Reaching betablockers target dose in elderly patients with chronic heart failure

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ABSTRACT

Despite overwhelming evidence of clinical efficacy, the use and dose of betablockers in elderly patients with chronic heart failure are often suboptimal. The underuse and undertreatment with betablockers in elderly may reflect true intolerability in older patients with comorbidities and with increased risk of side effects. Different betablockers may have different side-effects because of different pharmacological properties. Difference between betablockers use in the clinical practice and clinical trials might be explained by the fact that the major large-scale betablockers trials enrolled younger patients. The highest tolerability in elderly heart failure patients was reported for nebivolol. The tolerability of nebivolol in older patients might be explained by its unique pharmacological properties.

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Introduction

Chronic heart failure is an epidemic with high mortality, morbidity and significant quality of life impairment. Patients with stable chronic heart failure (CHF) from ischemic and non-ischemic etiology, reduced left ventricular ejection fraction (LVEF) and mild to severe symptoms should be treated with betablockers unless there is a contraindication. Betablockers are also recommended in patients with chronic heart failure and preserved LVEF [1]. Several, large, prospective, randomized, placebo controlled trials showed the clinical benefit of betablockers in patients with CHF and systolic left ventricular dysfunction with consistent mortality and morbidity reduction [2–7]. It was uncertain whether the benefits of betablockers (BBs) extended to older patients because previous BB trials included CHF patients who were younger (less than 80 years). Majority of patients with CHF in the community are elderly, with almost half being 80 years and older [8]. The underuse and underdose of BBs in the elderly may reflect true intolerability in older patients with comorbidities and with increased risk of side effects. Evidence of BBs use in elderly heart failure patients is limited.

Evidence of betablocker use in elderly heart failure patients

Tolerability of betablockers in older patients with chronic heart failure (CHF) was an objective of several studies. The second Carvedilol Open-Label Assessment (COLA II) aimed to evaluate the tolerability of BBs in 1030 subjects with chronic heart failure (CHF) with age greater than 70 years [9]. Patients with systolic CHF with left ventricular ejection fraction (LVEF <40%) and NYHA classes II–IV were included in the study. Tolerability of carvedilol was defined as dose ≥6.25 mg twice daily at the 6-month follow-up. Tolerability of carvedilol was high: 80% of patients enrolled in COLA II tolerated carvedilol and the tolerability was independent of gender and the presence of ischemic etiology of heart failure. Difference in tolerability between age ranges (70–75, >75–80 and >80) and other variables was tested by analysis of variance. Advanced age and the presence of obstructive airway disease were associated with lower tolerability while the presence of diabetes mellitus appeared to be a predictor of better tolerability. This surprising result was explained by the lower percentage of extreme elderly patients with diabetes receiving carvedilol. Titration of carvedilol to the target recommended dose was not the main objective of the COLA II study. The achieved dose was 29–33 mg per day with age difference: patients aged 70–75 achieved mean dose 33.3 mg per day whereas patients older than 80 years achieved mean dose 29.3 mg per day. There is limited information about the titration of betablockers to target dose in elderly CHF patients too.

Titrations of betablocker to target in elderly heart failure patients

Titration to target dose of different betablockers was the aim of the CIBIS-ELD Study [10]. The objective of the CIBIS-ELD trial (the Cardiac Insufficiency Bisoprolol Study in Elderly) was to evaluate the difference in achieving the target dose of carvedilol and bisoprolol. This was a randomized, double-blind trial with the primary endpoint tolerability of betablockers when used at recommended target doses in patients 65 years or older with systolic CHF, LVEF ≤45% and NYHA class ≥II, betablocker naïve or on less than 25% of the recommended target. The patients were seen every 2 weeks with a doubling of previous dose, the target dose of bisoprolol was 10 mg daily and for carvedilol 25 mg twice daily within 6 weeks with a final visit at 10 weeks. For patients weighing more than 85 kg, the target dose for carvedilol was 50 mg twice daily within 8 weeks and final visit at 12 weeks. The tolerability was defined as reaching the target dose. Secondary endpoints were change in NYHA class, heart rate, blood pressure, LVEF and parameters of diastolic function, distance in 6 min walk test, forced expiratory volume (one second – FEV1) and quality of life evaluation. The total number of 883 patients was randomized. In total, 75.7% of the subjects with mean age 72.8 years did not reach the primary endpoint with no difference between the bisoprolol group and the carvedilol group. Bradycardia was the most common cause of titration failure in the bisoprolol group whereas pulmonary adverse events were the most common reason for titration failure in the carvedilol group. There was no significant difference between the two groups in the incidence of worsening heart failure, hospital admission, hypotension and mortality. Only decrease in hemoglobin level was seen in the carvedilol group, mainly in patients’ betablocker naïve at randomization. Blood pressure decreased in both groups, NYHA, LVEF and 6 min walk test distance improved with no difference between bisoprolol and carvedilol groups. The CIBIS-ELD study showed that only 24% (resp. 25%) of the elderly heart failure subjects are able to reach target betablocker dose after 12 weeks titration (with dose doubling every 2 weeks as recommended in the ESC guidelines). Multivariate analysis showed that higher heart rate at baseline, BMI >25 kg/m and BB pre-treatment dose 25% were predictors of tolerability. Older age and NYHA III–IV classes were associated with not achieving the target dose. Different incidences of bradycardic events (higher in the bisoprolol group) and pulmonary events (higher in the carvedilol group) in the elderly patients with CHF in the CIBIS-ELD trial cohort might be explained by the different pharmacological properties of betablockers. Bisoprolol is the selective β1 - adrenoreceptor blocker, carvedilol is the non-selective α1-β1, β2 adrenoreceptor blocker. The CIBIS-ELD trial showed that titration of BBs in elderly heart failure patients is difficult. The proportion of patients achieving target doses should be higher than in the CIBIS-ELD trial when comparing data from other clinical trials with similar subjects (Table 1).

As shown in the table, the proportion of patients reaching target bisoprolol dose in the Cardiac Insufficiency Bisoprolol Study II (CIBIS II trial) was higher than that in the CIBIS-ELD study (43% vs. 24%, but lower than that on placebo – 61%). However, the mean age of the subjects in CIBIS II study was lower than that in the CIBIS-ELD cohort (61 years vs. 73 years). Titration scheme was somewhat different in these two trials: doubling of the dose every 2 weeks (1.25 mg of bisoprolol or placebo as a starting dose) in CIBIS-ELD, and increasing of
dose every week from 1.25 mg to 2.5, 3.75, 5.0, 7.5 and 10 mg in CIBIS II [3]. Not reaching the target bisoprolol dose was age dependent in the CIBIS II trial too. Similarly, higher proportion of patients were achieving target carvedilol dose in the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) than that in the CIBIS-ELD trial (65% vs. 25%) [5]. The COPERNICUS cohort was younger (mean age was 63 years) and patients were receiving an initial dose of 3.125 mg of carvedilol or placebo twice daily for 2 weeks with doubling the dose every 2 weeks with target dose 25 mg of carvedilol or placebo twice daily. The most important difference between COPERNICUS and CIBIS-ELD trials patients populations is that in COPERNICUS study total 100% of subjects were in NYHA class IV at baseline. In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), large proportions of subjects were reaching target metoprolol dose (64% on metoprolol but 82% on placebo), mean age of the cohort being 64 years. The starting dose was 25 mg of metoprolol CR/XL or placebo once daily (12.5 mg in NYHA III or IV) with doubling the dose every 2 weeks to reach target 200 mg once daily [4]. High tolerability of betablocker therapy in elderly heart failure patients was reported in the Study of Effects of Nebivolol Intervention and Outcomes and Rehospitalization in Senior with Heart Failure (The SENIORS Study) [6]. Nebivolol is a beta₁-selective adrenoceptor blocker with vasodilatory effect not dependent of alpha₁-receptor blockade [11]. Efficacy, tolerability and safety of nebivolol were tested in several studies. In the Efficacy of Nebivolol in the treatment of Elderly patients with chronic heart failure as add-on therapy (the ENECA) study 260 CHF patients older than 65 years were randomized to nebivolol or placebo [12]. The primary objective of the ENECA study was the change of LV EF, the secondary objective included other efficacy endpoints and tolerability and safety of nebivolol. Titration of nebivolol or placebo started with 1.25 mg and the dose was doubled every 2 weeks until the highest tolerated dose was reached or a maximum of 10 mg after 8 weeks (daily dose). The LVEF improved significantly more in the nebivolol group than in the placebo group (p=0.027) and the relative improvement was higher in the neboirol group than in the placebo group (p=0.008) as assessed by echocardiography. Nebivolol was well tolerated in the elderly patients with chronic heart failure. Severe adverse events were less frequent in the nebivolol group than in the placebo group (12% vs. 15%). Drug-related adverse events were more frequent in the nebivolol group and included bradycardia events, hypotension and dizziness. Worsening heart failure, ventricular tachycardia and new onset atrial fibrillation were less frequent in the nebivolol group; the difference was not statistically significant.

### Table 1 - Proportion of patients achieving target beta-blockers dose in heart failure trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Mean age</th>
<th>≥ 70 age</th>
<th>% on target BB</th>
<th>% on target placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENIORS</td>
<td>2128</td>
<td>76</td>
<td>2128</td>
<td>Nebivolol 68</td>
<td>80</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>3991</td>
<td>64</td>
<td>1245</td>
<td>Metoprolol 64</td>
<td>82</td>
</tr>
<tr>
<td>CIBIS-II</td>
<td>2647</td>
<td>61</td>
<td>539</td>
<td>Bisoprolol 43</td>
<td>61</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>2289</td>
<td>63</td>
<td>NA</td>
<td>Carvedilol 65</td>
<td>78</td>
</tr>
<tr>
<td>CIBIS-ELD</td>
<td>883</td>
<td>73</td>
<td>NA</td>
<td>Nebivolol 25</td>
<td>NA</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td></td>
<td></td>
<td></td>
<td>Metoprolol 24</td>
<td>NA</td>
</tr>
</tbody>
</table>

#### Effect of nebivolol on mortality in elderly patients with chronic heart failure

The SENIORS study aimed to assess the effects of nebivolol in patients 70 years and older [6]. The primary objective was to determine the effect of nebivolol on mortality and morbidity regardless of ejection fraction. The study was a parallel group, randomized, double-blind, multicentre, international trial. Patients 70 years and older with a history of CHF and one of the following features: documented hospital admission within the last 12 months before entry to the study or LV EF ≤ 35% within previous 6 months were included in the trial. Stable medical therapy more than 6 weeks and no change in the cardiovascular therapy within 2 weeks before randomization were required in all subjects. Patients were randomly assigned to nebivolol or placebo on a 1:1 basis. The initial dose was 1.25 mg with increasing the dose when tolerated to 2.5 mg and then to 5 mg every 1–2 weeks with a target dose of 10 mg over 16 weeks as a maximum. The primary objective of the SENIORS study was the composite of all cause mortality and cardiovascular hospital admission. Secondary endpoints included all cause mortality, all cause hospital admissions, cardiovascular mortality, and others. A total of 2135 patients were included in the study (1067 in the nebivolol group and 1061 in the placebo group were available for analysis) and followed from September 2000 to November 2003. Mean age of the SENIORS trial population was 76.1 years, NYHA classes II and III were most common (56% and 39%, respectively) at baseline, and mean LV EF was 36% (median 33% in the nebivolol group and 34% in the placebo group), 64% of subjects had LVEF ≤ 35% and 36% of patients had LV EF > 35%. From total 2128 patients at the end of the study, of the 65% subjects in the nebivolol group were on drug and of 64.2% patients in placebo group were on drug. The dose ≥ 5 mg was achieved in 80% of patients in the nebivolol group and in 87% of subjects in the placebo group. The target betablocker dose 10 mg daily was used in 68% of patients in the nebivolol group (68% of 65% on nebivolol at the end of the study) and 80% in the placebo group (80% of 64.2% on placebo at the end of the study). The effect of nebivolol on the primary endpoint was significant. The relative risk of death or cardiovascular hospital admission was reduced with nebivolol by 14% (hazard ratio 0.86, p=0.039). There was no statistical significant effect of nebivolol on all cause mortality and cardiovascular hospital admissions as an individual endpoint observed in the SENIORS study. In conclusion, the SENIORS study showed a positive effect of nebivolol on the reduction of the composite endpoint mortality and hospital admission.
admission for cardiovascular reasons in older patients with CHF. One-third of the SENIORS population had LV EF > 35%, 50% were 75 years and older and 37% of patients were women. Beneficial effect of nebivolol started 6 months after the beginning of treatment, the study medication was extremely well tolerated with 68% of patients achieving target betablocker dose [13]. The high tolerability of nebivolol in the elderly patients with chronic heart failure might be explained by its unique pharmacological properties.

Clinical pharmacology of nebivolol

Based on the results of the large randomized, placebo-controlled interventional mortality trials, European guidelines for the management of chronic heart failure recommends four: carvedilol, bisoprolol, metoprolol succinate (controlled released) and nebivolol. Carvedilol is the non-selective \( \alpha_2-\beta_1-\beta_2 \) adrenoreceptor blocker betablockers with antiproliferative and antioxidant properties. Metoprolol succinate CR/XL is the selective \( \beta_1 \)-adrenoreceptor blocker without important additional properties. Bisoprolol is the selective \( \beta_1 \)-adrenoreceptor blocker with higher selectivity to \( \beta_1 \)-receptor than metoprolol. Higher selectivity of bisoprolol might explain more bradycardia events as reported in the CIBIS-ELD study. Nebivolol is a beta-1 selective blocker with vasodilating properties. Nebivolol is a racemic mixture of two enantiomers with a highly selective beta-1-blocking activity and without an intrinsic sympathomimetic activity. Nebivolol has a unique haemodynamic and therapeutic profile, which is advantageous in essential hypertension, ischemic heart disease and congestive heart failure. Nebivolol does not compromise the left ventricular function; it increases stroke volume and does not have negative inotropic effect during exertion [11]. The vasodilating effect of nebivolol is not dependent on alfa-1-adrenoreceptor blockade, which usually produces symptomatic hypotension and postural drop in blood pressure mainly in the elderly patients. The vasodilating effect of nebivolol is explained by the inhibition of nitric oxide degradation. Nebivolol was first tested as an effective antihypertensive drug. The positive effect of nebivolol in chronic heart failure might be explained by the reduction of neurohormonal sympathetic activation, reduction of wall stress, reduction in heart rate with improved coronary perfusion, and reduction of incident coronary events. High tolerability of nebivolol in the elderly with a low frequency of adverse events might be explained by its high beta-1 selectivity (and low incidence of side effects usually reported in non-selective drugs, e.g. pulmonary events) and vasodilating properties providing peripheral tissue perfusion without rapid decrease of arterial pressure.

Conclusion

Several studies and surveys have shown that the use and dose of betablockers in CHF patients is not often optimal [14]. The underuse and underdose of betablockers are particularly evident in elderly patients [8]. Results from the CIBIS-ELD study showed that titration of BBs to target in elderly heart failure patients may be more difficult [10]. Not reaching target dose for carvedilol in the elderly heart failure subjects might be also explained by the strict recommendation of the previous guidelines recommending the target for carvedilol 50 mg bid for subjects weighting 85 kg and above [15]. Current guidelines do not mention weight dependence carvedilol dose with target dose range 25–50 mg bid [7].

High tolerability was reported for nebivolol in the SENIORS study [6,13]. Elderly patients are at a higher risk of side effects of BBs (mainly hypotension, bradycardia and pulmonary events); nevertheless, 68% of patients reached the target dose in the nebivolol group (68% of 65% on the drug at the end of the study). High tolerability of nebivolol in older patients with CHF might be explained by its pharmacological properties [11,12].

Several factors limit the use and dose of BBs in elderly patients with chronic heart failure, mainly the presence of comorbidities associated with relative contraindication to BBs therapy: chronic obstructive pulmonary disease, peripheral artery disease and the risk of postural hypotension and associated neurologic disorders. So, \( \beta_1 \)-adrenoreceptor blockers are the drug of choice in elderly patients with systolic CHF. Another factor leading to the underuse of BBs in older heart failure patients is the high prevalence of heart failure with preserved ejection fraction in the elderly (HF PEF). And there is lack of evidence of BBs benefit in HF PEF.

Conflict of interest

Nothing to declare.

Funding body

No funding.

Ethical statement

The research was done according to ethical standards.

REFERENCES


