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In-Hospital Management and Long-term Clinical Outcomes and Adherence in Patients With Acute Decompensated Heart Failure: Primary Results of the First Brazilian Registry of Heart Failure (BREATHE)

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ABSTRACT

Background: Heart failure (HF), a common cause of hospitalization, is associated with poor short-term clinical outcomes. Little is known about the long-term prognoses of patients with HF in Latin America.

Methods: BREATHE was the first nationwide prospective observational study in Brazil that included patients hospitalized due to acute heart failure (HF). Patients were included during 2 time periods: February 2011–December 2012 and June 2016–July 2018

Suggestion for rephrasing: In-hospital management, 12-month clinical outcomes and adherence to evidence-based therapies were evaluated.

Results: A total of 3013 patients were enrolled at 71 centers in Brazil. At hospital admission, 83.8% had clear signs of pulmonary congestion. The main cause of decompensation was poor adherence to HF medications (27.8%). Among patients with reduced ejection fraction, concomitant use of beta-blockers, renin-angiotensin-aldosterone inhibitors and spironolactone

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decreased from 44.5% at hospital discharge to 35.2% at 3 months. The cumulative incidence of mortality at 12 months was 27.7%, with 24.3% readmission at 90 days and 44.4% at 12 months.

Conclusions: In this large national prospective registry of patients hospitalized with acute HF, rates of mortality and readmission were higher than those reported globally. Poor adherence to evidence-based therapies was common at hospital discharge and at 12 months of follow-up. (*J Cardiac Fail 2023;00:1–12*)

Key Words: heart failure, registries, prescriptions, prognosis.

Heart failure (HF) is a global public health problem and is the most costly cardiovascular disease for health systems in many countries.[1–4] In Brazil, HF and coronary heart disease are the cardiovascular conditions with the greatest economic impact on the public health system.[4] This impact is predicted to worsen as people are living longer, since the likelihood of HF diagnosis increases with age.[5] Despite therapeutic advances, morbidity and mortality rates associated with HF remain high, and patients with HF are commonly readmitted within 90 days after hospital discharge.[6–10] In addition to compromising patients' quality of life and increasing costs to the health system, readmissions are 1 of the main factors associated with a risk of death in patients with HF.[8–10]

Several treatment strategies have been shown to be highly effective in patients with HF,[11–13] including beta-blockers, renin-angiotensin-aldosterone system blockade (with or without neprilysin inhibition), and sodium-glucose cotransporter-2 (SGLT2) inhibitors.[14] However, one of the factors frequently associated with HF readmission is inadequate therapy.[15,16] In addition to standard therapy for acute HF, interventions, such as cardiac resynchronization therapy, implantable cardioverter-defibrillators and ventricular devices, can be used; however, the appropriate use of these therapies must be based on optimized drug therapy, and there are limited data about their application in clinical practice in low- and middle-income countries.[11–13]

The BREATHE (Brazilian Registry of Heart Failure) was the first multicenter registry in acute HF to include patients from all regions of Brazil.[16,17] This allowed for the collection of comprehensive information, including hospital type (public or private) and short- and long-term prognoses. A previous publication from the first phase of BREATHE registry found that less than half of the population was taking the combination of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), associated with beta-blockers and spironolactone.[16] Despite the relevance of of these partial data from Breathe-I, the analysis had limitations because adherence data were collected in a cross-sectional study design, and changes in adherence during follow-up have not been reported so far. In addition, there is still a need to identify the real rate of events expected at 12 months post-hospitalization in patients with HF in Brazil.

The purpose of the present analysis is to describe the in-hospital management and 12-month clinical outcomes of patients in Brazil hospitalized due to acute HF.

Methods

The BREATHE registry was designed to identify gaps in the treatment of patients with acute HF in Brazil.[17] The study included patients from public and private hospitals from all regions of Brazil, and information was collected at hospital discharge and at 90, 180 and 365 days.

In the first phase of the study (February 2011–December 2012), an assessment of 1263 hospitalizations was conducted using data collected in-hospital.[16] The second phase of the study (June 2016–July 2018), BREATHE Extension, enabled a larger number of patients to enter and allowed a more robust analysis of in-hospital management. In addition, the current analysis evaluated clinical outcomes at 12 months in the entire study population (both phases of the registry).

Study Design

The rationale and design of the study has been published.[17] BREATHE was an observational, prospective, voluntary, multicenter study that included patients in public and private hospitals during 2 periods between 2011 and 2018. The selection of centers included all 5 regions in Brazil, and open invitations were sent to interested centers by the Brazilian Society of Cardiology and the coordinating center (HCor Research Institute, São Paulo). The study was initiated after approval by the Research Ethics Committee, and all patients included provided written informed consent. Data collection included in-hospital management until hospital discharge and longitudinal follow-up at 90, 180 and 365 days. The objectives were to measure adherence to evidence-based therapies and to assess the occurrences of

death and rehospitalizations. The study was developed by the Department of Heart Failure of the Brazilian Society of Cardiology (Rio de Janeiro, Brazil), and study operations were conducted by the HCOR Research Institute (São Paulo, Brazil).

Study Population

Patients admitted to public and private hospitals with clinical diagnoses of decompensated HF were invited to participate in the study and were included after providing written informed consent. The Boston criteria were recommended for diagnosing HF; patients had to have a score > 7 for a diagnosis of definitive HF.[17,18] Patients who underwent revascularization (angioplasty or surgery) in the previous month and those with signs of HF secondary to sepsis were excluded.[17] Patients were included consecutively through an active search in the various sectors of the hospital (emergency department, internal medicine, cardiology, and intensive care units).

Study Procedures

Admission. Data collection was initiated at admission with baseline data (baseline visit) and included etiology of HF, cause of decompensation, physical and clinical examinations, clinical and hemodynamic profiles, risk factors, laboratory tests, imaging tests, and medication use at home and in the hospital.[17] Cause of decompensation was determined by the local investigators according to the patients' records. Identification of comorbidities was also done by local investigators, and centers were instructed to follow current national and international guideline recommendations for diagnosis criteria. The clinical hemodynamic profile was defined according to the classification of Stevenson.[17,19]

Discharge and Post-discharge Follow-up. At hospital discharge, information regarding quality indicators, in-hospital cardiology procedures, medication use, and imaging tests were collected. Clinical follow-up visits were conducted at 90, 180 and 365 days to collect data on major cardiovascular events, medication use, cardiac procedures, and laboratory and imaging tests. Follow-up visits could take place in person during routine care or by telephone. Data about medication prescriptions were collected to assess adherence to evidence-based recommendations in accordance with evidence-based guidelines.[11–13] No information was collected on the effective use of the medication by patients.

All centers received training in the protocol and electronic case-report form, and support was available during the study. Quality-control checks of study data were conducted using various methods, including querying the electronic case-report form and checking central data.

Study Outcomes

The primary outcome was overall mortality at 12 months after discharge. Secondary outcomes included the proportion of patients undergoing interventions with proven benefits demonstrated by several indicators of quality of care (in patients with reduced left ventricular ejection fraction [LVEF]), in-hospital mortality and the following outcomes during 12 months of follow-up: hospital readmission overall, hospital readmission due to HF and a composite outcome (all-cause mortality or myocardial infarction [MI], stroke, or cardiac arrest), along with the individual components. All these clinical outcomes assessed during 12 months of follow-up were identified in the visits of 3 months, 6 months and 12 months. Variation in weight and heart rate between admission and hospital discharge were collected for exploratory analysis. For the assessment of potential predictors, we considered the outcome of cardiovascular death or hospital readmission due to HF within 12 months. These outcomes were reported by the investigator without the use of an independent committee for adjudicating events. At the time of the registry, the primary medications with proven impact on mortality rates in symptomatic patients with LVEF $< 40\%$ were beta-blockers, ACE inhibitors/ARBs (or angiotensin receptor-neprilysin inhibitors [ARNI]), and spironolactone.

Statistical Analysis

Quantitative variables are presented as means and standard deviation or medians with 25th or 75th percentiles, as appropriate, and qualitative variables are described as absolute and relative frequencies. In order to compare the use of medications at home and in the first 24 hours of hospitalization with the use of medications at hospital discharge, the McNemar test was performed. The paired *t* test and the Wilcoxon-signed rank test were used to compare heart rate and weight on admission and at discharge, respectively. Incidences rate and Kaplan-Meier curves were estimated for the nonischemic, ischemic and Chagas disease etiologies and compared without adjustment for covariates by using the log-rank test for composite outcome and overall death. These survival analyses were conducted only in patients included in the second phase of the study (BREATHE Extension), because the exact dates of events were not collected in the first phase of the study. Overall (considering patients from both phases), we did not record the exact dates of mortality, MI, stroke, and cardiac arrest in BREATHE. Instead, we recorded whether the clinical events

occurred within the 3-month, 6-month or 12-month period post-discharge. Thus, when modeling clinical events using data from both phases of the study, the cause-specific proportional odds model was used[20] based on intervals and not on specific dates of events. Cumulative incidences were estimated for each clinical outcome at 12 months, and the phases were compared using the cause-specific proportional odds model. For the outcome of cardiovascular death, noncardiovascular death was considered a competing risk. For the outcomes of MI, stroke, cardiac arrest, hospital readmission, and hospital readmission due to HF, death from any cause was considered a competing risk. We also conducted a multivariate analysis using the cause-specific proportional odds model[20] to evaluate potential predictors for cardiovascular death and/or readmission due to HF. We considered noncardiovascular death as a competing risk and excluded 5 patients who had missing information for at least 1 of the evaluated variables.

Patients undergoing to heart transplantation during follow-up were not excluded from the analysis because they represented very few patients (n = 27) and, as a consequence, would not influence the overall results. All analyses were performed using the statistical program R 4.0.2 (R Core Team, 2021; Vienna, Austria); a P value < 0.05 was considered to be statistically significant.

Results

A total of 3013 patients were included in the final analysis (Fig. 1). The median follow-up was 346 days (25th, 75th: 131, 365). Data from the 12-month follow-up visit were missing for 407 (13.5%) patients; follow-up data for these patients was censored at the date of last known contact. Patients were enrolled at 71 centers in Brazil (Graphical Abstract): 4 centers in the central-west region (5.63%), 15 in the northeast (21.13%), 7 in the north (9.86%), 36 in the southeast (50.7%), and 9 in the south (12.68%). Patients' care payers were predominantly public (73.1%), followed by supplementary/health plans (19.9%) and private payers (7%).

Baseline Characteristics

The population in BREATHE was 39.3% female, had a mean age of 65.2 (± 15.6) and a mean LVEF of 39.7% (± 17.5) (Table 1). Systemic arterial hypertension was the most common comorbidity and was present in almost 75% of patients (Table 1). The majority of patients had not completed high school (72%) and had a family income of up to 2 minimum wages (62%) (Table 1). De novo HF information was collected only in the BREATHE Extension phase and was reported in 21.4% of patients; the remaining 78.6% were decompensation of chronic HF.

Etiologies, Causes of Decompensation and Clinical Hemodynamic Profiles at Hospital Admission

Ischemic and hypertensive etiologies were predominant (48.9%) (Fig. 2A), and the main causes of HF decompensation were poor adherence to drug therapy (27.8%), followed by infections (21.3%) and arrhythmia (14.0%) (Graphical Abstract). At admission, the predominant clinical hemodynamic profile was wet-warm (2160 [71.7%]) while 388 (12.9%) patients did not present with signs of congestion or poor perfusion (Fig. 2B).

Body weight and heart rate were measured at admission and hospital discharge. Mean heart rate at admission was 87.6 (± 23.3) beats/minute and 74.7 (± 13.9) at discharge (Supplementary Table S1). Among patients with heart rate measurements at admission and discharge, we observed a reduction of 12.9 beats/minute (95% confidence interval [CI] 11.6−14.1). Mean body weights at admission were 73.7 (± 18.1) kg and 73.6 (± 19) kg at discharge (Supplementary Table S1). Among patients with bodyweight measurements at admission and discharge, there was a reduction of 2.3 kg (95% CI 1.9−2.7).

Quality Indicators of Evidence-based Therapies

At discharge, the combined use of beta-blockers, ACE inhibitors/ARBs/ARNI, and spironolactone was below 50% in both phases of the registry, and the use of these drugs was numerically different according to LVEF (Supplementary Table S2). In patients with reduced LVEF in the overall BREATHE population (phase I and Extension), the most common medications used during the 3 time periods evaluated (home use, first 24 hours of admission and hospital discharge) were beta-blockers (63.6%, 63.1%, 79.9%), followed by ACE inhibitors/ARBs/ARNI, and spironolactone (Table 2), (Graphical Abstract), (Supplementary Fig. S1). A numerical increase in the proportion of patients using the combination of beta-blockers, ACE inhibitors/ARBs/ARNI, and spironolactone was observed at hospital discharge, and the same pattern was seen for beta-blockers, nitrate, hydralazine, and spironolactone (Table 2) (Supplementary Fig. S1).

During the first 3 months of follow-up, the concomitant use of beta-blockers, ACE inhibitors/ARBs/ARNI, and spironolactone numerically decreased from 44.0%−35.6%, despite a slight numerical increase in the use of beta-blockers (Table 2) (Supplementary Fig. S1). Comparing the 2 phases of the registry among patients with LVEF $< 40\%$, the combined use of beta-blockers, ACE inhibitors/ARBs/ARNI, and spironolactone did not change at hospital discharge (Supplementary Table S2), but at 12

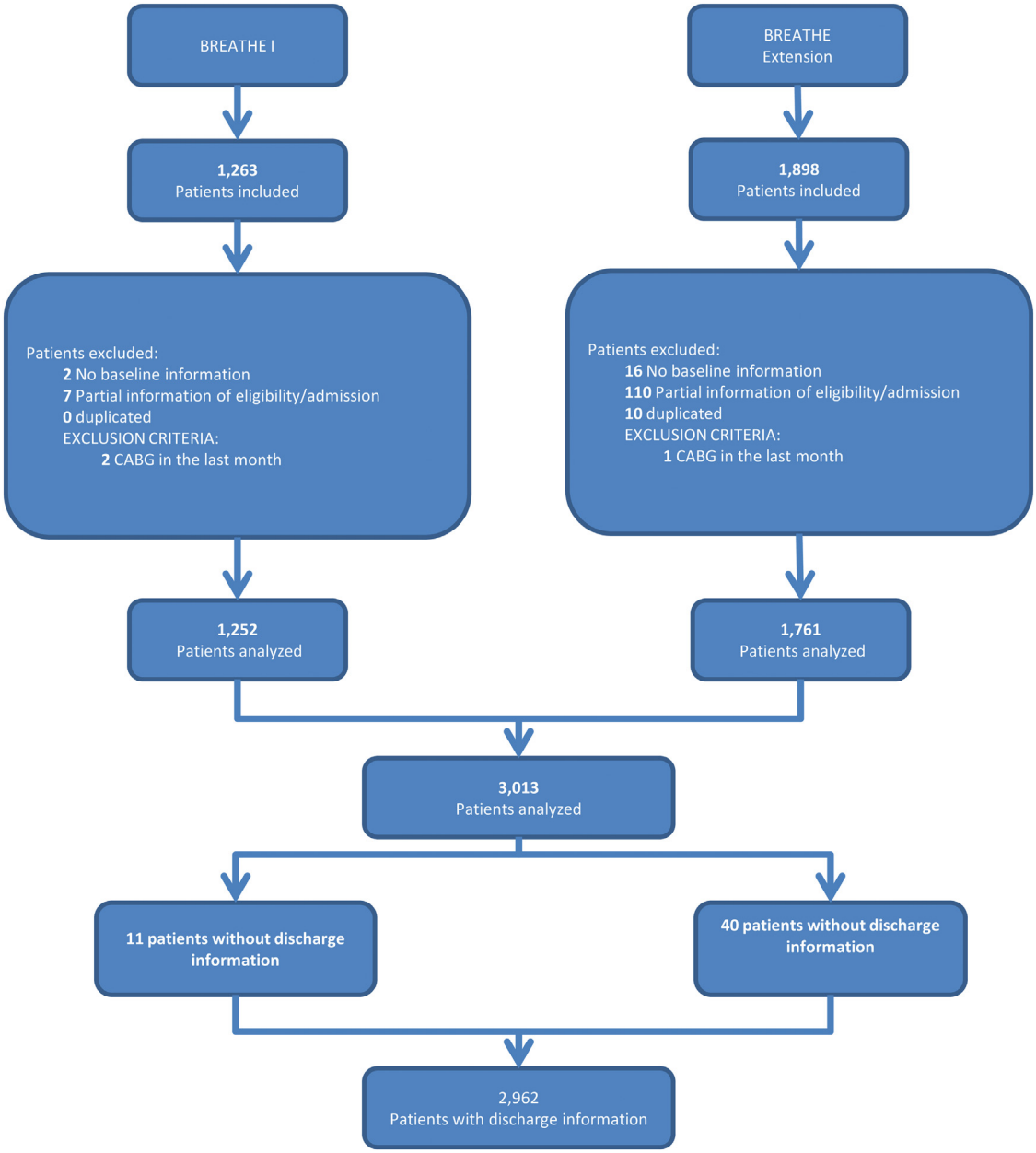

Fig. 1. Brazilian Registry of Heart Failure (BREATHE) registry flow diagram.

months, it increased from 34.2% to 46.4% (Supplementary Table S3).

Sacubitril/valsartan was available in 2017, and its incorporation during the first 3 years (until 2019) showed an increase to 14% (Supplementary Table S4).

Nonpharmacological recommendations given at hospital discharge were assessed in the study population and included guidance on diet (54.1%), instructions about correct drug usage (82.5%) and explanations about worsening symptoms and future consultations (69.1%). Physical activity was recommended for 38.8% of patients, and 61.8% of current smokers (155/251 smokers) were instructed to quit smoking.

Clinical Outcomes

A total of 324 (10.9%) patients died during hospitalization (Graphical Abstract), (Table 3). Of these, 37 (1.2%) died within 24 hours of admission. In-hospital procedures were infrequent; 272 (9.3%) patients underwent at least 1 cardiac procedure, including valve replacement (3.3%), angioplasty (2.1%) and cardiac pacemaker insertion (1.7%) (Table 3). In the overall population (BREATHE and Extension), the cumulative incidence of mortality at 12 months was 27.7%, with 24.3% readmission at 90 days and 44.4% at 12 months (Graphical Abstract) (Fig. 3A,B).

Table 1. Baseline characteristics

Variables	BREATHE (n = 1252)	BREATHE-Extension (n = 1761)	BREATHE Total (n = 3013)
Sociodemographic			
Age	64.2 ± 15.9	66 ± 15.4	65.2 ± 15.6
Female	502 (40.1%)	681 (38.7%)	1183 (39.3%)
Race			
White	738 (58.9%)	1013 (57.5%)	1751 (58.1%)
Black	194 (15.5%)	259 (14.7%)	453 (15%)
Asian	16 (1.3%)	17 (1%)	33 (1.1%)
Mixed	295 (23.6%)	467 (26.5%)	762 (25.3%)
Indigenous instead Indian?	9 (0.7%)	5 (0.3%)	14 (0.5%)
Level of education			
Illiterate/incomplete elementary	605 (48.3%)	890/1760 (50.6%)	1495/3012 (49.6%)
Complete elementary/incomplete high school	278 (22.2%)	396/1760 (22.5%)	674/3012 (22.4%)
Complete high school/incomplete college	228 (18.2%)	347/1760 (19.7%)	575/3012 (19.1%)
Complete college	141 (11.3%)	127/1760 (7.2%)	268/3012 (8.9%)
Family income			
≤1 minimum wage	257/872 (29.5%)	359/1759 (20.4%)	616/2631 (23.4%)
>1 to ≤2 minimum wages	338/872 (38.8%)	678/1759 (38.5%)	1016/2631 (38.6%)
>2 to ≤5 minimum wages	0/872 (0%)	481/1759 (27.3%)	481/2631 (18.3%)
>5 to ≤10 minimum wages	133/872 (15.3%)	160/1759 (9.1%)	293/2631 (11.1%)
>10 minimum wages	144/872 (16.5%)	81/1759 (4.6%)	225/2631 (8.6%)
Health Care			
Public	812 (64.9%)	1392 (79%)	2204 (73.1%)
Private	149 (11.9%)	61 (3.5%)	210 (7%)
Health insurance	291 (23.2%)	308 (17.5%)	599 (19.9%)
Risk Factors			
Previous MI	334 (26.7%)	429 (24.4%)	763 (25.3%)
Arterial hypertension	885 (70.7%)	1368 (77.7%)	2253 (74.8%)
Dyslipidemia	459 (36.7%)	722 (41%)	1181 (39.2%)
Previous stroke/TIA	158 (12.6%)	224/1758 (12.7%)	382/3010 (12.7%)
Atrial fibrillation	344 (27.5%)	536/1758 (30.5%)	880/3010 (29.2%)
Depression	170 (13.6%)	226/1759 (12.8%)	396/3011 (13.2%)
PAD	135 (10.8%)	261 (14.8%)	396 (13.1%)
CKD	302 (24.1%)	342 (19.4%)	644 (21.4%)
Diabetes mellitus	427 (34.1%)	707 (40.1%)	1134 (37.6%)
COPD/asthma	160 (12.8%)	324/1758 (18.4%)	484/3010 (16.1%)
Smoking status			
Current smoker	108 (8.6%)	177 (10.1%)	285 (9.5%)
Former smoker	461 (36.8%)	762 (43.3%)	1223 (40.6%)
Never smoked	683 (54.6%)	822 (46.7%)	1505 (50%)
LVEF, %	39.3 ± 16.2 (n = 491)	40.1 ± 18.4 (n = 713)	39.7 ± 17.5 (n = 1204)
<40	284 (57.8%)	397 (55.7%)	681 (56.6%)
40−49	88 (17.9%)	96 (13.5%)	184 (15.3%)
≥50	119 (24.2%)	220 (30.9%)	339 (28.2%)
Sodium, mean ± SD, mEq/L	137.6 ± 5.3 (n = 1134)	137.5 ± 5.2 (n = 1537)	137.5 ± 5.3 (n = 2671)
<135	263 (23.2%)	357 (23.2%)	620 (23.2%)
Potassium, mean ± SD, mEq/L	4.4 ± 0.8 (n = 1145)	4.4 ± 0.8 (n = 1426)	4.4 ± 0.8 (n = 2571)
Creatinine, mean ± SD, mg/dL	1.6 ± 1.5 (n=1190)	1.5 ± 1.2 (n=1609)	1.5 ± 1.3 (n=2799)
BNP, median (25th, 75th), pg/mL	1075 (518, 1890) (n = 97)	794.5 (391.8, 1500) (n = 160)	907 (439, 1590) (n = 257)
NT-proBNP, median (25th, 75th), pg/mL	5345.5 (2314.5, 19700.8) (n = 192)	5410 (2698, 11122) (n = 311)	5410 (2565, 13741) (n = 503)

Data presented as no./No. (%), unless otherwise indicated.

BNP, brain natriuretic peptide; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAD, peripheral artery disease; TIA, transient ischemic attack.

In-hospital mortality rates were lower in the second phase of the registry, but all-cause deaths at 3-, 6- and 12-month follow-ups were similar during both phases of the registry (Supplementary Table S5) (Supplementary Fig. S2, S3). Regarding other clinical outcomes, cardiovascular death, cardiac arrest and hospital readmission (including HF decompensation) were lower in the extension phase compared with phase I (Supplementary Fig. S2). Clinical outcomes after discharge in the overall registry were assessed at each visit; however, only patients included in the second phase of the study (BREATHE

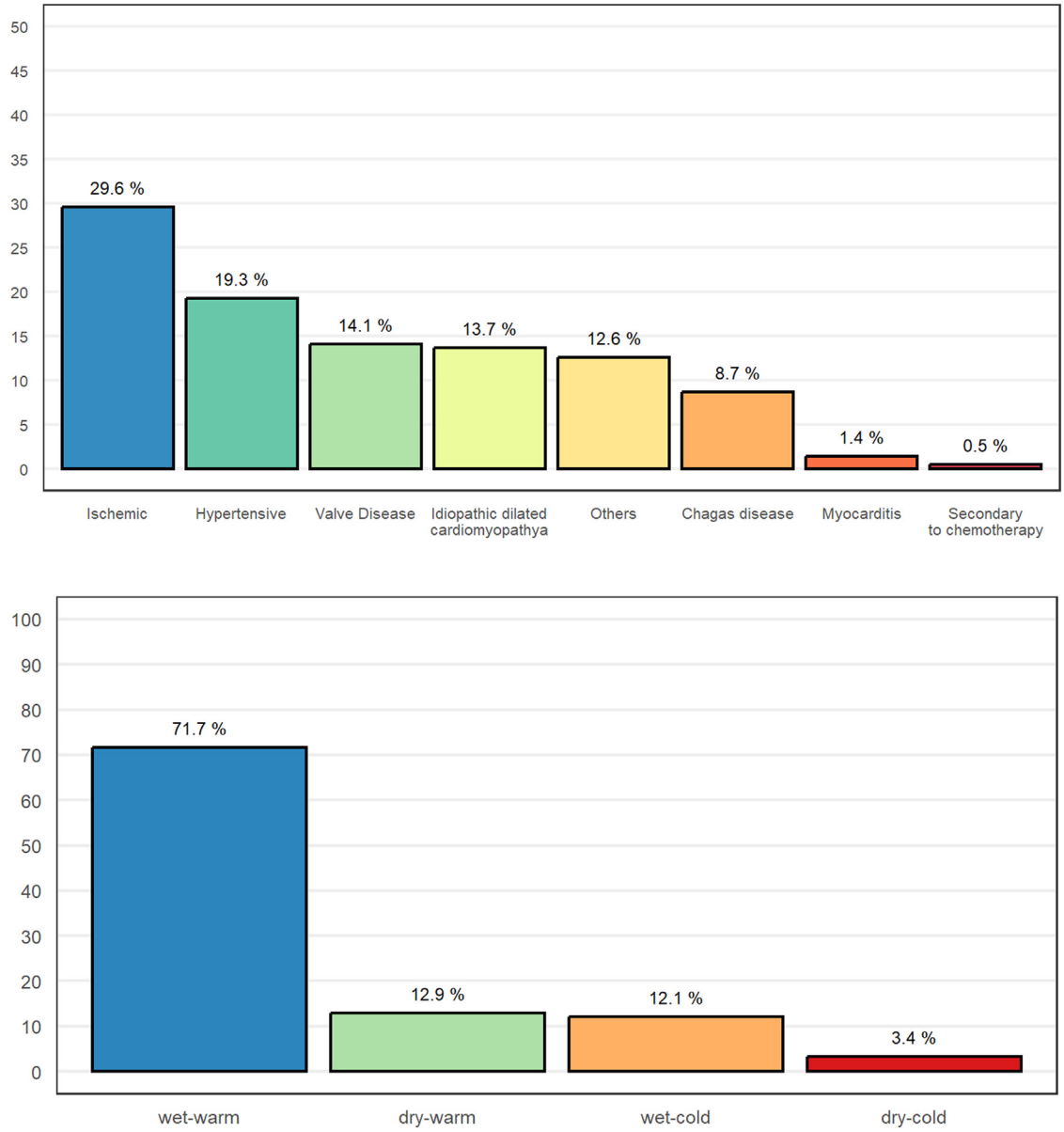

Fig. 2. A, Heart failure etiology in the overall population of the BREATHE (Brazilian Registry of Heart Failure) registry. B, Hemodynamic profile at hospital admission in the overall population of the BREATHE registry.

Extension) were included in the survival analysis curves, because the dates of death were not collected in the first phase of the study. In the survival analysis, patients were censored at 365 days (12 months) or on the date of last contact. The median follow-up time was 346 (142, 365) days, with an overall mortality rate of 31.3/100 patient-years. HF due to Chagas disease accounted for the highest mortality rate (48.04/100 patient-years), followed by ischemic etiology (35.2/100 patient-years), and nonischemic etiology (27.76/100 patient-years). In evaluating the composite outcome (death, MI, stroke, or cardiac arrest) (Fig. 3B) (Supplementary Fig. S3) and mortality from discharge to 12 months, we observed a statistical difference between the Chagas disease and nonischemic etiologies (Supplementary Fig. S4).

Multivariable analysis showed that registry phase, Chagas disease, previous MI, atrial fibrillation, chronic kidney disease, and diabetes mellitus were independently associated with cardiovascular death and/or hospitalization due to HF in the BREATHE population (Supplementary Table S6).

Discussion

The BREATHE registry evaluated more than 3000 patients hospitalized for acute HF in the 5 regions of Brazil, with a median follow-up of 346 days. The patient population was predominantly male, the average age was 65 years, and approximately half had HF of ischemic or hypertensive etiology. Upon admission, more than 80% of patients had signs of

Table 2. Medications before hospitalization (home use), first 24 hours of hospitalization, hospital discharge, and follow-up (among patients with ejection fraction <40%)

Medication	Home (n = 681)	First 24 hours (n = 681)	Discharge (n = 618)	3 months (n = 554)	6 months (n = 500)	12 months (n = 414)
Beta-blockers	433 (63.6%)	430 (63.1%)	494 (79.9%)	453 (81.8%)	403 (80.6%)	338 (81.6%)
Dosage < 50% of target		206 (30.2%)	172 (27.8%)	146 (26.4%)	115 (23%)	98 (23.7%)
Dosage > 50% but < 100%		122 (17.9%)	136 (22%)	102 (18.4%)	99 (19.8%)	75 (18.1%)
Target dosage		102 (15%)	185 (29.9%)	204 (36.8%)	189 (37.8%)	165 (39.9%)
ACEI	212 (31.1%)	275 (40.4%)	264 (42.7%)	205 (37%)	182 (36.4%)	144 (34.8%)
Dosge < 50% of target		24 (3.5%)	13 (2.1%)	9 (1.6%)	6 (1.2%)	6 (1.4%)
Dosge > 50% but < 100%		60 (8.8%)	58 (9.4%)	39 (7%)	37 (7.4%)	28 (6.8%)
Target dosage		176 (25.8%)	171 (27.7%)	134 (24.2%)	124 (24.8%)	99 (23.9%)
ARBs	199 (29.2%)	165 (24.2%)	160 (25.9%)	159 (28.7%)	154 (30.8%)	143 (34.5%)
Dosage < 50% of target		22/680 (3.2%)	16/616 (2.6%)	26/553 (4.7%)	22/497 (4.4%)	18 (4.3%)
Dosage > 50% but < 100%		63/680 (9.3%)	59/616 (9.6%)	56/553 (10.1%)	52/497 (10.5%)	54 (13%)
Target dosage		69/680 (10.1%)	67/616 (10.9%)	59/553 (10.7%)	60/497 (12.1%)	59 (14.3%)
ARNI	–	3 (0.4%)	7 (1.1%)	8 (1.4%)	11 (2.2%)	12 (2.9%)
Dosage < 50% of target		1 (0.1%)	4 (0.6%)	5 (0.9%)	8 (1.6%)	8 (1.9%)
Dosage > 50% but < 100%		1 (0.1%)	2 (0.3%)	2 (0.4%)	1 (0.2%)	2 (0.5%)
Target dosage		1 (0.1%)	1 (0.2%)	1 (0.2%)	2 (0.4%)	2 (0.5%)
ACEI or ARB or ARNI	405 (59.5%)	436 (64%)	424 (68.6%)	343 (61.9%)	337 (67.4%)	266 (64.3%)
Spironolactone	260 (38.2%)	339 (49.8%)	386 (62.5%)	306 (55.2%)	295 (59%)	250 (60.4%)
Dosage, median (25th, 75th), mg	–	25 (25, 25) (n = 183)	25 (25, 25) (n = 376)	25 (25, 25) (n = 300)	25 (25, 25) (n = 288)	25 (25, 25) (n = 243)
Hydralazine	42/397 (10.6%)	77 (11.3%)	113 (18.3%)	80 (14.4%)	60 (12%)	50 (12.1%)
Dose, median (25th, 75th), mg	–	50 (25, 75) (n = 77)	75 (50, 150) (n = 110)	75 (50, 100) (n = 80)	50 (25, 100) (n = 60)	75 (50, 100) (n = 50)
Nitrate	54/397 (13.6%)	87 (12.8%)	108 (17.5%)	91 (16.4%)	69 (13.8%)	60 (14.5%)
Dose, median (25th, 75th), mg	–	40 (20, 50) (n = 87)	40 (20, 60) (n = 107)	40 (20, 60) (n = 90)	40 (20, 60) (n = 69)	40 (20, 60) (n = 59)
Nitrate and hydralazine	24/397 (6%)	30 (4.4%)	60 (9.7%)	45 (8.1%)	27 (5.4%)	26 (6.3%)
Combined use of beta-blockers, ACEI/ARB/ARNI, and spironolactone	164 (24.1%)	197 (28.9%)	272 (44%)	197 (35.6%)	204 (40.8%)	169 (40.8%)
Combined use of beta-blockers, nitrate, hydralazine, and spironolactone	11/397 (2.8%)	12 (1.8%)	27 (4.4%)	18 (3.2%)	17 (3.4%)	16 (3.9%)
Combined use of beta-blockers, ACEI/ARB/ARNI (or nitrate and hydralazine), and spironolactone	118/397 (29.7%)	204 (30%)	288 (46.6%)	206 (37.2%)	214 (42.8%)	176 (42.5%)

*In BREATHE, information on home use of hydralazine and nitrate was not collected. Data are presented as no. (%), unless otherwise indicated.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor (available since 2017).

congestion; poor adherence to evidence-based therapies was identified as the primary cause of decompensation in almost 30% of patients. Overall, 44.5% of patients received the combination of beta-blockers, ACE inhibitors/ARBs/ARNI, and spironolactone at hospital discharge, and 40.1% were using all 3 classes of agents at 12 months.

Table 3. Mortality and procedures during in-hospital stay*

Mortality/Procedures	no./No. (%)
Mortality in the first 24 hours	37/3013 (1.2%)
In-hospital mortality	324/2962 (10.9%)
Cardiovascular procedures	272/2925 (9.3%)
Coronary artery bypass surgery	20/2925 (0.7%)
Valvular surgery	97/2925 (3.3%)
Percutaneous coronary intervention	61/2925 (2.1%)
ICD/CRT	33/2925 (1.1%)
Cardiac pacemaker	51/2925 (1.7%)
Transplant	27/2925 (0.9%)

*51 patients without discharge information (11 BREATHE and 40 BREATHE-Extension).CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator.

The population in BREATHE is a representative sample of patients in Brazil who are among the group of patients responsible for the highest number of hospitalizations due to cardiovascular diseases globally.[21] BREATHE included a broad population with very limited access to basic resources. As a consequence, even using the telephone for clinical follow-up, a relevant proportion did not have available 12-month follow-up information. Nevertheless, we consider it important to include this group of patients with social limitations because they were not commonly included in previous studies but do represent a relevant portion of the Brazilian population. It is essential to understand better

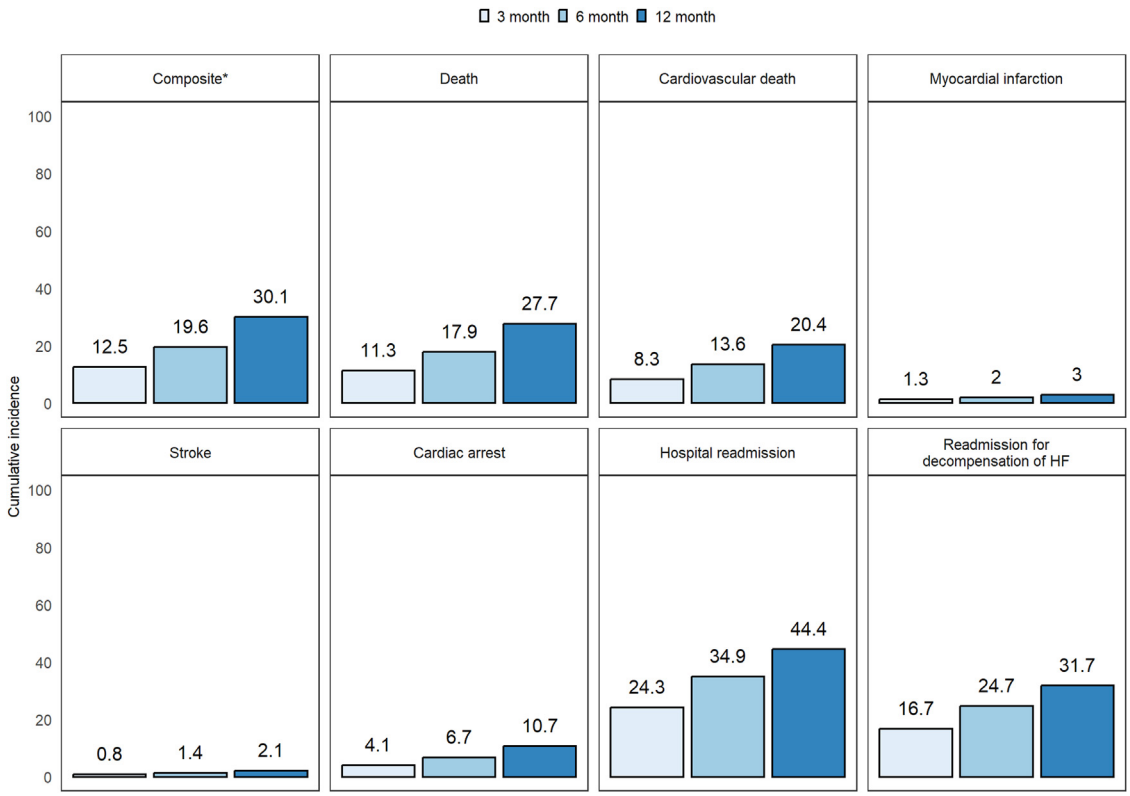

Fig. 3. A, Cumulative incidence of composite outcome (death, myocardial infarction, stroke, cardiac arrest, or hospital readmission) after discharge in the overall population of the BREATHE (Breathing REtraining for Asthma) registry. B, Cumulative incidence of composite outcome (death, myocardial infarction, stroke, or cardiac arrest) after discharge according to etiology in the overall population of the BREATHE registry

the characteristics of the population and the opportunities for improvements in the care of patients with HF in the "real world," especially in countries underrepresented in previous large registries.[22,23] The initial publication from BREATHE included 1263 patients and analyzed only in-hospital data.[16] In the present analysis, 1898 patients were added, bringing the total number enrolled to 3161, with 3013 patients eligible for analysis. In addition to the sample size increasing to more than twice the number of patients included in the previous report, the current study includes information about the prospective evaluation over the 12 months of follow-up after discharge. Thus, in addition to greater robustness in the assessment of baseline and in-hospital data, it was possible to include information on changes over time for all patients from both phases of the study. Despite the existence of large registries, especially in the United States[22] and Europe,[23] there was a lack of prospective and detailed information concerning large contemporary populations of patients with HF in other regions of the world. Previous registries in Latin America[24] were performed primarily in the first decade of the 2000s. Patients in these earlier registries were younger (~ 60 years) and had lower LVEF (average of 35%) than patients in BREATHE. A registry from Argentina during 2012 and 2013[25] that included 122 patients hospitalized due to HF had fewer women and an older population but had lower mortality rates at 12 months compared with the population in BREATHE. There was also a difference in the main causes of HF during this period. In previous registries in Latin America,[24] the primary HF etiologies were Chagas and ischemic disease; however, in BREATHE, Chagas was only the 6th cause, present in less than 10% of patients, whereas ischemic and hypertensive cardiac disease were responsible for almost half of the cases. These changes in etiology may reflect an improvement in the definition of the main cause of HF; cause was not determined in about one-third of cases in earlier registries but only 13.7% of patients in BREATHE registry. Also, comorbidities such as diabetes, hypertension and atrial fibrillation were less common in previous registries than in BREATHE. Thus, our findings indicate a trend toward an increase in etiologies related to lifestyle and age. As a result, the causes of HF in Latin America are becoming more like those seen in the United States and European registries.[26,27]

In evaluating prescription of evidence-based therapies to reduce cardiovascular risk, we found that almost 10% of patients did not receive any therapy, which had an impact on mortality due to HF at hospital discharge. Adherence to prescribed

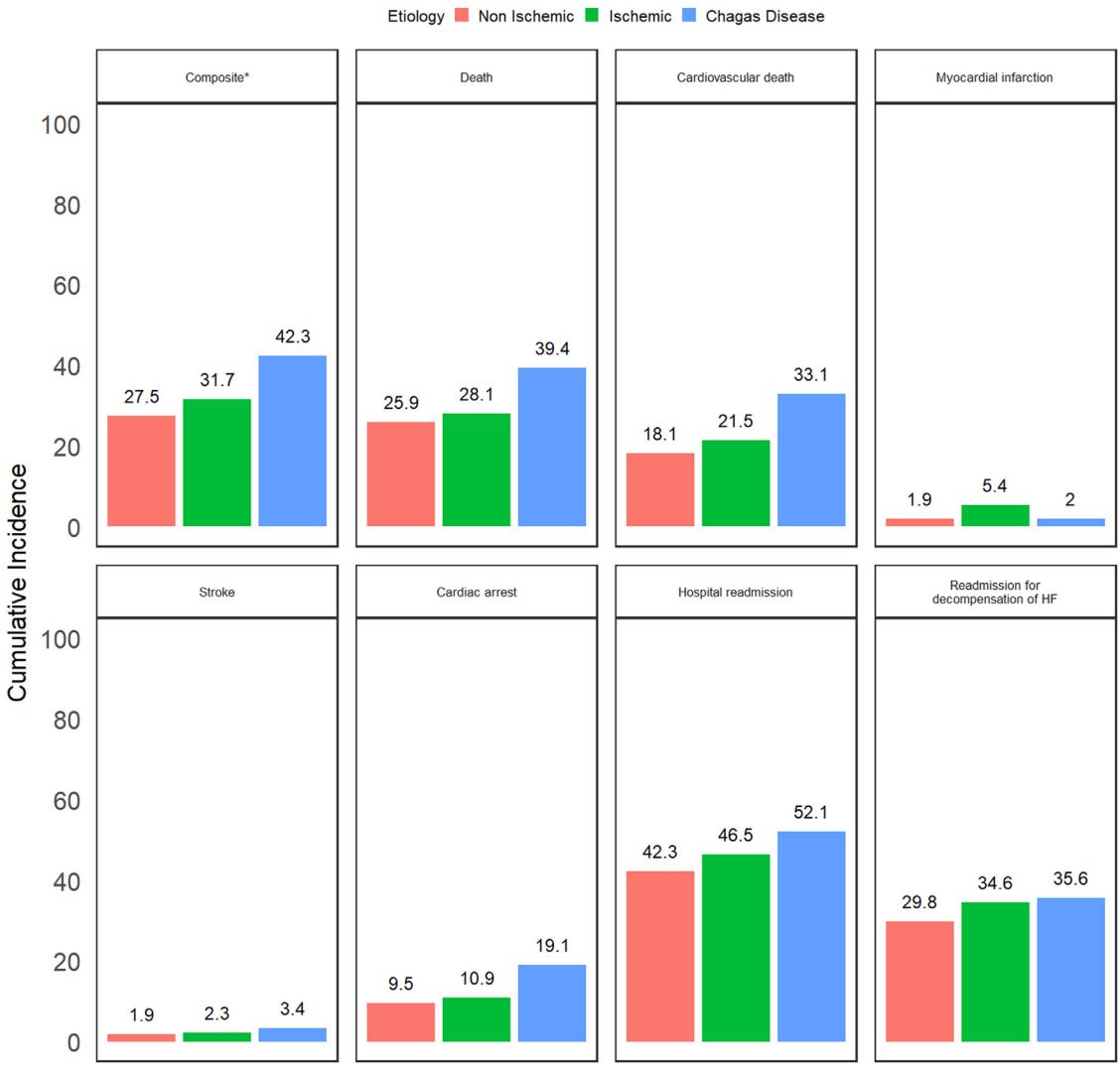

Fig. 3 Continued.

medications is a major problem in many chronic diseases.[28] Standard-of-care therapy for patients with HF includes a minimum of 3−5 medications that are usually added to other drugs for the management of common comorbidities.[29,30] Although drug adherence is related to better outcomes, medication adherence has been identified as a challenge in international registries of patients with HF.[21−25] In the BREATHE study, important gaps were identified in the application of evidence-based practices. In addition to this low use of evidence-based therapies at baseline, there was an absolute reduction of approximately 5% in the combined prescription of beta-blockers, ACE inhibitors/ARBs/ARNI, and spironolactone during the 12 months of follow-up. These findings illustrate the need to develop educational strategies to implement the use of evidence-based therapies that have been proven to be lifesaving for those with HF.

The 12-month follow-up period in BREATHE allowed for the analysis of complications after discharge and raised awareness about the prognoses of these patients. Thus, the need to improve medical care is reinforced by the fact that mortality and rehospitalization rates were higher in BREATHE than in international registries, assuming that improvement in the use of evidence-based therapies would lead to a reduction in these complications. Beyond a lesser use of evidence-based therapies, differences in the populations may explain the worse prognosis in the BREATHE registry. One interesting finding in BREATHE, which was also identified in previous studies, is that Chagas disease is, indeed, associated with worse long-term prognosis.[23,31] However, the analysis of in-hospital mortality showed a higher mortality rate among patients with ischemic etiology both in BREATHE and in previous registries that included patients with this etiology. This finding is probably related to a higher risk of complications in acute ischemic events, but after treating the ischemic event and compensating the patient, the disease is better controlled. In Chagas

disease, the risk still increases over time, and there is no specific intervention to control it. Thus, despite the administration of general treatments for HF, the progression of the disease is probably more intense and faster with Chagas disease than with other etiologies such as ischemic disease. It is necessary to evaluate new treatments for these patients, particularly because until now, no medical treatments that have a proven impact on relevant outcomes in patients with HF due to Chagas cardiac disease have been evaluated in appropriate randomized clinical trials.[32]

Study Limitations

Although the invitation was open to interested centers in all regions in Brazil, the north and central-western regions had proportionally low representation. In addition, because the participating centers have clinical research structures, and participants were included on a voluntary basis, the results may not be applicable to populations that do not fit these characteristics (eg, health facilities with fewer resources, especially in the northern and central-western regions). Nevertheless, even considering BREATHE sites as places with more favorable conditions, relevant gaps were identified in the application of evidence-based practices. Another limitation is the fact that data at 12 months were missing for 407 patients. However, the data losses occurred at different times, so we used cumulative incidence in BREATHE, and we performed a time-to-event analysis in BREATHE Extension with patients censored at the last recorded contact as a way to minimize variations in duration of follow-up. Finally, we did not collect information about the use of SGLT2 inhibitors, given the time the registry was conducted.

Conclusion

In this large national prospective registry of patients hospitalized with acute HF, mortality and readmission rates were higher than those reported globally. Poor adherence to evidence-based therapies was common both at hospital discharge and at 1 year of follow-up. Our study highlights important findings that should guide the implementation of quality-improvement interventions to help close the gap between scientific evidence and clinical practice in HF.

Lay Summary

- The BREATHE registry evaluated patients hospitalized due to acute heart failure in Brazil.
- Poor adherence to heart failure medications was the most common reason for heart failure decompensation.
- Even after hospitalization, more than half of the patients were discharged without concomitant use of beta-blockers, renin-angiotensin-aldosterone inhibitors and spironolactone.

Heart failure is a main cause of death and hospitalization worldwide; the use of evidence-based treatments can reduce complications related to heart failure. Nevertheless, adherence to these treatments is variable around the globe and, as a consequence, clinical outcomes also vary according to region. In the largest Brazilian study of a prospective cohort of patients with acute heart failure conducted thus far, some important messages could be identified, including an opportunity to improve the use of evidence-based therapies and, as a consequence, reduce clinical complications (eg, hospitalization, death) in this population.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2023.08.014.

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