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Sacubitril/Valsartan in Real-World Heart Failure with Reduced Ejection Fraction: Clinical, Echocardiographic, and Tolerability Outcomes — A Study of 300 Patients

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AUTHORS AND AFFILIATION

Sara Aouame
Hopital militaire moulay ismail

ABSTRACT

Background: Sacubitril/valsartan (ARNI) demonstrated superior outcomes versus enalapril in the PARADIGM-HF trial, yet real-world data on its comprehensive echocardiographic impact and tolerability in North African patients with high ischemic and comorbidity burden remain scarce.
Methods: We conducted a retrospective, observational, single-center study including 300 patients with HFrEF (LVEF <40%) treated with sacubitril/valsartan after optimized background therapy. Clinical, echocardiographic, and tolerability data were collected at baseline and 12 months. The primary endpoint was quality of life improvement (NYHA class). Secondary endpoints included LVEF change, reverse LV remodeling (indexed LVESV and LVEDV), functional mitral regurgitation (MR) regression, filling pressure normalization (E/E' ratio), and pulmonary artery pressure (PAPs) change.
Results: Mean age was 61.2 ± 5.3 years; 64% male. Ischemic etiology 68%, atrial fibrillation 48%, baseline LVEF 30.7 ± 6.5%. After 12 months, dyspnea prevalence decreased from 95% to 44%; NYHA I increased from 5% to 56%. LVEF improved from 30.7 ± 6.5% to 43.0 ± 7.3% ($p<0.001$); 61% recovered LVEF >40%. Indexed LVESV decreased from 61.5 ± 12.9 to 35.4 ± 15.9 mL/m² ($p<0.001$). Severe functional MR regressed from 21% to 10%. PAPs decreased from 48 ± 6 to 25 ± 8 mmHg; E/E' from 10.7 ± 3.2 to 6.3 ± 1.4 (both $p<0.001$). Target dose (200 mg twice daily) was achieved in 72% of patients; adverse events requiring discontinuation in only 6%.
Conclusions: Sacubitril/valsartan is highly effective and well tolerated in real-world HFrEF, including patients with ischemic etiology, atrial fibrillation, and multiple comorbidities. It induces comprehensive reverse LV remodeling, significant LVEF recovery, functional MR regression, and normalization of filling and pulmonary pressures, confirming its role as a cornerstone of modern HFrEF management.

KEYWORDS :

Heart failure with reduced ejection fraction, Sacubitril/valsartan, ARNI, Reverse remodeling, Echocardiography, Quality of life, Real-world, Functional mitral regurgitation

MAIN ARTICLE

1. BACKGROUND

Heart failure with reduced ejection fraction (HFrEF) remains a leading cause of morbidity, mortality, and healthcare resource utilization worldwide. Despite optimal background therapy including beta-blockers, ACE inhibitors or ARBs, and mineralocorticoid receptor antagonists (MRAs), a large proportion of patients continue to experience progressive deterioration and recurrent hospitalizations [15].

Sacubitril/valsartan (LCZ696) represents a breakthrough in HFrEF pharmacotherapy. By simultaneously blocking the renin-angiotensin-aldosterone system through valsartan and augmenting endogenous natriuretic peptide levels through neprilysin inhibition by sacubitril, this dual mechanism restores the neurohormonal imbalance characteristic of progressive heart failure [1, 2]. The landmark PARADIGM-HF trial demonstrated a 20% relative risk reduction in the composite of cardiovascular death and HF hospitalization, a 20% reduction in cardiovascular mortality, and a 21% reduction in HF hospitalizations versus enalapril, with consistent benefit across all pre-specified subgroups [1].

Following these results, sacubitril/valsartan received a Class I, Level of Evidence B recommendation in both ESC 2021 and ACC/AHA/HFSA 2022 guidelines for symptomatic HFrEF patients tolerating an ACE inhibitor or ARB [3, 4]. While the echocardiographic effects — notably reverse left ventricular remodeling and functional mitral regurgitation regression — have been reported in selected cohorts [8, 9], real-world data from North African and MENA region populations with a high prevalence of ischemic heart disease, atrial fibrillation, and multiple comorbidities remain scarce. The objective of this study was to evaluate the clinical, echocardiographic, and tolerability outcomes of sacubitril/valsartan in a real-world cohort of 300 HFrEF patients treated at a Moroccan military cardiology center.

2. METHODS

2.1. Study design and population

We conducted a retrospective, observational, single-center study at the Cardiology Department of Moulay Ismail Military Hospital, Meknes, Morocco. A total of 300 adult patients (age ≥18 years) with HFrEF (LVEF <40% by biplane Simpson method), who initiated sacubitril/valsartan after optimization of standard therapy (beta-blocker + ACE inhibitor or ARB + MRA at maximally tolerated doses), were consecutively included. This study was conducted in accordance with the Declaration of Helsinki and STROBE reporting guidelines for observational studies.

Eligibility criteria for sacubitril/valsartan initiation included: hemodynamic stability (systolic BP ≥100 mmHg), eGFR ≥30 mL/min/1.73m², serum potassium ≤5.4 mmol/L, and a minimum 36-hour washout period following ACE inhibitor discontinuation. Exclusion criteria included severe aortic stenosis, bilateral renal artery stenosis, history of angioedema, and pregnancy.

2.2. Treatment initiation and titration protocol

Sacubitril/valsartan was initiated at 50 mg twice daily and uptitrated every 2–4 weeks targeting 100 mg then 200 mg twice daily, according to BP tolerance and renal function. Clinical and biological monitoring (BP, renal function, serum potassium) was performed at 2 weeks, 1 month, 3 months, 6 months, and 12 months.

2.3. Data collection and endpoints

Data were extracted from electronic medical records at baseline (T0) and after 12 months of follow-up (T12). The primary endpoint was quality of life improvement, assessed by NYHA functional class change. Secondary endpoints included: LVEF improvement; reverse LV remodeling (change in indexed LVESV and LVEDV); regression of functional mitral regurgitation (EROA and regurgitant volume by PISA method); improvement in LV filling pressures (E/E' ratio); change in estimated systolic pulmonary artery pressure (PAPs).

Additional data collected included: baseline demographics and cardiovascular risk factors; comorbidities; ECG characteristics; coronary angiography results; prior medical therapy; sacubitril/valsartan dose achieved at 12 months; and adverse events requiring dose reduction or treatment discontinuation.

2.4. Statistical analysis

Statistical analysis was performed using SPSS Version 23. Continuous variables are expressed

as mean ± standard deviation; categorical variables as numbers and percentages. Pre-post comparisons used paired Student's t-test for continuous variables and McNemar's test for categorical variables. Statistical significance was defined as $p<0.05$.

3. RESULTS

3.1. Baseline population characteristics

Mean age was 61.2 ± 5.3 years (range 22–78 years); 64% were male (sex ratio 1.8). Cardiovascular risk factors: hypertension 60.5%, diabetes 40%, dyslipidemia 38.5%, smoking 35%, obesity 30%, family history of coronary disease 5%. Among women, 88% were postmenopausal.

Comorbidities: ischemic heart disease 68%, atrial fibrillation 48%, COPD 10%, chronic kidney disease 7%, prior stroke 5%, peripheral arterial disease 3%. Coronary angiography was performed in 77%, revealing: normal coronaries 9%, non-significant lesions 8%, single-vessel disease 21%, two-vessel disease 34%, three-vessel disease 28%.

Mean baseline BP was 132.1 ± 34.5/86.5 ± 16.3 mmHg, heart rate 84.2 ± 29 bpm, BMI 27.5 ± 7.3 kg/m², serum creatinine 10.1 ± 4.8 mg/L, eGFR 68.4 ± 22.7 mL/min/1.73m². ECG: sinus rhythm 42%, atrial fibrillation 48%, LBBB 38%, electrocardiographic LVH 29%, QRS >120 ms 42%.

All patients were on prior optimized therapy: beta-blockers 100%, ACE inhibitor/ARB 100%, MRA 88%, ivabradine 20%, diuretics 44%, CRT-P 1%.

3.2. Baseline echocardiographic parameters

Mean LVEF was 30.7 ± 6.5%. Indexed LVESV 61.5 ± 12.9 mL/m², indexed LVEDV 103.9 ± 11.1 mL/m². Functional MR: moderate in 28%, severe in 21%; mean EROA 0.24 ± 0.08 cm², regurgitant volume 31 ± 11 mL. Mean PAPs 48 ± 6 mmHg. Mean E/E' ratio 10.7 ± 3.2; elevated LV filling pressures (E/E' >14) in 38% of patients.

3.3. Primary endpoint: Quality of life and NYHA functional class

After 12 months of treatment, a significant improvement in quality of life was observed across all patients. NYHA class distribution shifted markedly: before treatment, 5% NYHA I, 28% II, 52% III, 15% IV; after 12 months, 56% NYHA I, 22% II, 18% III, 4% IV. The proportion of patients with dyspnea decreased from 95% to 44%; peripheral edema from 37.5% to 4%; asthenia from 95% to 22%; and functional limitation from 75% to 35%.

3.4. Secondary endpoints: Echocardiographic outcomes at 12 months

LVEF improved significantly from 30.7 ± 6.5% to 43.0 ± 7.3% ($p<0.001$). A total of 61% of patients recovered LVEF >40% and 12% achieved LVEF ≥50% (super-responders). Indexed LVESV decreased from 61.5 ± 12.9 to 35.4 ± 15.9 mL/m² ($p<0.001$) and indexed LVEDV from 103.9 ± 11.1 to 92.7 ± 14.3 mL/m² ($p<0.001$), confirming significant reverse LV remodeling.

Severe functional MR regressed from 21% to 10%. EROA decreased from 0.24 ± 0.08 to 0.16 ± 0.04 cm² ($p<0.001$) and regurgitant volume from 31 ± 11 to 24 ± 5 mL ($p<0.001$). PAPs decreased from 48 ± 6 to 25 ± 8 mmHg ($p<0.001$). E/E' ratio improved from 10.7 ± 3.2 to 6.3 ± 1.4 ($p<0.001$); the proportion of patients with elevated filling pressures decreased from 38% to 10%.

3.5. Dosing and tolerability

The target dose of 200 mg twice daily was achieved in 72% of patients, 100 mg twice daily in 20%, 50 mg twice daily in 6%, and 2% discontinued treatment. Adverse events requiring discontinuation occurred in only 6%: renal function deterioration 4%, symptomatic hypotension 2%, and no cases of angioedema (0%). Overall treatment tolerability was excellent, with 94% of patients completing follow-up without major adverse events.

Table 1. Baseline clinical, demographic, and biological characteristics (n=300)

Variable	Value (n=300)
Age (years)	61.2 ± 5.3
Male sex (%)	64% (n=192)
BMI (kg/m²)	27.5 ± 7.3
Systolic BP (mmHg)	132.1 ± 34.5
Diastolic BP (mmHg)	86.5 ± 16.3
Heart rate (bpm)	84.2 ± 29
Serum creatinine (mg/L)	10.1 ± 4.8
eGFR (mL/min/1.73m²)	68.4 ± 22.7
Ischemic etiology (%)	68%
Atrial fibrillation (%)	48%
Hypertension (%)	60.5%
Type 2 diabetes (%)	40%

Dyslipidemia (%)	38.5%
Smoking (%)	35%
Obesity (%)	30%
CKD (%)	7%
LBBB on ECG (%)	38%
QRS >120 ms (%)	42%
Sinus rhythm (%)	42%
Prior beta-blocker (%)	100%
Prior ACE-i/ARB (%)	100%
Prior MRA (%)	88%
Prior ivabradine (%)	20%
Prior diuretics (%)	44%

BP: blood pressure; BMI: body mass index; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; LBBB: left bundle branch block; MRA: mineralocorticoid receptor antagonist.

Table 2. Baseline echocardiographic parameters (n=300)

Echocardiographic parameter	Baseline value
LVEF (%)	30.7 ± 6.5
Indexed LVESV (mL/m²)	61.5 ± 12.9
Indexed LVEDV (mL/m²)	103.9 ± 11.1
Moderate functional MR (%)	28% (n=84)
Severe functional MR (%)	21% (n=63)
Mean EROA (cm²)	0.24 ± 0.08
Regurgitant volume (mL)	31 ± 11
Estimated PAPs (mmHg)	48 ± 6
E/e' ratio	10.7 ± 3.2
Elevated filling pressures E/e' >14 (%)	38% (n=114)

LVEF: left ventricular ejection fraction; LVESV/LVEDV: LV end-systolic/diastolic volume; MR: mitral regurgitation; EROA: effective regurgitant orifice area; PAPs: pulmonary artery systolic pressure.

Table 3. Clinical and echocardiographic outcomes at 12 months (n=300)

Parameter	Baseline	12 months	p-value
NYHA class I (%)	5%	56%	<0.001
NYHA class II (%)	28%	22%	<0.001
NYHA class III (%)	52%	18%	<0.001
NYHA class IV (%)	15%	4%	<0.001
Dyspnea (%)	95%	44%	<0.001
Peripheral oedema (%)	37.5%	4%	<0.001
Asthenia (%)	95%	22%	<0.001
LVEF (%)	30.7 ± 6.5	43.0 ± 7.3	<0.001
LVEF >40% recovery (%)	—	61% (n=183)	<0.001
LVEF ≥50% super-responders (%)	—	12% (n=36)	<0.001
Indexed LVESV (mL/m²)	61.5 ± 12.9	35.4 ± 15.9	<0.001
Indexed LVEDV (mL/m²)	103.9 ± 11.1	92.7 ± 14.3	<0.001
Severe functional MR (%)	21%	10%	<0.001
EROA (cm²)	0.24 ± 0.08	0.16 ± 0.04	<0.001
Regurgitant volume (mL)	31 ± 11	24 ± 5	<0.001
Estimated PAPs (mmHg)	48 ± 6	25 ± 8	<0.001
E/e' ratio	10.7 ± 3.2	6.3 ± 1.4	<0.001
Elevated filling pressures E/e' >14 (%)	38%	10%	<0.001

LVEF: LV ejection fraction; LVESV/LVEDV: LV end-systolic/diastolic volume; MR: mitral regurgitation; EROA: effective regurgitant orifice area; PAPs: pulmonary artery systolic pressure. Paired Student's t-test and McNemar's test.

Table 4. Sacubitril/valsartan dosing and tolerability at 12 months

Parameter	Value
Target dose achieved — 200 mg twice daily (%)	72% (n=216)
Intermediate dose — 100 mg twice daily (%)	20% (n=60)
Low dose maintained — 50 mg twice daily (%)	6% (n=18)
Treatment discontinuation (%)	2% (n=6)
Total adverse events requiring discontinuation (%)	6% (n=18)
— Renal function deterioration (%)	4% (n=12)

— Symptomatic hypotension (%)	2% (n=6)
— Angioedema (%)	0%
Patients completing 12-month follow-up without adverse events (%)	94% (n=282)

Adverse events defined as those requiring dose reduction or permanent treatment discontinuation.

4. DISCUSSION

Our real-world series of 300 HFrEF patients confirms the comprehensive clinical and echocardiographic benefits of sacubitril/valsartan observed in the PARADIGM-HF trial [1], extending them to a population with a high burden of ischemic heart disease (68%), atrial fibrillation (48%), and multiple comorbidities typically under-represented in randomized trials. The degree of LVEF recovery observed in our cohort — from 30.7 ± 6.5% to 43.0 ± 7.3% ($p<0.001$), with 61% of patients recovering LVEF >40% — is consistent with published real-world data from Bordeaux reporting a similar reverse remodeling response in 200 patients [8]. The paired LVESV reduction (from 61.5 ± 12.9 to 35.4 ± 15.9 mL/m², $p<0.001$) reflects true reverse eccentric remodeling rather than simple preload reduction, supporting the hypothesis that neprilysin inhibition favorably modifies myocardial biology beyond hemodynamic effects [2, 6].

The 12% super-responder rate (LVEF recovery ≥50%) in our series raises an important clinical question: whether guideline-directed medical therapy should be maintained, de-escalated, or switched following LVEF normalization. Current evidence from three small studies suggests that treatment discontinuation is associated with LV dysfunction recurrence in 20–30% of cases and HF rehospitalization in 33%, supporting the recommendation to maintain therapy indefinitely regardless of LVEF phenotype recovery [3].

The significant regression of severe functional MR (from 21% to 10%, $p<0.001$) with parallel reduction in EROA and regurgitant volume confirms data from the PRIME trial [9], which demonstrated the superiority of sacubitril/valsartan over valsartan alone in reducing functional MR through reverse LV remodeling. In our predominantly ischemic cohort, this finding is clinically meaningful: functional MR regression reduces volume overload, further supporting the reverse remodeling process and potentially avoiding or delaying the need for mitral intervention.

The dramatic reduction in PAPs (from 48 ± 6 to 25 ± 8 mmHg) and normalization of filling pressures (E/E' from 10.7 ± 3.2 to 6.3 ± 1.4) confirm that sacubitril/valsartan comprehensively

addresses the hemodynamic consequences of HFrEF — not merely neurohormonal — through genuine cardiac reverse remodeling. The reduction in elevated filling pressure prevalence from 38% to 10% has direct prognostic implications, as elevated filling pressures are a strong independent predictor of HF hospitalization and mortality [15].

The excellent tolerability profile — 6% adverse events requiring discontinuation, no angioedema, and a 72% rate of achieving target dose — in a population with significant CKD (7%), atrial fibrillation (48%), and elderly patients (mean age 61.2 ± 5.3 years) is consistent with the TITRATION study experience [12] and supports gradual uptitration as an effective and safe strategy. Importantly, the initial fear of renal deterioration or dangerous hypotension in this complex population appears overestimated in real-world practice.

5. CONCLUSIONS

Sacubitril/valsartan demonstrates comprehensive clinical, echocardiographic, and hemodynamic benefits in a real-world HFrEF population with high ischemic burden, atrial fibrillation, and multiple comorbidities. Beyond the well-established mortality and hospitalization reduction, it induces significant reverse LV remodeling, LVEF recovery in the majority of patients, regression of functional mitral regurgitation, and normalization of filling and pulmonary pressures. Its tolerability is excellent with a 6% adverse event rate and 72% target dose achievement. These real-world data from a Moroccan military hospital support the systematic use of sacubitril/valsartan as a cornerstone of modern HFrEF management and reinforce the importance of echocardiographic monitoring to document reverse remodeling and guide therapeutic decisions.

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Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of Moulay Ismail Military Hospital, Meknes, Morocco. Patient informed consent was waived due to the retrospective, non-interventional nature of the study.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Competing interests : The authors declare that they have no competing interests.

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