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Review article

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 underdose of 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 (LV EF) 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 LV EF [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 (LV EF $<$ 40%) and NYHA classes II–IV were included in the study. Tolerability of carvedilol was defined as dose $\geq$ 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, LV EF $\leq$ 45% and NYHA class $\geq$ 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 – FEV_1) 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, LV EF 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 β_1 - adrenoreceptor blocker, carvedilol is the non-selective α_1-β_1-β_2 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