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Heart failure signs and symptoms, hospital referrals, and prescription patterns in patients receiving sacubitril/valsartan in primary care and cardiologist settings in Germany

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Abstract

Aims The aim of this paper was to analyse heart failure (HF) signs and symptoms, hospital referrals, and prescription patterns in patients receiving sacubitril/valsartan (sac/val) in primary care and cardiology settings in Germany.

Methods and results A retrospective cohort study of electronic medical records identified 1263 adults (aged ≥18 years) in the German IMS® Disease Analyzer database who were prescribed sac/val during 2016 and had at least 6 months of data following sac/val initiation. Clinical characteristics were collected during the 12 months before the first recorded sac/val prescription (index date) and 6 months post-index. Details of sac/val dose and prescription patterns were also recorded in the 6 months post-index. HF signs, symptoms, and all-cause hospital referrals were evaluated for 90 days pre-index and 30–120 days post-index. Most patients (62%) were prescribed the lowest sac/val dose of 24/26 mg twice daily (b.i.d.) at index; only 14% of patients initiated on 24/26 mg or 49/51 mg b.i.d. were up-titrated to the 97/103 mg b.i.d. target dose during the 6 months post-index, while 6% of patients initiated on either 49/51 mg or 97/103 mg b.i.d. were stably down-titrated. Evaluation of prescription patterns in relation to clinical characteristics did not clearly explain the reluctance to up-titrate in the majority of patients. More patients experienced HF signs or symptoms or all-cause referrals to hospital during the 90 days pre-index than during the 30–120 days post-index.

Conclusions The majority of patients receiving sac/val are not up-titrated, contrary to recommendations of the EU summary of product characteristics; this is not fully explained by patients' clinical characteristics. Further research is required to understand the reasons for clinician inertia.

Introduction

Heart failure (HF) is a major public health challenge in developed countries owing to its impact on mortality, morbidity, and associated healthcare resource consumption.[1] The prevalence of HF in Germany in 2017 was estimated at approximately 4%.[2] HF is the leading cause of hospitalization in Germany, accounting for 2.3% of all inpatients in 2017,[3] and is consequently associated with substantial costs to the healthcare system.[4,5]

Sacubitril/valsartan (sac/val) is an angiotensin receptor–neprilysin inhibitor (ARNI) approved for adult patients with chronic HF with reduced ejection fraction (HFrEF), based on the results of the Prospective Comparison of ARNI with

Angiotensin-Converting-Enzyme Inhibitor (ACEI) to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.[6] PARADIGM-HF demonstrated that sac/val was associated with significant reductions in mortality, hospitalizations for HF, and the burden and frequency of HF symptoms and was also associated with improvements in health-related quality of life.[6,7] In addition, the real-world effectiveness of sac/val has been demonstrated in several studies.[8,9]

The 2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure recommend sac/val as a replacement for ACEI treatment in patients with HFrEF in ambulatory care who remain symptomatic despite treatment with a β-blocker (BB) and a mineralocorticoid receptor antagonist (MRA).[10] Sac/val was launched in Germany in January 2016 at a recommended starting dose of 49/51 mg twice daily (b.i.d.) for most patients.[11]

Several real-world studies have shown that, in clinical practice, there is reluctance to up-titrate patients with HFrEF to the recommended sac/val target dose of 97/103 mg b.i.d.;[12–14] this is consistent with the overall underdosing observed for HF medications in general.[6,7,11] It has been demonstrated that adherence to treatment and dosing guidelines by prescribing physicians is associated with more favourable clinical outcomes for patients,[15] and to our current knowledge, barriers to sac/val up-titration have not yet been explored comprehensively. Therefore, the purpose of this study was to define real-world sac/val prescription patterns in the context of patients' clinical characteristics before and after they initiate sac/val. This study also aimed to characterize changes in HF signs and symptoms and the number of referrals to hospital before and after initiation of sac/val, in primary care and cardiology settings in Germany.

Methods

Study design

This was a non-interventional, retrospective cohort study of adult patients (≥18 years of age) identified in the IMS® Disease Analyzer (DA) database in Germany, who were prescribed sac/val at least once in the inclusion period (between 1 January and 31 December 2016); patients were excluded if their age was not recorded. The full study period was between 1 January 2015 and 30 June 2017, giving a look-back period of 12 months before sac/val initiation and a minimum of 6 months of follow-up after sac/val initiation. Given that sac/val has been marketed in Germany since January 2016, no washout period before initiation of sac/val was implemented. In accordance with the German Federal Data Protection Act, no ethical review board approval was required for this study because it processed anonymous patient information from a secondary database.

Database

The German IMS® DA database contains anonymized, patient-level electronic medical record (EMR) data from general and specialist practices in Germany, on approximately 12 million individuals, from 1992 onwards. Its suitability for pharmacoepidemiologic studies has been demonstrated.[16] At the time of this study, the database included EMRs from 1061 primary care practices [representing 1310 general practitioners (GPs)] and 41 cardiologist practices (representing 62 cardiologists) that had continual data collection. The database includes both GPs and office-based cardiologists. The database covers around 3% of the total GPs and around 6% of cardiologists and has been found to be representative of the patient population.[16] Data collected include demographics, prescriptions, diagnoses, clinical characteristics, referrals to hospital or to other specialists, and clinical notes on signs and symptoms.

Study population

Patients with at least one prescription for sac/val during the inclusion period and who had attended practices with continual data delivery from 1 January 2015 were included. An index date was defined for each patient as the date of their first recorded sac/val prescription. Patients with a minimum of 6 months of post-index data (defined as at least one prescription for any Anatomical Therapeutic Chemical drug class, laboratory measurement, or diagnosis from 183 days or more post-index) were included.

Variables

Patient demographics and clinical characteristics

Patient demographics, comorbidities, and HF treatments were evaluated during the 12 month pre-index period. Clinical characteristics [New York Heart Association (NYHA) class, estimated glomerular filtration rate (eGFR), N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, systolic blood pressure (SBP), body mass index (BMI), and potassium (K^+) level] were collected during the 12 months pre-index and the 6 months post-index. In the case of multiple pre-index records for each clinical characteristic, the value recorded on the date closest to index was included.

Sacubitril/valsartan dose at index and prescription patterns

Sacubitril/valsartan dose at index and prescription patterns during the 6 months post-index were assessed in patients who had at least one sac/val prescription during this period. The below definitions were applied to classify the prescription patterns.

Up-titration and down-titration were subdivided into stable and unstable titration categories: unstable up-titration—

an increase in sac/val dose, after which at least one down-titration occurred; stable up-titration—up-titration with no subsequent down-titration; unstable down-titration —a decrease in sac/val dose, after which at least one up-titration occurred; and stable down-titration—down-titration with no subsequent up-titration.

Time to first sac/val dose titration and time to reach target sac/val dose were also assessed during the 6 months post-index and compared between the two settings of HF care (primary care and cardiology).

Symptoms and referrals to hospital

Heart failure signs and symptoms were identified from EMRs using International Classification of Diseases, 10th Revision diagnosis codes and free-text search strings for terms relating to dyspnoea, pulmonary oedema, peripheral oedema, fatigue, pain, chest pain, nausea, and cough. All-cause referrals to hospital, as recorded in patient EMRs, were stratified by sac/val dose at index and by treating specialist.

Heart failure signs, symptoms, and all-cause referrals to hospital were evaluated during the 90 days pre-index and the 30–120 days post-index (allowing 30 days for up-titration to the recommended sac/val target dose of 97/103 mg b.i.d., as recommended in the EU summary of product characteristics[11]). A sensitivity analysis was performed to assess HF signs, symptoms, and all-cause referrals to hospital during the 0–90 days post-index.

Statistical methods

Version 9.4 of the SAS statistical software (SAS Institute Inc., Cary, NC, USA) and R v3.0.1 were used for the data extractions, data management, and analyses. Normally distributed continuous variables were summarized with *n*, mean, and standard deviation (SD); continuous variables with a skewed distribution were summarized with median and interquartile range (IQR). Descriptive analyses included the proportion of missing data. Categorical variables were summarized with frequencies and percentages. Comparisons between sac/val 24/26 mg b.i.d. and 49/51 mg b.i.d. were assessed with *P* values calculated using Mann–Whitney *U* tests for continuous variables and χ^2 tests for categorical variables. Changes in HF signs and symptoms between the pre-index and 30–120 days post-index periods were compared using McNemar's test and Wilcoxon signed-rank test.

Results

Patient demographics and clinical characteristics

In total, 1263 patients with an index date between January 2016 and December 2016 and with 6 months of post-index data were identified. Patients' mean (SD) age at index was

71.4 (12.0) years and more than two-thirds of the study population (69%) were men (*Table 1*).

The most frequently recorded comorbidities in the 12 month pre-index period were hypertension and ischaemic heart disease, which were recorded in 49% and 42% of patients, respectively (*Table 1*). Use of cardiovascular medications was high: in the 12 month pre-index period, 37%, 30%, 68%, and 47% of patients had received prescriptions for ACEIs, angiotensin receptor blockers (ARBs), BBs, and MRAs, respectively (*Table 1*).

Data on clinical characteristics in the 12 months pre-index had limited availability: data on NYHA class, eGFR, NT-proBNP levels, SBP, BMI, and K+ levels were available for 9–48% of patients (*Table 1*). Of the patients with values recorded, most had HF of NYHA class III and almost half had an eGFR of 30–59 mL/min/1.73 m^2 (indicative of stage 3 chronic kidney disease). Patients' NT-proBNP levels were high [median (IQR): 1857 (856, 3545) pg/mL], as was SBP [mean (SD): 130 (21) mmHg]. The mean (SD) BMI across the cohort was 30 (6) kg/m^2, and the mean (SD) K+ level was 4.6 (0.6) mmol/L.

Sacubitril/valsartan dose at index and prescription patterns

Sacubitril/valsartan at index and in relation to pre-index clinical characteristics

At index, 62% of patients were prescribed sac/val 24/26 mg b.i.d., 31% were prescribed 49/51 mg b.i.d., and 7% were prescribed the target dose of 97/103 mg b.i.d.; the proportions of patients receiving each dose were similar in the two settings of HF care. Patients who received 24/26 mg b.i.d. at index were slightly older than those who received 49/51 mg b.i.d. (72.1 vs. 70.1 years of age, respectively; *P* = 0.011).

Higher mean SBP was associated with the prescription of a higher sac/val dose at index (128 mmHg for 24/26 mg b.i.d. vs. 133 mmHg for 49/51 mg b.i.d., *P* = 0.029). Of patients with a recorded NYHA class, 31% of those who were prescribed 24/26 mg b.i.d. at index had HF of classes I–II and 69% had HF of classes III–IV; 28% of patients who were prescribed 49/51 mg b.i.d. at index had HF of NYHA classes I–II and 72% had NYHA classes III–IV. Lower median (IQR) NT-proBNP levels were typically associated with higher sac/val doses at index [1995 (947, 3615) pg/mL for 24/26 mg b.i.d. vs. 1612 (697, 3736) pg/mL for 49/51 mg b.i.d., respectively]. Similarly, the mean (SD) eGFR was lower for patients receiving 24/26 mg b.i.d. than for those receiving 49/51 mg b.i.d. at index [57 (22) vs. 62 (21) mL/min/1.73 m^2; *P* < 0.01].

Prescription patterns in relation to clinical characteristics during the 6 months post-index

Overall, no records of titration were found in two-thirds of patients (67%) during the 6 months post-index. In total, 222 (17.6%) patients had only one prescription record in the first

Table 1 Pre-index demographics and clinical characteristics of patients prescribed sac/val

Characteristic	All patients (N = 1263)	Sac/val dose at index		
		24/26 mg b.i.d. (N = 781)	49/51 mg b.i.d. (N = 389)	97/103 mg b.i.d. (N = 93)
Mean age (SD), years	71.4 (12.0)	72.1 (11.7)	70.1 (12.3)	70.9 (12.9)
			P value 0.011	
Sex, n (%)				
Men	875 (69)	529 (68)	274 (70)	72 (77)
Women	388 (31)	252 (32)	115 (30)	21 (23)
			P value 0.348	
Comorbidities[b], n (%)				
Hypertension	613 (49)	383 (49)	187 (48)	43 (46)
			P value 0.755	
Ischaemic heart disease	533 (42)	333 (43)	161 (41)	39 (42)
			P value 0.684	
Atrial fibrillation/flutter	330 (26)	218 (28)	89 (23)	23 (25)
			P value 0.065	
Diabetes	327 (26)	222 (28)	87 (22)	18 (19)
			P value 0.027	
Chronic lower respiratory disease	244 (19)	161 (21)	68 (18)	15 (16)
			P value 0.203	
Valvular disease	193 (15)	124 (16)	54 (14)	15 (16)
			P value 0.371	
Dilated cardiomyopathy	184 (15)	112 (14)	60 (15)	12 (13)
			P value 0.622	
COPD	160 (13)	112 (14)	37 (10)	11 (12)
			P value 0.020	
Hypothyroidism	117 (9)	76 (10)	33 (9)	8 (9)
			P value 0.489	
Peripheral vascular disease	109 (9)	73 (9)	27 (7)	9 (10)
			P value 0.165	
CV medications[c], n (%)				
ACEI	463 (37)	296 (38)	146 (38)	21 (23)
			P value 0.903	
ARB (excluding sac/val)	384 (30)	227 (29)	124 (32)	33 (36)
			P value 0.323	
BB	861 (68)	541 (69)	263 (68)	57 (61)
			P value 0.564	
MRA	598 (47)	369 (47)	187 (48)	42 (45)
			P value 0.790	
Oral diuretics (excluding MRA)	965 (76)	604 (77)	291 (75)	70 (75)
			P value 0.336	
Antiplatelet drugs	382 (30)	243 (31)	113 (29)	26 (28)
			P value 0.470	
Lipid-lowering drugs	520 (41)	326 (42)	153 (39)	41 (44)
			P value 0.430	
Statins	504 (40)	318 (41)	147 (38)	39 (42)
			P value 0.335	
Non-CV medications[d], n (%)				
Glucose-lowering drugs	292 (23)	194 (25)	81 (21)	17 (18)
			P value 0.127	
NSAIDs	183 (15)	117 (15)	61 (16)	5 (5)
			P value 0.753	
Gout treatments	295 (23)	198 (25)	85 (22)	12 (13)
			P value 0.188	
COPD treatments	254 (20)	171 (22)	69 (18)	14 (15)
			P value 0.097	
Clinical characteristics				
SBP, mmHg				
Mean (SD)	130 (21)	128 (20)	133 (22)	133 (17)
			P value 0.029	
Unknown	859 (68)	526 (67)	274 (70)	59 (63)
BMI, kg/m^2				
Mean (SD)	30 (6)	29 (6)	30 (6)	31 (6)
			P value 0.062	
Unknown	956 (76)	583 (75)	305 (78)	68 (73)
NT-proBNP, pg/mL				
Median (IQR)	1857 (854, 3545)	1995 (947, 3615)	1612 (697, 3736)	1467 (1057, 1829)

(*Continues*)

Table 1 (continued)

Characteristic	All patients (N = 1263)	Sac/val dose at index		
		24/26 mg b.i.d. (N = 781)	49/51 mg b.i.d. (N = 389)	97/103 mg b.i.d. (N = 93)
		P value 0.508		
Unknown	1076 (85)	662 (85)	330 (85)	84 (90)
eGFR, mL/min/1.73 m^2, *n* (%)[a]				
Mean (SD)	59 (23)	57 (22)	62 (21)	59 (27)
		P value 0.006		
>90	49 (8)	27 (7)	17 (10)	5 (13)
60–90	219 (37)	137 (37)	71 (41)	11 (28)
30–59	274 (47)	176 (47)	79 (45)	19 (49)
15–29	42 (7)	32 (9)	7 (4)	3 (8)
<15	4 (1)	3 (1)	0 (0)	1 (3)
Unknown	675 (53)	406 (52)	215 (55)	54 (58)
K$^+$, mmol/L, *n* (%)				
Mean (SD)	4.6 (0.6)	4.6 (0.6)	4.6 (0.6)	4.8 (0.6)
		P value 0.459		
<3.5	10 (2)	9 (2)	1 (1)	0 (0)
3.5–3.9	47 (8)	34 (9)	11 (6)	2 (6)
4.0–4.4	182 (30)	115 (29)	62 (35)	5 (14)
4.5–4.9	218 (36)	137 (34)	66 (37)	15 (42)
5.0–5.9	140 (23)	93 (23)	34 (19)	13 (36)
6.0–6.4	10 (2)	9 (2)	1 (1)	0 (0)
≥6.5	4 (1)	1 (0)	2 (1)	1 (3)
Unknown	652 (52)	383 (49)	212 (54)	57 (61)
NYHA class, *n* (%)[a]				
I	4 (2)	3 (2)	0 (0)	1 (3)
II	71 (32)	37 (29)	18 (28)	16 (49)
III	124 (55)	68 (54)	42 (65)	14 (42)
IV	26 (12)	19 (15)	5 (8)	2 (6)
		P value 0.230		
Unknown	1038 (82)	654 (84)	324 (83)	60 (65)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; b.i.d., twice daily; BB, β-blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; IQR, interquartile range; K$^+$, potassium; MRA, mineralocorticoid receptor antagonist; NSAID, non-steroidal anti-inflammatory drug; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; sac/val, sacubitril/valsartan; SD, standard deviation.
For the percentages of patients with available data within each parameter, percentages may not sum to 100% owing to rounding. The *P* values included in the table represent the comparison between 24/26 mg and 49/51 mg.
[a]Calculated as percentage of patients with available data (except data for 'unknown', which are calculated based on the total number of patients).
[b]Ten most common comorbidities identified.
[c]Eight most common CV medications identified.
[d]Four most common non-CV medications identified.

6 months; therefore, any further titration efforts attempted on these patients would have not been captured. Among all patients, 30% were up-titrated during this period, of whom 85% were stably up-titrated, remaining on their up-titrated dose; stable down-titration was observed in 2% of patients. Of the patients who were prescribed 24/26 mg b.i.d. or 49/51 mg b.i.d. at index, 37% and 23% were up-titrated, respectively. Out of the 761 patients who were initiated on the lowest dose (24/26 mg b.i.d.) and had more than one prescription record, 367 (47%) did not titrate despite having received more than one prescription during the first 6 months. Of the patients who had a first recorded prescription of 97/103 mg b.i.d. at index, 90% had no titration records. Of the 10% of patients who experienced down-titration from the target dose, most (89%) were stably down-titrated. No titration was observed in 47%, 50%, and 67% of patients who were prescribed 24/26 mg b.i.d.,

49/51 mg b.i.d, and 97/103 mg b.i.d. (*Figure 1*). Titration patterns were similar in both care settings (Supporting Information, *Figure S1*).

Overall, the mean (SD) time to first dose titration was 61 (51) days. The mean (SD) time to reach the target dose of 97/103 mg b.i.d. within the 6 month post-index period was 61 (46) days; this was numerically longer in patients treated in a cardiology setting than in those treated in a primary care setting [64 (44) vs. 60 (47) days (*P* = 0.620), respectively].

Among patients who were prescribed sac/val 24/26 mg b.i.d. at index, there was no difference in mean (SD) SBP between those who were stably up-titrated and those who were not titrated [123 (17) mmHg vs. 122 (20) mmHg, respectively; *Table 2*] or in the proportion of patients with low SBP (<100 mmHg, 8% in both groups). Moreover, there were no patients with a recorded low SBP (<100 mmHg) among those

Figure 1 Titration patterns during the first 6 months post-index, stratified by sac/val dose at index. 'Unstable up-titration' corresponds to all patients who experience an initial increase in sac/val dose, after which at least one down-titration occurred; 'stable up-titration' corresponds to up-titrated patients who experienced no subsequent down-titration; 'unstable down-titration' corresponds to all patients who experienced an initial decrease in sac/val dose, after which at least one up-titration occurred; 'stable down-titration' corresponds to down-titrated patients who experienced no subsequent up-titration; and "unknown titration" corresponds to patients with a single prescription record during the 6 months analysis. The total of the grey categories are 'no recorded titration'. A proportion of all patients who were up-nitrated/down-titrated. b.i.d., twice daily; sac/val, sacubitril/valsartan.
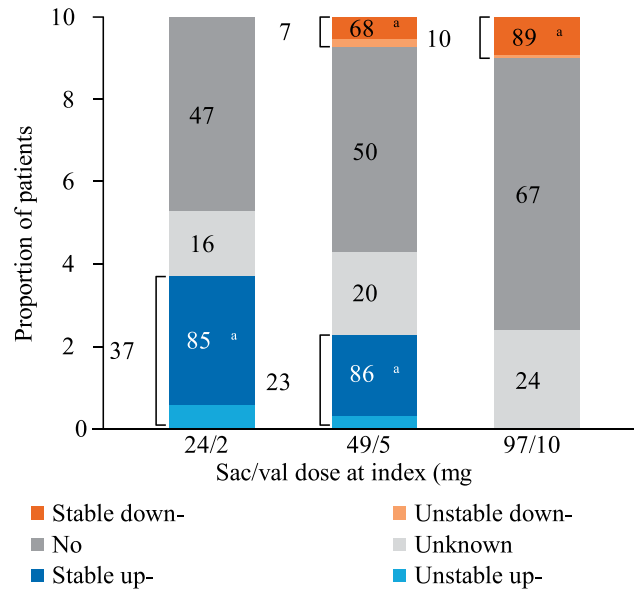
initiated on either 49/51 mg b.i.d. or 97/103 mg b.i.d. at index who were stably down-titrated; these patients had a lower mean (SD) SBP than those who were initiated on 49/51 mg b.i.d. at index and stably up-titrated [120 (15) vs. 134 (23) mmHg, respectively].

Similar mean (SD) K^+ levels were observed in patients who were stably up-titrated and those who were not titrated regardless of whether they had a starting dose of 24/26 mg b.i.d. or 49/51 mg b.i.d. at index [range: 4.6 (0.6)–4.7 (0.7) mmol/L]. Mean (SD) eGFR values were similar between patients who received 24/26 mg b.i.d. and who were stably up-titrated and those who were not titrated [54 (23) vs. 52 (22) mL/min/1.73 m^2, respectively]. Similar mean (SD) eGFR values were observed for patients who received 49/51 mg b.i.d. at index and were stably up-titrated, those who received 49/51 mg b.i.d. at index and were not titrated, and patients who had received either 49/51 mg b.i.d. or 97/103 mg b.i.d. and were stably down-titrated [61 (20) vs. 59 (23) vs. 62 (26) mL/min/1.73 m^2, respectively]. Among patients who were prescribed 24/26 mg b.i.d. at index, lower median (IQR) NT-proBNP levels were observed in those who were stably up-titrated than in those who were not titrated [1193 (642, 2576) vs. 1820 (789, 3424) mmol/L, respectively], although this difference was not statistically significant (P = 0.107). The

opposite trend was observed for patients prescribed 49/51 mg b.i.d. at index and stably up-titrated and those who were prescribed 49/51 mg b.i.d. at index and not titrated [median (IQR) NT-proBNP level of 1162 (432, 2711) vs. 850 (416, 1658) mmol/L, respectively].

Among patients who received 24/26 mg b.i.d. at index, mean (SD) post-index BMI values varied by titration stratum; patients who were stably up-titrated generally had higher BMI than those who were not titrated [31 (5) vs. 29 (6) kg/m^2], although this difference was not statistically significant (P = 0.051). Similar mean (SD) BMI value was observed for patients who received 49/51 mg b.i.d. at index and were stably up-titrated and those who were not titrated [both 30 (7) kg/m^2]. In patients prescribed 24/26 mg b.i.d. at index, lower NYHA classes tended to be observed in patients who were stably up-titrated than in those who were not titrated (NYHA classes I–II: 33% vs. 26%; NYHA classes III–IV: 67% vs. 74%, respectively). In contrast, among patients who were prescribed 49/51 mg b.i.d. at index, higher NYHA classes were generally observed in patients who were stably up-titrated than in those who were not titrated (NYHA classes I–II: 32% vs. 39%; NYHA classes III–IV: 68% vs. 61%, respectively).

Overall, no clear trends in differences in clinical characteristics were apparent across patients who were

Table 2 Patients reaching clinical thresholds during the 6 months post-index, by sac/val prescription pattern and index dose

Clinical characteristics

Sac/val dose at index, mg b.i.d.	Titration pattern[a]	SBP			K+ level			eGFR		
		Patients with data, n (N = 363, 29% of total population)	Mean, mmHg (SD)	<100 mmHg, n (%)[b]	Patients with data, n (N = 568, 45% of total population)	Mean, mmol/L (SD)	≥6 mmol/L, n (%)[b]	Patients with data, n (N = 542, 43% of total population)	Mean, mL/min/1.73 m² (SD)	<30 mL/min/1.73 m², n (%)[b]
24/26 mg	All	234	122 (19)	19 (8)	375	4.6 (0.6)	7 (2)	349	54 (22)	50 (14)
	No titration	139	122 (20)	11 (8)	213	4.7 (0.7)	6 (3)	196	52 (22)	28 (14)
	Other titration	20	126 (24)	2 (10)	39	4.6 (0.5)	1 (3)	33	57 (22)	2 (6)
	Stable up-titration	75	123 (17)	6 (8)	123	4.6 (0.6)	0 (0)	120	54 (23)	20 (17)
49/51 mg	All	96	128 (22)	2 (2)	158	4.7 (0.5)	1 (1)	159	60 (22)	11 (7)
	No titration	61	128 (22)	2 (3)	84	4.6 (0.5)	0 (0)	86	59 (23)	8 (9)
	Other titration	6	121 (23)	0 (0)	15	5.0 (0.3)	0 (0)	16	61 (26)	2 (13)
	Stable up-titration	24	134 (23)	0 (0)	43	4.7 (0.6)	1 (2)	43	61 (20)	0 (0)
49/51 mg or 97/103 mg	Stable down-titration	5	120 (15)	0 (0)	18	4.5 (0.6)	1 (6)	16	62 (26)	1 (6)
97/103 mg	All	33	134 (18)	0 (0)	35	4.9 (0.9)	3 (9)	34	60 (27)	4 (12)
	No titration	33	134 (18)	0 (0)	33	4.9 (0.9)	2 (6)	32	60 (27)	4 (12)

Clinical characteristics

Sac/val dose at index, mg b.i.d.	Titration pattern[a]	NYHA class			NT-proBNP			BMI		
		Patients with data, n (N = 219, 17% of total population)	I–II, n (%)[b]	III–IV, n (%)[b]	Patients with data, n (N = 221, 17% of total population)	Median, pg/mL (IQR)	≥400 pg/mL, n (%)[b]	Patients with data, n (N = 243, 19% of total population)	Mean, kg/m² (SD)	≥30 kg/m², n (%)[b]
24/26 mg	All	122	35 (29)	87 (71)	150	1543 (658, 2721)	124 (83)	168	30 (6)	71 (42)
	No titration	69	18 (26)	51 (74)	74	1820 (789, 3424)	61 (82)	92	29 (6)	32 (35)
	Other titration	7	2 (29)	5 (71)	18	1655 (461, 2707)	16 (89)	19	30 (5)	9 (47)
	Stable up-titration	46	15 (33)	31 (67)	58	1193 (642, 2576)	47 (81)	57	31 (5)	30 (53)
49/51 mg	All	67	25 (37)	42 (63)	61	989 (495, 2440)	49 (80)	54	30 (7)	23 (43)
	No titration	31	12 (39)	19 (61)	24	850 (416, 1658)	18 (75)	32	30 (7)	14 (44)
	Other titration	7	3 (43)	4 (57)	7	1694 (650, 1977)	7 (100)	2	40 (17)	1 (50)
	Stable up-titration	22	7 (32)	15 (68)	22	1162 (432, 2711)	17 (77)	17	30 (7)	7 (41)
49/51 mg or 97/103 mg 103 mg	Stable down-titration	11	5 (46)	6 (55)	10	1397 (518, 4119)	9 (90)	3	27 (3)	1 (33)
97/103 mg	All	30	15 (50)	15 (50)	10	1253 (855, 1595)	9 (90)	21	33 (7)	12 (57)
	No titration	26	13 (50)	13 (50)	8	1253 (741, 3281)	7 (88)	21	33 (7)	12 (57)

b.i.d., twice daily; BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; K+, potassium; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; sac/val, sacubitril/valsartan; SBP, systolic blood pressure; SD, standard deviation.

[a]Titration patterns were defined during the 6 months post-index. Stable up-titration corresponds to patients with no subsequent down-titration; stable down-titration corresponds to patients with no subsequent up-titration; no titration corresponds to no existing record of titration; and other titration corresponds to all patients with both up-nitration and down-titration.

[b]Proportions were calculated by dividing the number of patients with the characteristic in each titration pattern and dose index group by the total number of patients in each titration pattern and dose index group.

stably up-titrated, stably down-titrated, or not titrated (*Table 2*).

Symptoms and referrals to hospital

The overall frequency of recorded signs and symptoms in both the pre-index and post-index periods was low (recorded for less than 15% of patients). More patients experienced HF signs or symptoms during the 90 days pre-index than during the 30–120 days post-index (*Figure 2*). Except for nausea, fatigue, and pulmonary oedema, these differences were slightly more pronounced when comparing the pre-index and the 30–120 day post-index periods, than the pre-index and the 90 day post-index periods. The differences between the pre-index and the 30–120 day post-index periods were significant for peripheral oedema (3.7% vs. 2.4%, $P = 0.015$), dyspnoea (5.8% vs. 2.1%, $P < 0.001$), and chest pain (12.8% vs. 8.7%, $P < 0.001$; *Figure 2*).

Significantly fewer all-cause referrals to hospital occurred in the 30–120 day post-index compared with the 90 day pre-index period (10% vs. 19%, respectively, $P < 0.001$; *Figure 3*). A similar trend was observed in both care settings and across all sac/val doses at index. Slightly larger reductions in the proportions of patients referred to hospital between the pre-index and 30–120 day post-index periods were observed for patients prescribed higher index doses of sac/val (−9 percentage points for 49/51 mg b.i.d. vs. −7 percentage points for 24/26 mg b.i.d.; both $P < 0.001$). Among all

patients, the mean number of referrals to hospital per patient was approximately halved from the 90 day pre-index period to the 30–120 day post-index period (0.23 vs. 0.12, $P < 0.001$; data not shown). The results of the sensitivity analyses comparing the 0–90 days post-index and the 30–120 days post-index were consistent with the main analyses. In total, 13% of patients had one or two referrals to a cardiologist from their GP during the 12 months pre-index, compared with 16% of patients with one or two referrals to a cardiologist from their GP during the post-index period.

Discussion

This study has four main findings.

- Most patients were prescribed the lowest dose of sac/val at index and a small proportion was up-titrated to the target dose of 97/103 mg b.i.d. during the first 6 months post-index.
- The mean time to first up-titration was considerably longer than the 2–4 weeks recommended in the EU summary of product characteristics.[11]
- Post-index clinical characteristics, such as low SBP and eGFR and high K^+ levels, did not explain the reluctance to up-titrate the majority of patients.
- Initiation of sac/val was associated with a reduction in the occurrence of HF signs, symptoms, and all-cause referrals to hospital, regardless of sac/val dose at index and the setting of HF care.

Figure 2 Proportions of patients initiating sac/val who experienced HF signs and symptoms in the pre-index and post-index periods. *$P < 0.05$; **$P < 0.001$. HF, heart failure; sac/val, sacubitril/valsartan.
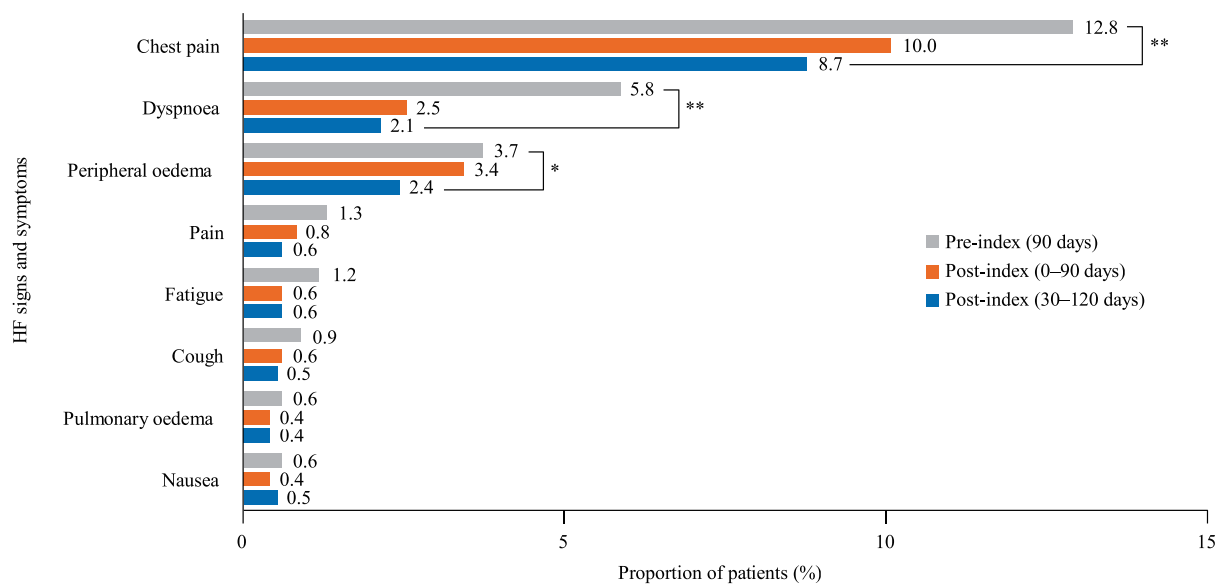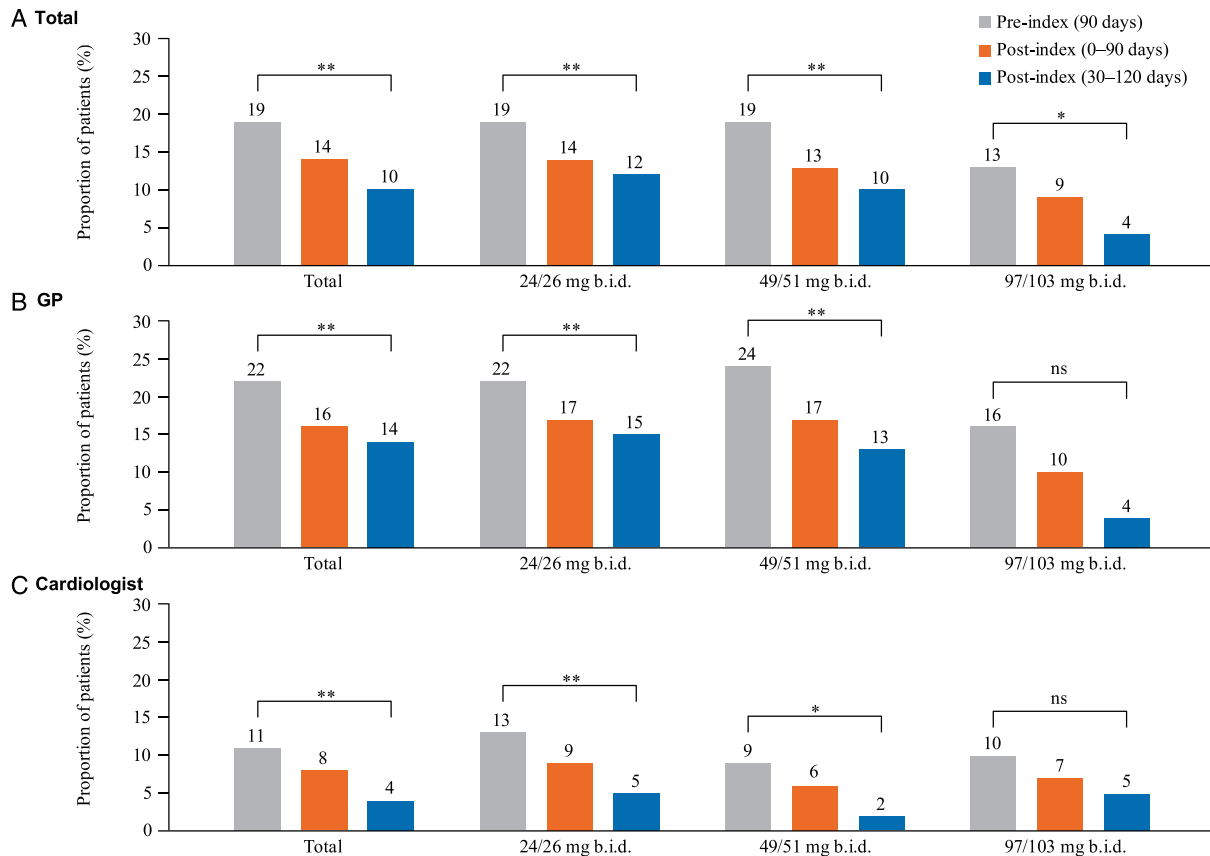
Figure 3 Proportions of patients initiating sac/val who experienced all-cause referrals to hospital in the pre-index and post-index periods, overall, and by sac/val index dose and treating specialist. $^*P < 0.05$; $^{**}P < 0.001$. b.i.d., twice daily; GP, general practitioner; ns, not significant; sac/val, sacubitril/valsartan.

Patient demographics and clinical characteristics

In this real-world study, the mean patient population age was higher than that of the PARADIGM-HF trial population, and there was a lower proportion of male patients than in the PARADIGM-HF trial (71 vs. 64 years and 69% vs. 79%, respectively).[6] This is consistent with the findings of other real-world studies of sac/val usage in Germany.[14]

Overall, the majority (55%) of patients had HF of NYHA class III, indicating that patients in real-world clinical practice have more severe HF than those enrolled in PARADIGM-HF, in which most patients (72%) had HF of NYHA class II[6]. The proportion of patients in this study with HF of NYHA class III is also higher than observed in other real-world studies of sac/val.[13,17] The differences in HF severity observed between the current study and other real-world studies may be partly explained by the low number of patients in the current cohort with a recorded NYHA class. Nevertheless, the overall higher severity of HF seen in these populations compared with PARADIGM-HF may partly explain the overall lower

dosing of sac/val at initiation in clinical practice. Indeed, in this study, patients with less severe HF (indicated by a lower NT-proBNP level, lower NYHA class, and higher eGFR) tended to receive higher index sac/val doses at index. The reasons for this are unknown; however, the presence of comorbidities might discourage physicians from prescribing higher index doses of sac/val.

Sacubitril/valsartan dose at index and prescription patterns

Overall, the majority of patients (62%) were prescribed the lowest sac/val dose of 24/26 mg b.i.d. at index, despite the recommendation of the EU summary of product characteristics to initiate most patients on a dose of 49/51 mg b.i.d.[11] Overall, no record of dose change in sac/val was found in two-thirds of patients during the 6 months post-index. The low frequency of down-titration observed in this study is reassuring, considering that high NT-proBNP levels, older

age, and lower SBP were among the identified significant predictors of dose reduction in a multivariable regression model of data from the PARADIGM-HF study.[18] More importantly, only a small proportion of patients was up-titrated to 97/103 mg b.i.d.; only 14% of patients initiated on 24/26 mg b.i.d. or 49/51 mg b.i.d. reached the target dose within 6 months post-index, vs. nearly 50% of patients as observed in the TRANSITION randomized controlled trial, indicating a gap in implementation of new therapies titrations in the real-world scenario.[19] Furthermore, the mean time to first titration was considerably longer than the recommended 2–4 weeks;[11] however, of the patients initiated on 49/51 mg b.i.d. who were up-titrated, 86% remained on 97/103 mg b.i. d., suggesting that the target dose of sac/val is well tolerated. The tolerability profile of initiation and up-titration of sac/val from 24/26 mg b.i.d. or 49/51 mg b.i.d. to 97/103 mg b.i.d has previously been demonstrated and is in line with other HF treatments.[20] Time to reach the target dose was significantly longer for patients initiated on 24/26 mg b.i.d. than for those initiated on 49/51 mg b.i.d.; this is to be expected considering that the recommendation is to up-titrate gradually and to monitor clinical and biochemical parameters. These findings confirm those of other studies that show that sac/val is underdosed and physicians' inability or unwillingness to up-titrate appears common in clinical practice.[12,13,21-] A recently published retrospective study of German adult patients on sac/val (aged ≥18 years) from the IMS® longitudinal prescriptions database also looked into treatment patterns and explored the barriers in up-titration.[14] This database consisted of patients from both the cardiology and primary care settings and reported that, overall, 64% of patients were prescribed the lowest dose of sac/val at index and that the mean time to first titration was 54 days. Interestingly, it shows that up-titration in patients on lower sac/val doses was not attempted and there were only marginal differences in the sac/val titration patterns between patients who were on different doses of prior ACEI vs. Renin-Angiotensin-Aldosterone-System (RAAS)-naïve. Additionally, patients who were up-titrated on sac/val tended to be prescribed lower daily diuretic doses post-index than those who were down-titrated on sac/val, suggesting a role of concomitant HF medication in the titration process.[14]

In the 6 months post-index, expected trends between index dose and clinical characteristics were observed, whereby patients who were prescribed 24/26 mg b.i.d. at index had lower SBP and eGFR than those prescribed higher index doses. Despite an expected correlation of SBP and eGFR with sac/val dose at index, when comparing the strata of titration patterns with sac/val dose at index, changes in clinical characteristics did not appear to justify titration inertia. Patients with lower SBP and eGFR were not less frequently up-titrated than those with higher SBP and eGFR, suggesting that the lack of up-titration cannot solely be explained by these clinical characteristics of the patients.

Symptoms and referrals to hospital

The occurrence of HF signs and symptoms and referrals to hospital can have a significant negative impact on patients' health-related quality of life, particularly in patients with more severe HF.[22] In this study, initiation of sac/val was associated with a reduction in the occurrence of HF signs and symptoms and referrals to hospital, regardless of sac/val dose at index. Overall, a reduction in the concomitant cardiovascular medication from pre- to post-index analysis was observed, suggesting that most patients who were initiated on sac/val not only discontinued ACEI/ARB therapy (from 37%/30% to 7%/9%, respectively; $P < 0.001$), but also slightly reduced the use of BB, MRAs, and diuretics (from 68%, 47%, and 76% to 64%, 44%, and 74%; $P < 0.001$, $P = 0.004$, and $P = 0.0641$). This is reassuring that the observed reduction in symptoms and hospital referrals is likely not a result of an optimization of other cardiovascular therapies. These findings have been observed in other real-world studies [8,23,24] and may prevent deterioration of health-related quality of life in patients receiving sac/val, as was observed in a secondary analysis of PARADIGM-HF.[25]

Additionally, the significant reduction of referrals to hospital post-index is consistent with the results of the PARADIGM-HF trial, in which significantly fewer patients experienced HF-related admissions to hospital after initiation of sac/val than before sac/val initiation.[26] Previous studies have shown that hospitalizations account for a substantial proportion of healthcare resource utilization and consequent economic burden of HF;[2,27] therefore, characterizing the impact of HF treatment on the reduction of hospitalizations is not only important from the perspective of improving outcomes for patients, but also from an economic perspective of reducing the burden to healthcare systems.

Strengths, limitations, and areas for future research

The strength of this study lies in the large sample size provided by the IMS® DA database,[16] which generates more precise estimates of the characterization of the real-world use and implementation of sac/val in Germany than smaller study populations. Additionally, the availability of clinical data allowed evaluation of correlations between sac/val dose, prescription patterns, and clinical characteristics, which builds upon titration data published in a previous study of the real-world use of sac/val.[12]

Limitations of this study include those inherent to the secondary use of data[28] and include the large unavailability of data on clinical parameters such as SBP, K^+ levels, NYHA class, NT-proBNP levels, BMI, and eGFR. Due to this limitation, statistical methods such as logistic regression could not be performed to further explore the potential associations

between these baseline parameters and titration. Additionally, the low clinical data recording has limited the choice of study design, including a potential matching based on propensity score matching for analysis. Namely, the lack of left ventricular ejection fraction data in this real-world database prevented the identification of a relevant comparator group of HFrEF patients who were not on sac/val. Other limitations include the lack of a closed healthcare system, meaning data from patients attending practices outside the scope of the IMS® DA database would not have been captured. This incomplete coverage may also account for the small proportion of patients who had a first recorded sac/val dose of 97/103 mg b.i.d., who may have previously received a lower initial dose of sac/val from centres not covered by the database. Additionally, information on the prescribed dose frequency is not captured within the database, and it was therefore assumed that sac/val was prescribed to be taken twice daily, in line with the approved posology. Situations of half-dosing are also not captured; this is particularly important for the recommended dose of 24/26 mg b.i.d., because it is possible that there may have been some occurrences in which physicians prescribe half the lowest sac/val dose at initiation. The influence of non-pharmacological interventions such as telemonitoring or nurse care was not captured in this data set.

Potential biases in the recording of HF signs and symptoms and hospital referrals in the EMRs need further investigation. The overall low frequency of HF signs and symptoms recorded in the EMRs both before and after sac/val initiation highlights the limitations of using EMR data to capture subjective patient outcomes, particularly because nearly all patients had HF of NYHA classes II–IV and were therefore symptomatic.

Furthermore, we were unable to assess the number of hospitalizations directly; therefore, hospital referrals were used as a proxy. Additionally, emergency hospitalizations and clinical outcomes are not captured by the IMS® DA database, and the cause of hospital referral is missing from structured EMRs.

Conclusions

This evidence from the real-world study of EMR data suggests an association between sac/val and reduction in the occurrence of HF signs, symptoms, and all-cause referrals to hospital. However, the majority of patients were prescribed the lowest sac/val dose of 24/26 mg b.i.d. at index and there was a low tendency to up-titrate patients to the target dose of 97/103 mg b.i.d. within the first 6 months after sac/val initiation. The lack of up-titration could not be fully explained by patients' clinical characteristics such as SBP, K^+ levels, or eGFR, and very few patients were down-titrated. Further research is required to understand the reasons for the lack of up-titration, and further educational efforts are warranted to promote

up-titration and to ensure that patients are treated to the maximum tolerated dose to achieve maximum clinical benefit.

Conflict of interest

R.W. has been a consultant for, or has received speaker's bureau honoraria from, Bayer, Berlin-Chemie, Boehringer Ingelheim, Bristol-Myers Squibb, CVRx, Gilead, Johnson & Johnson, Medtronic, Novartis, Pfizer, Relypsa, Sanofi, and Servier. His institution has received research funding from Boehringer Ingelheim, the EU, and The Federal Ministry of Education and Research. S.K. is an employee of Novartis Pharma GmbH, Nuremberg, Germany. B.B. and R.S. were employees of Novartis Pharma AG, Basel, Switzerland, at the time of the study. B.B. is now an employee of F. Hoffmann-La Roche Ltd, Basel, Switzerland. A.F.F. is an employee of Novartis Pharma AG, Basel, Switzerland. E.K. and J.E. were employees of IQVIA, Frankfurt, Germany, at the time of this study. S.B. W. was an employee of Novartis Sweden AB, Stockholm, Sweden, at the time of this study and is now an employee of Janssen-Cilag AB, Solna, Sweden. IQVIA was commissioned to conduct the study on behalf of Novartis Pharma AG and has ongoing consulting and research relationships with Novartis Pharma AG.

Author contributions

J.E. and E.K worked on the acquisition of data, and all authors contributed to the conception and design of the study, analysis and interpretation of data, and drafting and reviewing of the paper. All authors made substantial contributions to critically drafting and reviewing the article for important intellectual content and provided final approval of the version to be published.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Prescription patterns during the 6 months post-index, stratified by sac/val dose at index and care setting. 'Unstable up-titration' refers to patients who experienced an initial increase in sac/val dose, after which at least one down-titration occurred; 'stable up-titration' refers to up-titrated patients who experienced no subsequent down-titration; 'unstable down-titration' refers to patients who experienced an initial decrease in sac/val dose, after which at least one up-titration occurred; 'stable down-titration' refers to down-titrated patients who experienced no subsequent up-titration. b.i.d., twice daily; HF, heart failure; sac/val, sacubitril/valsartan; "no titration records" refers to no titration

Table S1. Pre-index demographic and clinical characteristics of patients prescribed sac/val stratified by setting of HF care

References

1. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CS, Sato N, Shah AN, Gheorghiade M. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014; **63**: 1123–1133.
2. Störk S, Handrock R, Jacob J, Walker J, Calado F, Lahoz R, Hupfer S, Klebs S. Epidemiology of heart failure in Germany: a retrospective database study. *Clin Res Cardiol* 2017; **106**: 913–922.
3. Statistics on hospital patients. German Federal Statistical Office, 2017. https://www.destatis.de/EN/FactsFigures/SocietyState/Health/Hospitals/Tables/20mostDiagnoses.html (23 January 2019).
4. Neumann T, Biermann J, Erbel R, Neumann A, Wasem J, Ertl G, Dietz R. Heart failure: the commonest reason for hospital admission in Germany: medical and economic perspectives. *Dtsch Arztebl Int* 2009; **106**: 269–275.
5. Christ M, Stork S, Dorr M, Heppner HJ, Muller C, Wachter R, Riemer U for the Trend HF Germany Project. Heart failure epidemiology 2000–2013: insights from the German Federal Health Monitoring System. *Eur J Heart Fail* 2016; **18**: 1009–1018.
6. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR for the PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371**: 993–1004.
7. Lewis EF, Claggett BL, McMurray JJV, Packer M, Lefkowitz MP, Rouleau JL, Liu J, Shi VC, Zile MR, Desai AS, Solomon SD, Swedberg K. Health-related quality of life outcomes in PARADIGM-HF. *Circ Heart Fail* 2017; **10**: e003430.
8. Martens P, Lambeets S, Lau C, Dupont M, Mullens W. Impact of sacubitril/valsartan on heart failure admissions: insights from real-world patient prescriptions. *Acta Cardiol* 2018; 1–8.
9. Antol DD, Casebeer AW, DeClue RW, Stemkowski S, Russo PA. An early view of real-world patient response to sacubitril/valsartan: a retrospective study of patients with heart failure with reduced ejection fraction. *Adv Therapy* 2018; **35**: 785–795.
10. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Group ESD. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.
11. Summary of Product Characteristics, Entresto. European Medicines Agency, 2015. https://www.ema.europa.eu/documents/product-information/entresto-epar-product-information_en.pdf (23 January 2019).
12. Wachter R, Viriato D, Klebs S, Grunow SS, Schindler M, Engelhard J, Proenca CC, Calado F, Schlienger R, Dworak M, Balas B, Bruce WS. Early insights into the characteristics and evolution of clinical parameters in a cohort of patients prescribed sacubitril/valsartan in Germany. *Postgrad Med* 2018; **130**: 308–316.
13. Martens P, Belien H, Dupont M, Mullens W. Insights into implementation of sacubitril/valsartan into clinical practice. *ESC Heart Fail* 2018; **5**: 275–283.
14. Wachter R, Fonseca AF, Balas B, Kap E, Engelhard J, Schlienger R, Klebs S, Bruce Wirta S, Kostev K. Real-world treatment patterns of sacubitril/valsartan: a longitudinal cohort study in Germany. *Eur J Heart Fail* 2019; **21**: 588–597.
15. Komajda M, Cowie MR, Tavazzi L, Ponikowski P, Anker SD, Filippatos GS. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. *Eur J Heart Fail* 2017; **19**: 1414–1423.
16. Rathmann W, Bongaerts B, Carius HJ, Kruppert S, Kostev K. Basic characteristics and representativeness of the German Disease Analyzer database. *Int J Clin Pharmacol Ther* 2018; **56**: 459–466.
17. DeVore AD, Mi X, Thomas L, Sharma PP, Albert NM, Butler J, Hernandez AF, Patterson JH, Spertus JA, Williams FB, Duffy CI, McCague K, Fonarow GC. Characteristics and treatments of patients enrolled in the CHAMP-HF registry compared with patients enrolled in the PARADIGM-HF trial. *J Am Heart Assoc* 2018; **7**: e009237.
18. Vardeny O, Claggett B, Packer M, Zile MR, Rouleau J, Swedberg K, Teerlink JR, Desai AS, Lefkowitz M, Shi V, McMurray JJ, Solomon SD. Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial. *Eur J Heart Fail* 2016; **18**: 1228–1,234.

19. Wachter R, Senni M, Belohlavek J, Straburzynska-Migaj E, Witte KK, Kobalava Z, Fonseca C, Goncalvesova E, Cavusoglu Y, Fernandez A, Chaaban S, Bøhmer E, Pouleur AC, Mueller C, Tribouilloy C, Lonn E, Al Buraiki J, Gniot J, Mozheiko M, Lelonek M, Noè A, Schwende H, Bao W, Butylin D, Pascual-Figal D; TRANSITION Investigators. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study.

20. Senni M, McMurray JJ, Wachter R, McIntyre HF, Reyes A, Majercak I, Andreka P, Shehova-Yankova N, Anand I, Yilmaz MB, Gogia H, Martinez-Selles M, Fischer S, Zilahi Z, Cosmi F, Gelev V, Galve E, Gómez-Doblas JJ, Nociar J, Radomska M, Sokolova B, Volterrani M, Sarkar A, Reimund B, Chen F, Charney A. Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens. *Eur J Heart Fail* 2016; **18**: 1193–1202.

21. Maggioni AP, Anker SD, Dahlstrom U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozdz J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavoliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L, Heart Failure Association of the ESC. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2013; **15**: 1173–1184.

22. Hobbs FDR, Kenkre JE, Roalfe AK, Davis RC, Hare R, Davies MK. Impact of heart failure and left ventricular systolic dysfunction on quality of life. A cross-sectional study comparing common chronic cardiac and medical disorders and a representative adult population. *Eur Heart J* 2002; **23**: 1867–1876.

23. Casebeer AW, Antol DD, DeClue RW, Stemkowski S, Russo PA. A reduction in physician-recorded heart failure signs and symptoms and all-cause hospitalizations following initiation of sacubitril/valsartan treatment among patients with heart failure and reduced ejection fraction in a real-world setting. *J Card Fail* 2017; **23**: S36.

24. Goh VJL, Koh N, Teoh CK, Hon JS, Teo LLY, Lim CP, Sim DKL. ARNI use leads to improved NYHA class and NT-proBNP levels in a Singaporean cohort. *Eur J Heart Fail* 2018; **20**: 267.

25. Chandra A, Lewis EF, Claggett BL, Desai AS, Packer M, Zile MR, Swedburg K, Rouleau JL, Shi VC, Lefkowitz MP, Katova T, McMurray JJV, Solomon SD. Effects of sacubitril/valsartan on physical and social activity limitations in patients with heart failure: a secondary analysis of the PARADIGM-HF trial. *JAMA Cardiol* 2018; **3**: 498–505.

26. Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Swedberg K, Zile MR, Solomon SD, Packer M, McMurray JJ, PARADIGM-HF Investigators and Committees. Importance of clinical worsening of heart failure treated in the outpatient setting: evidence from the prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). *Circulation* 2016; **133**: 2254–2262.

27. Lesyuk W, Kriza C, Kolominsky-Rabas P. Cost-of-illness studies in heart failure: a systematic review 2004–2016. *BMC Cardiovasc Disord* 2018; **18**: 74.

28. Cheng HG, Phillips MR. Secondary data analysis of existing data: opportunities and implementation. *Shanghai Arch Psychiatry* 2014; **26**: 371–375.