | | 0.59 |
| | 3 | N (%) | 204 | 6.06 | 2170 | 4.27 | | 8.11 | 163 | 5.33 | 327 | 5.34 | | 0.07 |
| | ≥ 4 | N (%) | 312 | 9.27 | 3104 | 6.10 | | 11.90 | 250 | 8.17 | 488 | 7.97 | | 0.72 |

| | | | Pre-match | | | | | | Post-match | | | | | |
|--|-----|-------|--------------------------|-------|----------|-------|-------------|-------|--------------------------|-------|----------|-------|---------|------|
| | | | Sacubitril/ valsartan | | ACEi/ARB | | p value | SMD | Sacubitril/ valsartan | | ACEi/ARB | | p value | SMD |
| Statistic | | | N | % | N | % | | | N | % | N | % | | |
| Previous HF specific outpatient visits | 0 | N (%) | 587 | 17.43 | 20368 | 40.04 | < 0.0001 | 51.58 | 587 | 19.18 | 1144 | 18.69 | 0.8213 | 1.25 |
| | 1 | N (%) | 635 | 18.86 | 10385 | 20.41 | | 3.91 | 609 | 19.90 | 1262 | 20.62 | | 1.79 |
| | 2 | N (%) | 458 | 13.60 | 6137 | 12.06 | | 4.60 | 428 | 13.99 | 872 | 14.25 | | 0.75 |
| | 3 | N (%) | 372 | 11.05 | 3777 | 7.42 | | 12.54 | 326 | 10.65 | 674 | 11.01 | | 1.16 |
| | ≥ 4 | N (%) | 1315 | 39.06 | 10205 | 20.06 | | 42.56 | 1110 | 36.27 | 2168 | 35.42 | | 1.77 |
| Previous HF specific ER visits | 0 | N (%) | 3182 | 94.51 | 49313 | 96.94 | < 0.0001 | 12.03 | 2904 | 94.90 | 5845 | 95.51 | 0.7086 | 2.83 |
| | 1 | N (%) | 154 | 4.57 | 1356 | 2.67 | | 10.23 | 128 | 4.18 | 230 | 3.76 | | 2.18 |
| | 2 | N (%) | 19 | 0.56 | 153 | 0.30 | | 4.02 | 19 | 0.62 | 32 | 0.52 | | 1.30 |
| | 3 | N (%) | 4 | 0.12 | 32 | 0.06 | | 1.86 | 4 | 0.13 | 7 | 0.11 | | 0.47 |
| | ≥ 4 | N (%) | 8 | 0.24 | 18 | 0.04 | | 5.48 | 5 | 0.16 | 6 | 0.10 | | 1.81 |

SD: Standard deviation; SMD: Standardized mean difference, HF: heart failure, ER: emergency room

SD: Standard deviation; SMD: Standardized mean difference, HF: heart failure, ER: emergency room

Propensity scores reported pre-and post-matching: Descriptive statistics for Truly naive sacubitril/valsartan cohort and Truly naive ACEi/ARB cohort

| | | Pre-match | | | | | | Post-match | | | | | | |
|----------------------|------------------------------|----------------------|------|----------|-------|---------|--------|----------------------|------|----------|------|---------|--------|------|
| | | Sacubitril/valsartan | | ACEi/ARB | | | | Sacubitril/valsartan | | ACEi/ARB | | | | |
| | Statistic | N | % | N | % | P value | SMD | N | % | N | % | P value | SMD | |
| Number of Patients | N (%) | 1230 | 100 | 26197 | 100 | | | 1225 | 100 | 2450 | 100 | | | |
| Sociodemographics | | | | | | | | | | | | | | |
| Age (years) at index | N (% non-missing) | 1230 | 100 | 26197 | 100 | 0.2224 | | 1225 | 100 | 2450 | 100 | 0.8461 | | |
| | Patients with estimated ages | 82 | 6.67 | 2941 | 11.23 | | | 81 | 6.61 | 218 | 8.90 | | | |
| | Mean | 65.38 | . | 65.87 | . | | | 65.36 | . | 65.45 | . | | | |
| | SD | 14.19 | . | 14.32 | . | | 3.39 | 14.19 | . | 14.34 | . | | 0.62 | |
| | Min | 21 | . | 18 | . | | | 21 | . | 20 | . | | | |
| | Max | 87 | . | 87 | . | | | 87 | . | 87 | . | | | |
| | 25% Percentile | 57 | . | 57 | . | | | 57 | . | 57 | . | | | |
| | Median | 67 | . | 67 | . | | | 67 | . | 66 | . | | | |
| | 75% Percentile | 77 | . | 78 | . | | | 77 | . | 77 | . | | | |
| Sex | Female | N (%) | 389 | 31.63 | 9617 | 36.71 | 0.0003 | 10.74 | 388 | 31.67 | 803 | 32.78 | 0.5010 | 2.36 |
| | Male | N (%) | 841 | 68.37 | 16580 | 63.29 | | 10.74 | 837 | 68.33 | 1647 | 67.22 | | 2.36 |
| Year of index | 2015 | | | | | < | | | | | | | | |
| | N (%) | 28 | 2.28 | 3417 | 13.04 | 0.0001 | 41.34 | 28 | 2.29 | 56 | 2.29 | 0.7144 | 0.00 | |

| | | | Pre-match | | | | | | Post-match | | | | | |
|---------------------|------------------|-------|----------------------|-------|----------|-------|----------|-------|----------------------|-------|----------|-------|---------|------|
| | | | Sacubitril/valsartan | | ACEi/ARB | | | | Sacubitril/valsartan | | ACEi/ARB | | | |
| Statistic | | | N | % | N | % | P value | SMD | N | % | N | % | P value | SMD |
| | 2016 | N (%) | 230 | 18.70 | 7501 | 28.63 | | 23.53 | 230 | 18.78 | 496 | 20.24 | | 3.71 |
| | 2017 | N (%) | 355 | 28.86 | 7378 | 28.16 | | 1.55 | 355 | 28.98 | 704 | 28.73 | | 0.54 |
| | 2018 | N (%) | 449 | 36.50 | 6329 | 24.16 | | 27.10 | 447 | 36.49 | 846 | 34.53 | | 4.09 |
| | 2019 | N (%) | 168 | 13.66 | 1572 | 6.00 | | 25.94 | 165 | 13.47 | 348 | 14.20 | | 2.13 |
| | | | | | | | | | | | | | | |
| Race | African American | N (%) | 194 | 15.77 | 3900 | 14.89 | 0.5415 | 2.46 | 192 | 15.67 | 407 | 16.61 | 0.8481 | 2.55 |
| | Asian | N (%) | 14 | 1.14 | 219 | 0.84 | | 3.06 | 14 | 1.14 | 27 | 1.10 | | 0.39 |
| | Caucasian | N (%) | 970 | 78.86 | 20911 | 79.82 | | 2.37 | 967 | 78.94 | 1904 | 77.71 | | 2.97 |
| | Other/Unknown | N (%) | 52 | 4.23 | 1167 | 4.45 | | 1.11 | 52 | 4.24 | 112 | 4.57 | | 1.59 |
| Ethnicity | Hispanic | N (%) | 34 | 2.76 | 915 | 3.49 | 0.1399 | 4.19 | 34 | 2.78 | 62 | 2.53 | 0.8753 | 1.52 |
| | Not Hispanic | N (%) | 1121 | 91.14 | 23938 | 91.38 | | 0.84 | 1117 | 91.18 | 2234 | 91.18 | | 0.00 |
| | Unknown | N (%) | 75 | 6.10 | 1344 | 5.13 | | 4.20 | 74 | 6.04 | 154 | 6.29 | | 1.02 |
| Geographical region | Midwest | N (%) | 493 | 40.08 | 11983 | 45.74 | < 0.0001 | 11.46 | 492 | 40.16 | 1015 | 41.43 | 0.7186 | 2.57 |
| | Northeast | N (%) | 206 | 16.75 | 3745 | 14.30 | | 6.78 | 204 | 16.65 | 435 | 17.76 | | 2.92 |
| | South | N (%) | 471 | 38.29 | 7755 | 29.60 | | 18.43 | 469 | 38.29 | 887 | 36.20 | | 4.31 |
| | West | N (%) | 33 | 2.68 | 1908 | 7.28 | | 21.26 | 33 | 2.69 | 65 | 2.65 | | 0.25 |
| | Other/Unknown | N (%) | 27 | 2.20 | 806 | 3.08 | | 5.50 | 27 | 2.20 | 48 | 1.96 | | 1.72 |

| | | Pre-match | | | | | | | Post-match | | | | | |
|------------------------------------|--------------------------|----------------------|------|----------|-------|-------|---------|----------------------|------------|----------|------|-------|---------|------|
| | | Sacubitril/valsartan | | ACEi/ARB | | | | Sacubitril/valsartan | | ACEi/ARB | | | | |
| | Statistic | | N | % | N | % | P value | SMD | N | % | N | % | P value | SMD |
| Geographical division | East North Central | N (%) | 367 | 29.84 | 8460 | 32.29 | <0.0001 | 5.31 | 367 | 29.96 | 741 | 30.24 | 0.8436 | 0.62 |
| | East South Central | N (%) | 82 | 6.67 | 1997 | 7.62 | | 3.71 | 82 | 6.69 | 150 | 6.12 | | 2.33 |
| | Middle Atlantic | N (%) | 138 | 11.22 | 1921 | 7.33 | | 13.43 | 136 | 11.10 | 309 | 12.61 | | 4.67 |
| | Mountain | N (%) | 21 | 1.71 | 1125 | 4.29 | | 15.21 | 21 | 1.71 | 39 | 1.59 | | 0.96 |
| | New England | N (%) | 68 | 5.53 | 1820 | 6.95 | | 5.87 | 68 | 5.55 | 126 | 5.14 | | 1.81 |
| | Pacific | N (%) | 12 | 0.98 | 775 | 2.96 | | 14.31 | 12 | 0.98 | 25 | 1.02 | | 0.41 |
| | South Atl/West South Crl | N (%) | 387 | 31.46 | 5731 | 21.88 | | 21.81 | 385 | 31.43 | 734 | 29.96 | | 3.19 |
| | West North Central | N (%) | 125 | 10.16 | 3501 | 13.36 | | 9.95 | 124 | 10.12 | 274 | 11.18 | | 3.44 |
| | Other/Unknown | N (%) | 30 | 2.44 | 867 | 3.31 | | 5.21 | 30 | 2.45 | 52 | 2.12 | | 2.19 |
| Elixhauser Comorbidity Index (ECI) | Low ECI Score <0 | N (%) | 7 | 0.57 | 136 | 0.52 | | 0.68 | 7 | 0.57 | 12 | 0.49 | | 1.12 |
| | Mild ECI score 0 | N (%) | 2 | 0.16 | 138 | 0.53 | | 6.22 | 2 | 0.16 | 11 | 0.45 | | 5.17 |
| | Moderate ECI Score 1-4 | N (%) | 30 | 2.44 | 859 | 3.28 | | 5.04 | 30 | 2.45 | 83 | 3.39 | | 5.58 |
| | Severe ECI Score ≥ 5 | N (%) | 1191 | 96.83 | 25064 | 95.68 | | 6.08 | 1186 | 96.82 | 2344 | 95.67 | | 6.01 |

| | | Pre-match | | | | | | Post-match | | | | | | |
|---------------------------------|---|----------------------|-----|----------|-------|---------|---------|----------------------|-----|----------|------|---------|--------|------|
| | | Sacubitril/valsartan | | ACEi/ARB | | | | Sacubitril/valsartan | | ACEi/ARB | | | | |
| | Statistic | N | % | N | % | P value | SMD | N | % | N | % | P value | SMD | |
| Comorbidities, signs & symptoms | Altered consciousness | N (%) | 39 | 3.17 | 2094 | 7.99 | <0.0001 | 21.12 | 39 | 3.18 | 81 | 3.31 | 0.8439 | 0.69 |
| | Anemia (including iron deficiency) | N (%) | 79 | 6.42 | 2258 | 8.62 | 0.0070 | 8.34 | 79 | 6.45 | 156 | 6.37 | 0.9240 | 0.33 |
| | Chronic Obstructive Pulmonary Disease | N (%) | 214 | 17.40 | 5817 | 22.20 | <0.0001 | 12.08 | 214 | 17.47 | 393 | 16.04 | 0.2716 | 3.83 |
| | Dementia | N (%) | 35 | 2.85 | 1569 | 5.99 | <0.0001 | 15.34 | 35 | 2.86 | 90 | 3.67 | 0.1981 | 4.59 |
| | Depression | N (%) | 125 | 10.16 | 3381 | 12.91 | 0.0049 | 8.60 | 125 | 10.20 | 241 | 9.84 | 0.7259 | 1.22 |
| | Diabetes mellitus | N (%) | 405 | 32.93 | 8336 | 31.82 | 0.4157 | 2.36 | 404 | 32.98 | 802 | 32.73 | 0.8815 | 0.52 |
| | Dyslipidemia (including hypercholesterolemia) | N (%) | 725 | 58.94 | 14413 | 55.02 | 0.0068 | 7.93 | 721 | 58.86 | 1447 | 59.06 | 0.9056 | 0.41 |
| | Edema and fluid overload | N (%) | 156 | 12.68 | 3333 | 12.72 | 0.9673 | 0.12 | 155 | 12.65 | 301 | 12.29 | 0.7502 | 1.11 |
| | Hypertension | N (%) | 802 | 65.20 | 17680 | 67.49 | 0.0947 | 4.84 | 802 | 65.47 | 1612 | 65.80 | 0.8442 | 0.69 |
| | Renal Disease | N (%) | 365 | 29.67 | 6804 | 25.97 | 0.0039 | 8.27 | 362 | 29.55 | 768 | 31.35 | 0.2661 | 3.90 |

| | | Pre-match | | | | | | Post-match | | | | | |
|---|--|----------------------|-------|----------|-------|----------|-------|----------------------|-------|----------|-------|---------|------|
| | | Sacubitril/valsartan | | ACEi/ARB | | P value | SMD | Sacubitril/valsartan | | ACEi/ARB | | P value | SMD |
| | Statistic | N | % | N | % | | | N | % | N | % | | |
| Cardiac specific comorbidities, signs, symptoms and devices | Renal Failure | | | | | < 0.0001 | 12.10 | | | | | 0.1653 | 4.88 |
| | N (%) | 249 | 20.24 | 6630 | 25.31 | | | 249 | 20.33 | 547 | 22.33 | | |
| | Shortness of breath (excluding sleep apnea) | | | | | 0.4410 | 2.25 | | | | | 0.6051 | 1.81 |
| | N (%) | 534 | 43.41 | 11666 | 44.53 | | | 531 | 43.35 | 1084 | 44.24 | | |
| | Sleep apnea | | | | | 0.0279 | 6.23 | | | | | 0.1505 | 4.99 |
| | N (%) | 189 | 15.37 | 3455 | 13.19 | | | 188 | 15.35 | 333 | 13.59 | | |
| | Angina Pectoris | | | | | 0.4446 | 2.19 | | | | | 0.1283 | 5.24 |
| | N (%) | 84 | 6.83 | 1647 | 6.29 | | | 84 | 6.86 | 137 | 5.59 | | |
| | Atrial Fibrillation | | | | | 0.0401 | 5.95 | | | | | 0.8309 | 0.75 |
| | N (%) | 502 | 40.81 | 9930 | 37.91 | | | 498 | 40.65 | 1005 | 41.02 | | |
| | Cardiac arrhythmia (excluding atrial fibrillation) | | | | | 0.0034 | 8.61 | | | | | 0.9807 | 0.08 |
| | N (%) | 451 | 36.67 | 10704 | 40.86 | | | 451 | 36.82 | 903 | 36.86 | | |
| | Cardio resynchronization therapy device | | | | | < 0.0001 | 36.31 | | | | | 0.4748 | 2.51 |
| | N (%) | 316 | 25.69 | 3079 | 11.75 | | | 314 | 25.63 | 655 | 26.73 | | |
| | Cerebrovascular disease | | | | | 0.0036 | 8.88 | | | | | 0.0172 | 8.48 |
| | N (%) | 130 | 10.57 | 3524 | 13.45 | | | 128 | 10.45 | 323 | 13.18 | | |

| | | Pre-match | | | | | | | Post-match | | | | | |
|--|-----------------------------|----------------------|------|----------|-------|---------|----------|----------------------|------------|----------|------|---------|--------|------|
| | | Sacubitril/valsartan | | ACEi/ARB | | P value | SMD | Sacubitril/valsartan | | ACEi/ARB | | P value | SMD | |
| | Statistic | N | % | N | % | | | N | % | N | % | | | |
| Medications | Antiarrhythmic and digoxin | N (%) | 724 | 58.86 | 18627 | 71.10 | < 0.0001 | 25.88 | 722 | 58.94 | 1504 | 61.39 | 0.1521 | 5.00 |
| | Beta-blockers | N (%) | 440 | 35.77 | 13498 | 51.52 | < 0.0001 | 32.17 | 440 | 35.92 | 899 | 36.69 | 0.6451 | 1.61 |
| | Calcium channel blockers | N (%) | 201 | 16.34 | 6962 | 26.58 | < 0.0001 | 25.12 | 201 | 16.41 | 413 | 16.86 | 0.7309 | 1.21 |
| | Lipid lowering drugs | N (%) | 651 | 52.93 | 15340 | 58.56 | < 0.0001 | 11.35 | 648 | 52.90 | 1316 | 53.71 | 0.6400 | 1.64 |
| | Loop diuretics | N (%) | 833 | 67.72 | 17748 | 67.75 | 0.9856 | 0.05 | 831 | 67.84 | 1648 | 67.27 | 0.7274 | 1.22 |
| | Nitroglycerin | N (%) | 683 | 55.53 | 16280 | 62.14 | < 0.0001 | 13.47 | 680 | 55.51 | 1395 | 56.94 | 0.4103 | 2.88 |
| | Potassium sparing diuretics | N (%) | 396 | 32.20 | 6381 | 24.36 | < 0.0001 | 17.47 | 394 | 32.16 | 822 | 33.55 | 0.3993 | 2.95 |
| Previous heart failure (HF) hospitalizations | 0 | N (%) | 1028 | 83.58 | 23442 | 89.48 | < 0.0001 | 17.37 | 1024 | 83.59 | 2037 | 83.14 | 0.9698 | 1.21 |
| | 1 | N (%) | 154 | 12.52 | 2168 | 8.28 | | 13.94 | 154 | 12.57 | 307 | 12.53 | | 0.12 |
| | 2 | N (%) | 29 | 2.36 | 388 | 1.48 | | 6.39 | 28 | 2.29 | 65 | 2.65 | | 2.37 |
| | 3 | N (%) | 9 | 0.73 | 106 | 0.40 | | 4.35 | 9 | 0.73 | 19 | 0.78 | | 0.47 |
| | ≥ 4 | N (%) | 10 | 0.81 | 93 | 0.36 | | 6.01 | 10 | 0.82 | 22 | 0.90 | | 0.89 |

| | | Pre-match | | | | | | Post-match | | | | | | |
|------------------------------------|--|----------------------|-------|----------|-------|----------|--------|----------------------|-----|----------|------|---------|--------|------|
| | | Sacubitril/valsartan | | ACEi/ARB | | | | Sacubitril/valsartan | | ACEi/ARB | | | | |
| | Statistic | N | % | N | % | P value | SMD | N | % | N | % | P value | SMD | |
| Left ventricular ejection fraction | Ischemic heart disease (including myocardial infarction) | N (%) | 789 | 64.15 | 17084 | 65.21 | 0.4426 | 2.23 | 785 | 64.08 | 1611 | 65.76 | 0.3154 | 3.51 |
| | Peripheral Artery Disease | N (%) | 70 | 5.69 | 1668 | 6.37 | 0.3415 | 2.84 | 69 | 5.63 | 155 | 6.33 | 0.4072 | 2.93 |
| | Peripheral vascular disease | N (%) | 102 | 8.29 | 2391 | 9.13 | 0.3198 | 2.96 | 102 | 8.33 | 215 | 8.78 | 0.6477 | 1.61 |
| | Tachycardia | N (%) | 274 | 22.28 | 5130 | 19.58 | 0.0203 | 6.63 | 272 | 22.20 | 553 | 22.57 | 0.8014 | 0.88 |
| | Valvular heart disease | N (%) | 577 | 46.91 | 11457 | 43.73 | 0.0282 | 6.38 | 574 | 46.86 | 1177 | 48.04 | 0.4982 | 2.37 |
| | N (% non-missing) | 1230 | 100 | 26197 | 100 | < 0.0001 | | 1225 | 100 | 2450 | 100 | 0.5368 | | |
| | Mean | 26.61 | . | 29.05 | . | | | 26.66 | . | 26.42 | . | | | |
| | SD | 8.31 | . | 8.21 | . | | 29.55 | 8.30 | . | 8.59 | . | | 2.76 | |
| | Min | 9.80 | . | 0 | . | | | 9.80 | . | 5 | . | | | |
| | Max | 40 | . | 40 | . | | | 40 | . | 40 | . | | | |
| 25% Percentile | 20 | . | 22.50 | . | | | 20 | . | 20 | . | | | | |
| Median | 27.25 | . | 30 | . | | | 27.50 | . | 26 | . | | | | |
| 75% Percentile | 34 | . | 35 | . | | | 34 | . | 35 | . | | | | |

| | | Pre-match | | | | | | | Post-match | | | | | | |
|--|-----|----------------------|------|----------|-------|---------|----------|----------------------|------------|----------|------|---------|--------|------|--|
| | | Sacubitril/valsartan | | ACEi/ARB | | P value | SMD | Sacubitril/valsartan | | ACEi/ARB | | P value | SMD | | |
| Statistic | | N | % | N | % | | | N | % | N | % | | | | |
| Previous all-cause hospitalizations | 0 | N (%) | 791 | 64.31 | 16557 | 63.20 | 0.8660 | 2.30 | 788 | 64.33 | 1505 | 61.43 | 0.3395 | 6.00 | |
| | 1 | N (%) | 255 | 20.73 | 5427 | 20.72 | | 0.04 | 254 | 20.73 | 533 | 21.76 | | 2.49 | |
| | 2 | N (%) | 90 | 7.32 | 2011 | 7.68 | | 1.36 | 89 | 7.27 | 192 | 7.84 | | 2.16 | |
| | 3 | N (%) | 41 | 3.33 | 940 | 3.59 | | 1.39 | 41 | 3.35 | 82 | 3.35 | | 0.00 | |
| | ≥4 | N (%) | 53 | 4.31 | 1262 | 4.82 | | 2.44 | 53 | 4.33 | 138 | 5.63 | | 6.01 | |
| Previous HF specific outpatient visits | 0 | N (%) | 320 | 26.02 | 12853 | 49.06 | < 0.0001 | 49.00 | 320 | 26.12 | 617 | 25.18 | 0.9498 | 2.15 | |
| | 1 | N (%) | 245 | 19.92 | 5301 | 20.24 | | 0.79 | 245 | 20.00 | 496 | 20.24 | | 0.61 | |
| | 2 | N (%) | 146 | 11.87 | 2754 | 10.51 | | 4.31 | 146 | 11.92 | 306 | 12.49 | | 1.75 | |
| | 3 | N (%) | 122 | 9.92 | 1559 | 5.95 | | 14.72 | 121 | 9.88 | 253 | 10.33 | | 1.49 | |
| | ≥ 4 | N (%) | 397 | 32.28 | 3730 | 14.24 | | 43.70 | 393 | 32.08 | 778 | 31.76 | | 0.70 | |
| Previous HF specific ER visits | 0 | N (%) | 1193 | 96.99 | 25594 | 97.70 | 0.0133 | 4.39 | 1188 | 96.98 | 2360 | 96.33 | 0.0756 | 3.63 | |
| | 1 | N (%) | 29 | 2.36 | 542 | 2.07 | | 1.96 | 29 | 2.37 | 81 | 3.31 | | 5.66 | |
| | 2 | N (%) | 5 | 0.41 | 48 | 0.18 | | 4.12 | 5 | 0.41 | 9 | 0.37 | | 0.66 | |
| | 3 | N (%) | 1 | 0.08 | 7 | 0.03 | | 2.35 | 5 | 0.41 | 9 | 0.37 | | 0.66 | |
| | ≥4 | N (%) | 2 | 0.16 | 6 | 0.02 | | 4.59 | 5 | 0.41 | 9 | 0.37 | | 0.66 | |

SD: Standard deviation; SMD: Standardized mean difference, HF: heart failure, ER: emergency room

Primary Outcome Result(s)

The rate of HF hospitalization events of the Naive sacubitril/valsartan cohort was similar compared with the Naive ACEi/ARB cohort; but this difference was not statistically significant (RR: 1.003, 95% CI: 0.907-1.108, p = 0.959).

Compare rates of HF hospitalization events for Naive sacubitril/valsartan cohort and Naive ACEi/ARB cohort

| Model variable information | RR estimate | Adjusted model 95% CI | | p value |
|----------------------------|-------------|--------------------------|-------|---------|
| | | Lower | Upper | |
| Pre-match | | | | |
| Treatment | | | | |
| Sacubitril/valsartan | 0.988 | 0.913 | 1.069 | 0.766 |
| ACEi/ARB | 1 (REF) | . | . | . |
| Post-match | | | | |
| Treatment | | | | |
| Sacubitril/valsartan | 1.003 | 0.907 | 1.108 | 0.959 |
| ACEi/ARB | 1 (REF) | . | . | . |

95% CI: 95% confidence interval, RR: rate ratio, REF: reference

Secondary Outcome Result(s)

The rate of HF hospitalization events of the Truly naive sacubitril/valsartan cohort was slightly higher compared with the Truly naive ACEi/ARB cohort; but this difference was not statistically significant (RR: 1.045; 95% CI: 0.890-1.227, p = 0.591)

**Compare rates of HF hospitalization events: Truly naive
sacubitril/valsartan cohort vs. Truly naive ACEi/ARB cohort**

| Model variable information | RR estimate | Adjusted model 95% CI | | p value |
|----------------------------|-------------|--------------------------|-------|---------|
| | | Lower | Upper | |
| Pre-match | | | | |
| Treatment | | | | |
| Sacubitril/valsartan | 1.018 | 0.891 | 1.163 | 0.797 |
| ACEI/ARB | 1 (REF) | . | . | . |
| Post-match | | | | |
| Treatment | | | | |
| Sacubitril/valsartan | 1.045 | 0.890 | 1.227 | 0.591 |
| ACEI/ARB | 1 (REF) | . | . | . |

95% CI: 95% confidence interval, RR: rate ratio, REF: reference

The time to first HF hospitalization events of the Naive Sacubitril/valsartan cohort was slightly higher compared with the Naive ACEi/ARB cohort in both the models; but this difference was not statistically significant (Option 1: HR: 1.024; 95% CI: 0.935-1.121, p = 0.61; Option 2: HR: 1.016; 95% CI: 0.928-1.113, p = 0.73)



Compare time to first HF hospitalization events: Naive sacubitril/valsartan cohort vs. Naive ACEi/ARB cohort

| | Adjusted model (Option 1) | | | | Adjusted model (Option 2) | | | |
|----------------------------|---------------------------|-------|-------|---------|---------------------------|-------|-------|---------|
| | 95% CI | | | | 95% CI | | | |
| Model variable information | HR estimate | Lower | Upper | p value | HR estimate | Lower | Upper | p value |
| Pre-match | | | | | | | | |
| Treatment | | | | | | | | |
| Sacubitril/valsartan | 1.059 | 0.985 | 1.138 | 0.12 | 1.037 | 0.962 | 1.118 | 0.34 |
| ACEi/ARB | 1 (REF) | . | . | . | 1 (REF) | . | . | . |
| Post-match | | | | | | | | |
| Treatment | | | | | | | | |
| Sacubitril/valsartan | 1.024 | 0.935 | 1.121 | 0.61 | 1.016 | 0.928 | 1.113 | 0.73 |
| ACEi/ARB | 1 (REF) | . | . | . | 1 (REF) | . | . | . |

95% CI: 95% confidence interval, HR: hazard ratio, REF: reference

The rate of HF hospitalizations and ER visit events of the Naive sacubitril/valsartan cohort was statistically significantly lower compared with the Naive ACEi/ARB cohort (RR: 0.86962; 95% CI: 0.80726-0.93680, p = 0.00023)

Compare rates of HF hospitalizations and ER visit events: Naive sacubitril/valsartan cohort vs. Naive ACEi/ARB cohort

| Model variable information | RR Estimate | Adjusted model 95% CI | | p value |
|----------------------------|-------------|--------------------------|---------|----------|
| | | Lower | Upper | |
| Pre-match | | | | |
| Treatment | | | | |
| Sacubitril/valsartan | 0.74601 | 0.70351 | 0.79107 | < 0.0001 |
| ACEi/ARB | 1 (REF) | - | - | - |
| Post-match | | | | |
| Treatment | | | | |
| Sacubitril/valsartan | 0.86962 | 0.80726 | 0.93680 | 0.00023 |
| ACEi/ARB | 1 (REF) | - | - | - |

95% CI: 95% confidence interval, RR: rate ratio, REF: reference

The time to first HF hospitalization or HF ER visit events of the Naive sacubitril/valsartan cohort was statistically significantly lower compared with the Naive ACEi/ARB cohort in both the models (Option 1: HR: 0.917, 95% CI: 0.858-0.981, $p = 0.011$; Option 2: HR: 0.912, 95% CI: 0.853-0.975, $p = 0.006$)

Compare time to first HF hospitalization or HF ER visit events: Naive sacubitril/valsartan cohort vs. Naive ACEi/ARB cohort

| Model variable information | Adjusted model (Option 1) | | | | Adjusted model (Option 2) | | | |
|----------------------------|---------------------------|--------|-------|---------|---------------------------|--------|-------|---------|
| | HR estimate | 95% CI | | p value | HR estimate | 95% CI | | p value |
| | | Lower | Upper | | | Lower | Upper | |
| Pre-match | | | | | | | | |
| Treatment | | | | | | | | |
| Sacubitril/valsartan | 0.863 | 0.817 | 0.911 | < 0.001 | 0.905 | 0.856 | 0.957 | < 0.001 |
| ACEi/ARB | 1 (REF) | . | . | . | 1 (REF) | . | . | . |
| Post-match | | | | | | | | |
| Treatment | | | | | | | | |
| Sacubitril/valsartan | 0.917 | 0.858 | 0.981 | 0.011 | 0.912 | 0.853 | 0.975 | 0.006 |
| ACEi/ARB | 1 (REF) | . | . | . | 1 (REF) | . | . | . |

95% CI: 95% confidence interval, HR: hazard ratio, REF: reference

The rate of all-cause hospitalization events of the Naive sacubitril/valsartan cohort was statistically significantly lower compared with the Naive ACEi/ARB cohort (RR: 0.867, 95% CI: 0.807-0.932, $p < 0.0001$)

**Compare rate of all-cause hospitalization events: Naive
sacubitril/valsartan cohort vs. Naive ACEi/ARB cohort**

| Model variable information | RR estimate | Adjusted model 95% CI | | p value |
|----------------------------|-------------|--------------------------|-------|---------|
| | | Lower | Upper | |
| Pre-match | | | | |
| Treatment | | | | |
| Sacubitril/valsartan | 0.711 | 0.673 | 0.751 | < 0.001 |
| ACEi/ARB | 1 (REF) | . | . | . |
| Post-match | | | | |
| Treatment | | | | |
| Sacubitril/valsartan | 0.867 | 0.807 | 0.932 | < 0.001 |
| ACEi/ARB | 1 (REF) | . | . | . |

95% CI: 95% confidence interval, RR: rate ratio, REF: reference

The time to first all-cause hospitalization events of the Naive sacubitril/valsartan cohort was statistically significantly lower compared with the Naive ACEi/ARB cohort in both the models (Option 1: HR: 0.850, 95% CI: 0.797-0.905, $p < 0.001$; Option 2: HR: 0.839, 95% CI: 0.788-0.894, $p < 0.001$)

Compare time to first all-cause hospitalization events: Naive sacubitril/valsartan cohort vs. Naive ACEi/ARB cohort

| Model variable information | Adjusted model (Option 1) | | | | Adjusted model (Option 2) | | | |
|----------------------------|---------------------------|--------|-------|---------|---------------------------|--------|-------|---------|
| | HR estimate | 95% CI | | p value | HR estimate | 95% CI | | p value |
| | | Lower | Upper | | | Lower | Upper | |
| Pre-match | | | | | | | | |
| Treatment | | | | | | | | |
| Sacubitril/valsartan | 0.738 | 0.700 | 0.777 | < 0.001 | 0.839 | 0.796 | 0.885 | < 0.001 |
| ACEi/ARB | 1 (REF) | . | . | . | 1 (REF) | . | . | . |
| Post-match | | | | | | | | |
| Treatment | | | | | | | | |
| Sacubitril/valsartan | 0.850 | 0.797 | 0.905 | < 0.001 | 0.839 | 0.788 | 0.894 | < 0.001 |
| ACEi/ARB | 1 (REF) | . | . | . | 1 (REF) | . | . | . |

95% CI: 95% confidence interval, HR: hazard ratio, REF: reference

The rate of CV hospitalization of the Naive sacubitril/valsartan cohort was slightly lower compared with the Naive ACEi/ARB cohort; but this difference was not statistically significant (RR: 0.939, 95% CI: 0.865-1.020, p = 0.13)

Compare rates of cardiovascular hospitalization events: Naive sacubitril/valsartan cohort vs. Naive ACEi/ARB cohort

| Model variable information | RR estimate | Adjusted model 95% CI | | p value |
|----------------------------|-------------|--------------------------|-------|---------|
| | | Lower | Upper | |
| Pre-match | | | | |
| Treatment | | | | |
| Sacubitril/valsartan | 0.837 | 0.785 | 0.892 | < 0.001 |
| ACEi/ARB | 1 (REF) | . | . | . |
| Post-match | | | | |
| Treatment | | | | |
| Sacubitril/valsartan | 0.939 | 0.865 | 1.020 | 0.13 |
| ACEi/ARB | 1 (REF) | . | . | . |

95% CI: 95% confidence interval, RR: rate ratio, REF: reference

Safety Results

Not applicable

Other Relevant Findings

None

Conclusion

The use of sacubitril/valsartan in Renin-angiotensin-aldosterone system inhibitors (RAASi)-naive patients with heart failure with reduced ejection fraction (HFrEF) resulted in lower rates of all-cause hospitalization and in a composite of Heart failure (HF) hospitalization and Emergency Rooms (ER) visit compared with ACEi/ARB treatment. The rates of HF and CV hospitalizations were similar between the two cohorts. These findings further strengthen the evidence base for sacubitril/valsartan in ACEi/ARB-naive patients. Initiating sacubitril/valsartan directly in RAASi-naive patients with HFrEF can reduce total hospitalizations, thereby reducing the clinical and economic burden of HFrEF in these patients.

Date of Clinical Study Report

15 October 2021