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EDITORIAL

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# Heart failure, aging and beta-blockers: the need for more data on tolerability and efficacy

Despite significant progress in its management during the last twenty years, contemporary large-scale trials, in both *acute* [13] and in *chronic* [8] heart failure (HF) show that this disorder is still associated with a high morbidity and mortality. Adherence to current guidelines is important as this improves outcome [9]. However, adherence is often far from optimal in HF patients [16], and compliance to other components of disease management, such as regular weighing and keeping a diet, is problematic especially in the elderly [19]. HF is also accompanied by many comorbidities in the elderly, such as diabetes, hypertension, atrial fibrillation, renal impairment, but also pulmonary disease and previous cancer, with exposure to (cardiotoxic) chemotherapy [7, 14, 18]. Because of the presence of these comorbidities, but also for other reasons, physicians may be inclined to withhold effective therapy from elderly patients, or use lower than optimal doses in them for assumed side-effects [11].

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Editorial to: "Bisoprolol vs carvedilol in elderly patients with heart failure: Rationale and design of the CIBIS-ELD".

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For all these reasons, HF is a true problem in the elderly, but in recent years, this has been increasingly recognized by the scientific community and by industry. As a result, the mean age of patients in HF trials has gradually increased in the last 10–20 years (for references see [1] and body text) (Fig. 1).

In this issue of the Journal, Düngen and colleagues present the design and rationale of the CIBIS-ELD trial, which is currently enrolling 780 elderly patients (≥ 65 years) with chronic HF [3]. CIBIS-ELD is a randomized, double blind, phase III trial, which will primarily compare the tolerability of bisoprolol with carvedilol, as measured by the number of patients that will tolerate target doses. Secondary endpoints will include echocardiography, laboratory assessment, time to treatment failure and adverse events, but not hard endpoints, such as death or hospitalisation.

Beta-blockers in elderly patients with HF have been investigated in a number of studies. The previous CIBIS (-III) study [21] was also conducted in patients >65 years, and compared first-line beta-blocker therapy with first-line ACE inhibitor treatment, followed by their combination; there was no significant different in outcome between the two arms. The SENIORS study [5] (which enrolled patients ≥ 70 years) was the largest study in elderly patients so far, and in a subanalysis, Dobre et al. recently reported the tolerability and efficacy of the beta-blocker nebivolol [2]. In that analysis 67% of all patients were able to tolerate the target dose of nebivolol. Importantly, a significant reduction in all-cause mortality or cardiovascular hospitalization was only reported in patients who were able to tolerate at least a medium-high dose, an effect that was not observed in patients who only tolerated the lower doses. Although this was a post-hoc subanalysis, another intriguing observation was that patients who could not tolerate any dose

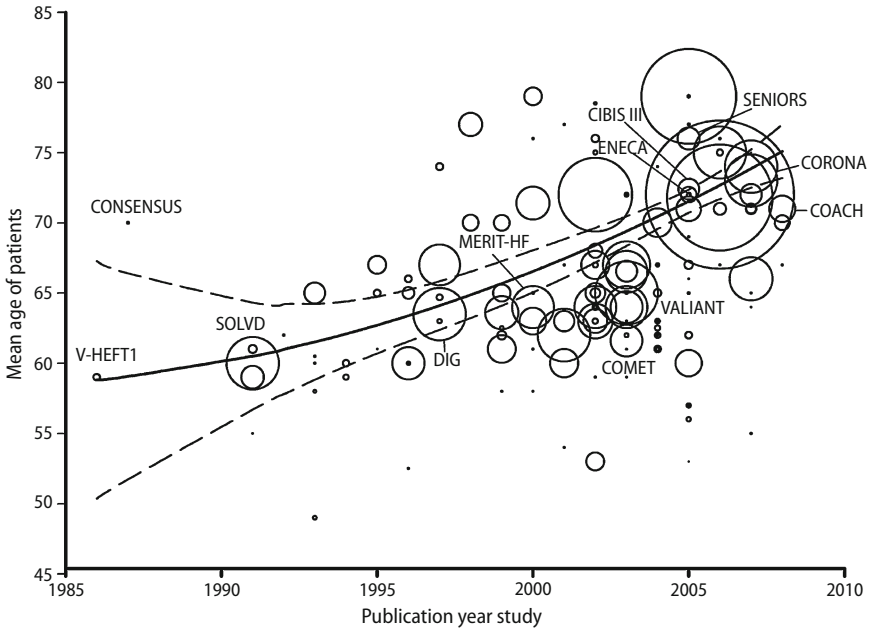


**Fig. 1** Relationship between year of publication of study and mean age of included patient. Shown are HF studies, including registries, clinical trials and observational cohort studies in the period 1985–2008. Included are acute as well as chronic heart failure studies, in combination with studies that included left ventricular dysfunction after myocardial infarction. Mean age is taken, irrespective of inclusion or exclusion criteria. Size of circles is relative to the study size. Some large and key trials are highlighted. The *solid line* represents the fitted regression line, weighted for study size. *Dashed lines* represent 95% confidence intervals

of the beta-blocker dose actually had a substantially increased risk for mortality. Remarkably, patients who could only tolerate low doses had almost comparable demographic characteristics, although they were slightly older, had lower blood pressure and worse renal function. Another trial, ENECA [4], included specifically patients with HF and ≥ 65 years, and investigated the effect of nebivolol on quality of life. In this trial, as many as 64% of patients were able to receive the target dose of nebivolol. Recently, another comparative study of beta-blockers in elderly HF was reported in this journal, whereby a different effect on insulin resistance between selective and non-selective beta-blockade was reported [10]. The CIBIS-ELD [3] study will provide more data on the tolerance of beta-blockade in the elderly, and will also allow a comparison between carvedilol and bisoprolol.

As discussed above, the presence of comorbidities has been associated with more conservative therapy and lower use of evidence based therapy [7, 11, 18]. Renal impairment, an important comorbidity in HF in general, but particularly in the elderly, is an important factor in this respect. Especially renin-angiotensin inhibitory medication, such as angiotensin converting enzyme inhibitors (ACEi), are frequently discontinued or not initiated when renal impairment is present or develops. Although renal function in patients with HF may initially slightly deteriorate, ACEi may also preserve renal function after myocardial damage, as was shown after (large) myocardial infarction [6]. Interestingly, beta-blocker prescription rates have also been shown to be decreased in patients with renal impairment in HF [12], even though renal impairment generally does not occur after institution of beta-blocker therapy. In the COMET trial, the occurrence of renal impairment was low, and was similar between carvedilol and metoprolol [17]. Presence of renal function at baseline may therefore be an important factor in the tolerance of beta-blocker therapy in CIBIS-ELD as well. In this respect, it will also be interesting to study the influence of baseline ACEi or angiotensin converting enzyme (ARB) therapy and their doses (are these drugs required in CIBIS-ELD at baseline and are there dose-requirements?) on whether beta-blockade is tolerated since it has been suggested that beta-blockers may possibly be less well-tolerated when there is no ACEi background therapy [21]. Vice versa, one could speculate that in HF patients with renal impairment who receive lower dosages of ACEi or ARB, there may less hypotension and more opportunity to uptitrate the beta-blocker.

Another important comorbidity in elderly patients with HF is atrial fibrillation [15]. In the recent CORONA trial (40% > 75 years), almost 25% had atrial fibrillation, but only patients with systolic dysfunction were studied [8]. In the SENIORS study, 35% had atrial fibrillation, but SENIORS also examined patients with HF and normal systolic function [5]. Beta-blockers may reduce the incidence of new-onset atrial fibrillation, as was observed in a subgroup analysis of the MERIT-HF study [20]. Tolerability of beta-blockers in patients with atrial fibrillation was slightly worse compared to those in sinus rhythm (16% Vs. 12% discontinuation) in MERIT-HF. It will be important to examine potential differences between

the two beta-blockers in CIBIS-ELD with regard to new onset atrial fibrillation, and of course to relate tolerability to the drugs to baseline presence of atrial fibrillation.

An interesting part of the CIBIS-ELD trial will be the difference in tolerability and efficacy of both carvedilol and bisoprolol in patients with preserved and reduced left ventricular ejection fraction. Most CHF trials that investigated the efficacy of beta-blockers have excluded patients with LVEF > 40%, while one third of patients in the SENIORS trial had a preserved LVEF [5].

In conclusion, CIBIS-ELD trial will provide important data on tolerability and efficacy of beta-blockers (carvedilol and bisoprolol) in the growing population of elderly patients with HF, and the results are eagerly awaited.

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