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# Tolerability and Feasibility of Beta-Blocker Titration in HFpEF Versus HFrEF

## Insights From the CIBIS-ELD Trial

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## ABSTRACT

**OBJECTIVES** This study evaluated the tolerability and feasibility of titration of 2 distinctly acting beta-blockers (BB) in elderly heart failure patients with preserved (HFpEF) and reduced (HFrEF) left ventricular ejection fraction.

**BACKGROUND** Broad evidence supports the use of BB in HFrEF, whereas the evidence for beta blockade in HFpEF is uncertain.

**METHODS** In the CIBIS-ELD (Cardiac Insufficiency Bisoprolol Study in Elderly) trial, patients >65 years of age with HFrEF (n = 626) or HFpEF (n = 250) were randomized to bisoprolol or carvedilol. Both BB were up-titrated to the target or maximum tolerated dose. Follow-up was performed after 12 weeks. HFrEF and HFpEF patients were compared regarding tolerability and clinical effects (heart rate, blood pressure, systolic and diastolic functions, New York Heart Association functional class, 6-minute-walk distance, quality of life, and N-terminal pro-B-type natriuretic peptide).

**RESULTS** For both of the BBs, tolerability and daily dose at 12 weeks were similar. HFpEF patients demonstrated higher rates of dose escalation delays and treatment-related side effects. Similar HR reductions were observed in both groups (HFpEF: 6.6 beats/min; HFrEF: 6.9 beats/min, p = NS), whereas greater improvement in NYHA functional class was observed in HFrEF (HFpEF: 23% vs. HFrEF: 34%, p < 0.001). Mean E/e′ and left atrial volume index did not change in either group, although E/A increased in HFpEF.

**CONCLUSIONS** BB tolerability was comparable between HFrEF and HFpEF. Relevant reductions of HR and blood pressure occurred in both groups. However, only HFrEF patients experienced considerable improvements in clinical parameters and left ventricular function. Interestingly, beta-blockade had no effect on established and prognostic markers of diastolic function in either group. Long-term studies using modern diagnostic criteria for HFpEF are urgently needed to establish whether BB therapy exerts significant clinical benefit in HFpEF. (Comparison of Bisoprolol and Carvedilol in Elderly Heart Failure [HF] Patients: A Randomised, Double-Blind Multicentre Study [CIBIS-ELD]; ISRCTN34827306) (J Am Coll Cardiol HF 2016;4:140–9) © 2016 by the American College of Cardiology Foundation.

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Chronic heart failure (HF) continues to be a major health problem in the community (1). Nearly one-half of HF patients have preserved left ventricular ejection fraction (HFpEF) (2), and the prevalence of HFpEF patients is increasing (3). Recent data suggest that mortality and readmission rates in HFpEF are higher than described and that the overall prognosis is comparable to HFrEF (2,3). Furthermore, although survival rates of HFrEF patients improved over the past decades, mortality remains unchanged in HFpEF patients (3). The diverging mortality trend reflects a lack of treatments with proven survival benefit for HFpEF, resulting partially, from the scarcity of large clinical trials in this condition (4).

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Robust evidence supports the use of beta-blockers (BB) in HFrEF, although their use in HFpEF remains controversial (5). BBs could theoretically be useful and recommended by guidelines to control HR in HFpEF (e.g., by lowering blood pressure [BP] and/or afterload, reducing left ventricular hypertrophy, lengthening diastolic filling time, and reducing high ventricular rates, which are poorly tolerated in this condition) (6). They also reduce the risk of ventricular arrhythmias, which are one of the most common modes of death in HFpEF (7). Registry data, 1 small randomized, controlled trial, and the large SENIOR study, have suggested a prognostic benefit due to beta-blockade in HFpEF (8–10). SENIOR study, however, using only a left ventricular ejection fraction (LVEF) cutoff value of >35% for the definition of HFpEF, has been criticized (9). On the other hand, the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry showed that the use of BBs in HFpEF patients was be related to poor outcomes (11), and another small observational study suggested that BB therapy may lead to a higher risk of rehospitalization in women with HFpEF (12).

However, little is still known about the tolerability of BBs in HFpEF. Although the overall tolerability of nebivolol was found to be similar for both HFrEF and HFpEF in the SENIOR study, prescription of BBs in both conditions remains low despite evidence of their prognostic benefit in HFrEF (13). The main results from the CIBIS-ELD (Cardiac Insufficiency Bisoprolol Study in Elderly) trial suggest that there is no difference in achieved doses and tolerability to target doses between bisoprolol and carvedilol in elderly HF patients (14). Although BBs are currently indicated to treat comorbidities associated with HFpEF, there are no recommendations of how to initiate BB treatment in HFpEF (15). Also according to the primary objective of the CIBIS-ELD trial, which addressed the superiority of bisoprolol versus carvedilol, in this pre-specified analysis, we therefore compared the tolerability and clinical effectiveness of these 2 differentially acting BBs on the burden of symptoms, functional capacity, and echocardiographic assessment of systolic and diastolic myocardial function in elderly HFrEF and HFpEF patients (16).

**ABBREVIATIONS AND ACRONYMS**

**BB** = beta-blockers

**HF** = heart failure

**HFpEF** = heart failure with preserved ejection fraction

**HFrEF** = heart failure with reduced ejection fraction

**HR** = heart rate

**LAVI** = left atrial volume index

**LVEF** = left ventricular ejection fraction

**LVMI** = left ventricular mass index

**QoL** = quality of life

## METHODS

**TRIAL DESIGN AND PATIENTS.** Details of the CIBIS-ELD trial design have been published previously (16). This investigator-initiated, randomized, double-blind, double-dummy, parallel group trial was performed in Germany, Montenegro, Serbia, and Slovenia. Patients eligible for inclusion were adults 65 years or older with symptomatic chronic HF consistent with NYHA functional class ≥II at presentation and either a reduced LVEF ≤45% (HFrEF patients) or a preserved ejection fraction (LVEF >45%) (HFpEF patients), with evidence of diastolic dysfunction as defined below. At baseline, eligible participants had to be BB naïve or currently taking ≤25% of the recommended BB dose for HFrEF (≤2.5 mg once daily for bisoprolol; ≤6.25 mg twice daily for carvedilol). They had to be clinically stable with no changes in HF medication for at least 2 weeks before randomization. Major exclusion criteria were known contraindications to BB treatment such as hypotension with a resting systolic BP < 90 mm Hg, severe pulmonary disease or severe asthma, bradycardia with a resting HR < 55 beats/min before commencement of therapy, second or third degree sinoatrial block (without pacemaker) and known sick sinus syndrome.

This is a pre-specified subgroup analysis of the differences between HFpEF and HFrEF in the CIBIS-ELD trial, which tested whether the target dose could be reached more often with bisoprolol than with carvedilol (14,16). Tolerability and clinical effectiveness of bisoprolol versus that of carvedilol on the burden of symptoms, functional capacity, and echocardiographic assessment of systolic and diastolic myocardial function in elderly HFrEF and HFpEF patients were compared. Tolerability was defined as tolerance (yes/no) of the study medication target dose as per cardiology guidelines recommended (primary endpoint). Further endpoints were time to treatment failure, % of target dose for long term treatment, number of adverse events or serious adverse events (14,16).

**TABLE 1 Baseline Characteristics**

| | All patients (N = 876) | HFpEF (N = 250) | HFrEF (N = 626) | p Value |
|---|---|---|---|---|
| Age, yrs | 72.8 ± 5.5 | 73.4 ± 6.0 | 72.6 ± 5.3 | 0.06 |
| Women (%) | 329 (38) | 164 (66) | 165 (26) | <0.001 |
| NYHA functional classes shown (%) | | | | 0.02 |
| I | 34 (4) | 2 (1) | 32 (5) | |
| II | 575 (66) | 191 (76) | 384 (61) | |
| III | 258 (30) | 57 (23) | 201 (32) | |
| IV | 9 (1) | 0 (0) | 9 (1) | |
| Peripheral edema (%) | 183 (21) | 88 (35) | 95 (15) | <0.001 |
| Heart rate on ECG, beats/min | 73.5 ± 14.3 | 70.7 ± 12.8 | 74.6 ± 14.8 | <0.001 |
| Blood pressure, mm Hg | | | | |
| Systolic | 137.1 ± 21.5 | 146.2 ± 23.6 | 133.5 ± 19.4 | <0.001 |
| Diastolic | 80.0 ± 11.8 | 80.4 ± 12.5 | 79.8 ± 11.5 | 0.49 |
| Body mass index, kg/m$^2$ | 27.7 ± 4.9 | 29.5 ± 5.9 | 27.1 ± 4.2 | <0.001 |
| Left ventricular ejection fraction (%) | 41.7 ± 13.6 | 58.9 ± 8.8 | 34.8 ± 7.9 | NA |
| NT-proBNP, pg/ml | 609 (255-1,614) | 253 (161-529) | 968 (409-2,091) | <0.001 |
| Time since first diagnosis of heart failure, yrs | | | | <0.001 |
| <1 | 197 (23) | 114 (46) | 83 (13) | |
| 1-5 | 305 (35) | 69 (28) | 236 (38) | |
| >5 | 248 (28) | 25 (10) | 223 (36) | |
| Unknown | 126 (14) | 42 (17) | 84 (13) | |
| Primary cause of heart failure | | | | <0.001 |
| CAD | 455 (52) | 79 (32) | 376 (60) | |
| DCM | 123 (14) | 4 (2) | 119 (19) | |
| Hypertension | 223 (25) | 140 (56) | 83 (13) | |
| Other | 75 (9) | 27 (11) | 48 (8) | |
| No. of hospitalizations for heart failure during the past 12 months (%) | 314 (36) | 51 (20) | 263 (42) | <0.001 |
| No. with medical history shown (%) | | | | |
| Current smoker | 76 (9) | 19 (8) | 57 (9) | 0.51 |
| Myocardial infarction | 347 (40) | 44 (18) | 303 (48) | <0.001 |
| PCI and/or CABG | 196 (22) | 42 (17) | 154 (25) | 0.01 |
| Pacemaker and/or ICD | 56 (6) | 7 (3) | 49 (9) | 0.005 |

*Continued on the next page*

The protocol and amendments were approved by all responsible national institutes for drugs and medical devices, as well as by national and local ethics committees. All patients provided written informed consent before enrolment, and all procedures related to the trial conformed to the principles outlined in the Declaration of Helsinki. CIBIS-ELD is registered at www.controlled-trials.com under the identifier ISRCTN34827306.

**STUDY MEDICATION.** Patients were randomized to either bisoprolol or carvedilol, independent of left ventricular function. All patients, investigators, and study personnel were blinded to treatment assignment. According to the titration scheme for HFrEF (on the basis of 2005 European Society of Cardiology guidelines), the blinded treatment was titrated to target doses over 10 weeks by doubling the dose every 2 weeks (17). Thus, with a starting dose of 2.5 mg of bisoprolol once daily or carvedilol, 6.25 mg twice daily, patients were scheduled to reach the target dose of 10 mg of bisoprolol or 25 mg of carvedilol twice daily within 6 weeks (or 50 mg twice daily within 8 weeks for patients receiving carvedilol with a body weight >85 kg). When clinically indicated, investigators were allowed to delay dose titration, reduce the dose or discontinue the study treatment. The titration phase was followed by a 4-week maintenance period. The final visit was conducted at 10 weeks (or 12 weeks for patients weighing >85 kg). Delayed up-titration to the target dose was any titration that did not follow the titration scheme (i.e. an up-titration step was postponed to the next visit, or the study medication was even temporarily down-titrated), but eventually, the target dose was reached after 3 months.

**LABORATORY MEASUREMENTS.** At baseline and at 12 weeks, blood samples were taken in standardized conditions by venous puncture after a 20-minute supine resting period. All samples were immediately

**TABLE 1 Continued**

| | All patients (N = 876) | HFpEF (N = 250) | HFrEF (N = 626) | p Value |
|---|---|---|---|---|
| Comorbidities | | | | |
| Hypertension | 724 (83) | 224 (90) | 500 (80) | 0.001 |
| Coronary artery disease | 510 (58) | 82 (33) | 428 (68) | <0.001 |
| Diabetes mellitus | 223 (26) | 57 (23) | 166 (27) | 0.27 |
| Hyperlipidaemia | 548 (63) | 165 (66) | 383 (61) | 0.19 |
| Peripheral vascular disease or stroke | 121 (14) | 30 (12) | 91 (15) | 0.39 |
| Atrial fibrillation | 164 (19) | 25 (10) | 139 (22) | <0.001 |
| Chronic obstructive pulmonary disease | 65 (7) | 22 (9) | 43 (7) | 0.32 |
| Renal dysfunction (GFR <60) | 338 (39) | 68 (27) | 270 (43) | <0.001 |
| Anemia (male: Hb <13 g/dl; female: Hb <12 g/dl) | 181 (21) | 38 (15) | 143 (23) | 0.01 |
| Occurrence of depression | 73 (8) | 35 (14) | 38 (6) | |
| In men | 31 (6) | 2 (2) | 29 (6) | 0.20 |
| In women | 42 (13) | 33 (20) | 9 (5) | <0.001 |
| Interaction sex × LV function | | | | 0.001 |
| No. taking cardiovascular medications shown (%) | | | | |
| Beta-blocker use at enrolment | | | | <0.001 |
| None | 349 (40) | 131 (52) | 218 (35) | |
| 12.5% of target dose equivalent | 149 (17) | 24 (10) | 125 (20) | |
| 25% of target dose equivalent | 378 (43) | 95 (38) | 283 (45) | |
| ACE inhibitor and/or ARB | 741 (85) | 190 (76) | 551 (88) | <0.001 |
| Aldosterone receptor antagonist | 275 (31) | 21 (8) | 254 (41) | <0.001 |
| Diuretic agent | 649 (74) | 146 (58) | 503 (80) | <0.001 |
| Cardiac glycoside | 129 (15) | 17 (7) | 112 (18) | <0.001 |
| Calcium channel blocker | 143 (16) | 62 (25) | 81 (13) | <0.001 |
| Nitrate | 277 (32) | 32 (13) | 245 (39) | <0.001 |
| Antiarrhythmic | 95 (11) | 5 (2) | 90 (14) | <0.001 |
| Statin | 342 (39) | 77 (31) | 265 (42) | 0.002 |
| Antiplatelet | 582 (66) | 122 (49) | 460 (73) | <0.001 |
| Anticoagulant agent | 220 (25) | 37 (15) | 183 (29) | <0.001 |

Values are mean ± SD, n (%), or median (interquartile range).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; DCM = dilated cardiomyopathy; GFR = glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; HRrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LV = left ventricle; NA = Non-applicable; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

centrifuged and stored below −80°C. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was analyzed using a commercially available Elecsys proBNP sandwich immunoassay on an Elecsys 2010 analyzer (Roche Diagnostics, Berlin, Germany).

**ECHOCARDIOGRAPHY.** Echocardiography was performed according to current guidelines of the American Society of Echocardiography, including comprehensive evaluation of diastolic function with Doppler and tissue Doppler techniques. All examinations were performed by experienced echocardiographers who were blinded to treatment assignment. LVMI and left atrial volume index (LAVI) were calculated as also recommended by the American Society of Echocardiography (18).

Diastolic function in CIBIS-ELD was evaluated and graded according to a standardized protocol developed by the nationwide German Competence Network Heart Failure (19,20).

**STATISTICAL ANALYSIS.** Baseline characteristics of HFpEF and HFrEF patients were compared by using the *t* test for quantities, by Kendall's tau for ordinal variables, and by Fisher exact test for frequencies. Changes in quantitative measurements from baseline to 12 weeks were assessed within each of the groups by t tests for paired variables, and were compared between groups by analysis of covariance with the 12 weeks value as dependent variable, the baseline value as covariate, and ventricular function as the group variable. Correlations of changes in functional variables and quality of life (QoL) were described by Kendall's tau for each of the functional groups separately, and the tau coefficients were compared between groups using the Gauss approximation test. Analyses were performed using SPSS version 15 software (SPSS Inc., Chicago, Illinois).

**FUNDING AND RESPONSIBILITIES.** The project was initiated and coordinated by investigators of the

Competence Network Heart Failure (Project Multicenter Trials), a group of investigators funded by the German Federal Ministry of Education and Research (19). The sponsor of the trial according to ICH-GCP was the Charité University Hospital in Berlin, Germany. Merck KGaA supported the trial with an unrestricted research grant without any rights to influence trial design, data collection, data analysis, and interpretation or publication of the results and thus did not interfere with the investigators' intellectual property rights. The senior biometrician and the corresponding author had full access to all data. The first and corresponding authors had final responsibility for the decision to submit the paper for publication.

## RESULTS

**PATIENTS.** Of 883 CIBIS-ELD patients, 876 patients (mean age: 72.8 ± 5.5, 38% female; mean LVEF 58.7 ± 8.8% in HFpEF, 34.9 ± 8.0% in HFrEF) received bisoprolol or carvedilol and were available for analysis. HFpEF was diagnosed in 250 patients (29%) and HFrEF in 626 patients (71%). In the HFrEF group, 317 patients (51%) received carvedilol, and 309 (49%) received bisoprolol. In the HFpEF group, 127 patients (51%) received carvedilol and 123 (49%) bisoprolol. Baseline characteristics are shown in Table 1. HFpEF patients were more frequently female and tended to be older, with greater body mass index (BMI), higher systolic BP and lower resting HRs at baseline, in lower NYHA functional classes, with more peripheral edema and lower NT-proBNP levels. More HFpEF patients were BB-naïve (52% vs. 35% in HFrEF) and had lower rates of coronary artery disease.

**TOLERABILITY TO TARGET DOSE AND MEAN DAILY BB DOSE.** At the end of the titration period 31% (n = 77) of HFpEF patients and 31% (n = 197) in HFrEF had reached the target dose (between group comparison p = 0.87), as presented on Figure 1. Among these patients, 62% of HFpEF patients (n = 48) reached the target dose as scheduled versus 84% of HFrEF patients (n = 166; HFpEF vs. HFrEF; p < 0.01). For both bisoprolol and carvedilol, delayed up-titration was observed more frequently in HFpEF patients than in HFrEF patients (bisoprolol, p = 0.001; carvedilol, p = 0.04); however, no significant differences were observed in mean daily doses following titration (bisoprolol: 4.93 ± 3.70 mg for HFrEF vs. 5.01 ± 3.61 mg for HFpEF; p = 0.83; whereas carvedilol: 29.1 ± 25.9 mg for HFrEF vs. 25.3 ± 18.6 mg HFpEF; p = 0.09). Of the total number of patients, 7% (n = 60) had a delay in up-titration to the target dose: 31 (5%) in HFrEF and 29 (12%) in HFpEF.

Forty-eight HFpEF patients (19%) vs. 166 HFrEF patients (27%) reached the primary endpoint of the CIBIS-ELD trial (defined as reaching the target dose through biweekly dose doubling with no more than 1 delayed titration step and with the target dose maintained for at least 10 days; p = 0.02). Fewer HFpEF patients reached the target dose than HFrEF patients, regardless of the treatment group (bisoprolol: 81, 26% vs. 21, 17%, carvedilol 85, 27% vs. 27, 21%; p = 0.52 for homogeneity of differences, p = 0.02 for agent-adjusted difference between HFpEF and HFrEF). When we adjusted for age, BMI, and NYHA functional class, this result remained the same, although the odds ratio (OR) of HFpEF versus HFrEF for reaching the primary endpoint (OR: 0.66; 95% confidence interval [CI]: 0.46 to 0.95; p = 0.02) became nonsignificant (OR: 0.79; 95% CI: 0.54 to 1.14, p = 0.21) when adjusting for baseline HR and BB pre-treatment.

More HFpEF patients experienced adverse events (79% vs. 58%, respectively, p < 0.001), regardless of agent. Bradycardia (51 [20%] vs. 66 [11%], respectively), dizziness (37 [15%] vs. 28 [4%]) and fatigue (44 [18%] vs. 25 [4%]) occurred more frequently in HFpEF patients (all p < 0.001). Differences remained significant even when we adjusted for baseline HR, BB pre-treatment, age, BMI, and NYHA functional class (p < 0.001).

**CLINICAL EFFECTS, FUNCTIONAL STATUS, AND QoL.** There were no significant differences between bisoprolol and carvedilol with regard to clinical parameters in either group. Although the reduction of HR was significantly higher with bisoprolol, the overall reductions of HR and diastolic BPs were comparable in HFrEF and HFpEF (drug by ventricular function interaction: p = 0.71, adjusted for BB pre-treatment). However, systolic BP reduction was more marked in HFpEF patients (Table 2). NYHA functional class improved to a lesser extent in HFpEF patients than in HFrEF patients. There was a significant increase in NT-proBNP in HFpEF patients, whereas NT-proBNP remained stable in HFrEF.

Scores for 6-minute-walk distances and physical QoL improved in the HFrEF group. In HFpEF patients, the reduction of HR was not associated with changes in subjectively or objectively measured parameters of physical and myocardial function (Tables 2 and 3). In HFrEF, HR reduction was associated with improvements in NYHA functional class, self-reported physical functioning (SF-36 PFS), and LVEF (all p < 0.05). Reduction of BP was not related to changes in QoL or functional status in either group.

**CHANGES IN SYSTOLIC AND DIASTOLIC FUNCTION.** LVEF and left ventricular end-diastolic diameter

(LVEDD) and left ventricle end-systolic diameter (LVESD) improved in HFrEF patients but not in HFpEF patients (Table 3). There were no changes in key parameters of diastolic function (E/e') or atrial remodelling (LAVI) in either group; however, an increase in E/A mitral flow ratio was observed in HFpEF patients only (baseline: EA 0.84 ± 0.32; at 12 weeks, E/A was 0.91 ± 0.36; $p < 0.001$). There were no differences between bisoprolol and carvedilol in regard to echocardiographic parameters.

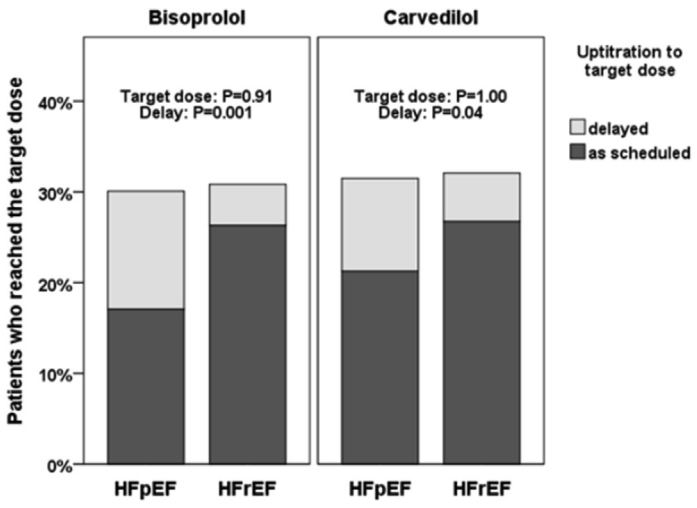
## DISCUSSION

This pre-specified subgroup analysis of the CIBIS-ELD trial is the first detailed comparison between of 2 commonly used BBs with distinct pharmacological profiles in elderly HFrEF versus HFpEF patients, and therefore gives valuable information about the use of BB in HFpEF, namely, BB titration was more difficult in HFpEF patients than in HFrEF patents and led to more titration delays and side effects. Only 19% of HFpEF patients versus 27% of HFrEF patients reached the primary endpoint defined as titration to the target dose without delay, although in both groups, 31% of the patients finally reached the target dose. This implies that it might take more time to titrate HFpEF patients on a BB dose than HFrEF patients. As there is no exact definition of "tolerability," one could discuss whether it is more important to reach a target dose rather than reach it without any delay.

We found no differences between the probabilities of HFpEF and HFrEF patients reaching the target dose, but HFpEF patients experienced more titration delays and more adverse events.

Both BBs were comparable regarding their tolerability and clinical effectiveness in HFrEF and HFpEF. Reduction of HR and BP was greater in HFpEF patients than in HFrEF patients, which is in concordance with previously published results (21). This finding therefore further supports the evidence regarding the substantial hemodynamic differences between HFpEF and HFrEF. Despite the significant reduction in HR and BP at 12 weeks, there was modest improvement in NYHA functional class, although self-reported physical functioning, 6-minute-walk distance, and echocardiographic parameters of systolic and diastolic functions did not improve in HFpEF, unlike those in HFrEF patients. We could not show a clear clinical benefit in the HFpEF group (except for the previously mentioned slight improvement in NYHA functional class, after BB titration), although the limitation of this trial was that we did not have a placebo group. It is also important to mention that there was a significant improvement in QoL in all subscales in HFrEF patients but not in those in HFpEF patients.

**FIGURE 1** Percentage of HFrEF and HFpEF Patients Reaching the Targeted Beta-Blocker Dose by the End of the 12-Week Titration Period




HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

**PATIENTS.** Although several small studies, registry data and post-hoc analyses of the SENIOR study seem to support the use of BBs in HFpEF, results regarding the clinical effectiveness of BBs in HFpEF patients remain inconsistent and tolerability was addressed only once previously (6,9). Differences in methodology, HFpEF definition and sample composition limit the comparability of previous studies. In our analysis the diagnosis of HFpEF was on the basis of HF signs and symptoms and on the absence of a reduced LVEF using a prognostically relevant cut-off value of 45% (22). Furthermore, as required by the current ESC and AHA/ACC guidelines, echocardiographic evidence of diastolic dysfunction was required for all HFpEF patients (20). In previous large trials investigating HFpEF, the presence of diastolic dysfunction as determined by echocardiography was often not required for study eligibility; treatment-related effects on diastolic function were often investigated in subgroups only (4). Stringent diagnostic criteria for HFpEF are essential to avoid the inclusion of falsely diagnosed patients in clinical trials, especially as common co-morbidities may mimic the HFpEF symptoms. Inhomogeneous HFpEF definition and differences in phenotyping may account for the failure of large trials. Our definition made possible to include HFpEF patients with typical clinical and

demographic characteristics. As shown in previous community-based and interventional studies, HFpEF patients in this study were in lower NYHA functional classes, less severely affected in QoL dimensions and less frequently treated with cardiovascular drugs (2,3,9). Furthermore, they demonstrated low rates of coronary artery disease, which has been proposed as an indicator of sample quality (23).

**TOLERABILITY OF THE TARGET DOSE AND MEAN DOSE.** After adjusting for baseline HR and BB pre-treatment, HFpEF patients achieved the primary tolerability endpoint of the CIBIS-ELD trial as often as HFrEF patients regardless of the BB used. In general, only 19% versus 27% fulfilled these criteria in both groups, which is markedly lower than previously reported for HFrEF (9). Similar mean daily doses for bisoprolol and carvedilol were observed at the end of titration in HFpEF and HFrEF patients. The SENIOR study reported that 67% of HF patients reached the maximal dose of nebivolol after titration period. Furthermore, they found no significant differences between HFrEF and HFpEF patients (24). The stringent definition of tolerability in our trial (including a time-to-target-dose criterion), the predominant inclusion of younger patients in former trials in HFrEF and differences in pharmacological profile of investigated BBs might be the most important contributors to the high rate of failure to reach primary endpoint in both HFpEF and HFrEF in our trial.

**MYOCARDIAL SYSTOLIC AND DIASTOLIC FUNCTION.** In HFrEF patients there is strong evidence that BB treatment results in LVEF improvement and has the potential to reduce left ventricular volumes (25). Similarly, we observed echocardiographic improvement in HFrEF patients regardless on the substance used. Not surprisingly, neither bisoprolol nor carvedilol had an effect on LVEF, LVEDD, or LVES in HFpEF patients.

**TABLE 2 Clinical Endpoints**

| | Treatment Group | | Difference |
|---|---|---|---|
| | HFpEF (N = 250) | HFrEF (N = 626) | HFpEF vs. HFrEF* |
| Heart rate on ECG (beats/min) | | | |
| Mean change (95% CI) | -6.6 (-8.0 to −5.2) p < 0.001 | −6.9 (-8.0 to −5.7) p < 0.001 | 1.2 (-0.8 to 3.2) p = 0.25 |
| Blood pressure systolic ( mm Hg) | | | |
| Mean change (95% CI) | -14.3 (-17.7 to −11.0) p < 0.001 | −7.5 (-9.1 to −5.9) p < 0.001 | −6.4 (−9.7 to 3.0) p < 0.001 |
| Diastolic blood pressure (mm Hg) | | | |
| Mean change (95% CI) | -5.2 (-6.9 to −3.5) p < 0.001 | −4.1 (−5.1 to −3.1) p < 0.001 | −0.7 (−2.6 to 1.3) p = 0.49 |
| NYHA functional class | | | |
| Mean change (95% CI) | -0.18 (-0.25 to −0.11) p < 0.001 | −0.31 (−0.35 to −0.26) p < 0.001 | 0.14 (0.05 to 0.23) p = 0.002 |
| 6-min walk distance (m) | | | |
| Mean change (95% CI) | 4 (-8 to 16) p = 0.52 | 20 (15 to 25) p < 0.001 | −15 (−26 to −4) p = 0.008 |
| Log 10 NT-proBNP | | | |
| Mean change (95% CI) | 0.05 (0.00 to 0.10) p = 0.03 | 0.00 (−0.04 to 0.03) p = 0.82 | 0.05 (−0.01 to 0.11) p = 0.13 |
| SF-36 PFS | | | |
| Mean change (95% CI) | 1.1 (−1.7 to 3.9) p = 0.44 | 4.9 (2.9 to 6.9) p < 0.001 | −4.3 (−8.2 to −0.4) p = 0.03 |
| SF-36 PCS | | | |
| Mean change (95% CI) | 1.1 (−0.1 to 2.2) p = 0.08 | 2.5 (1.8 to 3.3) p < 0.001 | −1.7 (−3.2 to −0.2) p = 0.02 |
| SF-36 MCS | | | |
| Mean change (95% CI) | 0.4 (−1.2 to 2.0) p = 0.61 | 3.8 (2.9 to 4.7) p < 0.001 | p < 0.001 |

*Adjusted for beta-blocker pre-treatment and study drug.

ECG = electrocardiography; NT-proBNP = N-terminal pro b-type natriuretic peptide; NYHA = New York Heart Association; SF-36 MCS = short-form quality of life health survey (SF-36) mental component su mmary score; SF-36 PCS = short-form quality of life health survey (SF-36) physical component summary score; SF-36 PFS = short-form quality of life health survey (SF-36) physical functioning score; SRH = self-rated health score.

**TABLE 3 Echocardiographically Determined Left Ventricular Dimensions and Myocardial Function**

| | Treatment Group | | Difference |
|---|---|---|---|
| | HFpEF (N = 250) | HFrEF (N = 626) | HFpEF vs. HFrEF |
| LVEF (%) | | | |
| Baseline, mean ± SD | 58.7 ± 8.8 | 34.9 ± 8.0 | |
| 12 weeks, mean ± SD | 59.0 ± 8.3 | 38.8 ± 9.1 | |
| Mean change (95% CI) | 0.4 (−0.6 to 1.4) | 3.8 (3.3 to 4.4) | −3.5 (−4.6 to −2.3) |
| | p = 0.47 | p < 0.001 | p < 0.001 |
| LVEDD (mm) | | | |
| Baseline, mean ± SD | 47.6 ± 7.5 | 60.3 ± 9.5 | |
| 12 weeks, mean ± SD | 47.9 ± 6.4 | 59.8 ± 8.7 | |
| Mean change (95% CI) | 0.2 (−0.5 to 0.9) | −0.5 (−0.9 to −0.1) | 0.6 (−0.1 to 1.4) |
| | p = 0.52 | p = 0.01 | p = 0.11 |
| LVESD (mm) | | | |
| Baseline, mean ± SD | 31.1 ± 7.1 | 47.8 ± 10.0 | |
| 12 weeks, mean ± SD | 31.4 ± 6.4 | 46.4 ± 9.8 | 1.7 (0.8 to 2.5) |
| Mean change (95% CI) | 0.3 (−0.5 to 1.1) | −1.4 (−1.8 to −0.9) | p < 0.001 |
| | p = 0.46 | p < 0.001 | |
| E/e′ | | | |
| Baseline, mean ± SD | 11.0 ± 5.6 | 12.2 ± 9.3 | |
| 12 weeks, mean ± SD | 10.7 ± 5.2 | 11.9 ± 9.6 | |
| Mean change (95% CI) | −0.3 (−0.9 to 0.3) | −0.3 (−1.0 to 1.4) | 0.0 (−1.2 to 1.1) |
| | p = 0.29 | p = 0.38 | p = 0.95 |
| E/A | | | |
| Baseline, mean ± SD | 0.84 ± 0.32 | 1.13 ± 0.91 | |
| 12 weeks, mean ± SD | 0.91 ± 0.36 | 1.15 ± 0.87 | |
| Mean change (95% CI) | 0.07 (0.03 to 0.11) | 0.01 (−0.05 to 0.08) | 0.04 (−0.07 to 0.15) |
| | p = 0.001 | p = 0.68 | p = 0.44 |
| DT (ms) | | | |
| Baseline, mean ± SD | 219 ± 75 | 219 ± 83 | |
| 12 weeks, mean ± SD | 217 ± 66 | 222 ± 79 | |
| Mean change (95% CI) | -2 (−11 to 8) | 4 (−3 to 10) | −6 (−18 to 5) |
| | p = 0.74 | p = 0.27 | p = 0.29 |
| IVRT (ms) | | | |
| Baseline, mean ± SD | 97.1 ± 27.6 | 114.1 ± 35.3 | |
| 12 weeks, mean ± SD | 102.6 ± 32.6 | 114.0 ± 32.7 | |
| Mean change (95% CI) | 5.6 (0.6 to 10.5) | 0.1 (−3.2 to 3.0) | 4.0 (−1.8 to 9.7) |
| | p = 0.03 | p < 0.94 | p = 0.18 |
| LAVI (ml/m$^2$) | | | |
| Baseline, mean ± SD | 28.0 ± 10.9 | 36.0 ± 14.4 | |
| 12 weeks, mean ± SD | 28.6 ± 10.8 | 35.7 ± 14.3 | |
| Mean change (95% CI) | 0.6 (−0.4 to 1.6) | −0.2 (−0.9 to 0.5) | 0.8 (−0.4 to 2.1) |
| | p = 0.24 | p = 0.53 | p = 0.20 |
| DD grade | | | |
| Baseline, mean ± SD | 1.22 ± 0.55 | 1.61 ± 0.75 | |
| 12 weeks, mean ± SD | 1.18 ± 0.57 | 1.58 ± 0.75 | |
| Mean change (95% CI) | −0.04 (−0.10 to 0.03) | −0.02 (−0.08 to 0.03) | −0.02 (−0.11 to 30.8) |
| | p = 0.28 | p = 0.36 | p = 0.74 |

DD = diastolic dysfunction; DT = deceleration time; E/e′ = E/e′ ratio; EA = E/A ratio; IVRT = isovolumic relaxation time; LAVI = left atrial volume index; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricle end-systolic diameter.

The severity of diastolic dysfunction is related to the functional capacity of HFpEF patients (26); thus an improvement of these properties is considered an appropriate target. Impaired relaxation and diastolic left ventricular filling, which are pathophysiological hallmarks of HFpEF (15), did not improve significantly over the 12-week titration period. The short observation period may account for the lack of diastolic improvement, however as reported previously in small trial of carvedilol in HFpEF with a 6-month

follow-up period we found a modest improvement in the E/A mitral inflow ratio (6).

**CLINICAL EFFECTS: FUNCTIONAL CAPACITY, QoL, AND NT-proBNP.** Despite greater reductions in BP and a similar reduction of HR at 12 weeks, HFpEF patients demonstrated no corresponding improvements in self-reported physical functioning, QoL or 6-minute-walk-distance. Of particular interest, NT-proBNP levels in HFpEF increased over this time period.

Although rate-lowering drugs are thought to improve left ventricular filling by lengthening the diastolic period thus increasing stroke volume and cardiac output, exercise intolerance was found to be more frequent in HFpEF patients treated with BBs in a recent study, possibly due to their negative inotropic properties (27,28). These findings are in concordance with the ELANDD trial, which show worsened exercise capacity in HFpEF patients treated with nebivolol (28). For this and other reasons the If-channel inhibitor ivabradine, which does not affect cardiac inotropy, has been studied in HFpEF. Recent small, placebo-controlled trials of ivabradine have shown improvements in exercise capacity and echocardiographic measures of diastolic dysfunction at rest (DT, E/E′ ratio, IVRT) and during exercise (E/A ratio) (29). However, despite no effect on E/E′ or LAVI in our study, NT-proBNP increased in HFpEF after BB titration, which rather indicates a worsening of left ventricular filling pressure.

Also the presence of the BB-related induction of chronotropic incompetence (CTI) is known to be a major contributor to exercise intolerance in this condition, might have influenced our results. CTI affects 25% to 30% of all HFpEF patients according to certain studies (27,30), whereas others show that the prevalence can be as high as 57% (31). Autonomic dysfunction is a main contributing factor to CTI (32), which is more common in patients receiving BBs (32). However, CTI was not investigated in our trial, wherefore only assumptions on the potential impact of CTI can be made.

**STUDY LIMITATIONS.** The intention of this trial was the comparison of bisoprolol versus carvedilol and therefore there was no placebo group and all the mentioned statements regarding changes from baseline, should be interpreted with caution. Because of the main target of this study to investigate tolerability of BB titration, only well compensated patients were enrolled and results should not be extrapolated towards more advanced HF. Although all echocardiographers were blinded to treatment allocation of the patients, the absence of an echocardiography core lab could potentially interact with the results.

Compared to HFrEF patients, we found no effects on relevant clinical or functional parameters in the HFpEF group. However, studies that would explore the effects of BB on these secondary parameters, would need to be powered for NT-proBNP or E/e' as primary endpoints.

For all the reasons mentioned above, a larger controlled trial with longer treatment and follow-up periods is urgently needed to gather more evidence about the value or harmfulness of BB treatment in HFpEF.

## CONCLUSIONS

Even though there were numerous differences in clinical response between elderly HFpEF and HFrEF patients, overall tolerability of BBs as defined by our protocol, was low, both in HFpEF and HFrEF. Despite BB titration in HFpEF and HFrEF was feasible and safe, titration delays and none severe side effects more often occurred in HFpEF. Nevertheless the need for a bigger outcome trial which would address the question of clinical effectiveness in terms of mortality reduction is evident.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** In most elderly patients with HFpEF, an algorithm-based up-titration of BB to a given target dose is not feasible. Our results suggest that BB titration in HFpEF patients is safe but that it should be carried out with caution because of adverse events and more delays in reaching an appropriate dose. These results, therefore, are of importance for the growing proportion of HFpEF patients within the HF population who are already taking BB for the treatment of comorbidities.

**TRANSLATIONAL OUTLOOK:** A large, prospective, randomized outcome trial is now urgently needed to define the role of BB in HFpEF.

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