Original Article

Association of Age with Optimal Medical Therapy in Patients with Chronic Heart Failure

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Abstract

Background: **The adherence to guideline-directed medical therapy in patients with heart failure (HF) remains suboptimal.**

Objectives: **We evaluated the association between age and adherence to guideline-directed medical therapy in patients with chronic HF and explored whether polypharmacy and comorbidities might explain this association.**

Methods: **We performed a cross-sectional study of 374 patients with chronic HF and left ventricle ejection fraction < 50% (23 to 89 years old, 33% women) between 2018 and 2019. GDMT was defined as using HF-related disease-modifying medications at the target dose according to guidelines. Patients were classified in 3 age groups (23 to 57, 58 to 67, and 68 to 89 years old).**

Results: **Older patients were less likely to receive optimal therapy (33% versus 24% versus 15%, p < 0.001 for each age category, respectively). After adjusting for potential confounders, the chances of receiving medical therapy at optimal dose significantly reduced for each age-decade increase (OR 0.66 [95% confidence interval 0.48 – 0.92], p = 0.013). The proportion of this association that was explained by polypharmacy (0% [0% – 3.5%]) or comorbidities (7% [0% – 41%]) was negligible.**

Conclusion: **We found that age was inversely associated with optimal drug therapy for HF, and polypharmacy or comorbidities do not appear to explain this.**

Keywords: **Heart Failure; Drug Therapy; Polypharmacy; Aging.**

Introduction

Heart failure (HF) affects 26 million people worldwide and is increasing in prevalence.[1] The expenditures are notable and will raise considerably in an aging population. HF has high mortality and morbidity, and treatment with different class of drugs can improve survival of these patients, as demonstrated in clinical trials.[2-10] Therapy using these drugs at target doses similar to those used in trials are paramount to modify the natural course of the disease, and they have been recommended by HF-related guidelines, which has been denominated guideline-directed medical therapy (GDMT).[11]

Despite the substantial evidence accumulated in the last 3 decades, the adherence to GDMT remains low. A previous study showed that only 1% of eligible patients with HF simultaneously received the target doses of angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB)/angiotensin II receptor-neprilysin inhibitor (ARNI), beta-blocker, and mineralocorticoid receptor antagonist (MRA) therapy recommended by guidelines.[12] Failure to achieve the target dose has been associated with worse survival.[13] The reasons for low compliance to GDMT are complex and likely multifactorial. A few studies have explored these reasons and suggested that drug optimization appear to be lower among older patients with HF, when compared to younger ones, but other factors may also play a role in the low treatment compliance, such as low income and health illiteracy.[14-16] However, there is a lack of studies evaluating rates of compliance to GDMT in low- and middle-income countries.

We, therefore, aimed to analyze the relation between age and GDMT in patients with HF treated in an institution from a middle-income country. We also explored whether the number of prescribed medications (polypharmacy) and number of comorbidities can help explain this association, as they might contribute to poor adherence to treatment.

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Methods

Study population

This is a cross-sectional observational study approved by the local institutional ethics committee under protocol number 3.227.412. We included consecutive patients over 18 years old referred to the Heart Failure Outpatient Clinic of the *Santa Casa de Misericórdia de Curitiba*, a tertiary university center dedicated to specialized care of patients with HF from Brazil's Unified Public Health System (SUS), from May 2018 to February 2019 in Curitiba, Paraná, Brazil. All of them were first diagnosed with HF and received medical treatment in primary care centers from SUS. They should be referred to the specialized center if they have been hospitalized for HF, or if they were considered refractory to medical treatment. Inclusion criteria were previous diagnosis of HF and left ventricle ejection fraction (LVEF) below 50%, measured by an echocardiogram performed within the previous 12 months. The patients were approchead during their routine consultation, and all the data were collected during the visit and from medical records. All patients provided written informed consent. Those who refused to participate in the study or had insufficient information, such as missing data on echocardiogram or laboratory exams, were excluded.

Exposure

Patients' ages were defined according to birth date as registered in medical records and evaluated as a continuous variable. The patients were also classified into 3 groups according to age tertiles: the first tertile from 23 to 57 years old, the second from 58 to 67 years old, and the third from 68 to 89 years old.

Outcome

The outcome was the proportion of patients under GDMT, i.e. using optimal medical treatment as recommended by the 2018 Brazilian Heart Failure Guidelines (*Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda*).[17] Patients were considered under GDMT if they were using the following drugs at the target dose according to European Society of Cardiology guidelines (Supplemental Table 1): 1) a HF-specific beta-blocker (carvedilol, metoprolol succinate or bisoprolol); 2) either an ACEI, ARB or ARNI; and 3) a MRA if symptomatic (New York Heart Association [NYHA] class II to IV).

Other covariates

Sex, etiology of HF, NYHA functional class, and creatinine blood levels were obtained from medical records. Blood pressure was measured during the patient's visit as recommended by international guidelines.[11,17] Height was measured in orthostatic position using a calibrated anthropometer, and weight was systematically measured on a calibrated scale. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared.

Time from the diagnosis of HF was the period in months between the diagnosis of HF and the date the patient was included in the study. The moment of diagnosis was estimated during patient interview based on either the first hospitalization due to HF or when they started to present typical symptoms of HF and were told they had HF, whichever happened first.

We estimated the severity of the disease by calculating the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score, which is a score that predicts the 1- and 3-year mortality in patients with HF.[18,19] This score combines 13 independent clinical variables such as LVEF, age, systolic blood pressure (SBP), BMI, creatinine levels, NYHA class, sex, current smoking status, diabetes, chronic obstructive pulmonary disease (COPD), first diagnosis of HF > 18 months, beta-blocker, and ACEI/ARB (Supplemental Table 2).

Polypharmacy and comorbidities

We defined polypharmacy as the use of medications belonging to pharmacologic classes other than those in the GDMT definition (i.e. ACEI, ARB, ARM, ARNI, or HF-specific beta-blocker).[11,17] They include medications related to HF, such as ivabradine, digoxin, loop diuretic, thiazide, hydralazine, and nitrate, as well as to comorbidities, such as statins, antiarrhythmics, anticoagulants, aspirin, clopidogrel, and others. For instance, if the patient was taking enalapril, carvedilol, digoxin, furosemide, statin, and aspirin, polypharmacy should be counted as four. As they are part of GDMT definition, enalapril and carvedilol did not count toward polyphamarcy.

The number of comorbities were defined according to the presence of hypertension, diabetes, coronary artery disease, chronic kidney disease, and COPD.

Statistical analyses

Continuous variables were evaluated for the Gaussian distribution of the data and were compared among the 3 age tertiles using ANOVA or Kruskal-Wallis test accordingly. Categorical variables were compared among groups using chi-squared test. To evaluate the independent association between age and GDMT, we performed multivariate logistic regression analysis with age as a continuous variable adjusted for sex, BMI, etiology of HF, LVEF, SBP, heart rate, NYHA functional class III/IV, MAGGIC score, and creatinine blood levels. Finally, we added polypharmacy and comorbidities to the model as potential mediators for the association between age and GMDT based on the previous hypothesis that elderly patients might take a greater number of medications and/or have more comorbidities, which might lead to less treatment optimization for HF due to drug side effects and lack of compliance. Structural equation models were built to assess the direct and indirect effects of age and to estimate the percentage of the total effect that is mediated by polypharmacy. All analyses were performed using Stata version 15 (Stata Corp, College Station, TX, USA).

Results

Study population

We evaluated 504 patients with HF from May 2018 to February 2019. Those with LVEF ≥ 50% (n = 123) or missing data (n = 7) were excluded, resulting in 374 patients for the present analysis. The mean age of the patients was 61 ± 12 (range 23 to 89) years old; 21 (6%) patients were octogenarians, and 33% were women. Table 1 displays the patients' characteristics according to age tertiles. Older patients had lower BMI, were more likely to present the ischemic and Chagas etiologies of HF, and had higher creatinine blood-levels and MAGGIC score, as compared to younger ones. LVEF, SBP, heart rate, functional class, and duration of HF were similar across age tertiles (Table 1). The proportion of patients using sodium-glucose cotransporter-2 inhibitors was very small (1 [0.8%], 1 [0.8%], and 2 [1.7%], p value = 0.48, in the three age tertiles, respectively).

Age and guideline-directed medical therapy

Older patients were less likely to receive optimal medical therapy according to GDMT. For each age decade increase, the chance of receiving optimal medical therapy significantly reduced (OR 0.67 [95% confidence interval 0.56 – 0.82], Table 2). This association remained significant after adusting for potential confounders, such as sex, BMI, etiology of HF, LVEF, SBP, heart rate, NYHA functional class III/IV, MAGGIC score, and creatinine blood levels (OR 0.66 [95% confidence interval 0.48 – 0.92], Table 2, Figures 1 and 2). There was no interaction between age and GDMT association and sex (p for interaction = 0.51).

Table 1 – Patient characteristics according to age tertile

Age tertiles	First tertile 23 a 57 y n=130	Second tertile 58 a 67 y n=128	Third tertile 68 a 89 y n=116	p value
Female, n (%)	39 (30)	42 (32.8)	42 (36.2)	0.59
BMI, kg/m²	29.6 ± 6.6	27.9 ± 5.2	26.5 ± 4.8	< 0.001
Etiology of HF, n(%)				< 0.001
Ischemic	41 (31.5)	53 (41.4)	59 (50.9)	
Chagasic	5 (3.8)	9 (7.0)	15 (12.9)	
Other	84 (64.6)	66 (51.6)	42 (36.2)	
Ejection fraction, %	33.4 ± 8.5	33.1 ± 8.9	32.1 ± 7.9	< 0.42
SBP, mmHg	112.1 ± 19.4	109.1 ± 18.8	110.2 ± 21.3	0.48
Heart rate, bpm	73.4 ± 13.7	71.9 ± 14.1	71.5 ± 13.1	0.53
NYHA 3 or 4, n(%)	35 (26.9)	34 (26.6)	32 (27.6)	0.98
Hypertension (%)	77 (59.2)	87 (67.9)	88 (75.9)	0.005
Diabetes (%)	31(23.8)	37 (28.9)	47 (40.5)	0.005
Coronary artery disease (%)	48 (36.9)	62 (48.4)	71 (61.2)	< 0.001
Chronic kidney disease	9 (6.9)	16 (12.5)	27 (23.3)	< 0.001
COPD	3 (2.3)	8 (6.2)	10 (8.6)	0.031
2 or more comorbities	49 (37.7)	67 (52.3)	80 (68.9)	< 0.001
Target dose according to GDMT, n(%)				
ACEI/ARB or ARNI	71(54.6)	60 (46.9)	45(38.3)	0.013
BB	80 (61.5)	71 (55.5)	57 (49.6)	0.06
MRA*	64 (80.0)	63 (80.8)	69 (75.0)	0.44
GDMT	43 (33.1)	31 (24.2)	17 (14.7)	< 0.001
MAGGIC score, points	12.9 ± 5.5	17.3 ± 6	24.2 ± 5.3	< 0.001
EGFR, mL/min per 1.73m²**	81.7±25.3	72.6±21.2	54.9±24.4	< 0.001
Onset of HF, years	3.3 [1.4-6.0]	4.2 [1.4-7.7]	2.6 [1.2-6.0]	0.35

*ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitors; BB: beta-blocker; BMI: body mass index; COPD: chronic obstructive pulmonary disease; Cr: creatinine; EGFR: estimated glomerular filtration rate; HF: heart failure; GDMT: guideline-directed medical treatment; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; SBP: systolic blood pressure. *Only for symptomatic patients **EGFR was estimated by the CKD-EPI formula.[30]*

Table 2 – Association between age and guideline-directed medical therapy after accounting for potential confounders

	N	OR	95% CI	p value
Age, for each 10-year increase				
Unajusted	374	0.67	(0.56-0.82)	<0.001
Adjusted for model 1	358	0.71	(0.57-0.88)	0.02
Adjusted for model 2	334	0.66	(0.48-0.92)	0.013

Model 1: Adjusted for sex, body mass index, etiology of heart failure, left ventricle ejection fraction, systolic blood pressure, heart rate, New York Heart Association functional class III/IV, and creatinine blood levels. Model 2: Adjusted for Model 1 + MAGGIC score. CI: confidence interval; OR: odds ratio.

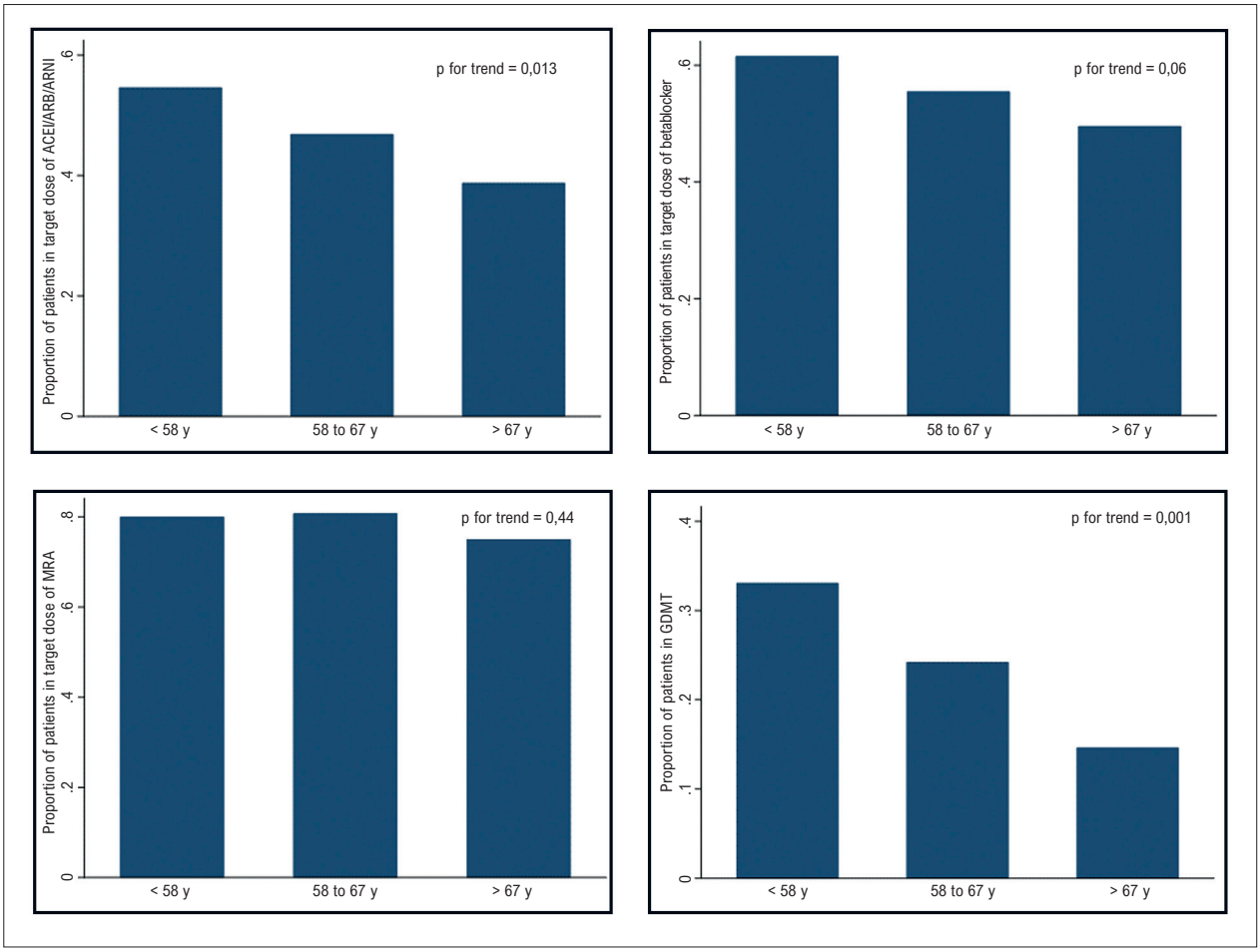

Figure 1 – *Proportion of patients at target dose of each heart failure medication as recommended by guidelines according to age tertiles. ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitors; GDMT: guideline-directed medical treatment; MRA: mineralocorticoid receptor antagonist.*

Polypharmacy and comorbidities

Older patients were more likely to use bisoprolol instead of carvedilol as HF-specific beta-blockers (Table 3). They were also more likely to use loop diuretics and statins (Table 3). Use of ACEI, ARB, MRA, digoxin, thiazide, hydralazine, nitrate, antiarrhythmic, anticoagulant, aspirin, and clopidogrel were similar between the age tertiles (Table 3). The proportion of the association between age and GDMT mediated by polypharmacy was 0% (0% – 3.5%). We also analyzed the number of comorbidities (hypertension, diabetes, coronary artery disease, chronic kidney disease, and COPD) to evaluate whether a high proportion of comorbidities might explain the inverse association between age and GDMT. We found that the number of comorbities mediated only 7% (0% – 41%) of this association.

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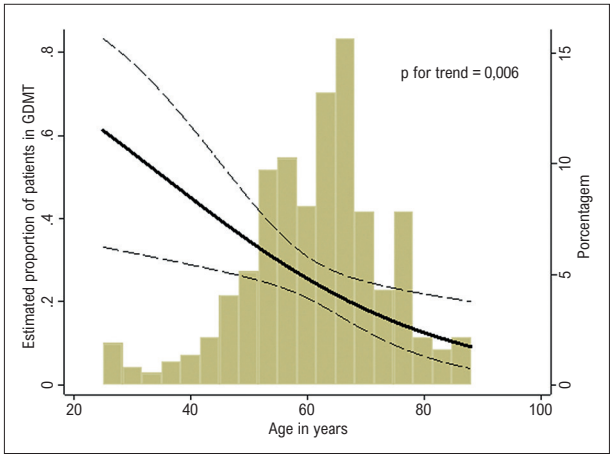

Figure 2 – *Association between medical treatment of heart failure according to guidelines and age after adjusting for potential confounders GDMT: guideline-directed medical treatment.*
**Adjusted for sex, body mass index, etiology of heart failure, left ventricle ejection fraction, systolic blood pressure, heart rate, New York Heart Association functional class III/IV, MAGGIC score, and creatinine blood levels*

Discussion

In this study of patients with chronic HF in a middle-income country, we found that optimal medical therapy for HF was significantly lower in elderly patients, compared to younger ones. This inverse association between age and optimal medical therapy was independent of heart rate, SBP, and disease severity. Also, this does not appear to be explained by polypharmacy or by the number of comorbidities, indicating treatment complexity, among elderly patients. It is noteworthy that the proportion of patients in GDMT was low across all ages. Our results show that there is much room for improvement in therapy for HF in clinical practice, which has the potential to improve survival in these patients.

Previous studies had suggested that older age can be related to lower rates of reaching target doses for HF-related medications.[15] In a study from Japan, it was shown that the presciption rates according to GDMT were significantly lower in patients 80 years old or older.[14] Another study, a survey from 36 countries worldwide found an inverse association between age and likelihood of receiving beta-blockers at the target dose in patients with HF with reduced ejection fraction.[15,20] They also found that rates of use of ACEIs and beta-blockers at target dose were quite

Table 3 – Association between use of medications and age categories

	First tertile	Second tertile	Terceiro tercil	p value
	23 to 57 y n=130	58 to 67 y n=128	68 to 89 y n=116	
Disease-modifying medications				
Carvedilol, n(%)	98 (75.4)	86 (67.2)	66 (56.9)	0.002
Metoprolol succinate, n(%)	11 (8.5)	11 (8.6)	12 (10.3)	0.61
Bisoprolol, n(%)	18 (13.8)	27 (21.1)	35 (30.2)	0.002
ACEI, n(%)	67 (51.5)	55 (43)	48 (41.4)	0.11
ARB, n(%)	34 (26.2)	47 (36.7)	30 (25.9)	0.98
ARNI, n(%)	24 (18.5)	22 (17.2)	27 (23.3)	0.36
MRA, n(%)	103 (79.2)	98 (76.6)	88 (75.9)	0.53
Other HF-related medications				
Ivabradine, n(%)	16 (12.3)	3 (2.3)	4 (3.4)	0.003
Digoxin, n(%)	34 (26.2)	24 (18.8)	24 (20.7)	0.29
Loop diuretic, n(%)	88 (67.7)	88 (68.8)	90 (77.6)	0.09
Thiazide, n(%)	19 (14.6)	15 (11.7)	10 (8.6)	0.15
Hydralazine, n(%)	32 (24.6)	29 (22.7)	21 (18.1)	0.22
Nitrate, n(%)	31 (23.8)	25 (19.5)	23 (19.8)	0.43
Other medications				
Statin, n(%)	75 (57.7)	93 (72.7)	90 (77.6)	<0.001
Antiarrhythmic, n(%)	14 (10.8)	5 (3.9)	9 (7.8)	0.34
Anticoagulant, n(%)	31 (23.8)	27 (21.1)	37 (31.9)	0.16
Aspirin, n(%)	63 (48.5)	79 (61.7)	66 (56.9)	0.17
Clopidogrel, n(%)	10 (7.7)	8 (6.2)	14 (12.1)	0.24

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitors; HF: heart failure; MRA: mineralocorticoid receptor antagonist.

low (28% and 15%, respectively), and adherence to guidelines varied across different regions around the world, which may result from different cultural and economic aspects.[15] Althought they included 5 continents, countries in South America were under-represented in this survey. Our study describes the rates of guideline-based prescriptions of drugs in HF in a Brazilian city, adding that older patients were also less likely to receive optimal medical therapy.[20] Conversely, we found higher rates of ACEIs and beta-blockers at target dose than those previous reports, probably reflecting patients treated in a referral center for HF, with access to medications free of cost.

The reasons for lower prescription according to guidelines in elderly patients are multifactorial. It has been suggested that elderly individuals are prone to hypotension and bradycardia, and these were important reasons for non-prescription of guideline-recommended medications in the QUALIFY survey.[15] Nevertheless, we did not find significant differences in SBP and heart rate among age tertiles in our study, and GDMT rates remained lower among elderly patients after adjusting for these parameters.[15] Therefore, there might be other factors, such as concern related to adverse effects and treatment inertia, which help explain the lower treatment optimization in this population. There is a well documented "risk-treatment paradox" in HF, where patients with a higher risk of mortality tend to receive less GDMT prescription.[12,21] Elderly patients are usually more complex, with more severe disease and co-morbidities, displaying higher mortality risk. Such complexity results in more unstable conditions that are more difficult to manage, and physicians may feel insecure in optimizing HF-related medications. Moreover, elderly patients may be less likely to report effort dyspnea, and physicians are less prone to optmize treatment when patients report themselves as asymptomatic. Also, physicians may prefer drugs that improve symptoms, with fewer potential adverse effects, instead of prescribing drugs that improve survival in elderly patients.[20]

Treatment complexity due to higher prevalence of comorbidities among elderly patients may also be a barrier to optimal medical treatment.[16] Cognitive impairment, which is prevalent in elderly patients with HF, has been reported as related with poor medication adherence.[22] On the other hand, an analysis from the QUALIFY study suggested that patients with HF and multiple comorbidities, such as coronary artery disease, hypertension, diabetes mellitus, vascular disease, and stroke/transient ischemic attack, were more likely to be at target dose of ACEIs, ARBs, and MRAs, which is expected, as these class of drugs are also indicated for these conditions.[15] This suggests that the presence of these comorbidities might actually contribute to optimal medical treatment for HF. Despite the mixed evidence, our results suggest that neither polypharmacy nor number of comorbidities accounted for the association between age and optimal medical treatment in HF.

Although they are excluded from most trials, elderly patients with HF are likely to benefit from GDMT.[23-25] An observational study showed that GDMT was associated with lower mortality in elderly patients with HF, and this association was consistent amont those 80 years old or older.[24] Our study highlights that there is much room to improve survival of patients with HF in clinical practice, particularly elderly patients. Efforts should be made to increase rates of GDMT in clinical practice, improving medical training and reducing medical inertia. For instance, a strategy called "start low go slow" for titration of the drugs and delivery of frequent educational reinforcements may help achieve the target dose for HF drugs in elderly patients.[25,26] Additionally, public policies may help improve comunication and establish goals for GDMT among patients with HF. Dissemination of cardiology guidelines and multidimensional practice-specific performance improvement interventions were associated with an increase in the use of GDMT.[15,27] A multilevel intervention that increases social support by relatives and healthcare providers and integrates different models of care, such as home care, telemedicine, primary care, and HF clinics, can help patients deal with treatment complexity and improve medical treatment.[20,25,28,29] Better rates of GDMT help reduce hospitalizations, with a significant economic impact.

Our study has some limitations that deserve attention. This is a cross-sectional study, which prevents us from establishing a temporal sequence relating patients aging and use of optimal drug doses. Furthermore, this design is subject to survival bias. We also cannot exclude the possibility that the differences and relations observed are due to other unmeasured confounding variables, such as income and education level. In addition, this is a single-center study of patients from SUS, and previous diagnosis of HF and LVEF below 50% may not necessarily reflect practices of others centers. The following specific characteristics of our study popuation should be noted: around 75% in NYHA funcional class I and II, which may reflect symptom improvement after treatment; 20% of patients used ARNI, even though this drug had elevated costs and it was not provided by the government at the time of the study; amost one third used ARB, even though they should be used only in patients who are intolerant to ACEI. Finally, the term "polypharmacy" has been defined in different ways in the literature, most commonly as the use of 5 or more medications, and no standard definition has been stablished.[30]

Conclusion

In this study of patients with HF in a middle-income country, we found that, overall, the rates of medical therapy of HF at the target dose was low. These rates were significantly lower in elderly patients, when compared to younger ones, and this does not appear to be explained by polypharmacy or the higher presence of comorbidities among the elderly.

Author Contributions

Conception and design of the research: Fernandes-Silva MM; Acquisition of data: Koga VAA, Dall'Asta L, Jacyntho TLP, De-Marchi LC, Mulinari RP, Ladeira BA, Nemeth MERF; Analysis and interpretation of the data: Koga VAA, Fernandes-Silva MM; Statistical analysis: Dall'Asta L, Fernandes-Silva MM; Writing of the manuscript: Koga VAA, Dall'Asta L, Jacyntho TLP, De-

Marchi LC, Mulinari RP; Critical revision of the manuscript for intellectual content: Silvestre OM, Bonatto MG, Moura LAZ, Fernandes-Silva MM.

Potential Conflict of Interest

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

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Study Association

This study is not associated with any thesis or dissertation work.

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