

Prevalence and Clinical Determinants of Optimized Pharmacological Therapy in Heart Failure with Reduced Ejection Fraction

Anderson Oliveira Estevan,¹ Ana Luísa Guedes de Franca e Silva,¹ Salvador Rassi Filho,¹ Aguiinaldo Figueiredo de Freitas Júnior,¹ Salvador Rassi¹

Universidade Federal de Goiás,¹ Goiânia, GO – Brazil

Abstract

Background: In heart failure with reduced ejection fraction (HFrEF), optimized medical therapy (OMT) with beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) (or sacubitril/valsartan), spironolactone, and sodium-glucose cotransporter-2 inhibitors (SGLT2i), at target or maximally tolerated doses, reduces morbidity and mortality. However, real-world data show its underuse.

Objective: To estimate the prevalence and clinical associations that influence the use of OMT in clinical practice. **Methods:** Cross-sectional observational study including outpatients with HFrEF treated at a tertiary hospital. Clinical factors associated with therapy were assessed using binary logistic regression (95% confidence interval).

Results: A total of 266 patients were analyzed (mean age 61 years; 62.4% male), 113 (42.5%) with Chagas disease etiology. Mean ejection fraction was 34.2%. Vasodilators, beta-blockers, spironolactone, and SGLT2i were prescribed in 88%, 95.9%, 85.3%, and 27.4% of patients, respectively. The prevalence of OMT was 7.9% (21 patients). Diabetes was associated with a higher likelihood of OMT use ($p = 0.034$). Chagas disease was associated with lower probability of receiving vasodilators ($p = 0.015$) and greater use of furosemide, amiodarone, and digoxin ($p < 0.005$). Chronic kidney disease (CKD), age > 60 years, systolic blood pressure < 100 mmHg, and use of furosemide were associated with lower use of vasodilators ($p = 0.003$; 0.025 ; 0.010 ; and 0.046). CKD was associated with lower use of spironolactone ($p = 0.002$). Diabetes ($p = 0.002$) and use of furosemide ($p = 0.005$) were associated with SGLT2i use.

Conclusion: Despite the high prevalence of prescription of disease-modifying drugs, the use of OMT was significantly lower than expected. CKD, advanced age, arterial hypotension, and concomitant use of furosemide were associated with a reduced likelihood of receiving these agents, whereas diabetes was associated with a higher probability of OMT use.

Keywords: Heart Failure; Systolic Heart Failure; Drug Therapy.

Introduction

Heart failure (HF) represents a significant challenge for global public health, demanding effective therapeutic approaches to improve patients' quality of life and survival.^{1,2} In recent decades, there has been substantial progress in understanding the pathophysiology of HF with reduced ejection fraction (HFrEF), which has led to the development of pharmacological treatments capable of modifying the prognosis of the disease.³⁻⁵

Initially, the management of HFrEF was guided by hemodynamic strategies focused on symptom relief, with the use of diuretics, digitalis, and vasodilators. However, this

approach proved insufficient to alter disease progression. With a better understanding of HF pathophysiology, modulation of the neurohormonal system became the focus of treatment.^{4,5} Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) represented a milestone in the treatment of HFrEF, with reductions in morbidity and mortality.⁶ Subsequently, mineralocorticoid receptor antagonists (MRAs) and beta-blockers (BBs) were incorporated into therapy, consolidating the "triple therapy" as the cornerstone of HFrEF management.⁷ More recently, Angiotensin Receptor–Neprilysin Inhibitors (ARNIs) as well as Sodium–Glucose Cotransporter-2 Inhibitors (SGLT2i) have demonstrated efficacy in clinical trials and have been incorporated into the therapeutic arsenal for HFrEF.^{8,9}

The use of these drugs has transformed the treatment of HFrEF, providing significant improvements in quality of life and survival. The use of quadruple therapy, at the recommended target doses or at the maximum dose tolerated by the patient, has become conventionally defined as Optimized Medical Therapy (OMT) for HFrEF.¹⁰⁻¹² Despite the clinical evidence and established guidelines, a significant gap persists between literature recommendations and the implementation of OMT in clinical practice, reflecting multifactorial challenges.^{13,14}

Mailing Address: Anderson Oliveira Estevan •

Universidade Federal de Goiás – Cardiologia - R. 235, s/n. Postal Code 74605-220, Setor Leste, Universitário Goiânia, GO - Brazil

E-mail: estevan.anderson@hotmail.com

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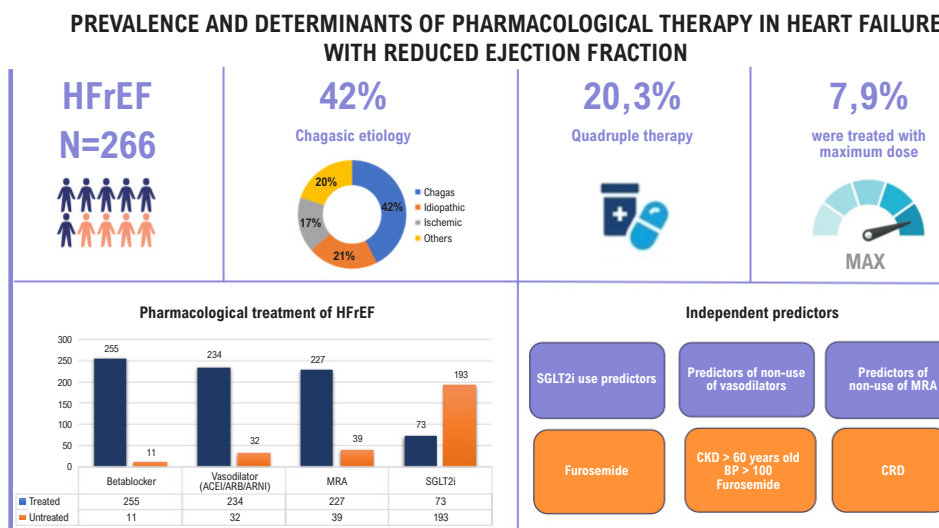
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Central Illustration: Prevalence and Clinical Determinants of Optimized Pharmacological Therapy in Heart Failure with Reduced Ejection Fraction



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ACEI: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; MRA: mineralocorticoid receptor antagonists; ARNIs: angiotensin receptor-neprilysin inhibitors; SGLT2i: sodium-glucose cotransporter-2 inhibitors; CKD: chronic kidney disease. Source: the authors.

The aim of this study was to estimate the prevalence of OMT prescription in a population of patients with HFrEF, according to current guidelines, as well as to identify possible clinical factors that may interfere with the use of the recommended pharmacological classes and their respective doses. Understanding the application of OMT in real-world patients contributes to identifying barriers and promoting strategies to improve treatment and, consequently, the prognosis of HFrEF.

Methods

Data collection

Data were collected over a 12-month period. The study was approved by the institutional Research Ethics Committee (REC) on 03/28/2022, under protocol number 5,315,449. The REC granted a waiver of the informed consent form, as provided by Resolution No. 466/2012. Information was collected through a structured questionnaire, based on the records of routine consultations of patients treated at the HF outpatient clinic of a tertiary university hospital.

The study included adults of both sexes aged 18 years or older with a diagnosis of HF with reduced left ventricular ejection fraction (LVEF $\leq$ 40%). Patients with at least two visits to the cardiology outpatient clinic were included. Exclusion criteria were palliative care (end-stage HF), hemodialysis, heart transplantation, and hospitalization within the three months

prior to the consultation, since such conditions could alter the prescription of HF pharmacological therapy.

Variables and definitions

The data assessment questionnaire included demographic variables (sex, age, and race), HF history (etiology and ejection fraction), clinical variables (functional class, blood pressure, and heart rate), laboratory variables (glomerular filtration rate, blood glucose, and electrolytes), and comorbidities. LVEF was measured using Simpson's method, based on the most recent echocardiogram.

Quadruple therapy was defined as the concomitant use of ACEI/ARB/ARNI combined with a beta-blocker, mineralocorticoid receptor antagonist, and SGLT2 inhibitor. OMT was defined as the concomitant use of quadruple therapy at target dose or at the maximum tolerated dose, according to the latest Update on Emerging Topics of the Brazilian Heart Failure Guideline – 2021.¹⁵ The maximum tolerated dose was defined by the presence of a previous unsuccessful attempt at dose escalation and by the presence of hypotension (blood pressure < 100 mmHg) and/or heart rate (HR) below 60 bpm. Dose titration was evaluated by comparing prescriptions over the last 12 months in a longitudinal manner.

Statistical analysis

The database was tabulated in EPIDATA® version 3.0, with double data entry and subsequent verification to minimize

typing errors. Analyses were conducted using IBM SPSS (Statistical Package for Social Science) version 26.0 (IBM Corp., Armonk, NY, USA), considering a significance level of 5% ($p < 0.05$). For comparison of categorical variables between groups, Pearson's chi-square test was used, while continuous variables were analyzed using Student's t-test for independent samples. Results were expressed as mean and standard deviation for continuous variables and as absolute and relative frequencies for categorical variables.¹⁶

The sociodemographic profile, etiologies, clinical and medication profiles were tested in five distinct models (use of OMT, vasodilators, beta-blockers, mineralocorticoid antagonists, and SGLT2 inhibitors). Each model consisted of two stages. First, a univariate logistic regression was performed to assess the association between each potential predictor variable and the response variable of each model. Variables with $p < 0.20$ in the first stage were included in the multivariate logistic regression analysis (second stage). Results were presented in terms of Wald statistics, pseudo- R^2 determination coefficient, odds ratio (OR) with 95% CI, and p-values.

Results

Data from 524 patients treated during the study period were evaluated. After applying inclusion and exclusion criteria, the final sample consisted of 266 patients with HFrEF.

Sample characteristics

The characterization of the total sample and according to OMT is presented in Table 1. The mean age of patients was 61.33 ± 13.24 years, with no significant difference between groups ($p = 0.583$). Most participants were male (62.4%), with no differences between groups with and without OMT ($p = 0.174$). LVEF was significantly lower in patients who received OMT ($29.57 \pm 8.94\%$) compared to those who did not receive this approach ($34.64 \pm 10.68\%$; $p = 0.049$). HR was also significantly lower in the OMT group (62.05 ± 8.15 bpm vs. 68.26 ± 12.41 bpm; $p = 0.045$).

Other variables, including hypertension, diabetes mellitus, Chronic Kidney Disease (CKD), and other comorbidities, did not show statistically significant differences between groups (Table 1). The most prevalent etiology of HF in this population was Chagas disease, representing 42.5% (113) of the sample, followed by

idiopathic dilated cardiomyopathy (21%) and ischemic etiology (16.5%).

Prevalence of OMT and medication classes

The prevalence of concomitant use of ACEI/ARB/ARNI, beta-blockers, MRAs, and SGLT2 inhibitors (quadruple therapy) was 20.3% (54 patients). The prevalence of OMT, defined as the use of quadruple therapy at target dose or maximum tolerated dose (as shown in the Central Figure), was 7.9% (21 patients). Vasodilators, beta-blockers, spironolactone, and gliflozins were prescribed in 88%, 95.9%, 85.3%, and 27.4% of patients, respectively.

Among the 116 patients using ACEIs, 96.5% (112) received enalapril, followed by 2.6% (3) captopril and 0.9% (1) ramipril. Among ARB users, 97.0% (64) were on losartan and 3.0% (2) on valsartan. A total of 12.0% (32) had a recorded contraindication to some vasodilator (renal dysfunction or hypotension). Regarding beta-blockers, carvedilol, metoprolol, and bisoprolol were used by 52.6% (134), 18.4% (47), and 29% (74) of patients, respectively. Contraindication to beta-blocker use was recorded in 2.3% (6), mainly due to severe asthma or bradycardia.

Spironolactone was the MRA used, and dapagliflozin was the SGLT2 inhibitor prescribed. MRA use was contraindicated in 5.3% (14), with renal dysfunction and hyperkalemia as the main causes. For SGLT2 inhibitors, 0.4% (1) had a reported contraindication described as "intolerance."

Dose evaluation

Figure 1 shows the distribution for each drug class according to the percentile of the target dose. It was observed that the BB class had the lowest proportion of patients receiving doses above 50% of the target dose, as shown in item C of Figure 1.

Etiology and pharmacological treatment

The logistic regression analysis between HF etiologies and pharmacological treatment revealed that patients with Chagas disease were 61% less likely to receive vasodilators (OR = 0.39; 95% CI = 0.18–0.85; $p = 0.015$). Conversely, these patients were more likely to be prescribed furosemide (OR = 2.40; 95% CI = 1.39–4.11; $p = 0.001$), amiodarone (OR = 4.98; 95% CI = 2.89–8.59; $p < 0.001$), and digoxin (OR = 3.75; 95% CI = 1.40–9.98; $p = 0.005$). Table 2 shows the associations found. No significant differences were observed in the use of HF medications across the other etiologies analyzed.

Table 1 – Characterization of the epidemiological profile and comorbidities in the total sample and according to optimized medical therapy (n = 266)

	Total	TMO		p
		No	Yes	
Age – year (Mean $\pm$ SD)	61.33 $\pm$ 13.24	61.20 $\pm$ 13.45	62.86 $\pm$ 10.77	0.583
Sex n (%)				
Female	100 (37.6)	95 (38.8)	5 (23.8)	0.174
Male	166 (62.4)	150 (61.2)	16 (76.2)	

Race n (%)				
Yellow	3 (1.1)	3 (1.2)	0 (0.0)	0.334
White	78 (29.3)	73 (29.8)	5 (23.8)	
Brown	162 (60.9)	150 (61.2)	12 (57.1)	
Black	23 (8.6)	19 (7.8)	4 (19.0)	
Etiology of HF n (%)				
Chagas	113 (42.5)	104 (42.4)	9 (42.9)	0.962
Idiopathic	56 (21.1)	52 (21.2)	4 (19.0)	
Ischemic	44 (16.5)	41 (16.7)	3 (14.3)	
Others	53 (19.9)	48 (19.6)	5 (23.8)	
SBP (mmHg) mean ± DP	111.91 ± 19.53	112.43 ± 19.33	105.81 ± 21.25	0.136
Ejection fraction (%)	34.54 ± 10.63	34.64 ± 10.68	29.57 ± 8.94	0.049
Heart rate (bpm)	67.77 ± 12.23	68.26 ± 12.41	62.05 ± 8.15	0.045
NYHA				
I	111 (41.7)	105 (42.9)	6 (28.6)	0.644
II	108 (40.6)	95 (38.8)	13 (61.9)	
III	40 (15.0)	38 (15.5)	2 (9.5)	
IV	7 (2.6)	7 (2.9)	0 (0.0)	
Use of devices n (%)				
No	189 (71.1)	175 (71.4)	14 (66.7)	0.644
Yes	77 (28.9)	70 (28.6)	7 (33.3)	
Comorbidities n (%)				
HAS	135 (50.8)	128 (52.2)	7 (33.3)	0.096
DLP	76 (28.6)	69 (28.2)	7 (33.3)	0.612
Atrial fibrillation	54 (20.3)	48 (19.6)	6 (28.6)	0.326
VT/VF	35 (13.2)	33 (13.5)	2 (9.5)	0.605
PAD	9 (3.4)	8 (3.3)	1 (4.8)	0.716
Depression	6 (2.3)	6 (2.4)	0 (0.0)	0.468
hypothyroidism	61 (22.9)	55 (22.4)	6 (28.6)	0.522
DM	58 (21.8)	50 (20.4)	8 (38.1)	0.064
AMI	32 (12.0)	29 (11.8)	3 (14.3)	0.741
CKD	45 (16.9)	39 (15.9)	6 (28.6)	0.138
Stroke	20 (7.5)	19 (7.8)	1 (4.8)	0.618
Anemia	37 (13.9)	34 (13.9)	3 (14.3)	0.959
COPD	26 (9.8)	25 (10.2)	1 (4.8)	0.420
Current smoker	17 (6.4)	17 (6.9)	0 (0.0)	0.212
Former smoker	72 (27.1)	66 (26.9)	6 (28.6)	0.876

*Pearson's chi-square; Student's t-test; n: absolute frequency; %: relative frequency; AMI: acute myocardial infarction; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DLP: dyslipidemia; DM: diabetes mellitus; HR: heart rate; M: mean; NYHA: New Yor Heart Association; OMT: optimized medical therapy; PAD: peripheral arterial disease; SAH: systemic arterial hypertension; SBP: systolic blood pressure; SD: standard deviation; VT/VF: ventricular tachycardia / ventricular fibrillation.

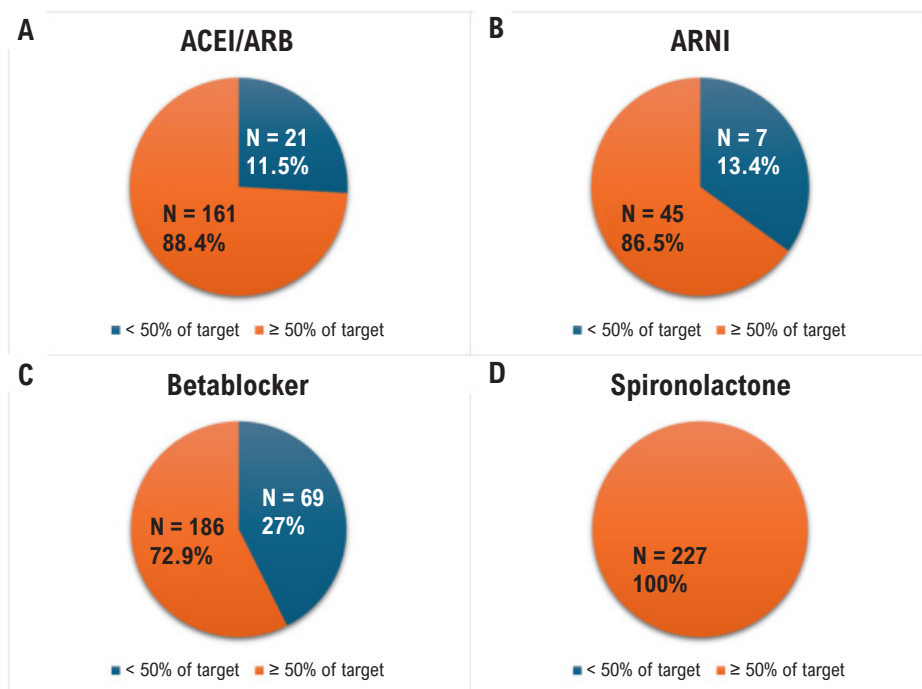


Figure 1 – Percentile of target dose in the pharmacological treatment of patients with heart failure with reduced ejection fraction (HFrEF); ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor–neprilysin inhibitor.

Table 2 – Result of the association between Chagas disease and pharmacological treatment of heart failure with reduced ejection fraction (n = 266)

Treatment	Chagas n (%)		OR (95%CI)	p
	No	Yes		
Quadruple therapy	33 (21.6)	21 (18.6)	0.83 (0.45–1.52)	0.550
OPT	12 (7.8)	9 (8.0)	1.01 (0.41–2.50)	0.971
Betablockers	149 (97.4)	106 (93.8)	0.40 (0.11–1.42)	0.147
Vasodilators	141 (92.2)	93 (82.3)	0.39 (0.18–0.85)	0.015
Spironolactone	129 (84.3)	98 (86.7)	1.21 (0.60–2.63)	0.581
SGLT2i	40 (26.1)	33 (29.2)	1.65 (0.68–2.00)	0.580
ACEI	73 (47.7)	43 (38.1)	0.67 (0.41–1.14)	0.116
ARB	43 (28.1)	23 (20.4)	0.65 (0.36–1.16)	0.148
ARNIs	25 (16.3)	27 (23.9)	1.60 (0.87–2.96)	0.125
Ivabradine	13 (8.5)	4 (3.5)	0.39 (0.12–1.24)	0.102
Furosemide	89 (58.2)	87 (77.0)	2.40 (1.39–4.11)	0.001
Amiodarone	30 (19.6)	62 (54.9)	4.98 (2.89–8.59)	<0.001
Digoxin	6 (3.9)	15 (13.3)	3.75 (1.40–9.98)	0.005

*Logistic regression; n: absolute frequency; %: relative frequency; ACEI: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; ARNIs: angiotensin receptor–neprilysin inhibitors; OTM: optimized pharmacological therapy; SGLT2i: sodium-glucose cotransporter-2 inhibitors.

Predictors of OMT use and medication classes

Table 3 shows the results of the multivariate logistic regression analyses

regarding the use of OMT and medication classes. In the multivariate analysis for OMT use, diabetes mellitus emerged as a significant predictor, increasing the likelihood of OMT use by 2.82 times (OR = 2.82; 95% CI = 1.07–7.24; $p = 0.036$). In addition, patients on OMT were more likely to present SBP < 100 mmHg (OR = 2.80; 95% CI = 1.03–7.02; $p = 0.043$).

In the final model for vasodilator use, the presence of CKD reduced the probability of using this drug class by 72% (OR = 0.28; 95% CI = 0.12–0.65; $p = 0.003$). Furthermore, SBP < 100 mmHg reduced the likelihood of vasodilator use by 68% (OR = 0.32; 95% CI = 0.14–0.76; $p = 0.010$). Age over 60 years (OR = 0.32; 95% CI = 0.12–0.87; $p = 0.025$) and furosemide use (OR = 0.35; 95% CI = 0.12–0.98; $p = 0.046$) were also associated with a lower probability of vasodilator use.

No variable showed statistical significance in the multivariate model regarding beta-blocker use.

Regarding the use of spironolactone, the multivariate analysis showed that patients with CKD were 74% less likely

to receive spironolactone (OR = 0.26; 95% CI = 0.11–0.62; $p = 0.002$). On the other hand, furosemide use was strongly associated with spironolactone use, tripling the likelihood of prescribing this medication (OR = 3.90; 95% CI = 1.85–8.20; $p < 0.001$). The variable “furosemide use” presented the highest Wald statistic (Wald = 12.87), indicating a strong association between these two drug classes.

For SGLT2 inhibitors, the final multivariate model indicated that the presence of diabetes mellitus increased the likelihood of use of this class by 2.63 times (OR = 2.63; 95% CI = 1.41–4.91; $p = 0.002$). Furosemide use was also a significant factor, with a 2.60-fold increase in the probability of SGLT2 inhibitor prescription (OR = 2.60; 95% CI = 1.34–5.03; $p = 0.005$).

Discussion

In the current scenario of high morbidity and mortality rates among patients with HF, it is crucial to improve pharmacological treatment to ensure a more favorable prognosis for these patients. A better understanding, with real-world data, of the determinants of non-adoption of evidence-based pharmacological therapy has a major impact on improving care for HF patients.¹⁷

Table 3 – Multivariate logistic regression analyses for the use of optimized pharmacological therapy (OPT) and the drug classes employed in heart failure with reduced ejection fraction

		No	Yes	Wald	r ²	OR (95%CI)	p
OPT							
	Male sex	150 (61.2)	16 (76.2)	1.42	0.08	1.91 (0.66–5.54)	0.231
	CKD	39 (15.9)	6 (28.6)	1.02		1.71 (0.60–4.86)	0.312
	DM	50 (20.4)	8 (38.1)	4.42		2.82 (1.07–7.24)	0.036
	SBP <100	43 (17.6)	7 (33.3)	4.08		2.80 (1.03–7.02)	0.043
Betablockers							
	Stroke	2 (18.2)	18 (7.1)	0.91	0.06	0.44 (0.08–2.37)	0.341
	Atrial fibrillation	4 (36.4)	50 (19.6)	0.48		0.63 (0.17–2.34)	0.490
	Chagas	7 (63.6)	106 (41.6)	0.25		0.71 (0.18–2.79)	0.618
	Amiodarone	7 (63.6)	85 (33.3)	2.17		0.36 (0.09–1.40)	0.140
Vasodilators							
	Age >60 years	26 (81.3)	129 (55.1)	5.05	0.20	0.32 (0.12–0.87)	0.025
	CKD	14 (43.8)	31 (13.2)	8.75		0.28 (0.12–0.65)	0.003
	Stroke	7 (21.9)	13 (5.6)	2.57		0.39 (0.13–1.23)	0.109
	VT/VF	10 (31.3)	25 (10.7)	1.10		0.56 (0.19–1.65)	0.294
	Chagas	20 (62.5)	93 (39.7)	0.87		1.61 (0.59–4.35)	0.352
	Idiopathic	2 (6.3)	54 (23.1)	1.89		3.10 (0.62–15.60)	0.169
	SBP <100	12 (37.5)	38 (16.2)	6.61		0.32 (0.14–0.76)	0.010
	Furosemide	27 (84.4)	149 (63.7)	3.97		0.35 (0.12–0.98)	0.046
	Amiodarone	19 (59.4)	73 (31.2)	1.26		0.58 (0.22–1.51)	0.262

Spironolactone						
Age > 60 years	27 (69.2)	128 (56.4)	0.24		0.82 (0.37–1.82)	0.621
CKD	12 (30.8)	33 (14.5)	9.34		0.26 (0.11–0.62)	0.002
PAD	3 (7.7)	6 (2.6)	1.89	0.15	0.34 (0.07–1.58)	0.169
SBP <100	2 (5.1)	48 (21.1)	4.74		5.27 (1.18–23.53)	0.029
HR	13 (33.3)	38 (16.7)	3.89		0.43 (0.19–1.00)	0.049
Furosemide	16 (41.0)	160 (70.5)	12.87		3.90 (1.85–8.20)	<0.001
SGLT2i						
Age > 60 years	107 (55.4)	48 (65.8)	0.33		1.20 (0.65–2.22)	0.567
DM	32 (16.6)	26 (35.6)	9.30		2.63 (1.41–4.91)	0.002
AMI	20 (10.4)	12 (16.4)	0.03		0.91 (0.28–2.90)	0.868
CKD	26 (13.5)	19 (26.0)	1.57	0.09	1.60 (0.77–3.35)	0.210
Stroke	10 (5.2)	10 (13.7)	1.91		2.07 (0.74–5.80)	0.167
Ischemic	27 (14.0)	17 (23.3)	1.27		1.82 (0.64–5.14)	0.260
Idiopathic	45 (23.3)	11 (15.1)	0.38		0.78 (0.36–1.72)	0.540
Furosemide	117 (60.6)	59 (80.8)	8.05		2.60 (1.34–5.03)	0.005

*Logistic regression; n: absolute frequency; %: relative frequency; AMI: acute myocardial infarction; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; HR: heart rate; OTM: optimized pharmacological therapy; PAD: peripheral arterial disease; SBP: systolic blood pressure; SGLT2i: sodium-glucose cotransporter-2 inhibitors; VT/VF: ventricular tachycardia / ventricular fibrillation.

The present study found a prevalence of 7.9% for the use of OMT. Real-world patients, with multiple comorbidities and particularities, may represent a challenge in initiating and titrating medications compared to clinical trials. Several factors may contribute to the underuse of evidence-based therapy in patients with HFrEF: factors related to the physician, the patient, and the healthcare system. Therapeutic inertia – defined as the tendency to maintain the current dose in clinically stable patients with low functional class – is also a limiting factor in achieving OMT. Lack of access to medical care (due to shortage of healthcare professionals or geographic limitations) may also hinder medication titration. In addition, drug costs may represent another barrier.^{13,14}

In this study, it was observed that 21.6% of patients were on quadruple therapy, while the prevalence of OMT (target dose or maximum tolerated dose of quadruple therapy) was 7.9%. In the CHAMP-HF registry, a U.S. observational study with 3,518 outpatients with HFrEF, only 1.1% were simultaneously on target doses of triple therapy (according to the guidelines available at the time of the study).¹⁸ The cited registry included non-specialized cardiology centers, which may explain the lower OMT rate observed compared to that found in the present study.

The IMPROVE-HF study demonstrated an increase in the prevalence of OMT from 14.1% to 22.8% in patients with HFrEF following the implementation of educational measures on HF treatment and management.¹⁹ Academic centers may achieve high rates of OMT utilization, and continuous medical education and training are

fundamentally important as the basis for maintaining high-quality care for HF patients.

A Brazilian observational study reported a prevalence of OMT (33.1%) in patients with HFrEF. However, this prevalence referred to the use of triple therapy,²⁰ differing from the present study, which included the use of SGLT2 inhibitors. Other studies have estimated the prevalence of concomitant use of HF drug classes,²¹ but analyzed only triple therapy and did not assess use at target or maximum tolerated doses.

The prevalence of vasodilator use (ACEI or ARB or ARNI) in the studied sample was 88%, with 49.5% (116), 28.2% (66), and 22.2% (52) using ACEIs, ARBs, and ARNIs, respectively. The prevalence of vasodilator use in this study is higher than those reported in international registries, which range from 73.4% to 85.8%.^{15,18,21,22} In the present study, ARNI use was 19.5% (52). This rate is higher than that observed in the U.S. population (13.0%) and in Middle Eastern registries (3.6%). The higher ARNI use is possibly associated with the recent availability (since 2021) of the drug in public high-cost medication distribution services in the studied region.^{18,21}

The prevalence of beta-blocker use was 95.9% (255). This high utilization rate of this drug class has also been reported in other Brazilian studies (ranging from 80% to 100%, depending on the region of the country).^{8,10,11} The prevalence of beta-blocker use in international registries varies from 67% to 86.2% in U.S. data, while in European studies it ranges from 52% to 84%.^{15,18,19,22,23}

The utilization rate of spironolactone was 85.3% (227). In international registries, lower frequencies of MRA use are

observed, ranging from 32.0% to approximately 56.0%.²⁴ Brazilian data show prescription rates for this drug class ranging from 64% to 93%.^{20,22}

The prevalence of SGLT2 inhibitor use was 27.4% (73). According to the literature, treatment rates with this class range from 12% to 20.1% in observational studies, which mostly included diabetic patients (11.9%) and few patients with HF (7.6%).^{25,26} Compared with the literature, we observed a higher prevalence of SGLT2 inhibitor prescription. This is possibly due to the high prevalence of diabetes in the studied population (21.8%), for whom this medication is more readily available in the public healthcare system.

Factors associated with the use of drug classes

Regarding vasodilator use, it was observed that the presence of CKD, advanced age, hypotension, and furosemide use were associated with a lower likelihood of prescribing this drug class. CKD is widely described in the literature as a limiting factor for the use of these medications.^{12,18,23} Similarly, advanced age is associated with non-use of ACEI/ARB, possibly reflecting a tendency toward under-medication in elderly patients, whether due to intolerance or therapeutic inertia.²⁷ Arterial hypotension may be a marker of more advanced disease and intolerance to this drug class.

Furosemide is not reported as a classic limiting factor for vasodilator use, but its negative association is possibly due to its hypotensive effect, which ultimately restricts the initiation or titration of vasodilators.^{28,29} This finding highlights the need for caution with other prescribed medications and their potential interactions in the pharmacological treatment of HFrEF.

The presence of CKD was an independent predictor of non-use of spironolactone. CKD is classically reported as a limiting factor for the use of this medication, with worsening renal function and hyperkalemia being the most frequent complications.^{12,23} In this study, no association was found between hyperkalemia and lower likelihood of MRA use. The positive association between spironolactone use and the presence of hypotension suggests that HF patients treated with this drug class tend to have lower blood pressure levels due to the hypotensive effect of MRAs.¹⁵

Furosemide use was positively associated with spironolactone use, which may reflect the commonly observed association in clinical practice, where more congested patients require concomitant use of both drugs. In a Swedish registry with more than 11,000 patients, it was observed that patients using other diuretics were more likely to use MRAs,²⁴ corroborating the findings of the present study.

Regarding the use of SGLT2 inhibitors, a positive association was observed between this drug class and the presence of diabetes mellitus (DM) as well as furosemide use. The association with DM may be explained by an indication bias, since patients with DM often receive SGLT2 inhibitors for glycemic control regardless of the HF indication, which increases OMT rates among diabetic patients. Although evidence shows a reduction in HF mortality regardless of the presence of DM,^{12,15} registries report higher prescription rates of SGLT2 inhibitors for patients with DM than for those with HF.²⁶ The association between SGLT2 inhibitors and

furosemide suggests that more congested and symptomatic patients may be more likely to receive concomitant loop diuretics and SGLT2 inhibitors. SGLT2 inhibitors tend to be more frequently prescribed in congested patients.²⁸

Chagas disease presents inherent autonomic dysfunction as well as progressive damage to the heart's electrical conduction system.³⁰⁻³² The use of amiodarone is frequent in this population due to the presence of severe arrhythmias, which justifies the observed association whereby Chagas etiology increases the likelihood of amiodarone use.^{33,34} Furthermore, the presence of Chagas disease was associated with a lower likelihood of vasodilator use, which may be explained by the borderline blood pressure commonly observed in this group,³⁵ preventing prescription of this drug class due to patient intolerance.

The STRONG-HF study investigated the impact of quadruple therapy in patients with HF. The results demonstrated that early intensification of treatment, combined with close follow-up, significantly reduced the rate of hospitalization for HF and all-cause mortality at 180 days compared with usual care.³⁶ In addition, improvements were observed in symptoms, quality of life, and biomarkers such as NT-proBNP. There was no significant increase in serious or fatal adverse events. These findings suggest that the implementation of an aggressive strategy for titration of quadruple therapy can substantially improve the prognosis of patients with HF, highlighting the importance of intensive and personalized management of these patients.

An observational study analyzed the impact of comorbidities on the prescription of pharmacological therapy in patients with HFrEF. Hypertension, DM, CKD, atrial fibrillation, and chronic obstructive pulmonary disease were the most prevalent comorbidities. The presence of multiple comorbidities negatively influenced the prescription of triple therapy, especially vasodilators and MRAs. However, the implementation of quadruple therapy, which included the addition of SGLT2 inhibitors, did not differ significantly between groups with different comorbidity burdens.³⁷ These findings suggest that although multimorbidity may hinder the prescription of triple therapy, the addition of SGLT2 inhibitors may be feasible regardless of the number of comorbidities. In the present study, no comorbidity was negatively associated with the use of SGLT2 inhibitors.

This study has limitations arising from its cross-sectional design, which restricts the assessment of adherence or therapeutic changes over time. Its single-center nature also limits the generalizability of the findings to other populations. Furthermore, the possibility of under-reporting contraindications in medical records may have influenced the classification of the therapies evaluated. These factors should be considered when interpreting the results.

The barriers to OMT use observed in the present study highlight the need for systematic strategies to overcome therapeutic inertia and ensure appropriate treatment in HFrEF. The implementation of outpatient dose-titration protocols, continuous medical education, and periodic systematic review of drug classes and doses are measures that should be adopted by specialized services. The findings

point to the need for a proactive and structured model of care focused on therapeutic progression in HF patients.

Conclusions

The present study found a high prevalence of the use of prognostic-modifying drugs in HFrEF; however, the use of target or maximum tolerated doses fell short of guideline recommendations. Chagas etiology, CKD, advanced age, arterial hypotension, and concomitant use of furosemide were associated with a reduced likelihood of receiving prognostic-modifying drugs in HFrEF, whereas the presence of diabetes was associated with a greater chance of OMT use.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Estevan AO, Silva ALGF, Rassi Filho S, Freitas Jr. A, Rassi S; Statistical analysis and Critical revision

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No potential conflict of interest relevant to this article was reported.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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