Titration of β -Blockers for Patients With Heart Failure

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Beta-blockers (BBs) are widely used in patients with heart failure (HF), based on several lines of clinical evidence,¹⁻³ but the dose of BBs used in clinical practice is still less than the target dose defined in clinical trials.^{4,5} In Japan, this tendency is more apparent than in the USA and Europe.⁶ The reasons suggested for insufficient up-titration of BBs are their short-term adverse hemodynamic effects, such as deterioration of left ventricular (LV) systolic function and lowering of blood pressure and heart rate, and intolerance in patients with advanced age, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), or other coexisting disorders. However, recent clinical findings have shown that BBs are tolerable even in patients with advanced age⁷ and are also effective in patients with COPD⁸ or CKD.⁹ According to those findings, up-titration of BBs in patients with HF has become more common in recent years, as is reported by Kato et al¹⁰ in this issue of the Journal. They examined 227 consecutive patients hospitalized for HF with reduced ejection fraction (HFrEF) in whom BBs were introduced on a de novo basis. They show that in recent years (after 2006), the prognosis for patients with HFrEF significantly improved compared with earlier years (before 2005). This improvement can be explained by an increased BB dose accompanied by lowered resting

heart rate. They also demonstrate that lower resting heart rate (≤ 71 beats/min) and higher BB dose (≥ 10 mg carvedilol) were significant determinants of better clinical outcomes, suggesting these parameters could be useful surrogate markers when titrating BBs in Japanese patients with HFrEF.

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Previous clinical studies have shown that the improvement in EF by BBs is dose-dependent, suggesting that higher doses of BBs would be better.^{6,11} However, intolerance of BB up-titration is relatively common in the Asian population. In fact, β_1 -receptor sensitivity is reported to be higher in Chinese than in Caucasians and African-Americans.¹² Moreover, it is sometimes difficult to maintain the incentive for up-titrating BBs in asymptomatic HF patients. Therefore, useful surrogate markers for titrating BBs have been anticipated.

It is known that a higher resting heart rate is associated with lower mortality in patients with HF.¹³⁻¹⁵ In a meta-analysis examining the effect of BBs on mortality in terms of heart rate reduction, a 14% risk reduction was observed with each 5 beats/min decrease in heart rate.¹⁶ In addition, the improvement in LVEF closely correlated with heart rate reduction.¹⁷

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However, heart rate reduction could be secondary to improved cardiac function and physical capacity by BB treatment. The causative effect of lowering heart rate itself has not been fully elucidated. A recent clinical study using a selective heart rate-lowering drug, an I_f current inhibitor (ivabradine), showed that heart rate reduction in patients with HFrEF, heart rate ≥ 70 beats/min, and sinus rhythm reduced the incidence of cardiovascular death and HF admission, suggesting the importance of heart rate reduction for treatment of HF.¹⁸ Although the precise mechanisms are still unclear, heart rate reduction possibly exerts its beneficial effects through decreased energy expenditure, increased coronary blood supply by prolonging diastole, improved force-frequency relation and restored vascular resistance.¹⁹

On the other hand, BB therapy reduces mortality even in patients undergoing cardiac resynchronization therapy with an implantable cardioverter defibrillator whose heart rate is fixed by the artificial pacemaker.²⁰ Because BB therapy has several beneficial effects, including reduction in myocardial ischemia, arrhythmias and LV wall stress and cardioprotection from neurohumoral activation, heart rate reduction is not the sole mechanism of the survival benefit of BBs (Figure).

The major clinical benefit of BBs is preventing sudden cardiac death (SCD). Because sympathetic activation plays a major role in the development of SCD, heart rate reduction is not necessarily required for SCD prevention. In fact, the SHIFT trial showed that ivabradine significantly reduced the risk of HF admission and death from HF, but not the risk of all cardiovascular death including SCD.¹⁸ Kato et al demonstrate that the BB dose, but not heart rate reduction, was an independent determinant of the composite endpoint of hospitalization for worsening HF and/or all-cause death by multivariate analysis.¹⁰ In contrast, the previous meta-analysis showed that the magnitude of heart rate reduction was statistically significantly associated with a decreased risk ratio of all-cause mortality by BBs in HF, whereas the dose of BB was not.¹⁶ However, the average dose in the meta-analysis was higher than that of the present study in Japan. Although the subanalysis of CIBIS II demonstrated that bisoprolol reduced mortality in HF patients at all tolerated dose levels and its withdrawal increased the risk of mortality, all-cause mortality was significantly reduced in the moderate dose (bisoprolol 5 or 7.5 mg/day) and high dose (bisoprolol 10 mg/day) groups compared with the low dose group (bisoprolol ≤ 3.75 mg/day). Because a dose of carvedilol < 10 mg is lower than the so-called “low dose” in Western countries, careful titration up to at least 10 mg carvedilol would be recommended to obtain survival benefit in Japanese patients with HFrEF.

Resting heart rate is a practical surrogate marker to titrate BBs. However, heart rate at peak exercise and 24-h average heart rate are also important to assess the degree of β -blockade. Further investigations will be required to establish a protocol to titrate BBs in individual patients with HF.

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