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Comparative Effectiveness of Sacubitril-Valsartan versus ACE/ARB Therapy in Heart Failure with Reduced Ejection Fraction

Nicholas Y. Tan, M.D., M.S.[a], **Lindsey R. Sangaralingham, M.P.H.**[b], **S. Jeson Sangaralingham, M.S., Ph.D.**[a], **Xiaoxi Yao, Ph.D, MPH**[b,c], **Nilay D. Shah, Ph.D.**[b,c,d], **Shannon M. Dunlay, M.D., M.S.**[a,b]

[a]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota

[b]The Robert and Patricia E. Kern Center for the Sciences of Healthcare Delivery, Mayo Clinic, Rochester, Minnesota

[c]Division of Health Care Policy and Research in the Department of Health Services Research, Mayo Clinic, Rochester, Minnesota

[d]OptumLabs, Cambridge, Massachusetts

Abstract

Background: Sacubitril-valsartan reduced risks of death and hospitalization for heart failure (HF) versus enalapril in ambulatory patients with HF and reduced ejection fraction in the PARADIGM-HF trial. However, the comparative effectiveness of sacubitril-valsartan and ACE inhibitors / angiotensin receptor blockers (ACE/ARB) in patients treated in routine clinical practice is unclear.

Objectives: To compare the effectiveness of sacubitril-valsartan and ACE/ARB in systolic HF.

Methods: We identified patients with systolic HF in a U.S. administrative claims database treated with sacubitril-valsartan or ACE/ARB from 07/01/15–02/01/18. One-to-one propensity score matching was used to balance patients on 29 clinical variables. Cox models were used to compare outcomes between treatment groups.

Results: A total of 7893 matched pairs were included; mean (SD) follow-up was 6.3 (5.4) months. Sacubitril-valsartan was associated with lower risks of all-cause mortality or all-cause hospitalization (HR 0.86, 95% CI 0.81–0.91, p<0.001), all-cause mortality (HR 0.80, 95% CI 0.66–0.97, p=0.027), and all-cause hospitalization (HR 0.86, 95% CI 0.80–0.91, p<0.001), but not HF hospitalization (HR 1.07, 95% CI 0.96–1.19, p=0.26). A lower risk of the primary outcome with sacubitril-valsartan was observed in whites (HR 0.83, 95% CI 0.76–0.90) but not blacks (21% of population, HR 1.00, 95% CI 0.88–1.15, interaction p=0.032). No statistically significant differences in treatment response by sex or age were observed.

Correspondence: Shannon M. Dunlay, M.D., M.S.,Department of Cardiovascular Medicine, Mayo Clinic 200 1st Street SW, Rochester, MN 55905, dunlay.shannon@mayo.edu, Phone: 507-284-8087 Fax: 507-284-1516.

Conclusion: Sacubitril-valsartan was associated with lower risks of death and hospitalization compared with ACE/ARB in a heterogeneous cohort of patients with systolic HF. However, our finding that outcomes with sacubitril-valsartan and ACE/ARBs were similar in black patients warrants further evaluation.

Keywords

heart failure; medication; mortality; hospitalization; sacubitril-valsartan

Introduction

Medical therapy for heart failure with reduced ejection fraction (HFrEF) has evolved over the last several decades due to the identification of effective pharmacotherapies that have significantly reduced morbidity and mortality. In 2014, the first-in-class small molecule LCZ696, which combined the neprilysin inhibitor sacubitril with the angiotensin II receptor blocker (ARB) valsartan, was shown to decrease all-cause mortality by 16% and HF hospitalization by 21% compared with enalapril in patients with symptomatic HFrEF enrolled in the Prospective Comparison of Angiotensin II Receptor Blocker Neprilysin Inhibitor with Angiotensin Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in HF (PARADIGM-HF) trial.(1) In July 2015, sacubitril-valsartan was approved by the U.S. FDA for use in chronic symptomatic HFrEF. Despite receiving a Class I recommendation in HF guidelines,(2,3) use of sacubitril-valsartan in clinical practice has been lower than expected.(4,5)

While numerous factors can impact the adoption of novel pharmacotherapies, uncertainty about the effectiveness of sacubitril-valsartan outside of clinical trial populations may have contributed to slow uptake. This uncertainty is especially pertinent for patient groups historically underrepresented in clinical trials, such as women, older individuals, and racial and ethnic minorities.(6) In PARADIGM-HF, only 5% of participants were black, and 21% were women, and as such, confidence in the effectiveness of sacubitril-valsartan in these populations is less robust. Furthermore, observational data suggest that clinicians are prescribing sacubitril-valsartan in ways that vary from the PARADIGM-HF treatment protocol.(5) Many patients initiated on sacubitril-valsartan have not been taking an angiotensin converting enzyme inhibitor (ACE) or ARB, and the effectiveness of sacubitril-valsartan in ambulatory ACE/ARB naïve patients is unknown.

To address potential uncertainties about the effectiveness of sacubitril-valsartan in real-world clinical practice, we compared differences in mortality and hospitalization in patients with HFrEF taking sacubitril-valsartan and ACE/ARB therapy represented in a large commercial insurance claims database.

Methods

Data Source.

This study was a retrospective cohort study from the OptumLabs® Data Warehouse (OLDW), which includes claims data for privately insured and Medicare Advantage

enrollees in a large, private, U.S. health plan.(7,8) We included individuals with both medical and pharmacy insurance coverage. The study was exempt from institutional board review as it used pre-existing de-identified data.

Study Population.

We identified all individuals at least 18 years of age that filled a prescription for sacubitril-valsartan or ACE/ARB between 07/01/2015 and 02/01/2018. We restricted to those with a prior diagnosis of systolic HF using International Classification of Diseases [ICD] billing codes (9^{th} Edition, 428.2X; 10^{th} Edition, I50.2X). This approach is 97.7% specific for individuals with HF and an ejection fraction (EF)<45%/(5,9) Patients were required to have ≥180 days of continuous enrollment in a medical health plan with prescription coverage prior to their index medication fill date to ensure adequate capture of baseline characteristics. The index date of the sacubitril-valsartan cohort was a patient's first prescription of sacubitril-valsartan, whereas the index date of the ACE/ARB cohort was the first fill of an ACE/ARB in the study period after patients met the 180 day enrollment requirement. Patients in the sacubitril-valsartan cohort could have ACE/ARB prescriptions prior to their index date.

Baseline Characteristics.

Clinical variables were defined by the presence of a claim with corresponding diagnosis codes, procedure codes, or prescription fills. Race in OLDW is classified based on self-report or derived rule sets (10,11), and is classified here as non-Hispanic white (white), non-Hispanic black (black) or other. Household income is estimated based on a model using both public and private consumer data. Comorbidities were captured by ICD-9 or ICD-10 codes in any position on claims in the 6 months prior to index prescription fill.(12) Prior hospitalizations,cardiologist, and primary care office visits were captured using medical claims. Prior medication use was defined as having a prescription fill within 120 days prior to the index date. The total daily dose of the ACE/ARB was categorized as low, intermediate or high (Supplementary Table S1).

Follow-Up.

Follow-up started from the index date and continued until end of treatment. End of treatment was defined as the earliest date of: discontinuation of index medication, end of enrollment in health plan, death, or end of the study period (February 1, 2018). Discontinuation of index medication was defined as not refilling a prescription within 30 days of end of supply.

We calculated adherence using the medical possession ratio (MPR).(13) Specifically, we used the prescription fill dates and days supply for each medication group (sacubitril-valsartan or ACE/ARB) to calculate total days supply and divided by the number of days in the follow-up period.

Study Outcomes.

The primary outcome was a composite of all-cause mortality or all-cause hospitalization. Mortality was identified using the Social Security Death Master File and discharge status of expired after a hospitalization.(14) All-cause hospitalization was captured using medical

claims. Secondary outcomes included all-cause mortality, all-cause hospitalization, and HF hospitalization. HF hospitalization was defined as a hospitalization with primary ICD-9 codes 428.X, 402.X1, 404.X1, 404.X3 or ICD-10 codes I11.0, I13.0, I13.2, or I50. (15–17) To assess differences in safety, we compared the risks of angioedema (ICD-9 995.1 or ICD-10 T78.3XXA), hypotension (ICD-9 458 or ICD-10 I95), and hyperkalemia (ICD-9 276.7 or ICD-10 E87.5) between treatment groups during follow-up. We included hospitalizations or outpatient visits where the ICD codes were listed as the primary diagnosis.

Statistical Analysis.

We used propensity score matching to identify patients treated with ACE/ARB who were similar to those treated with sacubitril-valsartan. Logistic regression was used to estimate the probability of being treated with sacubitril-valsartan. Covariates included in the logistic model were age, sex, race/ethnicity, census region, depression, renal failure, cardiac arrhythmia, peripheral vascular disease, valvular heart disease, anemia, hypertension, diabetes, prior myocardial infarction, dementia, cerebrovascular disease, chronic obstructive pulmonary disease, implantable cardioverter defibrillator (ICD), prior use of HF medications (beta blockers, loop diuretics, aldosterone antagonists, digoxin), strength of ACE/ARB dose (among prior/ current users), Charlson comorbidity index, office visit with a cardiologist and primary care provider, and hospitalization (all-cause, prior HF) in the last 6 months. One-to-one nearest-neighbor caliper matching was used to match patients based on the logit of the propensity score using a caliper equal to 0.2 of the standard deviation of the logit of the propensity score (18). To account for potential effects of initiating renin-angiotensin therapy, we exact matched new users of sacubitril-valsartan that had not used an ACE/ARB in the last 6 months to new users of ACE/ARB. For those switching to sacubitril-valsartan from ACE/ARB (had filled a prescription for ACE/ARB in prior 6 months), we matched to prevalent ACE/ARB users. Standardized difference was used to assess the balance of covariates after matching, with a difference of no more than 10% considered acceptable.(19)

Cox proportional hazards regression was used to compare the risk of outcomes between treatment groups in the propensity-matched cohort. Robust sandwich estimates were included to account for clustering within matched sets.(20) The proportional hazards assumption was tested on the basis of Schoenfeld residuals and found to be valid.(21) Differences in hazard ratios (HR) by subgroups of interest were tested using interaction terms. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC) and Stata version 14.1 (StataCorp).

Sensitivity Analyses.

First, we required at least 14 days of follow-up after cohort entry; results were similar (data not shown). Second, to ensure that the two treatment groups were well balanced following propensity matching, we compared laboratory values pre- and post-matching where available, including serum creatinine, calcium, albumin, hemoglobin and sodium (Supplementary Table S2). The values and the proportion of missing values were balanced after matching. Finally, analysis using a falsification endpoint was performed to test for

residual confounding.(22) Risk of outpatient urinary tract infection was selected as was unlikely to be impacted by treatment with sacubitril-valsartan versus ACE/ARB.

Results

Patient Characteristics.

A total of 8291 and 83318 adults filling a prescription for sacubitril-valsartan or ACE/ARB, respectively, were identified. Prior to matching, patients initiating sacubitril-valsartan were more often men, more often taking evidence-based HF medications, and more likely to have seen a cardiologist recently (Table 1). The final propensity-matched cohort included 7893 pairs taking sacubitril-valsartan or ACE/ARB. Overall, demographic and clinical characteristics were well-balanced between the two treatment groups (standardized differences <10%, Table 1). One-third of patients were women. There was excellent representation of racial and ethnic minority groups (20% black, 11% Hispanic). Over one-third of patients initiating sacubitril-valsartan had not filled a prescription for an ACE or ARB in the last 6 months. Adherence in both treatment groups was high, with mean MPRs of 0.94 (SD 0.096) and 0.98 (SD 0.05) and in the sacubitril-valsartan and ACE/ARB groups, respectively. Adherence to sacubitril-valsartan (mean MPR 0.93 vs. 0.95) and ACE/ARBs (mean MPR 0.97 vs. 0.98) was numerically slightly lower in black compared with white patients.

Outcomes.

The mean (SD) and median (IQR) follow-up times were 6.3(5.4) and 4.8(2.1–8.4) months, respectively. The primary outcome occurred in 1764(22.3%) individuals treated with sacubitril-valsartan and 2110(26.7%) individuals taking ACE/ARBs. Compared to ACE/ARB, sacubitril-valsartan was associated with a lower risk of all-cause mortality or all-cause hospitalization during follow-up (HR 0.86; 95% confidence interval [CI] 0.81 to 0.91, p<0.001, Central Illustration A).

Sacubitril-valsartan was also associated with lower risks of both components of the primary endpoint. During follow-up, 2.2% (n=170) of patients treated with sacubitril-valsartan died, compared with 2.9% (n=229) treated with ACE/ARB (HR 0.80, 95% CI 0.66 to 0.97, p=0.027, Central Illustration B). All-cause hospitalization occurred in 1716(21.8%) patients taking sacubitril-valsartan versus 2060(26.1%) taking ACE/ARBs (HR 0.86, 95% CI 0.80 to 0.91, p<0.001, Central Illustration C). The proportion of all-cause hospitalizations that included a code for HF in any position was 84.7% in the overall cohort (86.9% sacubitril-valsartan and 80.9% ACE/ARB group).During follow-up, 646(17.2%) patients treated with sacubitril-valsartan were admitted with a primary diagnosis of HF, compared with 648(15.9%) patients taking ACE/ARBs. Risk of HF hospitalization did not differ in patients taking sacubitril-valsartan and ACE/ARB (HR 1.07, 95% CI 0.96 to 1.19, p=0.26, Central Illustration D).Kaplan-Meier curves extended to two years of follow-up are included in the Supplementary Material (Figure S1).

Sacubitril-valsartan was associated with a higher risk of hypotension (3.4 vs. 2.5 events per 100 person-years, HR 1.35, 95% CI 1.05 to 1.75, p=0.022) compared with ACE/ARB

(Table S3). No difference in risk of hyperkalemia was observed (0.89 vs. 0.84 events per 100 person-years, HR 1.05, 95% CI 0.66 to 1.67, p=0.84). Angioedema risk was very low in both groups (<11 events total).

Subgroup Analyses.

Subgroup analyses for the combined endpoint of death or all-cause hospitalization are shown in Figure 1 and Tables S4-S7. Sacubitril-valsartan was associated with a lower risk of the combined endpoint compared with ACE/ARB in white patients (HR 0.83, 95% CI 0.76–0.90) and in non-black patients of other races/ ethnicities (HR 0.80, 95% CI 0.69–0.93), but not black patients (HR 1.00, 95% CI 0.88–1.15; interaction race* treatment p=0.032). A difference in the comparative risk of all-cause hospitalization in patients taking sacubitril-valsartan versus ACE/ARB by race was also observed (HR 0.83, 95% CI 0.76–0.90 in whites vs. HR 1.00, 95% CI 0.87–1.14 in blacks, interaction race*treatment p=0.045, Figure 2). There was a trend toward greater survival associated with sacubitril-valsartan use versus ACE/ARBs in white (HR 0.78, 95% CI 0.60–1.02) compared with black (HR 1.04, 95% CI 0.68–1.59) patients (Figure 3). To investigate if adherence impacted results observed, we excluded patients with poor adherence (MPR<0.80), and findings were similar. The HR (95% CI) associated with use of sacubitril-valsartan vs. ACE/ARB was 1.00 (0.87–1.12) for black patients, 0.82 (0.75–0.90) for whites, 0.81 (0.69–0.95) for other racial and ethnic groups (p value for interaction=0.040).

The magnitude of decreased risk of the primary outcome associated with sacubitril-valsartan was also more pronounced in patients without prior arrhythmia (HR 0.71, 95% CI 0.61–0.83) compared to patients with arrhythmias (HR 0.89, 95% CI 0.83–0.96; interaction arrhythmia*treatment p=0.006). This interaction of arrhythmia history and treatment was also observed for all-cause hospitalizations (p value for interaction<0.005, Figure 2) and HF hospitalizations (p value for interaction 0.024, Figure 4) Otherwise, treatment effects were similar by subgroup (p values for interaction>0.05, Figures 1–4). There were no differences in treatment response in men and women for all outcomes examined. There were no significant differences in treatment response by age (interaction >0.05 for all outcomes examined). For the combined endpoint of all-cause mortality or all-cause hospitalization, point estimates were similar in all three age groups examined (Figure 2). Conversely, sacubitril-valsartan was associated with a lower risk of HF hospitalization compared with ACE/ARB in younger patients, but the risk of HF hospitalization was higher with sacubitril-valsartan in the elderly (Central Illustration). However, differences in treatment response by age were not statistically significant (p value for interaction 0.07). Treatment effects were similar in patients who were and were not recently taking an ACE/ARB. While only a small percentage of patients (0.6%) initiated sacubitril-valsartan within one week of a HF hospitalization, the lower risk of the combined endpoint observed with sacubitril-valsartan compared with ACE/ARBs was similar in patients with and without a HF hospitalization in the last 6 months.

Sensitivity Analysis.

No difference in risk of urinary tract infection was observed in patients treated with sacubitril-valsartan versus ACE/ARB (HR 0.91, 95% CI 0.72–1.15, p=0.43).

Discussion

In this study of nearly 16,000 patients with HFrEF, those taking sacubitril-valsartan were significantly less likely to experience death or hospitalization from any cause compared with those on ACE/ARB therapy. The benefits observed with sacubitril-valsartan were similar in men and women and among those who were and were not taking an ACE/ARB previously. However, in contrast to patients of other races and ethnicities, outcomes with sacubitril-valsartan and ACE/ARBs were similar in black patients.

This study provides real-world effectiveness data comparing sacubitril-valsartan with ACE/ARB outside of a clinical trial. Our data suggest that patients prescribed sacubitril-valsartan in clinical practice are older (mean 68 vs. 64 years), more often women (33% vs. 22%), and more racially and ethnically diverse compared with participants in the PARADIGM-HF trial.(1) Despite these dissimilarities, the treatment benefits of sacubitril-valsartan were observed in both sexes and in patients with a variety of comorbidities. Sacubitril-valsartan was associated with better outcomes compared with ACE/ARB even in patients who had not been taking an ACE/ARB previously. The lower risk of all-cause mortality or all-cause hospitalization with sacubitril-valsartan was observed across the age spectrum. Hence, our data indicate that the benefits seen with sacubitril-valsartan in the PARADIGM-HF study are translatable to a representative population of patients with HFrEF in the U.S.

However, our observation that black patients had no better outcomes with sacubitril-valsartan compared with ACE/ARB suggests that further data are needed to fully understand the optimal treatment strategy for this population. Black patients were known to be underrepresented in PARADIGM-HF, with a total of 428 (5%) black patients included in both arms.(1) The recent PIONEER-HF trial enrolled a higher proportion of black patients (36%), but was a small study (n=881 total patients), so the absolute number of black patients enrolled was small.(23) Our study included more than 7 times the number of black patients in PARADIGM-HF and 10 times the number enrolled in PIONEER-HF. There is a growing body of literature demonstrating that the level of natriuretic peptides, which mediate a number of cardiorenal protective properties, vary across ethnic groups. African-Americans have lower natriuretic peptide levels, on average, than Caucasians.(24,25) This relative deficiency in natriuretic peptides has been hypothesized to contribute to an increased tendency for salt retention, hypertension, cardiac remodeling, and adverse cardiovascular outcomes.(26) Although the neprilysin inhibition from sacubitril may increase existing natriuretic peptide availability, this effect may be blunted in individuals who synthesize lower amounts of natriuretic peptides, providing a possible mechanism underlying the lack of benefit over ACE/ARBs we observed among black patients. More thorough investigation into potential racial differences in treatment effect and biological mechanisms mediating these differences are warranted.

Both patients with and without a history of arrhythmias experienced lower risk of the primary outcome with sacubitril-valsartan, but this effect was more pronounced among patients without a history of arrhythmias. Sacubitril-valsartan may be associated with decreased ventricular arrhythmia burden and ICD shocks, possibly due to reverse

remodeling (27,28). However, patients with arrhythmias may have also had more underlying comorbidities, which may have contributed to results observed. This finding is worthy of future study.

While patients treated with sacubitril-valsartan had lower risks of all-cause hospitalization compared with those treated with ACE/ARBs, the risk of hospitalization for HF was similar in both treatment groups. We were surprised by this given the large reduction in HF hospitalization risk with sacubitril-valsartan in PARADIGM-HF.(1) However, while we relied upon use of validated codes for HF hospitalization, the potential that differences in coding practices may have influenced the analysis of cause-specific hospitalization still exists. The fact that, despite matching on history of HF hospitalization in the baseline period, patients on sacubitril-valsartan still had a higher proportion of total hospitalizations where HF was coded in any position during follow-up, underscores that this may be the case. By selecting a measure that is not influenced by coding practices (all-cause hospitalization), we avoided this potential source of bias. Furthermore, while we found no statistically significant difference in treatment effects by age for outcomes examined in our study, there was some variation in point estimates of risk for HF hospitalization by age, suggesting that older patients on sacubitril-valsartan may have higher risk of HF hospitalization than those taking ACE/ARBs. Previously noted limitations to using codes to identify HF hospitalization may have contributed to these findings, which are in contrast to those observed in post-hoc analyses of PARADIGM-HF, where the benefits of sacubitril-valsartan were observed even in those 75 years and older.(29)

In-hospital initiation of sacubitril-valsartan was recently shown in an 881 patient randomized controlled trial to lead to a greater reduction in NT-proBNP compared with enalapril among patients hospitalized with acute decompensated HF.(24) In exploratory analyses, sacubitril-valsartan was also associated with greater reductions in risks of death and rehospitalization for HF at 8 weeks compared with enalapril. Our findings indicate that, to date, patients are rarely initiated on sacubitril-valsartan in the hospital. We suspect that practice patterns may change following publication of PIONEER-HF,(24) and the effectiveness of sacubitril-valsartan with ACE/ARB when initiated in hospitalized patients should be compared in future clinical practice studies.

Limitations and Strengths.

The OLDW includes patients enrolled in private and Medicare Advantage health plans; as such, our findings may not be generalizable to patients with other types of health insurance. The observational nature of the study precluded our ability to make conclusions regarding causality. The possibility of residual confounding between treatment groups cannot be ruled out despite the use of robust propensity matching techniques. The follow-up period was relatively short and it will be important to delineate long-term outcomes for sacubitril-valsartan in future investigations. Finally, there is the potential for misclassification when relying on billing codes for identifying comorbidities. However, to the best of our knowledge, this is the first study to compare risks of death and hospitalization in large numbers of patients with HFrEF prescribed sacubitril-valsartan and ACE/ARB therapies outside of a clinical trial. While randomized controlled trials are the gold standard way

to compare the effectiveness of two interventions, observational data can be incredibly helpful, as patients with HF treated in clinical practice are often different than those in clinical trials. Minorities, the elderly, women, and those with comorbidities have historically been underrepresented in clinical trials, but are treated with new therapies once available in clinical practice. Our study population is direct evidence of this phenomenon, as our population was older, had a higher proportion of women, blacks, and diabetics than patients enrolled in PARADIGM-HF. Furthermore, our study included nearly twice as many patients on sacubitril-valsartan as were enrolled in PARADIGM- HF. These data thereby add to our knowledge of the effectiveness of this novel HFrEF therapy in populations often underrepresented in clinical trials.

Conclusions.

In a large cohort of patients with HFrEF, sacubitril-valsartan was associated with lower risks of mortality and hospitalization when compared with ACE/ARB therapy. Our findings suggest that, unlike other racial and ethnic groups, outcomes with sacubitril-valsartan and ACE/ARBs were similar in black patients. More research is needed to determine if there are racial differences in treatment response to sacubitril-valsartan.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ACE/ARB	Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker
CI	confidence interval
COPD	chronic obstructive pulmonary disease
FDA	Food and Drug Administration
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
ICD	implantable cardioverter defibrillator

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Perspectives

Competency in Medical Knowledge:

In a large cohort of patients with systolic heart failure, use of sacubitril-valsartan was associated with lower risks of mortality or hospitalization compared with use ACE inhibitor / angiotensin receptor blocker (ACE/ARB) therapy.

Competency in Patient Care:

Sacubitril-valsartan is associated with lower risks of mortality and hospitalization compared with ACE/ARBs in patients with systolic heart failure.

Translational Outlook 1:

It will be essential to compare long term mortality and cardiovascular outcomes of sacubitril-valsartan against that of ACE/ARB therapy.

Translational Outlook 2:

More research is needed to determine if there are racial differences in treatment response to sacubitril-valsartan.

All-Cause Mortality or Hospitalization

Subgroup	Sacubitril-Valsartan No. of Patients	Sacubitril-Valsartan Event Rate per 100 Person-Years	ACE/ARB No. of Patients	ACE/ARB Event Rate per 100 Person-Years	HR (95%CI)	P for interaction
All Patients	7893	51.74	7893	60.12	0.86 (0.81, 0.91)	
Age, y						
18-64	2658	40.37	2787	50.18	0.80 (0.71, 0.90)	
65-74	2652	51.37	2633	59.09	0.87 (0.78, 0.97)	0.40
≥75	2583	64.30	2473	72.56	0.88 (0.80, 0.98)	
Gender						
Male	5268	48.88	5305	57.44	0.85 (0.78, 0.92)	0.71
Female	2625	57.84	2588	65.86	0.87 (0.78, 0.97)	
Race						
White	4690	47.79	4652	58.12	0.83 (0.76, 0.90)	
Black	1649	66.41	1608	62.50	1.00 (0.88, 1.15)	0.03
Other	1554	50.71	1633	63.82	0.80 (0.69, 0.93)	
Prior ACE/ARB						
No	2982	52.69	2982	65.60	0.80 (0.72, 0.89)	0.13
Yes	4911	51.23	4911	57.38	0.89 (0.82, 0.96)	
Renal Disease						
No	5280	40.73	5360	49.36	0.82 (0.76, 0.89)	0.18
Yes	2613	77.74	2533	86.88	0.90 (0.81, 0.99)	
Diabetes						
No	3620	40.92	3705	48.97	0.84 (0.76, 0.93)	0.55
Yes	4273	61.87	4188	70.47	0.87 (0.80, 0.94)	
Arrhythmia						
No	1816	35.30	1837	49.55	0.71 (0.61, 0.83)	<0.01
Yes	6077	56.69	6056	63.41	0.89 (0.83, 0.96)	
Prior HF Hospitalization						
No	6245	43.19	6283	49.47	0.87 (0.80, 0.94)	0.29
Yes	1648	90.36	1610	113.40	0.81 (0.72, 0.91)	

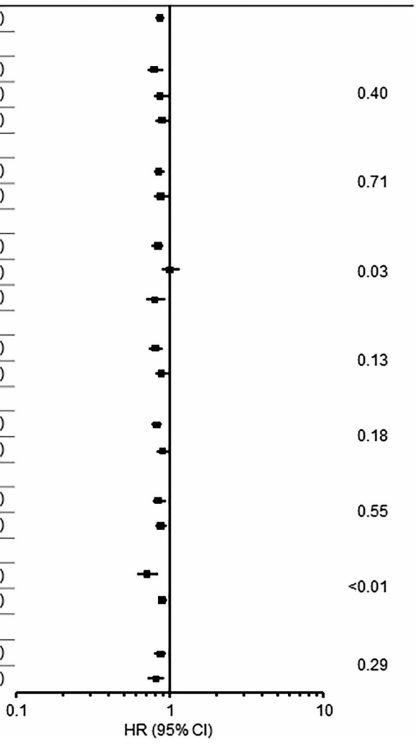


Figure 1: Differences in Risk of Mortality or All-Cause Hospitalization in Patients Taking Sacubitril-Valsartan Compared With ACE/ARB by Patient Characteristics

Differences in risk of all-cause hospitalization or mortality (HR, 95% CI and p value for interaction) according to patient baseline characteristics are shown.

All-Cause Hospitalization

Subgroup	Sacubitril-Valsartan No. of Patients	Sacubitril-Valsartan Event Rate per 100 Person-Years	ACE/ARB No. of Patients	ACE/ARB Event Rate per 100 Person-Years	HR (95%CI)	P for interaction
All Patients	7893	50.30	7893	58.66	0.86 (0.80, 0.91)	
Age, y						
18-64	2658	39.32	2787	49.43	0.79 (0.70, 0.89)	
65-74	2652	50.24	2633	57.73	0.87 (0.78, 0.97)	0.33
≥75	2583	62.14	2473	70.20	0.88 (0.80, 0.98)	
Gender						
Male	5268	47.40	5305	56.11	0.84 (0.78, 0.91)	0.60
Female	2625	56.52	2588	64.12	0.88 (0.79, 0.98)	
Race						
White	4690	46.63	4652	56.76	0.83 (0.76, 0.90)	
Black	1649	64.32	1608	61.13	1.00 (0.87, 1.14)	0.05
Other	1554	49.02	1633	61.95	0.80 (0.69, 0.93)	
Prior ACE/ARB						
No	2982	51.22	2982	64.64	0.79 (0.71, 0.88)	0.08
Yes	4911	49.82	4911	55.68	0.89 (0.82, 0.97)	
Renal Disease						
No	5280	39.63	5360	48.35	0.82 (0.75, 0.89)	0.15
Yes	2613	75.53	2533	84.31	0.90 (0.81, 0.99)	
Diabetes						
No	3620	39.81	3705	48.01	0.83 (0.75, 0.92)	0.48
Yes	4273	60.13	4188	68.55	0.87 (0.80, 0.94)	
Arrhythmia						
No	1816	34.27	1837	48.58	0.70 (0.60, 0.82)	<0.01
Yes	6077	55.14	6056	61.80	0.89 (0.83, 0.96)	
Prior HF Hospitalization						
No	6245	41.92	6283	48.42	0.86 (0.80, 0.93)	0.41
Yes	1648	88.18	1610	109.83	0.82 (0.73, 0.92)	

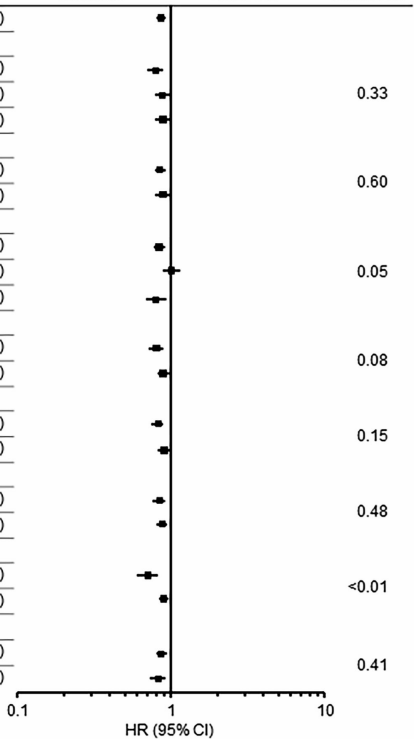


Figure 2: Differences in Risk of All-Cause Hospitalization in Patients Taking Sacubitril-Valsartan Compared With ACE/ARB by Patient Characteristics

Differences in risk of all-cause hospitalization (HR, 95% CI and p value for interaction) according to patient baseline characteristics are shown.

All-Cause Mortality

Subgroup	Sacubitril-Valsartan No. of Patients	Sacubitril-Valsartan Event Rate per 100 Person-Years	ACE/ARB No. of Patients	ACE/ARB Event Rate per 100 Person-Years	HR (95%CI)	P for interaction
All Patients	7893	4.31	7893	5.36	0.80 (0.65, 0.97)	
Age, y						
18-64	2658	2.06	2787	3.36	0.61 (0.38, 0.98)	
65-74	2652	4.52	2633	4.65	0.95 (0.68, 1.35)	0.28
≥75	2583	6.40	2473	8.28	0.77 (0.58, 1.02)	
Gender						
Male	5268	4.39	5305	5.37	0.82 (0.64, 1.04)	
Female	2625	4.14	2588	5.33	0.77 (0.54, 1.09)	0.82
Race						
White	4690	3.94	4652	4.99	0.78 (0.60, 1.02)	
Black	1649	5.50	1608	5.09	1.04 (0.68, 1.59)	0.24
Other	1554	4.37	1633	6.86	0.64 (0.41, 1.00)	
Prior ACE/ARB						
No	2982	3.93	2982	5.04	0.76 (0.54, 1.09)	
Yes	4911	4.51	4911	5.52	0.82 (0.64, 1.04)	0.80
Renal Disease						
No	5280	3.40	5360	4.00	0.84 (0.64, 1.11)	
Yes	2613	6.30	2533	8.44	0.74 (0.55, 0.99)	0.52
Diabetes						
No	3620	3.38	3705	4.87	0.69 (0.50, 0.95)	
Yes	4273	5.14	4188	5.77	0.88 (0.68, 1.14)	0.23
Arrhythmia						
No	1816	2.86	1837	3.89	0.75 (0.45, 1.25)	
Yes	6077	4.72	6056	5.79	0.81 (0.65, 1.00)	0.72
Prior HF Hospitalization						
No	6245	3.70	6283	4.17	0.88 (0.69, 1.13)	
Yes	1648	6.80	1610	10.34	0.65 (0.46, 0.92)	0.17

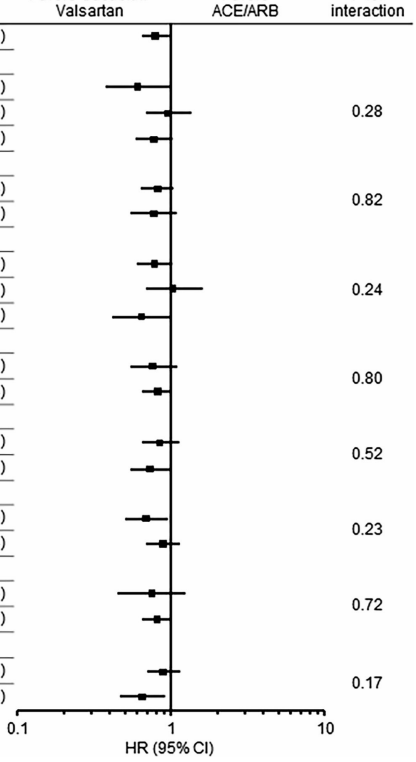


Figure 3: Differences in Risk of Mortality in Patients Taking Sacubitril-Valsartan Compared With ACE/ARB by Patient Characteristics

Differences in risk all-cause mortality (HR, 95% CI and p value for interaction) according to patient baseline characteristics are shown.

HF Hospitalization

Subgroup	Sacubitril-Valsartan No. of Patients	Sacubitril-Valsartan Event Rate per 100 Person-Years	ACE/ARB No. of Patients	ACE/ARB Event Rate per 100 Person-Years	HR (95%CI)	P for interaction
All Patients	7893	17.16	7893	15.93	1.07 (0.96, 1.19)	
Age, y						
18-64	2658	12.03	2787	13.62	0.87 (0.70, 1.08)	
65-74	2652	16.96	2633	15.81	1.07 (0.88, 1.29)	0.07
≥75	2583	22.78	2473	18.57	1.21 (1.02, 1.44)	
Gender						
Male	5268	15.73	5305	14.93	1.04 (0.91, 1.19)	0.62
Female	2625	20.16	2588	18.05	1.11 (0.93, 1.33)	
Race						
White	4690	15.50	4652	13.47	1.15 (0.99, 1.33)	
Black	1649	24.99	1608	21.72	1.08 (0.88, 1.33)	0.17
Other	1554	14.97	1633	17.29	0.88 (0.67, 1.14)	
Prior ACE/ARB						
No	2982	15.90	2982	16.16	0.97 (0.80, 1.17)	0.25
Yes	4911	17.82	4911	15.81	1.12 (0.98, 1.28)	
Renal Disease						
No	5280	12.28	5360	12.10	1.00 (0.86, 1.17)	0.31
Yes	2613	28.24	2533	24.89	1.13 (0.96, 1.32)	
Diabetes						
No	3620	12.15	3705	12.29	0.99 (0.82, 1.19)	0.30
Yes	4273	21.77	4188	19.13	1.11 (0.97, 1.27)	
Arrhythmia						
No	1816	9.66	1837	12.07	0.80 (0.60, 1.07)	0.024
Yes	6077	19.35	6056	17.09	1.12 (0.99, 1.26)	
Prior HF Hospitalization						
No	6245	11.87	6283	10.59	1.11 (0.96, 1.29)	0.33
Yes	1648	40.38	1610	40.44	0.99 (0.84, 1.17)	

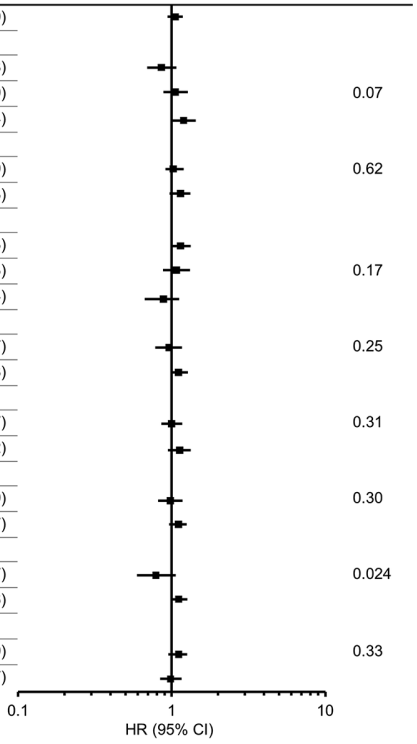
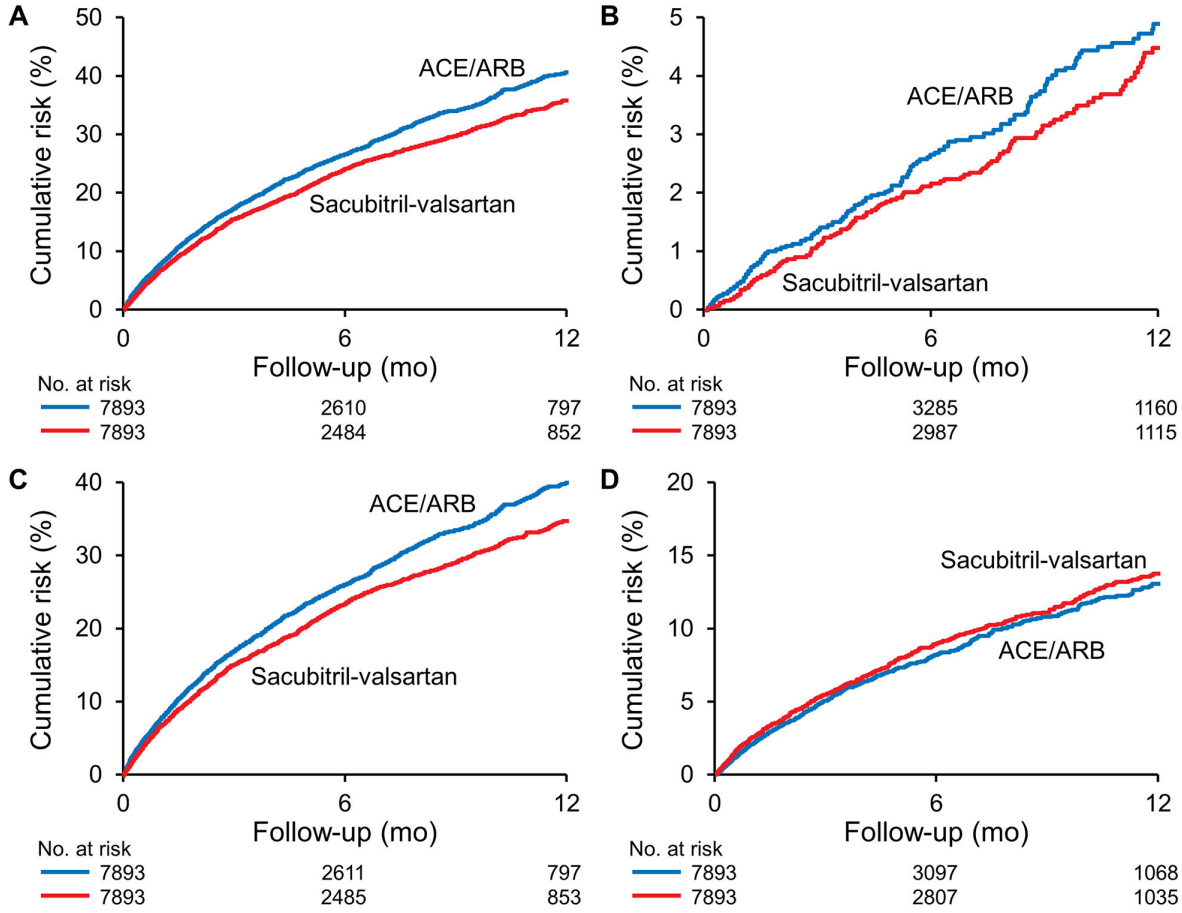


Figure 4: Differences in Risk of Heart Failure Hospitalization in Patients Taking Sacubitril-Valsartan Compared With ACE/ARB by Patient Characteristics

Differences in risk of hospitalization for heart failure (HR, 95% CI and p value for interaction) according to patient baseline characteristics are shown.



CENTRAL ILLUSTRATION: Cumulative Risk of Outcomes in Patients Treated with Sacubitril-Valsartan or ACE/ARB

Cumulative risk for the primary outcome (all-cause mortality or hospitalization; Panel A), all-cause mortality (Panel B), all-cause hospitalization (Panel C), and HF hospitalization (Panel D) for patients on sacubitril-valsartan or ACE/ARB are shown.

Table 1:

Baseline Characteristics Before and After Propensity Score Matching

Characteristic	Pre-Match			Post-Match		
	ACE/ARB (n=83318)	Sacubitril-Valsartan (n=8291)	*Std Diff*	ACE/ARB (n=7893)	Sacubitril-Valsartan (n=7893)	*Std Diff*
Age						
Mean (SD)	69.9 (12.2)	68.2 (12.0)	0.14	68.1 (11.9)	68.2 (12.0)	−0.01
Median	71	70		68	70	
Q1, Q3	62.0, 80.0	61.0, 77.0		61.0, 77.0	61.0, 77.0	
Sex						
Female	34318 (41.2%)	2719 (32.8%)	−0.17	2588 (32.8%)	2625 (33.3%)	0.01
Male	49000 (58.8%)	5572 (67.2%)	0.17	5305 (67.2%)	5268 (66.7%)	−0.01
Race						
Asian	1638 (2.0%)	168 (2.0%)	0.00	164 (2.1%)	160 (2.0%)	−0.01
Black	16246 (19.5%)	1741 (21.0%)	0.04	1608 (20.4%)	1649 (20.9%)	0.01
Hispanic	7062 (8.5%)	920 (11.1%)	0.09	900 (11.4%)	866 (11.0%)	−0.01
Unknown	5294 (6.4%)	531 (6.4%)	0.00	569 (7.2%)	528 (6.7%)	−0.02
White	53078 (63.7%)	4931 (59.5%)	−0.09	4652 (58.9%)	4690 (59.4%)	0.01
Income						
<$40,000	27263 (32.7)	2351 (28.4)	−0.09	2493 (31.6)	2242 (28.4)	−0.07
$40,000–$74,999	20394 (24.5)	2154 (26)	0.03	1865 (23.6)	2041 (25.9)	0.05
$75,000–$124,999	13826 (16.6)	1600 (19.3)	0.07	1278 (16.2)	1520 (19.3)	0.08
$125,000–$199,999	4349 (5.2)	570 (6.9)	0.07	374 (4.7)	536 (6.8)	0.09
$200,000+	1735 (2.1)	239 (2.9)	0.05	150 (1.9)	228 (2.9)	0.06
Missing	15751 (18.9)	1377 (16.6)	−0.06	1733 (22.0)	1326 (16.8)	−0.13
Patient Census Region						
Midwest	23865 (28.6%)	1671 (20.2%)	−0.20	1622 (20.5%)	1596 (20.2%)	−0.01
Northeast	12550 (15.1%)	1148 (13.8%)	−0.04	1047 (13.3%)	1054 (13.4%)	0.00
South	39389 (47.3%)	4973 (60.0%)	0.26	4715 (59.7%)	4759 (60.3%)	0.01
West	7514 (9.0%)	499 (6.0%)	−0.11	509 (6.4%)	484 (6.1%)	−0.01
Medical Comorbidities						

Characteristic	Pre-Match			Post-Match		
	ACE/ARB (n=83318)	Sacubitril-Valsartan (n=8291)	*Std Diff*	ACE/ARB (n=7893)	Sacubitril-Valsartan (n=7893)	*Std Diff*
Depression	18362 (22.0%)	1670 (20.1%)	−0.05	1423 (18.0%)	1523 (19.3%)	0.03
Renal Failure	28024 (33.6%)	2791 (33.7%)	0.00	2533 (32.1%)	2613 (33.1%)	0.02
Cardiac Arrhythmia	60174 (72.2%)	6461 (77.9%)	0.13	6056 (76.7%)	6077 (77.0%)	0.01
Peripheral Vascular Disease	35640 (42.8%)	4799 (57.9%)	0.31	4342 (55.0%)	4469 (56.6%)	0.03
Valvular Disease	41951 (50.4%)	4928 (59.4%)	0.18	4442 (56.3%)	4568 (57.9%)	0.03
Anemia	16628 (20.0%)	1536 (18.5%)	−0.04	1333 (16.9%)	1408 (17.8%)	0.02
Hypertension	76899 (92.3%)	7710 (93.0%)	0.03	7250 (91.9%)	7321 (92.8%)	0.03
Diabetes	44095 (52.9%)	4532 (54.7%)	0.04	4188 (53.1%)	4273 (54.1%)	0.02
History of Myocardial Infarction	26853 (32.2%)	3021 (36.4%)	0.09	2579 (32.7%)	2734 (34.6%)	0.04
Dementia	9485 (11.4%)	453 (5.5%)	−0.21	385 (4.9%)	427 (5.4%)	0.02
Cerebrovascular Disease	26086 (31.3%)	2377 (28.7%)	−0.06	2024 (25.6%)	2170 (27.5%)	0.04
COPD	40802 (49.0%)	4008 (48.3%)	−0.01	3554 (45.0%)	3716 (47.1%)	0.04
Pacemaker/ ICD	24851 (29.8%)	4058 (48.9%)	0.40	3739 (47.4%)	3781 (47.9%)	0.01
Medications						
β-blockers	59875 (71.9%)	7283 (87.8%)	0.41	6894 (87.3%)	6894 (87.3%)	0.00
Loop diuretics	43347 (52.0%)	5500 (66.3%)	0.29	5216 (66.1%)	5177 (65.6%)	−0.01
Aldosterone antagonist	14167 (17.0%)	3129 (37.7%)	0.48	2887 (36.6%)	2856 (36.2%)	−0.01
Digoxin	7830 (9.4%)	1202 (14.5%)	0.16	1094 (13.9%)	1107 (14.0%)	0.00
Prior ACE/ARB (120 Days Prior)	50449 (60.5%)	5309 (64.0%)	0.07	4911 (62.2%)	4911 (62.2%)	0.00
ACE	33651 (40.4%)	3138 (37.8%)	−0.05	2961 (37.5%)	2961 (37.5%)	0.00
ARB	16798 (20.1%)	2171 (26.2%)	0.14	1950 (24.7%)	1950 (24.7%)	0.00
Prior Dose (ACE/ARB)						
Low dose	16369 (32.4%)	1739 (32.8%)	0.01	1604 (32.7%)	1614 (32.9%)	0.00
Medium dose	20712 (41.1%)	2234 (42.1%)	0.02	2046 (41.7%)	2060 (41.9%)	0.00
High dose	13368 (26.5%)	1336 (25.2%)	−0.03	1261 (25.7%)	1237 (25.2%)	−0.01
Charlson Index Score						
Mean (SD)	5.2 (3.2)	5.3 (3.1)	−0.03	5.0 (2.9)	5.2 (3.1)	−0.07
Median (IQR)	5.0	5.0		5.0	5.0	

Characteristic	Pre-Match			Post-Match		
	ACE/ARB (n=83318)	Sacubitril-Valsartan (n=8291)	*Std Diff*	ACE/ARB (n=7893)	Sacubitril-Valsartan (n=7893)	*Std Diff*
Office Visit						
Cardiologist	45641 (54.8)	6641 (80.1)	0.56	6278 (79.5)	6269 (79.4)	0.00
Primary care	35281 (42.3)	3730 (45.0)	0.05	3500 (44.3)	3559 (45.1)	0.02
Prior Hospitalization						
“0”	49116 (59.0%)	5016 (60.5%)	0.03	4827 (61.2%)	4780 (60.6%)	−0.01
“1”	24021 (28.8%)	2214 (26.7%)	−0.05	2103 (26.6%)	2117 (26.8%)	0.00
“2+”	10181 (12.2%)	1061 (12.8%)	0.02	963 (12.2%)	996 (12.6%)	0.01
Prior HF Hospitalization						
“0”	69129 (83.0%)	6525 (78.7%)	−0.11	6283 (79.6%)	6245 (79.1%)	−0.01
“1”	12004 (14.4%)	1421 (17.1%)	0.07	1303 (16.5%)	1330 (16.9%)	0.01
“2+”	2185 (2.6%)	345 (4.2%)	0.09	307 (3.9%)	318 (4.0%)	0.01
Year of Index						
2015	39135 (47.0%)	162 (2.0%)	−1.23	191 (2.4%)	162 (2.1%)	−0.02
2016	22356 (26.8%)	2213 (26.7%)	0.00	2234 (28.3%)	2191 (27.8%)	−0.01
2017	20569 (24.7%)	5383 (64.9%)	0.88	5021 (63.6%)	5075 (64.3%)	0.01
2018	1258 (1.5%)	533 (6.4%)	0.25	447 (5.7%)	465 (5.9%)	0.01

ACE/ARB= angiotensin converting enzyme inhibitor/ angiotensin receptor blocker, COPD= chronic obstructive pulmonary disease; HF= heart failure