ORIGINAL ARTICLE

Outcomes with sacubitril/valsartan in outpatients with heart failure and reduced ejection fraction: The ARIADNE registry

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Abstract

Aims   ARIADNE aimed to assess the association between effects of sacubitril/valsartan and no sacubitril/valsartan treatment and clinical characteristics, functional capacity, and clinical outcomes (cause-specific mortality and hospitalizations) in outpatients with heart failure (HF) with reduced ejection fraction (HFrEF).

Methods   ARIADNE was a prospective European registry of 9069 patients with HFrEF treated by office-based cardiologists or selected primary care physicians. Of the 8787 eligible for analysis, 4173 patients were on conventional HF treatment (non-S/V group), whereas 4614 patients were either on sacubitril/valsartan treatment at enrolment or started sacubitril/valsartan within 1 month of enrolment (S/V group). We also generated a restricted analysis set (rS/V) including only those 2108 patients who started sacubitril/valsartan treatment within the month prior to or after enrolment.

Results   At the baseline, average age of patients enrolled in the study was 68 years, and 23.9% (2099/8787) were female. At the baseline, the proportions of patients with New York Heart Association (NYHA) Class III symptoms were 30.9 (1288/4173), 42.8 (1974/4614), and 48.2% (1015/2108), in non-S/V, S/V, and rS/V groups, respectively. After 12 months of treatment, the proportion of patients with NYHA Class III at baseline who improved to Class II was 32.0% (290/907) in the non-S/V group vs. 46.3% (648/1399) in S/V group and 48.7% (349/717) in rS/V group. The overall mortality rate was 5.0 per 100 patient-years. Rates of HF hospitalizations were high (20.9, 20.3, and 21.2 per 100 patient-years in the non-S/V, S/V, and rS/V groups, respectively). Emergency room visits without hospitalization occurred in 3.9, 3.2, and 3.9% of patients in the non-S/V, S/V, and rS/V groups, respectively.

Conclusions   This large HFrEF European registry provides a contemporary outcome profile of outpatients with HFrEF treated with or without sacubitril/valsartan. In a real-world setting, sacubitril/valsartan was associated with an improvement of symptoms in patients with HFrEF compared with the conventional HFrEF treatment.

Introduction

Heart failure (HF) appears to affect 1–2% of adults in Europe, with an incidence of about 5/1000 person-years in adults. The prognosis of HF is poor and reduces quality of life.[1] HF is responsible for over 1 million hospitalizations each year, imposing a heavy burden on the healthcare system.[2]

Based on the findings from the PARADIGM-HF trial, the 2021 European Society of Cardiology (ESC) HF guidelines recommend that an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blockers (ARB) is replaced by sacubitril/valsartan in ambulatory patients with heart failure with reduced ejection fraction (HFrEF) to improve symptoms, reduce the risk of HF hospitalization, and increase survival. Initiation of sacubitril/valsartan may be considered in patients with HFrEF who are ACEI/ARB naïve (*de novo* use).[1,3] Differences in healthcare systems and clinical practices may lead to variations in the use of sacubitril/valsartan across Europe.[4,5] Contemporary data on the use of sacubitril/valsartan in a real-life setting in Europe were limited shortly after approval.

The Assessment of Real lIfe cAre–Describing EuropeaN hEart failure management (ARIADNE) registry was designed to gather real-world data on the use and tolerability of sacubitril/valsartan for the treatment of patients with HFrEF in outpatient settings across Europe.[4]

The baseline characteristics of patients enrolled in ARIADNE have been reported recently.[6] Here, we describe the events (mortality, causes of death, and hospitalizations), and New York Heart Association (NYHA) functional class status during the first year of follow-up.

Methods

Study design and participants

The study design of the ARIADNE registry has been published.[4] Briefly, ARIADNE (EUPAS 13835) was a non-interventional and longitudinal registry of patients with chronic HFrEF treated by office-based cardiologists or selected primary care physicians (recognized as HF specialists). Patients were evaluated at baseline and then at 6 and 12 months. Between July 2016 and July 2019, data were collected from 687 study centres across 17 European countries, with 674 investigators participating in the study. Consecutive HF outpatients (aged ≥18 years) were included prospectively, irrespective of any changes in their treatment. Patients with concomitant or planned participation in any interventional clinical trial and those who were receiving ongoing treatment with sacubitril/valsartan initiated before market launch in their respective countries were excluded. Choice of therapy

was at the investigators' discretion. All data were captured prospectively. For some variables, retrospective data were obtained from the patients' medical records (such as medical history). Data were recorded by the physicians in electronic case report forms.

The registry was conducted in accordance with the Declaration of Helsinki tenets and with institutional review board/ethics committee approval at all sites. All patients provided written informed consent.[6]

Study assessments

This was a non-interventional study, and, to avoid interference with routine clinical care, no visit schedule was imposed on the participants. However, based on clinical experience, it seemed reasonable to assume that patients would visit physicians at least twice a year.

All patients were followed up for 12 months for the clinical outcomes of death or hospitalization, including emergency room visits. Additionally, NYHA status and left ventricular ejection fraction (LVEF) were assessed throughout the observation period. Clinical events such as myocardial infarction (MI), stroke, and cardiovascular (CV) and non-CV death were assessed. Investigators were asked to report all elective and non-elective hospitalizations (defined as at least one overnight stay) during study follow-up and to assign the primary reason for each hospitalization (HF, CV, or non-CV related). Additionally, emergency room or outpatient office visits were assessed.

Statistical analyses

All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA), with the main analysis set comprising all patients who fulfilled the minimal inclusion criteria, such as meeting the core baseline characteristics and providing informed consent before baseline. Patients were stratified according to their HF treatment as follows: (i) patients receiving conventional HF treatment without sacubitril/valsartan (including an ACEI/ARB; non-S/V group); (ii) patients receiving sacubitril/valsartan at enrolment, regardless of the timing of initiation of sacubitril/valsartan prior to enrolment into ARIADNE, or those who started sacubitril/valsartan within 1 month of enrolment (S/V group); and (iii) in order to assess the clinical outcomes that might be more closely related to the initiation and treatment effect of sacubitril/valsartan, a restricted analysis set was generated from the S/V group (rS/V) that included only those patients who started sacubitril/valsartan treatment within 1 month, prior to or after enrolment.

Continuous variables are reported as means and standard deviations (SDs). Categorical variables are presented as

means of frequency distribution or percentages. Baseline characteristics were compared using Student's *t*-test for continuous variables and the chi-squared test for categorical variables. The calculation of percentages was based on the observed data per variable, excluding patients with missing values. The frequency of clinical events was calculated by the incidence density rates per 100 patient-years.

Results

Patients

Of the total 9069 patients who were eligible for inclusion in the registry, 8787 patients were included in the present main analysis, and 282 (3.1%) patients were excluded for not meeting the minimum criteria for analysis.[6]

In total, 4614 (52.5%) patients were taking sacubitril/valsartan regardless of the timing of initiation prior to enrolment (S/V group). Of these, 2108 patients started sacubitril/valsartan within ±1 month of enrolment (rS/V group). Patients who continued on their previous individualized HF medication were included in the non-S/V group [4173 (47.5%)]. A total of 7596 (86.4%) [S/V group, 3999 (86.7%) and non-S/V group, 3597 (86.2%)] and 6338 (72.1%) [S/V group, 3346 (72.5%) and non-S/V group, 2992 (71.7%)] patients completed 6 months and 1 year of follow-up, respectively, with a median follow-up of 353 (1–631) days, of whom >90% had follow-up data on signs and symptoms (NYHA class), hospitalizations or emergency room visits, and healthcare resource utilization available. The most frequent reasons for non-completion of the study were patients not attending their routine visit or withdrawal of consent or lack of re-consent on the protocol amendment (*Figure S1*). There were 382 reported deaths during the year, leading to an incidence rate of 5.0 per 100 patient-years.

The baseline characteristics of the study population, including medications used at baseline, have been described previously.[6] Mean age was 68.1 (SD: 11.5) years, and 23.9% were female. The most frequent co-morbidities were arterial hypertension, coronary heart disease, and dyslipidaemia. The proportion of patients with any hospitalization within the last 12 months prior to enrolment was 44.0% in the S/V group, 42.1% in the rS/V group, and 39.3% in the non-S/V group, of which 73.3% were HF-related hospitalizations in the S/V group, 71.2% in the rS/V group, and 69.6% in the non-S/V group. At baseline, 84% of patients in the non-S/V group were on an ACEI/ARB. Overall, 79% of all patients were on β-blockers, and 54% were on mineralocorticoid receptor antagonists (*Table 1*). Around 8.0% of patients received ivabradine, and 7.5% of patients received digitalis. Logistic regression analysis showed that patients receiving sacubitril/valsartan tended to be younger (*P* ≤ 0.01), tended

to have a lower LVEF (*P* ≤ 0.0001), and were more likely to have NYHA Class III/IV symptoms (*P* ≤ 0.0001) compared with patients in the non-S/V group.[6]

Treatment response

Throughout the study, concomitant HF medication remained largely stable, with no major changes in the drug classes. *Table S1* shows the pharmacological treatments at follow-up. After 12 months, the proportion of patients with NYHA Class III or IV symptoms decreased from 32.1 to 25.2% in the non-S/V group, from 44.6 to 24.0% in the S/V group, and from 50.3 to 25.8% in the rS/V group (*Figure 1*). Baseline NYHA classification in the total patient population vs. classification in those patients with baseline and 1-year follow-up only were similar for each NYHA class, showing that patients with missing NYHA evaluation after 12 months were evenly distributed among NYHA classes (*Figures 1* and *S2*). In patients with NYHA classification available at baseline and 1-year follow-up, the proportion of patients with reported NYHA Class III at baseline who improved to Class II was 32.0% (290/907) in the non-S/V group vs. 46.3% (648/1399) in the S/V group and 48.7% (349/717) in the rS/V group, whereas the proportion of patients with reported NYHA Class II at baseline who improved to Class I was 12.4% (248/2007) in the non-S/V group vs. 20.0% (365/1829) in the S/V group and 22.6% (159/705) in the rS/V group (*Figure S2*).

Clinical events and incidence of non-elective hospitalizations and emergency room visits

The incidence of stroke was 0.50, 0.58, and 0.59 and of MI was 0.38, 0.64, and 0.71 per 100 patient-years in non-S/V, S/V, and rS/V groups, respectively (*Table 2*). The rates of reported cause-specific mortality are shown in *Figure 2*. In the overall cohort, hospitalization due to any reason was 17% between baseline and 6 months and 15% between 6 and 12 months. Of these, 46.8 and 42.2% were HF-related hospitalizations, respectively. The numbers of non-elective HF-related hospitalizations at various visits are given in *Table S2*.

The incidence rates of non-elective hospitalizations (in patients with at least one follow-up visit) and emergency room visits per 100 patient-years are shown in *Figure 3*. Mortality was lower in the S/V group compared with that in non-S/V groups [174 (4.4%) vs. 208 (5.8%)].

Discussion

The prospective ARIADNE registry is the largest study to provide a comprehensive picture of HF treatment practices in European outpatients and shows the way in which

Table 1 Demographics and baseline characteristics

Variables	Non-S/V group N = 4173	S/V group N = 4614	rS/V group (subset of S/V)[a] N = 2108
Age (years), mean ± SD	68.9 ± 11.3	67.3 ± 11.5***	68.0 ± 11.2**
<65 years, n (%)	1362 (32.6)	1794 (38.9)***	774 (36.7)**
≥65 years, n (%)	2811 (67.4)	2820 (61.1)***	1334 (63.3)**
Female, n (%)	1011 (24.2)	1088 (23.6)	526 (25.0)
BMI (kg/m², mean ± SD (n)	28.7 ± 5.3 (3909)	29.2 ± 5.5 (4282)***	29.2 ± 5.5 (1966)**
Smoking history, n (%)			
Never smoked	1435 (34.4)	1596 (34.6)**	737 (35.0)*
Current smoker	540 (12.9)	495 (10.7)**	219 (10.4)*
Former smoker	1496 (35.9)	1762 (38.2)**	780 (37.1)*
Unknown	700 (16.8)	755 (16.4)**	368 (17.5)*
NYHA class, n (%)***			
I	4 (0.1)	1 (0.0)[b]	0 (0.0)[b]
II	2831 (67.8)	2555 (55.4)[b]	1047 (49.7)[b]
III	1288 (30.9)	1974 (42.8)[b]	1015 (48.2)[b]
IV	50 (1.2)	81 (1.8)[b]	45 (2.1)[b]
LVEF, mean ± SD (n)***	35.4 ± 8.4 (4011)	32.7 ± 8.1 (4469)	32.3 ± 8.0 (2050)
Heart rate (bpm), mean ± SD (n)	71.6 ± 12.3 (4057)	71.5 ± 11.8 (4400)	72.3 ± 12.3 (2027)*
Blood pressure (mmHg), mean ± SD (n)			
Systolic blood pressure	127.0 ± 18.0 (4090)	123.2 ± 17.7 (4451)***	125.5 ± 17.7 (2053)**
Diastolic blood pressure	75.6 ± 10.6 (4090)	74.2 ± 10.6 (4449)***	75.4 ± 10.8 (2051)
NT-proBNP (pg/mL), median (25th–75th) (n)	998.0 (368.0–2558.0) (1025)	1133.5 (433.0–2528.0) (1370)	1354.0 (561.0–3022.0) (553)
<500 pg/mL, n (%)	332 (32.4)	385 (28.1)	118 (21.3)***
≥500 to <2000 pg/mL, n (%)	381 (37.2)	545 (39.8)	232 (42.0)***
≥2000 pg/mL, n (%)	312 (30.4)	440 (32.1)	203 (36.7)***
Co-morbidities, n (%)			
Coronary heart disease	2639 (63.5)	2798 (61.0)	1307 (62.4)
Atrial fibrillation	1626 (39.2)	1887 (41.0)	856 (40.8)
Chronic kidney disease	1054 (25.6)	1189 (26.0)	503 (24.1)
Diabetes mellitus Type 2	1374 (33.2)	1580 (34.3)	684 (32.5)
HF therapy, n (%)[c]			
ACEi	2362 (57.3)	19 (0.5)[d]	14 (0.7)[d]
ARB	1107 (26.9)	13 (0.3)[d]	8 (0.4)[d]
ARNI (sacubitril/valsartan)	0 (0)	4147 (100)	1872 (100)
β-Blocker	3352 (81.4)	3202 (77.2)	1458 (77.9)
MRA	2124 (51.6)	2319 (55.9)	1034 (55.2)
Loop diuretic	2411 (58.5)	2461 (59.3)	1117 (59.7)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; bpm, beats per minute; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; non-S/V group, conventional HF treatment without sacubitril/valsartan group; rS/V, restricted sacubitril/valsartan group; SD, standard deviation; S/V, sacubitril/valsartan group. Data are presented as n (%) and mean ± SD (n).
[a]For the comparison of patient profiles at sacubitril/valsartan initiation, the S/V group was restricted to patients who started sacubitril/valsartan ±1 month around baseline, and thus, a direct comparison between these two groups should be avoided.
[b]N = 4611 for the S/V group and N = 2107 for the rS/V group.
[c]N = 4120 for the non-S/V group, N = 4147 for the S/V group, and N = 1872 for the rS/V group.
[d]Values are presented as documented. For a low number of patients, concomitant use of either ACEI or ARB with sacubitril/valsartan was documented, although sacubitril/valsartan should not be co-administered with an ACEI or ARB as per the approved label; due to the potential risk of angioedema when used concomitantly with an ACEI, a wash-out period is mandatory.
*P ≤ 0.05.
**P ≤ 0.01.
***P ≤ 0.0001.

sacubitril/valsartan was introduced by office-based cardiologists and specialized primary care physicians in the real-world setting. Although this was an observational study, substantial data were available for most patients at the 12-month follow-up, especially with regard to clinical events, symptom improvement, and echocardiography, thus providing a unique insight into real-world HF treatment by HF specialists across Europe. Additionally, this study, which was initiated shortly after market approval of sacubitril/valsartan,

offers the first insights into the initial phase of introducing sacubitril/valsartan in several European countries. ARIADNE was the first observational registry to gather additional data on factors associated with physicians' decisions to introduce sacubitril/valsartan in real-life clinical practice.

The overall baseline characteristics of patients in the pivotal PARADIGM-HF study and ARIADNE were similar.[3] Nonetheless, we found that sacubitril/valsartan tended to be prescribed to younger patients with more severe HF in

Figure 1 Distribution of NYHA class at each visit. *Total patients includes all patients with NYHA classifications available at the respective visit.
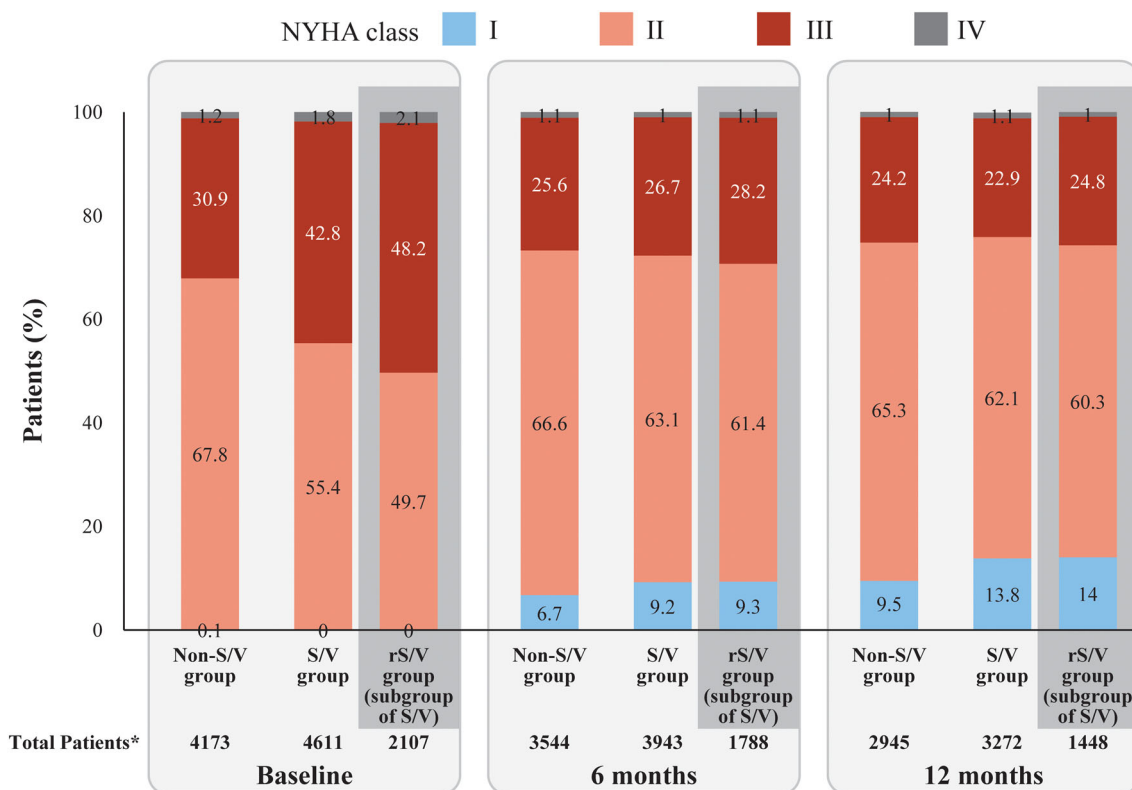
Table 2 Incidence rates of clinical events per 100 patient-years[a]

	Non-S/V group	S/V group	rS/V group (subset of S/V)[b]
Myocardial infarction	0.38	0.64	0.71
Stroke	0.50	0.58	0.59

HF, heart failure; non-S/V group, conventional HF treatment without sacubitril/valsartan group; rS/V group, restricted sacubitril/valsartan group; S/V group, sacubitril/valsartan group.
[a]Overall, 7877 main analysis set patients and 5608 restricted main analysis set patients had at least one follow-up visit, and if no event date was available, it was assumed that it occurred between two visits.
[b]For the comparison of patient profiles at sacubitril/valsartan initiation, the S/V group was restricted to patients who started sacubitril/valsartan ±1 month around baseline, and thus, a direct comparison between these two groups should be avoided.

ARIADNE than those included in PARADIGM-HF, as shown by lower LVEF and higher NYHA class and N-terminal pro B-type natriuretic peptide levels.[6] Some important findings in this real-world setting should be acknowledged. First, the reported mortality rate in patients with HFrEF was 5.3 per 100 patient-years, in a context in which 41.8% of patients had been hospitalized during the year prior to enrolment. In most studies, patients with HFrEF tended to have a higher risk of CV death and HF hospitalization than those with HF

and preserved ejection fraction.[7,8] Therefore, it seems reasonable that patients with HFrEF should be carefully evaluated to stratify prognosis and to identify those at higher risk who require close follow-up and frequent drug and dose optimization. However, in ARIADNE, the all-cause mortality rate was only 5.0 events per 100 patient-years, which is remarkably low compared with other real-world studies.[2,9,10] In an analysis of SwedeHF, which included 21 888 Swedish inpatients and outpatients registered between 2006 and 2013 in hospitals or outpatient clinics, there were 13.0 deaths per 100 patient-years over a follow-up period of 874 days.[11] In a prospective, multicentre, longitudinal study of patients with HF recruited between 2010 and 2014 in New Zealand and Singapore, the all-cause mortality rate in patients with HFrEF was 10.9 (95% confidence interval [CI]: 96–124) per 100 patient-years.[7] Data from ARIADNE hint at an overall improvement in HF management with a positive impact on patients' survival; however, the findings should be interpreted with caution because this was a real-world study, and as with other real-world studies, follow-up data on survival status were not confirmed for patients who did not complete a 12-month follow-up visit.

In ARIADNE, clinical events of stroke and MI occurred in low absolute numbers within 12 months with a higher incidence rate in the S/V group. This might be associated with

Figure 2 Cause of death during the first year of follow-up. Data are presented as *n* (%). Note: 382 deaths reported during the first year of follow-up.
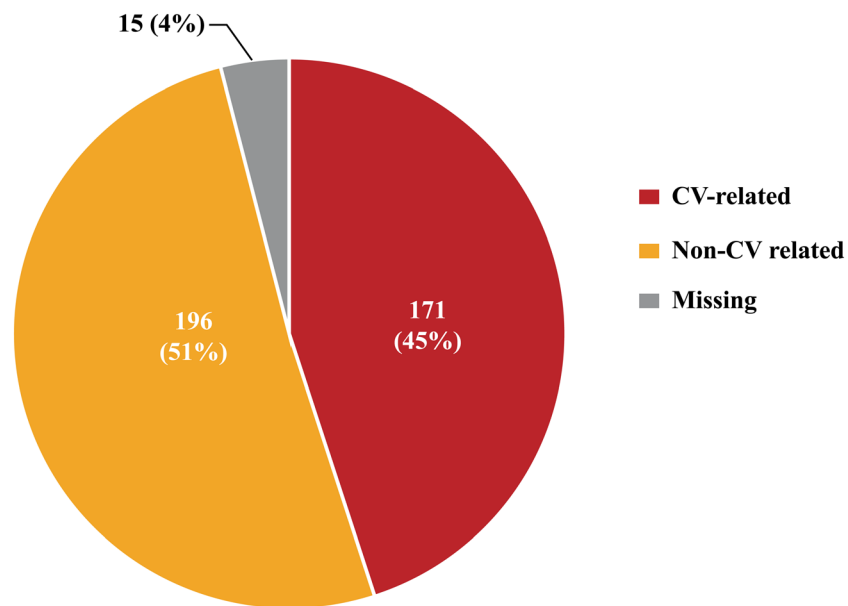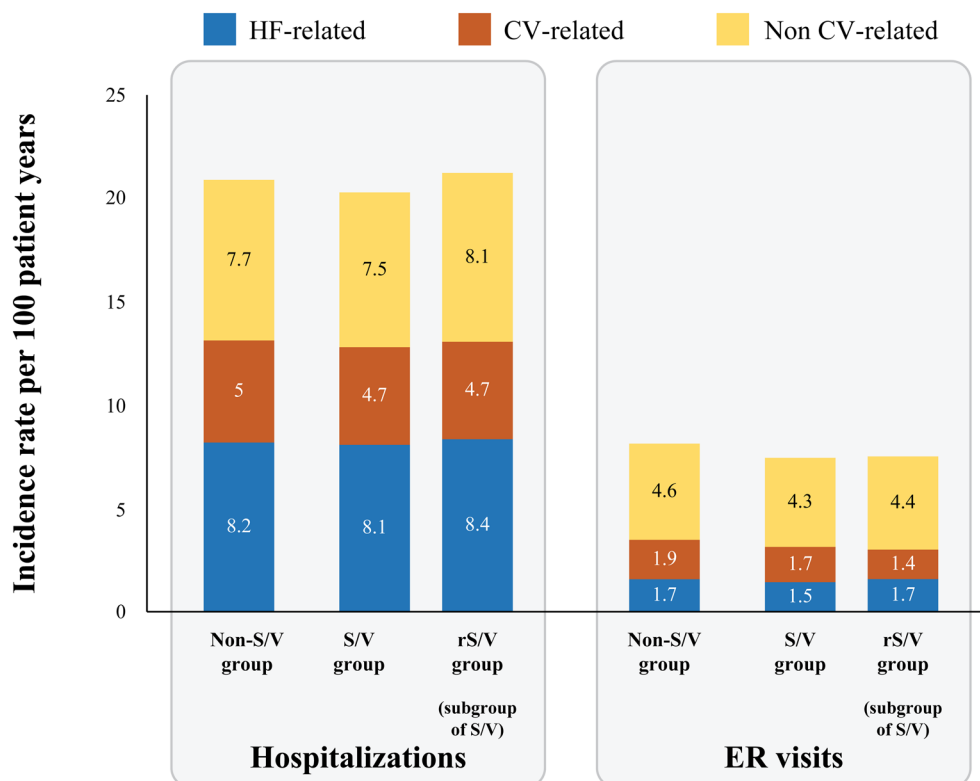

Figure 3 Incidence of non-elective hospitalizations and emergency room visits. Patients with at least one follow-up visit are included. ER, emergency room.

the characteristics of patients enrolled into the S/V group, which had more severe, more progressed HF, as shown earlier, thus were probably more likely to experience adverse clinical outcomes. In ARIADNE, CV events were responsible for almost half of the deaths, whereas in other real-world studies, two-thirds of the deaths were due to CV events in the overall cohorts (*Table 3*). Furthermore, the mortality rate from CV causes in clinical trials (~80%) may be higher than that in real-world studies due to the adjudication of all events to identify the cause of death in the clinical trial setting.[12] Indeed, the rates of CV deaths were reported to be 65.3% in the Italian Network on Heart Failure study[13] in 3755 outpatients with chronic HF compared with 54% in a multinational prospective study of Asian patients with HF (ASIAN-HF).[14]

ARIADNE reported a 20.9% hospitalization rate with most being related to HF. Other HF registries have shown a comparable incidence of HF hospitalizations. Notably, the HF-related hospitalization rate was 14.6% in the ESC-HF Long-Term registry[15] in outpatients with chronic HF (*N* = 9134), compared with 8.8% in the Italian Network on Heart Failure.[13] Over the course of the ARIADNE study, a large proportion of hospital admissions were not HF related. The rates of hospitalization due to non-CV-related reasons underscore the importance of non-cardiac co-morbidities in the general process of decompensation. Overall, a trend towards lower mortality together with an incidence of hospitalizations and emergency room visits in the ARIADNE registry, comparable with other HF registries,[13,16] indicates that despite HF becoming a condition that can be managed

and that patients can live with, rather than die from, there is still a considerable risk of clinical events in patients with HFrEF.

Although several observational HF registries are available (*Table 3*), data are lacking with regard to the real-world impact of sacubitril/valsartan on HF symptoms and clinical outcomes. We found that sacubitril/valsartan tended to be prescribed to patients with more severe symptoms with a higher NYHA class.[6] After 12 months' follow-up, HF symptoms improved in many patients. However, more than one-quarter of the patients still had NYHA Class III/IV symptoms after 12 months' follow-up, whereas, interestingly, concomitant HF medication remained largely stable during that time. A higher proportion of patients with NYHA Class II, III, or IV symptoms who were treated with sacubitril/valsartan reported improvements in NYHA class compared with those receiving conventional therapy. These results are in line with a recent observational study in 90 outpatients with HFrEF, among whom sacubitril/valsartan treatment was associated with an increase in LVEF (31.0% [interquartile range (IQR): 27.2–37.0] to 34.0% [IQR: 29.2–39.7]; *P* = 0.001) and NYHA class (NYHA II: from 52.2 to 78.2%; NYHA III: from 47.8 to 12.6%) at 6 months' follow-up.[17] However, despite the observed functional improvement in the ARIADNE study, hospitalization rates after 12 months of treatment were similar between the groups. With patients who received sacubitril/valsartan showing slightly higher hospitalization rates prior to enrolment, similar hospitalization rates could partly reflect an improvement in these patients.

Table 3 Comparison of ARIADNE with other outpatient registries

Registries	ARIADNE	ESC-HF Long-Term Registry (15)	Italian Network on Heart Failure (13)	ASIAN-HF (14)	CHAMP-HF (16)
Region/countries	Europe[a]	Europe[b]	Italy	Asia Pacific[c]	USA
Condition	HFrEF	HF	Chronic HF	HF	HFrEF
n	8787	9134	3755	6480	3518
Enrolment	Outpatients	Outpatients and inpatients	Outpatients	Outpatients and inpatients	Outpatients
Setting	Office-based cardiologists or selected primary care physicians (recognized as HF specialists)	Clinics and hospitals	Cardiology centres	Clinics and hospitals	Primary care and cardiology practices
Timeframe	2016–2019	2011–2015	2007–2009	2012–2015	2015–2017
Data collection	Both retrospective and prospective	Prospective	Prospective	Prospective	Prospective
All-cause mortality outcome (%)	5.0 per 100 patient-years	8.8	5.9	9.6	Data awaited
CV related	45	53.5	65.3	54	-
All-cause hospitalization (%)	20.9	28.1	22.7	-	-
HF related	42.2	14.6	8.8	-	-

ASIAN-HF, Asian Sudden Cardiac Death in Heart Failure; CHAMP-HF, Change the Management of Patients with Heart Failure; CV, cardiovascular; ESC-HF, European Society of Cardiology-Heart Failure; HF, heart failure; HFrEF, heart failure with reduced ejection fraction.
[a]Austria, Belgium, Bulgaria, Czech Republic, France, Germany, Greece, Ireland, Israel, Italy, Malta, Norway, Russia, Slovakia, Spain, Switzerland, and UK.
[b]Austria, Bosnia Herzegovina, Bulgaria, Czech Republic, Egypt, France, Greece, Hungary, Israel, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, and Turkey.
[c]China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand.

Furthermore, data from ARIADNE also support the findings from PARADIGM-HF (*N* = 8399)[18] and other real-world studies showing improvements in NYHA class and LVEF.[17,19–21]

Limitations

ARIADNE was an observational study in which the patients were recruited, and treatments were prescribed according to the decisions of the attending physician. The lack of blindness could, of course, have influenced subjective evaluation of symptoms. Being observational, the diagnosis of HF was made by the investigators according to their clinical judgement and was not validated centrally, including the LVEF assessments. Whereas LVEF data were available for almost all the patients at baseline (including echocardiography examinations up to 12 months prior), follow-up data were available for approximately 40% of the patients. The nature of this study was primarily descriptive, and no formal comparisons were made between treatment arms. Several variables, such as renal function and other laboratory variables, were collected only if available as a part of routine care and were therefore not always recorded. That almost half the patients from the overall ARIADNE cohort were from Germany could have affected the results. Other limitations include patient dropouts from the observational study for various reasons, including patients not attending routine visits and worsening of patients' health status. Thus, the available data (including symptoms and diagnostic examination) are potentially biased. In addition, follow-up data on mortality were not available for all patients. The results must be interpreted with caution.

The greater symptomatic benefit of sacubitril/valsartan over conventional therapy might be because those who did not complete 1-year follow-up may have had more advanced disease, thus not allowing for an unbiased comparison between the groups. However, there was a trend towards NYHA improvement among patients for whom data for all the visits were available.

Finally, participation in the study was limited to HF specialists; therefore, the population of patients is not fully representative of all patients with HF, of which a part of them are followed by other healthcare professionals, such as geriatricians, general practitioners, and internal medicine doctors.

Conclusions

ARIADNE showed a lower mortality and a slightly higher incidence of hospitalizations than that reported in other HF registries,[2,9,10] indicating progression of HF despite treatment by HF specialists. In a real-world setting, sacubitril/valsartan was associated with an improvement of symptoms in patients with HFrEF compared with the conventional HFrEF treatment.

Conflict of interest

APM reports personal fees from Novartis during the conduct of the study and personal fees from Bayer, personal fees from AstraZeneca, and personal fees from Fresenius, outside the submitted work. ALC reports personal fees and non-financial support from Novartis during the conduct of the study. VB declares grants and personal fees from Novartis during the conduct of the study and personal fees from Astra Zeneca and Boehringer Ingelheim-Lilly Alliance. TD reports grants and personal fees from Pfizer, grants and personal fees from Novartis, grants and personal fees from Bayer, and personal fees from Astra Zeneca, outside the submitted work. JD has nothing to disclose. CF reports personal fees from Novartis during the conduct of the study personal fees from Servier, personal fees and other from AstraZeneca, personal fees and other from Bayer, personal fees and other from Vifor Pharma, personal fees and other from Novartis, and other from Boehringer, outside the submitted work. LHL reports grants and personal fees from Novartis, during the conduct of the study; personal fees from Merck, personal fees from Sanofi, grants and personal fees from Vifor-Fresenius, grants and personal fees from AstraZeneca, grants and personal fees from Relypsa, personal fees from Bayer, grants from Boston Scientific, personal fees from Pharmacosmos, personal fees from Abbott, grants and personal fees from Mundipharma, personal fees from Medscape, personal fees from Myokardia, and grants and personal fees from Boehringer Ingelheim, outside the submitted work. SK is an employee of GKM (clinical research organization) contracted for data analysis by Novartis and received fees from Novartis during the conduct of the study. PCF and CK are employees of Novartis. RIH was an employee of Novartis when the study was conducted. UZ reports grants and personal fees from Novartis during the conduct of the study and grants and personal fees from Astra Zeneca, personal fees from Boehringer Ingelheim, grants and personal fees from BMS, personal fees from MSD, personal fees from Sanofi, grants and personal fees from Pfizer, personal fees from Trommsdorf, personal fees from Amgen, and grants and personal fees from Bayer, outside the submitted work.

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Supporting information

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

Figure S1. Study completion[a].
Figure S2. NYHA class improvement during the study in patients with NYHA class assessment at baseline and at the 12-month follow-up visit[a].
Table S1. Pharmacological treatments at follow-up.
Table S2. Number of non-elective HF-related hospitalisations[a].

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J 2021*; **42**: 3599–3726.

2. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlström U, Merkely B, Drozdz J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavoliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, Mebazaa A, on behalf of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail 2016*; **18**: 613–625.

3. 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.

4. Zeymer U, Clark AL, Barrios V, Damy T, Drożdż J, Fonseca C, Lund LH, di Comite G, Hupfer S, Maggioni AP. Management of heart failure with reduced ejection fraction in Europe: Design of the ARIADNE registry. *ESC Heart Fail 2020*; **7**: 727–736.

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

6. Zeymer U, Clark AL, Barrios V, Damy T, Drożdż J, Fonseca C, Lund LH, Kalus S, Ferber PC, Hussain RI, Koch C, Maggioni AP. Utilisation of sacubitril/valsartan in patients with heart failure with reduced ejection fraction: Real world data from the ARIADNE registry. *Eur Heart J Qual Care Clin Outcomes 2021*; **8**: 469–477.

7. Lam CSP, Gamble GD, Ling LH, Sim D, Leong KTG, Yeo PSD, Ong HY, Jaufeerally F, Ng TP, Cameron VA, Poppe K, Lund M, Devlin G, Troughton R, Richards AM, Doughty RN. Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. *Eur Heart J 2018*; **39**: 1770–1780.

8. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: An individual patient data meta-analysis. *Eur Heart J 2012*; **33**: 1750–1757.

9. Kalogeropoulos AP, Fonarow GC, Georgiopoulou V, Burkman G, Siwamogsatham S, Patel A, Li S, Papadimitriou L, Butler J. Characteristics and outcomes of adult outpatients with heart failure and improved or recovered ejection fraction. *JAMA Cardiol 2016*; **1**: 510–518.

10. Komajda M, Schöpe J, Wagenpfeil S, Tavazzi L, Böhm M, Ponikowski P, Anker SD, Filippatos GS, Cowie MR, QUALIFY Investigators. Physicians' guideline adherence is associated with long-term heart failure mortality in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. *Eur J Heart Fail 2019*; **21**: 921–929.

11. Lund LH, Carrero JJ, Farahmand B, Henriksson KM, Jonsson Å, Jernberg T, Dahlström U. Association between enrolment in a heart failure quality registry and subsequent mortality-A nationwide cohort study. *Eur J Heart Fail 2017*; **19**: 1107–1116.

12. Desai AS, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Chen F, Gong J, Rizkala AR, Brahimi A, Claggett B, Finn PV, Hartley LH, Liu J, Lefkowitz M, Shi V, Zile MR, Solomon SD. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. *Eur Heart J 2015*; **36**: 1990–1997.

13. Tavazzi L, Senni M, Metra M, Gorini M, Cacciatore G, Chinaglia A, di Lenarda A, Mortara A, Oliva F, Maggioni AP, on the behalf of IN-HF (Italian Network on Heart Failure) Outcome Investigators. Multicenter prospective observational study on acute and chronic heart failure: One-year follow-up results of IN-HF (Italian Network on Heart Failure) outcome registry. *Circ Heart Fail 2013*; **6**: 473–481.

14. MacDonald MR, Tay WT, Teng TK, Anand I, Ling LH, Yap J, Tromp J, Wander GS, Naik A, Ngarmukos T, Siswanto BB, Hung CL, Richards AM, Lam CSP, ASIAN-F investigators. Regional Variation of Mortality in Heart Failure With Reduced and Preserved Ejection Fraction Across Asia: Outcomes in the ASIAN-HF Registry. *J Am Heart Assoc 2020*; **9**: e012199.

15. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: An analysis of the ESC heart failure long-term registry. *Eur J Heart Fail 2017*; **19**: 1574–1585.

16. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, Hill CL, McCague K, Mi X, Patterson JH, Spertus JA, Thomas L, Williams FB, Hernandez AF, Fonarow GC. Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF registry. *J Am Coll Cardiol* 2018; **72**: 351–366.

17. Polito MV, Silverio A, Rispoli A, Vitulano G, D'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.

18. Packer M, McMurray JJ, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile M, Andersen K, Arango JL, Arnold JM, Bělohlávek J, Böhm M, Boytsov S, Burgess LJ, Cabrera W, Calvo C, Chen CH, Dukat A, Duarte YC, Erglis A, Fu M, Gomez E, Gonzàlez-Medina A, Hagège AA, Huang J, Katova T, Kiatchoosakun S, Kim KS, Kozan Ö, Llamas EB, Martinez F, Merkely B, Mendoza I, Mosterd A, Negrusz-Kawecka M, Peuhkurinen K, Ramires FJ, Refsgaard J, Rosenthal A, Senni M, Sibulo AS Jr, Silva-Cardoso J, Squire IB, Starling RC, Teerlink JR, Vanhaecke J, Vinereanu D, Wong RC, PARADIGM-HF Investigators and Coordinators. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation* 2015; **131**: 54–61.

19. Landolfo M, Piani F, Esposti DD, Cosentino E, Bacchelli S, Dormi A, Borghi C. Effects of sacubitril valsartan on clinical and echocardiographic parameters of outpatients with heart failure and reduced ejection fraction. *Int J Cardiol Heart Vasc* 2020; **31**: 100656.

20. De Vecchis R, Paccone A, Di Maio M. Sacubitril/valsartan improves left ventricular longitudinal deformation in heart failure patients with reduced ejection fraction. *Minerva Cardioangiol* 2019; **67**: 456–463.

21. Proudfoot C, Studer R, Rajput T, Jindal R, Agrawal R, Corda S, Senni M. Real-world effectiveness and safety of sacubitril/valsartan in heart failure: A systematic review. *Int J Cardiol* 2021; **331**: 164–171.