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RESEARCH ARTICLE

Prognostic role of β-blocker selectivity and dosage regimens in heart failure patients. Insights from the MECKI score database

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Aims

The use of β-blockers represents a milestone in the treatment of heart failure with reduced ejection fraction (HFrEF). Few studies have compared β-blockers in HFrEF, and there is little data on the effects of different doses. The present study aimed to investigate in a large database of HFrEF patients (MECKI score database) the association of β-blocker

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treatment with a composite outcome of cardiovascular death, urgent heart transplantation or left ventricular assist device implantation, addressing the role of β-selectivity and dosage regimens.

Methods and results In 5242 HFrEF patients, we investigated the role of: (i) β-blocker treatment vs. non-β-blocker treatment, (ii) β1-/β2-receptor-blockers vs. β1-selective blockers, and (iii) daily β-blocker dose. Patients were followed for 3.58 years, and 1101 events (18.3%) were observed; 4435 patients (86.8%) were on β-blockers, while 807 (13.2%) were not. At 5 years, β-blocker-patients showed a better outcome than non-β-blocker-subjects [hazard ratio (HR) 0.48, $P < 0.0001$], while also considering potential confounders. A comparable prognosis was observed at 5 years in the β1-/β2-receptor-blocker ($n = 2219$) vs. β1-selective group ($n = 2216$) (HR 0.95, $P =$ ns). A better prognosis was observed in high-dose (>2 5 mg carvedilol equivalent daily dose, $n = 1005$) patients than in both medium dose (12.5–25 mg, $n = 1431$) and low dose (<12.5 mg, $n = 1960$) (HR 1.97, $P < 0.001$; HR 1.95, $P = 0.001$, respectively), with no differences between the last two groups (HR 0.84, $P =$ ns).

Conclusion In a large population of chronic HFrEF patients, β-blockers were associated with a more favourable prognosis without any difference between β1- and β2-receptor-blockers vs. β1-selective blockers. A better outcome was observed in subjects receiving a high daily dose.

Keywords Heart failure • β-Blockers • Prognosis • β-Blocker selectivity • Equivalent dose

Introduction

Use of β-blockers is a mainstay of pharmacological treatment in patients affected by heart failure (HF) with reduced ejection fraction (HFrEF).[1,2] β-Blockers indicated for treatment of HFrEF differ in selectivity for adrenergic receptors, effects on peripheral circulation,[3] and on oxygen uptake and ventilatory parameters during exercise.[4–6] Carvedilol is a β1- and β2-receptor blocker with an α-receptor blocking action, metoprolol and bisoprolol are β1-selective blockers, and nebivolol is a β1-selective blocker with a nitric oxide releasing capacity.[1,2]

Randomized clinical trials have shown that carvedilol, bisoprolol and metoprolol improve survival and reduce cardiac hospitalizations in patients with HFrEF while nebivolol is effective in reducing cardiovascular (CV) hospital admissions but no effect on mortality has been shown.[7–11] However, few studies have compared β-blockers in HFrEF. The Carvedilol Or Metoprolol European Trial (COMET)[12] is the only randomized clinical trial that has compared two β-blockers on clinical outcomes in HFrEF patients and reported, despite some study design limitations,[13,14] a greater beneficial effect of carvedilol on all-cause mortality. Observational studies, analysis of nationwide registries, and clinical meta-analysis also tried to address this topic, yielding conflicting results and mainly focusing on the comparison between carvedilol and metoprolol.[15–18]

Moreover, few studies have shown that the beneficial role of β-blockers is dose-related,[15,19,20] although the concept of maximal tolerated dose in clinical practice is undefined. Even though guidelines[1,2] indicate the target doses for β-blockers in HFrEF, β-blocker titration in clinical practice is more often conducted up to the achievement of the 'clinical' maximal tolerated dose and not of the 'pharmacological' target dose, which is rarely reached in clinical practice.

Aim of the present study was to analyse in a large population of patients with chronic HFrEF, the beneficial role of β-blockers on long-term prognosis, investigating, in particular, the importance of β-selectivity and dosage regimens.

Methods

Population and study procedures

We retrospectively analysed data from a cohort of 6109 patients with a history of HFrEF, enrolled and prospectively followed in 23 Italian HFrEF centres participating in the Metabolic Exercise Cardiac Kidney Index (MECKI) score research group.[21] Inclusion criteria at the time of enrolment in the MECKI score database were history of HF [New York Heart Association (NYHA) functional class I–IV, stage B and C of American College of Cardiology (ACC)/American Heart Association (AHA) classification] and former documentation of reduced ejection fraction (EF) (<40%), unchanged HF medications for at least 3 months, ability to perform a cardiopulmonary exercise test (CPET), and no major CV treatment or intervention scheduled. Exclusion criteria were: history of pulmonary embolism, moderate-to-severe aortic and mitral stenosis, pericardial disease, severe obstructive lung disease, exercise-induced angina and significant electrocardiographic (ECG) alterations or presence of any clinical co-morbidity interfering with exercise performance.[22] At enrolment, clinical history and therapy information were recorded, then physical examination, laboratory analyses, ECG, transthoracic echocardiography, and CPET were performed, as described previously.[21]

Data analysis and study endpoints

To assess the prognostic role of β-blockers in HFrEF, data analysis was performed in different steps. The study endpoint was the composite of CV death, urgent heart transplantation (HTX) or left ventricular assist device (LVAD) implantation analysed at 5 years.

In the first step, we analysed the prognostic role of β-blocker treatment compared with patients not taking β-blockers. To do so from the whole population of 6109 patients, we selected those with complete treatment information, as regards presence or not of β-blocker

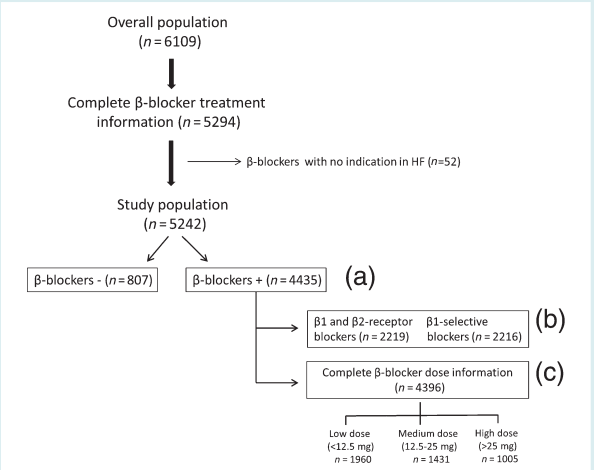

Figure 1 Study population and data analysis. From the whole population of 6109 patients, we selected those with complete treatment information as regard presence or not of β-blocker treatment ($n = 5294$). Afterwards we excluded patients treated with β-blockers not indicated for heart failure with reduced ejection fraction (HFrEF) ($n = 52$). As patients' enrolment in the Metabolic Exercise Cardiac Kidney Index (MECKI) score database started in 1993, some patients in the present analysis were treated with β-blockers not currently indicated for HRrEF. In particular, 14 patients were treated with atenolol, two patients were treated with acebutolol, two patients were treated with sotalol and 34 patients were treated with other β-blockers that were not specified. The final population analysed comprised 5242 subjects. In the first step, we compared β-blocker patients with patients not taking β-blockers (a). In the second step, we investigated the role of β-blockers selectivity (b). In the third step, we compared daily β-blocker equivalent doses (c).

treatment ($n = 5294$); afterwards, we excluded patients treated with β-blockers not indicated in HFrEF ($n = 52$), reaching a final population of 5242 subjects (*Figure 1*). Of those, 4435 were treated with β-blockers and 807 were not (*Figure 1a*). To compensate for intergroup variability, survival analysis was also done taking into account several potential confounders, specifically age, EF, oxygen uptake at peak exercise (peak VO_2) expressed as mL/min/kg, systolic blood pressure (SBP), resting heart rate measured on the cycle ergometer or treadmill ($n = 4957$ and $n = 285$, respectively) during the resting phase of CPET, haemoglobin, minute ventilation/carbon dioxide production relationship (VE/VCO_2) slope, renal function expressed as modification of diet in renal disease (MDRD), HF aetiology and presence of an implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy with defibrillator (CRT-D). The confounding variables analysed were chosen based on their recognized prognostic role in HFrEF, which would have affected survival analysis, as confirmed by the baseline differences observed in the patients enrolled.

In a second step, we investigated the role of β-blocker selectivity on the primary study outcome. Thus, patients were divided into two groups: the first group was composed of $\beta 1$- and $\beta 2$-receptor-blocker-treated patients (carvedilol), whereas the second group was composed of $\beta 1$-selective-blocker-treated subjects (bisoprolol, metoprolol, and nebivolol) (*Figure 1b*). Again, to overcome intergroup variability, survival analysis was corrected for the above-reported potential confounding factors.

Lastly, we aimed at investigating the role of β-blocker dose in predicting prognosis in HFrEF patients. Therefore, we compared three groups of HFrEF patients according to daily β-blocker equivalent dose (*Figure 1c*). Carvedilol equivalent dose was calculated for bisoprolol and nebivolol-treated subjects as dose $\times 5$, and for metoprolol-treated subjects as dose/4, again taking into account several possible confounders.[23] The three dose groups were also compared with patients not taking β-blockers.

Follow-up and data management

Patient follow-up and procedures of data management were performed as previously described.[21] In brief, follow-up was carried out according to the local HF programme, and it ended with the last clinical evaluation or with patients' death, urgent HTX or LVAD implantation. If a patient died outside the hospital where they were followed up, medical records of the event and the reported cause of death were considered. The study complied with the Declaration of Helsinki, was approved by local ethics committee on human research, and all patients signed an informed consent form at the time of enrolment (Protocol number CE no. R116/14-CCM127).

Statistical analysis

Continuous variables are presented as mean $\pm$ SD, and they were compared using the *t*-test for independent samples. Variables with skewed distributions were presented as median and interquartile range, and compared with the Wilcoxon rank-sum test. Categorical variables were reported as frequency and percentage, and they were compared using the chi-square test. Differences among β-blocker equivalent doses were assessed by ANOVA for continuous variables.

The association between use of β-blockers and endpoint (composite of CV death, HTX or LVAD implantation) was assessed by Cox regression analysis; the results are presented as hazard ratio (HR). Survival analysis was evaluated through Kaplan–Meier analysis and compared by log-rank test. Analyses were adjusted for the above-reported potential confounders. Missing data were considered as 'missing' during the statistical process because of an observed low rate of missing values for each variable considered. To assess if the size of our sample was adequate for the comparison among different β-blocker classes, we calculated the sample size of the two groups of β-blockers ($\beta 1$- and $\beta 2$-receptor-blockers and $\beta 1$-selective group). Assuming an incidence of the study outcome of respectively 8% and 11%, with a power of 80% the sample size needed was 1558 patients per group, and with a power of 90% 2063 per group of β-blockers. A *P*-value <0.05 was considered statistically significant. All data were collected in an Excel database, and analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 5242 HFrEF patients (81% male, mean age 61 $\pm$ 13 years) were included in the analysis. The mean EF of the entire population was 33 $\pm$ 10%; 72% of patients were in NYHA class I–II and 28% in class III–IV; mean peak VO_2 was 15 $\pm$ 5 mL/min/kg; in 2398 (46%) patients, HFrEF aetiology was an ischaemic cardiomyopathy.

The median follow-up period was 3.58 years (interquartile range 1.68–6.32), and 1101 events (18.3%) were observed (930 CV deaths, 159 HTX and 19 LVAD).

Prognostic role of β-blockers

A total of 4435 patients (86.8%) were treated with β-blockers currently indicated for HFrEF treatment. Specifically, 2219 (49.5%) patients were treated with carvedilol, 1923 (43%) with bisoprolol, 171 (3.8%) with metoprolol, and 122 (2.8%) treated with nebivolol. The characteristics of β-blocker and non-β-blocker groups ($n = 807$, 13.2%) are reported in *Table 1*. In particular, β-blocker-treated subjects were younger, showed a more compromised systolic function, had lower values of SBP and heart rate at rest, and exhibited a better exercise performance. The median overall follow-up was 3.58 years (interquartile range 1.68–6.29) in the β-blocker group and 3.48 years (interquartile range 1.65–6.39) in the non-β-blocker patients ($P = ns$).

At 5 years, an event rate of 29.8/1000 person-years was observed among β-blocker users, compared with 61.8/1000 person-years in non-β-blocker-treated subjects ($P < 0.001$).

At 5-year survival analysis, patients treated with β-blockers showed a significantly better outcome than non-β-blocker-treated subjects (HR 0.48, $P < 0.0001$) (*Figure 2a*, upper panel). The same results were observed after taking into account potential confounders (HR 0.57, $P < 0.001$) (*Figure 2a*, lower panel), as previously reported. Adjusting prognosis evaluation for other pharmacological treatment also did not affect results.

Prognostic role of β-selectivity

The β1- and β2-receptor-blocker group (carvedilol) comprised 2219 patients, while the β1-selective-blocker group (bisoprolol, metoprolol, nebivolol) comprised 2216 subjects. Patients' characteristics are reported in *Table 2*.

The β1-selective-blocker patients were older, showed a better systolic function, lower values of SBP and resting heart rate, and a better exercise performance than the carvedilol group. The median overall follow-up was 4.47 years (interquartile range 2.26–7.77) in the β1- and β2-blocker group and 2.74 years (interquartile range 1.26–5.17) in β1-selective-blocker patients ($P < 0.001$).

At 5 years, an event rate of 30.5/1000 person-years was observed in the β1- and β2-receptor-blocker group, compared to 29/1000 person-year in β1-selective blocker patients ($P = ns$).

In confounder non-adjusted and adjusted analyses, a similar prognosis was observed in patients treated with β1- and β2-blockers and β1-selective blockers (HR 0.95 and HR 0.99, respectively, $P = ns$ for both) (*Figure 2b*, upper and lower panel). The year of study enrolment was added as further variable with no impact on results. Similarly, results were not affected after adjusting for baseline differences in pharmacological treatment (angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, diuretics, allopurinol and digitalis).

Table 1 Characteristics of patients not treated and treated with β-blockers

	β-blockers − ($n = 807$)	β-blockers + ($n = 4435$)	*P*-value
Age, years	64.9 ± 12	60.4 ± 12.8	<0.0001
BMI, kg/m^2	26.2 ± 4.1	27.0 ± 4.4	<0.0001
EF, %	35.8 ± 12.7	32.7 ± 9.7	<0.0001
SBP, mmHg	120 ± 16	117 ± 17	0.0001
Heart rate at rest, b.p.m.	73 ± 13	71 ± 12	<0.0001
Peak VO_2, mL/min/kg	14.6 ± 5.1	15 ± 4.9	0.0173
VE/VCO_2 slope	33.4 ± 8.1	32.5 ± 7.7	0.0029
MDRD, mL/min/1.72 m^2	68.2 ± 24	72.9 ± 24.0	<0.0001
Haemoglobin, g/dL	13.3 ± 1.7	13.5 ± 1.6	0.0011
Gender, *n* (%)			
Female	171 (21)	809 (18)	0.0482
Male	636 (79)	3625 (82)	
NYHA, *n* (%)			<0.0001
I	92 (11)	747 (17)	
II	454 (56)	2454 (55)	
III	248 (31)	1183 (27)	
IV	13 (2)	50 (1)	
Atrial fibrillation, *n* (%)	181 (22)	636 (14)	<0.0001
ICD, *n* (%)	124 (15)	1622 (37)	<0.0001
CRT, *n* (%)	55 (7)	621 (14)	<0.0001
Aetiology, *n* (%)			<0.0001
Idiopathic	239 (30)	1862 (42)	
Ischaemic	371 (46)	2027 (46)	
Valvular	61 (8)	160 (4)	
Other	128 (16)	379 (9)	
ACE-inhibitors, *n* (%)	550 (68)	3318 (75)	<0.0001
ARBs, *n* (%)	135 (17)	875 (20)	0.0468
Diuretics, *n* (%)	595 (74)	3598 (81)	<0.0001
Statins, *n* (%)	243 (30)	2275 (51)	<0.0001
Allopurinol, *n* (%)	146 (18)	1296 (29)	<0.0001
MRAs, *n* (%)	335 (41)	2438 (55)	<0.0001
Anti-platelets, *n* (%)	388 (48)	2492 (56)	<0.0001
Oral anticoagulants, *n* (%)	286 (35)	1210 (27)	<0.0001
Digitalis, *n* (%)	225 (28)	735 (17)	<0.0001
Amiodarone, *n* (%)	245 (30)	1071 (24)	0.0002

BMI, body mass index; EF, ejection fraction; SBP, systolic blood pressure; Peak VO_2, oxygen uptake at peak exercise; VE/VCO_2 slope, minute ventilation/carbon dioxide production relationship (VE/VCO_2) slope; MDRD, Modification of Diet in Renal Disease; NYHA, New York Heart Association; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist.

An additional analysis was performed to address β-blockers' prognostic differences in selected subgroups. Thus, as subgroups, we considered gender categorization, EF <35% and ≥35%, NYHA classes I–II and III-IV, HFrEF ischaemic and idiopathic aetiology, peak $VO_2 \geq 12$ and <12 mL/min/kg, atrial fibrillation and sinus rhythm, VE/VCO_2 slope <34 and ≥34, MDRD <50 and ≥50 mL/min/1.73 m^2. Hazard ratios showed no differences between β1- and β2-receptor blockers and β1-selective-blockers in all subgroups analysed (see the Supplementary material online, *Figure S1*).

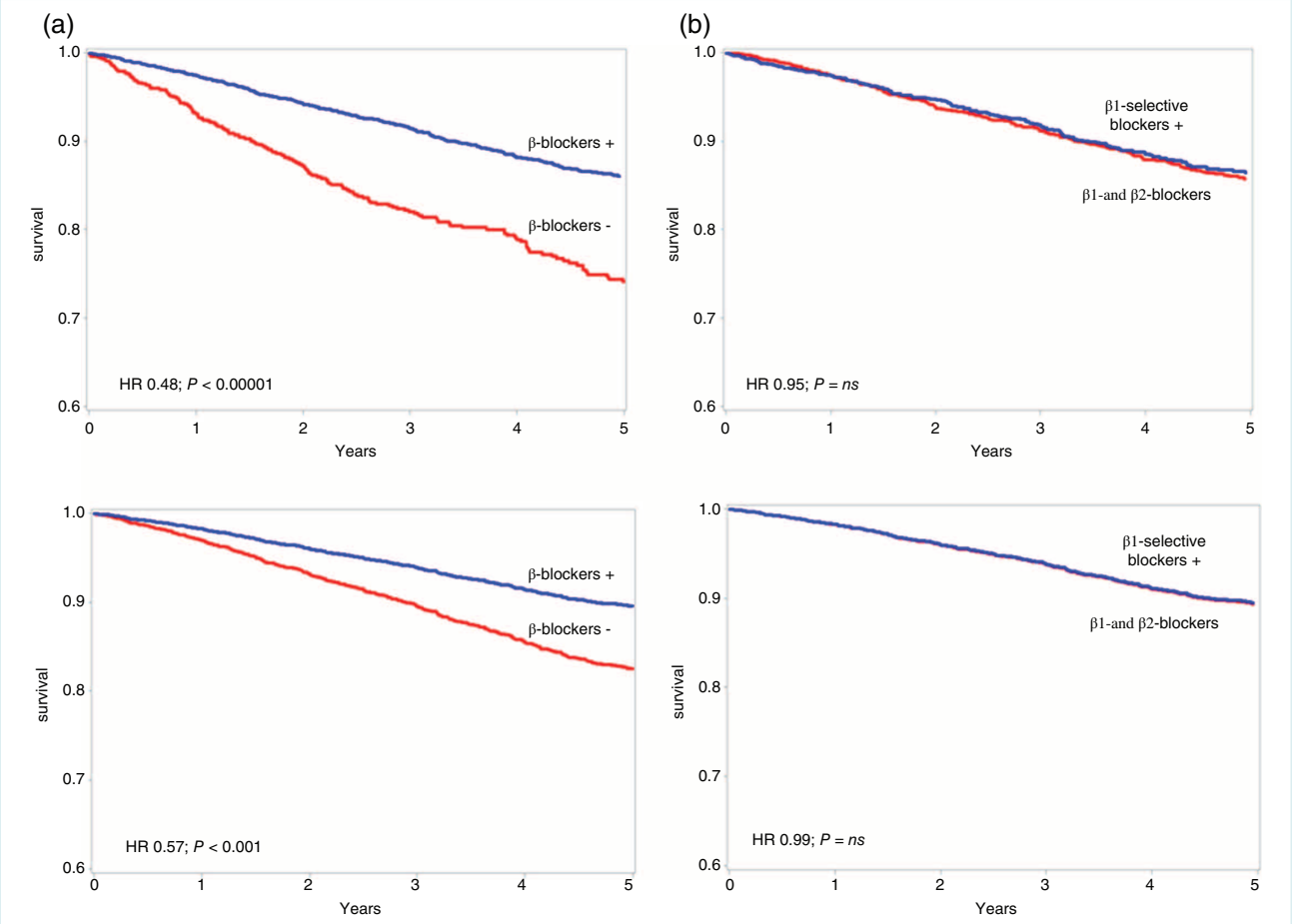

Figure 2 Prognostic role of β-blockers and of β-selectivity. (a) At 5 years, in non-adjusted analysis (upper panel), patients treated with β-blockers (blue line) showed a significantly better outcome than non-β-blocker subjects (red line). The same results were observed after correction for potential confounders (lower panel). (b) At 5 years, in non-adjusted analysis (upper panel), a similar prognosis was observed in patients treated with β1 and β2-blockers (red line) and β1-selective blockers (blue line). The same results were observed after correction for potential confounders (lower panel). HR, hazard ratio.

Prognostic role of β-blocker dose

To assess the prognostic role of β-blocker dose, patients were divided into three groups according to carvedilol equivalent doses. Daily β-blocker dose data were available in 4396 out of 5242 patients (82%). The low-dose group included patients with a carvedilol equivalent β-blocker dose <12.5 mg ($n = 1960$); the medium-dose group included patients with an equivalent dose between 12.5 and 25 mg (n = 1431), and the high-dose group included patients taking a carvedilol equivalent dose >25 mg ($n = 1005$). Patients' characteristics are reported in *Table 3*. Median follow-up was 3.26 years (interquartile range 1.50–5.92) in the low-dose group, 3.63 years (interquartile range 1.73–6.40) in the medium-dose group, and 3.88 years (interquartile range 1.95–6.58) in patients treated with high-dose β-blockers ($P = 0.002$).

At 5 years, the observed event rate was 35.1/1000 person-years in the low-dose group, 29.4/1000 person-years in medium-dose patients, and 17.8/1000 person-years in the high-dose group ($P < 0.0001$ between groups; P = ns between low and medium dose, $P < 0.001$ between low and high dose and medium and high dose).

A significantly better prognosis was observed in high-dose patients than in both medium- and low-dose regimens (HR 1.97, $P < 0.001$, and HR 1.95, $P = 0.001$, respectively); conversely, no differences were found between the last two groups (HR 0.84, P = ns) (*Figure 3a*). All the three groups showed significantly better prognosis when compared with patients not taking β-blockers (*Figure 3a*). The observed differences were also present after correction for potential confounding factors (*Figure 3b*).

Discussion

The present study reports an analysis of the role of β-blockers on long-term prognosis in a sizeable population of chronic HFrEF patients. This is the first multicentre study assessing in the same population several clinical relevant aspects of β-blocker treatment in HF. First, we confirmed the beneficial role of β-blocker

Table 2 Characteristics of patients treated with β1 and β2-selective blockers and β1-selective blockers

	β1- and β2- blockers (*n* = 2219)	β1-selective blockers (*n* = 2216)	*P*-value
Age, years	59.7 ± 12.8	61.2 ± 12.9	0.0004
BMI, kg/m^2	27 ± 4.4	26.9 ± 4.5	ns
EF, %	32.3 ± 9.8	33.1 ± 9.7	0.0372
SBP, mmHg	118 ± 17	116 ± 17	<0.0001
Heart rate at rest, b.p.m.	72 ± 12	70 ± 12	<0.0001
Peak VO_2, mL/min/kg	14.8 ± 4.6	15.2 ± 5.1	0.0178
VE/VCO_2 slope	32.3 ± 7.2	32.6 ± 8.1	ns
MDRD, mL/min/1.73 m^2	73.4 ± 23.6	72.5 ± 24.4	ns
Haemoglobin, g/dL	13.5 ± 1.6	13.6 ± 1.6	ns
Gender, *n* (%)			ns
Female	386 (17)	423 (19)	
Male	1833 (83)	1793 (81)	
NYHA, *n* (%)			ns
I	340 (15)	407 (18)	
II	1290 (58)	1164 (53)	
III	566 (26)	617 (28)	
IV	23 (1)	27 (1)	
Atrial fibrillation, *n* (%)	299 (13)	337 (85)	ns
ICD, *n* (%)	764 (34)	858 (39)	0.0066
CRT, *n* (%)	289 (13)	332 (15)	ns
Aetiology, *n* (%)			ns
Idiopathic	952 (43)	910 (41)	
Ischaemic	980 (44)	1047 (47)	
Valvular	81 (4)	79 (4)	
Other	205 (9)	174 (8)	
ACE-inhibitors, *n* (%)	1758 (79)	1560 (70)	<0.0001
ARBs, *n* (%)	371 (17)	504 (23)	<0.0001
Diuretics, *n* (%)	1835 (83)	1763 (80)	0.0266
Statins, *n* (%)	1122 (51)	1153 (52)	ns
Allopurinol, *n* (%)	613 (28)	683 (31)	0.0503
MRAs, *n* (%)	1217 (55)	1221 (55)	ns
Anti-platelets, *n* (%)	1228 (55)	1264 (57)	ns
Oral anticoagulants, *n* (%)	586 (26)	624 (28)	ns
Digitalis, *n* (%)	469 (21)	266 (12)	<0.0001
Amiodarone, *n* (%)	541 (24)	530 (24)	ns

BMI, body mass index; EF, ejection fraction; SBP, systolic blood pressure; Peak VO_2, oxygen uptake at peak exercise; VE/VCO_2 slope, minute ventilation/carbon dioxide production relationship (VE/VCO_2) slope; MDRD, Modification of Diet in Renal Disease; NYHA, New York Heart Association; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist.

treatment on a composite outcome of CV death, urgent HTX, or LVAD implantation. Second, we observed no prognostic differences between non-selective agents (carvedilol) and β1-selective blockers (bisoprolol, metoprolol, nebivolol), also taking into account potential confounders and in several subgroups analysed. Third, we showed that patients treated in the clinical practice with high β-blocker doses exhibit a better long-term prognosis than patients on medium- and low-dose regimens.

The positive role of β-blockers in chronic HFrEF has been well proven in several large randomized clinical trials.[7–10,23] β-blockers demonstrated a reduction in mortality and hospitalizations in HFrEF patients, and they are now indicated from the initial phase of the disease.[1,2] Several mechanisms are responsible for β-blockers effects on outcome, with an association between the degree of heart rate reduction and the improvement of survival, as demonstrated by the results of the Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT).[24,25] Our data reported, from an analysis of 5242 HFrEF patients, a better survival at 5 years in β-blocker treated patients with an HR of 0.48. Moreover, this association was also maintained after correction for potential confounding factors. Notably, the 13.2% of patients who were not treated with β-blockers did not have clear contraindication to treatment (*Table 1*), thus reinforcing the strength of our findings.

The second relevant observation of the present study was that β-blocker selectivity had no association with outcome in our population. In fact, only few studies tried to compare head-to-head β-blockers in patients with HFrEF. The COMET[12] is the only large randomized clinical trial that compared carvedilol with metoprolol

Table 3 Characteristics of patients treated with low, medium and high carvedilol equivalent doses of β-blockers

	Low dose ($n = 1960$)	Medium dose ($n = 1431$)	High dose ($n = 1005$)	ANOVA, *P*	Low vs. medium	Low vs. high	Medium vs. high
Age, years	62.5 ± 12.2	60.2 ± 12.9	56.7 ± 13	<0.0001	<0.0001	<0.0001	<0.0001
BMI, kg/m^2	24.5 ± 4.4	27.1 ± 4.3	27.6 ± 4.6	<0.0001	0.0003	<0.0001	0.0177
EF, %	32.8 ± 10	32.9 ± 9.6	32.4 ± 9.6	ns			
SBP, mmHg	116 ± 17	116 ± 17	119 ± 17	<0.0001	1	0.0001	0.0045
Heart rate at rest, b.p.m.	71 ± 13	70 ± 12	70 ± 12	ns			
Peak VO_2, mL/min/kg	14.8 ± 4.8	15.3 ± 5	15.2 ± 4.7	0.0149	0.0535	ns	ns
VE/VCO_2 slope	33.1 ± 8.1	32.2 ± 7.5	31.6 ± 7	<0.0001	0.0036	<0.0001	ns
MDRD, mL/min/1.73 m^2	71.2 ± 24.1	73.7 ± 23.5	75.3 ± 24.4	<0.0001	0.0158	0.0001	ns
Haemoglobin, g/dL	13.5 ± 1.6	13.6 ± 1.6	13.6 ± 1.6	0.0344	ns	ns	ns
Gender, *n* (%)				ns			
Female	356 (18)	257 (18)	187 (19)				
Male	1604 (82)	1174 (82)	818 (81)				
NYHA, *n* (%)				<0.0001	0.0002	<0.0001	ns
I	289 (15)	247 (17)	206 (20)				
II	1055 (54)	828 (58)	548 (55)				
III	585 (30)	346 (24)	241 (24)				
IV	30 (2)	10 (0.7)	10 (1)				
Atrial fibrillation, *n* (%)	286 (15)	199 (13.92)	144 (14.33)	ns			
ICD, *n* (%)	653 (33)	501 (35.03)	447 (44.57)	<0.0001	ns	<0.0001	<0.0001
CRT, *n* (%)	222 (12)	199 (14)	192 (19)	<0.0001	ns	<0.0001	0.0012
Aetiology, *n* (%)				0.0559	ns	ns	ns
Idiopathic	749 (38)	629 (44)	469 (47)				
Ischaemic	966 (49)	627 (44)	415 (41)				
Valvular	84 (4)	51 (4)	25 (2)				
Other	157 (8)	121 (8)	96 (10)				
ACE-inhibitors, *n* (%)	1428 (73)	1079 (75)	780 (78)	0.0149	ns	0.0317	ns
ARBs, *n* (%)	375 (19)	286 (20)	206 (20)	ns			
Diuretics, *n* (%)	1607 (82)	1154 (81)	803 (80)	ns			
Statins, *n* (%)	1017 (52)	731 (51)	504 (50)	ns			
Allopurinol, *n* (%)	583 (30)	421 (29)	278 (28)	ns			
MRAs, *n* (%)	1055 (54)	799 (56)	561 (56)	ns			
Anti-platelets, *n* (%)	1183 (60)	769 (54)	517 (51)	<0.0001	0.0007	<0.0001	ns
Oral anticoagulants, *n* (%)	531 (27)	392 (27)	279 (28)	ns			
Digitalis, *n* (%)	304 (16)	210 (15)	216 (21)	<0.0001	ns	0.0004	<0.0001
Amiodarone, *n* (%)	516 (26)	326 (23)	219 (22)	0.0083	ns	0.0416	ns

BMI, body mass index; EF, ejection fraction; SBP, systolic blood pressure; Peak VO_2, oxygen uptake at peak exercise; VE/VCO_2 slope, minute ventilation/carbon dioxide production relationship (VE/VCO_2) slope; MDRD, Modification of Diet in Renal Disease; NYHA, New York Heart Association; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist.

in HFrEF, reporting a 17% survival benefit in patients treated with carvedilol. However, this trial has been criticized for several study design limitations.[13] First of all, in the COMET trial a short-acting metoprolol formulation was used, as immediate-release metoprolol tartrate, which effects cardiac function and symptoms were described in patients with idiopathic dilated cardiomyopathy in the Metoprolol Dilated Cardiomyopathy trial,[26] but efficacy of this formulation on mortality in HFrEF has not been proven. Moreover, neither the optimal target dose of metoprolol nor dose equivalence between metoprolol and carvedilol was achieved in the COMET trial, confirming that the superiority of carvedilol over metoprolol tartrate cannot be sustained by the study results.[13] After the publication of the COMET trial, the debate on the 'best' β-blocker moved forward without consistent results. With regard to the comparison between carvedilol and metoprolol, Pasternak *et al.*[16] reported no differences in outcome between carvedilol- or metoprolol-treated patients with HFrEF, and similar results were confirmed in an analogous study on smaller numbers of patients.[18] In 2013, in a meta-analysis of 21 randomized trials, Chatterjee *et al.*[17] observed no differences between selective and non-selective β-blockers, although carvedilol showed a numerical benefit on mortality compared with other β-blockers. However, in this study, atenolol and bucindolol, currently not approved for HFrEF treatment, were also included. In contrast, in the same year, a meta-analysis of carvedilol vs. β1-selective blockers[27] in patients with acute ischaemic systolic dysfunction, reported a more favourable effect on outcome of

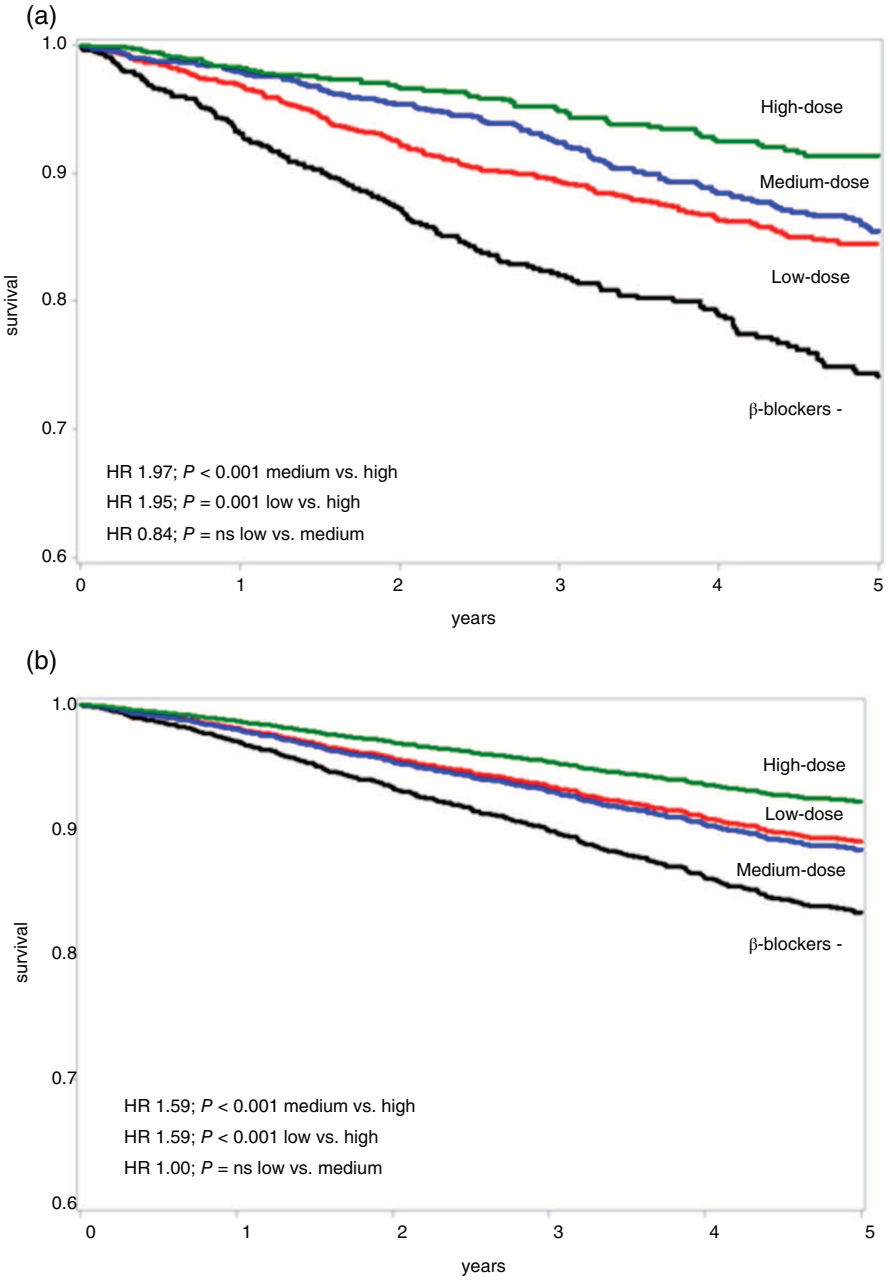

Figure 3 Prognostic role of β-blocker dose. At 5 years, in non-adjusted analysis (a), a significantly better prognosis was observed in high carvedilol equivalent dose (green line) patients than in both medium- (blue line) and low-dose (red line) regimens. Moreover, a significantly worst prognosis was observed in patients not taking β-blockers (black line) compared with high-, medium- and low-carvedilol equivalent doses (HR 0.32, $P < 0.001$ β-blockers - vs. high; HR 0.53, $P < 0.001$ β-blockers - vs. medium; HR 0.60 $P < 0.001$ β-blockers - vs. low). The same results were observed after correction for potential confounders (b) (for comparisons vs. patients not taking β-blockers: HR 0.44, $P < 0.001$ β-blockers - vs. high; HR 0.67, $P = 0.001$ β-blockers - vs. medium; HR 0.63, $P < 0.001$ β-blockers - vs. low. HR, hazard ratio.

carvedilol over selective agents, but this observation was hampered by the inclusion of atenolol and focused on a subgroup of HF patients.

In the present study, we tried to address the prognostic differences of β-selectivity considering patients with HFrEF in stable clinical conditions and therapeutic regimen, including only the β-blockers indicated for HFrEF treatment in the most recent guidelines.[1,2] Patients were grouped on the basis of adrenergic receptors' affinity, comparing carvedilol to bisoprolol, metoprolol and nebivolol. We found, in two numerically homogeneous groups (2219 vs. 2216 patients, respectively), no differences on a composite endpoint of CV death, urgent HTX or LVAD implantation

at 5 years. This result was also confirmed when the survival analysis was corrected for potential confounders. Moreover, a similar prognostic behaviour of selective vs. non-selective β-blockers was also evident in all subgroups analysed. A longer median follow-up was observed in carvedilol-treated subjects (4.47 years) vs. selective β-blockers (2.74 years); this difference could be related to the older, more consolidated experience with carvedilol of the enrolling centres, even if the final size of the two groups analysed was similar. However, adjusting the analysis for enrolment year did not affect results. The lack of differences between selective and non-selective agents has a pharmacologic and biologic support.[28] In particular, it has been stated that the majority of deleterious effects of the adrenergic hyperactivation in chronic HF are mediated through β1-receptor signalling.[28] Thus, no clear differences should be expected when comparing the different β-blockers in HFrEF patients at equivalent therapeutic doses. The choice of the type of β-blocker used was left to the physician in charge of the patients and no specific criteria for β-blocker selection were adopted in the present study. It is therefore possible, and even likely (but at present totally unproved), that an appropriate match between patients and drug characteristic can further improve HF patient outcome.[5]

The third observation of the present study was the association between β-blocker dose and prognosis, indicating a more favourable relationship with outcome in patients assuming the highest β-blocker doses. In our population, only 1005 out of 4396 (23%) patients received a high (>25 mg carvedilol equivalent) daily dose that was close to the suggested drug target dose, whereas the large majority of patients (77%) were treated with low or medium carvedilol equivalent doses. The reasons behind this finding are unknown as we do not know whether the β-blocker dose utilized was the highest possible in each patient or not. However, the treatment of HF patients with β-blockers not at target dose is frequent in clinical practice. An analysis of the SHIFT trial, which investigated the positive effects of ivabradine across groups of β-blocker doses,[25] reported that the distribution of reasons for not-achieving the target dose among the different dose categories of β-blocker users was similar to the reason for non-use of β-blocker (hypotension, fatigue, dyspnoea, decompensation, bradycardia). Indeed, target β-blocker doses are rarely reached in clinical practice because of patient tolerability, time needed, costs and practical issues related to proper therapy uptitration. A report from the Heart Failure Pilot Survey of the European Society of Cardiology also confirmed these data.[29] In particular, in an analysis of 5118 HF patients included in the survey the target dose of carvedilol, bisoprolol, and metoprolol was reached in 37.3, 20.7, and 21.4% of the subjects, respectively.[29] Moreover, the more recent results of a European long-term registry of 12 440 HF patients[30] showed that fewer than one-quarter of the subjects enrolled (17.5%) were at guideline-recommended β-blocker target doses, underlining that major efforts should be made to implement guideline recommendations.[1] In the previously mentioned analysis of the SHIFT trial,[25] despite investigators' efforts, only one-quarter of patients achieved β-blocker target doses and only half reached at least 50% of the target dose.

A few previous studies have reported that the beneficial role of β-blockers can be considered dose-dependent. In particular, the MOCHA study[20] was the only randomized parallel design dose–response study that demonstrated that carvedilol treatment accounted for dose-related improvements in systolic function and dose-related reductions in mortality and hospitalization in patients with mild to moderate HFrEF. Moreover, an analysis of the HF-ACTION trial showed an inverse relationship between β-blocker dose and the endpoint of all-cause death or all-cause hospitalization in HFrEF patients. In particular, in this study, a carvedilol equivalent dose was used, and patients in the high-dose group exhibited a better outcome in a follow-up of 2.5 years. In the present analysis, we also divided patients into three groups starting from carvedilol equivalent dose and, as previously reported, we found a better outcome in the high-dose group than in low- and medium-dose patients. These differences were confirmed both at baseline and after correction for potential confounders. Adjustment for confounders is particularly important in this setting, because HF severity was greater in the low-dose group, and the high-dose group seems to be treated more aggressively. Moreover, no differences were found between low and medium-dose regimens. This finding was unexpected. Patients receiving a low carvedilol equivalent dose showed a lower peak VO_2, MDRD and a higher VE/VCO_2 slope, suggesting a more severe HF, than patients receiving a medium dose. Moreover, the average low body mass index suggests that at least some of these patients had a reduced muscle mass. Indeed, looking at the unadjusted Kaplan–Meier curves, the prognosis of patients receiving a low carvedilol dose was worse than that of patients with other treatment dosages up to 3 years. In our analysis, 77% of patients were not treated with target doses, as frequently observed in clinical practice, with no clear motivation, also if we consider that baseline heart rate and SBP in low- and medium-dose groups would have allowed a further β-blocker titration (*Table 3*). Therefore, it is possible that, owing to a worse HF status, these patients did not tolerate higher β-blocker doses. However, after adjusting for potential confounders mainly related to severity of HF, the prognostic difference between low and medium doses of β-blockers disappeared. These data support the recommendation that β-blocker dose titration is crucial to confer a better outcome in patients affected by HFrEF. Indeed, there appear to be three degrees of prognostic benefit induced by β-blocker therapy, with the worst outcome in patients not receiving β-blockers, intermediate outcome in patients with a carvedilol equivalent dose up to 25 mg/day, and a further prognostic benefit in patients receiving a carvedilol equivalent dose >25 mg/day. Therefore, the results of the present study confirm that major efforts should be made to reach maximal clinical tolerated doses in all HFrEF patients.

Limitations

Our study has some important limitations. First, the analysis is based on HFrEF patients able to perform a CPET, and this may result in selection of a population not closely representative of a general population including subjects with worse HFrEF stages. Second, it should be noted that this analysis was performed

considering a static picture of the population at baseline without taking into account the possible changes in treatments during follow-up, which may carry a possible prognostic association. Third, heart rate value at rest was similar between β-blocker type and dosage groups, and it was relatively high. The last finding was unexpected. However, heart rate was measured during the resting phase of CPET with patients sitting on a cycle ergometer (95%) or standing on the treadmill (5%) with respiratory gas recording. Fourth, only <1% of patients were treated with ivabradine. The efficacy of adding ivabradine in patients with different doses of β-blocker is therefore unknown. In addition, we did not assess the prognostic role of heart rate reduction due to β-blocker treatment on patients' outcome. Indeed, it has been previously suggested that heart rate reduction and not β-blocker dose is the driving mechanism of β-blocker-related clinical improvement and survival benefit.[31] Our study was not designed to evaluate the role of heart rate reduction but we limited our analysis on β-blocker type and dose.

Moreover, it should be underlined that the β1-selective-blocker group mainly included patients treated with bisoprolol (87%), thus the results in this class are driven by the effects of bisoprolol. Last, the results of the present study can only be applicable to HFrEF patients, and the role of β-blockers in HF patients with preserved systolic function has not been addressed.

Conclusion

In a large population of HFrEF patients, β-blocker treatment was associated with a significantly more favourable clinical outcome. β-selectivity was not associated with prognosis, whereas patients assuming high-dose regimens showed better long-term outcome compared with those receiving lower doses. Thus, our findings reinforce the need for β-blocker use and dose uptitration to improve prognosis in patients with HFrEF.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Prognostic role of β-selectivity in subgroup analysis.

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