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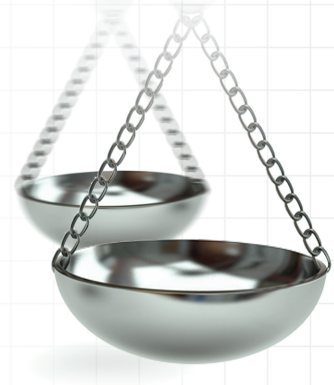

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Characteristics of early sacubitril/valsartan patients and considerations for studies in electronic health record data

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Aim: We examined characteristics of early sacubitril/valsartan users in a large US electronic health records database. **Patients & methods:** We identified three cohorts of patients with heart failure (HF): sacubitril/valsartan patients with a prior HF diagnosis; patients with HF with reduced ejection fraction; and patients with HF treated with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker and a β-blocker. **Results:** Sacubitril/valsartan patients were younger than patients in the other cohorts; the mean age of sacubitril/valsartan patients increased by 2 years in the first 15 months of marketing. Most sacubitril/valsartan patients had prior use of HF treatment. **Conclusion:** Overall, sacubitril/valsartan patients resembled those in the HF with reduced ejection fraction cohort, and commonly used other drugs for HF.

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Keywords: cardiology/cardiovascular • heart failure • observational research • outcomes research • sacubitril/valsartan • utilization

As a new drug is approved, it is important to understand how it is prescribed in real-world practice. Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), was approved by the US FDA in July 2015. The Prospective comparison of ARNI with angiotensin-converting enzyme inhibitor (ACEi) to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Phase III clinical trial found that, as compared with the ACEi, enalapril, plus recommended therapy for chronic HF, sacubitril/valsartan plus recommended therapy reduced the primary composite end point of cardiovascular mortality and HF hospitalization by 20% in adults with HF with reduced ejection fraction (HFrEF) [1]. The 2016 American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America updated their guidelines for the management of HF patients, recommending inhibition of the renin-angiotensin system with either an ACEi, an angiotensin receptor blocker (ARB), or an ARNI in conjunction with evidence-based β-blockers and mineralocorticoid receptor antagonists (MRA) to reduce morbidity and mortality in patients with chronic HFrEF [2]. The guidelines also indicate that replacement by an ARNI is recommended to further reduce morbidity and mortality in patients with chronic symptomatic HFrEF New York Heart Association (NYHA) class II or III who tolerate an ACEi or ARB.

For clinicians and patients seeking to make treatment decisions involving sacubitril/valsartan, it is critical to understand how PARADIGM-HF results translate to 'real-world' settings, in which patients might have different demographic and clinical characteristics, comorbidity profiles and medication use patterns than the typical PARADIGM-HF trial participant. An important first step in assessing the 'real-world' outcomes of a new drug is to explore characteristics of patients who receive sacubitril/valsartan to evaluate treatment dynamics in the early

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marketing period, where patient characteristics may change over relatively short periods of time [3,4]. Identification of an appropriate comparator is also essential for 'real-world' outcomes studies, but is challenging in the settings of chronic conditions such as HF, where patients often simultaneously use multiple treatments. In particular, comparator group selection may be complicated because sacubitril/valsartan is indicated in the USA only for symptomatic patients with HFrEF and many secondary electronic data sources currently lack structured ejection fraction data needed to define HFrEF and information on NYHA class needed to identify symptomatic patients.

The purpose of this study was to examine the characteristics of early sacubitril/valsartan patients as well as other patients with HF, including those with HFrEF and those with HF treated with ACEi or ARBs and β-blockers, in a large US electronic health records (EHR) database.

Methods

Data source

We used the Explorys data platform to conduct a descriptive cohort study of sacubitril/valsartan users and other patients with HF. The Explorys data platform is a data network comprising integrated information from 360 hospitals and approximately 31,700 providers, covering approximately 50 million patient lives and with data going back to the mid-1990s. The platform integrates data across the continuum of care including data from ambulatory EHRs, inpatient EHRs, laboratory, pharmacy, health plans, billing and accounting, data warehouses, patient portals, satisfaction surveys and care management systems. The database reflects EHR data for services provided in multiple care settings, including primary care, specialist encounters, hospitalizations, postacute care, long-term care and home care. The data are geographically diverse, updated regularly, and have been used for prior epidemiologic studies [5–8]. Because we focused on the time period around the US approval of sacubitril/valsartan, we used data predominantly from 2013 through November 2016; to ascertain HF status for the sacubitril/valsartan cohort, we used data going back as far as 1994.

Study population

We identified three cohorts of patients in the Explorys platform: patients with a prior diagnosis of HF who used sacubitril/valsartan, not conditional on left ventricular ejection fraction (LVEF) availability; patients with HFrEF, defined as those with a HF diagnosis and at least one available LVEF value of ≤40%, not conditional on pharmacotherapy; and patients with HF treated with an ACEi or ARB and a β-blocker (HF-ACEi/ARB + BB cohort), not conditional on LVEF. The HFrEF and HF-ACEi/ARB + BB cohorts were identified as indication- or treatment-based cohorts that could serve as potential comparison groups in a comparative effectiveness study.

For the sacubitril/valsartan cohort, we identified all patients in the Explorys data platform with at least one record of sacubitril/valsartan using both prescribing and dispensing data between July 2015 and October 2016. The date of first sacubitril/valsartan record was defined as the index date. We required patients in the sacubitril/valsartan cohort to have at least one HF diagnosis in the data any time prior to the index date. To define the cohort of patients with HFrEF, we identified patients with at least two HF diagnoses on different dates between the years 2013 and 2015 (inclusive), at least one medical encounter of any kind in 2013 and in 2015 and at least one LVEF measurement ≤40% at any time prior to the index date (not limited to the preceding year). The index date for this cohort was defined as 1 January 2016. To define the HF-ACEi/ARB + BB cohort, we identified patients with at least two HF diagnoses on different dates between the years 2013 and 2015 (inclusive), at least one medical encounter of any kind in 2013 and in 2015 and at least two ACEi or ARB records plus at least two β-blocker records in the year preceding the index date, which was also defined as 1 January 2016. Because sacubitril/valsartan is only approved for HF, we assumed that a single HF diagnosis in combination with a record for sacubitril/valsartan would identify patients using sacubitril/valsartan for HF with high specificity. As ACEi/ARBs and β-blockers are often used for other conditions, we required two diagnoses of HF to increase the likelihood that patients were using these medications for HF. Since we did not require HF pharmacotherapy for defining the HFrEF cohort, we required two diagnosis codes as evidence of HF.

The baseline period was defined as the 1-year period preceding the index date for members of each cohort. Only patients aged 18 years or older on the index date were included in each cohort and patients with missing age or sex information were excluded.

To examine the dynamics of sacubitril/valsartan initiators over time, we also created sequential cohorts of sacubitril/valsartan initiators defined by calendar quarter of their index dates. We did not require patients in the sequential cohorts to have a prior HF diagnosis. Although sacubitril/valsartan is approved only for HF, and

Table 1. Demographic characteristics of sacubitril/valsartan patients, heart failure with reduced ejection fraction patients and patients with heart failure treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and a beta-blocker.

Demographics	Sacubitril/valsartan patients (n = 1737)	HFrEF cohort (n = 9747)	HF-ACEi/ARB + BB cohort (n = 33,405)
Female gender, n (%)	531 (30.57)	3280 (33.65)	16,387 (49.06)
Age (years) at baseline, mean (SD)	65.28 (13.71)	70.57 (13.41)	71.86 (13.09)
Age categories (years), n (%):			
– <65	771 (44.39)	3074 (31.54)	9365 (28.03)
– ≥65	966 (55.61)	6673 (68.46)	24,040 (71.97)
Ethnicity, n (%):			
– Black	290 (16.70)	2056 (21.09)	5472 (16.38)
– Caucasian	1026 (59.07)	5928 (60.82)	20,635 (61.77)
– Other	421 (24.25)	1763 (18.13)	7298 (21.91)
Type of payer, n (%):			
– Private	338 (19.46)	1067 (10.95)	3095 (9.27)
– Medicare advantage/supplemental	502 (28.90)	3176 (32.58)	11,449 (34.27)
– Medicaid	63 (3.63)	314 (3.22)	1098 (3.29)
– Medicare + additional insurance	646 (37.19)	4027 (41.32)	13,731 (41.10)
– Other	188 (10.82)	1163 (11.93)	4032 (12.07)

HF: Heart failure; HF-ACEi/ARB + BB: Heart failure treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and a beta-blocker; HFrEF: Heart failure with reduced ejection fraction; SD: Standard deviation.

specifically for those with reduced LVEF, we sought to describe the evolution of all patients who started treatment with sacubitril/valsartan, including those who may not have had a prior diagnosis of HF or whose diagnosis may not have been recorded in the data at the time of starting treatment.

Analysis

We used the baseline year preceding the index date to characterize patients in the three cohorts based on a large number of factors, including demographics, resource utilization, comorbidities, medication use and laboratory values. All variables are listed in Table 1. Because this was a purely descriptive study, characteristics of each cohort are presented separately; no formal statistical comparisons were made. To examine the dynamics of new sacubitril/valsartan patients who initiated treatment in the early marketing setting, we also examined overall changes in baseline characteristics of sacubitril/valsartan patients over time by separately characterizing the sequential cohorts of sacubitril/valsartan users.

Ethics statement

This study was approved by the Brigham and Women's Hospital Institutional Review Board.

Results

Sacubitril/valsartan initiators

We identified 1737 eligible patients with HF who initiated sacubitril/valsartan in the Explorys data platform through November 2016 (Table 1; see Supplementary Table 1 for complete set of characteristics). The mean age of patients in the sacubitril/valsartan cohort was 65 years (standard deviation [SD]; 14) and 69% were male. Most sacubitril/valsartan patients had prior use of other drugs for HF: 54% had prior ACEi use, 29% had prior ARB use, 83% had prior β-blocker use and 45% had prior MRA use (Table 2; see Supplementary Table 2 for complete set of characteristics). With respect to comorbid conditions at baseline, 19% of patients had a recorded diagnosis of chronic kidney disease, 37% had a record of diabetes, 69% had a record of hypertension, 21% had a record of chronic obstructive pulmonary disease (COPD), 28% had peripheral vascular disease, 23% had a record of myocardial infarction (MI) and 28% had ischemic cardiomyopathy. The mean number of HF hospitalizations in the prior year was 0.82 (SD: 5.25) and the mean number of outpatient visits for HF was 2.73 (SD: 3.72).

The availability of baseline laboratory test and vital sign values ranged from 29% for LVEF to 95% for systolic blood pressure in the sacubitril/valsartan cohort (Table 3). Among the 27% of patients with an LVEF value recorded

Table 2. Clinical characteristics of sacubitril/valsartan patients, heart failure with reduced ejection fraction patients and patients with heart failure treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and a beta-blocker.

Baseline clinical characteristics	Sacubitril/valsartan patients (n = 1737)	HFrEF patients (n = 9747)	HF-ACEi/ARB + BB cohort (n = 33,405)
Health services utilization (12 months pre-index):			
– Number of HF hospitalizations, mean (SD)	0.82 (5.25)	0.75 (7.92)	1.22 (5.66)
– Number of HF outpatient visits, mean (SD)	2.73 (3.72)	2.90 (4.05)	2.63 (4.04)
– Number of all-cause hospitalizations, mean (SD)	2.39 (10.71)	2.09 (16.93)	4.42 (17.19)
– Number of all-cause outpatient visits, mean (SD)	13.92 (15.56)	12.84 (15.54)	17.25 (19.29)
Comorbidities (12 months pre-index, including index date), n (%):			
– Cardiomyopathy	485 (27.92)	1992 (20.44)	3290 (9.85)
– Chronic kidney disease	324 (18.65)	2463 (25.27)	9243 (27.67)
– COPD	368 (21.19)	2222 (22.80)	10,829 (32.42)
– Diabetes	650 (37.42)	3834 (39.34)	16,501 (49.40)
– Hypertension	1201 (69.14)	6716 (68.90)	29,205 (87.43)
– Myocardial infarction	402 (23.14)	2227 (22.85)	7668 (22.95)
– Peripheral vascular disease	478 (27.52)	3573 (36.66)	14,694 (43.99)
– Ischemic heart disease	754 (43.41)	4126 (42.33)	12,337 (36.93)
Medication use in the 12-month pre-index period, n (%):			
– Diuretics	1412 (81.29)	7042 (72.25)	29,091 (87.09)
– Potassium sparing	833 (47.96)	3145 (32.27)	9106 (27.26)
– Other diuretics	1307 (75.24)	6589 (67.60)	28,171 (84.33)
– Angiotensin-converting enzyme inhibitors	936 (53.89)	4818 (49.43)	24,254 (72.61)
– Angiotensin receptor blockers	497 (28.61)	1958 (20.09)	11,739 (35.14)
– Beta-blocker	1434 (82.56)	7643 (78.41)	33,405 (100.00)
– Mineralocorticoid receptor antagonists	829 (47.73)	3099 (31.79)	8704 (26.06)
– Digoxin/digitalis	370 (21.30)	1754 (18.00)	5213 (15.61)
HF clinical (12 months pre-index, including index date; if more than one measurement was available, the most recent value was used):			
– LVEF ≤40%, n (% of those with values available)	446 (89.02)	4980 (100.00)	2726 (39.34)
– LVEF ≤35%, n (% of those with values available)	388 (77.45)	3683 (73.96)	2088 (30.13)
– LVEF missing, n (% of all patients)	1236 (71.16)	4767 (48.91)	26,475 (79.25)

COPD: Chronic obstructive pulmonary disease; HF: Heart failure; HF-ACEi/ARB + BB: Heart failure treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and a beta-blocker; HFrEF: Heart failure with reduced ejection fraction; LVEF: Left ventricular ejection fraction; SD: Standard deviation.

in the prior year, 89% had at least one value ≤40%; the median value was 28% (interquartile range [IQR]: 21–35%). Among those with the respective blood pressure values available, the mean baseline systolic and diastolic blood pressures were 121.17 mmHg (SD: 21.52) and 69.47 mmHg (SD: 12.96), respectively. The mean BMI was 31.42 kg/m^2 (SD: 7.84), the mean estimated glomerular filtration rate (eGFR) was 55.34 ml/min/1.73 m^2 (SD: 21.87) and the mean heart rate was 81.40 beats per minute (SD: 15.92).

HFrEF patients

Among the 9747 patients who met criteria for the HFrEF cohort, the mean age (71 years [SD: 13]) was greater than that of the sacubitril/valsartan cohort, but a similar proportion was male (66%). As compared with the sacubitril/valsartan cohort, use of other medications for HF was similar for prior ACEi use (49%) and prior β-blocker use (78%), while prior use of ARB (20%) and MRA 32% was lower. Additionally, patients in the HFrEF cohort had a higher baseline prevalence of chronic kidney disease (25%) and peripheral vascular disease (37%) but had a similar prevalence of diabetes (39%), COPD (23%), MI (23%) and hypertension (69%) and a lower prevalence of ischemic cardiomyopathy (20%). Mean numbers of HF hospitalizations (0.75; SD: 7.92) and outpatient visits for HF (2.90; SD: 3.95) in the prior year were similar to those of the sacubitril/valsartan cohort.

By definition, all patients in the HFrEF cohort had an LVEF value available at some time before the index date, but only 51% had a value available in the year prior to the index date. The median LVEF value in the prior year (30%; IQR: 25–36%) was very similar to that in the sacubitril/valsartan cohort. HFrEF patients also had similar mean

Table 3. Clinical characteristics and laboratory values for sacubitril/valsartan patients, heart failure with reduced ejection fraction patients and patients with heart failure treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and a beta-blocker in 12 months pre-index, including index date.[†]

Characteristic	Sacubitril/valsartan patients (n = 1737)			HFrEF patients (n = 9747)			HF-ACEi/ARB+BB cohort (n = 33,405)		
	n with available data	Mean (SD)	Median (IQR)	n with available data	Mean (SD)	Median (IQR)	n with available data	Mean (SD)	Median (IQR)
LVEF (%)	501	29.43 (10.44)	28 (21–35)	4980	30.05 (8.05)	30 (25–36)	6930	45.86 (15.53)	48 (35–59)
Systolic BP (mmHg)	1653	121.17 (21.52)	119 (106–133)	9039	118.73 (22.81)	117 (102–132)	31,552	127.80 (24.09)	126 (111–142)
Diastolic BP (mmHg)	1651	69.47 (12.96)	69 (60–78)	9025	66.96 (13.25)	66 (58–76)	31,513	69.33 (13.53)	69 (60–78)
BMI (kg/m^2)	1652	31.42 (7.84)	30.2 (26.1–35.3)	8920	29.43 (7.43)	28.35 (24.33–33.33)	31,301	31.33 (8.72)	29.86 (25.24–65.9)
Urea	1535	25.00 (16.95)	22 (16–30)	7589	29.53 (26.90)	23 (17–34)	28,634	26.37 (22.65)	22 (16–31)
Hb (g/dl)	1418	12.67 (2.09)	12.7 (11.4–14.1)	7063	12.07 (2.25)	12.2 (10.5–13.7)	28,306	11.91 (2.17)	12 (10.4–13.4)
Heart rate (BPM)	1293	81.40 (15.92)	80 (69–95)	7973	84.38 (17.44)	86 (71–97)	27,323	80.98 (17.42)	80 (68–94)
eGFR (ml/min/1.73 m^2)	1070	55.34 (21.87)	53 (42–60)	5423	44.74 (23.27)	45.37 (32–55)	22,335	51.16 (23.25)	51 (38–59)
BNP (pg/ml)	371	1156.78 (3144.80)	375 (154–893)	945	1135.89 (3190.48)	391 (159.5–958)	7644	1202.06 (3154.50)	371.5 (147–924.25)
NT-proBNP (pg/ml)	705	5282.51 (7588.63)	2488 (987.5–5898.25)	3557	7807.95 (12,009.37)	3126 (1078.25–8606.25)	10,747	6022.31 (11,770.49)	2221 (738–6091)

[†]If more than one measurement was available, the most recent value was used.
BNP: B-type natriuretic peptide; BP: Blood pressure; BPM: Beats per minute; eGFR: Estimated glomerular filtration rate; g/dl: Grams per deciliter; HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; IQR: Interquartile range; Kg/m$_2$: Kilograms per meter squared; LVEF: Left ventricular ejection fraction; ml/min/1.73 m^2: Millimeters per minute per 1.73-meters squared; mmHg: Millimeters of mercury; NT-proBNP: N-terminal pro b-type natriuretic peptide; pg/ml: Pictograms per milliliter; SD: Standard deviation.

systolic (118.73 mmHg; SD: 22.81) and diastolic blood pressure (66.96 mmHg; SD: 13.25) as sacubitril/valsartan patients, but had slightly lower mean BMI (29.43 kg/m^2; SD: 7.43) and eGFR (44.74 ml/min/1.73 m^2; SD: 23.27) and a higher heart rate (84.38 beats per minute; SD: 17.44).

Patients with HF treated with an ACEi or an ARB and a β-blocker

We identified 33,405 patients who met criteria for the HF-ACEi/ARB + BB cohort. As compared with the sacubitril/valsartan cohort, patients in this cohort were older (mean age: 72 years [SD: 13]) and a lower proportion were male (51%). As compared with the sacubitril/valsartan cohort, a smaller proportion of patients (26%) had a record for MRA use in the prior year. The patients in the HF-ACEi/ARB + BB cohort also had a higher prevalence of chronic kidney disease (28%), diabetes (49%), hypertension (87%), COPD (32%) and peripheral vascular disease (44%), with similar baseline prevalence of MI (23%) and a lower prevalence of ischemic cardiomyopathy (10%). The mean number of HF hospitalizations in the prior year (1.22; SD: 5.66) was higher than that in the sacubitril/valsartan cohort; the mean number of outpatient visits (2.63; SD: 4.04) was similar.

Only 21% of patients in the HF-ACEi/ARB + BB cohort had an LVEF value available that was measured in the baseline year. Among those with available values, the median LVEF (48%; IQR: 35–59%) was higher than that in the sacubitril/valsartan cohort, and only 39% had an LVEF ≤40%. Among the 94% of patients with systolic blood pressure values available (n = 31,552), the mean value (127.80 mmHg; SD: 24.09) was higher than that in the sacubitril/valsartan cohort, but the mean diastolic blood pressure (69.33 mmHg; SD: 13.53) was similar. Mean BMI (31.33 kg/m^2; SD: 8.72) and heart rate (80.98 BM; SD: 17.42) were similar, but the mean eGFR was lower (51.16 ml/min/1.73 m^2; SD: 23.25).

Sequential sacubitril/valsartan cohorts

We formed five sacubitril/valsartan sequential cohorts comprising newly initiated patients between the third quarter of 2015 and the third quarter of 2016 to evaluate changes in sacubitril/valsartan patients in the early marketing period. The number of unique sacubitril/valsartan initiators in each quarter increased monotonically (Table 4; Supplementary Table 3 for complete set of characteristics). The average age of the sequential cohorts increased slightly from 64 years in quarter 3 of 2015 to 66 years in quarter 3 of 2016. The increase in average age was driven

Table 4. Demographic characteristics of sacubitril/valsartan patients by calendar quarter of index date.

Characteristic	Quarter 3, 2015 (n = 84)	Quarter 4, 2015 (n = 291)	Quarter 1, 2016 (n = 383)	Quarter 2, 2016 (n = 545)	Quarter 3, 2016 (n = 556)
Female gender, n (%)	23 (27.38)	91 (31.27)	116 (30.29)	170 (31.19)	179 (32.19)
Age (years) at baseline, mean (SD)	64.26 (14.06)	63.40 (13.28)	65.11 (13.16)	65.66 (13.97)	66.13 (13.55)
Ethnicity, n (%):					
– Black	17 (20.24)	41 (14.09)	67 (17.49)	84 (15.41)	93 (16.73)
– Caucasian	53 (63.10)	183 (62.89)	234 (61.10)	320 (58.72)	335 (60.25)
– Other	14 (16.87)	67 (23.02)	82 (21.41)	141 (25.87)	128 (23.02)

SD: Standard deviation.

Table 5. Clinical characteristics of sacubitril/valsartan patients by calendar quarter of index date.

Characteristic	Quarter 3, 2015 (n = 84)	Quarter 4, 2015 (n = 291)	Quarter 1, 2016 (n = 383)	Quarter 2, 2016 (n = 545)	Quarter 3, 2016 (n = 556)
Health services utilization (12 months pre-index):					
– Number of HF hospitalizations/ER visits, mean (SD)	0.77 (2.62)	0.97 (4.49)	0.55 (2.09)	0.83 (3.33)	1.07 (8.44)
– Number of HF outpatient visits, mean (SD)	3.2 (3.98)	3.16 (4.84)	2.29 (3.28)	2.30 (3.27)	2.76 (3.99)
– Number of hospitalizations/ER visits, mean (SD)	2.63 (10.42)	3.23 (10.93)	2.43 (9.32)	2.58 (8.98)	3.05 (15.66)
– Number of outpatient visits, mean (SD)	13.93 (16.14)	14.15 (17.59)	13.50 (15.67)	12.29 (13.58)	13.28 (14.30)
Comorbidities (12 months pre-index, including index date), n (%):					
– Cardiomyopathy	14 (16.67)	170 (58.42)	216 (56.40)	310 (56.88)	301 (54.14)
– Chronic kidney disease	21 (25.00)	50 (17.18)	60 (15.67)	80 (14.68)	136 (24.46)
– COPD	15 (17.86)	60 (20.62)	81 (21.15)	96 (17.61)	119 (21.40)
– Diabetes	35 (41.67)	110 (37.80)	135 (35.25)	176 (32.29)	212 (38.13)
– Hypertension	52 (61.90)	192 (65.98)	243 (63.45)	353 (64.77)	392 (70.50)
– Myocardial infarction	25 (29.76)	68 (23.37)	74 (19.32)	124 (22.75)	118 (21.22)
– Peripheral vascular disease	27 (32.14)	79 (27.15)	102 (26.63)	141 (25.87)	147 (26.44)
– Ischemic heart disease	38 (45.24)	118 (40.55)	158 (41.25)	209 (38.35)	246 (44.24)
Medication use in the 12 month pre-index period, n (%):					
– Diuretics	66 (78.57)	228 (78.35)	289 (75.46)	426 (78.17)	456 (82.01)
– Angiotensin-converting enzyme inhibitors	43 (51.19)	157 (53.95)	188 (49.09)	286 (52.48)	302 (54.32)
– Angiotensin receptor blockers	22 (26.19)	75 (25.77)	108 (28.20)	145 (26.61)	150 (26.98)
– Beta-blocker	64 (76.19)	240 (82.47)	290 (75.72)	452 (82.94)	452 (81.29)
– Mineralocorticoid receptor antagonists	38 (45.24)	147 (50.52)	171 (44.65)	234 (42.94)	248 (44.60)
HF clinical (12 months pre-index, including index date), n (%):					
– LVEF ≤40%, n (% of those with values available)	18 (56.25)	79 (91.86)	93 (85.32)	112 (87.50)	136 (88.89)
– LVEF ≤35%, n (% of those with values available)	16 (50.00)	64 (74.42)	83 (76.15)	94 (73.44)	121 (79.08)
– LVEF missing, n (% of all patients)	52 (61.90)	205 (70.45)	274 (71.54)	417 (76.51)	403 (72.48)

COPD: Chronic obstructive pulmonary disease; ER: Emergency room; HF: Heart failure; LVEF: Left ventricular ejection fraction; SD: Standard deviation.

by an increase in the proportion of patients aged 75 years or older. Other patient characteristics were relatively stable across the sequential cohorts (Tables 5 & 6; see Supplementary Table 4 for complete set of characteristics).

Table 6. Clinical characteristics and laboratory values sacubitril/valsartan patients by calendar quarter of index date.

Characteristic	Quarter 3, 2015 (n = 84)		Quarter 4, 2015 (n = 291)		Quarter 1, 2016 (n = 383)		Quarter 2, 2016 (n = 545)		Quarter 3, 2016 (n = 556)	
	n with available data	Mean (SD)	n with available data	Mean (SD)	n with available data	Mean (SD)	n with available data	Mean (SD)	n with available data	Mean (SD)
Systolic BP (mmHG)	82	122.78 (23.43)	264	120.78 (22.48)	360	120.90 (21.22)	513	120.08 (19.17)	538	122.40 (23.32)
Diastolic BP (mmHg)	82	71.30 (12.37)	262	69.82 (12.75)	359	68.62 (12.90)	513	69.68 (12.78)	538	68.94 (13.66)
eGFR (ml/min/1.73 m^2)	47	49.69 (17.45)	161	57.58 (22.70)	229	57.19 (23.24)	309	57.42 (23.48)	361	53.52 (20.04)
BMI (kg/m^2)	82	31.00 (6.72)	266	31.98 (7.28)	358	31.72 (7.93)	513	31.24 (7.79)	537	31.07 (8.16)
Hb (g/dl)	72	12.23 (1.84)	231	12.94 (2.01)	308	12.62 (2.04)	417	12.84 (2.36)	460	12.60 (1.94)
Heart rate (BPM)	62	76.54 (16.01)	208	80.76 (15.53)	267	82.83 (17.51)	392	82.07 (15.62)	428	81.56 (16.35)
BNP (pg/ml)	21	771.81 (1215.34)	63	493.30 (516.84)	82	963.44 (1950.75)	101	792.19 (2164.06)	115	1842.73 (4771.57)
NT-proBNP (pg/ml)	32	5614.33 (8626.59)	99	4197.92 (6126.25)	133	4836.90 (5811.07)	219	4977.36 (5801.30)	237	6345.50 (9776.48)

BNP: B-type natriuretic peptide; BP: Blood pressure; BPM: Beats per minute; eGFR: Estimated glomerular filtration rate; g/dl: Grams per deciliter; HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; Kg/m_2: Kilograms per meter squared; LVEF: Left ventricular ejection fraction; ml/min/1.73 m^2: Millimeters per minute per 1.73-meters squared; mmHg: Millimeters of mercury; NSAID: NT-proBNP: N-terminal pro b-type natriuretic peptide; pg/ml: Pictograms per milliliter; SD: Standard deviation.

Discussion

The objective of this descriptive study was to assess the characteristics of early sacubitril/valsartan patients in a 'real world' setting using a large US EHR database.

We observed a steady increase in sacubitril/valsartan initiation during the 15 months following its market authorization in the USA. The mean age of sacubitril/valsartan patients increased by approximately 2 years between quarter 3 of 2015 and quarter 3 of 2016, but we did not observe other major changes in characteristics of sacubitril/valsartan patients across calendar quarter of first identified sacubitril/valsartan use. In the first sequential cohorts, the mean age of sacubitril/valsartan patients was identical to that of PARADIGM-HF participants (i.e., 64 years). In subsequent sequential cohorts, the increase in average age was driven by an increase in proportion of sacubitril/valsartan patients who were older than 75 years. We also observed some differences between sacubitril/valsartan patients and trial participants, including a lower prevalence of previous MI and stroke. However, we measured comorbidities using a 1-year baseline period rather than considering histories of ever having these conditions, which could lead to differences in ascertainment. Overall, the results from this study suggest that initial patients using sacubitril/valsartan in 'real-world' practice settings are highly similar to trial participants and that prescribing appears to evolve to include other patients within the first year of market availability.

Overall, the characteristics of sacubitril/valsartan patients were similar to those of the HFrEF cohort. The two key differences in characteristics between the sacubitril/valsartan cohort and the HFrEF cohort were the younger age and the higher prevalence of ischemic cardiomyopathy in the sacubitril/valsartan patients. Although the mean age of sacubitril/valsartan patients was 65 years, the mean age of patients in the HFrEF cohort was 71 years. These findings are similar to those from the Get With the Guidelines – Heart Failure registry [9]. As described above, the younger age of sacubitril/valsartan patients may relate to the age of the PARADIGM-HF trial participants, which also represents a HFrEF cohort. The prevalence of ischemic cardiomyopathy was as high as 60% in the PARADIGM-HF trial, further suggesting that initial prescribing of sacubitril/valsartan may reflect the characteristics of trial participants. The prevalences of other comorbid conditions were also quite similar between sacubitril/valsartan patients and trial participants; namely, hypertension (71 vs 69%), diabetes (35 vs 37%) and atrial fibrillation (36 vs 37%).

As compared with patients with HF treated with an ACEi or an ARB and a β-blocker, but who do not necessarily have HFrEF, a large proportion of patients in the sacubitril/valsartan and the HFrEF cohorts was male and there was a lower prevalence of diabetes and hypertension. The difference in sex distribution could reflect a higher prevalence of HF with preserved EF in the HF-ACEi/ARB + BB cohort. Patients in the sacubitril/valsartan and HFrEF cohorts also had similar prior treatments for HF. Moreover, a similar proportion of patients in these cohorts had LVEF ≤35% and the distributions of LVEF were similar among those patients with values available. In contrast,

among those with results available, the majority of patients in the HF-ACEi/ARB + BB cohort did not have low LVEF values, further suggesting that many of these patients had HF with preserved EF.

Consistent with the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America guidelines for the management of HF and with the characteristics of patients in the PARADIGM-HF trial, most sacubitril/valsartan patients had prior use of other drugs for HF, including ACEi, ARB and β-blockers. The proportion of patients using these drugs was very similar between patients in the sacubitril/valsartan cohort and those in the HFrEF cohort. The prevalence of MRA use was higher in the sacubitril/valsartan initiator cohort (48%) than in the other cohorts, suggesting that sacubitril/valsartan may initially be more likely to be reserved for patients who have already exhausted other treatment options. This is also consistent with the prevalence of MRA use in PARADIGM-HF (56%).

The findings of this study have important implications for the design and conduct of future observational comparative effectiveness studies of sacubitril/valsartan. Consistent with the labeled indication, most sacubitril/valsartan patients with LVEF values available had reduced LVEF. The mean LVEF for sacubitril/valsartan patients was very similar to that for the HFrEF cohort, which was defined by requiring at least one recorded LVEF value of ≤40% in the database. Patients in the HF-ACEi/ARB + BB cohort had a much higher mean LVEF; 60% of patients with LVEF data available did not have any recorded values of ≤40%. Given that ejection fraction may be an important risk factor for mortality [10] and that sacubitril/valsartan is indicated only for patients with HFrEF, comparative effectiveness studies of sacubitril/valsartan will need to account for LVEF in the study design, especially when defining comparator cohorts. In the Explorys study database, information on LVEF was missing for 79% of patients in the HF-ACEi/ARB + BB cohort, even though many of these patients may have undergone echocardiography, which measures LVEF. Even for those with a value available, the most recently recorded value may not reflect a patient's LVEF at the time of cohort entry if, for example, LVEF worsened between the time of the measurement and the time of cohort entry. This reflects an important challenge in using secondary databases that rely on healthcare professionals to record test results. For future comparative studies, efforts will be needed to extract LVEF values from echocardiography notes using natural language processing algorithms so that this information can be made available in structured EHR data.

It is important to highlight the limitations of this study, which may also affect the interpretation of future comparative effectiveness studies in this setting. First, LVEF and other laboratory data were often missing for patients with HF in the Explorys data platform. Furthermore, information on NYHA classifications was not available. Another limitation of EHR data, in general, is that they lack enrollment information. To overcome this, we required demonstration of use of the system in the baseline period. However, even if patients have use of the system during a baseline, it is not possible to know whether all care for the patient occurs within health systems that contribute to the Explorys database and therefore whether data for the patient are complete. For example, if a patient is hospitalized at an institution that contributed data to Explorys but sees a general practitioner who is not part of a contributing system, inpatient data may be captured but outpatient physician visits would not be captured in the data. Another limitation of the data in the Explorys platform is that age for those older than 89 years is truncated. Thus, mean ages may be underestimated.

Conclusion & future perspective

In conclusion, using a large, representative sample of patients with HF in the USA, we observed increasing use of sacubitril/valsartan over time in the early postapproval period. Overall, sacubitril/valsartan patients shared many characteristics with patients in the HFrEF cohort and with PARADIGM-HF trial participants. The mean age of early sacubitril/valsartan patients was identical to that of the trial participants, but increased toward that of the HFrEF cohort over time. Given the observed LVEF values from the three cohorts, using EHR data to identify patients with HFrEF represents an important starting point for defining a comparison group for outcomes research studies involving sacubitril/valsartan, which will help ensure similar characteristics to sacubitril/valsartan patients. These results provide early insights into real-world characteristics of sacubitril/valsartan patients.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: https://www.futuremedicine.com/doi/suppl/10.2217/cer-2017-0088

Summary points

Aims

- It is important to understand how pre-approval trials translate to 'real-world' settings.
- This study examined characteristics of early sacubitril/valsartan patients and other patients with heart failure in a large US electronic health records database.

Patients & methods

- Sacubitril/valsartan patients with a prior heart failure diagnosis and two cohorts of other patients with heart failure were identified.
- Patients were characterized according to demographics, resource utilization, comorbidities, medication use, and laboratory values.
- Changes in baseline characteristics of sacubitril/valsartan patients over time were assessed.

Results

- Sacubitril/valsartan patients were younger than patients in the other cohorts.
- The mean age of sacubitril/valsartan patients increased over time.
- Most sacubitril/valsartan patients had prior use of heart failure medications.

Discussion

- Initial sacubitril/valsartan users were highly similar to participants in the pre-approval trial.
- Prescribing appeared to evolve to include other patients within the first year.
- Sacubitril/valsartan users were similar to other patients with heart failure with reduced ejection fraction.
- Sacubitril/valsartan users were quite different from patients with heart failure treated with other medications.

Conclusion

- Overall, sacubitril/valsartan patients resembled those with heart failure with reduced ejection fraction, and commonly used other drugs for heart failure.
- Using electronic health records data to identify patients with heart failure with reduced ejection fraction represents an important starting point for defining a comparison group for outcomes research studies involving sacubitril/valsartan.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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