ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 159–167
Published online 5 January 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12547

ORIGINAL RESEARCH ARTICLE

Sacubitril-Valsartan in a routine community population: attention to volume status critical to achieving target dose

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Abstract

Aims In the PARADIGM-heart failure trial, sacubitril-valsartan demonstrated a reduction in heart failure admissions and reduced all-cause mortality in patients with heart failure with reduced ejection fraction. Although real world data have shown similar benefits regarding efficacy and safety, there has been difficulty in achieving the target dose (TD). The factors preventing the achievement of TD remains unclear.

This study assesses the tolerability, ability to achieve, and factors linked to attaining TD in a routine clinical population.

Methods and results This is a retrospective single-centre review of patients switched from angiotensin-converting enzyme inhibitors/angiotensin receptor blockers to sacubitril-valsartan between May 2016 and August 2018. Baseline and follow-up clinical characteristics and biomarker profiles were collected. Univariate and multivariate analyses were used to analyse predictors of achieving TD. Clinical response to sacubitril-valsartan was defined as a reduction in N terminal pro BNP of $\geq$30%, or an increase in left ventricular ejection fraction of $\geq$5% compared with baseline values.

To date, a total of 322 patients (75% male patients) have been switched to sacubitril-valsartan. Those still in the titration phase were excluded (n = 25). Sacubitril-valsartan was not tolerated in 40 patients (12.4%). Those intolerant were older (73.4 years [68.3, 80.6] vs. 69.1 years [61.2, 76]; P = 0.003) and had worse renal function with estimated glomerular filtration rate (53.5 mL/min/1.72 m^2 [36.8, 60.2] vs 60 mL/min/1.72 m^2 [47, 77]; $P \leq 0.001$). Of the remaining 257 patients, TD (97/103 mg BD) was achieved in 194 patients (75.5%), while 37 patients (11.4%) were maintained on 49/51 mg BD and 26 patients (8.1%) remained on 24/26 mg BD. Symptomatic hypotension (74.6%) was the main impediment to attaining TD, followed by renal deterioration (12.7%), and to a lesser extent hyperkalaemia and gastrointestinal symptoms (4.8% each). Diuretic dose decrease was achieved in 37.2% of patients, and this was the strongest independent predictor of achieving TD (odds ratio = 2.1; 95% confidence interval [1.16, 3.8]; P = 0.014). Responder status by N terminal pro BNP criterion was observed in 99 of 214 patients (46.3%) while 70 of 142 (49.3%) attained the left ventricular ejection fraction response status. Achieving this response was independently linked to achieving TD.

Conclusions Sacubitril-valsartan was well tolerated. Achievement of TD was possible in the majority of the cohort and was linked to response metrics. Reduction in diuretic was required in a large percentage of the population and was the strongest predictor of attaining TD. Therefore, careful clinical attention to volume status assessment is essential to maximising the benefits of sacubitril-valsartan.

Keywords Heart failure; HF-rEF; Sacubitril-Valsartan; Diuretic dose decrease; Target dose; Real world

Received: 8 April 2019; Revised: 18 September 2019; Accepted: 23 September 2019
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Introduction

The recent demonstration by the PARADIGM-heart failure (HF) trial that sacubitril-valsartan significantly reduces mortality and morbidity among patients with reduced ejection fraction heart failure (HF-rEF) represents a further significant pharmacological advance in this syndrome.[1–3] In addition, more recent data have found it to be safe and effective when started during an acute decompensated HF admission.[4]

This agent is now licenced for use in certain well-defined circumstances.[5,6] However, as is always the case with novel therapeutic strategies, there is a need to look closely at how this agent performs in the routine community HF-rEF population, who are likely to be older,[7] more frail, and have increased burden of comorbidities.[8,9] This 'community testing' of a new compound may be of particular importance with sacubitril-valsartan, given its widespread biological effects on various neuroendocrine and signalling systems, potentially affecting these to different degrees in community patients compared with clinical trial patients.

Real world evidence to date has been in relatively small numbers of patients followed for short periods of time. In the main, observations have been in line with what has been reported in the clinical trial data.[10–13] However, there has been a lower rate of achievement of the target dose (TD), with the majority of studies reaching TD in less than 50% the patients,[14,15] including a large cohort in Germany.[16] To our knowledge, only one study to date had reported success in titration to TD in greater than 50% of the cases.[17] Given that achieving maximum dose seems to have an impact on outcome,[11,18] a fuller understanding is needed of the success and difficulties of titration of this agent in community HF-rEF.

Therefore, we report herein on our initial experience in excess of 300 patients switched to sacubitril/valsartan focusing on tolerability, dose achieved, and response patterns.

Methods

Study population and patients' characteristics

This is a single-centre retrospective observational analysis of patients with established HF-rEF [left ventricular ejection fraction (LVEF) $\leq$ 35%] managed in an outpatient HF unit. Stable HF-rEF patients who were on maximally tolerated doses of disease-modifying therapy were considered for sacubitril-valsartan from May 2016. Standard exclusion criteria to the use of sacubitril-valsartan were adhered to. These included patients who were haemodymically unstable, had previous angioedema with ACEi, hypersensitivity to sacubitril-valsartan, eGFR $\leq$ 30 mL/min/1.72 m^2 or severe liver impairment.[19–21] Clinical stability in HF was defined as absence of clinical deterioration in the previous month, defined as no hospitalisation for HF or outpatient escalation of diuretic therapy. In addition to being clinically stable, all patients had a clinic systolic blood pressure of $\geq$100 mmHg and serum potassium (K^+) of $\leq$5.4 mmol/L.

Baseline data collection

The following data were collected as part of the routine clinic management of this patient cohort.

i) Baseline demographics including age, gender, comorbidities, and HF aetiology.
ii) Clinical status including blood pressure, heart rate, and body mass index.
iii) Baseline therapies for HF and other prescribed drugs.
iv) Biomarker profile including haemoglobin, creatinine, potassium, urea, natriuretic peptide, and soluble ST2.

Dose titration and follow up

The initial dose of sacubitril-valsartan was 100 mg BD when the patient was on moderate to maximum recommended doses of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy (ACEi/ARB) or 50 mg BD if the patients were on lower doses of these agents and/or had a low clinic systolic blood pressure.

The titration visits (not less than a 2-week interval) were overseen by a staff cardiologist experienced in HF management. We closely monitored the patients' volume status, paying particular attention to the need for diuretic dose adjustment, based on the observation of a need for a reduction in diuretic strength in a significant number of patients in the PARADIGM-HF population.[22]

Outcome measurements

Primary endpoints

Tolerance of sacubitril-valsartan and achievement of target dose The primary outcomes were tolerability of sacubitril-valsartan and achievement of TD in the cohort. Characteristics of patients intolerant to sacubitril-valsartan were compared with those successfully initiated on this agent. Analysis was performed to determine the predictors of achieving TD. It should be noted that as a standard practice, an attempt was made to decrease diuretic dose before a patient was considered intolerant to sacubitril-valsartan because of hypotension.

Secondary endpoints

Responders to sacubitril-valsartan Our secondary analysis was a measure of patients' response to sacubitril-valsartan.

Response status was defined using changes in accepted metrics of prognosis in the HF-rEF syndrome. These were

i) Change in NT-proBNP

A reduction in N terminal pro BNP (NT-proBNP) of 30% or greater, comparing the most recent value taken at a time of clinical stability with the value obtained at the time of initiation of therapy with sacubitril-valsartan. This was accepted as a meaningful clinical change outside the range of the biological and assay variability of this natriuretic peptide.[23] Similar percent changes were used as either primary and secondary indicators of improving prognosis in patients on sacubitril-valsartan in the PARADIGM-HF, PIONEER-HF trials, PARADIGM *post hoc* analysis, and by Zile MR *et al.*[1,4,24,25]

ii) Change in LVEF

An increase in LVEF of greater than or equal to 5%, comparing follow-up Doppler-echocardiographic assessment with the observation taken prior to initiation of therapy, was accepted as a meaningful increase in LVEF outside of measurement variability.[26] Of note, a sub-analysis of PARADIGM found that a 5% decrease in EF was associated with a 9% increase in all-cause mortality.[25]

iii) Alteration of diuretic need

Third, we also analysed the impact of sacubitril-valsartan on diuretic use, noting the percentage of patients in whom it was possible to reduce diuretic dose and the overall impact of sacubitril-valsartan on diuretic need in the cohort. Diuretic need was expressed as furosemide equivalents with bumetanide 1 mg representing 40 mg of furosemide. Bumetanide and furosemide were the only loop diuretics prescribed in this cohort. The impact on ST2 values was also noted comparing stable values at the time of initiation of therapy with latest follow-up value.

Statistical analysis

R version 3.5.0[27] was used for all statistical analyses. Continuous variable summary statistics are reported as median [interquartile range (IQR)]. Categorical summary statistics are reported as numbers and percentages (%). *T*-test or Wilcoxon–Mann–Whitney test was used to compare continuous variables between groups as appropriate. Categorical variables were compared by chi-square or Fisher's exact test as appropriate. Univariate and multivariate logistic regression models were used to estimate odds ratios, including 95% confidence intervals. Two-sided *P*-value of $\leq$0.05 was considered statistically significant in all cases.

All patients who had at least one dose of sacubitril-valsartan and a gap of at least 10 days between their first sacubitril-valsartan prescription and their most recent prescription were included in the study. Baseline echocardiographic and laboratory tests were the most recent assessments performed before the first sacubitril-valsartan prescription. Follow-up tests were the most recent on record. Occasionally, values were missing, and these patients were excluded only from the particular statistical test that required it. The concern is that there may be some material difference in patients lost to follow-up analysis because of missing data. Therefore, additional analyses were carried out to compare those with and without follow up values to address this issue. In the interest of working only with actual collected data, no imputation of values was done; the exception being that if a comorbidity was not mentioned in patient medical history, we inferred it was not present.

Results

Patients' characteristics

We report on a population of 322 HF-rEF patients (75% male patients) switched to sacubitril-valsartan. Of this total cohort, 25 patients were in the titration phase at the time of data censoring and therefore are not included in the report. Median age was 70.0 years [61.9,76.2]. Before switching to sacubitril-valsartan, all patients were on either ACEi or ARB therapy. Other disease modifying therapies were prescribed in a high percentage of this group; 90.7% (274 patients) and 72.5% (219 patients) were on beta-blockers and mineralocorticoid receptor antagonists, respectively. Of these agents', TDs at baseline had been achieved in 28.9%, 13.2%, and 43.6% in ACEi/ARB, beta blockers, and mineralocorticoid receptor antagonists, respectively. The median LVEF was 28% [23.7, 33.0] (*Table 1*).

Sacubitril-valsartan tolerance

Among the 297 patients in the cohort, 40 (13.4%) did not tolerate sacubitril-valsartan. The main reasons for failure to tolerate were: symptomatic hypotension (20 patients, 50%); impairment of renal function (decline in eGFR of 30% or greater; 9 patients, 22.5%); gastrointestinal symptoms (5 patients, 12.5%); hyperkalaemia (4 patients, 10.0%); and others (2 patients, 5.0%) (*Figure 1A*). Those intolerant were older (73.4 years [68.3, 80.6] vs. 69.1 years [61.2, 76]; $P = 0.003$), had worse renal function with median eGFR (53.5 mL/min/1.72 m^2 [36.8, 60.2] vs. 60 mL/min/1.72 m^2 [47, 77]; $P \leq 0.001$), and had a higher but not statistically significant ST2 levels (43.6 ng/mL [25.3, 60.8] vs. 35.5 ng/mL [27.3, 51.8]; *P*

Table 1 Baseline patient characteristics. The table also shows comparison of patients' demographics between those who were able to reach maximum tolerated dose of sacubitril-valsartan with those who did not tolerate the compound

Variables	Total (N = 322)	Max tolerated dose (n = 257)	Intolerance (n = 40)	P-value
Age (years)	70 [61.9, 76.2]	69.1 [61.2, 76]	73.4 [68.3, 80.6]	0.003
Male	241 (75.1%)	191 (74.6%)	33 (82.5%)	0.520
CV risk factors				
Dyslipidaemia	32 (9.9%)	28 (10.9%)	2 (5.0%)	0.400
Hypertension	99 (30.7%)	83 (32.3%)	8 (20%)	0.120
Diabetes	56 (17.4%)	44 (17.1%)	7 (17.5%)	>0.99
Physical features				
Systolic BP (mmHg)	123 [112, 136]	124 [112, 136]	123 [114, 134]	0.710
Diastolic BP (mmHg)	65.5 [60, 74]	65 [60, 75]	65 [57, 71]	0.150
Heart rate (bpm)	68 [60, 76]	68 [60, 76]	67 [62, 76]	0.920
Body mass index (kg/m2)	29 [26.0, 33.0]	29 [26.0, 33.0]	26 [25.0, 29.0]	0.005
Primary aetiologies of heart failure				
Ischaemic	135 (41.9%)	104 (40.5%)	25 (62.5%)	0.015
Non-ischaemic	187 (58.1%)	153 (59.5%)	15 (37.5%)	
LVEF (%)	28 [23.7, 33.0]	28.4 [24.8, 35]	25 [24.6, 30.5]	0.310
Comorbidities				
Atrial fibrillation	139 (43.2%)	113 (44%)	21 (52.5%)	0.470
Chronic renal failure eGFR of ≤60ml/min/1.72m^2	116 (36.0%)	88 (34.2%)	25 (62.5%)	0.002
Anaemia	68 (21.1%)	51 (19.8%)	15 (37.5%)	0.030
COPD	36(11.2%)	29 (11.3%)	5 (12.5%)	>.99
Stroke/TIA	33 (10.2%)	25 (9.7%)	4 (10%)	>.99
Cancer	39 (12.1%)	29 (11.3%)	6 (15%)	0.790
Laboratory analysis				
Potassium (mmol/L)	4.5 [4.2, 4.8]	4.5 [4.2, 4.8]	4.5 [4.3, 4.8]	0.880
Haemoglobin(g/dL)	13.7 [12.6, 14.7]	13.9 [12.7, 14.8]	13 [12.2, 14]	0.006
Creatinine (μmol/L)	104 [83.2, 126]	102 [83, 123]	116.5 [104.2, 163]	0.002
Urea	8.2 [6.2, 11.3]	7.7 [6, 11.1]	10.2 [7.9, 15.7]	0.002
eGFR (ml/min/1.72m^2)	58.9 [46, 74]	60 [47, 77]	53.5 [36.8, 60.2]	0.001
Biomarkers				
BNP (pg/mL)	200.5 [99.1, 424.5]	191 [97.7, 400]	311 [154.5, 706.5]	0.038
NT-proBNP (pg/mL)	1092 [514.5, 2422.5]	1036 [481, 2314]	1194.5 [599.5, 3630.5]	0.480
ST2 (ng/mL)	36 [27.2, 51]	35.5 [27.3, 51.8]	43.6 [25.3, 60.8]	0.300
New York Heart Association				
I	33/317 (10.4%)	28/253 (11.1%)	3 (7.5%)	0.670
II	248/317 (78.2%)	198/253 (78.3%)	31 (77.5%)	
III	35/317 (11%)	26/253 (10.3%)	6/40 (15%)	
IV	1/317 (0.3%)	1/253 (0.4%)	0/40 (0%)	
Guidelines guided Heart Failure therapy				
Beta blocker	274 (90.7%)	220 (90.9%)	33 (86.8%)	0.300
ACEi	261(81.1%)	180 (74.4%)	24 (63.2%)	0.300
ARB	57 (18.9%)	46 (19.0%)	7 (18.4%)	>.99
Aldosterone antagonist	219 (72.5%)	179 (74%)	22 (57.9%)	0.069
Loop diuretics	249 (82.5%)	197 (81.4%)	33 (86.8%)	>.99
ICD	105 (32.6%)	87 (33.9%)	13 (32.5%)	0.970
CRT	8 (5.6%)	13 (5.1%)	3 (7.5%)	0.710

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB angiotensin receptor blocker; BNP, brain (B-type) natriuretic peptide; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronisation therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ICD, intracardiac defibrillator; LVEF, left ventricular ejection fraction; max tolerated, maximum tolerated; NT-proBNP, N terminal pro BNP; TIA, transient ischaemic attack.

= 0.30) in comparison with those who tolerated the compound.

In the remainder who tolerated sacubitril-valsartan, the median follow up was 519 days (range = 281–738 days). TD of sacubitril-valsartan (97/103 mg BD) was achieved in 194 patients (75.5% of those tolerating or 65.3% of the total assessed population). In the group that managed to achieve ACEi/ARB TDs, 72.0% of them were able to achieve sacubitril-valsartan TDs. Of the 63 patients who did not achieve TD of sacubitril-valsartan, 37 patients were prescribed the intermediate dose (49/51 mg BD) and 26 patients were on low dose (24/26 mg BD**)**. Symptomatic hypotension (47 patients, 74.6%) was the leading impediment to achieving maximum dose, followed by renal deterioration (8 patients, 12.7%), hyperkalaemia and gastrointestinal symptoms (3 patients, 4.8% each), and others (2 patients, 3.2%) (*Figure 1B*). Only 4.0% (13 out of 322) of patients on low dose and intermediate dose of sacubitril-valsartan were on TD of ACEi/ARB.

Multivariate analysis of factors related to achieving TD demonstrated that down-titration of diuretic therapy was the strongest independent predictor of reaching the 200-mg BD dose (*Table 2*).

Figure 1 (A) Reasons for failure to tolerate sacubitril-valsartan and (B) preventing patients reaching target dose. Percentages may not sum to 100 owing to rounding

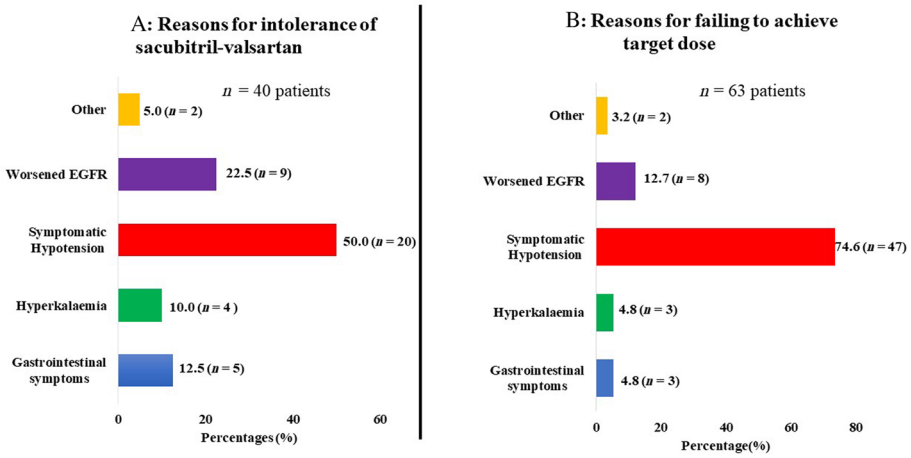


Table 2 Predictors of reaching maximum recommended dose of sacubitril-valsartan

	Univariate		Multivariable	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)	0.99 [0.97, 1.01]	0.23	1.01 [0.99, 1.04]	0.34
Male	1.04 [0.61, 1.78]	0.87	0.75 [0.38, 1.47]	0.400
Baseline log NT-proBNP	0.81 [0.66, 1.01]	0.056	0.85 [0.67, 1.09]	0.210
Baseline eGFR	1.02 [1.01, 1.03]	0.002	1.02 [1, 1.04]	0.029
Baseline haemoglobin	1.21 [1.04, 1.4]	0.015	1.14 [0.95, 1.36]	0.160
Diuretic dose decrease	1.77 [1.05, 2.97]	0.031	2.1 [1.16, 3.8]	0.014

Abbreviations: CI, coefficient interval; NT-proBNP, N-terminal pro B-type natriuretic peptide; OR, odds ratio; TD, target dose.

Population response to sacubitril-valsartan

Biomarker response was characterised by a significant reduction in NT-proBNP and ST2 with a trend towards an increase in BNP (B type). Minor changes in renal metrics were observed consistent with the use of an agent modulating the renin angiotensin aldosterone system. A significant improvement in LVEF was also noted. (*Table 3*)

A reduction of 30% or more in NT-proBNP was observed in 46.3% of the cohort, and an improvement in LVEF of 5% or greater was noted in 49.3% of the cohort. An improvement in at least one metric was achieved in 78.4% of the population, while we observed an improvement in both metrics in 18.9% of the group. Responders were noted to be younger, have better baseline renal function, and in sinus rhythm. Reduction in diuretic was an independent predictor of the occurrence of both metrics of response (*Tables 4A and 4B*).

Another measure of clinical response that we observed was the ability to reduce diuretic dose, as observed among 37.2% (93 of 250) of the population, with a mean reduction of 10 ± 38-mg furosemide equivalent across the entire population. (*Figure 2*). Among the patients who had their diuretic dose reduced, 31.2% (*n* = 29) did not achieve TD of sacubitril-valsartan, and 28.0% (*n* = 26) had their diuretics reduced to zero.

In addition, ST2 levels also reduced significantly in this population from 35.5 ng/mL [27.3, 51.8] to 30 ng/mL [21.9, 42.5] ($P \leq 0.001$).

Discussion

Sacubitril-valsartan represents one of the most significant advances in recent years in the management of HF with reduced ejection fraction. Impressive clinical trial data have demonstrated a reduction in mortality, improvement in several morbidity endpoints, and more recently, the capacity to initiate early post decompensation.[1,2,4] Real world data to complement this impressive clinical trial information are of importance to assess whether response is similar in a community population, who are invariably older and with more comorbidities.[11,28] To date, the limited published real world data indicate a similar positive experience.[10–12,14] Notably however, achievement of TD of sacubitril-valsartan appears to be more of a challenge in the community. Some studies have reported

Table 3 Biomarkers response and myocardial reverse remodelling because of the impact of sacubitril-valsartan

	Baseline	Follow up	*P*-value
BNP (pg/mL)	191 [97.7, 400]	213 [70.6, 478.9]	0.171
NT-proBNP (pg/mL)	1036 [481, 2314]	807.5 [257, 1867]	<0.001
ST2 (ng/mL)	35.5 [27.3, 51.8]	30 [21.9, 42.5]	<0.001
eGFR (ml/min/1.72m^2)	60 [47, 77]	57 [43.8, 76]	0.001
Potassium (mmol/L)	4.5 [4.2, 4.8]	4.6 [4.2, 4.8]	0.387
Haemoglobin (g/dL)	13.9 [12.7, 14.8]	13.6 [12.3, 14.6]	0.003
LVEF (%)	28.4 [24.8, 35]	32.5 [25.5, 40]	<0.001

Abbreviations: BNP, Brain (B-type) Natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; and NT-proBNP, N terminal pro BNP.

Table 4A Baseline characteristics between nonresponders and responders. Responder definition according to N terminal pro brain natriuretic peptide decrease by >30% and left ventricular ejection fraction increase >5%

Phenotypical features	Nonresponder	Responder	*P*-value
Age (years)	71.4 [62.7, 77.6]	65.1 [56.3, 72.5]	0.001
Creatinine (μmol/L)	107.5 [86, 131]	89 [69, 109.5]	0.002
eGFR (mL/min/1.72m^2)	58 [44, 70]	71 [55, 81]	0.010
DBP (mmHg)	64.5 [59.2, 72]	70 [62, 80]	0.015
Hypertension (*n*/*N*)	56/150 (37.3%)	6/35 (17.1%)	0.038
HF Isch (*n*/*N*)	42/146 (28.8%)	1/34 (2.9%)	0.001
Atrial Fib (*n*/*N*)	74/150 (49.3%)	9/35 (25.7%)	0.019

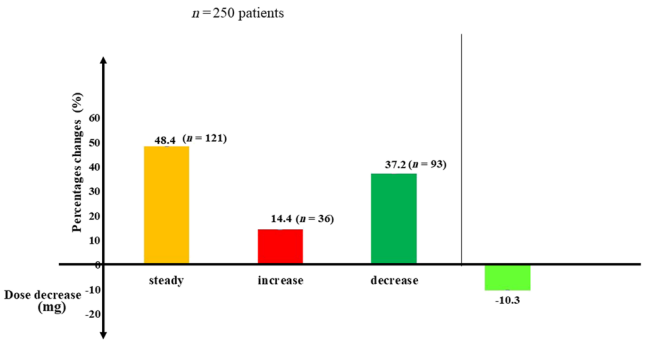
Abbreviations: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF Isch; heart failure because of ischaemia.

Table 4B Patients meeting the responder criteria

Secondary end points	*n*/*N*
NT-proBNP down >30% from baseline to follow up	99/214 (46.3%)
LVEF up >5% from baseline to follow up	70/142 (49.3%)
NT-proBNP down >30% and LVEF >5%	35/185 (18.9%)
NT-proBNP down >30% or LVEF >5%	134/171 (78.4%)
Diuretic dose decrease	93/250 (37.2%)

Abbreviations: LVEF, left ventricular ejection fraction; NT-proBNP, N terminal pro BNP.

Figure 2 Diuretic dose change patterns in the cohort.



rates as low as 17%, and the majority of studies achieved the maximum dose in less than 50% of individuals.[11,15,16] Given that emerging data indicate that the higher doses are associated with superior clinical response,[11,18] close analyses of the impediments to dose titration in the community are warranted in order to provide guidance on how best this agent in this setting.

Our data demonstrate that the clinical trial dose of sacubitril-valsartan can be achieved in a significant proportion of the population. Up to 75% of our population were titrated to and tolerated the TD. The strongest independent predictor of achieving maximum dose was the need to reduce diuretics. Response rates to sacubitril-valsartan in this cohort defined by biomarker or ejection fraction criteria were high and when determined by changes in both metrics were related to the achievement of TD. Together, these observations underline a positive clinical response to sacubitril-valsartan among community HF-rEF patients. Furthermore, the data highlight the importance of careful volume assessment to maximise the chances of achieving clinical trial dose and thereby maximising the chance of clinical response. The data presented herein, concerning the need to reduce diuretic therapy during titration of sacubitril-valsartan, are consistent with observations from within the PARADIGM cohort.[29]

Along with the observation that hypotension was the single greatest barrier to tolerance or successful titration of this

agent, these two observations indicate that accurate volume assessment is a critical aspect of successful use of this compound. The reasons for diuretic reduction are not certain but are likely multifactorial, including improved diuretic response with preservation of natriuretic peptides,[30] in addition to an overall improvement in ventricular function. A similar, though less impressive, response was observed with cardiac resynchronisation therapy with 19% of patients requiring down-titration of their diuretic therapy.[31] A heightened sensitivity to diuretics when co-administered with sacubitril-valsartan could also explain the reduction in diuretic need.[30] However, the limited data that are available on this interaction suggest that sacubitril-valsartan in fact reduces the effectiveness of the diuretics, an effect that opposes our finding of a reduction in diuretic need.[32]

While the importance of achieving the TD was not assessed in the larger clinical trials, a recent report by Martens *et al*. links the attainment of maximum dose to improved ventricular function.[18] Furthermore, within this data set, TD was linked to responder status, further supporting efforts to achieve maximum dose. Our data, while not reporting on clinical end points, indicate a similar community response in terms of natriuretic peptide and ST2 reduction, to that observed in PARADIGM-HF, and extend the clinical trial observations by demonstrating an increase in LVEF over time with this therapy.[1,17,33] We also noted that those responding to therapy tended to be younger and had better renal function. These data might indicate that earlier intervention with sacubitril-valsartan in the natural history of HF-rEF might be the most effective strategy in terms of improving the chances of a beneficial response. However, it should be noted that these data do not imply and that only younger patients benefit from the compound. As observed from the PARADIGM sub-analysis by Jhund PS *et al*., when the authors assessed the efficacy and safety of sacubitril-valsartan by age, they found that the superiority of sacubitril-valsartan over enalapril persisted across all age groups including the elderly, though the same efficacy gap decreased slightly in the older population.[34]

The clinical importance of these data is that they reinforce the positive observations from the clinical trial data,[1,33,35] and the emerging real world data,[14,15,17] and indicate that the majority of the cohort of community patients can tolerate the agent and benefit from the compound, in terms of either a reduction in NT-proBNP or an improvement in LVEF. More importantly, these data support the importance of achieving maximum dose and link this to a reduction in diuretic use, establishing clinical volume assessment as a critical feature in using this agent. This places a premium on medical assessment and careful clinical examination and might indicate that the process of titration cannot be as easily released to HF nurses as would be done with other disease modifying agents.

Limitations

In interpreting these data, certain aspects of this report need to be emphasized. First, this is an observational study from a clinical service and not a research cohort. Accordingly, some data are not available to us as a result of the data not being required for clinical decision making or are still awaited. The latter explains the absence of follow-up LVEF data on a significant number, with many still yet to undergo reassessment waiting for an appropriate time interval to pass following the last dose adjustment before reassessment. In some cases, a recheck of LVEF has not been planned as no change in therapy would be prescribed. Second, we have focused this report on assessment of change in important metrics of HF status to provide insight into the impact of sacubitril-valsartan. We have not reported on clinical events as we would have no meaningful comparator.

Conclusions

In summary, the impressive response to sacubitril-valsartan noted in the clinical trial arena is replicated in this community population. In addition, achievement of clinical trial dose can be managed in the majority of patients. The emerging link between dose achieved, clinical response, and the need for diuretic reduction underlines the importance of careful clinical assessment of volume status during the titration period.

Conflict of interest

Prof Ken McDonald/Prof Mark Ledwidge/Dr Joe Gallagher has received honoraria for speaking on behalf of Novartis at educational events.

Funding

No funding received.

Author contributions

RBP, MF, and KM conceptualised, drafted, and wrote the final manuscript, AM and ML reviewed and edited the final draft while MW, CS, KM, DO, JG, CW, and JB were involved in data curation. EO performed statistical analysis.

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