Efficacy and safety of sacubitril/valsartan in an outpatient setting: A single-center real-world retrospective study in HFrEF patients with focus on possible predictors of clinical outcome

Elisabeth J. Fröb[B–D,F], Jürgen R. Sindermann[E,F], Holger Reinecke[E,F], Izabela Tuleta[A,C–F]

Department of Cardiology I – Coronary and Peripheral Vascular Disease, Heart Failure, University Hospital Münster, Germany

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of the article

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Address for correspondence
Izabela Tuleta
E-mail: izat@gmx.de

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Abstract

Background. Currently, data on sacubitril/valsartan therapy from the real-world settings are scarce and the predictors of a good clinical responsiveness to this drug are unknown.

Objectives. To assess efficacy and safety profile of sacubitril/valsartan and to identify predictors for a better clinical outcome.

Materials and methods. Clinical, laboratory and echocardiographic data of 95 chronic heart failure (CHF) patients with reduced ejection fraction (HFrEF) were retrospectively analyzed. A good efficacy of sacubitril/valsartan was defined as the fulfilment of at least 2 of the following criteria: improvement of left ventricular ejection fraction (LVEF) or functional status, and reduction of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels or hospitalization rates.

Results. Under sacubitril/valsartan, major improvements were observed in LVEF, the New York Heart Association (NYHA) class, NT-proBNP levels, and hospitalization rates. Patients with a good efficacy of sacubitril/valsartan were characterized by initially worse LVEF (median (interquartile range (IQR)): 29.0% (23.0–33.0%) compared to 32.0% (28.5–38.0%) with more frequent nonischemic etiology (65.4% compared to 41.9%) and hospitalizations for CHF/month (0.016 (0.004–0.057) compared to 0.000 (0.000–0.012)), lower cholesterol (42.3% compared to 65.1%), higher C-reactive protein (CRP) levels at baseline (0.5 mg/L (0.5–1.0 mg/L) compared to 0.5 mg/L (0.5–0.5 mg/L)), and a shorter timespan between CHF diagnosis and the start of sacubitril/valsartan treatment (66.0 (11.0–127.0) compared to 111 (73.0–211.0) months) ($p < 0.05$ each). In a multivariate Cox analysis, only the last 2 parameters were shown to be independent predictors of good clinical responsiveness to sacubitril/valsartan (hazard ratio (HR) = 1.263, 95% confidence interval (95% CI) = [1.048; 1.521]; HR = 0.992, 95% CI = [0.987; 0.997], $p < 0.05$, respectively).

Conclusions. Sacubitril/valsartan improved LVEF, NYHA class, NT-proBNP levels, and hospitalization rates, mostly without relevant side effects. The independent predictors of a good clinical efficacy were higher CRP levels at baseline and a shorter delay between CHF diagnosis and the initialization of sacubitril/valsartan therapy.

Key words: CRP, sacubitril/valsartan, NYHA class, chronic heart failure with reduced left ventricular ejection fraction, hospitalization rates

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Background

Sacubitril/valsartan has been proven to be effective in the therapy of patients with chronic heart failure with reduced ejection fraction (HFrEF).[1] A post hoc analysis of the PARADIGM-HF study showed that the patients with HFrEF benefited equally in terms of the study endpoint, composed of cardiovascular (CV) death or hospitalization for heart failure (HF), regardless of baseline left ventricular ejection fraction (LVEF).[2] Moreover, benefits of sacubitril/valsartan over enalapril were consistent across subgroups of patients with different HF etiologies, although patients with nonischemic cardiomyopathy (NICM) were younger, more frequently female and had higher N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in comparison with ischemic cardiomyopathy (ICM) patients.[2] Furthermore, the presence of diabetes,[2] hospitalizations prior treatment[2] and the background pharmacological, interventional or device therapy did not have any relevant influence on the primary endpoint of the PARADIGM-HF study.[2,3] Also, the LVEF improvement, as a single endpoint in other study, did not differ between patients with different HF etiologies and comorbidities such as diabetes, arterial hypertension and atrial fibrillation. There was only a trend toward LVEF improvement in patients treated with medium/high doses of sacubitril/valsartan compared to the patients treated with the low ones.[4] Other authors reported that the LVEF improvement of at least 5% was more frequent in patients with lower LV dilation.[5] Therefore, no relevant specific parameters were identified up to date which would be connected to a significantly better responsiveness to sacubitril/valsartan therapy.

Objectives

The aim of our present study was to prove efficacy and safety of sacubitril/valsartan therapy in an outpatient real-world setting with an emphasis on potential predictors of a good clinical outcome under this medication.

Materials and methods

Study population, inclusion/exclusion criteria and data source

All procedures performed in this study involving human participants were in accordance with the ethical standards set by the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments. The local Ethics Committee of the Medical Faculty of the University of Münster, Germany, approved the study design.

All patients treated in our outpatient chronic heart failure (CHF) center between January 2018 and June 2019 were retrospectively screened for the therapy with sacubitril/valsartan (Fig. 1). Within this period, patients undergoing the sacubitril/valsartan therapy completed their last follow-up visit. The baseline visit before the initiation of sacubitril/valsartan treatment took place either within the abovementioned timeframe or before it, depending on the duration of the sacubitril/valsartan therapy (the earliest timepoint of sacubitril/valsartan prescription: mid-2016). Data collected within 3 months before the prescription of sacubitril/valsartan were considered baseline data. The inclusion criteria were as follows: age ≥18 years; clinical stability, defined as a status demanding no relevant changes in medication; and/or hospitalization in the last 3 months before baseline and follow-up. Patients who did not meet the inclusion criteria and for whom we were unable to collect all clinical, instrumental and laboratory data were excluded from the study. The decision to prescribe the sacubitril/valsartan therapy in patients enrolled was based on the European Society of Cardiology (ESC) guidelines, which recommend sacubitril/valsartan therapy in CHF patients with LVEF ≤ 40% who are still symptomatic despite adequate CHF therapy.[6]

Data sources included medical records from our clinic, patient information supplied by other healthcare providers such as primary care physicians and cardiologists, and the patient records from previous hospital admissions.

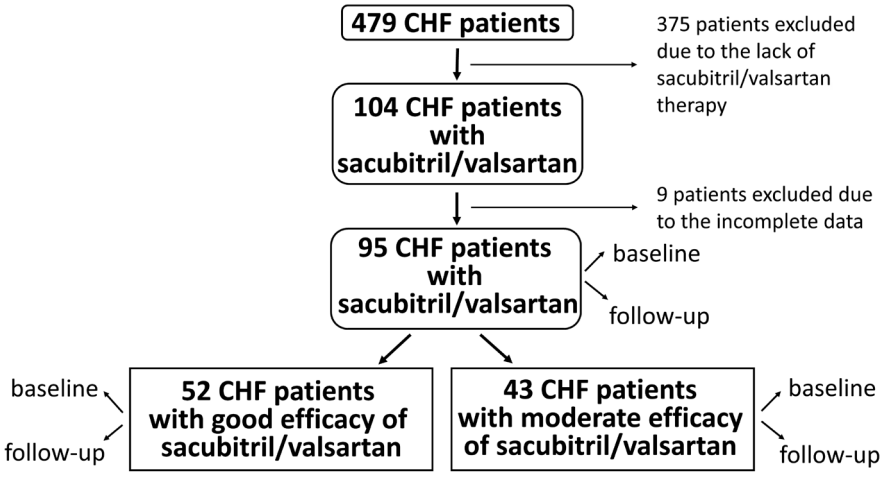

Fig. 1. Flowchart of the study design

CHF – chronic heart failure.

Patient cohorts and analyzed variables

Patient characteristics based on clinical, laboratory and instrumental results were compared before the initialization of sacubitril/valsartan therapy and during this therapy, at the last available follow-up within the data collection period (Table 1).

Clinical parameters included age, gender, body mass index (BMI), etiology of cardiomyopathy, observation period (timespan from the initial diagnosis to the start of sacubitril/valsartan treatment and the duration of sacubitril/valsartan therapy), dyspnea in daily activities according to the New York Heart Association (NYHA) classification, presence of cardiovascular risk factors, comorbidities, medication, and cardiac electronical devices. Instrumental diagnostics consisted of blood pressure and heart rate measurements, electrocardiogram (ECG), echocardiography, and laboratory analyses.

Endpoints and definitions

To examine whether patients notably benefited from the sacubitril/valsartan treatment, a score consisting of an improved LVEF of at least 5%,[2,3] decreased hospitalization rates for CHF (number of all hospitalizations divided by the observation period in months), better physical capacity (defined as an improvement in stair climbing of at least half a floor before stopping for dyspnea), and reduced NT-proBNP blood levels (reduction by at least 50%)[7] was used. Each attribute had a value of 1 point and if the total count amounted to at least 2 points, such case was assigned to a good efficacy group. Patients who did not fulfil these criteria constituted a group of a moderate efficacy. The abovementioned clinical, laboratory and instrumental findings were compared between both groups (Table 2).

Furthermore, side effects attributed to sacubitril/valsartan treatment were also evaluated (Table 3). When evaluating side effects, hypotension was defined as being clinically relevant if it caused orthostatic dizziness, affected everyday life and/or resulted in the reduction of HF medication. Anemia de novo was assessed under sacubitril/valsartan treatment according to the World Health Organization (WHO) definition (hemoglobin concentration <12 g/dL for women and <13 g/dL for men).[8] The deterioration in kidney function and the acute kidney injury (AKI) were diagnosed based on the Kidney Disease: Improving Global Outcome (KDIGO) criteria and defined as a reduction in glomerular filtration rate (GFR), resulting in a decrease in the classification of chronic kidney disease by at least 1 stage (deterioration in kidney function), and as an increase in serum creatinine of ≥0.3 mg/dL within 48 h, or ≥50% within 7 days, or urine output of <0.5 mL/kg/h for >6 h (AKI).[9,10]

Statistical analyses

The comparisons of qualitative dichotomous or polytomous variables between the same set of patients at baseline and at follow-up were conducted by means of the McNemar and marginal homogeneity tests, respectively (Table 1). For the calculations of potential differences between numerical parameters in patients prior to and under sacubitril/valsartan therapy, the Wilcoxon signed-rank test was

Table 1. Baseline characteristics and course of clinical, instrumental and laboratory findings under sacubitril/valsartan therapy

Parameter	Baseline (prior to sacubitril/valsartan) n = 95	Follow-up (under sacubitril/valsartan) n = 95	Test value	p-value
Age [years], median (IQR)	57.0 (50.0–69.0)	59.0 (52.0–70.0)	–7.716	<0.001*
Male gender, n (%)	71 (74.7)	–	–	–
BMI [kg/m^2], median (IQR)	27.8 (25.0–31.8)	28.7 (25.4–32.0)	–2.296	0.022*
Time from diagnosis to sacubitril/valsartan start [months], median (IQR)	92.5 (25.0–147.8)	–	–	–
Time from sacubitril/valsartan start to follow-up start [months], median (IQR)	–	17.0 (10.0–26.3)	–	–
NICM, n (%)	53 (55.8)	–	–	–
LVEF (%), median (IQR)	30.5 (25.0–35.0)	35.0 (30.0–43.3)	–5.330	<0.001*
LVEF improvement ≥5%, n (%)	–	48 (50.5)	–	–
LVEF improvement ≥5%, median (IQR)	–	12.0 (9.0–21.0)	–	–
NYHA class – NYHA I, n (%) – NYHA II, n (%) – NYHA III, n (%) – NYHA IV, n (%)	 7 (7.4) 21 (22.1) 62 (65.3) 5 (5.3)	 20 (21.1) 30 (31.6) 44 (46.3) 1 (1.1)	5.164 – – – –	<0.001* – – – –
Functional improvement (≥half a floor), n (%)	–	50 (52.6)	–	–
NT-proBNP [pg/mL], median (IQR)	843.0 (404.0–2591.0)	660.5 (231.5–2162.8)	–2.572	0.01*

Table 1. Baseline characteristics and course of clinical, instrumental and laboratory findings under sacubitril/valsartan therapy – cont.

Parameter	Baseline (prior to sacubitril/valsartan) n = 95	Follow-up (under sacubitril/valsartan) n = 95	Test value	p-value
NT-proBNP improvement ≥50%, n (%)	–	27 (28.4)	–	–
Hospitalizations for CHF per month, median (IQR)	0.009 (0.000–0.027)	0.000 (0.000–0.000)	–3.499	<0.001*
Improvement in hospitalizations for CHF per month, n (%)	–	51 (53.7)	–	–
Medical history at baseline				
Arterial hypertension, n (%)	63 (66.3)	–	–	–
Diabetes mellitus, n (%)	28 (29.5)	–	–	–
Dyslipidemia, n (%)	50 (52.6)	–	–	–
Smokers – current smokers, n (%) – previous smokers, n (%)	 14 (14.7) 46 (48.4)	 – –	 – –	 – –
Familiar history of cardiovascular disease, n (%)	41 (43.2)	–	–	–
Chronic kidney disease (eGFR ≤ 60 mL/min/1.73 m^2), n (%)	36 (37.9)	–	–	–
PAD, n (%)	20 (21.1)	–	–	–
CAD, n (%) – number of vessels, median (IQR) – number of MI, median (IQR)	45 (47.4) 0.0 (0.0–1.0) 0.0 (0.0–2.0)	– – –	– – –	– – –
CABG, n (%)	13 (13.7)	–	–	–
Stroke, n (%)	19 (20.0)	–	–	–
Hyperuricemia, n (%)	19 (20.0)	–	–	–
Obstructive lung diseases – COPD, n (%) – asthma, n (%)	 11 (11.6) 7 (7.4)	 – –	 – –	 – –
OSAS, n (%)	21 (22.1)	–	–	–
Medication				
BB, n (%)	93 (97.9)	95 (100.0)	–	–
BB (% of target dose), median (IQR)	0.5 (0.4–1.0)	0.5 (0.5–1.0)	–0.609	0.543
ACEI or ARB, n (%)	93 (97.9)	0 (0.0)	–	–
ACEI or ARB (% of target dose), median (IQR)	0.75 (0.5–1.0)	0.00	–	–
Sacubitril/valsartan, n (%)	0 (0.0)	95 (100.0)	–	–
Sacubitril/valsartan (% of target dose), median (IQR)	0.00	0.65 ±0.30	–	–
MRA, n (%)	80 (84.2)	80 (84.2)	–	–
MRA (% of target dose), median (IQR)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	–0.154	0.878
Diuretics, n (%)	79 (83.2)	77 (81.1)	23.765	0.791
Diuretics (% of target dose), median (IQR)	0.5 (1.0–2.0)	0.5 (1.0–2.0)	–0.665	0.506
Amiodarone, n (%)	14 (14.7)	14 (14.7)	–	–
Oral anticoagulation, n (%)	43 (45.3)	43 (45.3)	–	–
BP and heart rate				
Systolic BP [mm Hg], median (IQR)	117.5 (108.5–125.0)	110.0 (100.0–125.0)	–2.255	0.024*
Diastolic BP [mm Hg], median (IQR)	75.0 (70.0–80.0)	70.0 (68.5–80.0)	–0.502	0.616
Mean arterial pressure [mm Hg], median (IQR)	87.0 (82.3–93.3)	85.7 (76.7–93.3)	–1.290	0.197
Heart rate [bpm], median (IQR)	70.0 (60.0–76.0)	64.0 (58.0–74.0)	–2.803	0.005*
ECG/electronic cardiac device				
Atrial fibrillation (paroxysmal or permanent), n (%)	41 (43.2)	41 (43.2)	–	–
VA per month, median (IQR)	0.000 (0.000–0.004)	0.000 (0.000–0.000)	–0.206	0.837
Carrier of ICD, n (%) – for primary prophylaxis – for secondary prophylaxis	53 (55.8) 42 (44.2) 11 (11.6)	65 (68.4) 53 (55.8) 12 (12.6)	–2.840	0.005*
Left bundle branch block, n (%)	35 (36.8)	35 (36.8)	–	–

Table 1. Baseline characteristics and course of clinical, instrumental and laboratory findings under sacubitril/valsartan therapy – cont.

Parameter	Baseline (prior to sacubitril/valsartan) n = 95	Follow-up (under sacubitril/valsartan) n = 95	Test value	p-value
Carrier of CRT (as ICD upgrade or primary CRT-D implantation), n (%)	19 (20.0)	29 (30.5)	54.052	0.002*
Carrier of PM, n (%)	5 (5.3)	5 (5.3)	–	–
Echocardiography				
Moderate or severe mitral valve regurgitation, n (%)	18 (18.9)	14 (14.7)	15.598	0.454
Moderate or severe tricuspid valve regurgitation, n (%)	6 (6.3)	9 (9.5)	4.251	0.549
Moderate or severe aortic valve regurgitation, n (%)	2 (2.1)	2 (2.1)	–	–
LV enlargement, n (%)	mild: 14 (14.7) moderate: 20 (21.1) severe: 43 (45.3)	mild: 10 (10.5) moderate: 24 (25.3) severe: 33 (34.7)	–1.286	0.198
LA enlargement, n (%)	mild: 20 (21.1) moderate: 20 (21.1) severe: 27 (28.4)	mild: 10 (10.5) moderate: 21 (22.1) severe: 20 (21.1)	–3.178	0.001*
RV enlargement, n (%)	mild: 3 (3.2) moderate: 10 (10.5) severe: 3 (3.2)	mild: 4 (4.2) moderate: 6 (6.3) severe: 0 (0.0)	–1.325	0.185
RA enlargement, n (%)	mild: 11 (11.6) moderate: 13 (13.7) severe: 9 (9.5)	mild: 5 (5.3) moderate: 6 (6.3) severe: 8 (8.4)	–2.968	0.003*
Laboratory values				
Creatinine [mg/dL], median (IQR)	1.2 (1.0–1.4)	1.3 (1.0–1.6)	–3.767	<0.001*
Urea [mg/dL], median (IQR)	20.0 (15.0–26.0)	18.0 (14.0–27.0)	–0.623	0.533
GFR [mL/min], median (IQR)	66.0 (51.0–80.8)	60.0 (43.0–76.0)	–4.150	<0.001*
Uric acid [mg/dL], median (IQR)	6.8 (5.7–8.3)	6.6 (5.2–7.7)	–1.087	0.277
Hemoglobin [g/dL], median (IQR)	14.4 (12.9–15.1)	13.7 (12.6–14.8)	–1.923	0.054
Aspartate transaminase [U/L], median (IQR)	30.0 (24.0–36.5)	27.0 (24.0–32.0)	–2.554	0.011*
Potassium [mmol/L], median (IQR)	4.4 (4.2–4.8)	4.5 (4.2–4.8)	–1.300	0.194
CK [U/L], median (IQR)	105.0 (79.5–156.0)	108.5 (74.0–128.0)	–1.415	0.157
CRP [mg/dL], median (IQR)	0.5 (0.5–0.8)	0.5 (0.5–0.6)	–1.376	0.169

ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor blocker; BB – beta blocker; BMI – body mass index; BP – blood pressure; CABG – coronary artery bypass graft; CAD – coronary artery disease; CHF – chronic heart failure; COPD – chronic obstructive pulmonary disease; CRP – C-reactive protein; CK – creatinine kinase; CRT(-D) – cardiac resynchronization therapy (-implantable cardioverter defibrillator); ECG – electrocardiogram; (e)GFR – (estimated) glomerular filtration rate; HCT – hydrochlorothiazide; ICD – implantable cardioverter defibrillator; LA – left atrium; LV – left ventricle; LVEF – left ventricular ejection fraction; MI – myocardial infarction; MRA – mineralocorticoid receptor antagonist; NICM – nonischemic cardiomyopathy; NYHA – level of cardiopulmonal fitness according to the New York Heart Association; NT-proBNP – N-terminal pro-brain natriuretic peptide; OSAS – obstructive sleep apnea syndrome; PAD – peripheral artery disease; PM – pacemaker; RA – right atrium; RV – right ventricle; VA – ventricular arrhythmias. Data are presented as median (interquartile range (IQR)) (Wilcoxon signed-rank test) or n (%) (McNemar test for dichotomous variables and marginal homogeneity tests for polytomous variables). * – statistically significant value of $p < 0.05$. Target dose calculation (for most important drugs; others calculated as equivalent doses): ramipril 10 mg = 1.0; enalapril 20 mg = 1.0; candesartan 32 mg = 1.0; valsartan 320 mg = 1.0; irbesartan 300 mg = 1.0; sacubitril/valsartan 2 × 97/103 mg = 1.0; hydrochlorothiazide 25 mg = 1.0; bisoprolol 10 mg = 1.0; metoprolol 190 mg = 1.0; carvedilol 50 mg = 1.0; spironolacton 25 mg = 1.0; eplerenon 25 mg = 1.0; torasemid 10 mg = 1.0; hydrochlorothiazide 25 mg = 1.0; xipamid 20 mg = 1.0; furosemid 40 mg = 1.0.

used (Table 1). In order to compare measures between patients with a good and moderate sacubitril/valsartan efficacy, the Mann–Whitney U test for continuous variables (Table 2) and the χ^2 test for categorical data (Table 2,3) were applied. Quantitative values were expressed as a median (interquartile range (IQR)), and categorical measures were presented as a number of events (n) and their percentage in the total number of patients (%). Univariate (Table 4) and multivariate (Table 5) Cox regression analyses were performed for the identification of possible predictors of a good efficacy of sacubitril/valsartan therapy. The proportional hazards (PH) assumption based on the scaled Schoenfeld residuals showed a random pattern against time. No adjustment for multiple testing was performed since the analyses were regarded as explorative. Local, unadjusted p-values <0.05 were considered statistically significant. Statistical analysis was conducted using IBM SPSS Statistics v. 26 software (IBM Corp., Armonk, USA).

Table 2. Characteristics of patients with a good and moderate efficacy under sacubitril/valsartan

Parameters	Good efficacy of sacubitril/valsartan n = 52	Moderate efficacy of sacubitril/valsartan n = 43	Test value	p-value
Mean age [years], median (IQR)	prior s/v: 57.5 (50.0–69.8) under s/v: 59.0 (50.5–71.5)	prior s/v: 57.0 (50.0–63.0) under s/v: 58.0 (52.0–66.0)	–0.714 –0.752	prior s/v: 0.575 under s/v: 0.452
BMI [kg/m^2], median (IQR)	prior s/v: 27.4 (24.2–33.3) under s/v: 28.6 (25.1–34.3)	prior s/v: 28.4 (25.3–30.6) under s/v: 28.7 (25.4–30.8)	–0.082 –0.572	prior s/v: 0.934 under s/v: 0.567
Male gender, n (%)	38 (73.1)	33 (76.7)	0.168	0.682
Time from diagnosis to sacubitril/valsartan therapy start (months), median (IQR)	66.0 (11.0–127.0)	111.0 (73.0–211.0)	–2.672	0.008*
Time from sacubitril/valsartan therapy start to follow-up visit (months), median (IQR)	18.0 (8.0–27.0)	17.0 (10.0–23.0)	–0.300	0.764
NICM, n (%)	34 (65.4)	18 (41.9)	5.257	0.022*
LVEF (%), median (IQR)	prior s/v: 29.0 (23.0–33.0) under s/v: 38.0 (32.0–45.0)	prior s/v: 32.0 (28.5–38.0) under s/v: 30.0 (25.0–39.0)	–2.768 –3.625	prior s/v: 0.006* under s/v: <0.001*
NYHA class, n (%)	prior s/v: NYHA I: 5 (9.6) NYHA II: 10 (19.2) NYHA III: 34 (65.4) NYHA IV: 3 (5.8) under s/v: NYHA I: 17 (32.7) NYHA II: 18 (34.6) NYHA III: 17 (32.7) NYHA IV: 0 (0.0)	prior s/v: NYHA I: 2 (4.6) NYHA II: 11 (25.6) NYHA III: 28 (65.1) NYHA IV: 2 (4.7) under s/v: NYHA I: 3 (7.0) NYHA II: 13 (30.2) NYHA III: 26 (60.5) NYHA IV: 1 (2.3)	1.273 12.752	prior s/v: 0.736 under s/v: 0.005*
NT-proBNP [pg/mL], median (IQR)	prior s/v: 975.0 (470–3086.0) under s/v: 471.0 (208.5–1089.3)	prior s/v: 783.5 (263.8–2190.0) under s/v: 835.0 (341.0–2628.8)	–1.229 –1.772	prior s/v: 0.219 under s/v: 0.076
Hospitalizations for CHF per month, median (IQR)	prior s/v: 0.016 (0.004–0.057) under s/v: 0.000 (0.000–0.000)	prior s/v: 0.000 (0.000–0.012) under s/v: 0.000 (0.000–0.033)	–3.882 –3.047	prior s/v: <0.001* under s/v: 0.002*
Medical history at baseline				
Arterial hypertension, n (%)	35 (67.3)	28 (65.1)	0.051	0.822
Diabetes mellitus, n (%)	12 (23.1)	16 (37.2)	2.261	0.133
Dyslipidemia, n (%)	22 (42.3)	28 (65.1)	4.911	0.027*
Smokers – current smokers, n (%) – previous smokers, n (%)	 8 (15.4) 25 (48.1)	 6 (14.0) 21 (48.8)	0.038 – –	0.981 – –
Familiar history of cardiovascular disease, n (%)	22 (42.3)	19 (44.2)	0.034	0.854
Chronic kidney disease (eGFR ≤ 60 mL/min/1.73 m^2), n (%)	19 (36.5)	17 (39.5)	0.090	0.764
PAD, n (%)	11 (21.2)	9 (20.9)	0.108	0.948
CAD, n (%) – number of vessels, median (IQR) – number of MI, median (IQR) – CABG, n (%)	19 (36.5) 0.00 (0.00–2.00) 0.00 (0.00–0.75) 5 (9.6)	26 (60.5) 1.00 (0.00–2.00) 0.00 (0.00–1.00) 8 (18.6)	5.405 –1.529 –1.923 1.610	0.020* 0.126 0.055 0.204
Stroke, n (%)	9 (17.3)	10 (23.3)	1.064	0.588
Hyperuricemia, n (%)	10 (19.2)	9 (20.9)	0.042	0.837
Obstructive lung diseases – COPD, n (%) – asthma, n (%)	 6 (11.5) 4 (7.7)	 5 (11.6) 3 (7.0)	0.906 – –	0.924 – –
OSAS, n (%)	14 (26.9)	7 (16.3)	1.549	0.213
Medication				
BB, n (%)	prior s/v: 51 (98.1) under s/v: 52 (100.0)	prior s/v: 42 (97.7) under s/v: 43 (100.0)	0.019 –	prior s/v: 0.892 –
BB (% of target dose), median (IQR)	prior s/v: 0.5 (0.3–1.0) under s/v: 0.5 (0.4–1.0)	prior s/v: 0.5 (0.5–1.0) under s/v: 0.5 (0.5–1.0)	–0.412 –0.265	prior s/v: 0.681 under s/v: 0.791
ACEI or ARB, n (%)	prior s/v: 51 (98.1)	prior s/v: 42 (97.7)	0.816	prior s/v: 0.366
ACEI or ARB (% of target dose), median (IQR)	prior s/v: 0.5 (0.5–1.0)	prior s/v: 0.8 (0.5–1.0)	–0.899	prior s/v: 0.369
Sacubitril/valsartan, n (%)	under s/v: 52 (100)	under s/v: 43 (100)	–	–

Table 2. Characteristics of patients with a good and moderate efficacy under sacubitril/valsartan – cont.

Parameters	Good efficacy of sacubitril/valsartan n = 52	Moderate efficacy of sacubitril/valsartan n = 43	Test value	p-value
Sacubitril/valsartan (% of target dose), median (IQR)	under s/v: 0.5 (0.5–1.0)	under s/v: 0.5 (0.3–1.0)	–0.165	under s/v: 0.869
Mineralocorticoid receptor antagonists, n (%)	prior s/v: 44 (84.6) under s/v: 44 (84.6)	prior s/v: 36 (83.7) under s/v: 36 (83.7)	0.014 0.014	prior s/v: 0.905 under s/v: 0.905
Mineralocorticoid receptor antagonists (% of target dose), median (IQR)	prior s/v: 1.0 (1.0–1.0) under s/v: 1.0 (1.0–1.0)	prior s/v: 1.0 (1.0–2.0) under s/v: 1.0 (1.0–1.0)	–1.543 –0.150	prior s/v: 0.123 under s/v: 0.881
Diuretics, n (%)	prior s/v: 43 (82.7) under s/v: 40 (76.9)	prior s/v: 36 (83.7) under s/v: 37 (86.0)	0.018 1.276	prior s/v: 0.894 under s/v: 0.259
Diuretics (% of target dose), median (IQR)	prior s/v: 1.0 (0.5–2.0) under s/v: 1.0 (0.5–2.0)	prior s/v: 1.0 (1.0–2.0) under s/v: 1.0 (0.5–2.0)	–0.066 –0.249	prior s/v: 0.948 under s/v: 0.804
Amiodarone, n (%)	prior/under s/v: 6 (11.5)	prior/under s/v: 8 (18.6)	0.935	0.333
Oral anticoagulation, n (%)	prior/under s/v: 23 (44.2)	prior/under s/v: 20 (46.5)	0.049	0.824
BP and heart rate				
Systolic BP [mm Hg], median (IQR)	prior s/v: 120 (108.0–125.0) under s/v: 116.0 (104.0–130.0)	prior s/v: 115.0 (107.5–122.5) under s/v: 110.0 (96.3–118.5)	–0.642 –2.415	prior s/v: 0.521 under s/v: 0.016*
Diastolic BP [mm Hg], median (IQR)	prior s/v: 75.0 (70.0–80.0) under s/v: 76.0 (70.0–80.0)	prior s/v: 75.0 (69.0–80.0) under s/v: 70.0 (65.0–80.0)	–0.060 –1.688	prior s/v: 0.952 under s/v: 0.091
Mean arterial pressure, median (IQR)	prior s/v: 87.3 (82.0–95.0) under s/v: 90.0 (79.0–96.7)	prior s/v: 86.7 (82.3–93.3) under s/v: 83.3 (76.7–90.0)	–0.335 –2.205	prior s/v: 0.737 under s/v: 0.027*
Heart rate [bpm], median (IQR)	prior s/v: 70.0 (60.5–79.5) under s/v: 63.0 (58.0–72.0)	prior s/v: 68.0 (60.0–75.0) under s/v: 65.0 (57.0–75.0)	–0.591 –1.063	prior s/v: 0.554 under s/v: 0.288
ECG/electronic cardiac device				
Atrial fibrillation (paroxysmal or permanent), n (%)	prior/under s/v: 22 (42.3)	prior/under s/v: 19 (44.2)	0.034	prior/under s/v: 0.854
VA per month, median (IQR)	prior s/v: 0.000 (0.000–0.000) under s/v: 0.000 (0.000–0.000)	prior s/v: 0.000 (0.000–0.007) under s/v: 0.000 (0.000–0.000)	–0.847 –0.376	prior s/v: 0.397 under s/v: 0.707
Carrier of ICD, n (%)	prior s/v: 26 (50.0) under s/v: 33 (63.5)	prior s/v: 26 (60.5) under s/v: 30 (69.8)	1.040 0.419	prior s/v: 0.308 under s/v: 0.517
Left bundle branch block, n (%)	prior/under s/v: 22 (42.3)	prior/under s/v: 13 (30.2)	2.662	prior/under s/v: 0.264
Carrier of CRT (as ICD-upgrade or primarily CRT-D implantation), n (%)	prior s/v: 7 (13.5) under s/v: 12 (23.1)	prior s/v: 12 (27.9) under s/v: 17 (39.5)	3.070 3.006	prior s/v: 0.080 under s/v: 0.083
Carrier of PM, n (%)	prior/under s/v: 2 (3.8)	prior/under s/v: 3 (7.0)	0.463	prior/under s/v: 0.496
Echocardiography				
Moderate to severe mitral valve regurgitation, n (%)	prior s/v: 7 (13.5) under s/v: 5 (9.6)	prior s/v: 11 (25.6) under s/v: 9 (20.9)	2.251 2.398	prior s/v: 0.134 under s/v: 0.121
Moderate to severe tricuspid valve regurgitation, n (%)	prior s/v: 3 (5.8) under s/v: 3 (5.8)	prior s/v: 3 (7.0) under s/v: 6 (14.0)	0.058 1.838	prior s/v: 0.810 under s/v: 0.175
Moderate to severe aortic valve regurgitation, n (%)	prior s/v: 1 (1.9) under s/v: 2 (3.8)	prior s/v: 1 (2.3) under s/v: 0 (0.0)	0.019 1.689	prior s/v: 0.892 under s/v: 0.194
LV volume increase, n (%)	prior s/v: mild: 9 (17.3) moderate: 12 (23.1) severe: 21 (40.4) under s/v: mild: 5 (9.6) moderate: 11 (21.2) severe: 18 (34.6)	prior s/v: mild: 5 (11.6) moderate: 8 (18.6) severe: 22 (51.2) under s/v: mild: 6 (14.0) moderate: 13 (30.2) severe: 17 (39.5)	1.348 4.312	prior s/v: 0.718 under s/v: 0.230
LA volume increase, n (%)	prior s/v: mild: 12 (23.1) moderate: 10 (19.2) severe: 14 (26.9) under s/v: mild: 5 (9.6) moderate: 10 (19.2) severe: 7 (13.5)	prior s/v: mild: 8 (18.6) moderate: 12 (27.9) severe: 13 (30.2) under s/v: mild: 6 (14.0) moderate: 10 (23.3) severe: 13 (30.2)	1.565 6.919	prior s/v: 0.667 under s/v: 0.075

Table 2. Characteristics of patients with a good and moderate efficacy under sacubitril/valsartan – cont.

Parameters	Good efficacy of sacubitril/valsartan n = 52	Moderate efficacy of sacubitril/valsartan n = 43	Test value	p-value
RV volume increase, n (%)	prior s/v: mild: 3 (5.8) moderate: 5 (9.6) severe: 3 (5.8) under s/v: mild: 2 (3.8) moderate: 1 (1.9) severe: 0 (0.0)	prior s/v: mild: 0 (0.0) moderate: 5 (11.6) severe: 0 (0.0) under s/v: mild: 2 (4.7) moderate: 5 (11.6) severe: 0 (0.0)	5.309 3.837	prior s/v: 0.151 under s/v: 0.147
RA volume increase, n (%)	prior s/v: mild: 6 (11.5) moderate: 7 (13.5) severe: 5 (9.6) under s/v: mild: 5 (9.6) moderate: 2 (3.8) severe: 3 (5.8)	prior s/v: mild: 6 (14.0) moderate: 7 (16.3) severe: 5 (11.6) under s/v: mild: 1 (2.3) moderate: 4 (9.3) severe: 5 (11.6)	0.525 4.097	prior s/v: 0.913 under s/v: 0.251
Laboratory values				
Creatinine [mg/dL], median (IQR)	prior s/v: 1.1 (0.9–1.4) under s/v: 1.3 (1.0–1.5)	prior s/v: 1.2 (1.0–1.4) under s/v: 1.3 (1.1–1.6)	–1.303 –1.078	prior s/v: 0.193 under s/v: 0.281
Urea [mg/dL], median (IQR)	prior s/v: 20.0 (14.0–29.5) under s/v: 17.0 (14.0–27.8)	prior s/v: 20.0 (18.0–25.8) under s/v: 20.5 (15.8–26.3)	–0.036 –1.081	prior s/v: 0.971 under s/v: 0.280
GFR [mL/min], median (IQR)	prior s/v: 67.0 (51.0–87.0) under s/v: 60.0 (43.3–76.0)	prior s/v: 62.0 (51.0–76.0) under s/v: 59.0 (42.0–73.0)	–0.837 –0.666	prior s/v: 0.402 under s/v: 0.505
Uric acid [mg/dL], median (IQR)	prior s/v: 7.0 (5.7–9.0) under s/v: 6.1 (5.1–7.5)	prior s/v: 6.7 (5.7–7.8) under s/v: 6.8 (5.4–7.7)	–0.908 –0.780	prior s/v: 0.364 under s/v: 0.436
Hemoglobin [g/dL], median (IQR)	prior s/v: 14.1 (12.7–15.1) under s/v: 13.7 (12.7–14.7)	prior s/v: 14.4 (13.1–15.3) under s/v: 13.7 (12.4–15.1)	–0.582 –0.259	prior s/v: 0.560 under s/v: 0.796
Aspartate transaminase [U/L], median (IQR)	prior s/v: 30.0 (21.0–38.0) under s/v: 26.0 (24.0–31.0)	prior s/v: 30.0 (25.0–36.0) under s/v: 28.0 (23.0–33.0)	–0.343 –0.498	prior s/v: 0.731 under s/v: 0.619
Potassium [mmol/L], median (IQR)	prior s/v: 4.5 (4.2–4.8) under s/v: 4.5 (4.3–4.7)	prior s/v: 4.4 (4.2–4.6) under s/v: 4.5 (4.2–4.9)	–0.368 –0.203	prior s/v: 0.713 under s/v: 0.839
CK [U/L], median (IQR)	prior s/v: 102.5 (80.8–142.5) under s/v: 106.0 (73.0–131.0)	prior s/v: 108.0 (72.2–186.0) under s/v: 111.0 (74.0–128.0)	–0.810 –0.383	prior s/v: 0.418 under s/v: 0.701
CRP [mg/L], median (IQR)	prior s/v: 0.5 (0.5–1.0) under s/v: 0.5 (0.5–0.6)	prior s/v: 0.5 (0.5–0.5) under s/v: 0.5 (0.5–0.6)	–1.977 –0.386	prior s/v: 0.048* under s/v: 0.700

ACEI – angiotensin-converting enzyme inhibitors; ARB – angiotensin-II-receptor blockers; BB – beta blocker; BMI – body mass index; BP – blood pressure; CABG – coronary artery bypass graft; CAD – coronary artery disease; CHF – chronic heart failure; COPD – chronic obstructive pulmonary disease; CRP – C-reactive protein; CK – creatinine kinase; CRT-D – cardiac resynchronization therapy (-implantable cardioverter defibrillator); ECG – electrocardiogram; (e)GFR – (estimated) glomerular filtration rate; ICD – implantable cardioverter defibrillator; LA – left atrium; LV – left ventricle; LVEF – left ventricular ejection fraction; MI – myocardial infarction; MRA – mineralocorticoid receptor antagonist; NICM – nonischemic cardiomyopathy; NT-proBNP – N-terminal pro-brain natriuretic peptide; NYHA – level of cardiopulmonal fitness according to New York Heart Association; OSAS – obstructive sleep apnoea syndrome; PAD – peripheral artery disease; PM – pacemaker; RA – right atrium; RV – right ventricle; s/v – sacubitril/valsartan; VA – ventricular arrhythmias. Data are presented as median (interquartile range (IQR)) (Mann–Whitney U test) or n (%) (χ^2 test). * – statistically significant value of $p < 0.05$. Target dose calculation (for most important drugs; others calculated as equivalent doses): ramipril 10 mg = 1.0; enalapril 20 mg = 1.0; candesartan 32 mg = 1.0; valsartan 320 mg = 1.0; irbesartan 300 mg = 1.0; 2 × sacubitril/valsartan 97/103 mg = 1,0; hydrochlorothiazide 25 mg = 1.0; bisoprolol 10 mg = 1.0; metoprolol 190 mg = 1.0; carvedilol 50 mg = 1.0; spironolacton 25 mg = 1.0; eplerenon 25 mg = 1.0; torasemid 10 mg = 1.0; hydrochlorothiazide 25 mg = 1.0; xipamid 10 mg = 0.5; furosemid 40 mg = 1.0.

Results

Patient characteristics before and after the initiation of sacubitril/valsartan therapy

Out of the total number of 479 CHF patients, 104 patients were under sacubitril/valsartan treatment (Fig. 1). After the exclusion of patients with missing data, 95 patients were enrolled in our study. Within the period of data collection, no patient on sacubitril/valsartan therapy died. The median duration of sacubitril/valsartan therapy amounted to 17.0 (IQR: 10.0–26.3) months. Until then, the sacubitril/valsartan treatment was intermittently paused for a short period due to the side effects and thereafter prescribed again in 7 patients. In 3 cases, sacubitril/valsartan treatment had to be permanently withdrawn because of the drug intolerance and the data collection

Table 3. Side effects under sacubitril/valsartan therapy

Clinical symptom	Total number of patients, n = 95	Good efficacy of sacubitril/valsartan, n = 52	Moderate efficacy of sacubitril/valsartan, n = 43	Test value	p-value
Hypotension, n (%)	48 (50.5) (thereof without clinical relevance: 13 (13.7))	28 (53.8) (thereof without clinical relevance: 5 (9.6))	20 (46.5) (thereof without clinical relevance: 7 (16.3))	0.236	0.627
Orthostatic dizziness, n (%)	35 (36.8) (thereof without clinical relevance: 15 (15.8))	21 (40.4) (thereof without clinical relevance: 9 (17.3))	14 (32.6) (thereof without clinical relevance: 6 (14.0))	0.620	0.431
Kidney functional deterioration, n (%)	29 (30.5) (thereof with AKI: 4 (4.2))	19 (36.5) (thereof with AKI: 1 (1.9))	10 (23.3) (thereof with AKI: 3 (7.0))	1.958	0.162
Anemia de novo, n (%)	8 (8.4)	3 (5.8)	5 (11.6)	1.048	0.306
Hyperkalemia, n (%)	7 (7.4)	1 (1.9)	6 (14.0)	4.991	0.025*
Indefinite dizziness, n (%)	4 (4.2)	1 (1.9)	3 (7.0)	1.490	0.222
Headache, n (%)	2 (2.1)	2 (3.8)	0 (0.0)	1.689	0.194
Diarrhea, n (%)	2 (2.1)	2 (3.8)	0 (0.0)	1.689	0.194
Cough, n (%)	1 (1.1)	1 (1.9)	0 (0.0)	0.836	0.361
Angioedema, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	–	–

AKI – acute kidney injury according to Kidney Disease: Improving Global Outcome (KDIGO) criteria. Data are presented as n (%) (χ^2 test). * – statistically significant value of $p < 0.05$.

Table 4. Univariate Cox regression analysis predicting good clinical efficacy of sacubitril/valsartan

Parameters	Probability of a good sacubitril/valsartan efficacy	p-value
LVEF prior to sacubitril/valsartan	HR = 0.982, 95% CI = [0.948; 1.018]	0.318
NICM	HR = 2.523, 95% CI = [1.371; 4.644]	0.003*
Hospitalizations for CHF per month prior to sacubitril/valsartan	HR = 1.632, 95% CI = [0.944; 2.818]	0.079
Dyslipidemia	HR = 1.872, 95% CI = [1.062; 3.302]	0.030*
CRP levels prior to sacubitril/valsartan therapy	HR = 1.289, 95% CI = [1.080; 1.539]	0.005*
Time from diagnosis to sacubitril/valsartan start	HR = 0.993, 95% CI = [0.989; 0.997]	<0.001*

CHF – chronic heart failure; CRP – C-reactive protein; LVEF – left ventricular ejection fraction; NICM – nonischemic cardiomyopathy. Data are presented as hazard ratio (HR) with 95% confidence interval (95% CI) and p-values (univariate Cox regression analysis). * – statistically significant value of $p < 0.05$.

Table 5. Multivariate Cox regression analysis predicting a good clinical efficacy of sacubitril/valsartan; the final model

Parameters	Probability of a good sacubitril/valsartan efficacy	p-value
LVEF prior to sacubitril/valsartan	–	N/S: 0.928
NICM	–	N/S: 0.267
Hospitalizations for CHF per month prior to sacubitril/valsartan	–	N/S: 0.467
Dyslipidemia	–	N/S: 0.434
CRP levels prior to sacubitril/valsartan therapy	HR = 1.263, 95% CI = [1.048; 1.521]	0.014*
Time from diagnosis to sacubitril/valsartan start	HR = 0.992, 95% CI = [0.987; 0.997]	<0.001*

CHF – chronic heart failure; CRP – C-reactive protein; LVEF – left ventricular ejection fraction; NICM – nonischemic cardiomyopathy. Data are presented as hazard ratio (HR) with 95% confidence interval (95% CI) and p-values for selected variables. For non-selected variables (N/S), p-values of score test are displayed (multivariate Cox regression analysis). * – statistically significant value of $p < 0.05$.

was stopped at this timepoint. Baseline characteristics of all patients enrolled in the study are listed in Table 1. The patients were 57.0 (50.0–69.0) years old, mostly male, with a high prevalence of cardiovascular risk factors and presenting both ischemic and nonischemic etiologies of CHF. Almost all patients received optimal CHF drug therapy. The median time between the HF diagnosis and the initiation of the sacubitril/valsartan therapy was 92.5 (25.0–147.8) months. In 5 patients in the good efficacy group and in 3 patients in the moderate efficacy group, sacubitril/valsartan was prescribed within 1 month after the diagnosis of HF (de novo HF caused by either myocarditis, acute coronary ischemia or unclear nonischemic cardiomyopathy). Under sacubitril/valsartan therapy, the following parameters significantly improved: LVEF, NYHA class, NT-proBNP levels, the hospitalization rates, and the left (LA) and right (RA) atrial volumes, whereas the left ventricular (LV) and right ventricular (RV) volumes

demonstrated a decreasing trend. The heart rate was relevantly slower at a follow-up. Aspartate transaminase blood concentrations significantly decreased, probably as a reflection of a better cardiac function. In contrast, kidney function defined as changes in serum creatinine and GFR relevantly declined.

Characteristics of patients with a good and moderate efficacy of sacubitril/valsartan therapy, and possible predictors of outcome

When comparing patients with a good to moderate sacubitril/valsartan efficacy at baseline, the first group was characterized by relevantly worse LVEF of a predominantly nonischemic etiology, higher hospitalization rates for CHF, shorter period between CHF diagnosis and the initiation of sacubitril/valsartan therapy, and lower cholesterol and higher C-reactive protein (CRP) blood levels (Table 2). The good efficacy group showed by definition significantly higher LVEF, lower NYHA classes, reduced hospitalization rates for CHF, and a strong trend toward decreasing NT-proBNP levels at a follow-up.

Univariate and multivariate Cox regression analyses of good efficacy

The parameters which significantly differed between the groups with a good and moderate efficacy at baseline, such as LVEF, NICM, hospitalizations for CHF, dyslipidemia, CRP levels, and the time from diagnosis to the initiation of sacubitril/valsartan treatment, were included in the univariate Cox regression analysis (Table 4). The multivariate Cox regression analysis found only 2 parameters to be independently associated with a good efficacy (Table 5): higher CRP levels prior to sacubitril/valsartan therapy (hazard ratio (HR) = 1.263, confidence interval (95% CI) = [1.048; 1.521], p = 0.014), and a shorter time between CHF diagnosis and the initialization of sacubitril/valsartan treatment (HR = 0.992, 95% CI = [0.987; 0.997], p < 0.001).

Side effects

The most common side effects of sacubitril/valsartan treatment in our study were well-known adverse effects of this medication, such as arterial hypotension, worsening of kidney function followed by (less frequent) anemia, hyperkalemia, non-orthostatic dizziness, gastrointestinal disorders, headache, and cough (Table 3). Clinically relevant angioedema was not detected in any case. Interestingly, comparing the side effects in patients with a good to moderate efficacy, hyperkalemia was significantly more common in patients benefiting less from valsartan/sacubitril. In contrast, a tendency toward a more deteriorated kidney function (but not AKI), as defined in "Endpoints and definitions" section, was found in the good efficacy group.

Discussion

Our present study is a real-world research on sacubitril/valsartan therapy, identifying the parameters of a good clinical outcome under this treatment. In comparison with the patient population from the PARADIGM-HF study,[1] patients in our trial were in average younger, more frequently in NYHA class III than II, had more comorbidities, presented more often NICM as a CHF etiology, and were more frequently treated with mineralocorticoid antagonists and the implantable cardioverter-defibrillator (ICD)/cardiac resynchronization therapy (CRT) (Table 1).

In line with other studies, sacubitril/valsartan improved cardiac function with reversal of cardiac remodeling and positively influenced functional status, NT-proBNP levels and hospitalization rates.[1,2,11] The overall tolerance of sacubitril/valsartan was good, without major adverse effects, and did not differ between patients with a good and moderate efficacy, except for more frequent hyperkalemia in the moderate efficacy group (Table 3), which could be an effect of a slightly worse kidney function resulting from more reduced LVEF, with a consequent hypotension and/or more frequently present cardiovascular risk factors for generalized atherosclerosis in this group. Anemia was not pronounced in both groups at baseline and there was no significant decrease in hemoglobin (Hb) levels under sacubitril/valsartan therapy in either of the groups. This is an important information, as it is known that anemia increases hospitalization and mortality rates in CHF patients.[12] However, this does not allow to draw any conclusions about the iron status in patients enrolled in this study, since anemia is mostly driven by the upregulation of neurohumoral and inflammatory cytokines and a concomitant renal disease in CHF patients, and not by iron deficiency.[12] Iron deficiency itself is an independent risk factor of poor outcomes in CHF patients with reduced LVEF, regardless of Hb levels.[13] So far, there are no data supporting relevant adverse effects of sacubitril/valsartan on iron metabolism.

In total, 52 out of 95 patients (54.7%) reached the clinical endpoint of a good efficacy of sacubitril/valsartan, defined as an improvement of at least 2 parameters out of 4, including LVEF, NT-proBNP, NYHA class, and hospitalization rates. The decision to take into consideration at least 2 of the abovementioned parameters to judge the clinical efficacy under sacubitril/valsartan therapy was due to the fact that single non-mortality-related endpoints may be less reliable in adequately reflecting a good clinical responsiveness to therapy than composite endpoints. Indeed, it is known that NYHA class change alone may not properly assess a good clinical effectiveness of the CHF treatment, as CHF patients may not accurately report on their symptoms or may complain only few or even no symptoms due to the avoidance of physical activity.[14] Furthermore, the addition of LVEF with NT-proBNP and hospitalization frequency under sacubitril/valsartan therapy to our clinical endpoint, makes such an endpoint also relevant

for the survival estimation, as both reduced LVEF and increased hospitalization rates enhance mortality.[1,15]

Patients in a good efficacy group had significantly lower LVEF, more NICM, more frequent hospitalization rates for CHF, less dyslipidemia, higher CRP levels at baseline, and a shorter time between CHF diagnosis and the start of sacubitril/valsartan therapy. Additionally, they were characterized by a tendency toward less frequent diabetes (Table 2).

A multivariate Cox regression analysis evaluating relevant parameters significantly different at baseline between the groups, demonstrated that only 2 factors, higher blood CRP levels at baseline and a shorter time between the diagnosis of CHF and the start of sacubitril/valsartan therapy, were independent predictors of clinical success under this therapy.

Sacubitril/valsartan, as a composite drug of sacubitril and valsartan, was shown to exert, besides a positive influence on cardiac structure and function, also beneficial extracardiac impact such as metabolic effects with HbA1c level reductions, suggesting potential pleiotropic effects of this medication.[2] Valsartan was demonstrated to lower inflammatory levels and microalbuminuria in patients with metabolic syndrome,[16] and had protective effects against smoking-induced LV systolic dysfunction by attenuating oxidative stress, cardiomyocyte apoptosis and inflammation.[17] Similarly, the combination of a low dose of fluvastatin and valsartan was proven to act anti-inflammatory and antioxidative in apparently healthy middle-aged men[18] and in patients with type II diabetes.[19] Moreover, the coadministration of captopril and valsartan reduced inflammation levels in patients after the interventional therapy for acute myocardial infarction.[20] Studies on sacubitril/valsartan revealed that sacubitril/valsartan ameliorated atherosclerosis and inflammation in apoE–/– mice, as compared with valsartan alone.[21] Sacubitril/valsartan improved renal function by reducing the oxidative stress, inflammation and fibrosis beyond the effects of therapy with valsartan alone.[22] Furthermore, sacubitril/valsartan prevented cardiac rupture after myocardial infarction, due to the inhibition of inflammation and degradation response of macrophages.[23]

Thus, better effects of sacubitril/valsartan on clinical outcome in patients with higher inflammatory levels prior to sacubitril/valsartan therapy in our study could suggest that sacubitril/valsartan acts in this patient subpopulation even more effectively, as it may additionally unfold its further property, namely the anti-inflammatory one. Indeed, higher inflammation levels in the good efficacy group were decreased under sacubitril/valsartan therapy, and reached the levels comparable to those in the moderate efficacy group at the last follow-up in our study (Table 2). Since the inflammation is associated with left ventricular dysfunction[24,25] and higher mortality,[26] the attenuation of this process could explain better results of sacubitril/valsartan treatment in patients with enhanced inflammation before the start of sacubitril/valsartan therapy.

The second parameter which positively influenced the responsiveness to sacubitril/valsartan therapy in our study was a shorter time between the CHF diagnosis and the start of sacubitril/valsartan treatment. It may be assumed that this finding could be associated with the fact that early after CHF diagnosis, the magnitude of heart structure and function deterioration is not so high and the pathological changes are still at least partly reversible, compared to those in advanced CHF. In line with this assumption, sacubitril/valsartan seemed to be less effective in NYHA class III and IV patients for the primary endpoint of the PARADIGM-HF study, but not for death from cardiovascular causes.[2] However, because of the underrepresentation of NYHA class III and IV in the PARADIGM-HF study, these results should be proven in further trials. Similarly, the improvement of LVEF was associated with lower LV dilation prior to sacubitril/valsartan treatment,[5] indicating that sacubitril/valsartan therapy should be initiated earlier, when the cardiac remodeling is not advanced yet.[5] This result could also have another explanation connected to the findings stating that in acute HF with elevated BNP and NT-proBNP levels, neprilysin catalytic activity is inhibited.[27] Analogically, in advanced CHF with high BNP and NT-proBNP blood concentrations, the neprilysin catalytic activity could be suppressed, thus potentially affecting the actions of sacubitril/valsartan. In contrast, risk scores such as the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) score with independent predictors of all-cause mortality, cardiovascular mortality and hospitalizations for CHF including baseline characteristics, comorbidities and concurrent medication, as well as the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) risk score with 10 independent risk factors showed that the subgroups of patients with different quartiles benefited from sacubitril/valsartan over enalapril, and the greatest absolute benefit was detected in patients with the highest risk, defined, among others, by a more advanced, long-lasting HF.[28] However, in the high-risk patient groups, the levels of inflammation could have been higher than in the other ones, so that the anti-inflammatory effect of sacubitril/valsartan could possibly outweigh the attenuated effectiveness, due to a longer persistence of HF before the start of sacubitril/valsartan therapy.

Another aspect of our finding is that the inclusion criteria for sacubitril/valsartan should not exclude patients who do not perfectly match the inclusion criteria of the PARADIGM-HF study, or due to the concerns about potential side effects. Also, hasty withdrawal or significant reduction of sacubitril/valsartan dose only because of minor, clinically not significant adverse effects should be avoided. Another important issue are patients in NYHA class I with low NT-proBNP levels who were not enrolled in the PARADIGM-HF study. Since NYHA class or NT-proBNP levels do not reliably predict the clinical benefit of sacubitril/valsartan treatment, withholding this therapy from those patients could possibly put them at risk of disease

progression. Therefore, further investigations on this issue are urgently needed, since the current European Guidelines still recommend sacubitril/valsartan treatment in patients with a persistence of symptomatic CHF who had to previously undergo angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) therapy.[7]

Limitations

Our study has some limitations, primarily arising from its retrospective design and the associated bias. Additionally, the study's meaningfulness could potentially be affected by a relatively small sample size and the limited follow-up time. Furthermore, NYHA class reported by patients was not verified using functional tests. Also, as a single-center experience in an outpatient setting in Germany, the results might represent local practice and cannot be uncritically extrapolated to more advanced CHF stages demanding hospitalizations. Moreover, a control group treated with standard HF medication is lacking since, after the approval of sacubitril/valsartan, all patients fulfilling the indication criteria for sacubitril/valsartan in our outpatient section were gradually switched to this drug. Also, the target dose of sacubitril/valsartan was not reached in many cases because of already occurring side effects or preventive actions aimed at avoiding possible adverse effects under higher medication doses. However, according to the PARADIGM-HF study, lower sacubitril/valsartan doses are still effective and more beneficial in terms of outcome than the comparable ACEI/ARB doses. Another limitation of our study is the documentation of LV performance through the assessment of LVEF, without the calculation of strain in a speckle tracking analysis. Although the strain measurement could be useful to better estimate the magnitude of LV dysfunction, such analysis was not routinely performed in our patient collective, as it may be of a higher importance in population with apparently preserved LV function to detect early changes in LV.[29] Moreover, the vast majority of patients who fulfilled the criterion of the LVEF improvement of at least 5%, had an increase in LVEF relevantly higher than 5% (median (IQR): 12% (9–21%)), so that the potential errors in the LVEF estimation over the course of time resulting from the inaccuracy of the method seem to be limited.

Nevertheless, despite all the above limitations, our findings present real-world data which confirm the safety and efficacy of this quite new drug, with an emphasis on potential factors predicting the best clinical results.

Conclusions

In conclusion, our present study found worse LVEF, increased hospitalization rates for CHF, less frequent hyperlipidemia and increased CRP at baseline together with more predominant NICM and a shorter time between CHF diagnosis and the start of sacubitril/valsartan therapy to be associated with a good clinical response and outcome under sacubitril/valsartan therapy, defined as an improvement of at least 2 of the following parameters: LVEF, NT-proBNP, NYHA class, or the hospitalization rates. However, only increased CRP blood levels at baseline and a shorter time from the CHF diagnosis to the initiation of sacubitril/valsartan therapy turned out to be independently associated with a good clinical response to sacubitril/valsartan treatment in a multivariate Cox regression analysis. Thus, this study may contribute to optimized patient selection and help to predict clinical prognosis of patients undergoing sacubitril/valsartan therapy. However, further prospective studies with a larger number of patients are required to definitely prove these findings.

ORCID iDs

Elisabeth J. Fröb https://orcid.org/0000-0002-4269-558X
Jürgen R. Sindermann https://orcid.org/0000-0002-1370-0060
Holger Reinecke https://orcid.org/0000-0002-4515-1609
Izabela Tuleta https://orcid.org/0000-0002-8482-591X

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