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The prognostic impact of cardioselectivity of beta-blockers prescribed during hospitalization for decompensated heart failure.

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Abstract

Background

Beta-blockers (BBs) show considerable variation in cardioselectivity (i.e., the relative affinity to the β_1 receptor), even among those with evidence of benefit in the treatment of chronic heart failure (HF). We aimed to evaluate whether the cardioselectivity of BBs prescribed at discharge from hospitalization for decompensated HF will affect the long-term prognosis of patients.

Methods

In the prospective study, we followed 4053 patients hospitalized for decompesated HF. The entire cohort was divided into subgroups based on the cardioselectivity of the BBs prescribed at discharge.

Results

After complex adjustment, patients treated with a highly selective BBs (bisoprolol) showed significantly lower five-year cardiovascular mortality than those with a lesser degree of cardioselectivity (mainly metoprolol) [HRR 0.69 (95%CIs:0.52–0.92), p = 0.011]. This difference remained in patients with HF with reduced ejection fraction (HFrEF) [HRR 0.58 (95%CIs:0.37–0.89), p = 0.013], but was not yet significant in HF with preserved ejection fraction [HRR 0.66 (95%CIs:0.43–1.02), p = 0.063]. In HFrEF patients only, highly cardioselective BBs also showed a lower risk of cardiovascular mortality than nonselective BBs with α-blocking activity (mainly carvedilol) [HRR 0.55 (95%CIs:0.33–0.93, p = 0.025].

Conclusion

The choice of a beta-blocker regarding the degree of its cardioselectivity may have a prognostic impact in chronic HF patients.

1. Introduction

Chronic heart failure (HF) is an end-stage complication of most cardiovascular diseases[1]. Its clinical manifestation range from asymptomatic (and in several cases undiagnosed) mild functional insufficiency of the filling of the left ventricle up to highly symptomatic, seriously impaired ejection fraction. From a clinical point of view, patients in whom the chronic heart failure suddenly progressed into the need for hospitalization are indeed one of the most affected groups in terms of the staging of the disease, also showing a significantly worse prognosis. In our previous analysis on these patients, fewer than 45% of subjects being hospitalized for acute decompensated HF survived for more than five years [2]. The long-term prognosis of these patients is not significantly influenced by acute-phase

management (which is largely standard), but rather by long-term treatment in the chronic stage of the disease.

Beta-blockers (BBs) were historically only the second drug class (after angiotensin-converting enzyme inhibitors) to be shown to have a prognostic benefit in patients with chronic HF. Use of BBs in chronic HF was to some extent counterintuitive (and even initially contraindicated) until the groundbreaking studies[3-5]from the turn of the century demonstrated the key role of blockade of sympathetic activity at the myocardial level in terms of patient prognosis (although only for the "phenotype" of heart failure with reduced ejection fraction, i.e. HFrEF). However, with respect to the pharmacodynamic effects of BBs, there is substantial heterogeneity within the BBs group. This pharmacological class was initially "designed" more as an antihypertensive, where the impact at the heart level (manifested as a decrease in heart rate) was an undesirable property preventing higher dosage. From the standpoint of blood pressure, a vasodilating effect of some members of BB class (a phenomenon known as intrinsic sympathomimetic activity) was more desirable, but paradoxically, it led to an increase in heart rate (which is undesirable in a failing left ventricle). In contrast, the desired pharmacodynamic effect in HFrEF is the preference of b_1 receptor over b_2 (a phenomenon known as cardioselectivity), leading to a decrease in sympathetic stimulation at the myocardial level, and at the same time, minimal effect on peripheral vascular resistance (i.e., no intrinsic sympathomimetic activity). The practical impact of this heterogeneity was that only four BBs showed benefit in the treatment of chronic HF (i.e., bisoprolol, metoprolol succinate, carvedilol, and nebivolol[3-6]). In contrast, the effect of several other class members was neutral or even harmful [7].

If we accept the theory that the key component of the benefit of BBs in chronic HF is cardioselectivity, it must be stated that the difference in this pharmacodynamic property across the BBs is indeed significant. The oldest propranolol was practically completely nonselective (or even affected b_2 receptors about 1.8 times more than b_1), later representatives (such as metoprolol, atenolol, or betaxolol) have about 20-35 times higher affinity for the b_1 receptor, while the most selective bisoprolol has up to 75 times higher [8]. For the sake of completeness, primary nonselective carvedilol has more complex pharmacodynamic properties (i.e., shows additive α-blocking activity, the ability to modulate nitric oxide signaling, and other mechanisms), and a different mechanism than cardioselectivity probably mediates its cardiovascular benefit.

In this study, we raised the question of whether the choice of beta-blocker in terms of cardioselectivity, prescribed (recommended) at discharge from hospitalization for acute decompensated HF, somehow affects the prognosis of patients in the long-term perspective. The secondary question was to what extent BBs lacking evidence of benefit in the treatment of chronic HF are still used in "real-world" clinical practice (despite clear recommendations from the Guidelines[9, 10]) and to what extent this also affects patient prognosis.

2. Methods

The independent institutional board (Ethical Committee of the University Hospital and Medical Faculty Pilsen) approved the study protocol. All study procedures were performed according to the Good Clinical Practice principles and ethical standards formulated in the 1964 Declaration of Helsinki and its later amendments. The study subjects signed a written informed consent at admission to the hospital (i.e., baseline visit). The data were stored and evaluated in accordance with the GDPR issued by the European Committee.

Design and Study Population

The analysis represents a prospective follow-up study and was performed in patients hospitalized de novo for acute decompensated HF at the University Hospital Pilsen. The main qualifying criterion was based on diagnosis, as formally stated in the discharge report as the primary cause of hospitalization. Details of the selection process were reported elsewhere [2] and are also depicted in Figure 1. In the first step, we identified 10,792 individual patients hospitalized between January 1, 2000, and September 29, 2020 (in case of recurrent hospitalization for HF in the same patient, we used the data from the first hospitalization during the observation period). In the second step, we excluded 4988 patients hospitalized for HF before January 1, 2010 (in our or any other Hospital). In this way, we created a sample of 5804 individual patients without a history of HF hospitalization in the previous ten years. From this initial pool, 1140 were older than 85 years, 138 subjects were excluded after a review of their documentation; usually because the HF was not found to be the primary cause of their hospitalization, but we also excluded patients with end-stage diseases or medical circumstances, presumptively limiting patient survival to less than one year. Another 429 patients died during hospitalization and 44 patients were excluded due to lost of follow-up (these patients were not citizens of the Czech Republic and therefore are not included in the national population register) The final sample consisted of 4053 subjects, aged ≤85 years, with the first manifestation of HF requiring hospitalization (and being not previously hospitalized for at least ten years for HF) and surviving the qualifying hospitalization. The date of admission to the hospital was used as a baseline point for the follow-up analysis.

Data collection

The details of the study protocol were reported elsewhere [2, 11]. Briefly, we extracted the following data from the hospital information system: history of cardiovascular diseases, coronary revascularizations, diabetes mellitus, hypertension, known malignancies, and smoking history. We critically assessed the presumed leading etiology of HF (coronary artery disease-related or not) based on available documentation. At the same time, we derived the ejection fraction (EF) from echocardiography performed during hospitalization and the presence of atrial fibrillation/flutter from the ECG. We also extracted the recommended pharmacotherapy (including doses) from the discharge report regarding the drugs of particular interest: furosemide, beta-blockers (BBs), renin-angiotensin system (RAS) blockers (angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor-neprilysin inhibitors (ARNI) were included in this group), mineralocorticoid receptor antagonists (MRA), and statins. These drug classes were managed in a binary way (i.e., treated versus non-treated). In contrast, for furosemide, we

applied further stratification by dose at discharge (i.e., ≤40 mg, >40 & <125 mg, and ≥125 mg). In addition, we also considered a specific representative of beta-blockers (the exact stratification will be mentioned later).

Essential laboratory examinations (glycemia, serum lipids, creatinine, and natriuretic peptides) were done as a part of the routine clinical management in the central hospital laboratory (Department of Clinical Biochemistry and Hematology, University Hospital Pilsen; only standard commercial kits and analytical platforms were used, namely COBAS 8000 analytical platform, ROCHE Diagnostics, Basel, Switzerland). The regular quality control system involves all procedures (instruments, laboratory estimations, etc.). We also calculated estimated glomerular filtration rate (eGFR) from individual creatinine values using the CKD-EPI formula [12].

The individual vital status of all patients was ascertained by the National Population Registry (Institute of Health Information and Statistics, Ministry of Health of the Czech Republic). The death date was recorded if the patient died between discharge and September 30, 2025 (the follow-up reference day). To specify the cause of death, we also reviewed death certificates and available documentation in hospital information systems.

Data management

We stratified the sample by reported [8, 13] degree of cardioselectivity or concomitant a-blocking activity: "highly cardioselective "(i.e., bisoprolol, group A); "with a-blocking activity "(i.e., carvedilol or nebivolol, group B); "cardioselective "(i.e., atenolol, betaxolol, metoprolol-succinate or metoprolol-tartarate, group C); "nonselective or none "(i.e., acebutol, celiprolol, pindolol or betablocker not prescribed, group D)—these subgroups we used one to each other as exposure. For the second analysis, we divided the sample into 3 categories according to the level of evidence of beta-blocker prescribed: "evidence-based BBs" (i.e., bisoprolol, carvedilol, metoprolol-succinate, and nebivolol, group a); "non-evidence-based BBs "(i.e., acebutol, celiprolol, atenolol, betaxolol, metoprolol-tartarate, and pindolol, group b); "no BBs "(betablocker not prescribed at discharge, group c).

As outcomes, we used all-cause mortality and cardiovascular mortality at 5 years. Moreover, a subanalysis was done with 5-year all-cause mortality, after excluding death from malignancy or external causes (and was labeled as all-cause/non-malignant).

We used the following definitions for covariates: EF was dichotomized into two categories: ≤40% and ≥41%. All cases with a history of myocardial infarction, myocardial revascularization, or angiographically proven coronary artery stenosis greater than 50% were considered "coronary artery disease." Similarly, patients with hypertension but without any apparent secondary etiology of HF (dilated, post-inflammatory, or tachycardia-induced cardiomyopathy, valvular disease, etc.) fall into this category. Other comorbidities and conditions we defined as follows: hypertension, if this diagnosis was explicitly mentioned in the documentation or if the patient was treated with antihypertensives beyond those used in the treatment of HF; diabetes mellitus, if the highest fasting glucose during hospitalization was ≥7 or

non-fasting glucose ≥11.1 mmol/L or Hba1c ≥70 mmol/mol, as well as treatment with antidiabetics or history of diabetes mentioned in the documentation. Hypercholesterolemia was defined as LDL-cholesterol ≥1.8 mmol/L, while markedly increased brain natriuretic peptide (BNP) was defined as a peak concentration ≥10 times the upper limit of normal (ULN), i.e., BNP ≥1000 or N-terminal proBNP ≥3000 ng/L. History of malignancy means this diagnosis was documented anywhere in the patient's available documentation, irrespective of current staging or grading. Other drug classes of special interest (RAS blockers, MRA, statins, …) were managed in a binary way (i.e., treated versus non-treated), while for furosemide we applied further stratification by dose at discharge (i.e., ≤40, >40 & <125 mg, and ≥125 mg). Treatment with SGLT-2i (sodium-glucose cotransporter-2 inhibitors) was not included in the analysis, as only a minority of patients with HF were treated with this new drug class at the time of discharge (before 2020).

Statistical analyses were performed using STATISTICA 8 (StatSoft Inc, Tulsa, OK, USA) and STATA 8 (STATA Corp LP, College Station, TX, USA). We applied conventional descriptive methods (i.e., the mean and standard deviation for continuous variables and frequencies for categorical variables). To determine the relative role of exposure on defined outcomes, we used a set of Cox proportional hazard models (including potential covariates to ensure exposure independence). In the first step, we fit the model with only basic covariates (age, gender, and ejection fraction), while in the second step, we performed the full adjustment. Power calculations indicated that our patient population was sufficiently large to estimate the expected incidence of the specified outcomes with 5% relative precision.

3. Results

In total, 4053 initially stabilized chronic HF patients were followed in this study; their baseline characteristics are listed in Table 1. During the median 1502 days (IQR: 512-2524) of follow-up, 2729 patients (67.3%) died, and 1550 of them died of cardiovascular causes; corresponding five-year all-cause and cardiovascular mortality were 41.8 and 24.7%. respectively. Moreover, five-year all-cause/non-malignant mortality (see Methods for definition) was 35.1%.

In the first step, we used a multivariate Cox proportional hazards model to identify covariates associated with five-year mortality risk (Table 2). Following baseline factors increased the risk of death for any case during five years (first column): age decade, male gender, history of malignancy, highly increased BNP during hospitalization, and need for higher dose of furosemide at discharge. In contrast, treatment with RAS blockers, statins, and implanted cardioverter-defibrillator, as well as recent hospitalization, appeared to be a protective factor in terms of mortality risk. With few exceptions, we generally observed a similar pattern when using cardiovascular death as the endpoint (mid column), and the same is true for all-cause mortality after excluding deaths from malignancy or any external cause (all-cause/non-malignant mortality, left column). In all three models, BB treatment showed a protective effect but did not reach statistical significance.

Cardioselectivity of BBs

The survival curve for the prescribed BBs cardioselectivity is shown again in Figure 2 (left panels). Both, BBs with high cardioselectivity (group A) or with a-blocking activity (group B) were associated with apparently better survival than moderately cardioselective (group C) or nonselective/none BBs (group D). Highly cardioselective BBs (group A) were also associated with slightly better survival than those with α-blocking activity (group B), but this is true only when we assessed only cardiovascular outcomes (Figure 2, bottom right panel) or when we excluded death from malignancy or external causes (not shown in the Figure).

Multivariate regression models also confirmed this pattern, after complex adjustment (Table 3). Patients treated with highly selective BBs showed significantly lower mortality risk than those treated with moderately cardioselective (group C) or nonselective/none BBs (group D). Highly cardioselective BBs also showed a lower risk of fatal CV events than those with a-blocking activity (group B); however, the difference did not reach statistical significance. However, if only deaths from malignancies/external causes were excluded, the difference in risk of death again became statistically significant (the bottom row of Table 3).

Cardioselectivity of BBs and phenotype of HF

Generally, we repeated all analyses separately for patients with EF≤40% (i.e., HFrEF) and EF>40% (i.e., heart failure with preserved ejection fraction, HFpEF). The prescription rate of BBs was lower in HFpEF than in HFrEF, but still relatively high (72.8% versus 83.2%, P<0.0001 by χ^2 test). The relative proportions of defined BB subgroups (A, B, …) also differed statistically (P < 0.0001, χ^2 test). In HFrEF patients, we found markedly higher prescription of BBs with α-blocking activity (group B, 71.8% versus 28.2%) and also in highly selective BBs (group A, 56.9% versus 43.1%). Surprisingly, patients with HFrEF did not show significantly higher risk of 5-year mortality, and when we repeated the analyses in Table 2 separately for HFrEF and HFpEF, the results were essentially the same. Namely, treatment with any BB (regardless of cardioselectivity or level of evidence) was not associated with a significant benefit in either phenotype.

Table 4 repeats the analyses from Table 3, but separately for both HF phenotypes. In HFrEF, patients treated with highly cardioselective BBs (group A) showed significantly lower mortality than those treated with moderately cardioselective BBs (group C), with α-blocking activity (group B), or nonselective/none. In contrast, this pattern was not observed in HFpEF.

Evidence-based *versus* non-evidence-based BBs

The survival curves among these subgroups of BBs are in Figure 2 (right panels). Evidence-based BBs (subgroup a) showed better survival than non-evidence-based BBs (subgroup a). Similar survival characteristics were observed for death from any cause, cardiovascular events only, and all-cause/non-malignant outcomes (*not* in the Figure). In the next step, we tested the independence of this association using a Cox proportional hazards model (Table 5). In the partially adjusted model (age, age, and ejection fraction only), evidence-based BBs showed a greater reduction in the five-year all-cause mortality risk than non-evidence-based BBs (22% vs. 17%, respectively, compared with non-treated patients), and the

difference was statistically significant in both subgroups. If cardiovascular mortality was used as an outcome, we observed a significant risk reduction only with evidence-based BBs, not with non-evidence-based BBs.

In fully adjusted models, any significant effect of BBs on mortality reduction generally disappeared, except for a marginally significant benefit in patients treated with evidence-based BBs compared with BB-naïve patients. Very similar results were also observed using all-cause/non-malignant cause of death as the outcome. Finally, we did not observe any significant difference between evidence-based and non-evidence-based BBs in a direct comparison (a *versus* b subgroups).

4. Discussion

In a prospective observational study, we demonstrated that, even in real-world practice, the choice of a specific BB in the treatment of patients with overt heart failure can play a relatively important role in their prognosis. It is generally accepted that only evidence-based (guidelines-determined) BBs should be prescribed in CHF, but we observed a significantly different prognostic impact even within this subgroup. Patients treated with a highly cardioselective beta-blocker had about a 30% lower risk of death from cardiovascular causes than those treated with a BBs with a lower degree of cardioselectivity (even after comprehensive adjustment for other factors that could potentially affect mortality). We observed an even greater benefit of highly selective BBs when only a subset of patients with HFrEF was analyzed (≈42% lower risk of fatal CV event, compared to BBs with a lower degree of cardioselectivity). A similar pattern was observed for all-cause mortality, even if death from malignancies was excluded. BBs with a lower degree of cardioselectivity (group B) consisted mainly of metoprolol (1678 of 1756 patients), while highly selective BBs (group A) represented in this context only bisoprolol. However, the risk of death from cardiovascular causes remained virtually the same in the same comparison (i.e., A *versus* C) even if we excluded 78 patients treated with betaxol or atenolol (both lack evidence/indication in treatment of chronic HF) from group C [HRR 0.69 (0.51-0.93, p=0.014, fully adjusted model]. It should also be emphasized that, although metoprolol succinate has a robust evidence base for the treatment of chronic HF [4], metoprolol tartrate lacks such evidence. We therefore performed an additive analysis, excluding 568 patients treated with metoprolol tartrate. The results were again confirmatory [HRR 0.69 (0.51-0.93, p=0.014, for A *versus* C comparison with fully adjusted model] and the differences in the prognosis of patients treated with both drugs (i.e., bisoprolol versus metoprolol) persist even after we have excluded or taken into account factors that could potentially confound this result. There is no extensive randomized study comparing bisoprolol and metoprolol succinate in chronic heart failure; on the contrary, both drugs have the highest level of evidence for benefit in the treatment of chronic HF[3, 4]. Even indirect data from registries do not show a fundamental difference between the two drugs [14]. The virtually only difference in pharmacodynamic effect between both agents therefore remains in the degree of cardioselectivity, where bisoprolol belongs to the representatives with practically the highest cardioselectivity, while the affinity of metoprolol to the β_1 receptor is less than half. On the other hand, it is necessary to stress that the current Guidelines[9] also recognize both drugs as equivalent and do not

favor highly β_1-selective agents over less selective agents for prognostic benefit in chronic heart failure; drug selection is primarily guided by clinical tolerance, comorbidities, and hemodynamic profile rather than receptor selectivity per se. No consistent difference in β-blocker selectivity was demonstrated in a large network meta-analysis conducted by Bangalore and colleagues [15]. Therefore, our results remain "isolated," so they do not yet allow us to make any more categorical recommendations.

The comparison of highly selective BBs with a group of BBs with α-blocking activity yielded similar results. Although highly selective bisoprolol showed a modest benefit compared to BB with alpha-blocking activity in terms of overall mortality (or overall mortality after "cleaning" for deaths from malignancy/external causes), if we only considered cardiovascular events, the difference between the two groups disappeared after adjustment. However, if HFrEF patients were only analyzed, subjects treated with highly cardioselective bisoprolol had about 45% lower risk of fatal cardiovascular event than those treated with BBs with α-blocking activity. It is also necessary to stress that the group of BB with α-blocking activity almost exclusively consisted of patients treated with carvedilol, since only 37 patients were treated with nebivolol (in fact, we compared bisoprolol and carvedilol here). We have only limited evidence regarding the comparison of bisoprolol and carvedilol. A relatively small study (241 Japanese patients with HFrEF) found no difference in tolerability between BBs; in terms of effectiveness, bisoprolol showed a greater reduction in heart rate, while carvedilol showed a greater decrease in BNP [16]. A marginal difference in pharmacological effects was observed with some biomarkers: bisoprolol showed greater efficacy in reducing inflammation, while carvedilol showed greater efficacy in reducing oxidative stress [17]. A registry-based cohort study of more than 106,000 Taiwanese patients with HF showed similar mortality among carvedilol and bisoprolol-treated patients (although this analysis did not include a direct comparison of the two BBs)[18]. A retrospective study of 655 patients with NYHA III-IV showed no difference in survival between those treated with bisoprolol and those treated with carvedilol over 18 months [19]. Our study provided an analysis on a larger sample and with longer follow-up.

It is necessary to stress again that BBs have convincing evidence in HFrEF but nearly completely lack it in HFpEF. This fact is also reflected in the Guidelines [9, 10]; in HFrEF, BBs are considered one of the cornerstones of treatment, whereas in HFpEF, they are recommended only for other indications (heart rate control in atrial fibrillation, coronary heart disease, or hypertension). The reason is that randomized trials in HFpEF have generally not shown any benefit of BBs [6, 20-22]. This phenomenon also has a pathophysiological explanation. Patients with HFpEF have a small stroke volume, a rigid left ventricle, and an inability to increase end-diastolic volume during exercise. Their rate-dependent cardiac output is much higher, so beta-blockers remove the main compensatory mechanism. Conversely, in HFrEF, BBs suppress maladaptive chronic sympathetic activation in the long term, thereby limiting myocardial remodeling, arrhythmias, and allowing recovery of left ventricular function[20]. Our observations are essentially confirmatory in this way. We observed a benefit of BB treatment only in the HFrEF subgroup, but not in patients with HFpEF (although a non-significant trend was observed here as well). On the other hand, we observed, that in the "real world," BBs prescription in HFpEF remains very high (73%), although we cannot confirm to what extent this is always indicated.

Our analysis also revealed that a relatively large number of patients (about 17%) were not prescribed evidence-based (guideline-determined) BB at discharge, but rather an agent lacking evidence for the treatment of chronic HF. Similar therapeutic inertia is definitely not specific to our study sample; rather, it is a relatively common phenomenon in clinical practice (and underdosing of BBs is even more common) [23]. Although we did not demonstrate a significant impact of prescribing non-evidence-based BBs on mortality risk, this does not mean this practice is correct. There is no medical or economic reason for it, "guidelines-determined" BBs have been fully available in the Czech Republic for many years and are practically completely covered by health insurance. The good news is that this practice has been on the decline during the observed period. Between 2010-2015, 75.6% of prescribed BBs were "guidelines-determined "(after excluding untreated patients), while in the period 2016-2020 this ratio increased to 83%. It is also necessary to stress that the vast majority of prescribed non-evidence-based BBs (568 out of 664 patients) were metoprolol tartrate (which, again, does not make sense given the availability of evidence-based metoprolol succinate). The randomized interventional COMET study demonstrated that treatment with (non-evidence-based) metoprolol tartrate was associated with a significantly worse prognosis than treatment with (evidence-based) carvedilol [24].

Our analysis completely omitted one of the most essential drug classes in the treatment of chronic HF in the last decade, i.e., SGLT-2 inhibitors. The reason was that our analysis covers the period 2010-2020, when this essential drug class had a formal indication (and thus reimbursement by the health insurance) only for the treatment of diabetes. In our cohort, only 28 patients would be prescribed SGLT-2 inhibitor at discharge. Over time in outpatient care, this number increased somewhat (to 20.1% among 975 patients alive at the end of 2022) [17], but the exploratory analysis indicated that this did not significantly affect our results. Similarly, the newest drugs in HF, already mentioned in the Guidelines [10] (such as vericiguat), have not yet been implemented.

Study limitations

Our study has several limitations. The main one is the observational/non-randomized nature of our analysis. On the other hand, for both financial and perhaps ethical reasons, it is not realistic to expect that an interventional randomized trial comparing the 2 types of BBs would ever be conducted. Another limitation is that classification into the appropriate BB group was based on prescription at discharge rather than on chronic (outpatient) treatment. According to our subanalysis published elsewhere [25], over time in outpatient care the prescription of evidence-based BBs significantly increased (up to ≈74%), while prescription of nonselective BBs decreased to zero. However, from the perspective of cardioselectivity of the chosen drug, BB prescription has not fundamentally changed in outpatient care. The same applies to the dosage of BBs, where, for example, only 12.5% of patients used the highest dose of BBs both at discharge and in the outpatient setting. Our study also did not take into account the chronic NYHA classification of patients, and the advanced staging of chronic heart failure is determined primarily by the fact that patients required hospitalization for acute decompensated HF. However, the individual staging of the disease indirectly reflects the time the patient was hospitalized before receiving compensation, which we included in the regression model. Our cohort also includes patients

hospitalized in only one hospital (albeit large and containing several departments providing cardiovascular care), which may affect the generalizability of our results. Finally, based on the new personal data protection regulation, we were unable to individually reliably analyze the risk of re-hospitalization for HF, as we no longer have available data on hospitalizations outside our hospital.

Conclusions

In the prospective study, we observed that HFrEF patients who were prescribed a highly cardioselective BB during hospitalization for acute decompensated HF subsequently showed a significantly better prognosis, with up to 42% reduction in the risk of fatal cardiovascular event over the next five years. Although "guidelines-determined" BBs are generally perceived as equivalent in the treatment of chronic HF, it cannot be ruled out that their individual pharmacodynamic characteristics may play a role beyond their class effect.

Declarations

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Disclosure statement

There are no conflicts of interest to disclose

Author Contributions

OM participated in the conception and design of the study, data collection, data analysis and interpretation, and drafting the article; JJ participated in data collection. JF participated in data interpretation and critically revised the article for important intellectual content. The manuscript has been seen and approved by all authors.

Data Availability

The data are not publicly available due to ethical restrictions, but are available from the corresponding author upon reasonable request and approval by the institutional ethics committee.

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Tables

Tables 1 to 5 are available in the Supplementary Files section.

Figures

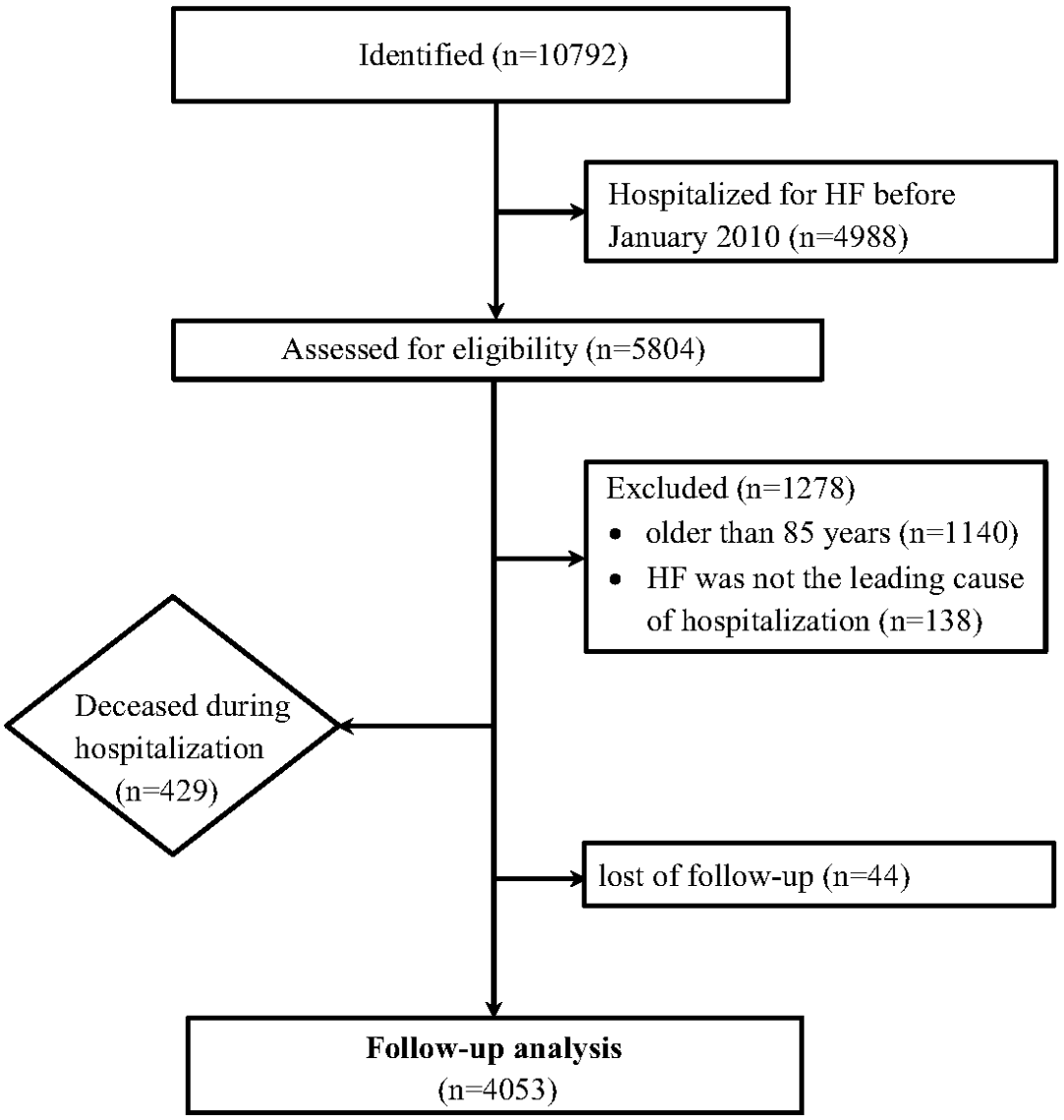


Figure 1

Study sample selection process

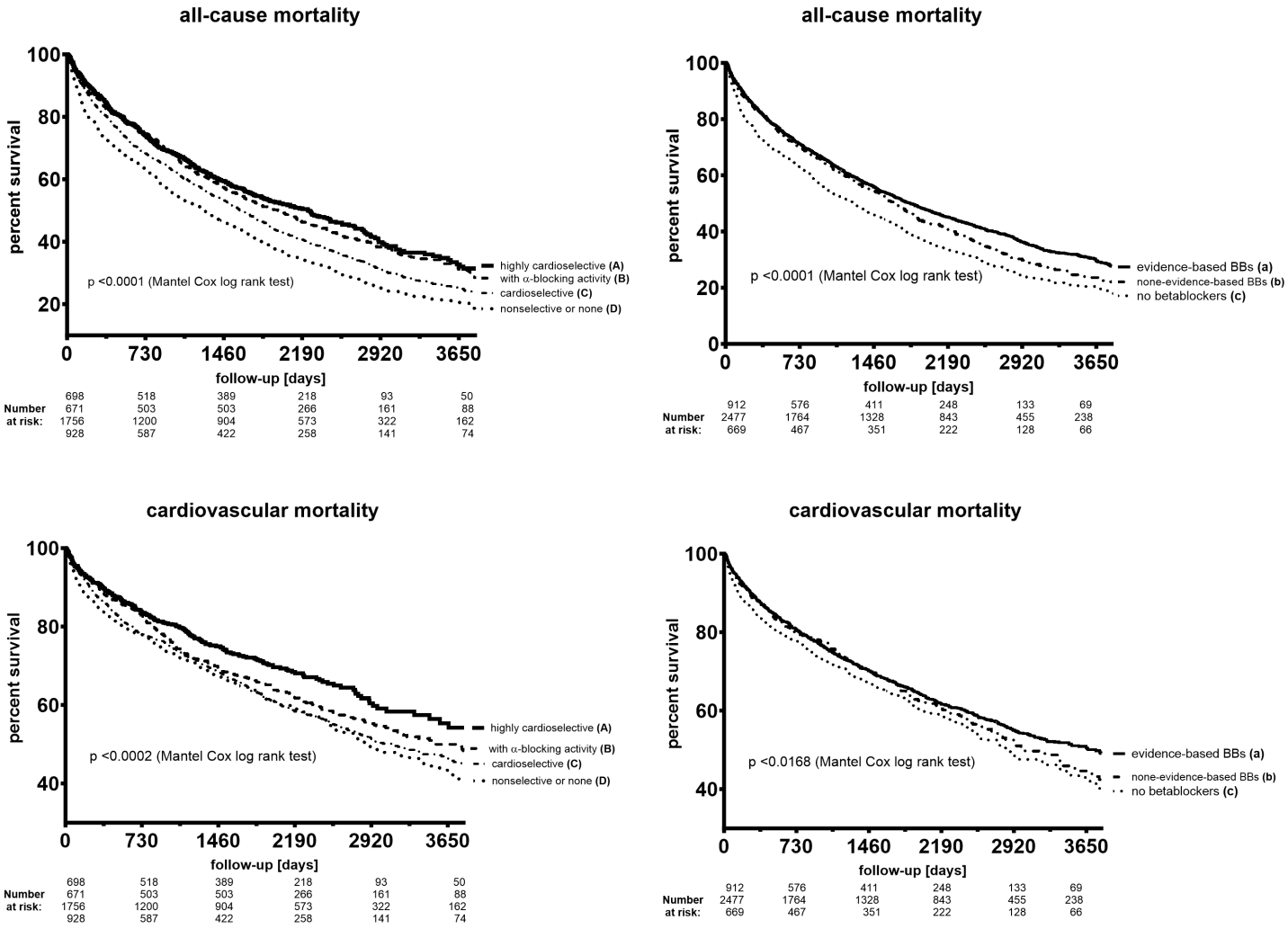


Figure 2

Kaplan-Meier survival curves according to the prescribed beta-blocker characteristics

Supplementary Files

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- Table1.docx
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