

Clinical Representativeness of the PARADIGM-HF Study in an Outpatient Cohort of Patients with Heart Failure, Including Chagas Disease, Treated According to Guideline-directed Medical Therapy: Prospective Study, in a Single Center in Brazil

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Authors' contributions

This work was carried out in collaboration among all authors. Author RMFLS designed the study, performed the statistical analysis and wrote the first draft of the manuscript. Authors PVCG and EKII collected data and managed the analysis of the study. All authors read and approved the final manuscript.

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ABSTRACT

Background: In the PARADIGM-HF trial there was a 20% reduction in hospitalization and cardiovascular mortality in patients with heart failure (HF) and treated according to guideline-directed medical therapy. Eligibility for the use of sacubitril/valsartan in the real world has varied between 12% and 76%. There are no studies on the national scene on this eligibility.

Aims: To investigate the clinical eligibility of the PARADIGM-HF trial in patients with HF in the outpatient clinic of a university institution, which also includes Chagas disease, and to compare the profile of the two populations.

Study Design: This is a single center, prospective, observational study.

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Place and Duration of Study: Department of Internal Medicine, Faculty of Medicine, Hospital das Clínicas, Federal University of Minas Gerais, Brazil, duration 6 consecutive months.

Methods and Results: We included 136 consecutive outpatients with HF, 53 women, and mean age of 54.2 years, underwent clinical and laboratory evaluation. The main etiologies of HF were ischemic, Chagas disease and idiopathic. The means of baseline variables were 117.2 mmHg for systolic blood pressure, 78.4 bpm for heart rate, 1.8 for dyspnea functional class, 0.39 for ejection fraction (EF) and 74.2 mL/min for creatinine clearance. The exclusion criteria considered in the PARADIGM-HF trial and present in this study were systolic blood pressure less than 95 mmHg in 15.4% and creatinine clearance less than 30 mL/min in 5.1% of patients. 22.1% had mid-range EF and 55.9% had reduced EF. Comparing this cohort of patients with the population of the PARADIGM-HF trial, age, systolic blood pressure, proportion of male patients, ischemic etiology, hypertension, patients with atrial fibrillation, use of angiotensin-converting enzyme inhibitor, furosemide and beta-blocker were lower in this study ($p \leq 0.01$, chi-square and Student's t tests). The proportion of diabetic patients, use of angiotensin receptor blocker, aldosterone antagonist and digoxin were similar between groups as well as proportion of patients with cardiac resynchronization therapy.

Conclusions: Up to 44% of patients in this study did not meet the main randomized trial criteria. Chagas disease was one of the main etiologies. Furthermore, systolic blood pressure, proportion of hypertensive patients was lower, which may have influenced the underutilization of some medications.

Keywords: Sacubitril/valsartan; angiotensin receptor-neprilysin inhibitor; chronic heart failure; chagas disease; eligibility; guideline-directed medical therapy.

1. INTRODUCTION

Heart failure (HF) is a clinical syndrome with symptoms and/or signs of intolerance to efforts and/or water retention [1]. The decrease in cardiac output and the increase in intracardiac pressures that occur in HF trigger neurohumoral activation mechanisms [2,3]. With decreased cardiac output, there is less action of central inhibitory signals by baroreceptors, with activation of the sympathetic nervous system. The norepinephrine resulting from this activation induces peripheral vasoconstriction, maintaining perfusion to the vital organs, and increases heart rate and myocardial contraction. The decrease in cardiac output also leads to reduced renal perfusion and decreased detected sodium load in the macula densa in the distal tubule. This action and that of the sympathetic nervous system will result in activation of the renin-angiotensin-aldosterone system through the juxtaglomerular cells. There is also pro-inflammatory cytokine production due to the mechanical overload of cardiomyocytes and less parasympathetic action, among others. All this sustained neurohumoral activation is responsible for the desensitization of the adrenergic receptor, for fibrosis, endothelial and baroreflex dysfunction. Another system is activated early, the counter-regulator system, which mainly includes natriuretic peptides, bradykinin, nitric oxide, prostaglandins and prostacyclins. Thus, the pharmacological

treatment of HF is based on these neurohumoral mechanisms in order to reduce morbidity and mortality [1].

PARADIGM-HF trial was randomized, double-blind study, with the inclusion of 4187 patients for use of sacubitril/valsartan and 4212 for use of enalapril [3]. All patients, at least 18 years old, had heart failure (HF), with NYHA (New York Heart Association) functional class II-IV, ejection fraction (EF) $\leq 40\%$ and with B-type natriuretic peptide (BNP) ≥ 150 pg/dL or NT-proBNP ≥ 600 pg / dL, or with a history of hospitalization in the last 12 months. There was an early interruption of the study, at 27 months, because intermediate results showed a reduction of about 20% in hospitalization and cardiovascular mortality in patients who were already receiving other drugs such as beta-blockers and mineralocorticoid-receptor antagonists. In view of these results, the use of angiotensin receptor-neprilysin inhibitor (ARNI) is class I of recommendation for patients with chronic symptomatic HF with reduced ejection fraction in NYHA class II or III who tolerate an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). ARNI should be administered 36 h after the suspension of ACEI and should not be used in patients with a history of angioedema [4].

Despite this evidence, the eligibility of patients for the use of ARNI is variable in the real world,

between 12% and 76%, due to the inclusion criteria of the randomized study and the adverse effects of the drug [5-8].

In Brazil, its use was approved in May 2017 by ANVISA (Agência Nacional de Vigilância Sanitária) and only in August 2019 for use in the National Health System [9]. Data on ARNI and HF due to Chagas disease are scarce and should be interpreted with caution given the particularities of this etiology [10]. There are no studies on the national scene on this eligibility.

Therefore, the main objectives of this study are to investigate the clinical eligibility of the PARADIGM-HF trial in patients with HF in the outpatient clinic of a university institution, which also includes Chagas disease, and to compare the profile of the two populations.

2. METHODS

2.1 Patients and Methods

This is a prospective, observational study of 136 consecutive patients with HF from a single university hospital center included in an outpatient visit after patient invitation and acceptance. Patients underwent clinical and laboratory evaluation (electrocardiogram, echocardiogram and clinical medicine analysis). BNP was not evaluated for its unavailability. The diagnosis of HF was initially made by the attending physician of cardiology outpatient clinic based on history, symptoms, physical signs and validated by trans-thoracic echocardiogram. Patients with HF due to heart valve disease and pregnant women were excluded. The treatment was done by the attending physicians of the patients, without the influence of the researchers. After treatment according to guideline-directed medical therapy and with tolerable titrated doses of medications, patients were included for 6 consecutive months (until May 2019).

2.2 Statistical Analysis

All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS, Inc. Chicago, IL, USA) - SPSS (version 14.0) software. The Kolmogorov-Smirnov test was applied and the population distribution of this study was normal. The results were expressed in numbers and proportions, for categorical variables, and data as mean \pm standard deviation (SD), for continuous variables. Chi-square test and Fisher's exact test, as appropriate, were

used to study associations between categorical variables. The continuous variables of the two groups (this study and PARADIGM-HF trial) were compared using the Student's t test. Multiple comparisons were performed using analysis of variance (ANOVA). The level of statistical significance was 5%.

3. RESULTS

3.1 Baseline Characteristics of the Participants

The mean age of patients was 54.2 years (\pm 15.1), ranging from 19 to 86 years, 53 women, with a mean EF 0.39 (calculated by Teichholz's formula). Thirty patients (22.1%) had mid-range EF and 76 (55.9%) had reduced EF. The means of baseline variables were 117.2 (\pm 21.5) mmHg for systolic blood pressure, 73.1 (\pm 12.5) for diastolic blood pressure, heart rate 78.4 (\pm 18.6) bpm (in patients without atrial fibrillation), NYHA functional class 1.8 (\pm 0.8), body mass index 26.1 (\pm 5.8 kg/m²) and creatinine clearance 74.2 (\pm 31.2) mL/min. Regarding NYHA class, 39% of patients were in class I and 46.3% were in class II.

The exclusion criteria considered in the PARADIGM-HF trial and present in this study were systolic blood pressure less than 95 mmHg in 15.4% and creatinine clearance less than 30 mL/min in 5.1% of patients. No patient had a history of angioedema or unacceptable side effects during receipt of ACEI or ARB.

3.2 Etiologies of HF and Comparison of the Variables in This Study

The main etiologies of HF were ischemic, Chagas disease and idiopathic. The other etiologies of HF were alcoholic (5.9%), peripartum (3 patients) and post-chemotherapy (one patient) cardiomyopathies, and viral myocarditis (2 patients). The proportions of the main etiologies of HF are shown in Fig. 1.

The mean age and EF were lower in patients with Chagas disease than in patients with ischemic heart disease (54.0 versus 62.5 years; 0.35 vs 0.42; $p=0.01$ and 0.03 , respectively).

Baseline systolic blood pressure was lower in idiopathic HF compared to chagasic and ischemic patients (103.5 ± 15.6 vs 113.9 ± 21.2 vs 118.4 ± 22.0 mmHg, respectively, $p=0.01$).

3.3 Comparison between Data from the Present Study and the PARADIGM-HF Trial

The proportion of diabetic patients (29.4% in the study versus 34.7% in the PARADIGM-HF, $p=0.36$), use of ARB (24.3% vs 22.2%, $p=0.07$), use of aldosterone antagonist (55.1% vs 54.2%, $p=0.88$) and digoxin (35.3% vs 29.2%, $p=0.36$) were similar between groups. The average daily doses were 61.8 (\pm 33.6) mg of losartan, 50.5 (\pm 28.2) mg of captopril and 16.7 (\pm 9.3) mg of enalapril in this study. Only one patient was using valsartan (80 mg daily).

The proportion of patients with cardiac resynchronization therapy was also no different between groups (1.5% vs 7.4%, $p=0.08$). Data comparisons of other variables are shown in Table 1.

4. DISCUSSION

This study demonstrated a different scenario of patients with HF in a specialty clinic in a center of the National Health System in a middle-income country, including Chagas disease among the three main HF etiologies.

Randomized clinical trials are performed with a highly selected population, with good adherence and the study is conducted in a well-controlled environment. For this reason, these studies may not have clinical representativeness in the real world even with evidence-based practice. In the real world, the conditions are not ideal, the patient population is heterogeneous and their adherence to treatment may be low [11].

There are some studies addressing the real-life eligibility of using sacubitril/valsartan with cohort of patients with chronic HF, medical records and HF Long-Term Registry [6-8,12-14].

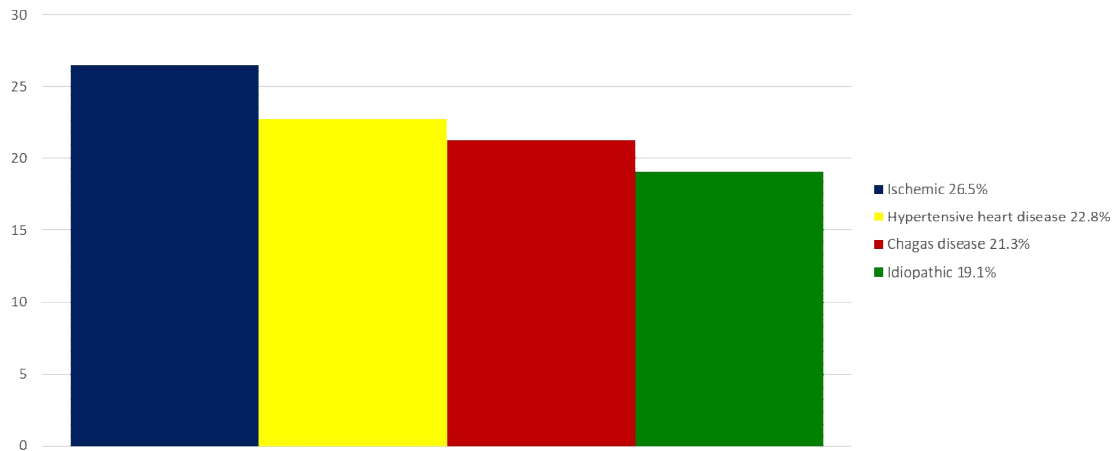


Fig. 1. Proportion of the main etiologies of HF in the study population

Table 1. Comparison between data from the present study and the PARADIGM-HF trial regarding clinical variables and drugs

Population/variables	This study	PARADIGM-HF trial	P-value
Age (years)	54.2	63.8	0.0001
Male (%)	61.0	79.0	0.0055
NYHA functional class \geq II (%)	46.3	94.7	0.0001
Systolic blood pressure (mmHg)	117.2	122.0	0.0003
Ischemic etiology (%)	26.5	59.9	0.0001
Hypertension (%)	47.0	70.9	0.0006
Patients with atrial fibrillation (%)	14.7	36.2	0.0007
ACEI (%)	54.4	78.0	0.0003
Furosemide (%)	64.7	80.3	0.0175
Beta-blocker (%)	55.9	93.0	0.0001

NYHA: New York Heart Association class; ACEI: Angiotensin-converting enzyme inhibitor

Cohort studies were prospective or retrospective, with 196, 224 and 452 patients with chronic HF [6,12,13]. In the study by Rodrigues et al [6], with 196 outpatients with HF, 44 had preserved EF. Therefore, 22% of patients with HF did not have mid-range EF or reduced EF, a proportion similar to this study. Of the 152 patients with reduced EF, 41.4% did not have $EF \leq 35\%$ and 30.9% did not use ACEI or ARB at doses equivalent to 20 mg per day of enalapril. About two in five of the patients with systolic HF would be considered eligible for PARADIGM-HF considering their inclusion and exclusion criteria.

Retrospective study of 224 patients with optimized guideline-directed medical therapy demonstrated that the indication for sacubitril/valsartan would be for 38.4% of patients [12]. One of the reasons for this ineligibility was the impossibility of using ACEI or ARB in 22.3% of patients, a proportion also similar to that of the present study, which was 21.3%.

In the real-world experience from Taiwan [13], the retrospective analysis of 452 patients from three medical institutes showed that the serum creatinine level was higher than in PARAFIGM-HF by about 36% (1.5 versus 1.1 mg/dL). Furthermore, 41.6% of patients received less than half the standard dose of sacubitril/valsartan. This demonstrates that renal impairment is one of the criteria of ineligibility for the use of that drug. In the study by Rodrigues [6], besides renal function impairment with 7.2% of patients with a glomerular filtration rate below 30 mL/min/1.73 m², greater than that of this study (5.1%), systolic blood pressure below 95 mmHg in 3.9% of patients were also identified as one of the criteria for the impossibility of indicating sacubitril/valsartan. Regarding blood pressure, the percentage of patients with systolic blood pressure below 95 mmHg in this study was higher [15.4%]. This can be explained by hemodynamic instability (lower systolic blood pressure and heart rate) in patients with chagasic cardiomyopathy, who are also younger (mean age of 51.8 years) [15]. In the studies cited there were no patients with Chagas disease as the etiology of HF, unlike this study with 21.3% with this etiology.

Comparing the Chagas disease with other HF etiologies (other nonischemic cardiomyopathy and ischemic cardiomyopathy), patients with Chagas disease are younger, have a low prevalence of arterial hypertension, but have worse health-related quality of life and higher

rates of hospitalization and mortality [16]. There are also differences in pharmacological treatment. Patients with HF due to Chagas disease receive the same proportion of ACEI as other patients with HF. However, they are treated less frequently with beta-blockers and digitalis, but with a higher proportion of mineralocorticoid receptor antagonists. Regarding the use of sacubitril/valsartan, data are scarce, since only 7.6% of the PARADIGM-HF trial and the ATMOSPHERE trial (Aliskiren Trial of Minimizing OutcomeS in Patients With HEart Failure) had Chagas disease [17].

The low representativeness of the PARADIGM-HF profile is also seen in larger studies. Among 1924 patients diagnosed with HF from medical records, only 5% were eligible for treatment with sacubitril/valsartan, reaching 24% among 401 patients with $EF \leq 35\%$ [14]. Data from the Swedish Heart Failure Registry with 12866 outpatients in NYHA functional class II – IV and $EF \leq 40\%$ showed that between 34 and 76% of them were eligible for the use of sacubitril/valsartan [7]. The most common reason for ineligibility was a low level of natriuretic peptide, followed by low systolic blood pressure in 7.9% of patients. Among 5443 outpatients from the ESC-EORP-HFA HF-LT Registry [8], only 12% and 28% met the PARADIGM-HF criteria, considering the doses of at least 20 mg and 10 mg of enalapril, respectively. The absent criteria were suboptimal pharmacotherapy (74%) and hypotension (7%).

In the PARADIGM-HF trial screening consultation, daily doses of enalapril were 16.4 ± 8.3 mg and losartan were 67.1 ± 30.2 mg. There was no use of captopril [4]. Therefore, the doses in this study were similar, despite the lower proportion of patients using ACEI and other medications for HF. The low proportion of patients reaching target ACEI or ARB target doses in clinical practice was also seen in the community HF clinic with 1396 patients. In this population, only 27.5% were on target doses at initial visit and 12% were eligible for the PARADIGM-HF criteria [18]. In addition to the ineligibility criteria such as problems such as renal dysfunction, hypotension and low proportion of target doses, the low prescription rate for sacubitril/valsartan is another aggravating factor. In the Veterans Administration Health System in the United States, among 27% of eligible patients, only 3.5% received the prescribed medication [19]. In another real-world clinical setting in a recent publication, with 1355 patients with HF, 20%

were eligible for use of sacubitril/valsartan and only 13% received the medication [20].

The comparison between this study and the PARADIGM-HF trial [4] pointed out other differences. The patients in this study were younger and this can be explained by the lower proportion of hypertensive patients and the presence of Chagas disease as one of the main etiologies. Consequently, the proportion of patients with atrial fibrillation was lower. Another difference was the NYHA functional class. This cohort consisted of outpatients. For this reason, the majority was stable. Other studies that assessed the eligibility of PARADIGM-HF also showed proportions of 88.1% and 79% of patients in NYHA class II [6,18]. This reflects the differences between real-world clinical practice and that of randomized trials.

There were geographic variations in the PARADIGM-HF trial with respect to age, symptoms, comorbidity, background therapy [21]. Among 17% of patients in Latin America, a higher proportion of women and patients in NYHA class II and less frequency of ischemic etiology were observed. It has also been shown that patients with HF due to Chagas Disease have lower systemic blood pressure and lower dose of ACEI or ARB and beta-blockers in comparison with other etiologies. For these particularities, HF due to Chagas disease has been considered an "Achilles' heel" in the interpretation of the PARADIGM-HF results [22]. Additionally, enalapril has never been tested in large randomized double prospective studies in patients with HF due to Chagas disease [23].

There are other barriers to the use of sacubitril/valsartan in addition to adverse effects and conditions such as renal failure and angioedema. The cost presents a barrier to the use of this drug. Among patients with an income greater than \$ 100,000 a year, 40% would not accept its use for the price [24]. Among Medicare beneficiaries the costs are high, but there was a 156% increase in the use of sacubitril/valsartan from 2016 to 2017 [25]. Therefore, the cost has an impact on patients' adherence to the use of sacubitril/valsartan according to their socioeconomic status and this has implications for the cardiovascular outcomes of these patients.

5. LIMITATIONS

This study has some limitations, such as the small number of patients, inclusion of patients

with a history of clinical HF independent of EF and the lack of BNP measurement. The etiologies of HF are different from those of developed countries.

6. CONCLUSIONS

Up to 44% of the patients in this study had the main exclusion criteria from the randomized trial also considering the left ventricular ejection fraction. Chagas disease was one of the main etiologies. Furthermore, systolic blood pressure, proportion of hypertensive patients was lower, which may have influenced the underutilization of some medications. This may impact the recommendation based on the PARADIGM-HF trial.

CONSENT

The authors declare that written informed consent was obtained from the patients.

ETHICAL APPROVAL

All authors declare that the research was approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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