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Titration to target dose of bisoprolol vs. carvedilol in elderly patients with heart failure: the CIBIS-ELD trial

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Aims Various beta-blockers with distinct pharmacological profiles are approved in heart failure, yet they remain underused and underdosed. Although potentially of major public health importance, whether one agent is superior in terms of tolerability and optimal dosing has not been investigated. The aim of this study was therefore to compare the tolerability and clinical effects of two proven beta-blockers in elderly patients with heart failure.

Methods and results We performed a double-blind superiority trial of bisoprolol vs. carvedilol in 883 elderly heart failure patients with reduced or preserved left ventricular ejection fraction in 41 European centres. The primary endpoint was tolerability, defined as reaching and maintaining guideline-recommended target doses after 12 weeks treatment. Adverse events and clinical parameters of patient status were secondary endpoints. None of the beta-blockers was superior with regards to tolerability: 24% [95% confidence interval (CI) 20–28] of patients in the bisoprolol arm and 25% (95% CI 21–29) of patients in the carvedilol arm achieved the primary endpoint ($P = 0.64$). The use of bisoprolol resulted in greater reduction of heart rate (adjusted mean difference 2.1 b.p.m., 95% CI 0.5–3.6, $P = 0.008$) and more, dose-limiting, bradycardic adverse events (16 vs. 11%; $P = 0.02$). The use of carvedilol led to a reduction of forced expiratory volume (adjusted mean difference 50 mL, 95% CI 4–95, $P = 0.03$) and more, non-dose-limiting, pulmonary adverse events (10 vs. 4%; $P < 0.001$).

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Conclusion Overall tolerability to target doses was comparable. The pattern of intolerance, however, was different: bradycardia occurred more often in the bisoprolol group, whereas pulmonary adverse events occurred more often in the carvedilol group.
This study is registered with controlled-trials.com, number ISRCTN34827306.

Keywords Heart failure • Beta-blocker • Elderly • Tolerability • Target dose • Lung function

Introduction

Chronic heart failure is a growing epidemic associated with high mortality, morbidity, and quality of life (QoL) impairment and is a substantial burden on health systems.[1] Three key trials have randomized nearly 9000 patients with systolic heart failure to beta-blocker (bisoprolol, carvedilol, or metoprolol succinate controlled release) or placebo and demonstrated a consistent 30% reduction in mortality and a 40% reduction in hospitalizations.[2–4] Nevertheless, recent large international surveys have shown that only 20–40% of heart failure patients are taking beta-blockers and the mean dose is half the recommended target.[5,6]

The underuse and underdosing of beta-blockers may reflect a reluctance to change practice stemming from their long-standing contraindication in heart failure. Conversely, it may reflect a true lack of tolerability of beta-blockers in patients who are typically relatively old, have co-morbidities, and are taking a range of other drugs. It is noteworthy that many previous beta-blocker trials included heart failure patients who were younger (mean age 61–64) than those encountered in routine practice (mean age 71–75).[2–4,7,8]

Class effects may not be uniform and tolerability may differ between the commonly used beta-blockers, reflecting their distinct pharmacological profiles such as selectivity for the β_1-adrenoceptor subtype (bisoprolol) or vasodilatory activity (carvedilol). However, differences in tolerability have not been systematically studied. If one proven beta-blocker were better tolerated than another it could be of considerable public health importance. Results of the Carvedilol Or Metoprolol European Trial (COMET), suggested that overall tolerability of carvedilol vs. metoprolol tartrate does not differ,[8] but it has been suggested that this interpretation is problematic because doses were not equivalent.[9] The second Carvedilol Open-Label Assessment found good tolerability for carvedilol in older heart failure patients,[10] but no previous double-blind randomized trial had tolerability as the primary endpoint.

Beta-blocker therapy in patients with preserved left ventricular ejection fraction (LVEF) is associated with an improvement in echocardiographic parameters[11] and international guidelines provide an expert-based recommendation of heart rate lowering using beta-blockers in these patients[12] despite a lack of proven reduction in mortality.

We therefore designed the Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD) to investigate the tolerability of two of the most widely used beta-blockers in elderly heart failure patients with impaired and preserved LVEF. This is the first randomized, double-blind trial to have as its primary endpoint the tolerability of bisoprolol vs. carvedilol when used at their guideline-recommended target doses.

Methods

Trial design and patients

We undertook this investigator-initiated, randomized, double-blind, parallel-group trial in 21 centres in Germany, 1 in Montenegro, 15 in Serbia, and 4 in Slovenia. The CIBIS-ELD protocol was approved by all relevant federal institutes for drugs and medical devices as well as by national and local ethics committees. Patients provided written informed consent and the trial conforms to the principles outlined in the Declaration of Helsinki. Details of the CIBIS-ELD trial design have been published elsewhere.[13] This study is registered with controlled-trials.com, number ISRCTN34827306.

Patients were recruited between April 2005 and April 2008 (*Figure 1*). Eligible patients were 65 years or older with symptomatic chronic heart failure consistent with New York Heart Association (NYHA) functional class $\geq$II at time of enrolment or with an LVEF $\leq$ 45%. At baseline, participants had to be beta-blocker naïve or on $\leq$25% of the guideline-recommended target or equivalent dose.[14] Patients who had been on suboptimal doses previously were included to investigate titration success following pretreatment. Patients had to be clinically stable and on stable medication for 2 weeks prior to randomization.

Major exclusion criteria were: known contraindications to beta-blocker treatment, such as hypotension with a resting systolic blood pressure $<$90 mmHg, severe pulmonary disease or severe asthma, heart rate $<$55 b.p.m. prior to commencement of therapy, second or third degree sinoatrial block (without pacemaker), and known sick sinus syndrome.

Procedures

Patients were recruited through primary care physicians, and secondary and tertiary care hospitals. Upon enrolment, they were randomly assigned to either bisoprolol or carvedilol. For each centre, a random sequence of permuted blocks of variable length was generated by the Clinical Trial Centre Leipzig. Patients, investigators, and study personnel were blinded to treatment assignment for the duration of the trial.

During the initial titration phase of the study, patients were seen at fortnightly intervals. According to the titration scheme [based on the 2005 European Society of Cardiology (ESC) guidelines],[14] the dose was scheduled to double at every visit to reach the target dose of 10 mg bisoprolol once daily or 25 mg carvedilol twice daily within 6 weeks (50 mg twice daily within 8 weeks for patients $>$85 kg). Investigators were free to delay titration or reduce the dose if clinically indicated. The titration phase was followed by a maintenance period lasting 4 weeks and the final visit was at 10 weeks (12 weeks for patients $>$85 kg).

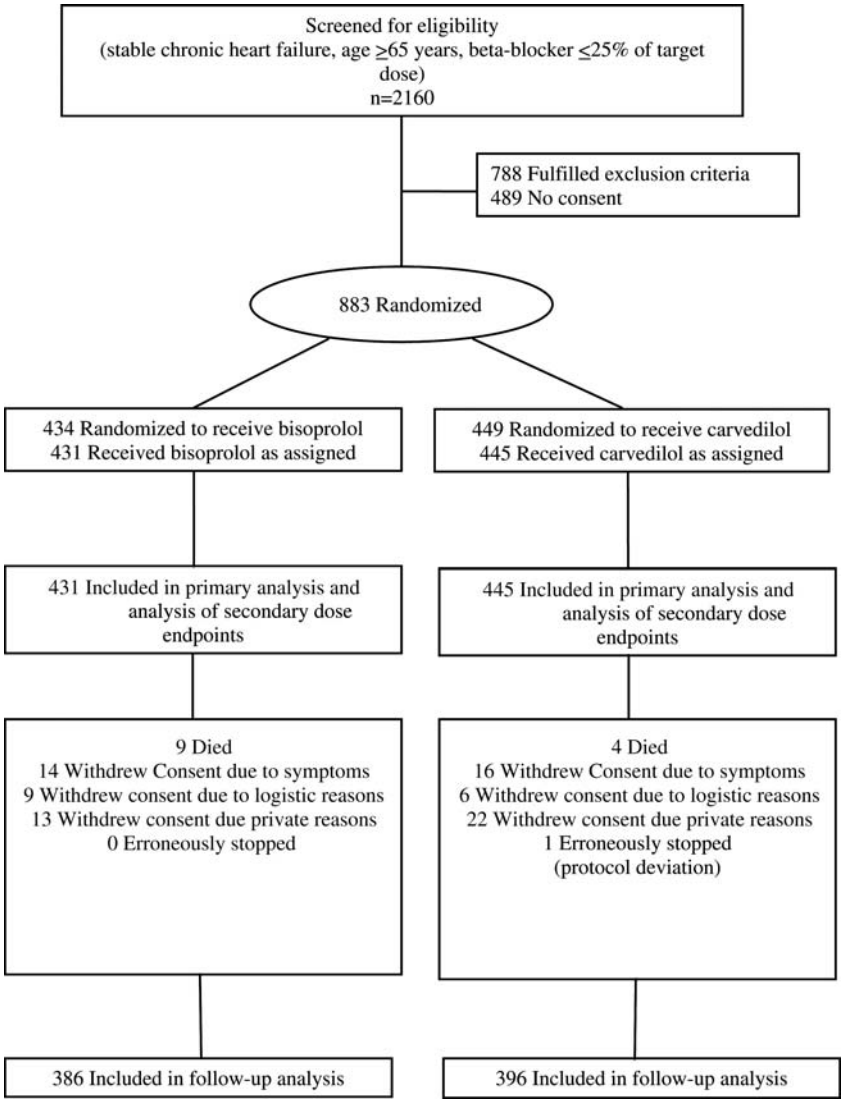

Figure 1 Participant flow through the study. Target dose based on the 2005 European Society of Cardiology guidelines.

Outcome measures

The primary endpoint of tolerability was defined as reaching the target dose through the process of fortnightly doubling with no more than one delayed increase and with the target dose maintained for at least 10 days. Titration failure was defined as failure to up-titrate more than once or as down-titration after receiving the target dose level. Predefined secondary endpoints were the percentage of target dose achieved at the end of the study, and the dose achieved prior to first titration failure. Occurrences of adverse events were recorded and their association with dose adjustment was assessed by odds ratios. For titration failures with no simultaneous adverse event, we implemented a blinded endpoint committee consisting of experts with sound clinical experience in heart failure therapy and research who evaluated the circumstances of titration failure based on data from all visits and additional investigator comments. Multiple reasons could be specified by the endpoint committee (Appendix).

Predefined clinical secondary endpoints were: NYHA functional class, heart rate, blood pressure (measured prior to dose titration at each visit) and LVEF, assessment of diastolic function, 6 min walk distance, 1 s forced expiratory volume (FEV_1) and the physical and psychosocial component scores on the short-form QoL health survey (SF36) at the end of the study, adjusted for baseline.

Statistical analysis

All analyses were carried out by intention to treat, including all patients who received the first dose of allocated study medication. Patients who died or prematurely stopped treatment were judged not to have fulfilled the conditions for the primary endpoint. A sensitivity analysis was performed counting deaths as drop-outs. The primary null hypothesis that equal percentages of patients would tolerate the target doses of the two agents was tested against the two-sided alternative by Fisher's exact test. This was designed to discover the superiority of one beta-blocker assuming 60 vs. 50% tolerability

Table 1 Baseline characteristics

	All patients (n = 876)	Bisoprolol (n = 431)	Carvedilol (n = 445)
Women, no. (%)	329 (38)	167 (39)	162 (36)
Age, mean (SD), years	72.8 (5.5)	72.9 (5.6)	72.7 (5.5)
NYHA class			
I	34 (4)	15 (4)	19 (4)
II	575 (66)	272 (63)	303 (68)
III	258 (30)	139 (32)	119 (27)
IV	9 (1)	5 (1)	4 (1)
Hospitalization for heart failure during the past 12 months, no. (%)	314 (36)	143 (33)	171 (38)
Heart rate on ECG, mean (SD), b.p.m.	73 (14)	74 (15)	73 (14)
Blood pressure, mean (SD), mmHg			
Systolic	137 (21)	137 (21)	137 (22)
Diastolic	80 (12)	80 (12)	80 (12)
LVEF, mean (SD), %	42 (14)	42 (14)	42 (13)
LVEF > 45%, no. (%)	250 (29)	123 (29)	127 (29)
6 min walk distance, mean (SD), m	322 (110)	319 (103)	325 (116)
NT-pro-BNP, median (IQR), pg/mL	609 (255–1614)	596 (236–1699)	630 (284–1587)
Haemoglobin, mean (SD), g/dL	13.7 (1.6)	13.7 (1.6)	13.7 (1.6)
FEV_1, mean (SD), mL	2192 (675)	2185 (712)	2197 (638)
FEV_1, predicted for age and sex (%), mL	90.8 (23.9)	90.4 (24.8)	91.2 (23.1)
Peripheral oedema, no. (%)	183 (21)	88 (20)	95 (21)
Body mass index, mean (SD), kg/m^2	27.7 (4.9)	28.0 (5.0)	27.6 (4.7)
Medical history, no. (%)			
Current smoker	76 (9)	41 (10)	35 (8)
Myocardial infarction	347 (40)	163 (38)	184 (41)
PCI and/or CABG	196 (22)	90 (21)	106 (24)
Pacemaker and/or ICD	56 (6)	23 (5)	33 (7)
Co-morbidities[a]			
Hypertension	724 (83)	353 (82)	371 (84)
Diabetes mellitus	223 (26)	107 (25)	116 (26)
Hyperlipidaemia	548 (63)	261 (61)	287 (65)
Peripheral vascular disease or stroke	121 (14)	59 (14)	62 (14)
Atrial fibrillation	164 (19)	83 (19)	81 (18)
COPD	65 (7)	28 (7)	37 (8)
Renal dysfunction [GFR < 60]	338 (39)	165 (38)	173 (39)
Anaemia [male: Hb < 13 g/dL; female: Hb < 12 g/dL]	181 (21)	86 (20)	95 (21)
Depression	73 (8)	34 (8)	39 (9)
Cardiovascular medication, no. (%)			
Beta-blocker			
None	349 (40)	175 (41)	174 (39)
12.5% of target dose equivalent	149 (17)	75 (17)	74 (17)
25% of target dose equivalent	378 (43)	181 (42)	197 (44)
ACE inhibitor and/or ARB	741 (85)	374 (87)	367 (83)
Aldosterone receptor antagonist	275 (31)	145 (34)	130 (29)
Diuretic	649 (74)	323 (75)	326 (73)
Cardiac glycoside	129 (15)	64 (15)	65 (15)
Calcium channel blocker	143 (16)	80 (19)	63 (14)
Nitrate	277 (32)	131 (30)	146 (33)
Antiarrhythmic	95 (11)	48 (11)	47 (11)
Statin	342 (39)	159 (37)	183 (41)
Antiplatelet	582 (66)	287 (66)	295 (66)
Anticoagulant	220 (25)	102 (24)	118 (26)

Continued

Table 1 *Continued*

	All patients ($n = 876$)	Bisoprolol ($n = 431$)	Carvedilol ($n = 445$)
QoL, mean (SD)			
SF-36 physical component score	38.2 (9.5)	37.9 (9.3)	38.5 (9.7)
SF-36 psychosocial component score	45.4 (12.1)	44.5 (11.8)	46.2 (12.4)

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; GFR, glomerular filtration rate; Hb, haemoglobin; FEV_1, forced expiratory volume in the first second; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.
[a]Co-morbidities determined during medical examination or as defined in square brackets.

Table 2 Tolerability and dose endpoints

	Patients in treatment groups		*P*-value
	Bisoprolol ($n = 431$)	Carvedilol ($n = 445$)	
Primary endpoint achieved[a], no. (%)	102 (24)	112 (25)	0.64
95% CI for rate	20–28	21–29	
Dose level at follow-up, no. (%)			0.58
0 (study medication stopped before follow-up)	46 (11)	51 (11)	
12.5% (1.25 mg bisoprolol or 3.125 mg carvedilol)	47 (11)	45 (10)	
25% (2.5 mg bisoprolol or 6.25 mg carvedilol)	108 (25)	97 (22)	
50% (5 mg bisoprolol or 12.5 mg carvedilol)	98 (23)	110 (25)	
100% (10 mg bisoprolol or 1–2 × 25 mg carvedilol)	132 (31)	142 (32)	

[a]Primary endpoint achieved: the patient was up-titrated to the guideline-recommended target dose and remained on this dose level until follow-up. The dose was never reduced but delay of titration was allowed.

to target doses. Doses achieved at follow-up were compared by the Mann–Whitney *U* test. Percentages of patients achieving the target dose free of titration failure are presented as Kaplan–Meier analyses. Prespecified baseline variables were examined for being predictors for achievement of target dose by multiple logistic regression. Only 26 patients (bisoprolol $n = 11$, carvedilol $n = 15$) reached the higher dose level applicable to patients >85 kg; therefore data for this group were not analysed separately.

Changes in clinical endpoints are presented as mean differences and their significance assessed within each treatment group by paired *t*-test. Comparison across groups was carried out by analysis of covariance (ANCOVA) with the follow-up measurement as dependent variable, the randomized agent as factor, and the baseline measurement as covariate (or as categorical co-factor in case of NYHA class). Patients with a pacemaker were excluded from the analysis of change in heart rate. Percentages of patients who had an adverse event were compared using Fisher's exact test. Analyses were performed using SPSS Version 15 (SPSS Inc., Chicago, IL, USA).

Sample size

The study was designed to detect a 10% difference between arms with a power of 80–90% on the assumption that at least 50% of all patients would meet the criterion for tolerability. We therefore needed to recruit 760–1040 patients at a significance level of 5%. In April 2008, we had enrolled 883 patients, leading to a power of 85%. For the detection of 25 vs. 35% tolerability, power was 90%. Since the primary endpoint was defined for all patients, no adjustment for drop-outs was necessary.

Results

A total of 883 patients were randomized (Germany $n = 300$, Montenegro $n = 18$, Serbia $n = 535$, and Slovenia $n = 30$), 876 of whom received the first dose of the study medication. One patient was erroneously excluded from further trial participation by an investigator; no patient was lost to follow-up (*Figure 1*). Baseline characteristics are shown in *Table 1* and there were no imbalances between treatment groups.

Primary endpoint

None of the beta-blockers was superior with regards to tolerability according to the primary endpoint of reaching the respective target doses when following the recommended titration scheme (*Table 2*). This result remained the same when adjusting for treatment effect covariates (*Figure 2*). Kaplan–Meier estimates show that the percentage of patients reaching the ascending dose levels in line with the titration scheme did not differ between groups (*Figure 3*). Overall, 31% of patients reached the full, and 55% tolerated at least half of the target doses (*Table 2*). The mean daily dose reached at follow-up was 5.0 mg for bisoprolol and 23.9 mg for carvedilol in patients ≤85 kg (47.7 mg in patients >85 kg). Factors associated with reaching the primary endpoint are shown in *Figure 2*.

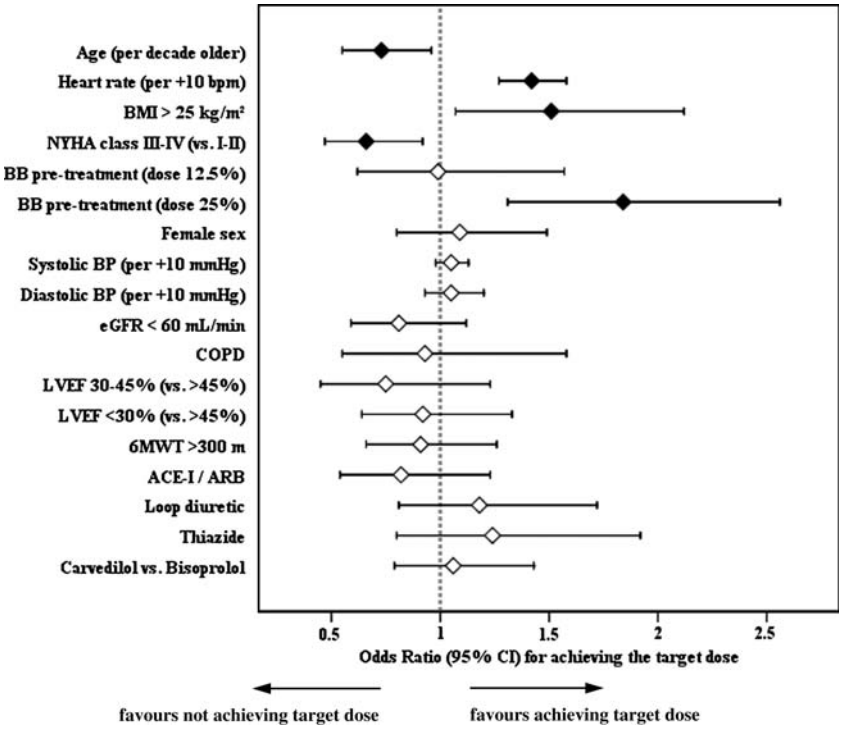

Figure 2 Predictors of tolerability. Filled diamonds indicate factors significantly related to outcome.

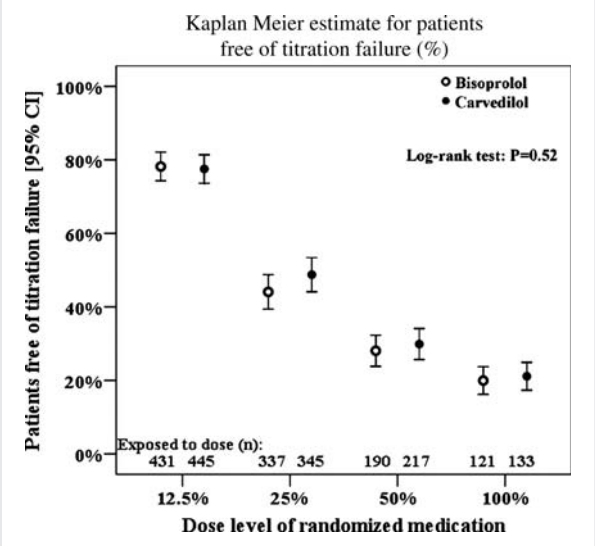

Figure 3 Kaplan–Meier estimate showing that the percentage of patients reaching the ascending dose levels in line with the titration scheme did not differ between groups. White circles indicate bisoprolol and black circles indicate carvedilol.

Safety and reasons for titration failure

In total, 668 patients (75.7%) did not reach the primary endpoint and experienced at least one titration failure. While there was no overall difference between the two groups, bradycardia (defined as heart rate <55 b.p.m. or a heart rate below 60 b.p.m. plus a decrease of more than 15%) was the most common reason for titration failure and occurred more often in the bisoprolol group (*Table 3*). These episodes were associated with more dose reductions ($P = 0.003$) as well as a lower likelihood of achieving the target dose ($P < 0.001$).

Pulmonary adverse events, which included a change in FEV_1 of $\geq$20%, or clinical symptoms such as breathing difficulty, obstructive ventilatory disorders, and bronchospasm occurred more often in the carvedilol group than among patients taking bisoprolol. However, pulmonary adverse events were not dose-limiting nor led to withdrawal of carvedilol. Anaemia occurred more often in patients taking carvedilol (*Table 3*). A decrease in mean haemoglobin was seen in the carvedilol group (*Table 4*), and this effect was more pronounced in patients who were beta-blocker naïve at baseline (interaction term: $P < 0.01$). Other adverse events with no difference between groups were worsening heart failure, hypotension, hospital admission, and mortality (*Table 3*).

Potential reasons for down-titration, slowed titration, or discontinuation defined by the blinded endpoint committee included undesirable reduction in heart rate $\leq$60 b.p.m. ($n = 70$, 8.0%); undesirable reduction in blood pressure $\leq$100 mmHg systolic/$\leq$60 mmHg diastolic ($n = 21$, 2.4%), logistical reasons ($n = 14$, 1.6%), and patient refusing the medication for unknown reasons ($n = 31$, 3.5%). Patients in the bisoprolol group were more likely to be affected by an undesirable

Table 3 Adverse events and relationship to target dose

	Number of adverse events			
	Bisoprolol	**Carvedilol**	***P*-value**	
Any adverse event, no. (%)	281 (65)	284 (64)	0.67	
Death	9 (2)	4 (1)	0.17	
Hospitalization	13 (3)	14 (3)	1.00	
Worsening heart failure	95 (22)	94 (21)	0.74	
Bradycardia	70 (16)	47 (11)	0.02	
New AV block	46 (11)	39 (9)	0.36	
Hypotension	37 (9)	44 (10)	0.56	
Fatigue/ drowsiness	46 (11)	23 (5)	0.003	
Vertigo	32 (7)	32 (7)	1.00	
Pulmonary	16 (4)	44 (10)	0.01	
Renal dysfunction	36 (8)	29 (7)	0.31	
Anaemia	29 (7)	52 (12)	0.01	
Hyperuricaemia	20 (5)	20 (5)	1.00	
Hyperlipidaemia	22 (5)	23 (5)	1.00	
	Odds ratio for relationship of BB titration with AE			
	Bisoprolol		Carvedilol	
	Any titration failure	Dose reduction	Any titration failure	Dose reduction
Any adverse event	2.10**	2.88***	2.08**	1.04
Death	†			
Hospitalization	0.79	6.62***	3.58	3.75*
Worsening heart failure	1.19	1.36	1.53	1.52
Bradycardia	1.60	3.04***	4.35**	0.91
New AV block	1.75	1.09	2.49	0.92
Hypotension	1.66	0.87	2.23	1.28
Fatigue/ drowsiness	12.75***	3.90***	2.93	4.58***
Vertigo	1.38	2.30*	2.03	3.15**
Pulmonary	1.08	1.26	1.23	0.66
Renal dysfunction	1.04	0.64	0.83	0.29*
Anaemia	0.77	0.42	1.32	0.09***
Hyperuricaemia	2.31	0.91	0.80	0.46
Hyperlipidaemia	1.13	0.26	0.75	0.39

Anaemia = male: Hb $<$ 13 g/dL; female: Hb $<$ 12 g/dL; bradycardia $\leq$ 55 b.p.m. or $<$60 b.p.m. with 15% change from previous visit; hyperlipidaemia $\geq$ 260 mg/dL or increase by 30%; hyperuricaemia $\geq$ 6.5 mg/dL or increase by 30%; hypotension $\leq$ 90 mmHg systolic/$<$60 mmHg diastolic; pulmonary, clinical assessment of breathing difficulty; obstructive ventilatory disorders or bronchospasm or drop of FEV_1 by $\geq$20%; renal dysfunction, GFR $<$ 60.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
†, odds ratio not applicable.

reduction in heart rate [$n = 45$ (12%) vs. carvedilol $n = 25$ (6%); $P = 0.01$]. There were no differences between bisoprolol and carvedilol with regards to the other reasons for down-titration, slowed titration, or discontinuation.

Change in New York Heart Association class, left ventricular ejection fraction, 6 min walk distance, quality of life, heart rate, and 1 s forced expiratory volume

New York Heart Association functional class, LVEF, 6 min walk distance and QoL improved to the same extent over the period of the study in each treatment group; blood pressure was lowered equally. Heart rate decreased in both groups from baseline to follow-up, but the reduction was greater in the bisoprolol group. Mean FEV_1 decreased in the carvedilol group whereas it remained stable in the bisoprolol group (*Table 4*).

Discussion

In this first head-to-head comparison trial of two approved beta-blockers in elderly heart failure patients, we found no superiority of bisoprolol vs. carvedilol or vice versa with regards to tolerability to target doses, but the reasons for not reaching the primary endpoint and the clinical reaction to the beta-blockers differed.

Table 4 Clinical endpoints

	Bisoprolol (B)	Carvedilol (C)	Difference B–C from ANCOVA
NYHA functional class	($n = 386$)	($n = 396$)	
Mean change (95% CI)	−0.29 (−0.35 to −0.24)	−0.25 (−0.30 to −0.20)	−0.01 (−0.08 to +0.05)
P-value	<0.001	<0.001	0.71
Heart rate on ECG[a], b.p.m.	($n = 367$)	($n = 369$)	
Mean change (95% CI)	−8.4 (−9.8 to −7.0)	−6.0 (−7.2 to −4.7)	−2.1 (−3.6 to −0.5)
P-value	<0.001	<0.001	0.008
Systolic blood pressure, mmHg	($n = 386$)	($n = 396$)	
Mean change (95% CI)	−9.3 (−11.4 to −7.3)	−9.5 (−11.7 to −7.3)	+0.6 (−1.7 to +2.9)
P-value	<0.001	<0.001	0.60
Diastolic blood pressure, mmHg	($n = 386$)	($n = 396$)	
Mean change (95% CI)	−4.7 (−5.9 to −3.5)	−4.2 (−5.4 to −3.0)	−0.3 (−1.6 to +1.1)
P-value	<0.001	<0.001	0.69
LVEF, %	($n = 383$)	($n = 394$)	
Mean change (95% CI)	+3.0 (+2.3 to +3.7)	+2.7 (+2.0 to +3.4)	+0.4 (−0.5 to +1.4)
P-value	<0.001	<0.001	0.36
6-min-walk distance, m	($n = 357$)	($n = 358$)	
Mean change (95% CI)	+19 (+11 to +26)	+13 (+6 to +19)	+5 (−4 to +14)
P-value	<0.001	<0.001	0.25
Haemoglobin, g/dL	($n = 358$)	($n = 373$)	
Mean change (95% CI)	−0.07 (−0.20 to +0.06)	−0.24 (−0.37 to −0.11)	+0.15 (−0.02 to +0.32)
P-value	0.28	<0.001	0.07
FEV_1, mL	($n = 349$)	($n = 365$)	
Mean change (95% CI)	+3 (−32 to +39)	−42 (−73 to −11)	+50 (+4 to +95)
P-value	0.86	0.007	0.03
SF-36 physical component score	($n = 289$)	($n = 295$)	
Mean change (95% CI)	+2.4 (+1.6 to +3.3)	+2.0 (+1.1 to +2.9)	+0.4 (−0.7 to +1.5)
P-value	<0.001	<0.001	0.49
SF-36 psychosocial component score	($n = 289$)	($n = 295$)	
Mean change (95% CI)	+3.5 (+2.4 to +4.7)	+2.6 (+1.5 to +3.7)	+0.4 (−1.0 to +1.7)
P-value	<0.001	<0.001	0.61

CI, confidence interval; FEV_1, forced expiratory volume in the first second; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.[a]Excluding patients with pacemaker.

Pharmacological differences and heart rate

Recent publications have confirmed heart rate reduction as an important target in the treatment of heart failure.[15,16] The selective β_1-adrenoceptor-blocker bisoprolol was associated with a larger heart rate reduction and more bradycardic adverse events than the non-selective α_1-, β_1-, and β_2-adrenoceptor-blocker carvedilol. Sole alpha-blockade is known to increase heart rate and the combination of alpha- and beta-blockade in one molecule appears to weaken its heart rate lowering effect.[17] Although this difference in selectivity may explain our results, CIBIS-ELD is the first comparison trial to provide evidence of its clinical relevance in heart failure patients. In multivariate analysis, higher baseline heart rate predicted better tolerability of target doses, regardless of treatment group. Of note, the baseline mean heart rate was relatively low in this study (73 b.p.m.) when compared with other heart failure trials such as CIBIS II (80 b.p.m.),[2] CIBIS III (79 b.p.m.),[18] and COMET (81 b.p.m.).[8] The lower baseline heart rate of patients in this trial may explain at least in part why the mean daily dose reached (bisoprolol: 5.0 mg; carvedilol: 23.9 mg for patients ≤85 kg; and 47.7 mg for patients >85 kg) was lower than that observed, for example, in CIBIS III (mean bisoprolol dose 8.3 mg),[18] and in COMET (mean carvedilol dose 41.8 mg, compared with a target of 50 mg).[8]

Pharmacological differences and pulmonary function

Beta-blockers are frequently not up-titrated or even withheld for fear of bronchoconstriction.

In this trial carvedilol was associated with more pulmonary adverse events than bisoprolol and with a reduction of FEV_1, which is in line with its pharmacodynamic properties. Incidence of pulmonary adverse events was nonetheless moderate in both groups. In contrast to pre-existing opinions, neither these

adverse events nor the reduction in FEV_1 with carvedilol were a significant limitation for up-titration. Furthermore, the presence of chronic obstructive pulmonary disease (COPD), which was the most powerful independent predictor of beta-blocker underutilization in the EuroHeart Failure Survey,[6] was not predictive of less ability to titrate dose upwards in our trial. In a study that looked specifically at heart failure patients with COPD receiving bisoprolol or placebo, bisoprolol was associated with a 5% reduction in FEV_1.[19] However, this did not cause pulmonary symptoms or impair QoL.

Tolerability of beta-blocker therapy in CIBIS-ELD

Titration scheme

The observation that only 31% of patients reached their target dose contrasts with findings from previous trials, in which 42–87% of patients reached the recommended target doses.[2–4,8,18,20] However, these previous trials enrolled younger patients (60–63 years), allowed a longer duration of titration (10–16 weeks and longer if clinically indicated), and also allowed more than one delay in titration, and/or intermediate dose steps (for bisoprolol 3.75 and 7.5 mg) instead of a doubling of the dose every fortnight as recommended by the 2005 ESC guidelines. The new 2008 ESC guidelines adopt the titration schemes of these larger beta-blocker trials without citing new evidence, but our findings appear to support this change.[21]

Target doses

Although a dose-related reduction in mortality and hospitalization rates was shown in younger patients receiving carvedilol,[22] a recent meta-analysis of 23 beta-blocker trials failed to show an association between beta-blocker dose and survival benefit in heart failure.[16] Our study was not designed to address the relationship of dose benefit; however, it does clearly raise the question of the achievability of currently recommended targets.

Predictors of tolerability

In agreement with other investigators, our findings show that younger age and NYHA functional class II predicted patients' ability to tolerate higher beta-blocker doses.[10,23] Beta-blocker pretreatment was a further predictor of tolerability in CIBIS-ELD, which may be in favour of a slower approach to titration and is in line with clinical observations that a quarter of the recommended beta-blocker dose is a hurdle to be overcome. A body mass index >25 kg/m^2 being predictive of achieving higher doses may be due to adverse effects probably being linked to the volume of distribution, but is an observation that to our knowledge has not been reported before.

Adverse effects

We expected that the vasodilatory effects of carvedilol might lead to lower tolerability as a result of hypotension. In a review of selective vs. non-selective beta-blockers, the most frequent adverse effects were reported to be worsening heart failure with bisoprolol, and hypotension and dizziness with carvedilol.[24] Our results do not confirm these findings. Anaemia as an adverse event was observed more frequently in patients receiving carvedilol. These results are in line with findings from the COMET trial.[25]

Limitations

A correlation between tolerability to the target doses or titration success and mortality cannot be established on the basis of our data due to the short follow-up. Another limitation might be that there is no recommended beta-blocker target dose for patients with preserved LVEF. However, despite a lack of proven reduction in mortality, there is an expert-based recommendation of heart rate lowering using beta-blockers in diastolic heart failure and for reasons of comparison, we used the same dose.[26] In addition, recent data from SENIORS suggest that beta-blockers may possibly be effective in patients with LVEF $>35\%$.[27] It may be considered a limitation that only 25% of patients reached the primary endpoint though a target of 50% was planned. However, this should first be seen as an unexpected outcome which deserves consideration when speaking about the meaning of target dose, and second, it is not a true limitation as the power of the study was not reduced. Further, it was not mandatory for CIBIS-ELD investigators to document reasons for titration failure. Therefore, a blinded endpoint committee assessed the patients' clinical data at the time of titration failure (for failures unrelated to adverse events) and potential reasons for titration failure were recorded where possible.

Conclusion and clinical implications

In CIBIS-ELD, we found no difference in achieved doses and tolerability to target doses between bisoprolol and carvedilol in elderly patients with heart failure, although the patterns of adverse effects differed. With both agents, it appears that clinicians should follow an individualized, slower, titration scheme. For patients with low resting heart rates, physicians might prefer prescription of carvedilol, and for patients with lung disease, the favourable beta-blocker might be bisoprolol.

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Appendix

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