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ORIGINAL RESEARCH ARTICLE

Eligibility for sacubitril–valsartan in patients with acute decompensated heart failure

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Abstract

Aims Large-scale clinical trials have demonstrated clinical benefits of sacubitril–valsartan in symptomatic heart failure with reduced ejection fraction patients (PARADIGM-HF), with potential benefits in patients hospitalized for acute decompensated heart failure (ADHF) (PIONEER-HF) and fewer benefits in patients with heart failure with preserved ejection fraction (PARAGON-HF). The aim of this study was to evaluate eligibility for sacubitril–valsartan using criteria described in PIONNER-HF in non-selected patients hospitalized for ADHF.

Methods and results Between November 2014 and May 2019, 799 patients were recruited in a prospective registry of acute heart failure at the University Hospitals of Geneva (ClinicalTrials.gov: NCT02444416). The cohort consists of consecutive patients admitted to the Department of Medicine with ADHF. Eligibility for sacubitril–valsartan was determined using criteria described in PIONEER-HF, including left ventricular ejection fraction, clinical parameters, and co-morbidities. Of 799 patients, 123 (15.39%) were eligible for sacubitril–valsartan treatment. Clinical outcomes including all-cause mortality and readmission were similar in eligible and non-eligible groups, hazard ratio 1.02 (95% confidence interval 0.81–1.29, P = 083).

Conclusions Using current criteria from randomized controlled trials, only 15% of non-selected patients admitted for ADHF are theoretically eligible for sacubitril–valsartan. Eligibility for sacubitril–valsartan using published criteria is not associated with worse outcome, suggesting that further evaluation of benefits of sacubitril–valsartan in heart failure patients based on parameters other than left ventricular ejection fraction may be of interest.

Keywords Heart failure; Acute; Sacubitril-valsartan

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Introduction

Acute decompensated heart failure (ADHF) is a leading cause of hospitalizations and mortality in patients older than 65 years, and prognosis remains poor.[1–4] Recent prospective randomized studies have tested the angiotensin receptor–neprilysin inhibitor sacubitril–valsartan in various heart failure (HF) populations.[5] The PARADIGM-HF study enrolled 8842 ambulatory, symptomatic patients with a left ventricular ejection fraction (LVEF) <35% who were receiving a stable dose of angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) and a beta-blocker. Sacubitril–valsartan, as compared with enalapril, was superior in reducing the risk of death for cardiovascular cause and hospitalization for HF. The PIONEER-HF study enrolled 887 patients with HF and LVEF < 40% who were hospitalized for ADHF. Early initiation of sacubitril–valsartan led to a greater reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) at 4–8 weeks.[6] There was a trend towards a favourable impact of early initiation of sacubitril–valsartan on mortality and rehospitalization, but the study was underpowered for this issue. More recently, PARAGON-HF did not demonstrate a lower rate of hospitalizations for HF or death from cardiovascular causes among 4822 ambulatory patients with HF and LVEF > 45%.[7] Exclusion criteria in the PIONEER-HF study included the requirement of treatment

with both ACE-I or ARB, estimated glomerular filtration rate <30 mL/min/1.73 m^2, serum potassium >5.2 mEq/L, isolated right HF due to severe pulmonary disease, presence of haemodynamically significant mitral or aortic valvular disease, hypertrophic cardiomyopathy, or known hepatic impairment (total bilirubin >3 mg/dL).[6] In an outpatient setting, the proportion of patients with HF with reduced ejection fraction (HFrEF) eligible to receive sacubitril–valsartan have already been shown to be limited.[8] The prognosis of patients with HF is associated with factors such as age, renal function, blood pressure, LVEF, brain natriuretic peptide (BNP) levels, and certain co-morbidities.[9–12] The purpose of this study was to evaluate the eligibility for initiation of sacubitril–valsartan in a non-selected prospective cohort of consecutive patients hospitalized with ADHF.

Methods

Patients

Between November 2014 and May 2019, consecutive patients with ADHF admitted to the Department of Medicine were recruited in a prospective registry of acute HF at the University Hospitals of Geneva (ClinicalTrials.gov: NCT02444416). The study included patients with symptoms of HF based on the European Society of Cardiology definition, such as dyspnoea, ankle swelling and fatigue, accompanied by signs of HF such as elevated jugular venous pressure, pulmonary crackles, or peripheral oedema due to structural and/or functional cardiac abnormality.[10] Additional inclusion criteria were elevated BNP levels >100 ng/L or pro-BNP levels >300 ng/L. All patient data were reviewed by a senior investigator, with expertise in the diagnosis and management of HF. The protocol was approved by the institutional ethics committee (protocol CER 14-019), and all patients gave written informed consent.

Patients were classified according to European Society of Cardiology guidelines as having HF with reduced ejection fraction (HFrEF) if LVEF was $<40\%$. For LVEF $>40\%$, elevated natriuretic peptides and relevant structural heart disease or diastolic dysfunction were additional criteria.[10]

Characteristics, including age, gender, weight, smoking status, a full medical history, and medical therapy at admission, throughout hospital stay, and at discharge, were recorded. Clinical presentation, including New York Heart Association dyspnoea class, and clinical parameters, such as blood pressure, heart rate, and weight, were also recorded at admission and throughout hospital stay. Further investigations carried out on all patients included full blood count, urea and electrolytes, electrocardiography, and echocardiography. Echocardiography was analysed by experienced staff cardiologists.

Outcomes were collected at 3, 12, and 24 months and yearly afterwards and included mortality, readmission, clinical state, and medication. Follow-up was carried out through contact with treating physicians and examination of hospital medical records.

Sacubitril–valsartan eligibility criteria

Criteria were adapted from the PIONEER-HF study, with patients classified as eligible for sacubitril–valsartan (Group 1) if all the following characteristics were present: >18 years of age, hospitalized with a primary diagnosis of HF, including symptoms and signs of fluid overload, haemodynamically stable with a systolic blood pressure >100 mmHg, an LVEF $< 40\%$, and elevated natriuretic peptides (NT-proBNP $\geq$ 1600 pg/mL or BNP $\geq$ 400 pg/mL).[6] Patients with one of the above criteria of exclusion but with LVEF $< 40\%$ were classified in Group 2 (HFrEF but contraindications for sacubitril–valsartan). Group 3 comprised all patients with LVEF $> 40\%$ (*Figure 1*).

Study outcomes

Patients hospitalized for ADHF were grouped based on eligibility criteria for sacubitril–valsartan. Based on this categorization, measured clinical outcomes were all-cause mortality and readmission, cardiovascular death and readmission, and the components of these outcomes.

Statistical analysis

We used median (inter-quartile range) for continuous data and number (%) for categorical data, as appropriate. Student's *t*-test or Mann–Whitney–Wilcoxon test was used for comparing quantitative data and χ^2 test or Fisher's exact test for categorical comparisons. The distribution of these variables was tested, and non-parametric tests were used for non-normal distribution. For the study outcomes, we used survival analysis with log-rank test for the unadjusted analysis, Kaplan–Meier plots, and Cox proportional hazard models for multivariate exploration, as previously described in the cohort.[13] The multivariate model included variables that were associated with outcome on unadjusted analysis ($P < 0.2$), as well as commonly recognized variables identified in previous studies. Statistical analysis was performed using the R statistical software package, Version 3.1.1 (www.cran.r-project.org).

Results

Baseline characteristics

Between November 2014 and May 2019, 799 consecutive patients were included. Of these patients, 538 (67.33) had an

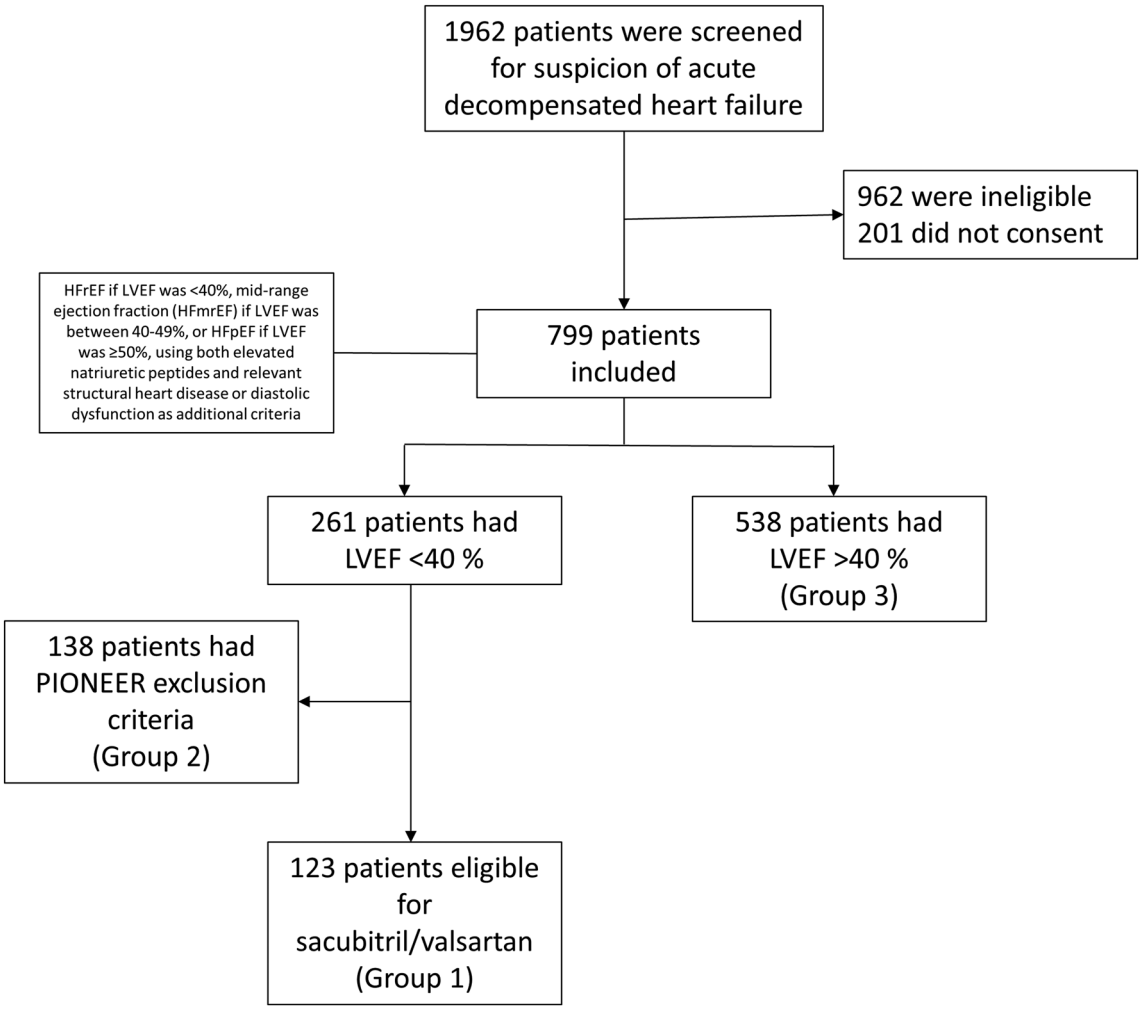

Figure 1 Screening and eligibility groups. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction.

LVEF $>$ 40% and 261 (32.7%) had an LVEF $<$ 40% (*Figure 1*). Based on the specified eligibility groups, the median age was 73.34 years in Group 1 (eligible for sacubitril–valsartan), 75.53 years in Group 2 (non-eligible LVEF $<$ 40%), and 79.82 years in Group 3 (non-eligible LVEF $>$ 40%) (*Table 1*). Overall median age was 78.40 years. Of the 261 patients with an LVEF $<$ 40%, 11 (4.2%) had a systolic pressure $<$100 mmHg at admission, 1 (0.38%) had both ACE-Is and ARBs, 36 (13.79%) had estimated glomerular filtration rate $<$30 mL/min/1.73 m^2, 22 (8.43%) had serum potassium $>$5.2 mEq/L, 86 (32.95%) had haemodynamically significant mitral and/or aortic disease, and 17 (6.5%) had NT-proBNP $<$ 1600 pg/mL or BNP $<$ 400 pg/mL. According to these criteria, there were 123 (15.39%) patients of the 799 meeting the specified inclusion criteria, with no specified exclusion criteria of PIONEER-HF and therefore potentially eligible for sacubitril–valsartan therapy (Group 1) (*Table 3*). There were 138 (17.27%) patients in Group 2, comprising patients with LVEF $<$ 40% but with exclusion criteria. There were 538 patients with LVEF $>$ 40% (*Tables 1* and *3*). There were six patients treated with sacubitril–valsartan at admission, and for the purposes of the analysis, none were excluded.

At admission, and as compared with patients with LVEF $<$ 40%, patients with LVEF $>$ 40% had a slightly greater median age, were more likely to be female, had proportionally more hypertension and proportionally less moderate or severe mitral or aortic valvular disease, and had lower median BNP and NT-proBNP levels (*Table 1*). Other characteristics such as body mass index (BMI) and co-morbidities such as diabetes, chronic kidney disease, and chronic obstructive pulmonary disease were similar in all three groups. Clinical parameters such as New York Heart Association class at admission, systolic and diastolic blood pressure, and heart rate were similar across the groups.

Medication at admission, including HF-specific medication such as ACE-Is, ARBs, mineralocorticoid receptor antagonists, and other classes, was similar across the groups, irrespective of LVEF (*Table 2*).

Table 1 Baseline patient characteristics according to sacubitril–valsartan eligibility status

	All patients in cohort, $N = 799$ (%)	Group 1 LVEF < 40% eligible, $N = 123$ (15.39%)	Group 2 LVEF < 40% non-eligible, $N = 138$ (17.27%)	Group 3 LVEF > 40% non-eligible, $N = 538$ (67.33%)
Median age, years (IQR)	78.4 (70.15–84.89)	73.34 (63.2–81.69)	75.53 (66.2–82.64)	79.82 (72.95–85.52)
Gender				
Male (%)	462 (57.82)	83 (67.48)	93 (67.39)	286 (53.16)
Female (%)	337 (42.18)	40 (32.52)	45 (32.61)	252 (46.84)
Median BMI, kg/m^2 (IQR)	25.47 (22.24–29.94)	24.18 (21.18–28.65)	24.68 (21.68–28.31)	26.29 (22.64–31.38)
De novo heart failure (%)	251 (31.41)	47 (38.21)	35 (25.36)	169 (31.41)
Medical history				
Hypertension	632 (79.1)	88 (71.54)	99 (71.74)	445 (82.71)
Diabetes	266 (33.29)	40 (32.52)	49 (35.51)	177 (32.9)
CKD	283 (35.49)	29 (23.58)	51 (36.96)	203 (37.73)
COPD	119 (14.89)	13 (10.57)	18 (13.04)	88 (16.36)
Chronic anaemia	334 (41.8)	38 (30.89)	58 (42.02)	238 (44.24)
Valvular disease[a]	232 (29.04)	0 (0)	86 (62.32)	146 (27.14)
NYHA class				
I	8 (1.00)	0 (0)	2 (1.45)	6 (1.12)
II	53 (6.63)	8 (6.5)	5 (3.62)	40 (7.43)
III	295 (36.92)	47 (38.21)	57 (41.3)	191 (35.5)
IV	443 (55.44)	68 (55.28)	74 (53.62)	301 (55.95)
Median SBP at admission, mmHg (IQR)	140 (122–157)	137 (123–151)	132 (114–149)	143 (125–160)
Median DBP at admission, mmHg (IQR)	80 (69–93)	86 (79–97)	80 (70–93)	79 (67–91)
Median heart rate at admission, b.p.m. (IQR)	87 (73–104)	96 (82–114)	90 (77–108)	84 (71–99)
Median BNP ($n = 118$), ng/L (IQR)	883 (459–1432)	1307 (877–1785)	1312 (861–1921)	705 (375–1107)
Median NT-ProBNP ($n = 681$), ng/L (IQR)	4275 (1904–9869)	7400 (3938–13 358)	7408 (3832–13 522)	3266 (1457–7642)
Median Hb, g/L (IQR)	125 (108–140)	133 (118–144)	129 (113–144)	122 (106–137)
Median eGFR, mL/min/1.73 m^2 (IQR)	51 (36–69)	57 (44–74)	46 (29–63)	51 (34–69)

BMI, body mass index; BNP, brain natriuretic peptide; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DPB, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; IQR, inter-quartile range; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.
[a]Defined as moderate or severe mitral or aortic valve stenosis or regurgitation.

The median follow-up period in this cohort was 15.5 months (inter-quartile range 7–25 months); there were a total of 618 patients with events during this period including 274 deaths and 518 readmissions. Median survival without all-cause death or readmission was 5 months (inter-quartile range 2–14 months) (*Table 3*).

In survival analysis, risk of all-cause hospitalization and death, as well as cardiovascular hospitalization and death, did not differ between the three groups (*Figure 2*). In particular, Group 1 patients eligible for sacubitril–valsartan therapy did not have worse outcomes. In univariate analysis, eligibility for sacubitril–valsartan was not associated with the secondary outcomes. To further investigate this, multivariate analysis in a model comprising age, gender, BMI, and co-morbidities, such as chronic kidney disease and chronic obstructive pulmonary disease, confirmed no increased hazard ratio for the primary or secondary outcomes with eligibility status (*Table 4*).

Discussion

In this prospective cohort of consecutive patients admitted for ADHF, only 15.39% were eligible to receive sacubitril–valsartan based on criteria adapted from the PARADIGM-HF, PIONEER-HF, and PARAGON-HF studies. This limited number of patients eligible in a real-life cohort owing to the strict inclusion and exclusion criteria used in the princeps trials relativizes the expected benefits of this therapy at the population level. Interestingly, our study further shows that clinical outcomes of patients are not different between groups based on eligibility criteria for sacubitril–valsartan, suggesting that patients shown to benefit from this treatment do not inherently have a dissimilar prognosis.

Whilst sacubitril–valsartan conveys a clinically significant benefit in addition to other treatments of HF in strictly defined patients, the criteria used in the PARADIGM-HF and PARAGON-HF studies limit the number of patients who are eligible for this new treatment.[5] The primary efficacy outcome in the PIONEER-HF was the change in NT-proBNP concentration, with only exploratory clinical outcomes, further rendering the potential benefit of sacubitril–valsartan in the general HF population unclear.[6] In our cohort, the high prevalence of impaired kidney function and hyperkalaemia suggests that existing co-morbidities are common in the general HF population and play an important role in patient

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Table 2 Medication at admission

	All patients in cohort, $N = 799$ (%)	Group 1, LVEF $< 40\%$, eligible, $N = 123$ (15.39%)	Group 2, LVEF $< 40\%$, non-eligible, $N = 138$ (17.27 %)	Group 3, LVEF $> 40\%$, non-eligible, $N = 538$ (67.33%)
ACE inhibitors	219 (27.41)	39 (31.7)	49 (35.5)	131 (24.35)
AR blockers	232 (29.04)	26 (21.13)	26 (18.84)	180 (33.46)
Loop diuretics	421 (52.69)	49 (39.84)	72 (52.17)	300 (55.76)
Beta-blockers	443 (55.44)	66 (53.66)	82 (59.42)	295 (54.83)
Calcium channel blockers	202 (25.28)	16 (13.01)	18 (13.04)	168 (31.23)
Sacubitril/valsartan	6 (0.75)	4 (3.25)	1 (0.72)	1 (0.19)
Antiarrythmics	77 (9.64)	13 (10.57)	16 (11.59)	48 (8.92)
Antiplatelets	350 (43.8)	57 (46.34)	74 (53.62)	219 (40.71)
Oral anticoagulants	304 (38.05)	35 (28.46)	44 (31.88)	225 (41.82)
Cholesterol lowering	360 (45.06)	45 (36.59)	68 (49.28)	247 (45.91)
Mineralocorticoid receptor antagonist	106 (13.27)	27 (21.95)	33 (23.91)	46 (8.55)
Digoxin	39 (4.88)	8 (6.5)	6 (4.34)	25 (4.65)
Oral antidiabetics /insulin	238 (29.79)	32 (26.02)	45 (32.61)	161 (29.93)
NSAIDs/ corticosteroids	66 (8.26)	9 (7.32)	11 (7.97)	46 (8.55)
Implantable defibrillator	65 (8.14)	20 (16.26)	24 (17.39)	21 (3.9)
CRT device	76 (9.51)	16 (13.01)	27 (19.57)	33 (6.13)

ACE, angiotensin-converting enzyme; AR, angiotensin receptor; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; NSAIDs, non-steroidal anti-inflammatory drugs.

management decisions. The PIONEER-HF study concluded that angiotensin–neprilysin inhibition in ADHF led to a greater reduction in the NT-proBNP concentration and furthermore suggested that in exploratory clinical outcomes, the in-hospital initiation of sacubitril–valsartan therapy was associated with a lower rate of rehospitalization for HF at 8 weeks than enalapril therapy. Rates of renal dysfunction, hyperkalaemia, and hypotension did not differ significantly. These findings are restricted to patients included in the study. Our results suggest that very few patients with ADHF are eligible for sacubitril–valsartan and that the optimal moment for starting this medication is not yet demonstrated. The lack of a demonstrable benefit in patients with HF with preserved ejection fraction (HFpEF) in the PARAGON-HF study shows that this entity remains a therapeutic challenge and will have to be further investigated.[7] Dissecting underlying mechanisms of HFpEF and pathophysiological pathways leading to cardiac dysfunction may reveal new therapeutic targets of inflammation or other forms of stress.[14] Pre-specified subgroup analysis of the PARAGON-HF study suggests that certain patients may yet benefit. Both women and patients with a median LVEF $< 57\%$ had fewer total hospitalizations and death from cardiovascular causes in the sacubitril–valsartan group. The definition of HFpEF has evolved over time and may still require further refinement.

We found no difference in overall rates of hospitalization or death, or hospitalization or death from cardiovascular causes between patients eligible and those not eligible for

Table 3 Distribution of exclusion criteria in patients with LVEF $< 40\%$ (261 of 799 patients)

	LVEF $< 40\%$, $N = 261$ (32.67%)
Systolic blood pressure <100 mmHg	11 (4.2)
NT-proBNP < 1600 pg/mL, BNP < 400 pg/mL	17 (6.5)
Treatment with both ACE-I and ARB	1 (0.38)
eGFR < 30 mL/min/1.73 m^2	36 (13.79)
Potassium >5.2 mEq/L	22 (8.43)
Moderate or severe mitral or aortic valve disease	86 (32.95)
1 or more exclusion criteria	138 (53)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

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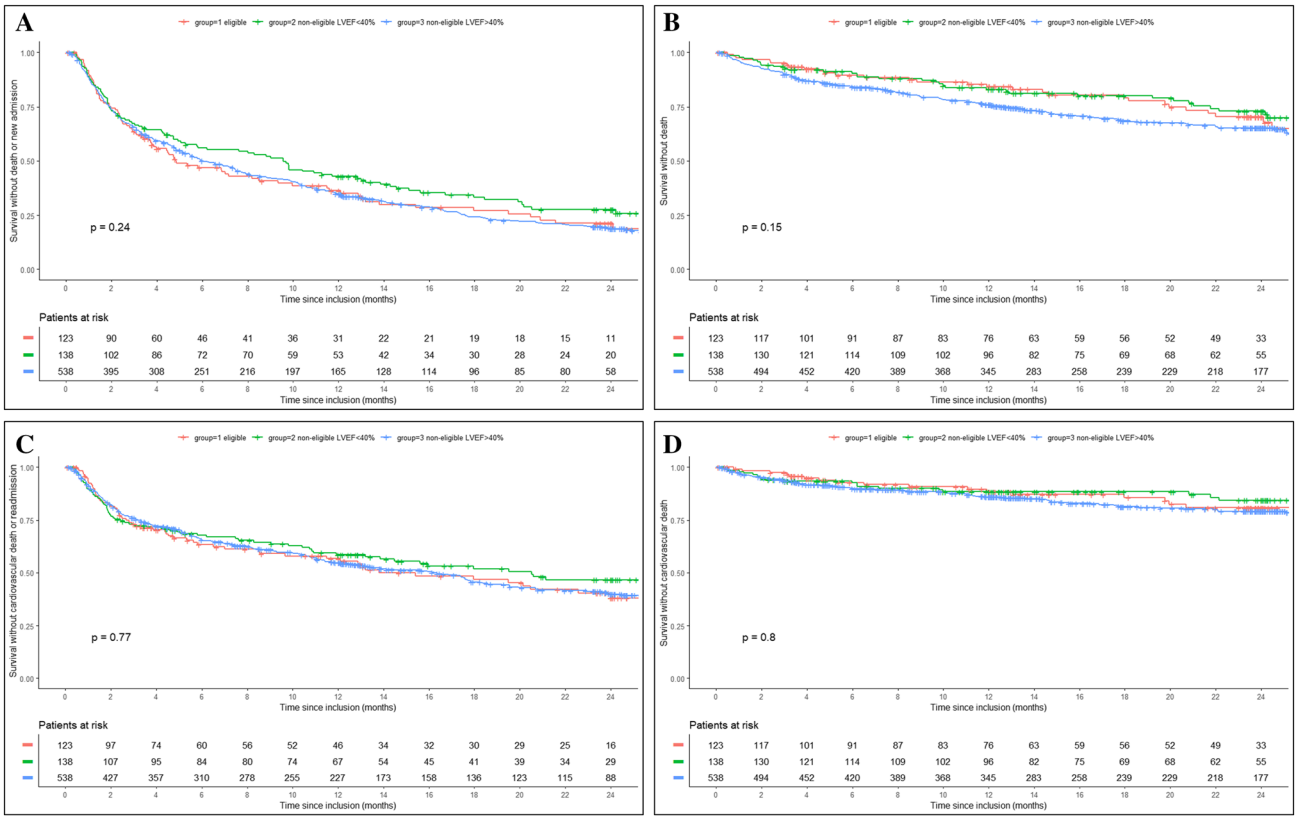

Figure 2 Kaplan–Meier survival analysis for clinical outcomes in patients according to eligibility group: (A) all-cause mortality and readmission, (B) all-cause mortality, (C) cardiovascular mortality and readmission, and (D) cardiovascular mortality. LVEF, left ventricular ejection fraction.

sacubitril–valsartan therapy, regardless of LVEF. This suggests that patients with decreased LVEF, as included in the PARAGON-HF as well as in the PIONEER-HF populations, do not intrinsically have a worse prognosis, adding to the argument that LVEF is in itself a poor predictor of outcome in patients with HF and ADHF.[15–17] We and others have previously shown that other echocardiographic parameters are more robustly associated with poor clinical outcomes.[13] Determining prognosis in HF is complex, and LVEF is perhaps not in itself the most valid discriminating parameter. Despite PARAGON-HF not showing that sacubitril–valsartan results in a decrease in death or hospitalization rates in patients with LVEF $>$ 45%, further studies will have to investigate other parameters to identify patients who may benefit from this therapy. Patients' co-morbidities, baseline characteristics, including BMI, and other cardiac function parameters may play a determining role.[9,11,18]

Despite the multitude of medical therapies available today for the treatment of HFrEF, overall improvement of survival remains limited, and disease-modifying therapies for HFpEF are lacking.[2,19–21] Long-term incidence of HF stretching back to 1950 has not decreased in men, with a slight decrease in women.[2] With respect to survival, the modest effective increase contrasts sharply with the expected cumulative benefits extrapolated from the large randomized clinical trials of beta-blockers, ACE-Is, and ARBs and other medications.[20–23] Explanations for this discrepancy lie in the epidemiology of HF and obligatory restrictiveness of randomized trials. In our cohort, as in other real-life studies, the average age was higher than in the PARADIGM-HF study (76.23 vs. 63.8 years), the prevalence of HFpEF was above 50%, and a significant number of patients had severe co-morbidities such as chronic kidney disease.[24] This is more representative of the overall HF population, and benefits of recommended therapies in these elderly and multi-morbid patients are not adequately demonstrated. Furthermore, evidence-based eligibility limits the number of patients who can truly receive given therapies and notably sacubitril–valsartan. Finally, distinguishing between chronic or stable HF and patients presenting with ADHF appears to be important, and prognosis may be different when this distinction is made.

Whilst not undermining the value of sacubitril–valsartan in selected patients, this study suggests that achieving an improvement of survival in a greater proportion of HF patients, and in particular in patients with ADHF, still requires both a

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Table 4 Adjusted association of sacubitril–valsartan eligibility with clinical outcomes

	All-cause mortality or readmission, HR (95% CI)	*P* value	All-cause mortality, HR (95% CI)	*P* value	Cardiovascular mortality or readmission, HR (95% CI)	*P* value	Cardiovascular mortality, HR (95% CI)	*P* value
Group 1, LVEF < 40%, eligible[a]	1.02 (0.81–1.29)	0.83	0.87 (0.6–1.27)	0.47	1.13 (0.86–1.48)	0.38	1.03 (0.63–1.68)	0.9
Age[b]	1.00 (1.0–1.01)	0.41	1.03 (1.02–1.05)	<0.001	1.01 (1.00–1.00)	0.27	1.04 (1.02–1.07)	<0.001
Gender, female[c]	0.90 (0.77–1.07)	0.24	0.82 (0.65–1.07)	0.16	0.91 (0.75–1.12)	0.38	1.11 (0.59–1.17)	0.28
BMI > 25 kg/m^2[d]	0.87 (0.74–1.03)	0.11	0.64 (0.5–0.83)	<0.001	0.93 (0.76–1.14)	0.51	0.68 (0.47–0.96)	0.03
Chronic kidney disease	1.43 (1.2–1.7)	<0.001	1.6 (1.25–2.05)	<0.001	1.5 (1.23–1.84)	<0.001	1.5 (1.07–2.13)	0.02
History of COPD	1.51 (1.21–1.87)	<0.001	2.22 (1.66–2.97)	<0.001	1.63 (1.27–2.1)	<0.001	2.67 (1.81–3.95)	<0.001

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LVEF, left ventricular ejection fraction.
[a]As compared with non-eligible patients.
[b]With 1 year increments.
[c]As compared with male.
[d]As compared with BMI < 25 kg/m^2.

better understanding of factors affecting prognosis, as well as more effective implementation of proven therapies and medical compliance. Extending the indication of sacubitril–valsartan to less selected patients, with older age and more co-morbidities, should be the focus of future studies. Implementation and prescription of target dose of existent therapies for HFrEF, as well as medical adherence, remain a priority and should be an aim in itself in HF management. Indeed, in similar studies to our own, only 27% patients had target dose of an ACE-I or ARB.[8]

Our study has limitations. First, because of their observational nature, our findings are limited to association and not causality, and despite multivariate analysis, there is residual confounding. Further limitations include the low sample size as well as the single-centre nature of the cohort. The strengths of our study are its prospective design, the consecutive inclusion of patients admitted with ADHF, and the use of robust clinical and biological inclusion criteria based on accepted guidelines and definitions for the identification of patients with HF.[10,12,25,26] The cohort corresponds to a real-life representation of patients hospitalized with ADHF, characterized by co-morbidities that often co-exist, and the results may be generalizable and have external validity. We specifically chose certain objective and measurable exclusion criteria. Applying all criteria used in the PIONEER-HF study would have further limited the number of eligible patients.

Conclusions

In non-selected patients admitted for ADHF, applying criteria from randomized controlled trials shows that eligibility for sacubitril–valsartan is limited. Eligibility for sacubitril–valsartan using published criteria is not associated with a worse outcome, suggesting that further evaluation of benefits of sacubitril–valsartan in HF patients based on parameters other than LVEF may be of interest.

Conflict of interest

None declared.

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