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Bisoprolol vs. carvedilol in elderly patients with heart failure: rationale and design of the CIBIS-ELD trial

■ **Abstract** *Background* Chronic heart failure (CHF) is a widespread disease with severe quality of life impairment and a poor prognosis. Beta-blockers are the mainstay of CHF therapy; yet they are under-prescribed and under-dosed in clinical practice. This is particularly evident in elderly patients, which may be due to a fear of side-effects or intolerance. Beta-blockers have further not been adequately tested in patients with diastolic CHF, which is particularly common in elderly patients. Finally, comparative data on the use of different beta-blockers in patients with CHF is scarce. *Aim* To compare the tolerance of bisoprolol and carvedilol in elderly patients with CHF. *Methods* CIBIS-ELD is an investigator-initiated, multi-centre, 1:1 randomised, double-blind, phase III trial comparing bisoprolol and carvedilol in patients ≥ 65 years with systolic or diastolic CHF. Recruitment started in April 2005 and is anticipated to be completed by April 2008 with at least 800 patients enrolled. *Perspective* This is the first large scale head to head beta-blockers trial in an elderly population with CHF. Besides determining which of two standard beta-blockers is best tolerated in elderly patients with systolic or diastolic CHF, we expect to gain further insight into the treatment of the particular population of patients with diastolic CHF.

■ **Key words** chronic heart failure – bisoprolol – carvedilol – tolerance – head-to-head

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Introduction

Chronic heart failure (CHF) is a highly prevalent disease with a profound impact on quality of life and has been found to be as malignant as many common types of cancer [25]. In combination with a rising prevalence and incidence in people over 65 years [12], it is a growing epidemic with a not to be underestimated burden on health care systems.

Despite major advances in the treatment of CHF since the pioneering work on the use of beta-blockers 30 years ago [28], prognosis remains poor for patients with systolic CHF [4]. To date, the use of beta-blockers in CHF has been studied extensively in more than 20,000 patients in randomised controlled trials [9, 23] and according to latest ESC guidelines [26], beta-blockers should be used in symptomatic patients with left ventricular systolic dysfunction and in patients with asymptomatic systolic dysfunction due to ischaemic heart disease. Nevertheless, it appears that beta-blockers remain underused and under-dosed particularly in the elderly, both in primary care [7, 20] as well as tertiary care [13] and in patients managed primarily by cardiologists [15]. It is noteworthy that approximately 20% of patients in a large randomised controlled trial received an suboptimal beta-blocker dose or remained completely untreated [8].

More than half of all hospitalised patients with CHF are older than 75 years but recommendations for the use of beta-blockers in the ESC guidelines are regardless of patients' age despite the fact that elderly have been underrepresented in CHF trials [24] and therefore evidence for the use of beta-blockers in this

often multi-morbid population is not as strong as for their younger counterparts.

Beta-blockers are easily available and have proven cost-effective for CHF therapy [27], but comorbidity, polypharmacy as well as fear of intolerance appear to complicate adherence to effective treatment regimens further [2]. The investigators of one non-randomized trial (COLA II) reported good tolerance of beta-blocker therapy in elderly patients with systolic CHF [14]. However, it has been criticised that in this study, 1/4 of the carvedilol target dose was accepted to assess tolerance [6]. Results of the COMET trial suggest that carvedilol improves survival and is better tolerated than metoprolol tartrate [22].

In view of the above described problems, particularly regarding the insufficient evidence in the senior CHF population and tolerance of beta-blockers in this group, investigators initiated the CIBIS-ELD trial. This is the first large scale randomised double blind trial to compare two beta-blockers in an elderly population with CHF. Bisoprolol and carvedilol are compared for tolerance in CHF patients in three months titration, during which the individual maximally tolerated beta-blocker dose is determined.

Design of the CIBIS-ELD trial

The authors confirm that the investigation conforms to the principles outlined in the Declaration of Helsinki. The national and locally appointed ethics committees have approved the research protocol and written informed consent has been obtained from all subjects.

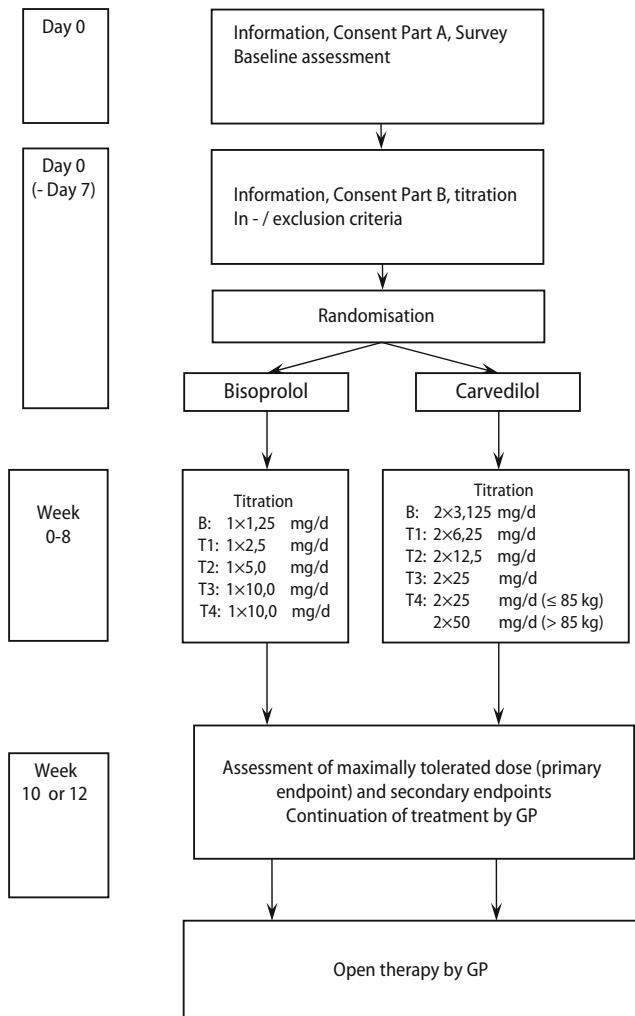


Fig. 1. Flow chart of the CIBIS-ELD trial

CIBIS-ELD is an investigator-initiated multi-centre randomised parallel, double-dummy, double-blind group phase III trial with ≥ 65 -year-old patients with moderate to severe diastolic or systolic chronic HF. The overall aim of the study is to compare the tolerance of bisoprolol and carvedilol in elderly patients with CHF. The trial is performed in 55 centres in four countries (Germany, Serbia, Montenegro and Slovenia). Fig. 1 shows details of the study flow. Eligible patients are randomised in a 1:1 fashion to receive either bisoprolol or carvedilol; bisoprolol with a 10 mg/d target dose and carvedilol with a target dose of 25 mg b.i.d (patients > 85 kg; 50 mg b.i.d.) (see Fig. 1).

■ Role of the funding sources and conflict of interest

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01GI0205). Some of the authors have received honoraria for speaking on aspects of cardiology by different pharmaceutical companies. No member of the committees is an employee of the pharmaceutical industry nor is paid for attending at meetings or for consulting relating to this trial. Merck KGaA gave an unrestricted grant to support the trial without any rights to influence trial design, data collection, data analysis or publication and will not interfere with the investigators intellectual property rights. The study was initiated and coordinated by investigators of the subproject "multicenter trials" of the Competence Network Heart Failure and is scientifically led by a steering committee consisting of independent researchers. This committee has full responsibility for the study protocol and publications about the study. Sponsor of the trial according to ICH-GCP was Charité - Universitätsmedizin Berlin university hospital. Producer of study medication was the pharmacy of Charité - Universitätsmedizin Berlin. Statistical Analysis is performed by the Coordination Centre for Clinical trials in Leipzig, which is publicly funded as well.

■ Patient selection

Inclusion and exclusion criteria are listed in Table 1. Patients are identified by their General Practitioners (GPs) or cardiologists, contacted by them and referred to the trial sites for initial assessment. Since April 2005, 670 patients have entered the study. Recruitment is anticipated to be completed by April 2008 with at least 800 patients enrolled (see Table 1).

■ Up-titration

The internationally recommended target dose for bisoprolol is 10 mg o.d., for carvedilol at 25 and 50 mg b.i.d. for patients > 85 kg. To monitor whether these doses achieve a comparable degree of beta-blockade, spiroergometry is performed on a subgroup of 60 patients. The beta-blocker dose is increased to the target dose at fortnightly intervals. Dose titration differs according to the previous medication schedule of each patient. After the initial dose, therapy is commenced with either dose increment 1 or 2 (see Fig. 2). Patients > 85 kg receive dose increment five after six or eight weeks. This increment indicates an increase in dosage in the carvedilol group only; in the bisoprolol group the increment is only technically treated like a dose increase for blinding purposes. The highest tolerated dose increment is maintained until the primary endpoint is reached (final visit in week 10 or 12). In case of medication intolerance, patients are instructed not to reduce the dose without medical advice. The trial physician determines whether the intolerance is

Table 1 Key inclusion and exclusion criteria for patients in the CIBIS-ELD trial

Inclusion criteria	<ul style="list-style-type: none"> • Age \geq 65 years • Current diagnosis of HF with symptoms consistent with NYHA II or above • Left ventricular ejection fraction (LVEF) \leq 45 % (documented by echocardiography, levocardiography or magnetic resonance imaging (MRI)) and/or echocardiographic parameters of diastolic dysfunction Stage \geq I • Chronic heart failure was stable for the previous two weeks • Written informed consent
Exclusion criteria <i>Major</i>	<ul style="list-style-type: none"> • Previously prescribed medical HF therapy was changed within the last two weeks before the study • Intake of beta-blockers for longer than 14 days within the last three months in a dose which is more than $\frac{1}{4}$ of the recommended daily intake. • Other systemically administered beta-blockers except for the study medication during participation • Acute or de-compensated HF • Cardiogenic shock • Acute pulmonary embolism • Obstructive or restrictive cardiomyopathy • Severe pulmonary dysfunction or severe asthma as determined by the responsible investigator • Uncontrolled hypertension (systolic BP $>$ 190 mmHg or diastolic BP $>$110 mmHg) • Endocarditis and myocarditis • History of heart transplant surgery within two months prior to the study or planned • Uncontrolled hypo – or hyperthyroidism • Clinically relevant abnormal lab results • Known alcohol or drug abuse • Participation in another clinical study within the last 30 days • Legal incapacity or reduced legal capacity
<i>Relating to cardiovascular disease</i>	<ul style="list-style-type: none"> • Known hypersensitivity to bisoprolol or carvedilol • Advanced peripheral vascular disease and/ or Raynaud's disease • Hypotension • Bradycardia with less than 55 bpm prior to commencement of the therapy • First or second degree sinoatrial or atrioventricular block (without pacemaker) or known sick sinus syndrome • Strict fasting • Current desensitisation therapy • Known or suspected pheochromocytoma
<i>Contraindications to beta-blocker therapy</i>	<ul style="list-style-type: none"> • Inotropic substances with the exception of digoxin • Ergotamine derivates • Calcium-channel-blockers of the phenylalkylamine type • Clonidine • Rifampicin • Antiarrhythmic medications except amiodarone • Monoamine oxidase inhibitors (except MAO-B inhibitors) • α1-Antagonists or α2-Agonists

avoidable by changing the concomitant medication. Is this not the case, the dose is reduced by one increment. The medication is then not further up-titrated to minimise the risk of non-adherence by repeatedly provoking symptoms of intolerance. Is up-titration delayed (e.g. by adjusting concomitant medication) but the dose not reduced, GPs are encouraged to up-titrate to target doses during subsequent treatment, even if it was not attained during the study treatment phase. Due to the exacerbation of sympathetic activity, the beta-blocker is not to be abruptly discontinued after the 12-week therapy phase. GPs are advised to continue prescribing the beta-blocker as standard treatment after study completion.

■ Endpoints

Primary endpoint

The primary endpoint of CIBIS-ELD is tolerance (yes/no) of the study medication target dose as per cardiology guidelines. Tolerance (=yes) is defined when the target dose was achieved and the study medication dose was not reduced during the titration phase. It is irrelevant whether unscheduled titration-visits took place if the titration target was not affected. Further, the patient is taking the respective target dose at the end of the study and has done so for at least ten consecutive days.

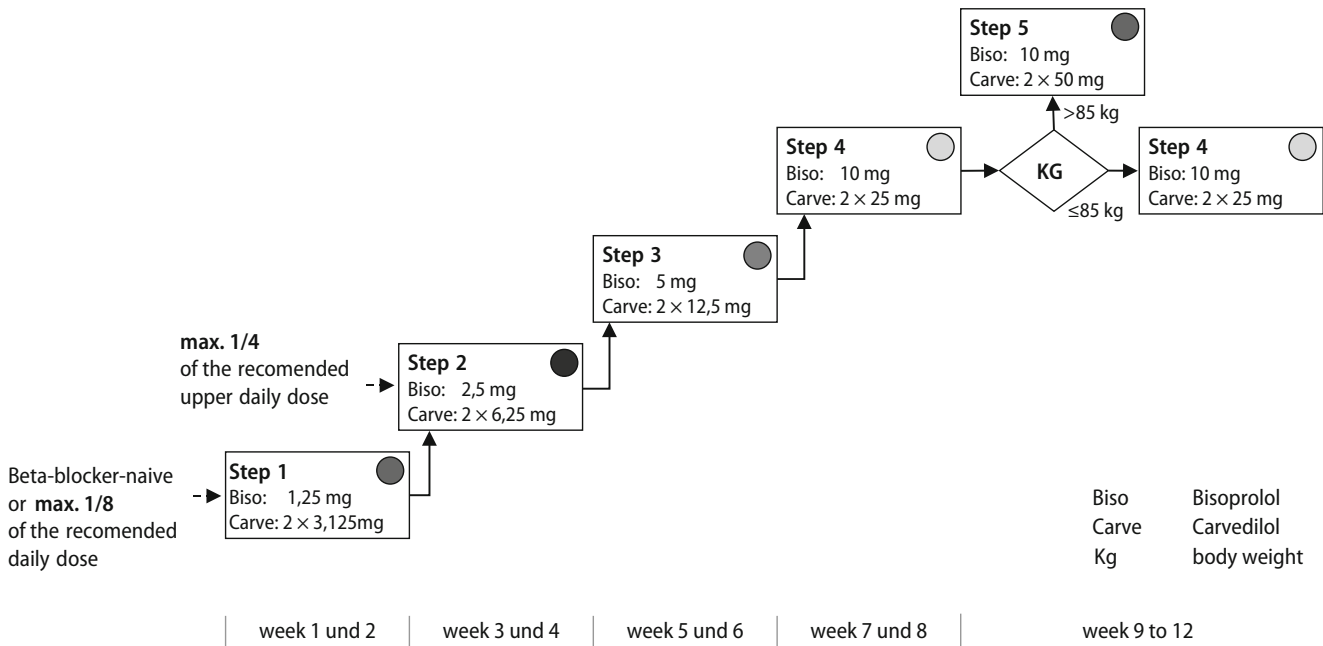


Fig. 2. Titration of beta-blockers

Secondary endpoints

- Time to treatment failure (TTF)
- Dose increment attained (% of target dose) for long term treatment
- Number of adverse events (AE) or serious adverse events (SAE) in total as well as itemised according to their relationship to dose reduction/ discontinuation of treatment
- NYHA class
- 6-min walk test
- Echocardiography (left ventricular dimensions, wall thickness, EF according to Simpson or visually determined by an experienced echocardiographer; diastolic function according to ASE including mitral valve Doppler, tissue Doppler, flow propagation time, and pulmonary vein Doppler) before and after beta-blocker titration.
- Quality of life, depression and physical well-being (measured with the following assessment instruments: SF-36, PHQ-D and FEW-16)
- Heart rate at rest and under stress
- Plasma- Brain Natriuretic Peptide (NT-proBNP and BNP) concentration
- Alteration of total cholesterol, HDL, LDL and triglycerides plasma concentration
- Investigation of medical treatment parameters at baseline:

Frequency and dose of concomitant medication including beta-blockers, diuretics, ACE-inhibitors or angiotensin receptor antagonists
Qualitative and quantitative survey of other therapeutic non-pharmacological actions

- Lung function (vital capacity (VC), forced expiratory volume in the first second (FEV1), peak expiratory flow (PEF) and maximal mid-expiratory flow (MEF50))
- Hospitalisations
- Days alive and days out of hospital

■ Laboratory parameters

Blood samples are taken at baseline and during follow up at every visit in order to look for a correlation between both NT-pro BNP and BNP and the influence of beta-blocker therapy. In selected centres these analyses are done at every titration visit to correlate titration performance and BNP/ NT-pro BNP levels. Further blood sample analysis includes haemoglobin, erythrocytes, leucocytes and thrombocytes, sodium, potassium and creatinine serum levels, uric acid, total cholesterol, high and low density lipoprotein and triglycerides as well as CYP P450 2D6 polymorphism testing. In addition, blood samples (1x serology, 2x complete blood count) are taken for the central database from patients who consented to DNA analysis.

■ Statistical hypothesis and sample size considerations

The major hypothesis of the CIBIS-ELD trial is that the target dose can be reached more often with bisoprolol than with carvedilol. In order to present the difference in the case of opposite direction, the null-hypothesis postulates equality and the alternative hypothesis a difference in any of the two directions. It is estimated that 50% of the patients in the inferior subgroup will tolerate the target dose. Relevant superiority of the other subgroup is ascertained when 60% of patients tolerate the target dose. For the primary endpoint, the Accurate Mann–Whitney U-test will be applied for biometrical analysis. Secondary endpoints: Mann–Whitney contrast with censorship (days alive out of hospital), analysis of variance (metric endpoints), stratified Odds Ratios with Cochrane-Mantel-Haenszel with Breslow-Day-Homogeneity-Test (binary endpoints) and Kaplan Meier (time to event). Exploratory: multiple regression analyses. Guided by power analysis for sample size considerations for a power of 90%, a sample size of 1,040 was determined to be optimal for the purpose of this study. A power of 80% is achieved with 760 patients.

Subgroup analysis

The study will stratify for patients with preserved and impaired LVEF ($\leq 45\%$), and the findings in these two subgroups will be a secondary endpoint. Further, patients with atrial fibrillation will be analysed as a subgroup to determine potential differences in the effect of beta-blockers in this group.

Discussion

There is an ongoing discussion in clinical practice as to which beta-blocker is advantageous because of their differences in pharmacodynamics and pharmacokinetics. Bisoprolol and metoprolol succinate as selective beta-1-receptor-blockers, and carvedilol as an alpha-1-, beta-1- and beta-2-receptor-blocker have shown to be effective in reducing the risk of all cause mortality in patients with CHF by approximately 35% with a supporting ACE-inhibitors therapy, whereas results for nebivolol were partly disappointing (non-significant 12% fall in all cause mortality) [5, 10, 17, 19]. Bisoprolol shows the strongest beta-1-selectivity of all beta-blockers approved for CHF therapy. The strong selectivity might be a possible benefit for CHF patients with accompanying chronic obstructive pulmonary disease [16]. On the other hand it has been discussed whether

the anti-adrenergic effects of carvedilol in addition to beta-1-blockade prolongs survival [18].

The effectiveness of beta-blockers specifically in elderly CHF patients has been investigated prospectively in two major trials: In CIBIS III bisoprolol, when compared with enalapril, reduced overall mortality by 28% (secondary endpoint) in patients ≥ 65 years after 6 months mono-therapy [29]. In SENIORS, nebivolol reduced the risk for the combined endpoint of all cause mortality or cardiovascular hospital admission in heart failure (HF) patients (HR 0.86, 95% CI 0.74–0.99, $P = 0.039$) [10]. Although the benefit of nebivolol appeared to be less in patients > 75 years, there was no significant interaction between age as continuous or categorical variable and the effect of nebivolol.

Beta-blocker therapy is approved for patients with HF due to severe systolic dysfunction only [3]. Patients with an LVEF $> 35\%$ have been excluded from almost every beta-blocker trial. Nevertheless, CHF with normal or mildly impaired systolic function has received much attention over the last years. A recent trial showed that isolated diastolic dysfunction is present in more than 40% of patients with CHF [4]. More than half of CHF patients have a preserved EF—their mortality rate is as high as in systolic CHF. So far there is no proven treatment for these patients. There is some evidence for AT1-Blockers from the CHARM-Preserved trial, which showed a non-significant reduction in the composite endpoint of cardiovascular death or HF hospitalisation with candesartan [21]. The benefit of digoxin could not be shown in a subgroup analysis of the DIG trial [1]. An objective measurement of diastolic function was not performed in these trials, though. Therefore results do not permit any conclusion about the treatment of diastolic heart failure. From a pathophysiologic point of view it is worth asking for the role of beta-blockers in the treatment of diastolic HF as they prolong the diastole and energy is preserved for the relaxation process. In the SENIORS trial, nebivolol reduced the composite of all-cause mortality and cardiovascular hospital admission, regardless of EF, in patients ≥ 70 -years-old [10]. More than 700 Patients had an EF $\geq 35\%$. Although an improvement in EF and a reduction of ventricular size could be shown in patients with systolic HF, the mechanism of benefit in the patients with preserved HF remained unclear. No changes of diastolic function assessed by pulsed mitral valve Doppler-echocardiography could be found. Tissue Doppler was not performed.

The authors argue that elderly patients and those with preserved diastolic function should not be excluded from beta-blocker trials any longer, as a high percentage of HF patients have a preserved EF and especially the elderly are affected. It appears mandatory to evaluate the possible mechanisms leading to

clinical improvement by thorough assessment of diastolic function. This can be achieved by tissue Doppler, which is one of the examinations performed in the CIBIS-ELD trial.

Further trials are needed to evaluate the effect of beta-blockers on mortality concentrating on patients with CHF and preserved EF or diastolic heart failure. The J-DHF trial, which assesses the effects of beta-blockers in diastolic heart failure, is expected to finish in 2009 [11]. The results of CIBIS-ELD will be helpful in identifying the beta-blocker with the best tolerance in elderly patients with CHF.

Perspective

Beta-blockers are standard therapy in heart failure, though they are still under-prescribed. Good tolerance of beta-blockers is a key factor in successfully initiating therapy, reaching the target dose and establishing it for long term therapy. Elderly patients were under-represented in almost every CHF-trial, even though they present the largest group of CHF patients. They are thought to be particularly affected by intolerance to beta-blocker therapy. CIBIS-ELD is the first trial comparing the tolerance of two commonly used beta-blockers in heart failure patients as the primary outcome measure. The beta-blocker identified as being better tolerated should be used as standard for the therapy of elderly CHF patients. In addition, this study will provide important insights into the therapy of patients with diastolic heart failure, and results will need to be considered in the further development of guidelines.

Committees

■ Steering committee

Members are Prof. Dr. Hans-Jürgen Becker (Frankfurt/M.), Dr. Hans-Dirk Düngen (Berlin), Prof. Dr. Thomas Eschenhagen (Hamburg), PD Dr. Roland Hardt (Trier), Prof. Dr. Friedrich Luft (Berlin), Prof. Dr. Bernhard Rauch (Ludwigshafen), Prof. Dr. Elisabeth Steinhagen-Thiessen (Berlin), Prof. Dr. Ruth Strasser (Dresden), Prof. Dr. Finn Waagstein (Göteborg).

The Committee advises on the scientific direction of the trial, protocol design, scientific policies, monitoring of trial progress, sub-studies, co-operation with the Data and Safety Monitoring Committee, as well as on the reporting and publication of trial

results. The Committee is scheduled to meet once per year during the trial, and is informed regarding trial progress, protocol adherence and other aspects as necessary. A decision on premature termination of the trial will be made by the steering committee after consultation of the funding organisation, the external advisory board, the DMSC, and the biometrician.

■ Independent data and safety monitoring committee (IDSMC)

Members are Dr. Ulrike Bauer (Berlin), Dr. Stephan Beckmann (Berlin) and Dr. Jürgen Waigand (Berlin). The principal responsibility of the IDSMC is protecting the safety of patients in the trial.

■ External advisory board

Members are Univ.-Prof. Dr. Georg Ertl (Würzburg), Herr Prof. Dr. Ferenc Follath (Zürich) and Prof. Dr. Thomas Meinertz (Hamburg).

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