Optimized Treatment and Heart Rate Reduction in Chronic Heart Failure

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Abstract

Background: Heart failure (HF) is a syndrome that leads to poor outcome in advanced forms. The neurohormonal blockade modifies this natural history; however, it is often suboptimal.

Objective: The aim of this study is to assess at what percentage cardiologists used to treating HF can prescribe target doses of drugs of proven efficacy.

Methods: A total of 104 outpatients with systolic dysfunction were consecutively enrolled, all under stabilized treatment. Demographic and treatment data were evaluated and the doses achieved were verified. The findings are shown as percentages and correlations are made between different variables.

Results: The mean age of patients was 64.1 ± 14.2 years, with SBP =115.4 ± 15.3, HR = 67.8 ± 9.4 bpm, weight = 76.0 ± 17.0 kg and sinus rhythm (90.4%). As for treatment, 93.3% received a RAS blocker (ACEI 52.9%), all received beta-blockers (BB), the most often prescribed being carvedilol (92.3%). As for the doses: 97.1% of those receiving an ARB were below the optimal dose and of those who received ACEI, 52.7% received an optimized dose. As for the BB, target doses were prescribed to 76.0% of them. In this group of patients, most with BB target dose, it can be seen that 36.5% had HR ≥ 70 bpm in sinus rhythm.

Conclusion: Cardiologists used to treating HF can prescribe target doses of ACEI and BB to most patients. Even though they receive the recommended doses, about one third of patients persists with HR > 70 bpm and should have their treatment optimized. (Arq Bras Cardiol. 2013;101(5):442-448)

Keywords: Heart Failure; Heart Rate; Ventricular Dysfunction, Left; Digoxin.

Introduction

Heart failure (HF) is a prevalent and potentially progressive syndrome and individuals with HF at advanced stages have high morbidity and mortality[1,2]. The neurohormonal blockade carried out with adequate doses of drugs can modify its natural history; however, it is often suboptimal[2-4]. Data from clinical trials, HF registries and from patients referred for a second opinion show that often the target doses of drugs with proven efficacy in HF are not prescribed and it is likely that this fact contributes to the possible risk of hypotension, bradycardia and lack of tolerance by patients[3,4]. In the Euro Heart Survey Programme it was observed that 36.9% of patients with HF had a beta-blocker (BB) prescription and only 17.2% received a combination of diuretics, angiotensin-receptor inhibitors and beta-blockers[4].

In advanced HF, even when patients are adequately treated, the mortality rate is still higher than desired, which suggests that new therapeutic approaches should be investigated or implemented[1].

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Experience shows that the HF treatment is not always easy, as the patients, especially the most severe ones, have reduced blood pressure levels, a clinical finding that may complicate the prescription of several medications. There is, however, evidence that HF treatment specialists and HF Clinics can optimize treatment and obtain better results[5,6]. Few analyses have been carried out on the quality of HF treatment in Brazil. In InCor, the prescription of drugs was described at the pre-beta-blockers time[7].

In search of data on drug prescription and its form, we proposed to analyze the prescription of drugs of proven efficacy in patients with HF, treated in medical offices, by doctors used to treating HF. We aimed to verifying which medications were being prescribed and, among patients receiving BB, how many were receiving target doses of the drugs and clinical features of patients receiving this type of prescription. We also aimed to answer a more recent question: how many patients would have a HR > 70 beats per minute while receiving optimized treatment?

Methods

The aim of the study was to determine how patients with HF are treated by cardiologists used to treating this syndrome, especially if the medication doses tested in large clinical trials can be prescribed to these patients and whether they would be well tolerated by patients.

To perform this research, we evaluated the treatment of patients with HF treated by three cardiologists used to treating this syndrome. From October 2011 to May 2012 a total of 104 patients with HF and left ventricular systolic dysfunction were consecutively enrolled. Patients undergoing HF treatment for more than two months, who received a BB and optimized treatment at the time of study enrollment, were included in this cross-sectional cohort. Demographic data, heart disease etiology, heart rhythm, blood pressure, heart rate, weight and drug treatment data were assessed, verifying the doses prescribed of different drugs.

The inclusion criteria included patients receiving BB, who had an echocardiogram documenting systolic dysfunction with ejection fraction < 45% on a test performed within six months prior to study enrollment.

Patients were considered to be adequately managed when they were prescribed the three medications that have been proven to modify the natural history of HF: Angiotensin-Converting Enzyme (ACE) inhibitor; or Angiotensin Receptor Blockers (ARBs) II; BB and spironolactone and in those with renal failure, if they received hydralazine and nitrate instead of ACE inhibitor or ARBs. The dose considered correct for ACE inhibitor was 20 mg of enalapril 2x/day or equivalent doses of captopril (150 mg/day) or ramipril (10 mg/day) [2].

For ARBs, the correct dose was considered as 150 mg/ day of losartan. For candesartan, the target dose was 32 mg/day and for valsartan, 320 mg/day [2]. For spironolactone, the target dose was 25 mg/day. For beta-blockers, the full dose was considered as 25 mg 2x/day for carvedilol to patients up to 80 kg, 50 mg 2x/day for those with more than 80 kg [2]. For bisoprolol, the target dose was considered as 10 mg/day, and for metoprolol succinate, 200 mg/day [2].

We also identified the percentage and prescription dose of digoxin, hydrochlorothiazide, furosemide and amiodarone, medications often prescribed to patients with HF.

For the statistical analysis, considering that the most often prescribed medications were enalapril, losartan and carvedilol, equivalent doses were adopted when the prescribed medications were not one of those.

Statistical Analysis

Continuous variables are shown as mean ± standard deviation and categorical variables as frequencies and percentages. The comparison of treatment among patients who reached the target dose of BB was performed using the Kolmogorov-Smirnov test for normal distribution of continuous variables (Table 1), and all analyzed variables (age, SBP, DBP, HR, weight, LVEF, LVDD, LA) showed a normal distribution using the Kolmogorov-Smirnov test ($p > 0.05$). Thus, the Student's *t* test was used to compare the means of these variables regarding the "target dose" of BB. In the comparison of the characteristics, the chi-square or Fisher's exact test were used for categorical variables.

The sample size was estimated at 98 patients to determine the mean dose of BB (carvedilol) in the population of patients with HF on optimized treatment, with a confidence interval of 95% and a variation of ± 3.5 mg in the standard deviation, taking as basis the standard deviation of the mean dose of carvedilol in the SHIFT study[8], which was 17.8 mg. Thus, 104 patients were included in the study.

The p values are two-tailed, with a significance level of <0.05.

Results

The main characteristics of the study population are shown in Table 1.

As for the treatment, 93.3% received a renin-angiotensin system blocker and 52.9% an ACE inhibitor and 40.4%, an ARB; all received beta-blockers, with carvedilol being the most often prescribed medication (92.3%). Spironolactone was being prescribed to 69.2% of patients and digoxin, to 16.3% of them.

Table 2 shows the mean dose of prescribed drugs. As for the doses, 82.1% of those treated with an ACE inhibitor received the target dose and 97.1% of those receiving an ARB received a dose that was less than optimal.

As for the BB, 76.0% of the patients were prescribed target doses or higher. In patients over 80 kg, the percentage of patients receiving the target dose of 50 mg 2x/day was 21.6%.

Regarding the ACE inhibitors, the non-prescription of target doses was associated with lower systolic blood pressure (112.6 + 14.5 mmHg vs. 122.7 + 15.1 mmHg, $p = 0.0003$).

Regarding the beta-blockers, the non-prescription of target doses was associated with the etiology of heart disease, with prescription of doses below the target dose in 82% of patients with Chagas disease. Patients with functional class III and IV also received lower doses of beta-blockers. On the other hand, patients with ischemic heart disease received more often the target doses of beta-blockers (Table 1).

At the HR analysis of patients in sinus rhythm with optimized treatment, it was observed in this population that 36.5% had HR > 70 bpm; of these patients, 71.1% received carvedilol at a dose of 50 mg/day or more (Figure 1). When comparing the clinical characteristics and pharmacological treatment of patients with HR > or < 70, we found no differences in the degree of cardiac involvement. The EF (37.3 ± 8.9% vs. 37.4 ± 8.34%, $p = 0.921$) and LVEDD (63.8 ± 8.9 vs. 64.7 ± 6.5 mm, $p = 0.426$) were similar in both groups. Among the clinical variables, systolic BP differed between the two groups, being lower in the group with HR < 70 bpm (119.2 ± 15.4 vs. 112.8 ± 14.8 mmHg, $p = 0.035$).

Comments

The patients analyzed in this cross-sectional cohort received optimized treatment from the therapeutic point of view, as most were receiving the drugs indicated in the Guidelines for the treatment of HF and the target dose was prescribed and tolerated by most[2,9]. The data showed that cardiologists used to treating HF can achieve the target doses indicated in the Guidelines for most patients.

The data also showed that these results, regarding quality of

Table 1 - Clinical characteristics of the study population and comparison between patients who achieved and did not achieve the target dose of beta-blocker

	Total		Beta-blocker ("target dose")		
Characteristics	(n = 104)	P (K-S)	Yes (n = 79)	No (n = 25)	p*
Age (years)	64.1 ± 14.2	0.521	64.5 ± 13.8	63.0 ± 15.7	0.202
Male sex	69 (66.3)	-	53 (67.1)	16 (64.0)	0.776
Etiology:					
Chagas	11 (10.6)	-	2 (2.5)	9 (36.0)	<0.001
Ischemic	52 (50.0)	-	45 (57.0)	7 (28.0)	0.012
Non-ischemic	41 (39.4)	-	32 (40.5)	9 (36.0)	0.688
SBP (mmHg)	115.4 ± 15.3	0.985	116.1 ± 14.8	113.2 ± 17.0	0.611
DBP (mmHg)	73.8 ± 10.0	0.539	74.6 ± 9.8	71.4 ± 10.7	0.590
HR (bpm)	67.8 ± 9.4	0.158	67.2 ± 8.6	69.7 ± 11.8	0.340
Weight (kg)	76.0 ± 17.0	0.542	76.9 ± 16.5	73.2 ± 18.6	0.659
AF	10 (9.6)	-	9 (11.4)	1 (4.0)	0.445
Class (NYHA):					
I	17 (16.3)	-	14 (17.7)	3 (12.0)	0.757
II	78 (75.0)	-	61 (77.2)	17 (68.0)	0.354
III	7 (6.7)	-	3 (3.8)	4 (16.0)	0.055
IV	2 (1.9)	-	1 (1.3)	1 (4.0)	0.425
FC = III/IV	9 (8.7)	-	4 (5.1)	5 (20.0)	0.035
HR ≥70 bpm	43 (41.3)	-	31 (39.2)	12 (48.0)	0.438
LVEF (%)	37.3 ± 8.6	0.723	37.7 ± 8.8	36.1 ± 7.9	0.784
LVEDD (mm)	64.3 ± 7.6	0.741	64.2 ± 7.8	64.8 ± 7.0	0.488
LA (mm)	45.8 ± 7.8	0.852	45.6 ± 7.8	46.2 ± 7.8	0.782

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; AF: atrial fibrillation; NYHA: New York Heart Association; FC: functional class; LVEF: left ventricular ejection fraction; LVEDD: left ventricular-end diastolic diameter; LA: left atrial diameter. p, p value (Student's t test, Chi-square test or Fisher's exact test). P (K-S), Kolmogorov-Smirnov test (p > 0.05 = normal distribution).*

Table 2 - Percentage of prescription and mean dose of prescribed medications for the treatment of heart failure in the outpatient clinic

Medication	n (%)	Mean dose (mg/day)
Carvedilol	104 (100.0)	49.8 ± 24.1
Enalapril	55 (52.9)	32.2 ± 27.6
Losartan	42 (40.4)	95.8 ± 48.6
Espironolactona	72 (69.2)	25.7 ± 5.5
Digoxin	17 (16.3)	0.15 ± 0.05
Hydrochlorothiazide	27 (26.0)	32.9 ± 12.6
Furosemide	48 (46.2)	49.6 ± 27.1
Hydralazine	11 (10.6)	172.7 ± 104.6
Nitrates	9 (8.7)	80.00 ± 31.6
Amiodarone	8 (7.7)	115.6 ± 58.2

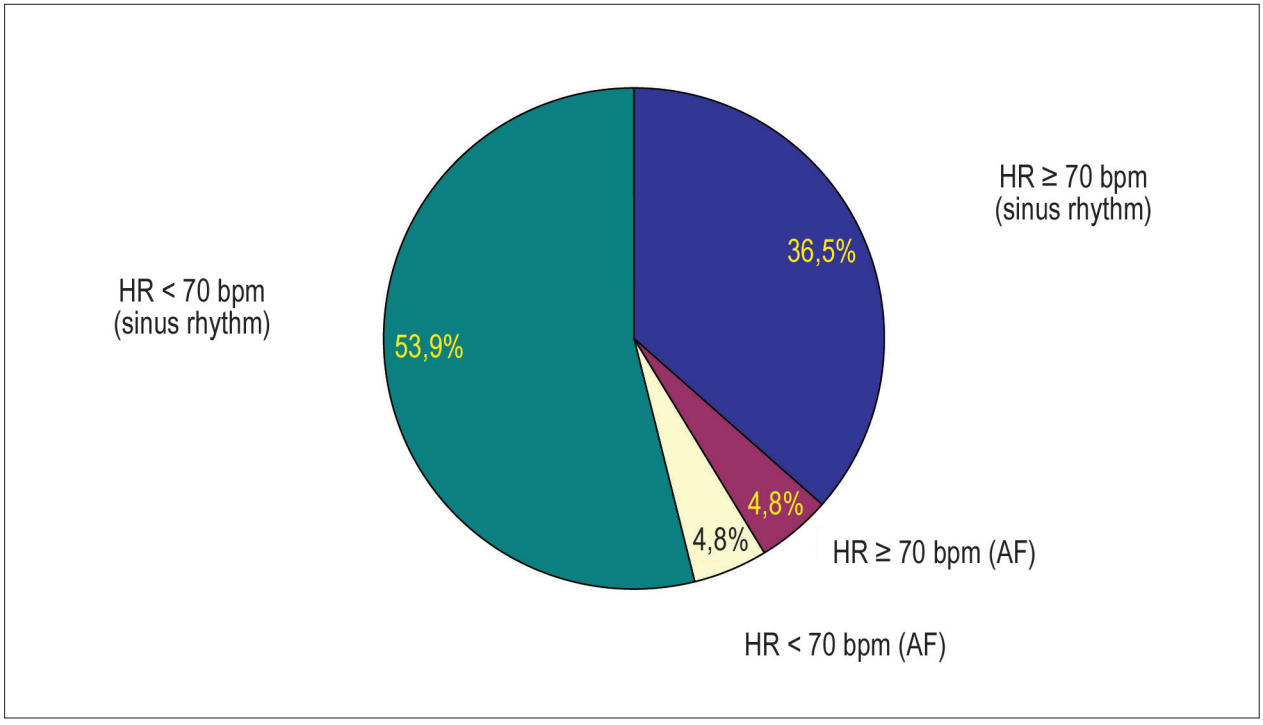

Figure 1 – *Patients that met the criteria for further heart rate reduction: 36.5% of patients in sinus rhythm had heart rate (HR) ≥ 70 bpm, who could benefit from further HR reduction.*

treatment, were better than those usually described in registries and even in some clinical trials[4,8,10,11].

In this patient population, the percentage that received a renin-angiotensin system blocker was similar to that described in the registries, with more than 90% of patients receiving such drugs; however, the percentage receiving the target dose was higher in our series[4,11] .

As for the spironolactone, the prescription frequency was higher than that observed in the registries and similar to those observed in the most recent clinical trials[4,8,10,12]. In the ADHERE Registry, aldosterone blockers were prescribed to 34.6%; in the European registry, to 20.5%, and in the SHIFT study, to 60% of cases, and in our series, to 69.2% of cases[4,8,10].

As for beta-blockers, all patients were receiving the drug by selection criteria. The prescribed dose was higher than that described in the Registries and even higher than in several clinical trials of these drugs. Citing two recent studies, in the CIBIS - ELD study the mean prescribed dose of carvedilol was 23.9 mg, and 31% received the target dose of 50 mg/day[11]. In the SHIFT study, the mean dose was 25.0 mg/day and 26% received the target dose, while in our series the mean dose of carvedilol was 49.8 mg/day and 76% received the target dose of 50 mg/day[8].

The issue of the BB dose is not fully elucidated, but the MOCHA and REVERT studies and the analyses of CIBS-II, CIBIS-III and SENIORS studies indicate that higher doses result in better outcomes with greater reversal of cardiac dilatation and morbimortality reduction[13-17]. Analysis of data from the HF-ACTION study of 2012 again confirmed the importance of higher doses, with patients showing better outcomes when treated with target doses, a more significant result than with lower doses[18].

Our results showed that it is possible to administrate the target dose to most patients, while demonstrating that Chagas disease was associated with greater difficulty in prescribing the target doses of beta-blockers. These findings show us that physicians used to treating HF can most often prescribe and achieve the target doses of drugs of proven efficacy in HF[2,9]. It also showed that Chagas disease, probably due to higher cardiac impairment and clinical forms, makes it difficult to achieve the target doses of these drugs[19,20]. The higher degree of involvement and nonprescription / no tolerance to target doses may explain the worse outcomes in patients with this disease when they have HF[19,20].

There is increasing evidence that the HR can be a good parameter to indicate the quality of treatment, considering that the therapeutic regimen should promote HR reduction, aiming at achieving a HR of around 70 beats per minute or less[8,12,21,22]. The presence of HR > 70 bpm would be an indicator of the need to review the treatment and optimize it.

The issue of HR and treatment of HF is a controversial one and not fully understood, and its interpretation is necessary to consider different variables. For instance, in Chagas disease and in elderly patients, HF is often lower, and thus cannot be used as a good indicator of treatment quality. Incidentally, this was one of the results of this study, when we observed that the doses of BB prescribed to chagasic patients were lower than those prescribed to nonchagasic ones.

In recent years, however, evidence started to appear that higher HR would be an important prognostic marker. The BEAUTIFUL and SHIFT studies demonstrated that patients with HR > 70 bpm have a poorer prognosis than patients with lower basal HR[8,21]. Similar results have been reported in different databases, such as in the CHARM and DIG studies and in case series[22-24]. These data leave no doubt that HR should be considered an important prognostic factor and should be targeted for treatment, as it has been shown that its reduction with ivabradine resulted in a decrease in hospital admissions due to decompensated HF and from all causes, and reduced HF mortality, with no difference in cardiovascular and all-cause mortality.

In our study, we analyzed the HR in patients after treatment optimization and observed that a third of them, even after receiving full doses of beta-blockers, persisted with basal HR > 70 bpm.

This result is similar to that described in several European HF registries and even clinical trials; there were, however, no Brazilian data on this clinical finding[3,4,24,25].

When analyzing our series, we tried to verify whether the clinical characteristics and those related to the treatment of patients could explain this finding of HR > 70 bpm. To analyze the data, we divided the patients into two groups: those with HR > and < 70 bpm. In this comparison, we found no differences that could explain the finding, as the two groups were similar regarding clinical characteristics, as well as the medical treatment received. Moreover, there was no association between the prescribed dose of BB and HR of the patient when undergoing stabilized and optimized drug therapy. Our results overlap those observed in the SHIFT study, showing that the observed HR was not associated with the dose of BB that patients were receiving[8,12].

Overall, our data and the literature indicate that HF treatment should be individualized. When patients receive treatment instructions, physicians should seek to prescribe drugs of proven efficacy at doses that have shown benefits. We confirmed that the majority of office patients tolerate these doses.

Notwithstanding the optimized treatment, patients persisted with HR > 70 bpm, a finding indicative of worse prognosis, indicating the need for treatment reevaluation and possibly improved optimization, aiming at a reduction in HR. For that purpose, one can prescribe digitalis, increase the dose of beta-blockers or prescribe ivabradine. Of these drugs, ivabradine is the one of which effectiveness has been documented, randomly analyzed in a large clinical trial, the SHIFT study[8].

Study limitations

This pilot observational study demonstrated that cardiologists used to treating HF prescribe medications that have been shown to improve the prognosis of HF, as recommended by the Guidelines; however, we do not know how these patients are treated by most generalists at public health units, and what the impact is on clinical outcomes (prognosis, HF hospitalizations), when comparing the treatment of HF performed by clinicians and cardiologists. Additional studies are needed to understand the treatment of HF in our country.

Conclusion

The results of this analysis showed that, in a population treated at medical offices, most patients tolerate the drugs of proven efficacy in the treatment of HF and the target doses can be prescribed and are tolerated by most patients. It also showed that about one third of patients with optimized treatment remain with HR > 70 bpm, allowing us to conclude that the treatment could be revised and further optimized. These findings require further investigations to help in the planning of new studies in this area, enabling a better understanding of HF treatment in the real world and thus assist in the care of patients with this malignant and debilitating syndrome, in an attempt to reverse this trend.

Author contributions

Conception and design of the research, Acquisition of data and Critical revision of the manuscript for intellectual content: Moreno IB, Del Carlo CH, Pereira-Barretto AC; Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Del Carlo CH, Pereira-Barretto AC.

Potential Conflict of Interest

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

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Study Association

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