

Evidence Based Treatment of Heart Failure: Challenges of Drug Access

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Abstract

Heart failure (HF) is a complex clinical syndrome with high prevalence, significant morbi-mortality and is the leading cause of hospital admissions of Brazilian patients over 65 years of age. Drug therapy plays a key role in the care of HF patients, aimed to control symptoms, improve functional classification, reduce hospital readmissions and HF-related mortality rates. Despite the evidence of drug therapy proven benefits in HF, their access through the Unified Health System (Sistema Único de Saúde, SUS) remains unexplored. The present study aims to analyze the dynamics of access to HF therapy, based on the list of drugs made available by the SUS through a descriptive and documental methodology. Data were collected from the Municipal Lists of Essential Medicines in a metropolitan region in southern Brazil. Municipalities with a population over 80,000 inhabitants were included, and the respective lists of available drugs were reachable electronically by the health departments themselves. The results showed a partial access to HF treatment via the SUS, especially spironolactone and furosemide, present in 72.7% and 81.8% of the municipalities, respectively. Although drug treatment for HF has proven a high level of evidence, access via SUS represents a challenge to overcome in the continuum of care of patients with heart failure in Brazil

Introduction

Heart failure (HF), a complex syndrome with high levels of morbidity and mortality, and is currently the leading cause of hospitalization for people over 65 years of age in Brazil.¹ Heart failure is also responsible for approximately 5% of public health funding in the country.²

Drug therapy plays an important role in the process of care of HF patients, aiming to improve not only symptoms control and functional class, but, in particular, HF-related outcomes, such as reduction in hospital readmissions and disease-related mortality rates.²⁻⁴ Different classes of drugs,

used in combination, have demonstrated proven benefits in large clinical trials.⁵ However, patients' access to these drugs through the Unified Health System (SUS) remains a challenge.

Thus, the present study aims to analyze the dynamics of access, through SUS, to HF evidence-based drug therapy.

Methods

A descriptive, documental and exploratory study was carried out based on data collected through the Municipal List of Essential Medicines (REMUMEs): a list of drugs selected according to the needs of each city, based on the National List of Essential Medicines (RENAME), from municipalities in a metropolitan area in southern Brazil.

The study included lists from cities with a population over 80,000 inhabitants, made available electronically by the municipal health departments themselves. From the guideline-oriented treatment², data were collected, analyzed and described from HF drugs available at each municipality.

Results and Discussion

Twelve cities were included in the study and in one case the list was not available for electronic access, so 11 REMUMEs were analyzed. The 11 lists described the access, via the basic component of pharmaceutical assistance, to essential drugs for 80.86% of the overall metropolitan area population. The results showed a partial access to drug therapy in HF (Central Figure). All municipalities have some type of beta-blocker with proven benefit in HF as part of their list, mostly carvedilol and metoprolol (although in tartrate form) in most cases, as described in Table 1. Published studies use metoprolol succinate for HF treatment, however the use of tartrate shows as an possible alternative due to its vast availability in the SUS; therefore requiring a prescription adaptation.

Beta-blockers prescription is one of the four pillars of HF treatment⁴ and its main objective is to preserve ventricular function, either through the negative chronotropic effect or the inhibition of cardiomyocyte sympathetic activity. Trials such as US Carvedilol,⁵ CIBIS II and III,^{6,7} MERIT-HF⁸ and COPERNICUS⁹ showed benefits for improving functional class, reducing symptoms progression and hospitalizations, and in beneficial myocardial remodeling, in addition to reducing mortality.

However, it is important to highlight that beta-blockers do not have a class benefit in HF: only a sort of them showed benefits in HF primary endpoints. Atenolol and propranolol are not a therapeutic choice to HF patients; despite their vast availability in the SUS (therefore devoted to Hypertension treatment). In addition, beta-blockers have differences among their

Keywords

Heart Failure; Drug Therapy; Access to Essential Medicines and Health Technologies; Health Services Accessibility

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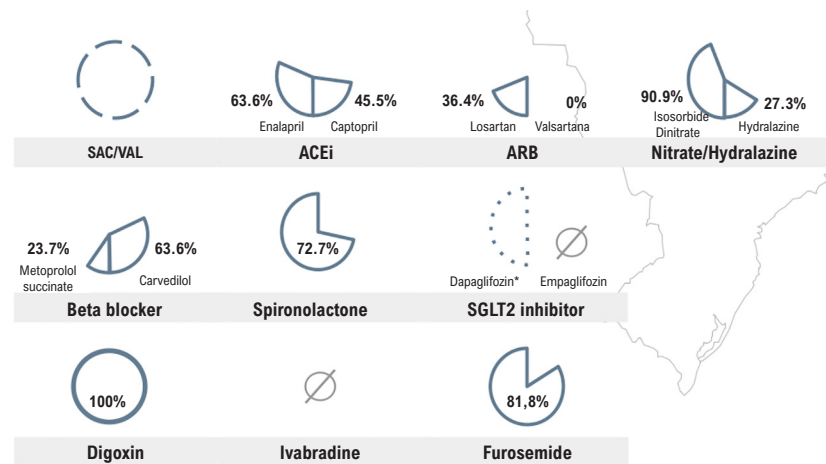
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Central Illustration: Evidence Based Treatment of Heart Failure: Challenges of Drug Access



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Graphic representation on HF drugs presence as part of Essential Medicine Lists from metropolitan municipalities in southern Brazil. Source: the authors. Sac/Val: sacubitril/valsartan, access through the specialized component of pharmaceutical assistance according to the criteria of the Brazilian Ministry of Health Guidelines (Heart Failure international code disease I50.0; I50.1; or I50.9, age between 18 and 75 years, NYHA II, BNP > 150 pg/mL or NT-ProBNP > 600 pg/mL, LVEF ≤ 35%, and symptomatic despite optimal clinical treatment; source: Brazil, 2020); ACEi: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blockers; SGLT2i: Sodium Glucose Cotransporter 2 inhibitors. * Patients above 65 years, cardiovascular disease and type 2 diabetes mellito. Source: Brasil, 2023.

cardioselectivity: their selectivity for β_1 rather than peripheral β_2 receptors differs, which makes it essential to individualize the choice of medication for each patient. Bisoprolol, the most cardioselective beta-blocker in HF, as cited in the guidelines, is not available in any of the REMUME in our study.

Like beta-blockers, spironolactone (only mineralocorticoid antagonist available by SUS) is one of the four pillars of heart failure therapy, with evidence of reducing disease-related mortality and hospitalizations, both observed in RALES¹⁰ clinical trials. However, spironolactone is part of only 72.7% of the medication lists from the cities included in the study, which ends up restricting its access, being available to the patients only by the “Popular Pharmacy Program”.

Regarding the third pillar of treatment in HF, the Brazilian Guidelines for Heart Failure,² aligned with the ESC³ and the HFSA⁴ treatment guidelines, brings the co-crystal Sacubitril/Valsartan, an angiotensin receptor and neprilysin inhibitors (ARNI), as an evidence 1A (high level of evidence, and strong recommendation) drug in therapy.

Access to Sacubitril/Valsartan, in the dosage forms of 50mg, 100mg and 200mg, is available without payment via SUS through the Brazilian Specialized Component of Pharmaceutical Assistance: the purchase and distribution of this drug is a federal responsibility by the Ministry of Health, according to the Clinical Protocol and Therapeutic Guidelines (CPTG)¹¹ criteria, and its dispensation is carried out by states and municipalities after evaluating the documentation submitted by patients. Therefore, even if the drug is not part of the municipal drug lists, its distribution is guaranteed by SUS to patients that meet the criteria established in the CPTG guidelines (left ventricular

ejection fraction ≥ 35%, BNP > 150 pg/mL or NT-ProBNP > 600 pg/mL, aged between 18 and 75 years, with NYHA functional class of II and/or symptomatic despite optimized clinical drug treatment). If the patient develops drug intolerance, there is no drug availability for dispensing onsite, or the patient do not meet the above, the options continue to be the use of an angiotensin converting enzyme inhibitors (ACEi), an angiotensin II receptor blockers (ARB II) or the association of nitrate and hydralazine, available by municipalities through primary care units.

Our analysis of the REMUMEs revealed that in four cases, none of ACEi or ARB are available, limiting the patients' access through the “Popular Pharmacy Program” or the solicitation of Sacubitril/Valsartan via the Specialized Component of Pharmaceutical Assistance.

Lisinopril, ramipril, perindopril, valsartan, candesartan, telmisartan and irbesartan were not found in the municipalities drug lists review, and were excluded from data shown in Table 1.

The last and fourth pillar of the treatment of Heart Failure are the Sodium Glucose Cotransporter 2 inhibitors (SGLT2i). Recent studies, such as DAPA-HF¹² and EMPEROR-REDUCED,¹³ have shown the benefit of this drug class (previously used for the treatment of type 2 diabetes mellitus) in HF outcomes in patients with and without a diagnosis of diabetes; for both dapagliflozin and empagliflozin. In the SUS, dapagliflozin is included in the CPTG of type 2 diabetes mellitus (DM2) for patients meeting criteria;¹⁴ or then through co-payment via the Brazilia “Popular Pharmacy Program”. None of the municipalities in the study had drugs of this class composing their list of essential medicines.

Brief Communication

Table 1 – Dosage forms (mg) of heart failure drugs in the lists of essential medicines from municipalities in a southern Brazil metropolitan area

	Popular Pharmacy Program ¹⁶	Porto Alegre ¹⁷	Alvorada ¹⁸	Cachoeirinha ¹⁹	Canoas ²⁰	Esteio ²¹	Guaíba ²²	Gravataí ²³	Novo Hamburgo ²⁴	Sapucaia do Sul ²⁵	São Leopoldo ²⁶	Viamão ²⁷
Beta blockers												
Metoprolol succinate	25	-	-	25 50	-	-	50	-	50	-	-	-
Metoprolol tartrate	-	100	100	100	100	100	-	100	-	-	100	100
Carvedilol	-	6,25	6,25	6,25 25	-	-	12,5	-	6,25	6,25 25	-	6,25 12,5
Bisoprolol	-	-	-	-	-	-	-	-	-	-	-	-
Mineralocorticoid receptor antagonist												
Spironolactone	25	25	25	-	-	25	25	25	25	25	-	25
Angiotensin Receptor and Neprilysin Inhibitors (ARNI), Angiotensin Converting Enzyme Inhibitors (ACEi), Angiotensin II Receptor Blockers (ARB II), Nitrate/ Hydralazine												
Sac/Valsartan	-						PCDT†					
Enalapril	10	10	10	-	10 20	-	10	-	5	10	-	10
Captopril	25	25	25	-	25	-	25	-	-	-	-	25
Losartan	50	50	-	-	-	-	50	-	-	50	-	50
Hydralazine	-	-	25	25	-	-	-	-	-	-	-	25
Isosorbide Dinitrate	-	5	5	5	5	5	5	5	5	5	-	5
Isosorbide Mononitrate	-	20	40	20 40	40	40	-	40	20	40	20	40
SGLT2 inhibitors												
Dapagliflozin	10*						PCDT‡					
Empagliflozin	-	-	-	-	-	-	-	-	-	-	-	-
Loop diuretic												
Furosemide	40	40	40	-	40	40	40	40	40	40	-	40
Other												
Digoxin	-	0,25	0,25	0,25	0,25	0,25	0,25	0,25	0,25	0,25	0,25	0,25
Ivabradine	-	-	-	-	-	-	-	-	-	-	-	-

Source: the authors.

* Patients above 65 years, cardiovascular disease and type 2 diabetes mellito. Font: Brasil, 2023.¹⁶† Heart Failure international code disease (I50.0; I50.1; I50.9), age between 18 and 75 years, NYHA II, BNP > 150 pg/mL (or NT-ProBNP > 600 pg/mL), LVEF ≤ 35%, and symptomatic (symptoms such as dyspnea, signs of congestion, clinical worsening with recent hospitalizations) despite optimal clinical treatment (usage of maximum tolerated dosages of ACEi or ARB II, beta-blockers, spironolactone and diuretics in case of congestion. Font: Brasil, 2020.¹⁴‡ Non-insulin dependent diabetes mellitus international code disease (E11.2 a E11.9), age ≥ 65 years, without adequate glycemic levels and cardiovascular disease (previous acute myocardial infarction, coronary artery bypass surgery, coronary angioplasty, stable or unstable angina, previous ischemic stroke, previous transient ischemic attack, and LVEF ≤ 35% heart failure). Fonte: Brasil, 2020.¹⁶

Lastly, and reasonably most remarkable, given the clinical impact of the lack of access to this drug, was the finding that not all cities have furosemide as part of their list of essential drugs. Loop diuretic of choice for outpatient management of congestion and therefore crucial in preventing admissions and emergency visits due to decompensation,¹⁵ furosemide is not available in 2 of the municipalities analyzed. Together, they represent 360,000 inhabitants who, if they have HF diagnosis and do not acquire their pharmacotherapy with their own

resources, will not have access to the medicine except through the Popular Pharmacy Program.

The main limitation of this study, along with its small size and regionalized focus, is the fact that only the official lists of each municipality were analyzed, and not their real-life availability in primary care centers to dispensation for patients. There is a possibility that, even being part of the list, some of the drugs in question may be missing from municipal stocks. Further studies should be carried out regarding patients' access to HF drug treatment.

Conclusions

Although drug therapy for HF has proven a high level of evidence from literature, and even with the advent of new therapeutic classes among its options, free access via SUS represents a challenge to overcome in the construction of the HF *continuum* of care. Studies on pharmacoeconomics and implementation sciences must be carried out to face HF in a country of continental dimensions like Brazil, which is going through an important demographic transition with a growing demand for the triple burden of diseases in its health system. Ensuring access to drug therapy in Heart Failure is also a way of saving funding resources, which are finite, in the health sector.

Author Contributions

Conception and design of the research and Writing of the manuscript: Einsfeld L; Acquisition of data, Analysis and interpretation of the data and Critical revision of the

manuscript for important intellectual content: Einsfeld L, Pilger D, Roman C; Statistical analysis: Einsfeld L, Roman C.

Potential conflict of interest

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

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Ethics approval and consent to participate

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

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