ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 3547–3556
Published online 2 August 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13547

ORIGINAL RESEARCH ARTICLE

Sacubitril/valsartan in real-life European patients with heart failure and reduced ejection fraction: a systematic review and meta-analysis

Stefano Giovinazzo[1†], Luca Carmisciano[2†], Matteo Toma[1], Stefano Benenati[1,3], Daniela Tomasoni[4], Maria Pia Sormani[2], Italo Porto[1,3], Marco Canepa[1,3], Michele Senni[5], Marco Metra[4] and Pietro Ameri[1,3]*

[1]*Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, IRCCS Italian Cardiology Network, Genoa, Italy;* [2]*Department of Health Sciences, Section of Biostatistics, University of Genova, Genoa, Italy;* [3]*Department of Internal Medicine, University of Genova, Genoa, Italy;* [4]*Cardiology Unit, ASST Spedali Civili and Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; and* [5]*Cardiology Division, Cardiovascular Department, Ospedale Papa Giovanni XXIII, Bergamo, Italy*

Abstract

Aims We systematically reviewed the European real-world evidence (RWE) about sacubitril-valsartan for heart failure with reduced ejection fraction.

Methods and results Twenty-one articles, including 16 952 subjects, were identified until 31 October 2020. Taking as reference the PARADIGM-HF cohort, few baseline characteristics were presented in >80% of these studies, most often with high heterogeneity. In random-effects model meta-analysis, age was higher (mean difference +3.84, 95% CI 1.92–5.76), ischaemic aetiology (OR 0.76, 95% CI 0.64–0.91), hypertension (OR 0.55, 95% CI 0.37–0.82), and diabetes (OR 0.77, 95% CI 0.64–0.92) were less common, and the use of mineralocorticoid receptor antagonists was more frequent (OR 3.54, 95% CI 2.27–5.53) in real-life than in PARADIGM-HF. Other clinical and medical features were presented in 19–76% of the selected publications and suggested more severe heart failure with reduced ejection fraction. Sacubitril-valsartan was titrated to 97/103 mg b.i.d. in 35% (95% CI 23–47) and discontinued in 12.8% (95% CI 7.4–18.3) patients. When reported, the incidence of hyperkalaemia (six studies, no. 1076), all-cause mortality (five studies, no. 684), and any hospitalization (three studies, no. 390) was 12 (95% CI 5–19)/100 person-year, 8 (95% CI 4–12)/100 person-year, and 24 (95% CI 5–42)/100 person-year, respectively. Knowledge contribution, a metric measuring the proportion of RWE provided by each article based on the number of reported variables and the sample size, was 58.8% and 13.6% for the two biggest investigations (12 082 and 2037 patients), and <5% for all others (most with <100 subjects).

Conclusions Limited-quality RWE indicates that there are important differences between European patients prescribed sacubitril-valsartan and the PARADIGM-HF population, including the frequency of target dose achievement.

Keywords Sacubitril-valsartan; ARNI; Heart failure; Real-word; Real-life

Received: 19 April 2021; Revised: 22 June 2021; Accepted: 16 July 2021
**Correspondence to: Pietro Ameri, IRCCS Ospedale Policlinico San Martino – IRCCS Italian Cardiology Network & Department of Internal Medicine, University of Genova, Viale Benedetto XV, 6, 16132 Genoa, Italy. Phone: +390103538928; Fax: +390105556513. Email: pietroameri@unige.it*
†These authors contributed equally to this work.

Introduction

Sacubitril-valsartan, the first-in-class angiotensin receptor neprilysin inhibitor (ARNI), represents a major advance in the pharmacotherapy of heart failure with reduced ejection fraction (HFrEF). The pivotal phase 3 Prospective Comparison of ARNI with an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial compared sacubitril-valsartan with enalapril in patients with chronic HFrEF and was stopped prematurely because of an overwhelming benefit of ARNI for the primary outcome of cardiovascular (CV) death or HF hospitalization.[1] All-cause mortality was also significantly lower in the sacubitril-valsartan than in the enalapril arm.[1]

By following the design of PARADIGM-HF, current guidelines from the European Society of Cardiology (ESC)

recommend sacubitril-valsartan for patients with HFrEF, who remain symptomatic, with left ventricular ejection fraction (LVEF) $\leq$ 35%, and with high brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) levels, despite treatment with beta-blocker, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), and mineralocorticoid receptor antagonist (MRA) at the target or highest tolerated doses.[2]

It has been argued that these indications, which replicate the PARADIGM-HF inclusion and run-in criteria, preclude treatment of subjects who may benefit from sacubitril-valsartan.[3] Of 5443 HFrEF outpatients included in the ESC-European Observational Program (ESC-EORP) Long-Term Heart Failure (HF-LT) Registry between 2011 and 2013, 84% had NYHA class II–IV and LVEF $\leq$40% and, thus, were eligible for sacubitril-valsartan according to the European Medicines Agency and Food and Drug Administration labels. However, only 12% could have received sacubitril-valsartan when following PARADIGM-HF criteria and ESC guidelines.[4]

Moreover, after publication of the results of PARADIGM-HF, it has been shown that sacubitril-valsartan may favourably modify the trajectory of HFrEF by inducing reverse cardiac remodelling[5,6] and decreasing the risk of ventricular arrhythmias.[7,8] Based on these data, early use of sacubitril-valsartan in HFrEF has been advocated.

Real-world evidence (RWE) is fundamental to determine to which patients sacubitril-valsartan has been prescribed so far in clinical practice. Hence, we undertook a systematic analysis of the articles describing the use of sacubitril-valsartan for HFrEF in Europe.

Methods

This meta-analysis was registered on PROSPERO (registration number CRD42021226366).

Study selection

A systematic literature search was performed in MEDLINE and Scopus, from 11 September 2014 (date of publication of PARADIGM-HF) until 31 October 2020, to identify the articles focusing on real-world use of sacubitril-valsartan in European patients with HFrEF. The key words were: 'sacubitril/valsartan', 'heart failure', 'heart failure with reduced ejection fraction', 'real-world', and 'real-life'. The search was integrated by reviewing the bibliographies of the retrieved articles, as well as of review articles about sacubitril-valsartan. Studies involving $\leq$10 subjects, regarding the prescription of sacubitril-valsartan for conditions other than outpatient HFrEF, published without peer revision, or in languages other than English were excluded.

Data extraction

Two authors (S. G. and M. T.) independently reviewed the literature. In case of articles describing partially overlapping populations or periods of evaluation, the one with the biggest sample or with the longest observation was included. Any disagreement was resolved by asking the revision of senior authors and by discussion.

By reasoning that the studies about sacubitril-valsartan in the real-word setting should take PARADIGM-HF as a reference, in order to integrate the knowledge basis set by this trial, we determined to which extent the baseline characteristics of the PARADIGM-HF population were assessed in the selected articles. Moreover, the following information was extracted: (i) follow-up duration; (ii) dose of sacubitril-valsartan achieved and frequency of sacubitril-valsartan discontinuation; (iii) rates of hyperkalaemia and worsening renal function; (iv) all-cause death and all-cause hospitalization. The Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations were followed (Supporting Information, *Table S1* and *Figure S1*).

Statistical analysis

Mean and standard deviation (SD) or count and percentage were used to describe the pooled patients' characteristics, as computed from the aggregated data using weighted averages.

The characteristics of the subjects in the selected articles were compared with those of the PARADIGM-HF cohort by performing a meta-analysis using a random-effects model for each variable. Mean difference (MD) and standardized mean difference were used to compare continuous variables, and proportion (%) and odds ratio (OR) to compare binary ones. For each measure, 95% confidence intervals (95% CI) are given.

The proportion of variation across studies attributed to heterogeneity rather than to chance was evaluated by I^2 statistic ($I^2 < 25\%$: low heterogeneity; I^2 25–50%: moderate heterogeneity; $I^2 > 50\%$: high heterogeneity), and the quality of the articles was assessed by the ROBINS-I tool. This latter explores seven domains, in which systematic differences may occur between a non-randomized, observational study and an ideal pragmatic randomized trial that the study attempts to emulate.[9]

The frequency of full dose sacubitril-valsartan achievement was calculated by dividing the number of subjects reaching the highest dosage of the drug (i.e. 97/103 mg b.i.d.) at any time by the number of individuals included in the study.

The incidence rates of all-cause mortality and all-cause hospitalization were estimated based on the number of events reported over 100 person-year, as derived by the total number of participants and the median follow-up. The

influence of age and sex on these outcomes was investigated by meta-regression with linear models weighted for the number of patients and adjusted for the length of follow-up, in which age and sex were explanatory variables. The other baseline characteristics were too underreported to be added to the analysis.

To establish how each article contributed to the depiction of real-world patients taking sacubitril-valsartan, a specific metric was conceived. First, the number of reported variables among those describing the PARADIGM-HF population was multiplied by the number of evaluated subjects, to obtain a number that is referred to as 'study knowledge'. Then, 'knowledge contribution' (KC) was calculated as the ratio between the specific study knowledge and the sum of all studies' knowledge. The higher the number of reported variables and the study sample, the higher the metric.

R version 3.6.3 was used for all statistical analyses with the package 'metafor' version 2.1-0.[10]

Results

Characteristics of the patients described in the selected articles

Twenty-one articles, 10 retrospective and 11 prospective, were selected[11–31] (Supporting Information, *Figure S1* and *Tables S2* and *S3*). Collectively, these studies included 16 952 patients: 12 082 (71.3%) were accounted for by a single article,[16] while the sample size of the other ones varied from 11 (0.06%) to 2037 (12.0%) subjects.[11–15,17–31] Four investigations included patients in NYHA class I (Lopez-Azor[23]: 1.1%; Vicent[18]: 1.2%; Kakuzna[11]: 3.0%; and Pharithi[24]: 10.4%).

Taking as reference the PARADIGM-HF cohort, only age and sex were reported for all patients (*Table 1*). Information about systolic blood pressure, ischaemic aetiology, diabetes, hypertension, and therapy with beta-blockers or MRA was available in >80% of the studies (*Table 1*). The other baseline characteristics were presented in 19–76% of the articles. None of the studies contained data about prior myocardial infarction or stroke (*Figure 1*).

Heterogeneity was most often high (*Table 1*). All investigations had a moderate to high risk of bias in at least one domain; the overall risk was low in 16 (76%) and moderate in 5 (24%). It was mainly related to baseline assessment (bias due to confounding and participant selection) and reporting of outcomes (bias due to missing data, measurement of the outcomes and, especially, selection of the results) (Supporting Information, *Figure S2*).

Considering the variables available in >80% of the retrieved articles, real-life HFrEF patients in Europe were older, had less often an ischaemic aetiology of HF, hypertension, and diabetes, and were more likely to being treated with MRA than participants in PARADIGM-HF (*Table 1*; the relevant forest plots are shown in Supporting Information, *Figures S3–S7*). Among the characteristics less frequently reported, NYHA class III-IV was more common in real-life cohorts, while previous hospitalization for HF was less frequent (*Table 1*, Supporting Information, *Figures S8–S9*). Concentrations of creatinine were higher in real-life than PARADIGM-HF patients, and a trend for higher levels of NT-proBNP was also found (*Table 1*, Supporting Information, *Figures S10–S11*). Furthermore, when sacubitril-valsartan was started, the frequency of ARB (rather than of ACEi), ICD, and CRT was higher than in PARADIGM-HF (*Table 1*, Supporting Information, *Figures S12–S14*). Digoxin was instead used less often than in PARADIGM-HF (*Table 1*, Supporting Information, *Figure S15*).

Sacubitril-valsartan management and side effects, all-cause mortality, and all-cause hospitalization

Sacubitril-valsartan was titrated to 97/103 mg b.i.d. in 35% (95% CI 23–47) of the article patients, with no clear trend of full-dose achievement over time and no significant relation with age or sex. Based on nine of the reviewed studies, the proportion of subjects interrupting sacubitril-valsartan was 12.8% (95% CI 7.4–18.3).

Hyperkalaemia was assessed in six investigations (1076 individuals in total), in which it occurred at a rate of 12 (95% CI 5–19)/100 person-year. Renal function was evaluated in 16 of the selected articles, but only six reported the rate of worsening renal function, and the definition of this event was given in two (≥0.3 mg/dL increase in serum creatinine in 18 and ≥30% decline in estimated glomerular filtration rate in 24). With these limitations, worsening renal function was observed in 5.1% (95% CI 2.8–7.4) of treated patients.

All cause-mortality was reported in five studies covering 684 subjects, with the incidence rate being 8 (95% CI 4–12)/100 person-year.[11,18,19,26,27] The hospitalization rate, as inferred by three studies with 390 patients in total, was 24 (95% CI 5–42)/100 person-year.[11,17,18] While there was no relationship between age or sex and all-cause mortality, male sex was negatively associated with hospitalization (weighted linear regression, $\beta = -2.44$, 95% CI -4.04 to -0.84; $P = 0.03$).

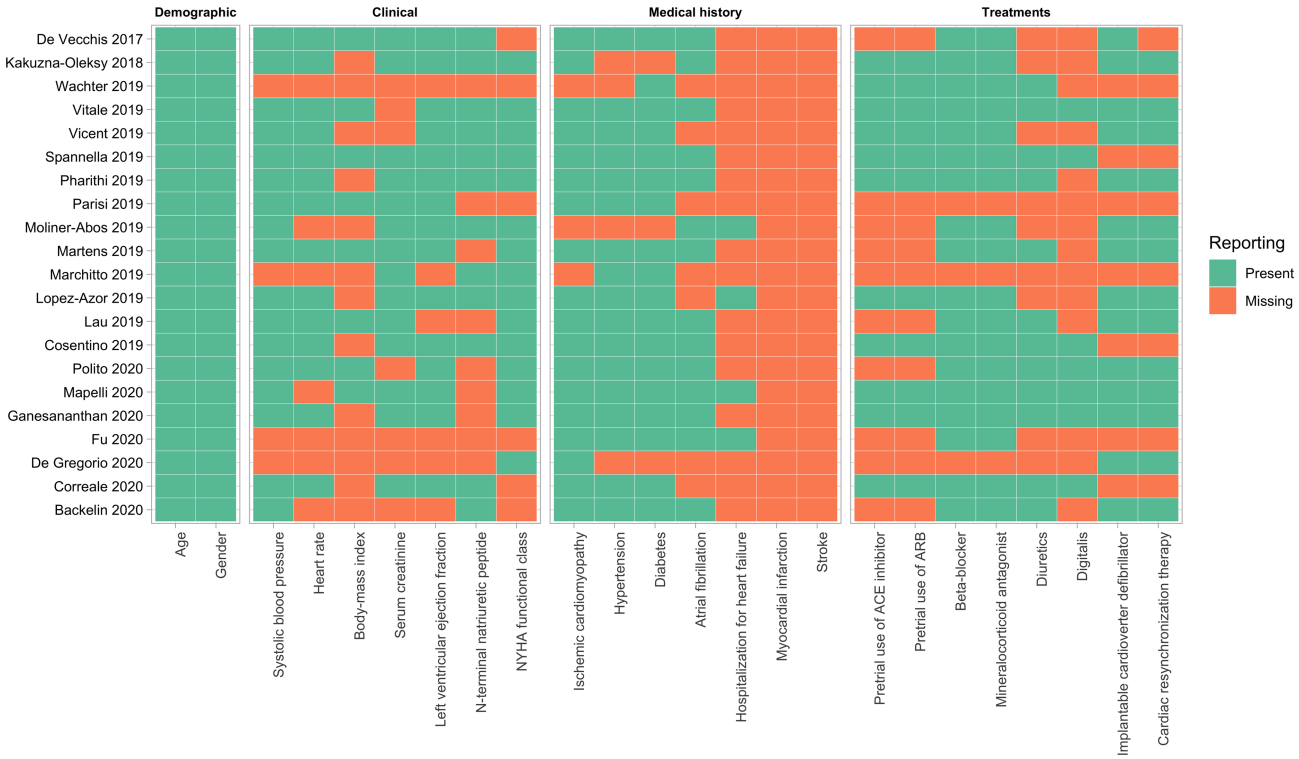
Two studies compared mortality and HF hospitalization in patients receiving sacubitril-valsartan or ACEi/ARB: De Vecchis *et al*. found that the rate of all-cause death was 6.8% with sacubitril-valsartan and 34% with ACEi/ARB (OR 0.14, 95% CI 0.04–0.49), and the rate of HF hospitalization 4.5% and 59%, respectively (OR 0.03, 95% CI 0.01–0.14)[19]; while in the cohort described by Polito *et al*. the rate of any death was 8.9% versus 12.2% ($P < 0.05$) and the one of HF hospitalization 5.6% versus 13.3% ($P = 0.04$).[26] The overall

Table 1 Baseline characteristics of the patients included in the articles describing the use of sacubitril-valsartan in European clinical practice, compared with those of the participants in PARADIGM-HF

	No. (%) of reporting articles	No. (%) of reported patients	Pooled population	PARADIGM-HF (ref. 1)	Pooled population vs. PARADIGM-HF
Age (years)	21 (100%)	16 952 (100%)	70.3 ± 11.9	63.8 ± 11.5	MD = +3.84 (1.92, 5.76; $P < 0.001$) $I^2 = 97.11\%$, $P < 0.0001$
Female sex	21 (100%)	16 952 (100%)	6629 (39.1)	879 (21.0)	OR = 1.12 (0.91, 1.37; $P = 0.28$) $I^2 = 87.09\%$, $P < 0.0001$
SBP (mmHg)	17 (81%)	2780 (16%)	120 ± 33	122 ± 15	MD = −1.09 (−2.96, 0.78; $P = 0.23$) $I^2 = 60.67\%$, $P = 0.019$
HR (b.p.m.)	14 (67%),	2376 (14%)	69 ± 13	72 ± 12	MD = −1.89 (−4.51, 0.72; $P = 0.28$) $I^2 = 96.44\%$, $P < 0.0001$
BMI (kg/m^2)	8 (38%)	1104 (7%)	27 ± 7	28.1 ± 5.5	MD = −0.59 (−1.50, 0.32; $P = 0.78$) $I^2 = 8.9\%$, $P = 0.24$
Serum creatinine (mg/dL)	14 (67%)	2080 (12%)	1.21 ± 0.62	1.13 ± 0.30	MD = +0.08 (0.02, 0.14; $P = 0.008$) $I^2 = 84.88\%$, $P < 0.0001$
Ischaemic aetiology	18 (86%)	4751 (28%)	2528 (53)	2506 (59.9)	OR = 0.76 (0.64, 0.91; $P = 0.003$) $I^2 = 0.01\%$, $P = 0.51$
LVEF (%)	15 (71%)	2484 (15%)	29.5 ± 7	29.6 ± 6.1	MD = 0.05 (−0.21, 0.3; $P = 0.73$) $I^2 = 96.45\%$, $P < 0.0001$
NT-proBNP (pg/mL)	12 (57%)	1804 (11%)	2280 ± 990	1631 (885–3154)	MD = +1369 (−218, +2956; $P = 0.08$) $I^2 = 97.56\%$, $P < 0.0001$
NYHA III–IV	16 (76%)	2664 (16%)	882 (33.1)	1002 (23.9)	OR = 2.01 (1.38, 2.93; $P < 0.001$) $I^2 = 91.31\%$, $P < 0.0001$
Hypertension	17 (81%)	4692 (28%)	2676 (57.0)	2969 (70.9)	OR = 0.55 (0.37, 0.82; $P = 0.003$) $I^2 = 78.24\%$, $P < 0.0001$
Diabetes	18 (86%)	16 774 (99%)	5584 (33.3)	1451 (34.7)	OR = 0.77 (0.64, 0.92; $P = 0.004$) $I^2 = 45.89\%$, $P = 0.12$
Atrial fibrillation	14 (67%)	3789 (22%)	1579 (41.7)	1517 (36.2)	OR = 1.10 (0.92, 1.32; $P = 0.31$) $I^2 = 73.68\%$, $P = 0.001$
Prior HF hospitalization	4 (19%)	2873 (17%)	1004 (34.9)	2607 (62.3)	OR = 0.27 (0.17–0.41) $P < 0.001$ $I^2 = 92.96\%$, $P < 0.0001$
Myocardial infarction	0 (0%)	—	—	1818 (43.4)	-
Stroke	0 (0%)	—	—	355 (8.5)	-
Prior ACEi	11 (52%)	13 909 (82%)	8064 (58.0)	3266 (78.0)	OR = 0.61 (0.48, 0.78; $P < 0.001$) $I^2 = 77.17\%$, $P < 0.001$
Prior ARB	11 (52%)	13 909 (82%)	4935 (35.5)	929 (22.2)	OR = 1.32 (1.06, 1.65; $P = 0.01$) $I^2 = 81.05\%$, $P < 0.001$
Beta-blocker	18 (86%)	16 885 (99.6%)	15 471 (91.6)	3899 (93.1)	OR = 1.34 (0.93, 1.91; $P = 0.11$) $I^2 = 52.53\%$, $P = 0.08$
MRA	18 (86%)	16 885 (99.6%)	11 632 (68.8)	2271 (54.2)	OR = 3.54 (2.27, 5.53; $P < 0.001$) $I^2 = 96.47\%$, $P = 0.0001$
Diuretics	12 (57%)	13 714 (81%)	11 568 (84.3)	3363 (80.3)	OR = 0.96 (0.52, 1.77; $P = 0.89$) $I^2 < 0.01\%$, $P = 0.23$
Digoxin	7 (33%)	613 (4%)	67 (11)	1223 (29.2)	OR = 0.32 (0.18, 0.57; $P = <0.001$) $I^2 = 93\%$, $P < 0.0001$
ICD	14 (67%)	2665 (16%)	1276 (48)	623 (14.9)	OR = 4.87 (3.50, 6.78; $P < 0.001$) $I^2 = 96.4\%$, $P < 0.0001$
CRT	13 (62%)	2621 (15%)	736 (28)	292 (7)	OR = 4.52 (2.91, 7.04; $P < 0.001$) $I^2 = 8.61\%$, $P = 0.55$

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CRT, cardiac resynchronization therapy; HF, heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure.
Data are presented as mean ± SD, median (interquartile range) or number (%). Mean differences (MD) and odds ratios (OR) are given with 95% CI in brackets.

Figure 1 Reported baseline characteristics of patients receiving sacubitril-valsartan in Europe. Reported (green) and missing (red) baseline characteristics in the selected articles, which are ordered by date of publication.



risk of bias in these investigations was low and moderate, respectively (Supporting Information, *Figure S2*).

Underreporting in the selected articles

In the only two articles including >1000 patients, more than 60% of the PARADIGM-HF baseline variables were missing (*Table 2*). KC was 58.8% for the biggest study,[16] driven by the very high number of evaluated subjects, and 13.6% for the second biggest one,[29] which however analysed a sample that was 6 times smaller. The percentage of missing variables in the other articles ranged from 16.7% to 75%, and KC was always <5% (*Table 2*). Ten (47.6%) of the selected articles were from Italy. Of these, only one described more than 100 subjects,[31] and it was also characterized by a relatively low proportion of missing variables; KC was 1.8%. The other nine studies from Italy yielded a KC < 1% each (*Table 2*). Underreporting was constant over time (Supporting Information, *Figure S16*).

Around 40% of the real-world investigations were supported by Novartis, and another 40% was funded by other sources; the remaining 20% did not have specific funding declared. KC was 89% for the studies sponsored by Novartis and 5% for the others, mainly because of the difference in the number of patients evaluated (ratio >10:1, see Supporting Information, *Table S4*).

Discussion

This systematic review highlights important dissimilarities between the population that, so far, has received sacubitril-valsartan for HFrEF in Europe and the one enrolled in PARADIGM-HF, based on which current ESC guidelines define the eligibility to ARNI. A second major finding is that only 35% of European patients appear to be titrated to the highest dose of sacubitril-valsartan in clinical practice. Third, the quality of RWE about sacubitril-valsartan in Europe is poor.

Age was reported by all the articles on sacubitril-valsartan prescription in Europe, and it was significantly higher than in PARADIGM-HF. Similarly, subjects with HFrEF initiated on sacubitril-valsartan the USA[32,33] and Asia[44] were older than those recruited in PARADIGM-HF.

The other characteristics of European HFrEF patients given sacubitril-valsartan have been delineated less consistently by the scientific literature examined in this work. In particular, the biggest study, accounting for more than two thirds of the described real-word population, did not include essential

DOI: 10.1002/ehf2.13547

Table 2 Missing data and knowledge contribution in the articles describing the use of sacubitril-valsartan in European clinical practice

		No. (%) of patients	Missing variables (%)[a]	Study-specific KC (%)[b]	Country-specific KC (%)[c]
Lau (2019)	Belgium	201	33.3	2.0	6.0
Martens (2019)		401	29.2	4.0	
Wachter (2019)	Germany	12 082	66.7	58.8	58.8
Pharithi (2019)	Ireland	322	20.8	3.7	3.7
Correale (2020)	Italy	60	33.3	0.5	5.8
Cosentino (2019)		29	25.0	0.3	
De Gregorio (2020)		42	75.0	0.4	
De Vecchis (2017)		44	37.5	0.4	
Mapelli (2020)		201	16.7	1.8	
Marchitto (2019)		11	70.8	0.1	
Parisi (2019)		14	58.3	0.1	
Polito (2020)		90	29.2	0.8	
Spannella (2019)		54	20.8	0.5	
Vitale (2019)		99	16.7	0.9	
Kakuzna-Oleksy (2018)	Poland	28	33.3	0.3	0.3
Lopez-Azor (2019)	Spain	527	25.0	5.0	10.1
Moliner-Abos (2019)		108	45.8	1.0	
Vicent (2019)		427	33.3	4.1	
Backelin (2020)	Sweden	95	45.8	0.6	14.3
Fu (2020)		2037	62.5	13.6	
Ganesananthan (2020)	UK	80	20.8	0.9	0.9

KC, knowledge contribution.
[a]Proportion of missing variables among those describing the PARADIGM-HF population.
[b]For each study, the number of reported variables was multiplied by the number of evaluated patients, obtaining a number defined as 'study knowledge'. Then, each study knowledge was divided by the sum all studies' knowledge to obtain KC.
[c]Sum of the KC of all articles from a certain country.

information about clinical features and medical history, apart from diabetes. Furthermore, heterogeneity across articles was most often high. Therefore, caution should be paid in making additional comments on the type of patients treated with sacubitril-valsartan in real-life as compared with PARADIGM-HF.

With this premise, an ischaemic aetiology of HF was less common than in PARADIGM-HF. The prevalence of hypertension and diabetes was also lower than in PARADIGM-HF, and this result may be related to the lower frequency of ischaemic heart disease. On the other side, the diagnosis of CV co-morbidities may have not been accurate in the investigations we reviewed. According to an interim analysis of Change the Management of Patients With Heart Failure (CHAMP-HF), a US registry of outpatients with HFrEF, the PARADIGM-HF population generally reflects the one encountered in clinical practice, but the prevalence of both hypertension (71% vs. 82%) and diabetes (34% vs. 41%) is lower in the former than in the latter.[34] It is also possible that the lower rates of hypertension and diabetes in our analysis are the consequence of enrichment strategies adopted in PARADIGM-HF.

Although it cannot be inferred whether there has actually been a preferential real-life use of sacubitril-valsartan in non-ischaemic HFrEF, it must be noted that, in PARADIGM-HF, sacubitril-valsartan was effective irrespective of the aetiology of HF.[35]

Overall, real-world patients might have somehow more severe HFrEF than participants in PARADIGM-HF, with NYHA classes III and IV being more frequent, creatinine and NT-proBNP concentrations higher, and implanted devices more common. Additional European RWE, published after the period covered by this systematic review, is in agreement with this interpretation. In a recent investigation, 1043 individuals prescribed sacubitril-valsartan in Ireland in 2018 had lower LVEF and higher NYHA class than the subjects randomized in PARADIGM-HF.[36]

The sicker phenotype of European patients receiving sacubitril-valsartan in clinical practice may also be, at least partly, the consequence of their older age. Indeed, renal function and NT-proBNP are function of age. However, more advanced HFrEF has also been outlined in real-world cohorts younger than the PARADIGM-HF one.[37]

The explanation for the apparently diverse use of sacubitril-valsartan in European patients as compared with PARADIGM-HF may also lie in the indications provided by ESC guidelines. Participants in PARADIGM-HF had NYHA class II-IV, elevated BNP or NT-proBNP, and a LVEF $\leq$35% (after amending the original protocol, in which the LVEF cut-off was set at 40%). They were on beta-blocker and ACEi or ARB, and more than 50% was also taking MRA. Furthermore, tolerance to the maximum dose of enalapril and sacubitril-valsartan was sequentially tested in a run-in period preceding randomization.[38] European guidelines recommend that all these criteria be applied.[2] Thus, patients who are initiated on sacubitril-valsartan by definition have uncontrolled, progressive HFrEF.

Almost 70% of real-life patients received MRA, as compared with not only 54% in PARADIGM-HF, but also 30%–60% in prior registries.[39] Because real-world subjects on

sacubitril-valsartan were symptomatic with about 30% in NYHA class III-IV, it is possible that MRA were prescribed for the diuretic effect, rather than to antagonize the detrimental actions of aldosterone. Remarkably, RWE indicates that HFrEF patients initiated on sacubitril-valsartan have higher creatinine levels than in PARADIGM-HF, and the rate of hyperkalaemia we could calculate was 12 per 100 patient-years, as compared with 10 and 7.3 per 100 patient-years in MRA-treated and untreated participants in PARADIGM-HF, respectively.[40] While emphasizing that the combination of sacubitril-valsartan and MRA must be judicious, it is noteworthy that, among patients on MRA in PARADIGM-HF, severe hyperkalaemia was less likely during treatment with sacubitril/valsartan than with enalapril.[40]

According to our analysis, about 1 in 10 subjects discontinued sacubitril-valsartan and about one third reached the full dose. Because the articles we examined may be biased towards more experienced prescribing physicians, the prevalence of individuals on the highest dose of sacubitril-valsartan might be even lower. The low rate of prescription of sacubitril-valsartan at the maximum dose may be due to the old age and frail phenotype of real-life patients. Clinical inertia is also to be considered. A recent analysis included a subgroup of the sample in reference 15, consisting of 1263 German adults.[41] Of them, 62%, 31%, and 7% were prescribed sacubitril-valsartan 24/26 mg b.i.d., 49/51 mg b.i.d., and 97/103 mg b.i.d., respectively, at the index visit, and only 14% of those initiated on 24/26 mg or 49/51 mg b.i.d. were up-titrated to 97/103 mg b.i.d. during the subsequent 6 months. Although features of less severe HF (lower NT-proBNP level, lower NYHA class, and higher estimated glomerular filtration rate) were associated with higher dose of sacubitril-valsartan, the patients' clinical characteristics did not clearly explain the reluctance to treatment up-titration.[41] Organizational issues, related to the need to see the patients multiple times, may play a role in sacubitril-valsartan underdosing.

Unfortunately, we could not assess the correlates of non-achievement of the maximal dose of sacubitril-valsartan, nor of discontinuation, owing to the lack of sufficient data.

Interestingly, sacubitril-valsartan titration seems to be lax worldwide. In a large USA insurance database, almost 60% of patients were initiated on 24/26 mg b.i.d., and only 24.5% of those who continued sacubitril-valsartan for 180 days after initiation were taking 97/103 mg b.i.d. by the end of the study period.[32] In the Prospective, Multicenter, Open Label, Post-Approval Study Aimed at Characterizing the Use of LCZ696 at 97 mg Sacubitril/103 mg Valsartan bid in Patients With HFrEF (PARASAIL), an open-label, phase IV, multicenter investigation involving Canadian HFrEF outpatients, 65% and 62% subjects were on sacubitril/valsartan 97/103 b.i.d. after 6 and 12 months, respectively.[42]

Given these considerations, it is reassuring that, in PARADIGM-HF, those requiring dose reduction still derived benefit of sacubitril-valsartan over enalapril at lower than target dosing, when the dose was maximally tolerated.[45]

RWE about treatment of European HFrEF patients with sacubitril-valsartan is weak. The articles included in this analysis either presented data from big, but very poorly characterized cohorts, or gave quite detailed descriptions of small samples. Hence, KC, a metric incorporating both the number of subjects evaluated and the degree of their characterization, was invariably low. The poverty of the RWE on sacubitril-valsartan is further revealed by the very scant data about worsening renal function (most often undefined) and by the fact that only 2 studies compared the effectiveness of sacubitril-valsartan with that of ACEi/ARB. It is also striking that the articles funded by the manufacturer of sacubitril-valsartan had more missing data than the others.

These results prompt the question of whether research on sacubitril-valsartan in real-life, particularly sponsored but also independent, could have been better planned and carried out. The efforts spent to perform multiple investigations with relatively few patients from the same country, especially Italy, could have been coordinated and finalized into a single, accurate, and well-sized study. On the other hand, prescription data with no clinical information were intrinsically flawed, even when they regarded thousands of individuals.

The limits of the RWE we systematically reviewed also underline the challenges in collecting good-quality real-life data to know and possibly improve clinical practice. Importantly, these considerations also apply to the RWE about sacubitril-valsartan from other regions, such as the USA.[32,33] With this respect, initiatives such as the ESC-EORP[43] or CHAMP-HF[34] are of utmost value.

We acknowledge that the literature presented here is likely affected by biases, especially in the reporting domain. Nonetheless, we believe that an updated and comprehensive representation of the use of sacubitril-valsartan in real-life is needed.

We did not assess the articles describing the initiation of sacubitril-valsartan in inpatients admitted for acutely decompensated HFrEF, because this approach is not approved in all European countries and is not mentioned in the current ESC guidelines. Future analyses are expected to address this topic.

In conclusion, RWE of modest quality indicates that, in European clinical practice, sacubitril-valsartan was prescribed to patients with major differences from the population that participated in PARADIGM-HF. The highest dose of the drug, which should be targeted according to guidelines, was prescribed in around one third of treated subjects.

Conflict of interest

S.G. received speaker and advisor fees from Novartis for topics related to the present study, and speaker and advisor

fees from Boehringer Ingelheim outside the scopes of the submitted work. I.P. received speaker and/or advisor fees from Biotronik, ABIOMED, Terumo, Philips, Sanofi, Amgen, Daiichi-Sankyo, and Bayer, all outside the scopes of the submitted work. M.C. received speaker and/or advisor fees from Akcea Therapeutics, Menarini, Novartis, Pfizer, Sanofi, Sanofi Genzyme, and Vifor Pharma, and two investigator-initiated grant from Pfizer, all outside of the scopes of the submitted work. M.S. received advisor fees from Novartis, Vifor Pharma, Astra Zeneca, Abbott, and Boehringer Ingelheim for topics related to the present study, and advisor fees from MSD and Bayer outside the scopes of the submitted work. M.M. received speaker and/or advisor fees from Servier, Amgen, Abbott, Vifor Pharma, and Astra Zeneca for topics related to the present study, and speaker and/or advisor fees from Bayer, Edwards therapeutics, LivaNova, Actelion, and WindTree Terapeutics outside of the scopes of the submitted work. P.A. received speaker and/or advisor fees from Novartis and Astra Zeneca for topics related to the present study, and speaker and/or advisor fees from Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Janssen, and MSD outside the scopes of the submitted work. The other authors have no conflicts of interest to disclose.

Funding

This study was not supported by specific funding.

Supporting information

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

Table S1. PRISMA checklist.
Table S2. Patient characteristics in the selected articles: demographic data and clinical presentation.
Table S3. Patient characteristics in the selected articles: comorbidities and treatments.
Table S4. Missing data and knowledge contribution in the articles describing the use of sacubitril-valsartan in European clinical practice according to the source of funding.
Figure S1. PRISMA flow diagram.
Figure S2. Risk of bias in the selected articles.
Figure S3. Mean age in the selected articles as compared with the PARADIGM-HF cohort.
Figure S4. Frequency of ischemic etiology in the selected articles as compared with the PARADIGM-HF cohort.
Figure S5. Frequency of hypertension in the selected articles as compared with the PARADIGM-HF cohort.
Figure S6. Frequency of diabetes in the selected articles as compared with the PARADIGM-HF cohort.
Figure S7. Frequency of MRA use in the selected articles as compared with the PARADIGM-HF cohort.
Figure S8. Frequency of NYHA class I-II vs. III-IV in the selected articles as compared with the PARADIGM-HF cohort.
Figure S9. Frequency of prior HF hospitalization in the selected articles as compared with the PARADIGM-HF cohort.
Figure S10. Mean serum creatinine concentration in the selected articles as compared with the PARADIGM-HF cohort.
Figure S11. Mean NT-proBNP concentration in the selected articles as compared with the PARADIGM-HF cohort.
Figure S12. Prior use of ACEi or ARB in the selected articles as compared with the PARADIGM-HF cohort.
Figure S13. Frequency of implantable cardioverter defibrillators in the selected articles as compared with the PARADIGM-HF cohort.
Figure S14. Frequency of cardiac resynchronization therapy in the selected articles as compared with the PARADIGM-HF cohort.
Figure S15. Frequency of digoxin use in the selected articles as compared with the PARADIGM-HF cohort.
Figure S16. Temporal distribution of underreporting of the baseline characteristics of patients receiving sacubitril-valsartan in Europe.

References

1. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014; **371**: 993–1004.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 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.
3. Pellicori P, Urbinati A, Shah P, MacNamara A, Kazmi S, Dierckx R, Zhang J, Cleland JGF, Clark AL. What proportion of patients with chronic heart failure are eligible for sacubitril-valsartan? *Eur J Heart Fail* 2017; **19**: 768–778.
4. Kapelios CJ, Lainscak M, Savarese G, Laroche C, Seferovic P, Ruschitzka F, Coats A, Anker SD, Crespo-Leiro MG, Filippatos G, Piepoli MF, Rosano G, Zanolla L, Aguiar C, Murin J, Leszek P,

McDonagh T, Maggioni AP, Lund LH, Heart Failure Long-Term Registry Investigators. Sacubitril/valsartan eligibility and outcomes in the ESC-EORP-HFA Heart Failure Long-Term Registry: bridging between European Medicines Agency/Food and Drug Administration label, the PARADIGM-HF trial, ESC guidelines, and real world. *Eur J Heart Fail* 2019; **21**: 1383–1397.

5. Januzzi JL Jr, Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, Camacho A, Piña IL, Rocha RA, Shah AM, Williamson KM, Solomon SD, PROVE-HF Investigators. Association of change in N-terminal Pro-B-Type Natriuretic Peptide following initiation of Sacubitril-Valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA*. 2019; **322**: 1085–1095.
6. Kang DH, Park SJ, Shin SH, Hong GR, Lee S, Kim MS, Yun SC, Song JM, Park SW, Kim JJ. Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation. *Circulation* 2019; **139**: 1354–1365.
7. de Diego C, González-Torres L, Núñez JM, Centurión Inda R, Martin-Langerwerf DA, Sangio AD, Chochowski P, Casasnovas P, Blazquéz JC, Almendral J. Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices. *Heart Rhythm* 2018; **15**: 395–402.
8. Martens P, Nuyens D, Rivero-Ayerza M, Van Herendael H, Vercammen J, Ceyssens W, Luwel E, Dupont M, Mullens W. Sacubitril/valsartan reduces ventricular arrhythmias in parallel with left ventricular reverse remodeling in heart failure with reduced ejection fraction. *Clin Res Cardiol* 2019; **108**: 1074–1082.
9. Sterne JA, Hernán MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; **355**: i4919.
10. Viechtbauer W.Conducting meta-analyses in R with the metaphor package. *J Stat Softw* 2010; **36**, 1–48. https://doi.org/10.18637/jss.v036.i03
11. Kaluzna-Oleksy M, Kolasa J, Migaj J, Pawlak A, Lelonek M, Nessler J, Straburzynska-Migaj E. Initial clinical experience with the first drug (sacubitril/valsartan) in a new class - angiotensin receptor neprilysin inhibitors in patients with heart failure with reduced left ventricular ejection fraction in Poland. *Kardiol Pol* 2018; **76**: 381–387.
12. Vitale G, Romano G, Di Franco A, Caccamo G, Nugara C, Ajello L, Storniolo S, Sarullo S, Agnese V, Giallauria F, Novo G, Clemenza F, Sarullo FM. Early effects of Sacubitril/Valsartan on exercise tolerance in patients with heart failure with reduced ejection fraction. *J Clin Med* 2019; **8**: 262.
13. Cosentino ER, Degli Esposti D, Miceli R, Bentivenga C, Landolfo M, Fg Cicero A, Berardi E, Spinardi L, Magri G, Dugato V, Borghi C. Sacubitril/valsartan improves both functional and echocardiographic parameters in patients with chronic heart failure with reduced ejection fraction. *Curr Med Res Opin* 2019; **35**: 9–12.
14. Marchitto N, Sindona F, Mobilia P, Dalmaso SG, Raimondi G. Effect of low-dose sacubitril/valsartan on body composition, bioelectrical impedance analysis, heart rate variability and T-peak to T-end index in elderly patients with severe chronic heart failure: a pilot experience. *Curr Med Res Opin* 2019; **35**: 13–15.
15. Parisi C, De Giusti M, Castello L, Dito E, Proietti F, Tomai F. Sacubitril/valsartan: preliminary experience in post-acute stabilized patients with reduced ejection fraction heart failure. *Curr Med Res Opin* 2019; **35**: 17–20.
16. Wachter R, Fonseca AF, Balas B, Kap E, Engelhard J, Schlienger R, Klebs S, Wirta SB, Kostev K. Real-world treatment patterns of sacubitril/valsartan: a longitudinal cohort study in Germany. *Eur J Heart Fail* 2019; **21**: 588–597.
17. Moliner-Abós C, Rivas-Lasarte M, Pamies Besora J, Fluvià-Brugues P, Solé-González E, Mirabet S, López López L, Brossa V, Pirla MJ, Mesado N, Álvarez-García J, Roig E. Sacubitril/Valsartan in real-life practice: experience in patients with advanced heart failure and systematic review. *Cardiovasc Drugs Ther* 2019; **33**: 307–314.
18. Vicent L, Ayesta A, Esteban-Fernández A, Gómez-Bueno M, De-Juan J, Díez-Villanueva P, Iniesta ÁM, Rojas-González A, Bover-Freire R, Iglesias D, García-Aguado M, Perea-Egido JA, Martínez-Sellés M. Sex influence on the efficacy and safety of Sacubitril/Valsartan. *Cardiology* 2019; **142**: 73–78.
19. De Vecchis R, Ariano C, Di Biase G, Noutsias M. Sacubitril/valsartan for heart failure with reduced left ventricular ejection fraction : A retrospective cohort study. *Herz* 2019; **44**: 425–432.
20. Lau CW, Martens P, Lambeets S, Dupont M, Mullens W. Effects of sacubitril/valsartan on functional status and exercise capacity in real-world patients. *Acta Cardiol* 2019; **74**: 405–412.
21. Martens P, Verluyten L, Van de Broek H, Somers F, Dauw J, Dupont M, Mullens W. Determinants of maximal dose titration of sacubitril/valsartan in clinical practice. *Acta Cardiol* 2019: 1-10. https://doi.org/10.1080/00015385.2019.1686226. Online ahead of print.
22. Spannella F, Marini M, Giulietti F, Rosettani G, Francioni M, Perna GP, Sarzani R. Renal effects of Sacubitril/Valsartan in heart failure with reduced ejection fraction: a real life 1-year follow-up study. *Intern Emerg Med* 2019; **14**: 1287–1297.
23. López-Azor JC, Vicent L, Valero-Masa MJ, Esteban-Fernández A, Gómez-Bueno M, Pérez Á, Díez-Villanueva P, De-Juan J, Manuel-Iniesta Á, Bover R, Del Prado S, Martínez-Sellés M. Safety of sacubitril/valsartan initiated during hospitalization: data from a non-selected cohort. *ESC Heart Fail.* 2019; **6**: 1161–1166.
24. Pharithi RB, Ferre-Vallverdu M, Maisel AS, O'Connell E, Walshe M, Sweeney C, Barton J, McDonald K, O'Hare D, Watson C, Gallagher J, Ledwidge M, McDonald K. Sacubitril-Valsartan in a routine community population: attention to volume status critical to achieving target dose. *ESC Heart Fail* 2020; **7**: 158–166.
25. Correale M, Mallardi A, Mazzeo P, Tricarico L, Diella C, Romano V, Ferraretti A, Leopizzi A, Merolla G, Di Biase M, Brunetti ND. Sacubitril/valsartan improves right ventricular function in a real-life population of patients with chronic heart failure: The Daunia Heart Failure Registry. *Int J Cardiol Heart Vasc* 2020;**27**:100486. https://doi.org/10.1016/j.ijcha.2020.100486.eCollection 2020 Apr.
26. Polito MV, Silverio A, Rispoli A, Vitulano G, Auria F, De Angelis E, Loria F, Gigantino A, Bonadies D, Citro R, Carrizzo A, Galasso G, Iaccarino G, Vecchione C, Ciccarelli M. Clinical and echocardiographic benefit of Sacubitril/Valsartan in a real-world population with HF with reduced ejection fraction. *Sci Rep* 2020; **10**: 6665.
27. Nordberg Backelin C, Fu M, Ljungman C. Early experience of Sacubitril-Valsartan in heart failure with reduced ejection fraction in real-world clinical setting. *ESC Heart Fail.* 2020; **7**: 1049–1055.
28. de Gregorio C, Laterra G, Vaccaro V, Bitto R, Dattilo G. Time-based clinical and functional achievements in real-life HF patients on ARNI treatment. *Eur J Intern Med* 2020; **76**: 115–117.
29. Fu M, Vedin O, Svennblad B, Lampa E, Johansson D, Dahlström U, Lindmark K, Vasko P, Lundberg A, Costa-Scharplatz M, Lund LH. Implementation of sacubitril/valsartan in Sweden: clinical characteristics, titration patterns, and determinants. *ESC Heart Fail.* 2020; **7**: 3633–3643.
30. Ganesananthan S, Shah N, Shah P, Elsayed H, Phillips J, Parkes A, Morgan A, Yousef Z. Real-world treatment switching to sacubitril/valsartan in patients with heart failure with reduced ejection fraction: A cohort study. *Open Heart.* 2020; **7**: e001305. https://doi.org/10.1136/openhrt-2020-001305

31. Mapelli M, Salvioni E, de Martino F, Mattavelli I, Bonomi A, Sassi V, Gugliandolo P, Vignati C, Magini A, Rovai S, Paolillo S, Agostoni P. Sacubitril/valsartan use in a real-world population of patients with heart failure and reduced ejection fraction. *J Cardiovasc Med (Hagerstown)* 2020; **21**: 882–888.
32. Sangaralingham LR, Sangaralingham SJ, Shah ND, Yao X, Dunlay SM. Adoption of Sacubitril/Valsartan for the management of patients with heart failure. *Circ Heart Fail* 2018; **11**: e004302.
33. Albert NM, Swindle JP, Buysman EK, Chang C. Lower hospitalization and healthcare costs with Sacubitril/Valsartan versus angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker in a retrospective analysis of patients with heart failure. *J Am Heart Assoc* 2019; **8**: e011089.
34. DeVore AD, Mi X, Thomas L, Sharma PP, Albert NM, Butler J, Hernandez AF, Herbert Patterson J, 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.
35. Balmforth C, Simpson J, Shen L, Jhund PS, Lefkowitz M, Rizkala AR, Rouleau JL, Shi V, Solomon SD, Swedberg K, Zile MR, Packer M, McMurray JJV. Outcomes and of treatment according to etiology in HFrEF: an analysis of PARADIGM-HF. *JACC Heart Fail* 2019; **7**: 457–465.
36. Kennedy C, Smith A, Doran S, Barry M. Sacubitril/valsartan (Entresto) utilisation and prescribing patterns in the context of a reimbursement application system. *Br J Clin Pharmacol* 2021; **87**: 406–413.
37. Dashwood A, Vale C, Laher S, Chui F, Rheault H, Gan J, Wong YW. Impact of Patient and Model of Care Factors on Titration and Tolerability of Sacubitril/Valsartan: An Early Australian Real-World Experience. *Heart Lung Circ* 2020; **29**: 1688–1695.
38. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau J, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Committees and Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail* 2013; **15**: 1062–1073.
39. Savarese G, Carrero JJ, Pitt B, Anker SD, Rosano GMC, Dahlström U, Lund LH. Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2018; **20**: 1326–1334.
40. Desai AS, Vardeny O, Claggett B, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Zile MR, Lefkowitz M, Shi V, Solomon SD. Reduced risk of hyperkalemia during treatment of heart failure with mineralocorticoid receptor antagonists by use of Sacubitril/Valsartan compared with enalapril: a secondary analysis of the PARADIGM-HF Trial. *JAMA Cardiol* 2017; **2**: 79–85.
41. Wachter R, Klebs S, Balas B, Kap E, Engelhard J, Schlienger R, Bruce Wirta S, Fonseca AF. Heart failure signs and symptoms, hospital referrals, and prescription patterns in patients receiving sacubitril/valsartan in primary care and cardiologist settings in Germany. *ESC Heart Fail* 2020; **7**: 2318–2330.
42. Haddad H, Bergeron S, Ignaszewski A, Searles G, Rochdi D, Dhage P, Bastien N. Canadian real-world experience of using Sacubitril/Valsartan in patients with heart failure with reduced ejection fraction: insight from the PARASAIL study. *CJC Open* 2020; **2**: 344–353.
43. Rossignol P, Lainscak M, Crespo-Leiro MG, Laroche C, Piepoli MF, Filippatos G, Rosano GMC, Savarese G, Anker SD, Seferovic PM, Ruschitzka F, Coats AJS, Mebazaa A, McDonagh T, Sahuquillo A, Penco M, Maggioni AP, Lund LH, Heart Failure Long-Term Registry Investigators Group. Unravelling the interplay between hyperkalaemia, renin-angiotensin-aldosterone inhibitor use and clinical outcomes. Data from 9222 chronic heart failure patients of the ESC-HFA-EORP Heart Failure Long-Term Registry. *Eur J Heart Fail* 2020; **22**: 1378–1389.
44. Pathadka S, Yan VKC, Li X, Tse G, Wan EYF, Lau H, Lau WCY, Siu DCW, Chan EW, Wong ICK. Hospitalization and Mortality in Patients With Heart Failure Treated With Sacubitril/Valsartan vs. nalapril: A Real-World, Population-Based Study. *Front Cardiovasc Med.* 2021; **7**:602363. https://doi.org/10.3389/fcvm.2020.602363.eCollection 2020.
45. Vardeny O, Claggett B, Packer M, Zile MR, Rouleau J, Swedberg K, Teerlink JR, Desai AS, Lefkowitz M, Shi V, McMurray JJ, Solomon SD, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Investigators. 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**: 1228–1234.