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ORIGINAL RESEARCH

# Sacubitril/Valsartan Initiation Among Veterans Who Are Renin-Angiotensin-Aldosterone System Inhibitor Naïve With Heart Failure and Reduced Ejection Fraction

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**BACKGROUND:** Sacubitril/valsartan, a first-in-class angiotensin receptor neprilysin inhibitor, received US Food and Drug Administration approval in 2015 for heart failure with reduced ejection fraction (HFrEF). Our objective was to describe the sacubitril/valsartan initiation rate, associated characteristics, and 6-month follow-up dosing among veterans with HFrEF who are renin-angiotensin-aldosterone system inhibitor (RAASi) naïve.

**METHODS AND RESULTS:** Retrospective cohort study of veterans with HFrEF who are RAASi naïve defined as left ventricular ejection fraction (LVEF) ≤40%; ≥1 in/outpatient heart failure visit, first RAASi (sacubitril/valsartan, angiotensin-converting enzyme inhibitor [ACEI]), or angiotensin-II receptor blocker [ARB]) fill from July 2015 to June 2019. Characteristics associated with sacubitril/valsartan initiation were identified using Poisson regression models. From July 2015 to June 2019, we identified 3458 sacubitril/valsartan and 29 367 ACEI or ARB initiators among veterans with HFrEF who are RAASi naïve. Sacubitril/valsartan initiation increased from 0% to 26.5%. Sacubitril/valsartan (versus ACEI or ARB) initiators were less likely to have histories of stroke, myocardial infarction, or hypertension and more likely to be older and have diabetes mellitus and lower LVEF. At 6-month follow-up, the prevalence of ≥50% target daily dose for sacubitril/valsartan, ACEI, and ARB initiators was 23.5%, 43.2%, and 47.1%, respectively.

**CONCLUSIONS:** Sacubitril/valsartan initiation for HFrEF in the Veterans Administration increased in the 4 years immediately following Food and Drug Administration approval. Sacubitril/valsartan (versus ACEI or ARB) initiators had fewer baseline cardiovascular comorbidities and the lowest proportion on ≥50% target daily dose at 6-month follow-up. Identifying the reasons for lower follow-up dosing of sacubitril/valsartan could support guideline recommendations and quality improvement strategies for patients with HFrEF.

**Key Words:** angiotensin receptor neprilysin inhibitor ■ heart failure ■ medication ■ reduced ejection fraction ■ titration

Recent heart failure (HF) guidelines recommend initiating sacubitril/valsartan as an alternative to angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-II receptor blockers (ARBs) to reduce morbidity and mortality in patients with HF with reduced ejection fraction (HFrEF).[1] The recommendations are based on findings from the PARADIGM-HF (Prospective Comparison of Angiotensin Receptor-Neprilysin

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## CLINICAL PERSPECTIVE

### What Is New?

- In the Veterans Health Administration, the largest integrated healthcare system in the United States, sacubitril/valsartan initiation for patients with heart failure with reduced ejection fraction who were previously renin-angiotensin-aldosterone system inhibitor naïve steadily increased during the 4 years immediately following Food and Drug Administration approval.
- Most patients did not receive guideline-directed medication titration within 6 months of an initial pharmacy fill for a renin-angiotensin-aldosterone system inhibitor for heart failure with reduced ejection fraction in the Veterans Health Administration outpatient setting and the proportion of patients at <50% target dose at 6-month follow-up was highest for sacubitril/valsartan initiators (versus angiotensin-converting enzyme inhibitor or angiotensin receptor blocker initiators).

### What Are the Clinical Implications?

- Increasingly, research suggests that sacubitril/valsartan for heart failure with reduced ejection fraction is safe, effective, and well tolerated among patients who are renin-angiotensin-aldosterone system inhibitor naïve and hemodynamically stable. Thus, it is important for healthcare providers and teams to follow up with their patients to ensure they receive guideline-directed medication titration, where tolerated, to maximize the benefits of heart failure with reduced ejection fraction pharmacotherapy.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **HFrEF** | heart failure with reduced ejection fraction |
| **PARADIGM-HF** | Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with Angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and morbidity in Heart Failure |
| **RAASi** | renin-angiotensin-aldosterone system inhibitor |
| **VHA** | Veterans Health Administration |

Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) randomized trial that showed that sacubitril/valsartan was superior to enalapril in reducing the risks of death and hospitalization for HFrEF. However, PARADIGM-HF included mostly participants who were pretrial users of either an ACEI or an ARB. Overall, the uptake of sacubitril/valsartan in the United States has been slow.[2–5] However, data are limited on the use of sacubitril/valsartan among an outpatient HFrEF population who have never used an ACEI or an ARB (ie, a renin-angiotensin-aldosterone system inhibitor [RAASi]-naïve population).

We, therefore, sought to describe (1) the quarterly rate of and factors associated with sacubitril/valsartan initiation, and (2) initial and 6-month follow-up RAASi doses among veterans with HFrEF who were previously RAASi naïve. We used Veterans Health Administration (VHA) data to answer this question as it contains comprehensive pharmacy and electronic heath record data on more than 9 million veterans and, because of fixed and low copays for prescription medications, it provides an opportunity to study sacubitril/valsartan in a setting where cost is less of a barrier to medications. Data on sacubitril/valsartan initiation, associated baseline characteristics, and 6-month follow-up dosing among veterans with HFrEF who were previously RAASi naïve may provide important insights such as identifying characteristics of veterans with HFrEF who could benefit from but were not initiated on sacubitril/valsartan.

## METHODS

The data and study materials cannot be made available by the author to other researchers for purposes of reproducing the results or replicating the procedure, per Veterans Affairs (VA) policy. However, all data used in the analyses are available to VA researchers through the VA Informatics and Computing Infrastructure.

### Study Design

Among veterans with HFrEF who were RAASi naïve, we conducted a retrospective cohort study using national VHA data. Our cohort included veterans with 1 or more outpatient pharmacy fill(s) through the VHA for a RAASi during the cohort identification period: July 7, 2015 (date of sacubitril/valsartan Food and Drug Administration approval) to June 13, 2019 (Figure S1).

We defined the index date as the date of the first RAASi fill during the cohort identification period. We used the 1-year period immediately preceding the index date for each veteran (1-year preindex period) to further define study eligibility and baseline characteristics. Because our goal was to understand medication use in veterans with HFrEF who were RAASi naïve, we restricted the cohort to veterans with a reduced left ventricular ejection fraction (LVEF, ≤40%) and no VHA pharmacy fills for a RAASi during the 1-year preindex period.

Because some veterans did not have a documented LVEF during the 1-year preindex period, we defined HFrEF using both LVEF values and the *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* (*ICD-CM-9/10*) diagnosis codes (Table S1). First, if a veteran had a documented LVEF during the 1-year preindex period, we excluded those whose most recent (to the index date) value was >40%. Second, for ACEI or ARB initiators, if a veteran had a most recent value that was ≤40%, we required at least 1 *ICD-CM-9/10* diagnosis code for HF (inpatient or outpatient) during the 1-year preindex period.[6] Third, for ACEI or ARB initiators who did not have a documented LVEF during the 1-year preindex period, we required the *ICD-CM-9/10* code to specifically indicate systolic HFrEF. We performed the second and third steps because ACEIs and ARBs are often used for indications other than HFrEF, whereas, during the study period, sacubitril/valsartan use was specific to HFrEF. We excluded veterans who did not have at least 1 VHA clinical encounter(s) including pharmacy claims or in/outpatient services during the 1-year preindex period.

## Data Sources

We accessed demographic, pharmacy, clinical, and medical history data from the national VHA Corporate Data Warehouse. Data were accessed using the VA Informatics and Computing Infrastructure workspace. This study was sponsored by Novartis Pharmaceuticals Corporation. The University of Utah Institutional Review Board and the Salt Lake City Veterans Affairs Health Care System Research and Development Office approved this study. Informed consent was not required for this study.

## Veteran Characteristics

Veteran age was determined on the index date and categories of race/ethnicity included non-Hispanic White, non-Hispanic Black, Hispanic, other (Non-Hispanic American Indian/Alaska Native, Non-Hispanic Asian, Non-Hispanic Multirace, Non-Hispanic Native Hawaiian/Other Pacific Islander), and unknown. We used inpatient and/or outpatient diagnosis *ICD-9/10* codes to ascertain clinical characteristics and medical history corresponding to the 1-year preindex period (Table S1). For each veteran, we created medication profiles using the most recent pharmacy fill data before or overlapping the index date. If a veteran's medication supply (according to the fill date and number of days' supply dispensed) overlapped the veteran's index date, then the veteran was considered to be a current user of the medication on the index date. At baseline, we examined current users of beta blockers and mineralocorticoid receptor antagonists. We also examined use of beta blockers specifically indicated for HFrEF (ie, metoprolol succinate, carvedilol, bisoprolol) at any time in the 1-year preindex period as a sensitivity analysis.

To obtain LVEF values, the VA Informatics and Computing Infrastructure created a validated natural language processing tool to extract LVEF values from text notes, because these data are not readily accessible from structured data.[7] The tool was applied to all clinical documents within the Corporate Data Warehouse and a new data set with structured LVEF data was created and was updated regularly.

## Initial and 6-month Follow-up Dose of RAASi

We ascertained total daily doses in mg per day for RAASi medications at baseline and 6-month follow-up. We chose a 6-month follow-up period to maximize the number of study participants with full follow-up since the date of sacubitril/valsartan Food and Drug Administration approval and to represent a clinically meaningful time frame for follow-up medication titration.[8] In addition, a 6-month follow-up period provides sufficient time to observe whether providers follow the 2015 VA Sacubitril and Valsartan Drug Monograph recommendation of "starting therapy with sacubitril/valsartan at 24/26 mg twice daily and doubling the dose every 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated."[9] We defined the baseline or initial dose as the total daily dose of the pharmacy fill overlapping the index date. The dose at 6-month follow-up corresponded to the last pharmacy fill date during the 6-month period after the index date. We converted ACEI and ARB medications into lisinopril and valsartan equivalents using standard conversions (Table S2). We defined 3 dose levels at each time point: <50% target daily dose, 50 to <100% target daily dose, and ≥100% target daily dose based on the lower bound of the maximum dose in the 2017 American College of Cardiology/American Heart Association/Heart Failure Society of America HF Guideline Update.[1] For example, doses of 97/103 mg twice daily (194/206 mg total daily), 20 mg daily, and 160 mg twice daily (320 mg total daily) defined target daily dosing for sacubitril/valsartan, lisinopril equivalents, and valsartan equivalents, respectively. We also explored differences in initial and 6-month follow-up dose of sacubitril/valsartan overall by whether or not a visit with primary care or cardiology occurred on the index date, by mean systolic blood pressure (measured during the 1-year preindex and during the 6-month follow-up periods), and by hypotension diagnosis during the 6-month follow-up period.

## Statistical Analysis

Rates of sacubitril/valsartan initiation were calculated for each quarter from July 2015 to June 2019 by dividing the number of new sacubitril/valsartan initiators by the number of all new RAASi initiators within each quarter. Veterans were included only in the calculation

for the quarter corresponding to their index date (initiation rates were not cumulative across the quarters). Summary statistics were calculated for baseline characteristics of the study population and were compared between sacubitril/valsartan initiators and ACEI or ARB initiators. In instances where there were few veterans who contributed to a table cell or figure count (eg, <5 veterans), we used the notation "<" so as to avoid reporting potentially identifiable information in accordance with VHA policy. We calculated the percentage of veterans on various combinations of HFrEF medications on the index date including sacubitril/valsartan, ACEI, ARB, beta blockers, and mineralocorticoid receptor antagonists. To identify characteristics associated with initiating sacubitril/valsartan (versus an ACEI or ARB), we used multivariable adjusted Poisson regression models to calculate prevalence ratios and 95% CIs. All baseline characteristics were included in our multivariable adjusted regression model and were presented as a forest plot. Sankey plots were generated to visualize the transition in the proportion of veterans across the 3 initial and 6-month follow-up target dose categories (ie, <50% target daily dose, 50 to <100% target daily dose, and ≥100% target daily dose).[10] Statistical analyses were performed with SAS software v 9.4 (SAS Institute, Cary, NC).

# RESULTS

## Veteran Characteristics

Overall, our study population included mostly male (97.7%) non-Hispanic, White (69.1%) veterans. Compared with ACEI or ARB initiators, sacubitril/valsartan initiators had a lower prevalence of female veterans (1.1% versus 2.4%) and non-Hispanic Black (14.2% versus 20.3%) and Hispanic (2.4% versus 4.8%) race/ethnicity (Table). The mean (SD) age, estimated glomerular filtration rate, and LVEF for sacubitril/valsartan versus ACEI or ARB initiators was 73.1 (10.8) versus 70.6 (11.5) years, 62.1 (20.3) versus 66.5 (25.8) mL/min per 1.73 $m^2$, and 27.0% (7.5%) versus 28.6% (8.2%), respectively.

## Rate of Sacubitril/Valsartan Initiation

Among study eligible veterans newly initiated on a RAASi in the outpatient setting for HFrEF from July 7, 2015 to June 13, 2019, 3458 (10.5%) initiated sacubitril/valsartan and 29 367 (89.5%) initiated an ACEI or ARB. The proportion initiating sacubitril/valsartan increased from 0% in Q3 of 2015 to 26.5% in Q2 of 2019 (Figure 1A and Figure S2).

## Factors Associated With Sacubitril/Valsartan Initiation

After adjusting for all baseline characteristics, sacubitril/valsartan initiators (versus ACEI or ARB initiators) were less likely to be female; Hispanic (versus non-Hispanic White); and have a history of stroke, myocardial infarction, or hypertension and more likely to be older, have a history of atrial fibrillation, diabetes mellitus, have an implantable cardioverter defibrillator, a lower LVEF, and an estimated glomerular filtration rate <60 mL/min per 1.73 $m^2$ (Figure 2). Also, sacubitril/valsartan initiators were less likely to have a pharmacy fill for a beta blocker and more likely to have a pharmacy fill for a mineralocorticoid receptor antagonist that overlapped the index date.

## Baseline HF Medication Regimens

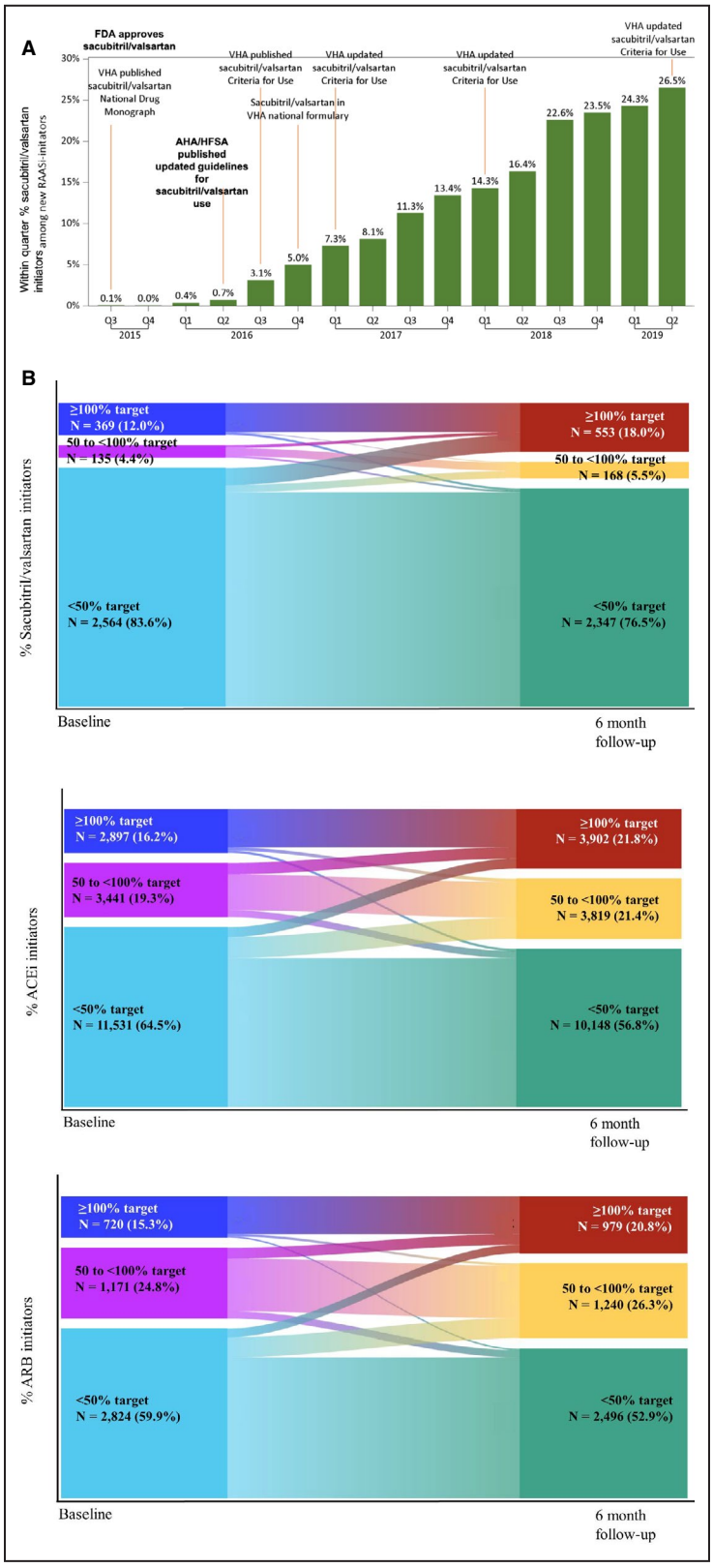
In unadjusted analyses just over half of sacubitril/valsartan initiators (55.4%), versus most ACEI or ARB initiators (79.6%), also had a pharmacy fill for 1 or more HF medication classes including beta blockers and/or mineralocorticoid receptor antagonists that overlapped the index date (Table). This finding was largely due to the low prevalence of veterans with beta blocker fills overlapping the index date among sacubitril/valsartan (36.2%) versus ACEI or ARB (62.4%) initiators.

## Initial and Follow-up RAASi Dosing

Analysis of RAASi dosing was restricted to 88.8% (N=3068) of sacubitril/valsartan initiators, 76.8% (N=17 869) of ACEI initiators, and 77.5% (N=4715) of ARB initiators who had 6-month follow-up dosing information available. The proportion of veterans on ≥50% of target dose initially and at 6-month follow-up was lowest for sacubitril/valsartan (≥97/103 mg/day, 16.4% initially and 23.5% at follow-up) versus ACEI (≥10 mg/day, 35.5% initially and 43.2% at follow-up) or ARB initiators (≥160 mg/day, 40.1% initially and 47.1% at follow-up) (Figure 1B). Changes from baseline to 6-month follow-up in the <50% target dose group were similar

**Figure 1. Initiation rate, and initial and 6-month follow-up dose of sacubitril/valsartan vs ACEI or ARB in veterans with HFrEF who were previously RAASi-naïve.**

**A**, Initiation rates were calculated for each quarter from July 2015 to June 2019 by dividing the number of new sacubitril/valsartan initiators by the number of new RAASi initiators within each quarter and were not cumulative across the quarters. **B**. Sankey plots visualize the transition in the proportion of veterans across the 3 initial and 6-month follow-up target dose categories. Doses of 97/103 mg twice daily (194/206 mg total daily), 20 mg daily, and 160 mg twice daily (320 mg total daily) defined 100% target daily dosing for sacubitril/valsartan, lisinopril (for ACEI) equivalents, and valsartan (for ARB) equivalents. ACEI indicates angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin-II receptor blocker; FDA, Food and Drug Administration; HFrEF, heart failure with reduced ejection fraction; HFSA, Heart Failure Society of America; RAASi, renin-angiotensin aldosterone system inhibition; and VHA, Veterans Health Administration.




among sacubitril/valsartan, ACEI, and ARB initiators, down 7.1%, 7.7%, and 7.0%, respectively, from baseline to 6-month follow-up. Among a small subset of sacubitril/valsartan initiators who had data on outpatient provider seen on the index date (N=534), we found that veterans who were seen in primary care (versus cardiology) had a lower prevalence of sacubitril/valsartan dose at ≥100% target daily dose both initially (10.2%

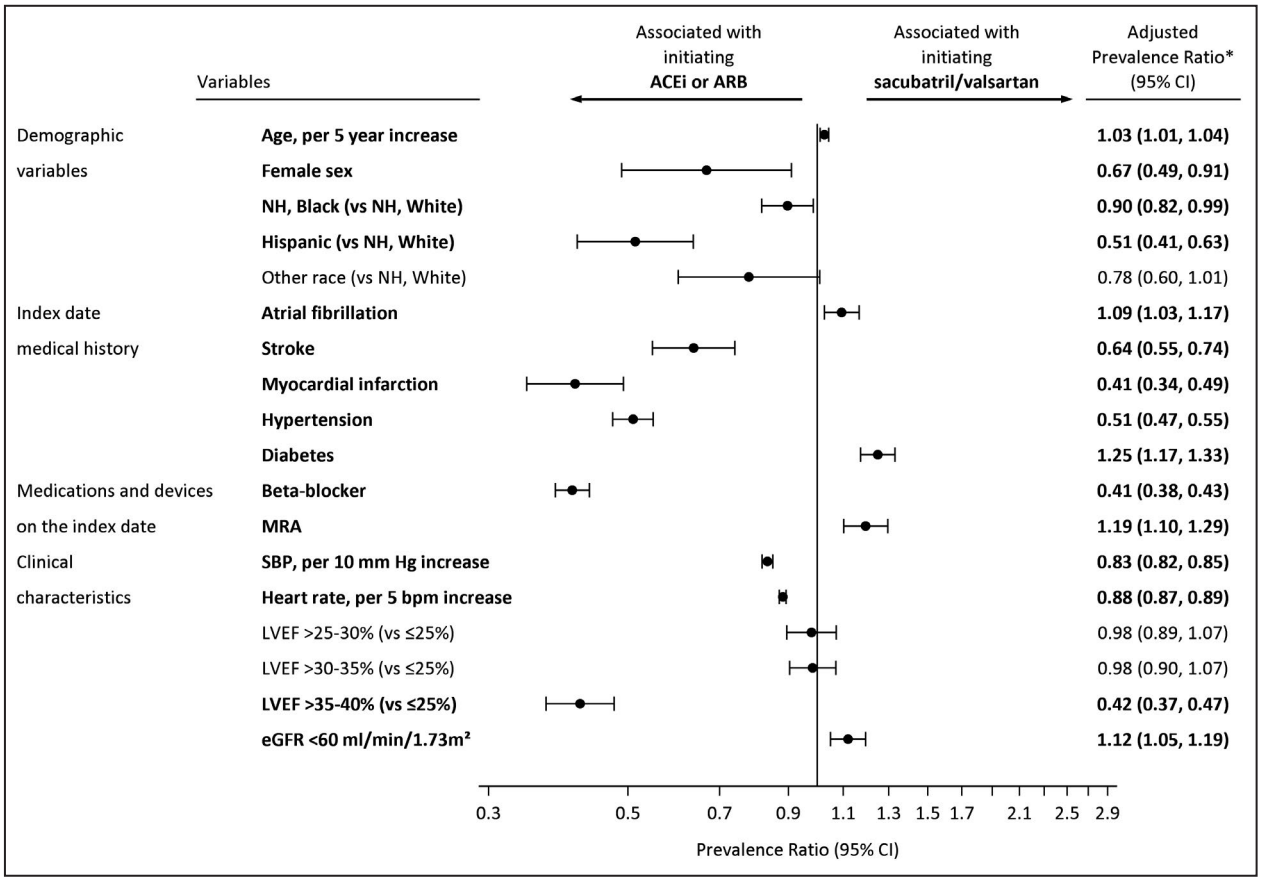



**Figure 2. Baseline characteristics associated with initiating sacubitril/valsartan vs an ACEI or ARB among veterans with HFrEF.**

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NH, non-Hispanic; and SBP, systolic blood pressure. *Prevalence ratios were estimated from multivariate-adjusted (including all variables in 1 model) Poisson regression models with robust standard errors.

versus 12.6%) and at 6-month follow-up (13.6% versus 18.4%) (Table S3). Also, among a subset of sacubitril/valsartan initiators who had 6-month follow-up dose and systolic blood pressure data (N=2190 [71.4%]) we observed that veterans whose dose either decreased or was maintained (versus increased) had lower mean systolic blood pressures over the 6-month follow-up period. Mean systolic blood pressure (SD) for veterans whose dose was decreased (N=109) was 115.7 (16.5) mm Hg, for veterans whose dose was maintained (N=1636) was 117.0 (16.7) mm Hg, and for veterans whose dose was increased (N=445) was 121.9 (16.5) mm Hg (Table S4).

## DISCUSSION

Sacubitril/valsartan initiation among veterans with HFrEF who were RAASi naïve increased during the 4 years immediately following Food and Drug Administration approval. In Q2 of 2019, 27 in 100 study eligible veterans initiated sacubitril/valsartan. Sacubitril/valsartan (versus ACEI or ARB) initiators were more likely to be older, male, have a lower LVEF, estimated glomerular filtration rate <60 mL/min per 1.73 $m^2$, diabetes mellitus, or have an implantable cardioverter defibrillator and less likely to be Hispanic (versus non-Hispanic White), have a history of stroke, myocardial infarction, hypertension, or a concurrent beta blocker pharmacy fill. The proportion of veterans on ≥50% of target dose at 6-month follow-up was lowest for sacubitril/valsartan (23.5%) versus ACEI (43.2%) or ARB initiators (47.1%).

Initial studies suggested slow uptake of sacubitril/valsartan, including our prior study that showed the prevalence was only 3.5% overall from 2015 to 2017.[11] Low sacubitril/valsartan initiation of 3.5% was also reported in a separate study of veterans from the VA Greater Los Angeles Healthcare System in 2017 among those who met eligibility criteria of the PARADIGM-HF study.[12] In the VHA, where out-of-pocket costs are typically no more than $11 for a 30-day supply of sacubitril/valsartan, it is more likely that factors including stricter criteria for use, described previously, rather than cost to veterans, led to low initiation.[11,13] Briefly,

**Table. Baseline* Characteristics of Sacubitril/Valsartan and ACEI or ARB Initiators With HFrEF Who Were RAASi-Naïve in the One-Year Pre-index Period**

| Characteristic | Sacubitril/valsartan (N=3458) | ACEI or ARB (N=29 367) |
|---|---|---|
| Age, y, mean (SD) | 73.1±10.8 | 70.6±11.5 |
| Female sex, n (%) | 39 (1.1) | 706 (2.4) |
| Race or ethnic group, n/total n (%) | | |
| Non-Hispanic, White | 2654 (77.2) | 20 024 (68.6) |
| Non-Hispanic, Black | 487 (14.2) | 5935 (20.3) |
| Hispanic | 81 (2.4) | 1404 (4.8) |
| Other‖ | 54 (1.6) | 544 (1.9) |
| Missing | 162 (4.7) | 1277 (4.4) |
| Clinical characteristics | | |
| Systolic blood pressure, mm Hg, mean (SD)† | 123.0 ± 16.4 | 130.5 ± 17.6 |
| Heart rate, bpm, mean (SD)† | 74.6 ± 11.8 | 80.6 ± 14.5 |
| LVEF, %, median (IQR) | 27.5 (20.5, 33.0) | 30.0 (22.5, 35.0) |
| LVEF ≤25% | 1196 (34.6) | 8646 (29.4) |
| LVEF >25%–30% | 541 (15.6) | 3819 (13.0) |
| LVEF >30%–35% | 660 (19.1) | 4604 (15.7) |
| LVEF >35%–40% | 289 (8.4) | 5453 (18.6) |
| LVEF Missing, n % | 772 (22.3) | 6845 (23.3) |
| eGFR, mL/min per 1.73 $m^2$, median (IQR)† | 59.0 (48.2, 74.2) | 65.0 (50.3, 81.8) |
| eGFR <60 mL/min per 1.73 $m^2$, n (%)† | 1375 (51.5) | 10 657 (42.3) |
| Medical history, n (%) | | |
| Atrial fibrillation | 1358 (39.3) | 10 242 (34.9) |
| Stroke | 161 (4.7) | 2347 (8.0) |
| Myocardial infarction | 122 (3.5) | 3435 (11.7) |
| Hypertension | 901 (26.1) | 12 978 (44.2) |
| Diabetes mellitus | 1386 (40.1) | 10 909 (37.1) |
| Heart failure medication regimen at time of RAASi initiation/index date, n (%)‡ | | |
| RAASi only§ | 1541 (44.6) | 5995 (20.4) |
| RAASi+beta blocker | 1251 (36.2) | 18 331 (62.4) |
| RAASi+MRA | 133 (3.8) | 672 (2.3) |
| RAASi+beta blocker+MRA | 533 (15.4) | 4369 (14.9) |

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and RAASi, renin-angiotensin-aldosterone system inhibitor.

*Timing of baseline defined as overlapping or on the index date for the following: age, sex, race. Timing of baseline defined using the mean of all values during the 1-year preindex date period: systolic blood pressure, heart rate, eGFR. Timing of baseline variables defined using a single value closest to the index date and up to 1-year preindex: LVEF. Timing of baseline variables defined using *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* code(s) occurring during the 2-year preindex date period: atrial fibrillation, stroke, myocardial infarction hypertension, diabetes mellitus.

†The following variables have missing values: systolic blood pressure (174 sacubitril/valsartan, 3692 ACEI or ARB), heart rate (66 sacubitril/valsartan, 244 ACEI or ARB), eGFR (788 sacubitril/valsartan, 4170 ACEI or ARB).

‡Veterans were considered to be a current user of the medication at baseline/on the index date if the medication supply (according to the fill date and number of days' supply dispensed) overlapped the veteran's index date.

§RAASi only was defined as users of only sacubitril/valsartan or ACEI or ARB on the index date, without fills for beta blockers or MRA that overlapped the veteran's index date.

‖Other includes Non-Hispanic American Indian/Alaska Native, Non-Hispanic Asian, Non-Hispanic Multirace, Non-Hispanic Native Hawaiian/Other Pacific Islander.

during the study period, some of the stricter VHA criteria for use (versus American College of Cardiology/American Heart Association/Heart Failure Society of America HF Guidelines) for sacubitril/valsartan initiation included lower LVEF (≤35% versus ≤40%), restricted initial prescriptions through cardiology (versus no restriction to cardiology), and recommended receipt of a stable dose (ie, ≥ 4 weeks) of an ACEI or ARB (versus no explicit recommendation for prior receipt of ACEI or ARB).[1,13]

The current study shows that the prevalence of sacubitril/valsartan initiation from 2015 to 2019 was 10.5%

(N=3458/29 367) among veterans who were RAASi naïve and 18.4% (N=8499/37 704) in treated veterans with HFrEF, or an overall prevalence of 15.1%. Among ACEI or ARB initiators who were RAASi naïve, 0.2% (54/29 367) had at least 1 fill for sacubitril/valsartan (switched to sacubitril/valsartan) over the 6-month follow-up period. The more recent increases in sacubitril/valsartan use may be related to recently implemented educational trainings on the approved criteria for use and other VHA efforts to increase awareness,[12] greater clinical experience, and more studies demonstrating safety and benefit.[14]

Veteran characteristics associated with sacubitril/valsartan initiation were generally consistent with prior studies[2–4,11] including the association with lower LVEF, which is also consistent with the VHA recommendation for sacubitril/valsartan initiation among patients with LVEF ≤35%.[13] However, the unadjusted difference in median LVEF was small (27.5% sacubitril/valsartan versus 30.0% in ACEI or ARB initiators) and there was a high prevalence of missing values for LVEF (22.3% in sacubitril/valsartan and 23.3% in ACEI or ARB initiators).

The 2017 American College of Cardiology/American Heart Association/Heart Failure Society of America HF Guideline Update for patients with HFrEF recommends several medication classes, including beta blockers and mineralocorticoid antagonists in conjunction with RAASi treatment.[1] We found that nearly half of sacubitril/valsartan (versus a minority of ACEI or ARB) initiators did not have concurrent fills for beta blockers at baseline. Our findings did not change when we excluded veterans with fills for guideline-directed beta blockers in the 1-year preindex period (those who potentially had HFrEF longer [Table S5]). It is possible that our criteria for defining concurrent fills, that is, medication supply (according to the fill date and number of days supply dispensed) that overlapped the index date, was too strict and under classified concurrent users. It is also possible that providers used a stepped approach and later initiated veterans on beta blockers and other HFrEF medications, after they initiated veterans on RAASi treatment. Further research is needed to understand whether prescribing of sacubitril/valsartan without concurrent beta blockers is common as well as potential reasons for initiating veterans on sacubitril/valsartan alone, such as using a stepped approach across HFrEF medication classes.

At 6-month follow-up, a minority of (23.5%) sacubitril/valsartan initiators were at ≥50% target daily dose recommended by the 2017 American College of Cardiology/American Heart Association/Heart Failure Society of America HF Guideline Update, compared with approximately half of ACEI (43.2%), and ARB (47.1%) initiators.[1] Although Greene et al in the CHAMP-HF (Change the Management of Patients with Heart Failure) study similarly found that most HFrEF patients were titrated to less than target doses of ACEI, ARB, or sacubitril/valsartan at any point during 12 months of follow-up, initiation or dosing increases were higher for patients on sacubitril/valsartan (10%) versus an ACEI or ARB (7%).[15] The lack of titration is not unique to sacubitril/valsartan and there are several possible explainations.[15,16] First, early on, when there was less guidance for healthcare providers, it may have been common to prescribe lower than target doses. Our exploratory analysis examined whether provider specialty seen on the index date, a proxy for provider familiarity with sacubitril/valsartan, was related to sacubitril/valsartan dose. Our results suggest that veterans seen in primary care, where there may be lower familiarity with sacubitril/valsartan (versus cardiology), were prescribed lower doses of sacubitril/valsartan at baseline and follow-up (Table S3). Second, lower sacubitril/valsartan doses may have been chosen because of perceived benefit at lower doses as supported by evidence from a post hoc PARADIGM-HF analysis.[17] However, any dose reduction from the target dose in the post hoc analysis, regardless of assignment to sacubitril/valsartan or enalapril, was associated with a higher risk of cardiovascular death or heart failure hospitalization. Third, the blood pressure lowering effects of sacubitril/valsartan were either anticipated by patients' healthcare providers or were experienced by patients and therefore prescriptions for lower doses were maintained.[18] Results from our exploratory analysis support the possibility that veterans were maintained at lower doses because of lower blood pressures observed during the 6-month follow-up period (Table S4).

Multiple approaches that target patients, healthcare providers and healthcare systems may be needed to overcome therapeutic inertia and to increase guideline-directed medical therapy for patients with HFrEF. Possible patient/provider targeted strategies include increased education, electronic health record embedded clinical decision support tools, remote monitoring, and protocolized care such as the biomarker-guided care intervention tested in the GUIDE-IT (Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment) trial.[5,19–21] Healthcare system targeted strategies may include increased alignment across guidelines and performance metrics. Peri-Okonny et al noted that current performance measures do not include medication intensity information, highlighting an opportunity to support guideline-directed medical therapy.[5,22] However, these interventions need to be guided by a greater understanding of the reasons for deviations from guideline-directed medical therapy. In the GUIDE-IT trial the most common reasons for lack of titration documented among experienced HF cardiologists was "clinically stable" and "already at maximally tolerated therapy."[20] This finding led Fiuzat et al to speculate that the low prevalence of achieved guideline-directed medical therapy in their study may have been due to unrealistic goals, in

addition to therapeutic inertia. Carefully designed implementation studies are needed to identify barriers to guideline adoption in clinical care, whether there is a need to reevaluate recommendations and to design or adapt strategies to address barriers that can be scaled across healthcare settings.[23]

## Limitations

Our study should be considered in the context of potential limitations. First, the veteran population is mostly male and practices within the VA may be unique, and thus our findings may not generalize to the broader US population or populations from other healthcare systems. Second, although we cannot exclude possible differences in the timing and presence of initial HFrEF diagnoses across sacubitril/valsartan versus ACEI or ARB initiators, we applied strict eligibility criteria using both LVEF values and diagnosis codes to define HFrEF. Third, veterans may have sought HFrEF care outside the VHA. We anticipate that the prevalence of pharmacy use outside the VHA in our study was low, because a prior study of veterans who either used VA-reimbursed pharmacies exclusively or VA and Medicare Part D-reimbursed pharmacies for ACEI prescriptions (N=42 539 veterans) found only 1.9% of VA and Medicare Part D users filled their ACEI prescriptions through both.[24] Fourth, we had a high proportion of veterans who were missing LVEF values and 6-month follow-up dose for RAASi inhibitors, which limited our analysis of these characteristics. Fifth, the current study did not include New York Heart Association functional class data, which is part of the sacubitril/valsartan criteria for use. This information was not included because it is not systematically or routinely collected as structured data, and our prior analysis revealed that despite using natural language processing to extract New York Heart Association class more than 50% of HFrEF patients were still missing New York Heart Association functional class.[11] Because this was an observational study, we cannot exclude the possibility that residual confounding may have led to some of the associations observed between baseline characteristics and sacubitril/valsartan initiation. For example, we did not anticipate that veterans with higher blood pressures were more likely to initiate an ACEI or ARB (versus sacubitril/valsartan), although this association may be partly explained by residual confounding from associations with other cardiovascular conditions (eg, myocardial infarction, stroke) that may have been more likely to be treated with an ACEI or ARB.

# CONCLUSIONS

In conclusion, during the first 4 years following US Food and Drug Administration approval, quarterly outpatient initiation of sacubitril/valsartan in the VHA increased from 0% to 26.5% among veterans with HFrEF who were previously RAASi naïve. Sacubitril/valsartan (versus ACEI or ARB) initiators had fewer baseline cardiovascular comorbidities and were less likely to have a concurrent beta blocker fill. At 6-month follow-up the proportion of veterans on ≥50% of target dose was lowest for sacubitril/valsartan versus ACEI or ARB initiators. These findings highlight an opportunity to improve the pharmacotherapy management of veterans with HFrEF who are RAASi naïve.

## ARTICLE INFORMATION

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### Supplementary Material

Figures S1–S2
Tables S1–S5

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# SUPPLEMENTAL MATERIAL

**Table S1. Variable Definitions**

| Variable | Definition | Data Source |
|---|---|---|
| Index date | The date of the first pharmacy fill for sacubitril/valsartan, and if none, then the date of the first fill for an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker (ACEi or ARB) in the cohort identification period. The cohort identification period was from 07 July 2014 through 13 June 2019. For instances where Veterans had a fill for both sacubitril/valsartan and ACEi or sacubitril/valsartan and ARB or ACEi and ARB, the index medication was determined by the next pharmacy fill in the follow-up period. If there was no fill in the follow-up period, these Veterans were excluded. | CDW |
| **Clinical Characteristics** | | |
| Systolic blood pressure (SBP), mm Hg | Mean of all SBP values measured in cardiology, renal, or the primary care outpatient setting, in the 1-year pre-index period. SBP values were dropped if any of the following was true: missing value, systolic less than diastolic, systolic >300 mm Hg, and systolic <60 mm Hg. | CDW |
| Heart rate (HR), bpm | Mean of all HR values measured in the outpatient setting in the 1-year pre-index period. HR values dropped if >300 bpm. | CDW |
| Left Ventricular Ejection Fraction (LVEF),% | The LVEF value closest to the index date in the pre-index period. Since LVEF values are non-structured data in VINCI, a validated natural language processing tool was used to extract quantitative LVEF values from the medical notes.<br><br>1. Apply cleaning rule to all LVEF values: if the range of 2+ LVEF values on a given day was >10% drop all LVEF values for that date. | CDW, NLP |

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| | 2. After applying the cleaning rule, determine the LVEF value for each Veteran that was closest to the index date in the pre-index period. | |
| Baseline estimated glomerular filtration rate (eGFR), mL/min/1.73 $m^2$ | Used reported eGFR as the primary eGFR, if missing used calculated eGFR from serum creatinine and the Modification of Diet in Renal Disease (MDRD) equation.<br><br>Reported eGFR values from the CDW: defined using the mean of all eGFR values in the 1-year pre-index period.<br><br>Calculated eGFR: used age, sex, race/ethnicity, and serum creatinine using the MDRD equation(1). If race was missing, assume race = non-African American. | CDW |
| **Medical History** | | |
| History of atrial fibrillation | ≥1 inpatient or outpatient encounter with an ICD-9 code of 427.3, 427.31, or 427.32 (any position) or ICD-10 code of I48.0, I48.2, I48.91 during the 2-year period before the index date | CDW |
| History of stroke | ≥1 inpatient or outpatient encounter with an ICD-9 code of 430.xx- 432.xx, 433.x1, 434.xx, 435.xx 436.xx or ICD-10 code of G45.0, G45.1, G45.2, G45.8, G45.9, G46.0, G46.1, G46.2, G97.31, G97.32, I60.00, I60.01, I60.02, I60.10, I60.11, I60.12, I60.20, I60.21, I60.22, I60.30, I60.31, I60.32, I60.4, I60.50, I60.51, I60.52, I60.6, I60.7, I60.8, I60.9, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I63.00, I63.02, I63.011, I63.012, I63.019, I63.031, I63.032, I63.039, I63.09, I63.10, I63.111, I63.112, I63.119, I63.12, I63.131, I63.132, I63.139, I63.19, I63.20, I63.211, I63.212, I63.219, I63.22, I63.231, I63.232, I63.239, I63.29, I63.30, I63.311, I63.312, I63.319, I63.321, I63.322, I63.329, I63.331, I63.332, I63.339, I63.341, I63.342, I63.349, I63.39, I63.40, I63.411, I63.412, I63.419, I63.421, I63.422, I63.429, I63.431, I63.432, I63.439, I63.441, I63.442, I63.449, I63.49, I63.50, I63.511, I63.512, I63.519, I63.521, I63.522, I63.529, I63.531, I63.532, I63.539, I63.541, I63.542, I63.549, | CDW |

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| | I63.59, I63.6, I63.8, I63.9, I66.01, I66.02, I66.03, I66.09, I66.11, I66.12, I66.13, I66.19, I66.21, I66.22, I66.23, I66.29, I66.3, I66.8, I66.9, I67.841, I67.848, I67.89, I97.810, I97.811, I97.820, I97.821 (any position) during the 2-year period before the index date (2). | |
| History of myocardial infarction | ≥1 inpatient ICD-9 code of 410.xx (except 410.x2, indicates subsequent episode of care) or 412.x (any position) or ICD-10 code of 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 during the 2-year period before the index date (3,4). | CDW |
| Hypertension | At least 1 inpatient or outpatient claim (any position) with an ICD-9 diagnosis code of 401.x–405.x 437.2 or ICD-10 code of H35.031, H35.032, H35.033, H35.039, 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, I67.4, N26.2 during the 2-year period before the index date (5). | CDW |
| Diabetes | Any one of the following during the 2-year period before the index date (6):<br><br>(a) At least 1 inpatient claim with discharge ICD-9 diagnoses (any position) of 250.xx, 357.2, 362.0x, or 366.41 or an ICD-10 code for diabetes (listed below)<br><br>(b) At least 2 outpatient claims occurring at least 7 days apart with ICD-9 diagnoses (any position) of 250.xx, 357.2, 362.0x, or 366.41 or an ICD-10 code for diabetes (listed below).<br><br>(c) At least 1 pharmacy fill for an oral anti-diabetes medication or insulin fills<br><br>ICD-10 codes: E08.00, E08.01, E08.10, E08.11, E08.21, E08.22, E08.29, E08.311, E08.319, E08.321, E08.329, E08.331, E08.339, E08.341, E08.349, E08.351, E08.359, E08.36, E08.39, E08.40, E08.41, E08.42, E08.43, E08.44, E08.49, E08.51, E08.52, E08.59, E08.610, E08.618, | CDW |

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| | E08.620, E08.621, E08.622, E08.628, E08.630, E08.638, E08.641, E08.649, E08.65, E08.69, E08.8, E08.9, E09.00, E09.01, E09.10, E09.11, E09.21, E09.22, E09.29, E09.311, E09.319, E09.321, E09.329, E09.331, E09.339, E09.341, E09.349, E09.351, E09.359, E09.36, E09.39, E09.40, E09.41, E09.42, E09.43, E09.44, E09.49, E09.51, E09.52, E09.59, E09.610, E09.618, E09.620, E09.621, E09.622, E09.628, E09.630, E09.638, E09.641, E09.649, E09.65, E09.69, E09.8, E09.9, E10.10, E10.11, E10.21, E10.22, E10.29, E10.311, E10.319, E10.321, E10.329, E10.331, E10.339, E10.341, E10.349, E10.351, E10.359, E10.36, E10.39, E10.40, E10.41, E10.42, E10.43, E10.44, E10.49, E10.51, E10.52, E10.59, E10.610, E10.618, E10.620, E10.621, E10.622, E10.628, E10.630, E10.638, E10.641, E10.649, E10.65, E10.69, E10.8, E10.9, E11.00, E11.01, E11.21, E11.22, E11.29, E11.311, E11.319, E11.321, E11.329, E11.331, E11.339, E11.341, E11.349, E11.351, E11.359, E11.36, E11.39, E11.40, E11.41, E11.42, E11.43, E11.44, E11.49, E11.51, E11.52, E11.59, E11.610, E11.618, E11.620, E11.621, E11.622, E11.628, E11.630, E11.638, E11.641, E11.649, E11.65, E11.69, E11.8, E11.9, E13.00, E13.01, E13.10, E13.11, E13.21, E13.22, E13.29, E13.311, E13.319, E13.321, E13.329, E13.331, E13.339, E13.341, E13.349, E13.351, E13.359, E13.36, E13.39, E13.40, E13.41, E13.42, E13.43, E13.44, E13.49, E13.51, E13.52, E13.59, E13.610, E13.618, E13.620, E13.621, E13.622, E13.628, E13.630, E13.638, E13.641, E13.649, E13.65, E13.69, E13.8, E13.9 | |
| **Baseline treatments** | | |
| ACEi | ≥ 1 pharmacy fill where the days supply of the medication overlaps the index date for captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril, benazepril, and moexipril. | CDW |

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| ARB | ≥ 1 pharmacy fill where the days supply of the medication overlaps the index date for candesartan, losartan, valsartan, azilsartan, eprosartan, irbesartan, olmesartan, or telmisartan. | CDW |
| Beta-blocker | ≥ 1 pharmacy fill where the days supply of the medication overlaps the index date for acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, labetalol, metoprolol succinate, metoprolol tartrate, nadolol, nebivolol, propranolol, penbutolol, pindolol | CDW |
| Mineralocorticoid receptor antagonist | ≥ 1 pharmacy fill where the days supply of the medication overlaps the index date for spironolactone or eplerenone. | CDW |
| **Follow-up variables** | | |
| Hypotension | ≥1 inpatient or outpatient diagnosis (any position) with an ICD-9 code of 458.x or ICD-10 code of I95.x documented during the 6-month follow-up period. | |
| Systolic blood pressure (SBP), mm Hg | Mean of all SBP values measured in cardiology, renal, or the primary care outpatient setting, in the 6-month follow-up period. SBP values were dropped if any of the following was true: missing value, systolic less than diastolic, systolic >300 mm Hg, and systolic <60 mm Hg. | |

**Table S2. Conversions for ACEi and ARB medications into lisinopril and valsartan equivalents**

| **ARB Medications** | **Daily dose achieved in valsartan equivalents = daily dose of ARB medication * z, where z equals:** |
|---|---|
| Candesartan | 5.0 |
| Olmesartan | 4.0 |
| Telmisartan | 2.0 |
| Azilsartan | 2.0 |
| Losartan | 1.6 |
| Valsartan | 1.0 |
| Irbesartan | 0.533 |
| Eposartan | 0.133 |
| **ACEi Medications** | **Daily dose achieved in lisinopril equivalents = daily dose of ACEi medication * x, where x equals:** |
| Trandolapril | 5.0 |
| Ramipril | 4.0 |
| Perindopril | 2.5 |
| Enalapril | 2.0 |
| Lisinopril | 1.0 |
| Benazepril | 1.0 |
| Quinapril | 1.0 |
| Fosinopril | 1.0 |
| Captopril | 0.2 |

| | |
|---|---|
| Moexipril | 0.133 |

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker

**Table S3. Sacubitril/valsartan dose assessed at baseline and during the 6 months follow-up period by provider specialty seen on the index date**

| Sacubitril/valsartan Dose | Primary Care Visit on Index Fill Date (N = 176) | Cardiology Visit on Index Fill Date (N = 358) |
|---|---|---|
| **Baseline– no. (%)** | | |
| Index fill <50% target | 151 (85.8) | 288 (80.4) |
| Index fill 50-<100 target | 7 (4.0) | 25 (7.0) |
| Index fill ≥100% target | 18 (10.2) | 45 (12.6) |
| **6-months follow-up– no. (%)** | | |
| Follow-up fill <50% target | 143 (81.3) | 266 (74.3) |
| Follow-up fill 50-<100% target | 9 (5.1) | 26 (7.3) |
| Follow-up fill ≥100% target | 24 (13.6) | 66 (18.4) |

**Table S4. Systolic blood pressure and sacubitril/valsartan dose changes from baseline to 6 months follow-up**

| | Dose stayed the same N = 2,365 | Dose increased N = 562 | Dose decreased N = 141 |
|---|---|---|---|
| Baseline mean SBP– mm Hg, mean (SD) | 122.5 (16.3) | 125.9 (16.4) | 121.8 (15.2) |
| Baseline SBP missing– no. (%) | 111 (4.7) | 22 (3.9) | 9 (6.4) |
| Follow-up mean SBP 6 mo overall– mm Hg, mean (SD) | 117.0 (16.7) | 121.9 (16.5) | 115.7 (16.5) |
| Follow-up SBP 6 mo overall missing– no. (%) | 729 (30.8) | 117 (20.8) | 32 (22.7) |
| Hypotension follow-up– no. (%)* | 71 (3.0) | 11 (2.0) | 7 (5.0) |

Abbreviations: SBP, Systolic Blood Pressure; SD, standard deviation.

* Hypotension was defined as ≥1 inpatient or outpatient diagnosis (any position) with an ICD-9 code of 458.x or ICD-10 code of I95.x documented during the 6-month follow-up period.

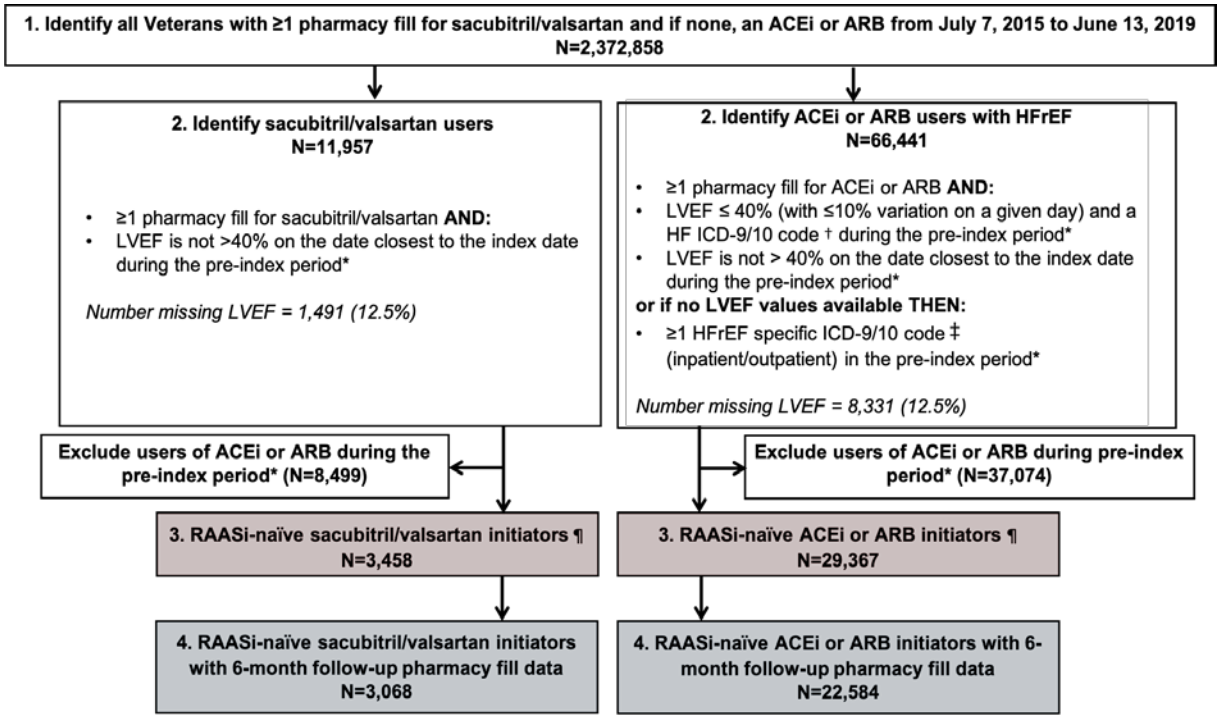
**Table S5. Baseline heart failure medication classes of sacubitril/valsartan and ACEi or ARB initiators with HFrEF who were previously RAASi-naïve, excluding Veterans with ≥1 pharmacy fill(s) for beta blockers recommended for HF in the 1-year pre-index period**

| Heart failure medication regimen at time of RAASi initiation | Sacubitril/valsartan (N =1,812) | | ACEi or ARB (N =10,434) | |
|---|---|---|---|---|
| | N | (%) | N | (%) |
| RAASi only | 1,541 | 85.0 | 5,995 | 57.5 |
| RAASi + Beta blocker | 116 | 6.4 | 3,326 | 31.9 |
| RAASi + MRA | 133 | 7.3 | 672 | 6.4 |
| RAASi + Beta blocker + MRA | 22 | 1.2 | 441 | 4.2 |

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin aldosterone system inhibitor.

Beta blockers recommended for HF included pharmacy fills for metoprolol succinate, carvedilol, or bisoprolol.

**Figure S1. Eligibility criteria applied to the VHA population**




Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HFrEF, heart failure with reduced ejection fraction; ICD-9/10, International Classification of Diseases-9th/10th Revision-Clinical Modification; LVEF, left ventricular ejection fraction; RAASi, renin angiotensin-aldosterone system inhibitor; VHA, Veterans Health Administration.

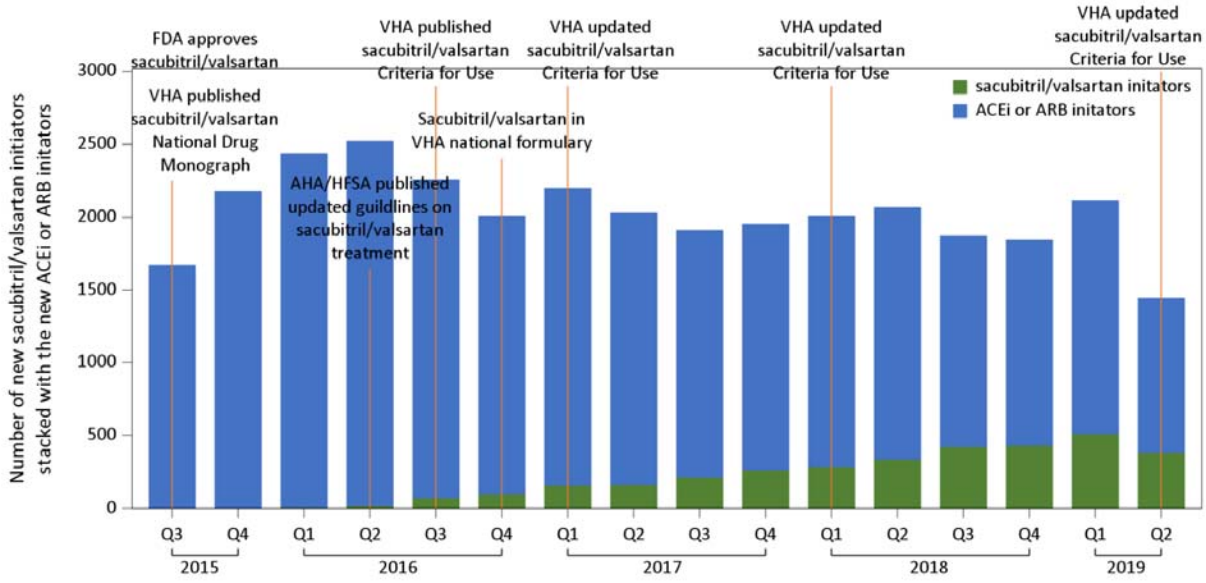
*Pre-index period = 1 year before the index date defined as 1st fill of sacubitril/valsartan and if none, 1st fill of ACEi or ARB.

† HF ICD-9/10 codes: 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9/I09.81, I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40. I50.41, I50.42, I50.43, I50.9.

‡ HFrEF ICD-9/10 codes (i.e., systolic HF): 428.20, 428.21, 428.22, 428.23, 428.40, 428.41, 428.42, 428.43/I50.20, I50.21, I50.22, I50.23, I50.40, I50.41, I50.42, I50.43.

¶ RAASi naïve defined as no VHA pharmacy fills for ACEi or ARB in the pre-index period.

**Figure S2. Number of new sacubitril/valsartan overlaid on new ACEi or ARB initiators, with HFrEF and who are RAASi-naïve, by quarter of initiation from July 2015 to July 2019 ***




Abbreviations: AHA, American Heart Association; FDA, Food and Drug Administration; HFSA, Heart Failure Society of America; VHA, Veterans Health Administration.

*The number of new Veterans is not cumulative across study quarters. The current study ended on June 13, 2019, therefore we excluded June 2019 from this figure and Q2 of 2019 does not include a full quarter of data.

Supplementary References

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