Safety analysis of sacubitril/valsartan in patients with heart failure in Vitória, Espírito Santo

Safety analysis of sacubitril/valsartan in HFrEF

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ABSTRACT

Background: Sacubitril/valsartan has proven its efficacy to reduce cardiovascular mortality, all-cause mortality and sudden death in heart failure with reduced ejection fraction (HFrEF). Thus, it becomes important to evaluate the safety profile of the medication in clinical practice.

Objectives: This study aimed to assess safety outcomes on the use of sacubitril/valsartan in patients with HFrEF attended in a Brazilian specialized service.

Methods: Prospective observational study that included patients with HFrEF from a specialized ambulatory service, in functional class II-IV, initiated on sacubitril/valsartan as per clinical indication, with a four-month follow-up. Primary outcomes were the occurrence of symptomatic arterial hypotension, hyperkalemia and reduction of renal function. Serum potassium values, blood pressure and creatinine clearance were analyzed at inclusion and at the end of follow-up. A 5% significance level was considered for comparisons.

Results: Twenty-six patients were analyzed, 57.7% male, mean age 57.8 ± 10 years, average left ventricle ejection fraction 29.9 ± 7.7%. Symptomatic hypotension occurred in 53.8%, hyperkalemia in 19.2% and reduction of renal function in 6.7%. There was significant difference from initial to final systolic (122 ± 24mmHg versus 109 ± 15mmHg; p=0.024) and diastolic (76 ± 18mmHg versus 66 ± 12mmHg; p=0.022) blood pressure, but no difference in serum potassium (4.8 ± 0.4mEq/L versus 5.0 ± 0.3mEq/L; p=0.07) and creatinine clearance (65 ± 23mL/min/1.73m² versus 66 ± 29mL/min/1.73m²; p=0.89).

Conclusions: Symptomatic hypotension was the most frequent side-effect of sacubitril/valsartan. Reduction of blood pressure was observed at the end of follow-up, but no reduction of renal function or significant increase of serum potassium.

INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF) is a chronic disease with high morbidity and mortality, affecting over 26 milllion individuals around the globe.[1] From diagnosis, clinical evolution is insidious despite medical treatment, causing death in at least in fourth of the patients after five years.[2] In Brazil and other developing countries, the scenario is even worse, with urgent need to implement the best therapies available to reduce adverse outcomes. The BREATHE registry (*Brazilian Registry of Heart Failure - Clinical aspects, care quality and hospitalization outcomes*) highlighted the real-world national mortality of 12.6%, four times higher than in countries such as the United States.[3,4]

Important therapeutic milestones with prognostic impact in HFrEF arised throughout the years and decades. In the late 1980's and early 1990's, angiotensin–converting-enzyme inhibitors (ACEI) proved their efficacy in HFrEF by reducing mortality in more than 30%.[5,6] In 1997 the use of mineralocorticoid receptor antagonists, such as spironolactone showed a significant benefit in HFrEF as an add-on medication.[7] In 2001, metoprolol succinate and carvedilol confirmed the irrefutable role of beta-blockers in HFrEF almost simultaneously, defining the pharmacological triad that sustains the treatment of the disease until nowadays.[8,9] After that, only in 2014 the PARADIGM-HF study (*Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial)* revealed sacubitril-valsartan as a new treatment option with significant survival benefit.[10]

National and international guidelines recommend to prescribe sacubitril/valsartan to patients with symptomatic HFrEF despite optimal medical treatment.[11-13] However, possible side-effects, such as arterial hypotension, hyperkalemia and acute renal dysfunction can inhibit its use in some populations. Local and regional analysis are desirable in HFrEF and contribute to the knowledge concerning medical therapy in HFrEF. Thus, the aim of this study was to

assess tolerability and safety outcomes of sacubitril/valsartan in patients with HFrEF who were refractory to optimized medical treatment.

METHODS

Study Design

Observational prospective study.

Population

We analyzed patients with HFrEF from an ambulatory specialized service that belongs to Brazilian public health system, included from April to August 2018, with clinical follow-up of at least four months. One-hundred and five patients were initially identified in regular appointments in the specialized ambulatory service.

Inclusion Criteria

Patients 18 years of age or older, with previous diagnosis of HFrEF – left ventricle ejection fraction (LVEF) lower than 40% by Simpson method on echocardiogram performed in the last two years. Patients were in New York Heart Association (NYHA) functional class II to IV despite optimal medical therapy, and were initiated on sacubitril/valsartan by medical indication. Optimal medical treatment was considered as the use of ACEI or angiotensin II receptor blocker (ARB), beta-blocker and mineralocorticoid receptor antagonist, in target-doses or in maximum tolerated doses. Sacubitril/valsartan was initiated in a 24/26mg dose BID, with up-titration to 49/51mg and 97/103mg BID in two to four weeks if tolerated. Whenever it was not possible to increase doses, medical staff kept the dose in use. In case of serious adverse events, such as sever hyperkalemia (>6.0mEq/L), acute renal failure or symptomatic hypotension attributed to sacubitril/valsartan, the medication was discontinued

and resumed upon clinical resolution of the complication. Patients with symptomatic hypotension could be managed individually, with attempts to reduce symptoms by simple recommendations such as reducing diuretics or other anti-hypertensive drugs, mantaining the HFeRF medications whenever possible.

Exclusion Criteria

Patients were excluded if creatine clearance was lower than 30mL/min/1.73m² by *Modification of Diet in Renal Disease Study* (MDRD) formula, hyperkalemia (serum potassium higher than 5.5 mEq/L), systolic blood pressure lower than 100mmHg or medical history of allergy or angioedema after using valsartan. We also excluded patients that interrupted the medication with no medical orientation and no clinical reason for discontinuation, and patients that discontinued medical follow-up in the institution for any reason.

Data Collection and Variables

Data from medical evaluations and complementary exams were obtained from medical registries at admission and after the four-month folllow-up. Data collected included age, gender, comorbidities (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation and pulmonary artery hypertension), etiology of HFrEF, and medications in use (ACEI or ARB, beta-blockers, spironolactone, diuretics and anticoagulants). Data referring to study outcomes, such as serum potassium, creatinine clearance and blood pressure, were routinely measured after admission and throughout follow-up by medical staff. Patients were systematically questioned about the occurrence of symptomatic hypotension. Blood pressure was measured at least twice in every medical appointment, in both arms, with digital equipment (Omron®), after five to ten minutes rest, in sitting position, with the back of the body leaned on the chair, legs uncrossed and feet flat on the floor.

Routine evaluations were done weekly during the first month of medication usage, and every 15 or 30 days after one month, depending on individual clinical conditions. Laboratory assessment was done every 30 days, according to institutional protocol, or within shorter intervals if complications occurred. Patients who did not return for appointments were contacted by telephone for rescheduling and data collection.

Outcomes

Clinical events considered as safety outcomes of the study were: symptomatic arterial hypotension (systolic blood pressure lower than 90mmHg accompanied by at least one of the following symptoms: syncope, pre-syncope, temporary visual blurring or dizziness with no other reasons), hyperkalemia (serum potassium higher than 5.5 mEq/L) and acute reduction of renal function with creatinine clearance lower than 30mL/min/1.73 m² by MDRD formula or reduction of serum creatinine higher than 25% from baseline. Orthostatic hypotension, if symptomatic, were equally considered as symptomatic hypotension. Initial and final average values of blood pressure, serum potassium and creatinine clearance were compared. Efficacy outcomes of LVEF and NYHA functional class at admission and end of follow-up were analyzed as exploratory data, with no statistical power to detect differences in such comparisons. Clinical hard endpoints were also computed – death and hospitalization due to decompensated HFeRF.

Sample Size Calculation

For sample size effect, considering an alfa error of 5% and confidence level of 95%, with an estimation of outcomes occurrence of 30% in sample throughout follow-up, we estimated a sample size of 24 patients, with 80% power. Due to prediction of loss of follow-up in up to 15%, we calculated a sample size of 30 patients to be included in the study.

Ethical Aspects

The study was approved by the institutional Research Ethics Comittee under the number 2.618.469 and developed under ethical principles of the Helsinki declaration, complying with resolution 466/2012. All patients included in the study received the medication from the institution at no charge. Sacubitril/valsartan was prescribed as per institutional protocol, with no specific interventions from the research team. All patients read, comprehended and signed the free informed consent for participation in the study.

Statistical Analysis

Categorical variables were described as absolute numbers and percentages, and continuous variables were described as mean and standard-deviation when they presented normal distribution. Comparative analysis were made on Statistical Package for the Social Sciences *(*SPSS) software version 23.0, using the Chi-Square test, the Fisher test and the paired t-student test, adopting a significance level of 5%.

RESULTS

Amongst HFrEF oupatients in ambulatory follow-up throuhout the inclusion period, 31 patients met inclusion criteria and were prescribed sacubitril/valsartan in place of an ACEI or an ARB. Five patients were excluded and 26 (83.9%) completed the four-month follow-up, compounding the analyzed sample (Figure 1). Etiology of HFrEF was mostly ischemic cardiomyopathy or idiopathic dilated cardiomyopathy. Wide usage of mortality reducing medications was observed at inclusion. Table 1 highlights the baseline clinical characteristics. Symptomatic arterial hypotension occurred in 14 patients (53.8%). Five patients (19.2%) presented hyperkalemia throughout clinical follow-up. No patients had serum potassium dosage above 6.0 mEq/L. Two patients (6.7%) presented reduction of creatinine clearance greater than 25% from baseline, and no patients had reduction of creatinine clearance below 30mL/min/1.73m². No patients needed definitive discontinuation of medication due to blood

pressure, hyperkalemia or acute renal dysfunction. Temporary discontinuation due to symptomatic hypotension was necessary in 11 patients (78.6% of those who presented symptomatic hypotension) and due to hyperkalemia in five patients (100% of those who presented hyperkalemia). No patients needed to discontinue medication, even temporarily, due to acute renal dysfunction. Initial and final mean values of systolic and diastolic blood pressure, serum potassium and creatinine clearance are described in Table 2. Among patients who needed to interrupt sacubitril/valsartan by medical indication, the average number of days in use of maximum dose was 78.8 days in those who presented symptomatic hypotension versus 77.4 days in those who did not (p=0.48), and 73.0 days in those who presented hyperkalemia versus 78.9 days in those who did not (p=0.65).

Mean LVEF on admission and end of follow-up was respectively 29.9 ± 7.7% and 34.0 ± 7.8% (p=0.04). Mean NYHA functional class at both moments was 2.1 ± 0.5 and 1.1 ± 0.3 (p=0.01). Twenty-two patients (84.6%) improved functional class, and 21 (80.8%) were on functional class I at the end of follow-up. No patients presented worsening NYHA functional class. One death (3.8%) and one hospitalization due to decompensated HFrEF (3.8%) occurred throughout follow-up.

DISCUSSION

As a recently-approved medication that is still being incorporated in therapeutic arsenal of HFrEF in Brazil, there is paucity of real-world safety studies for sacubitril/valsartan in Brazilian population. In our sample, composed of refractory HFrEF patients on optimal medical therapy, the occurrence of symptomatic hypotension was high, although with good clinical control through simple medical end behavioral management in most cases. We also

observed, in lower extent, hyperkalemia and reduction of renal function, both with no significant clinical repercussion.

Sacubitril/valsartan promotes important vasodilation, once it inhibits degradation of natriuretic peptides, leading to increased natriuresis, diuresis and systemic vasodilation.[14] In PARADIGM-HF, group sacubitril/valsartan had significant reduction of blood pressure after eight months when compared to group enalapril. Symptomatic hypotension occurred in 14.0% of patients on sacubitril/valsartan and in 9.2% of patients on ACEI ($p<0.001$).[10] In a French pharmacovigilance study, arterial hypotension was also the main side-effect of sacubitril/valsartan, affecting 18% of patients on use of medication.[15] In our study, more than half of patients on sacubitril/valsartan presented symptomatic hypotension whenever questioned. Nevertheless, no patients needed to interrupt the medication definitively, and the presence of symptoms did not cause reduction of days in use of target-dose. We attributed the higher occurrence of this side-effect in our study due to frequent clinical monitoring, with active investigation during medical appointments by questioning symptoms. Dealing with a drug that was recently inserted in clinical practice, this approach was embraced in order to reduce possible serious adverse events during follow-up. Methods of questioning and interviewing might have influenced theses results, since a number of HFrEF patients often tolerate hypotension with no relevant symptoms. When questioned, these might have confirmed symptoms, increasing the report of this outcome.

The occurrence of hyperkalemia and plasmatic elevation of nitrogenous compounds is common during natural history of HFrEF, especially during decompensating episodes.[16,17] In the PIONEER-HF study, the incidence of hyperkalemia in hospitalized patients was 11.6% in those who initiated sacubitril/valsartan versus 9.3% in those who received enalapril (relative risk 1.25; 95% confidence interval 0.84-1.84).[18] Even in outpatients, mainly in those with associated chronic kidney disease, the risk of hyperkalemia is higher.[12] Advanced age, male

gender, baseline hyperkalemia, diabetes and blockage of renin-angiotensin-aldosterone system (RAAS) are predisposing factors for hyperkalemia.[19] The last one is an integrant part of optimal medical therapy, once the use of mineralocorticoid receptor antagonists reduces the risk of death in HFrEF significantly.[20,21] Our study showed a mild increase in average serum potassium, not carrying higher risk of serious outcomes such as cardiac arrythmias and, therefore, interruption of medication. Noteworthy, it is not recommended to initiate spironolactone if baseline creatinine level is higher than 2.5mg/dl or if serum potassium is higher than 5.0mEq/L.[11] Once spironolactone is initiated, close monitoring of serum potassium and creatinine is necessary.[11] Interruption criteria include serum potassium dosage higher than 6.0mEq/L or serum creatinine higher than 3.5mg/dl. For potassium dosages between 5.6 and 6.0mEq/L, or creatinine between 2.5 and 3.5mEq/L, dose reduction and frequent laboratory monitoring are recommended.[12]

RAAS blockage can initially cause hemodynamic renal alterations, although not promoting severe worsening of glomerular filtration.[22] Yet, strict observation is necessary, since multiple mechanisms of reducing glomerular filtration may exist in the association between cardiac and renal dysfunction.[23,24] In PARADIGM-HF, no differences of renal function were observed between groups sacubitril/valsartan and enalapril (2.2% versus 2.6%; relative risk 0.86; 95% confidence interval 0.65-1.13; p=0.28).[10] According to these findings concerning safety of sacubitril/valsartan, the drug does not seem to impact renal function negatively, despite the high frequency of symptomatic hypotension. Equally important to note, patients with creatinine clearance <30mL/min/1.73m² were excluded, thus the safety profile of the medication in this population remains unknown.

Recent therapeutic innovations have been described for HFrEF with improving survival, which was not seen for years in clinical trials.[10,25-27] Sacubitril/valsartan represents a new pharmacological option in HFrEF, capable of reducing mortality in 16%, cardiovascular

mortality in 20%, and hospitalizations due to HFrEF in 21%.[10] With clinically relevant net benefit and favourable safety profile as shown in real-world studies, sacubitril/valsartan must be included in the frontline therapeutic arsenal of HFrEF. Tolerability issues seem to lay mostly on symptomatic hypotension, a less critical event that can generally be managed with reduction or interruption of diuretics, demystification of water restriction, and postural and behavioral education. However, it is important to address local and regional individual data, since ethnical and body constitution differences can interfere on pharmacological tolerance. Thus, focus on therapeutic adherence and administration of mortality-reducing drugs may can play its role to prolong life and improve quality of life in patients with HFrEF.

Although relevant in our population, our study has limitations, especially those related to the small sample size. Despite demonstrating significant clinical benefit related to LVEF and NYHA functional class on follow-up, this study did not have sufficient power for this efficacy analysis. Besides, the study was conducted in a HFrEF specialized center located in a medical teaching institution, with major initiatives to promote higher therapeutic adherence, such as continuous education, family meetings and frequent medical appointments. Then, these results must be regarded carefully, since most national public institutions lack these resources and protocols and might have higher rates of drug interruption.

CONCLUSIONS

Sacubitril/valsartan demonstrated to be safe in Brazilian clinical practice, in a high-risk and refractory group of patients with HFrEF treated in a specialized ambulatory service. Symptomatic aterial hypotension was mentioned at some moment of follow-up by more than half of included patients. Nevertheless, definitive drug interruption was not necessary in any cases. Hyperkalemia and worsening of renal function were less frequent adverse outcomes.

Knowing adverse effects of medications used for HFrEF is a major concern for multidisciplinary teams to provide timely actions and aggressive, yet safe, treatments. Finally, enabling the use of survival-improving medications such as sacubitril/valsartan is one of the primary challenges in clinical management of patients with HFrEF.

DATA AVAILABILITY STATEMENT

Data can be provided by corresponding author Roberto Ramos Barbosa on reasonable request.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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None.

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FIGURE CAPTION

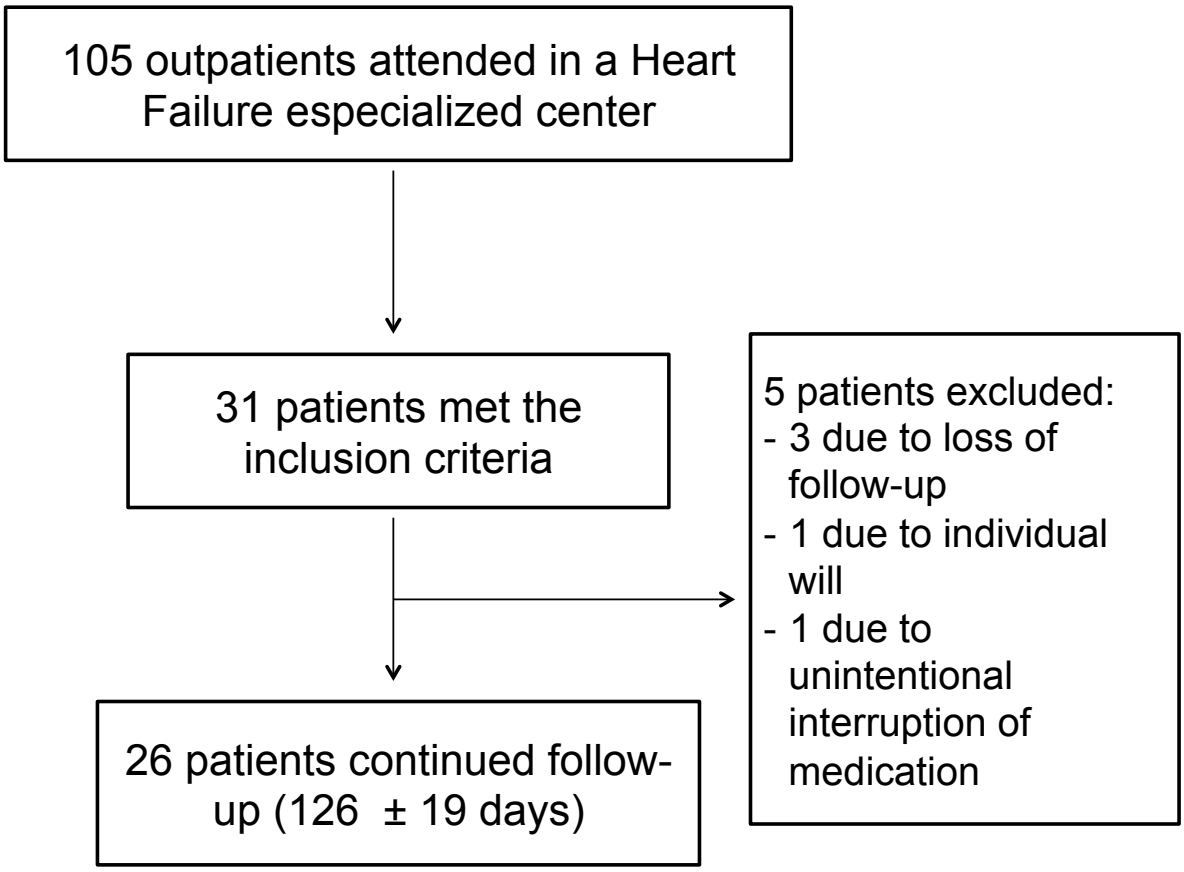

Figure 1. Fluxogram of inclusion and exclusion in the study.

TABLES

Table 1. Baseline clinical characteristics of patients with heart failure with reduced ejection fraction that initiated sacubitril/valsartan.

	Total (n=26)
GENDER, n (%)	
Male	15 (57.7)
Female	11 (42.3)
AGE**, median ± SD*	57.8 ± 10
ETIOLOGY, n (%)	
Ischemic	8 (30.8)
Idiopathic	8 (30.8)
Alcoholic	7 (26.9)
Chemotherapy	1 (3.8)
Others	2 (7.7)
COMORBIDITIES, n (%)	
Hypertension	18 (69.2)
Dyslipidemia	17 (65.9)
Diabetes mellitus	13 (50.0)
Atrial fibrillation	7 (26.9)
Pulmonary artery hypertension	5 (19.2)
Previous ACEI†/ARB‡, n (%)	26 (100.0)
ACEI	13 (50.0)
ARB	13 (50.0)
MEDICATIONS*, n (%)	
Beta-blocker	26 (100.0)
Carvedilol	23 (88.5)
Metoprolol succinate	3 (11.5)
Spironolactone	23 (88.5)
Diuretics	15 (57.7)
Furosemide	7 (26.9)
Thiazides	8 (30.8)
Anticoagulants	9 (34.6)
Warfarin	5 (19.2)
Dabigatran	4 (15.4)

* Standard-deviation; † Angiotensin-converting-enzyme inhibitor; ‡ Angiotensin II receptor blocker.

Table 2. Safety outcomes of patients with heart failure with reduced ejection fraction that initiated sacubitril/valsartan.

Variables	Mean ± standard-deviation	p-value
Systolic blood pressure (mmHg)		
Initial	122 ± 24	p = 0.024
Final	109 ± 15	
Diastolic blood pressure (mmHg)		
Initial	76 ± 18	p = 0.022
Final	66 ± 12	
Serum potassium (mg/dl)		
Initial	4.8 ± 0.4	p = 0.07
Final	5.0 ± 0.3	
Creatinine clearance (ml/min/1.73m²)		
Initial	65 ± 23	p = 0.89
Final	66 ± 29	

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Sacubitril/valsartan demonstrated a favourable safety profile in heart failure outpatients in Vitória, Espírito Santo. This single-center study showed a major occurrence of symptomatic hypotension (53.8%), although with an intensive questioning method. Nevertheless, serious adverse outcomes such as hyperkalemia and reduction of renal function were rare. This new knowledge in this specific population is important to allow wide use of prognostic-improving therapies in heart failure.

AUTHORS CONTRIBUTIONS

Conception and design of the research: Barbosa RR, Gomes NSSC, Batista LB, Lima PD, Serpa RG, Calil OA, Barbosa LFM. Acquisition of data: Barbosa RR, Gomes NSSC, Batista LB, Lima PD, Serpa RG, Calil OA, Barbosa LFM. Analysis and interpretation of the data: Barbosa RR, Gomes NSSC, Batista LB, Lima PD, Barbosa LFM. Statistical analysis: Barbosa RR. Obtaining financing: None. Writing of the manuscript: Barbosa RR, Gomes NSSC, Batista LB. Critical revision of the manuscript for intellectual content: Barbosa RR, Barbosa LFM.