Elevated heart rate (HR) is a recognized independent prognostic risk factor in heart failure (HF). However, a progressive increase in HR with increasing severity of HF is considered to be a compensatory response to the limited cardiac reserve via activation of sympathetic activity. This concept raises concern that a limitation of increases in HR could deteriorate clinical status, especially in patients with severe HF. However, a post hoc analysis of the Systolic Heart Failure treatment with the I inhibitor ivabradine Trial (SHIFT) demonstrated consistent efficacy and safety of ivabradine even in severe HF with left ventricular ejection fraction (LVEF) ≤20% and/or New York Heart Association (NYHA) functional class IV. Therefore, ivabradine is considered to be effective irrespective of the severity of HF.

Low systolic blood pressure (SBP) is also known to be associated with greater risk for cardiovascular death and HF. A post hoc analysis of SHIFT has also shown that a combination of low SBP and high HR is a significantly higher risk for mortality and morbidity. Patients with low SBP were more likely to have severe HF as characterized by lower LVEF and higher NYHA functional class. However, importantly, baseline SBP (<115, 115 to <130, and ≥130 mmHg) did not change the effect of HR reduction with ivabradine on clinical outcomes in HF. There was a similar beneficial effect on both the primary composite endpoint and on the selected secondary endpoints in these groups, with comparable absolute risk reductions for the primary endpoint in patients with low, intermediate, and high SBP. The neutral effect on BP relative to placebo whatever the SBP at baseline is not unexpected, given the mode of action of ivabradine, which acts solely by I inhibition in the sinus node with no effects on cardiac function other than HR. This is unlike β-blockers, for which tolerability is sometimes poor in severe HF patients with low SBP. Therefore, in severe HF patients, low SBP indicates greater severity and such patients are more dependent on activation of sympatholytic activity.

Dr. Okada et al raised an important point regarding the possibility that the reduction of SBP during the early period (4 weeks) after the initiation of ivabradine might be associated with the long-term clinical outcome based on their own experience. Following to their suggestion, we performed a post hoc analysis of J-SHIFT focusing on the reduction of SBP during the early phase. Patients in the ivabradine group (n=124) were divided into three groups according to the change of SBP at 4 weeks from baseline; ≥1 (n=65), 1> to >−10 (n=28), and ≤−10 (n=31) mmHg. The primary endpoint, cardiovascular death or hospital admission for worsening HF, occurred among 14 (21.5%), 4 (14.3%), and 6 (19.4%) patients, respectively. The adjusted hazard ratios of the 1> to >−10 and ≤−10 mmHg groups were 0.47 (95% confidence interval 0.14–1.56) and 0.51 (0.18–1.42), respectively, as compared with the ≥1 mmHg group, demonstrating that the reduction in SBP during the early period was not associated with long-term clinical
outcome in the J-SHIFT. Nevertheless, we agree with Dr. Okada that we need to further determine the clinical effect of early SBP reduction associated with HR reduction. Reduction of SBP and HR can occur by ivabradine, especially during the initiation period and particularly in severe HF, which might be associated with adrenergic hyperactivity. Therefore, caution is definitely needed when starting ivabradine in a severe HF patient with very low LVEF of 18% and markedly dilated LV with a diastolic diameter of 95 mm, as reported by Dr. Okada et al.

Disclosures
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References

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