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ORIGINAL RESEARCH ARTICLE

Early experience of Sacubitril–Valsartan in heart failure with reduced ejection fraction in real-world clinical setting

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Abstract

Aims Sacubitril/Valsartan (Sac/Val) was proven more effective than enalapril for symptomatic patients with heart failure (HF) with reduced ejection fraction (HFrEF). This study aimed to investigate eligibility, titration, and tolerability for Sac/Val in a real-world clinical setting.

Methods and results This retrospective cohort study consists of two parts. In Part 1 (eligibility study), all patients discharged from Sahlgrenska University Hospital due to HF were consecutively included during 1 year. Data from the patients' medical records were collected. Patients were adjudicated to be eligible based on European Society of Cardiology (ESC) criteria for angiotensin receptor neprilysin inhibitor (ARNI) with the exception of N-terminal (NT)-proBNP levels. Patients who received $<$50% of target dose angiotensin-converting enzyme/angiotensin receptor blocker and otherwise fulfilled ESC criteria were adjudicated to be potentially eligible. In Part 2 (tolerability study), all patients receiving Sac/Val during the same period were included. Medical data regarding dose, titration, and adverse effects and events were registered. A total of 1355 patients (mean age 78 ± 13 years) were hospitalized for HF and 619 patients had an EF $\leq$40%. Twenty percent were eligible for initiation of ARNI, and additionally 8% were potentially eligible. In all 95 patients (mean age 65 ± 12 years) were initiated with Sac/Val, which correlates to 13%. The patients who were initiated were younger (65 years), more often had dilated cardiomyopathy (31%), more often were on guideline-directed medical therapy, and had a higher frequency of cardiac resynchronization therapy and implantable cardioverter–defibrillator compared with the patients who did not receive Sac/Val. Of the initiated patients, 59% reached target dose of Sac/Val, and 15% discontinued due to adverse effects. The most common cause of discontinuation was benign gastrointestinal adverse effects, followed by elevated creatinine, malaise, and vertigo. Female gender [odds ratio (OR) 3.58; 95% CI 1.07–2.00; P = 0.038] and NT-proBNP $\geq$ median level (OR 0.48; 95% CI 0.26–0.90; P = 0.021) was associated with termination of the medication.

Conclusions Among HFrEF patients in this real-world cohort, 20% were eligible for ARNI; however, only 13% received the treatment. Sac/Val was well tolerated, but 41% of the patients did not reach target dose. How this affects outcome is not known and needs further investigation.

Keywords Chronic heart failure; Eligibility; HFrEF; Pharmacological Treatment; Sacubitril–Valsartan; Tolerability

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Introduction

Heart failure (HF) is a syndrome that affects approximately 26 million patients worldwide,[1] and the prevalence is estimated to approximately 2% in the western world. [2,3] In Sweden, it is among the most common causes of hospitalization.[4] Despite guideline-directed medical therapy (GDMT) including ACE inhibitor (ACEI) or angiotensin II receptor blocker (ARB) together with beta-blocker (BB) and mineral corticoid receptor antagonist (MRA), both mortality and morbidity remain high.[3,5]

Sacubitril/Valsartan, an angiotensin receptor neprilysin inhibitor (ARNI) is a novel treatment of HF with reduced ejection fraction (HFrEF) and was shown in the PARADIGM-HF trial to be more effective than enalapril for symptomatic HFrEF patients in reducing mortality and morbidity.[6] However, the HF population in real-world differs from patients in randomized controlled trials in many aspects. The population in the PARADIGM-HF trial was younger and excluded patients who could not tolerate enalapril 20 mg daily during a run-in phase in the trial. This raised serious concern of applicability of the trial results in a real-world setting in which the main body of HF population do not tolerate target dose of GDMT.[7,8] Therefore, it remains uncertain what proportion of patients with HF that would be eligible for ARNI, and if so, how well is ARNI tolerated? In this study, we sought to assess the representativeness of the PARADIGM-HF trial in a real-world population of patients with HFrEF by investigating eligibility and tolerability of ARNI during the early implementation in Sahlgrenska University Hospital in Gothenburg, Sweden.

Methods

This retrospective cohort study was made in two parts: eligibility and tolerability study. The study complies with the Declaration of Helsinki and was approved by the Swedish ethical committee.

Eligibility study

All patients from Sahlgrenska University Hospital (Mölndal, Sahlgrenska, and Östra Hospital) who were hospitalized in any ward and discharged with the main diagnosis of HF (ICD10 I.50) were consecutively included from the 1st of November 2016 until the 31st of October 2017. The hospitals have a catchment area of approximately 800 000 people. We manually extracted data from the hospital's medical records according to a standardized protocol. Data from the time of hospitalization regarding age, gender, ejection fraction, laboratory results, blood pressure, aetiology and duration of HF, medical therapy, dosing, and device therapy were registered and then later validated by a second reviewer. Comorbidities were registered from the text of the journals.

Patients with left ventricular ejection fraction (LVEF) $\leq$40% were considered fully eligible for ARNI if they fulfilled the safety criteria of S-Potassium (s-K) $\leq$5.2 mmol/L, estimated glomerulation filtration rate (eGFR) $\geq$30 mL/h/L, and 73 m^2 and systolic blood pressure (SBP) of $\geq$100 mmHg and were treated with BB and at least 50% of target dose of ACEI/ARB. Patients were considered potentially eligible for ARNI if the ACEI/ARB dose were $<$50% of target dose. We considered all patients symptomatic because they were hospitalized due to HF. The eGFR was calculated with the chronic kidney disease epidemiology collaboration formula.[9]

Tolerability study

All patients from the eligibility study who were prescribed ARNI, either during hospitalization or during follow up at the outpatient clinic, were included. To this cohort, we added patients with HFrEF from the HF outpatient clinic who were initiated with ARNI during the same period of time. This made the cohort more numerous and also more comparable with the paradigm study in which only ambulatory patients were included. The titration of ARNI was performed in a nurse-based HF outpatient clinic. Information of titration rate, all adverse effects, hospitalizations, mortality, laboratory results, blood pressure, medication, dosage, and discontinuation were collected from the hospital's medical records during the titration period. The follow-up period regarding mortality was 12 months after initiation.

Statistical analysis

Categorical variables are presented as numbers (*n*) and percentages (%). For continuous variables mean, standard deviation, median (min; max) is presented. For comparison between the groups, Fisher's exact test was used for dichotomous variables, and the Mann–Whitney *U*-test was used for continuous variables. The impact of selected variables [age, sex, SBP, diastolic blood pressure, ischemic heart disease, N-terminal (NT)-proBNP, renal disease, number of different types of comorbidities, and the starting doses of Sac/Val registered at first up-titration] on the incidence of discontinuation of ARNI was evaluated by applying age-adjusted univariable logistic regression. Odds ratio (OR) and 95% confidence interval (CI) were presented along with area under the receiver operating characteristic curve, area under the curve for receiver operating characteristic curve, as a goodness-of-fit statistics.

All tests were two tailed and conducted at 0.05 significance level. All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Eligibility study

During 1 year, 1355 patients were hospitalized due to HF of which 603 patients had LVEF $>$40%, 619 patients had LVEF $\leq$40%, and 133 patients had missing data of LVEF. There were 64 patients with missing data of SBP (*n* = 36), eGFR (*n* = 21), or s-K (*n* = 7), leaving 555 patients included in the eligibility study. Of the patients, 62.9% were diagnosed with HF for 6 months or longer, and the most common aetiology of HF was ischemic heart disease (43%; *n* = 237). The mean age

was 74.0 ± 13.9 years, and the median age was 76.0 years (min; max 18.0; 100.0). Of the patients, 30.5% were women.

Medication with ACEI or ARB were used by 376 (67.7%) patients, and 208 (37.5%) were prescribed ≥50% of target dose of ACEI or ARB. Of the patients 88,5% (n = 491) were on treatment with BB, and 42.7% (*n* = 237) were on MRA.

In the hospital cohort, 111 patients (20%) were fully eligible for initiation of ARNI according to ESC criteria with the exception of NT-proBNP level. Additional 45 (8%) of the patients were considered potentially eligible. The main reason for not being fully eligible is insufficient basic medication, predominantly ACEI and ARB.

Tolerability study

In the tolerability part of the study, 73 patients from the hospital cohort and 22 patients from the outpatient ward, in total 95 patients, were initiated and up-titrated with ARNI (*Figure 1*). Comparison between the groups, in total 577 patients (555 from the hospital cohort and 22 from the outpatient ward), is shown in Table *1a*. The patients who were treated with ARNI were younger, with lower NT-proBNP, and more often on GDMT (100% with BB and 100% with MRA) Table *1b*. The aetiology was more often dilated cardiomyopathy in the ARNI group. Of the patients initiated on ARNI, 58.9% reached target dose after up-titration. Adverse effects of ARNI during the titration period are illustrated in Figure *2*. Of the patients, 25% (*n* = 24) were rehospitalized for HF, and the mortality rate was 12% (*n* = 11) during the 1 year of follow up. With the exception of discontinuation due to death, mechanical assist, or heart transplantation, 14.7% discontinued ARNI medication. The most common cause of discontinuation was gastrointestinal adverse effects, followed by elevated creatinine, malaise, and vertigo (*Figure 3*). Age-adjusted logistic regression analysis showed that female gender (OR 3.58; 95% CI 1.07–2.00; *P* = 0.038) and a NT-proBNP higher than the median level of 2860 ng/L (OR 0.48; 95% CI 0.26–0.90; *P* = 0.021) predicted discontinuation of the treatment.

Discussion

During the first year of introduction of ARNI in Sahlgrenska University Hospital, 13% of the hospitalized HFrEF patients were initiated with ARNI, despite that 20% of the patients were eligible and 28% were potentially eligible. Side effects

Figure 1 Inclusions of patients in the tolerability part of the study and the up-titration of ARNI. Data is presented in numbers. ARNI, angiotensin receptor neprilysin inhibitor

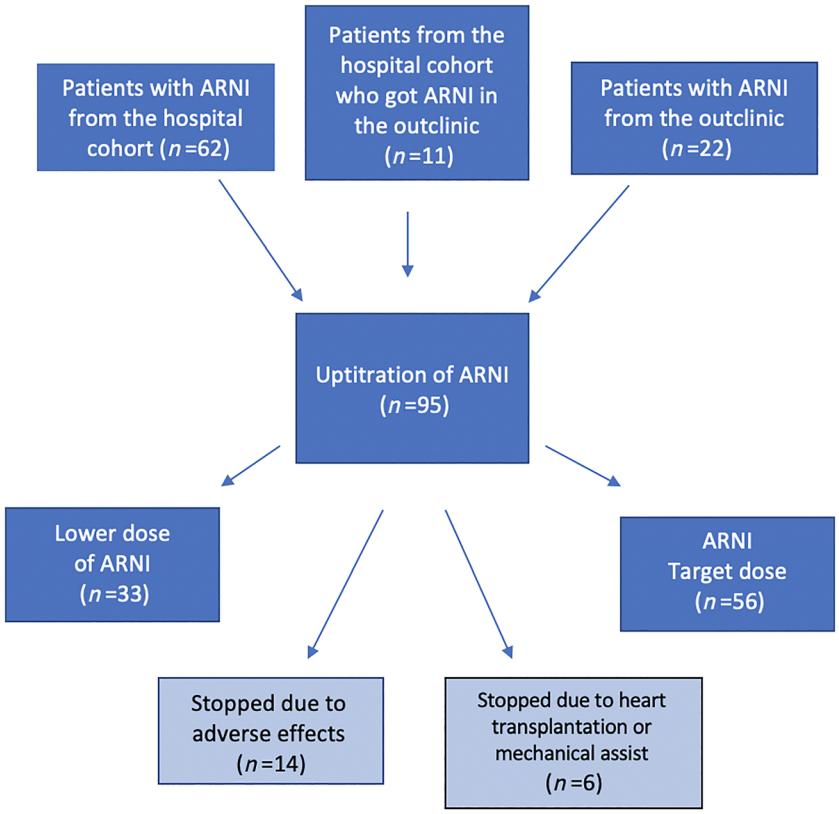
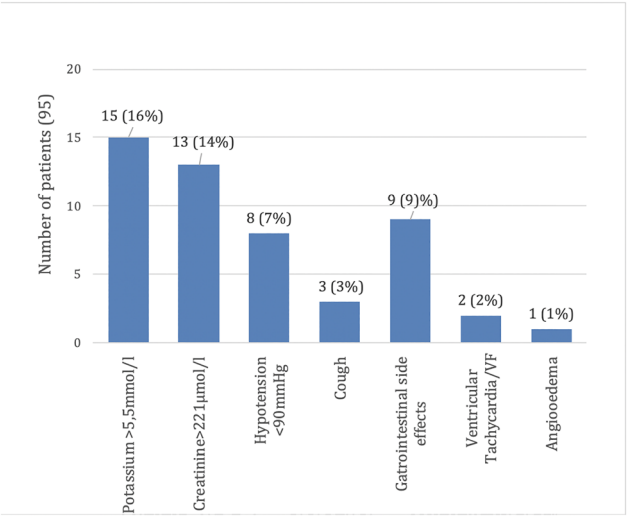


Figure 2 Adverse events during up-titration of angiotensin receptor neprilysin inhibitor. Data is presented in numbers and percentage. Patients can have multiple adverse events and be registered several times



and discontinuation rates were comparable to those observed in the PARADIGM-HF trial.

In the PARADIGM-HF trial, there was a single-blind run-in period, during which all patients received enalapril at target dose, followed by a single-blind run-in period during which all patients received Sac/Val at target dose. This was to ensure an acceptable side-effect profile of the study drug at target doses and to minimize discontinuation rates in the trial. However, this raised serious concern about representativeness of the trial in the real-world clinical setting. Moreover, similar inclusion and exclusion criteria were adopted by European and Swedish guideline recommendations for selecting patients for ARNI. However, in our daily clinical practice, it is impossible to provide run-in prior to initiation of ARNI. More than one third of the HF patients in this study did not tolerate the target dose. Therefore, experience of early implementation of ARNI is important.

In our study, 20–28% of all hospitalized HF patients were eligible, and this is in line with previous studies.[10–12] However, a recent publication from the Swedish Heart failure Registry showed that 34–76% of the patients were eligible to ARNI.[13] The patients registered in the Swedish Heart failure Registry are real-world patients but still a selected group from cardiology clinics with an interest of HF.

In our study, all hospitalized HF patients, from all clinics, not only cardiology wards, at the hospitals were consecutively included and might reflect the "real-world" HF population in a more correct manor.

Another recent Swedish study comparing eligible and noneligible patients showed that eligible patients had lower all-cause mortality than those who were noneligible although they still had higher mortality compared with the PARADIGM-HF trial population.[14]

Table 1a

Patient characteristics	Total (n = 577)	Hospitalized non-ARNI patients (n = 482)	ARNI patients (n = 95)	P-value
Male	402 (69.7%)	327 (67.8%)	75 (78.9%)	
Female	175 (30.3%)	155 (32.2%)	20 (21.1%)	0.038
Age	73.8 (13.6)	75,4 (13.2)	65,4 (12.2)	<0.0001
	76.0 (18.0; 100.0)	78.0 (18.0; 100.0)	66.0 (36.0; 86.0)	
	n = 577	n = 482	n = 95	
SBP and lab results				
SBP (mmHg)	129.3 (23.0)	131.7 (23.0)	116.6 (18.7)	<0.0001
	129.0 (68.0; 224.0)	130.0 (68.0; 224.0)	116.0 (80.0; 180.0)	
	n = 573	n = 482	n = 91	
Potassium (mmol/L)	4.2 (0.54)	4.2 (0.52)	4.5 (0.55)	<0.0001
	4.2 (2.20; 7.10)	4.1 (2.20; 7.10)	4.5 (2.90; 6.10)	
	n = 572	n = 482	n = 90	
NT-proBNP (ng/L)	9172 (13 371)	9945 (14 249)	5627 (7308)	<0.0001
	5680 (66; 218 000)	6420 (87; 218 000)	2860 (66; 34 200)	
	n = 441	n = 362	n = 79	
eGFR (CKD-EPI)	59.6 (29.2)	58.8 (29.1)	63.6 (29.2)	0.10
	57.8 (4.3; 292.2)	56.7 (4.3; 292.2)	61.9 (24.3; 265.9)	
	n = 576	n = 482	n = 94	
Aetiology of HF				
Hypertension	102 (17.7%)	87 (18.0%)	15 (15.8%)	0.72
IHD	237 (41.1%)	210 (43.6%)	27 (28.4%)	0.0076
DCM	65 (11.3%)	35 (7.3%)	30 (31.6%)	<0.0001
HCM	3 (0.5%)	1 (0.2%)	2 (2.1%)	0.14
Valve disease	28 (4.9%)	24 (5.0%)	4 (4.2%)	1.00

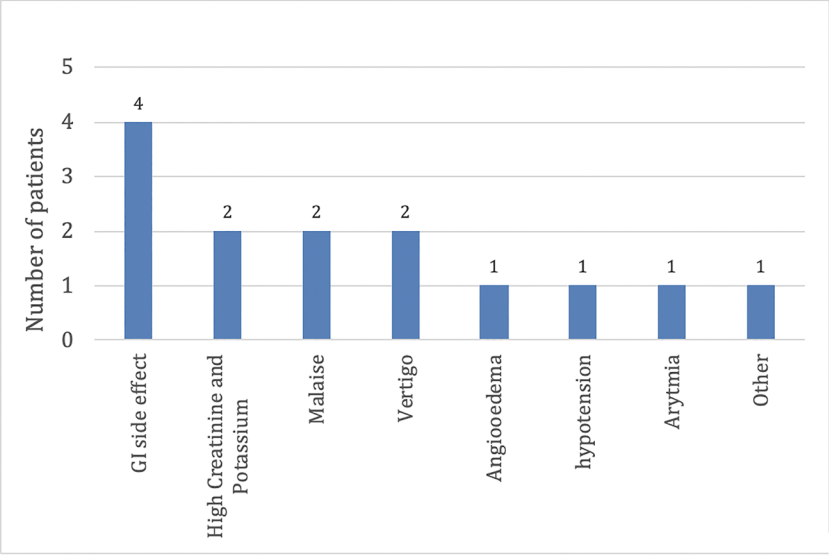
ARNI, angiotensin receptor neprilysin inhibitor; CKD-EPI, chronic kidney disease epidemiology collaboration; DCM, dilated cardiomyopathy; EF, ejection fraction; eGFR, estimated glomerulation filtration rate; HCM, hypertrophic cardiomyopathy; HF, heart failure; IHD, ischemic heart disease; NT-proBNP, N-terminal pro BNP; SBP, systolic blood pressure.
Table 1a Comparison of non-ARNI patients and ARNI patients. For categorical variables, n (%) is presented. For continuous variables, mean (*SD*)/median (min; max)/*n*= is presented.

Table 1b

Comorbidities	Total (n = 577)	Hospitalized non-ARNI patients (n = 482)	ARNI patients (n = 95)	P-value
Number of different types of comorbidities	2.6 (1.41) 2.0 (0.00; 6.00) n = 577	2.6 (1.43) 3.0 (0.00; 6.00) n = 482	2.2 (1.25) 2.0 (0.00; 6.00) n = 95	0.011
Hypertension	280 (48.5%)	249 (51.7%)	31 (32.6%)	0.0009
Myocardial infarction	233 (40.4%)	199 (41.3%)	34 (35.8%)	0.38
Atrial fibrillation	293 (50.8%)	248 (51.5%)	45 (47.4%)	0.54
Diabetes type 1	9 (1.6%)	7 (1.5%)	2 (2.1%)	0.90
Diabetes type 2	162 (28.1%)	138 (28.6%)	24 (25.3%)	0.59
Stroke	74 (12.8%)	64 (13.3%)	10 (10.5%)	0.59
Renal disease	124 (21.5%)	111 (23.0%)	13 (13.7%)	0.052
COPD	60 (10.4%)	58 (12.0%)	2 (2.1%)	0.0022
Asthma	25 (4.3%)	23 (4.8%)	2 (2.1%)	0.38
Sleep apnea	33 (5.7%)	25 (5.2%)	8 (8.4%)	0.32
Malign cancer	94 (16.3%)	84 (17.4%)	10 (10.5%)	0.12
Valve disease	98 (17.0%)	90 (18.7%)	8 (8.4%)	0.016
RA	16 (2.8%)	14 (2.9%)	2 (2.1%)	0.99
Thyroid disease	67 (11.6%)	57 (11.8%)	10 (10.5%)	0.88
Medication				
Beta blockers	515 (89.3%)	420 (87.1%)	95 (100.0%)	<0.0001
MRA	278 (48.2%)	183 (38.0%)	95 (100.0%)	<0.0001
Ivabradine	3 (0.5%)	1 (0.2%)	2 (2.1%)	0.14
Loop diuretics	447 (77.5%)	391 (81.1%)	56 (58.9%)	<0.0001
Anticoagulant	280 (48.5%)	229 (47.5%)	51 (53.7%)	0.32
Device				
Pacemaker	51 (8.8%)	50 (10.4%)	1 (1.1%)	0.0016
CRT without ICD	27 (4.7%)	23 (4.8%)	4 (4.2%)	1.00
CRT with ICD	39 (6.8%)	21 (4.4%)	18 (18.9%)	<0.0001
ICD without CRT	43 (7.5%)	27 (5.6%)	16 (16.8%)	0.0010

ARNI, angiotensin receptor neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; MRA, mineralcorticoid receptor antagonist; RA, rheumatoid arthritis.
Table 1b Comparison of non-ARNI patients and ARNI patients.For categorical variables, n (%) is presented. For continuous variables, mean (*SD*)/median (min; max)/n= is presented.

Figure 3 Reasons for discontinuation of angiotensin receptor neprilysin inhibitor during follow up, 1 year after initiation. Data is presented in numbers



The patients from our cohort who were initiated with ARNI were younger, more often had dilated cardiomyopathy as the aetiology, with a lower NT-proBNP, and more often were on GDMT (100% with BB, 100% with MRA, and a higher frequency of CRT/ICD) compared with the patients who did not receive ARNI. This means that patients treated with ARNI, during the first year of introduction, were highly selected. Accordingly, great potential exists for further improvement in

clinical implementation of ARNI in a broader HFrEF population.

We have shown that ARNI was well tolerated among this selected group. Only 14.7% of the patients discontinued treatment, and the most common cause of discontinuation was surprisingly benign gastrointestinal side effects. Women had a greater risk of discontinuation. Among adverse events, high potassium and elevation of creatinine occurred in 16% and 14% of the patients, respectively, and these numbers are in line with the PARADIGM-HF study.[6] The strict selection of HFrEF patients for initiation of ARNI is not optimal but is apparent from the clinical reality of today. At present, many HFrEF patients, including patients from this study, are to a large extent on suboptimal medical therapy although the majority of the patients were diagnosed with HF for 6 months or more. Only around 1/3 were on target dose of BB and renin–angiotensin–aldosterone system inhibitor. Because the baseline therapy is far from optimal, adding treatment with ARNI is not the first step based on available guidelines. This under treatment is an international problem and has been shown repeatedly in previous studies.[7,15,16] There is also a large variation in prescriptions of ACEI/ARB reported in Swedish Heart failure Registry between older and younger patients (70% and 90%, respectively). The annual reports are available at www.SwedeHF.se.

If more patients get GDMT in accurate dose, it is possible that more would be eligible to ARNI as the next step according to the guidelines. Another possibility is that more patients would improve and then not be eligible for ARNI. At present, available international and national guidelines vary because of uncertainty about how to manage dose level of background therapy with ACEI/ARB before initiation of ARNI. However, it is shown that the benefit of Sac/Val, over Enalapril, was consistent regardless of background therapy or BB dose.[17] Therefore, increasing the awareness of under treatment among physicians at all levels is an urgent matter and should receive high priority.

Only 58.9% of the patients reached target dose of ARNI, lower than in the TITRATION study in which 75.9% reached target dose.[18] This most likely illustrate the differences between randomized controlled trials and clinical practice. The effect of a lower dose is not known despite subgroup analysis from the PARADIGM-HF trial showed that Sac/Val is still more effective than enalapril if both are in lower dose.[19] Further studies are warranted to investigate the effect of lower dosage. However, in the TITRATION study, a more careful titration approach seemed beneficial in reaching target dose in patients with lower blood pressure.

The readmission rate of our ARNI population was higher than in PARADIGM-HF even though follow-up time was shorter. The possible explanation might be that our cohort is frailer compared with the patients in the PARADIGM-HF trial because the majority of our patients were hospitalized due to HF and had almost 10-fold higher NT-proBNP levels on average. The readmission rate in the PIONEER study, which also included hospitalized patients, was 8% in 8 weeks, suggesting a higher readmission rate in hospitalized HF patients.[20] However, the mortality rate in this study was in line with PARADIGM-HF and other previous studies.[21]

Limitations

Our study has included only a limited number of patients. However, a consecutive inclusion was applied without any exclusions to ensure representativeness from real-world clinical settings. The number of patients who received ARNI is small, but this was from the first year of implementation of Sac/Val. Despite some data missing, all data in this study were validated by reviewing patients' medical records by two reviewers.

Conclusions

In the present study, from a cohort of patients with HFrEF, 20% are fully and 28% are potentially eligible for ARNI. However, only 13% received the treatment. ARNI was well tolerated, but 41% of the patients did not reach target dose. How this affects outcome is not known. The use of GDMT in accurate dose in a real-world clinical setting is far from optimal in patients with HFrEF. Our study highlights the immediate need for improved HF therapy in real world.

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Conflict of interest

Michael Fu and Charlotta Ljungman have received honoraria for lectures by Novartis. Charlotte Nordberg Backelin has no conflict of interest to disclose.

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