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Optimization of Heart Failure Treatment by Heart Rate Reduction

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ABSTRACT

Heart failure (HF) treatment should be optimized in addition to guideline-directed and recommended drugs to achieve an appropriate heart rate (i.e. 50–60 bpm) by ivabradine in patients with a heart rate >70 bpm in sinus rhythm and with an ejection fraction ≤35%. Heart rate reduction was to reduce cardiovascular death and HF hospitalization dependent on baseline resting heart rate. In particular in patients at a heart rate >75 bpm, a reduction in cardiovascular death, all-cause death, HF death, HF hospitalization and all-cause hospitalization has been observed. The optimal heart rate achieved appears to be between 50–60 bpm, if well tolerated as in these patients the lowest event rate is observed on treatment. Heart rate reduction is, therefore, a treatable risk factor in chronic HF. Observational studies support the concept that it is a risk indicator in other cardiovascular and non-cardiovascular conditions. Whether heart rate reduction is also modifying risk in other conditions than chronic HF should be explored in prospective clinical trials.

Keywords: Heart rate; Chronic heart failure; Ivabradine; Patient outcomes; Cardiovascular comorbidities; Heart rhythm

INTRODUCTION

Elevated resting heart rate (RHR) is associated with cardiovascular outcomes in the general population,[1] cardiovascular risk factors like obesity[2] and diabetes,[3] hypertension,[4] coronary heart disease,[5] coronary heart disease with impaired left ventricular function[6] and chronic heart failure (HF).[7] Thus, it has an impact on prognosis throughout the cardiovascular continuum. Although, the association of RHR to morbidity and mortality, generally at a threshold above 70 bpm, is convincing, effective RHR reduction with beta-blockers or ivabradine have not always shown significant risk reductions like in stable coronary artery disease[8] and coronary artery disease and impaired left ventricular function.[9] However, in chronic HF, the reduction of RHR with ivabradine was associated with a reduction of cardiovascular death and HF hospitalization.[10] Therefore, in cardiovascular conditions in general, elevated RHR might be a useful risk indicator, while only in HF RHR represents a significantly modifiable risk factor.[11] This concept is summarized in **Figure 1**.[11]

Conflict of Interest
MB received grants and honoraria from Servier and was Executive Boar Member of the SHIFT trial.
The other authors have no financial conflicts of interest.

Author Contributions
Writing - original draft: Böhm M; Writing - review & editing: Böhm M, Bewarder Y, Kindermann I, Slawik J, Wintrich J, Werner C.

I_F INHIBITION TO REDUCE HEART RATE

RHR reduction is achieved, however, often not sufficiently, by beta-blocker therapy, which beyond a negative chronotropic effect might also antagonize direct toxic effects of catecholamines and reduce oxygen consumption by negative inotropic effects. Ivabradine was the first clinically available drug to reduce RHR by inhibition of I_f—f stands for "funny" due to the unusual gating behavior this nonspecific cation current (I)—mediated by hyperpolarization-activated cyclic nucleotide–gated (HCN) channels, which are expressed exclusively in sinus nodal cells.[12] Therefore, ivabradine acts on sinoatrial node pacemaker cells without any other known cardiovascular effects and does not reduce RHR in atrial fibrillation. It serves as a tool to study specific effects of heart rate reduction in cardiovascular diseases.[11] Ivabradine binds the inner side of the HCN channel, when it is in its open state.[12] Therefore, ivabradine has the highest binding capacity, when a large number of channels are in the open state, which is usually the case when RHR is high.[12][13] Therefore, the binding capacity and the negative chronotropic effect is most pronounced at high RHR and only small RHR reductions are achieved when RHR is low.[14] This might create important implications for cardiovascular safety.[14]

RISK ASSOCIATIONS IN CHRONIC HEART FAILURE

Elevated RHR has been associated with incident HF in a general population (Rotterdam Study)[15] in patients after myocardial infarction and HF (DIAMOND)[16] and in chronic HF (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial [SHIFT])[7] (**Figure 2**). Interestingly, high RHR at discharge (>84 bpm) was associated with cardiovascular death the year thereafter.[17][18] Beta-blockers are associated with improved outcomes in patients with chronic HF representing guideline-recommended standard treatments.[19-21] The

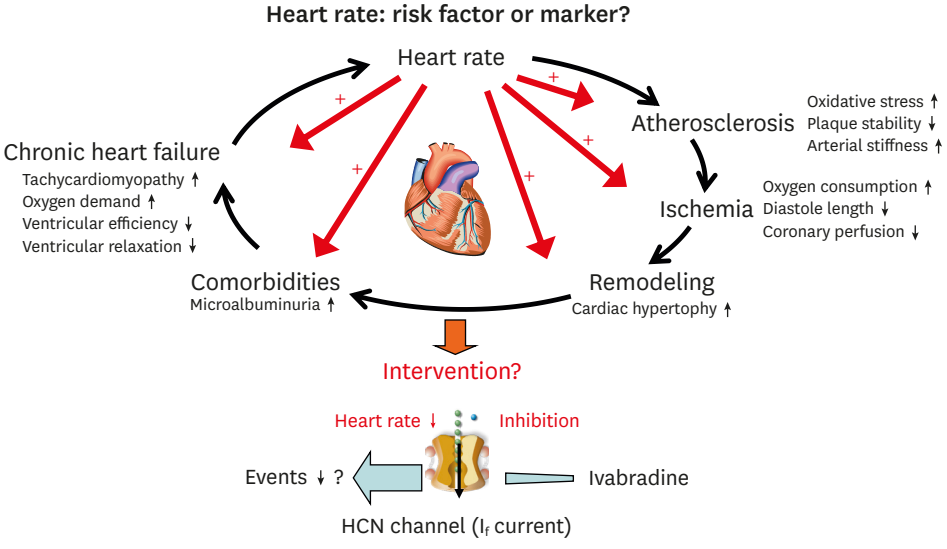

Figure 1. Heart rate in the cardiovascular continuum and the potential influence of ivabradine. Heart rate is a risk indicator in all cardiovascular conditions but a modifiable risk factor only in chronic heart failure. Ivabradine binds to the HCN channel inhibiting I_f currents, thereby reducing the phase IV depolarization of the action potentials leading to heart rate reduction. Modified according to 11.
HCN = hyperpolarization-activated cyclic nucleotide–gated.

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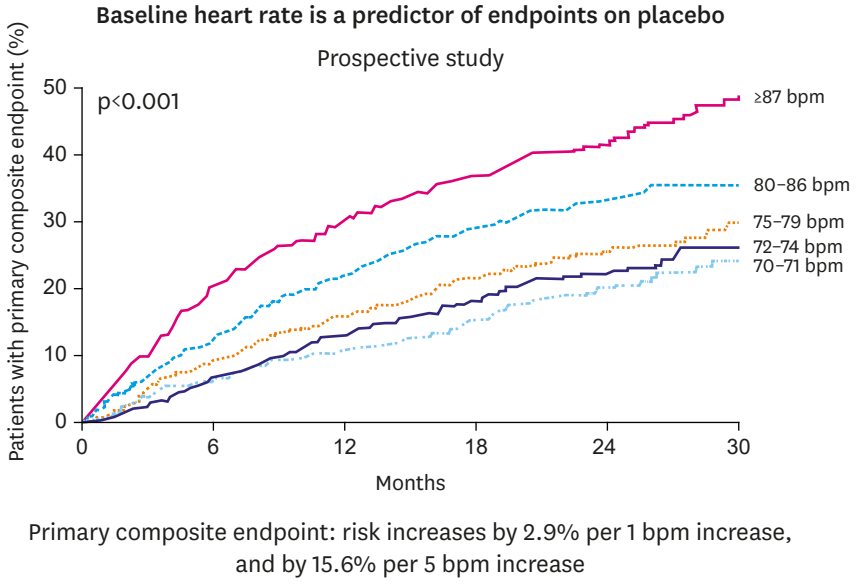

Figure 2. Kaplan Meier cumulative event curves for the primary composite endpoint (cardiovascular death or heart failure hospitalization) according to patient groups defined by quintiles of heart rate at 28 days on placebo. Log rank p values show the difference between the groups. Modified according to 7.

number of heart beats reduced was associated with improvements of ejection fraction.[22] Reductions of the absolute numbers of heart beats reduced is also associated with risk reduction. The heart rate achieved on beta-blockers was associated with a reduction in annualized mortality.[22] However, the average RHR and the lowest RHR achieved in beta-blocker trials was only 70 bpm.[22] Allover, RHR achieved on treatment with beta-blockers was more closely associated with a reduction of risk than the dose of the beta blockers applied.[23] These findings point towards a significant role of RHR and RHR reduction in patients with HF to improve outcomes.

HEART RATE REDUCTION IN HEART FAILURE: RESULTS OF THE SHIFT TRIAL

Results from the SHIFT demonstrated that ivabradine safely lowers RHR in patients with sinus rhythm above 70 bpm.[10] Treatment with ivabradine with a starting dose of 5 mg bid up-titrated to 7.5 mg bid or down-titrated to 2.5 mg bid according to RHR changes below 50 bpm resulted in a placebo-controlled RHR reductions of 10.9 bpm at 28 days, 9.1 bpm at 1 year and 8.1 bpm at the end of the study[10] (**Figure 3**). Treatment with ivabradine was associated with a reduction of the composite primary endpoint cardiovascular death or hospital admission for worsening of HF compared with placebo.[10] This result was primarily driven by hospital admission for HF.[7][10] In patients with RHR above the median (RHR of 75 bpm) not only the composite and HF hospitalization were significantly reduced, but also all-cause death, cardiovascular death and death for HF[24] (**Figure 4**). Patients with the highest RHR had a greater reduction of RHR and a greater reduction of risk.[7] Similarly, RHR achieved between 50–60 bpm after up-titration (at 28 days) resulted in a 50% lower number of subsequent cardiovascular outcomes compared to patients who remained at a RHR >75 bpm on treatment.[7] In general, treatment was safe. However, more symptomatic bradycardia (5% on ivabradine compared to 1% on placebo) requiring dose reductions

(5% vs. 1%) were observed. A small, however, significant increase by 1% in incident atrial fibrillation was detected.[10] In the population of SHIFT, the early re-hospitalization after an index hospitalization markedly increased death in the following year regardless of whether the cause of hospitalization was due to HF or myocardial infarction.[25] In patients after HF hospitalization, the treatment effect of ivabradine was similar compared to the overall population[26] and the relative risk reduction was similar in patients with severe impairment of left ventricular function[27] resulting in a large absolute reduction of events prevented. In addition, the nominal effect of risk reduction was independent from the beta-blocker dose applied, but on RHR at the beginning of treatment.[28]

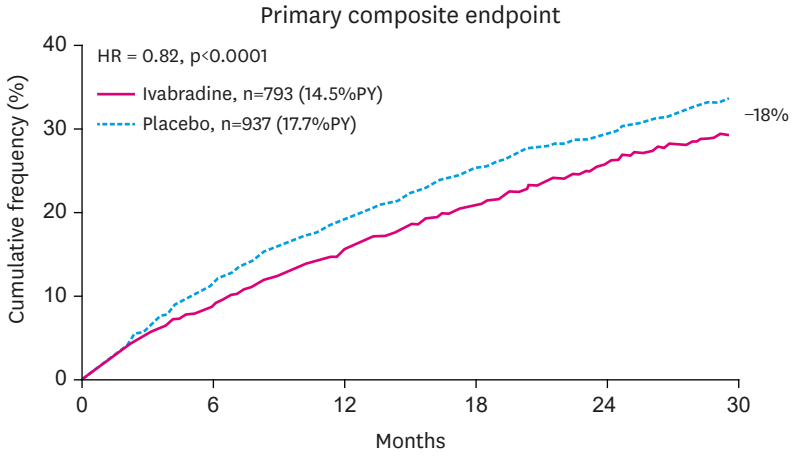

Figure 3. Kaplan Meier cumulative event curves for the primary composite endpoint (cardiovascular death or heart failure hospitalization) for ivabradine or placebo. Primary results of the SHIFT study. Modified according to 10.
HR = hazard ratio; SHIFT = Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial.

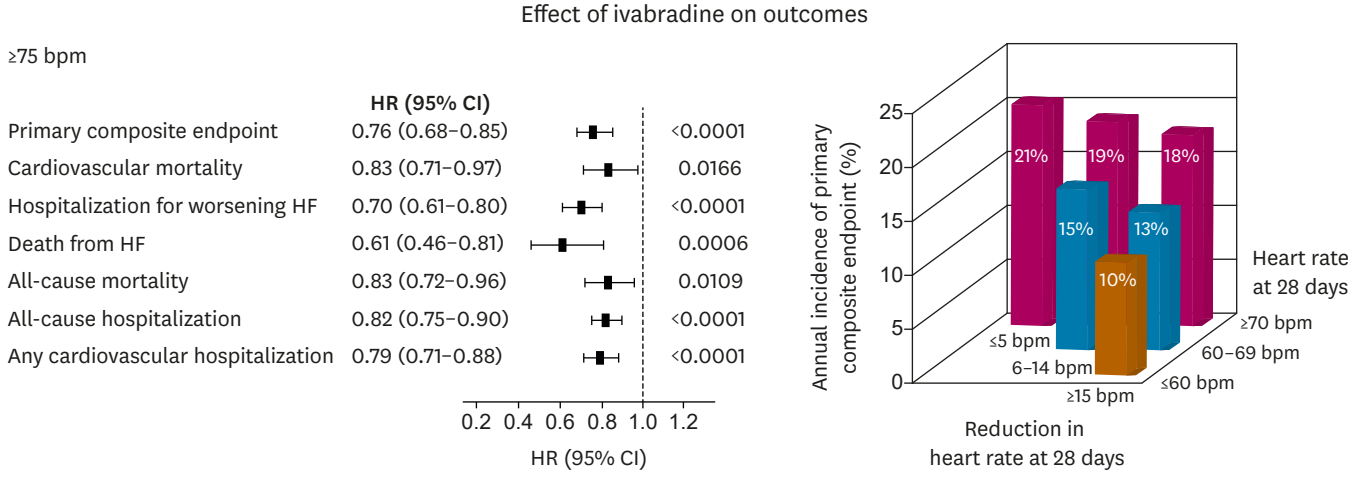

Figure 4. Forest plots (left) demonstrating the hazard ratio (with 95% CIs) for the primary composite endpoint (cardiovascular death or HF hospitalization), cardiovascular mortality, hospitalization for worsening of HF, death from HF, all-cause mortality, all-cause hospitalization and any cardiovascular hospitalization for ivabradine compared to placebo. On the right hand side, the annual incidents of the primary composite endpoint are given according to heart rate achieved after up-titration of ivabradine at 28 days or reduction of heart rate at 28 days. Please note that all endpoints were significantly reduced and this reduction is closely associated with heart rate achieved and heart rate reduction in patients with chronic HF at a heart rate ≥ 75 bpm. Modified according to 24.
CI = confidence interval; HF= heart failure; HR = hazard ratio.

RISK CONDITIONS AND ACCOMPANYING CARDIOVASCULAR OR NON-CARDIOVASCULAR COMORBIDITIES

A low systolic blood pressure (<120 mmHg) is prevalent in 15–25% of HF patients and is associated with a greater risk for post-discharge mortality, in-hospital mortality and worsening of HF.[29)30)] These patients are usually under-treated, because physicians are afraid of further reducing blood pressure with guideline-recommended treatments although they have shown efficacy on morbidity and mortality. However, at low blood pressure, ivabradine had a similar treatment effect compared to patients with higher blood pressures,[31)] and treatment with ivabradine was associated with a nominal increase of 2 mmHg on treatment.[10)] In patients at increased age, an under-treatment with beta-blockers and mineralocorticoid antagonists has been reported,[32)] even though the risk for hospitalization is higher in this population and these drugs have shown efficacy on mortality and morbidity.[33)] In patients above an age of >75 years, the treatment effect of ivabradine was maintained and not different over the whole spectrum of age groups.[34)] In patients with left bundle branch block, the treatment effects were also maintained.[35)] The concern here was that left bundle branch block might select patients with conduction disorders making them more prone for brady-arrhythmic complications after I_f-inhibition. However, no significant signals in Holter studies were detected.[36)]

In patients with comorbidities like diabetes, cardiovascular complications and hospitalizations were higher in HF patients with diabetes compared to patients without diabetes.[37)] In the post-hoc analysis of SHIFT, the treatment effect of heart rate reduction in diabetes was not impaired and similar to patients without diabetes.[38)] Similar findings were observed in patients with impaired renal function.[39)] While higher RHR is a significant predictor of worsening of renal function,[39)40)] effects of RHR reduction on renal function decline were not shown.[39)] Pulmonary disease and in particular chronic obstructive pulmonary disease (COPD) are highly prevalent in the HF population.[41)] In the SHIFT population, there was no significant difference in the treatment effect of RHR reduction with ivabradine compared to patients without COPD.[42)] Finally, the cumulative comorbidity load according to numbers of comorbidities was studied in SHIFT.[43)] There was an increasing mortality and morbidity in patients with increasing comorbidities compared to 4 or more comorbidities, the relative treatment effect of ivabradine was maintained[43)] (**Figure 5**).

PRACTICAL CONSIDERATIONS AND CLINICAL PERSPECTIVES

In the failing heart, there is a negative force-frequency relationship[44)45)] (**Figure 6**). The positive force-frequency relationship (so called "Treppe") was first discovered by Bowditch[46)] in 1871. On exercise, the maximal oxygen uptake is achieved at a heart rate of approximately 80 bpm in HF patients, while the maximum in patients without HF is around 160 bpm.[47)] Therefore, a reduction of RHR and exercise HR rate might be associated with an increase in contractility. In line with this suggestion are clinical experiments in patients with significant HF (New York Heart Association [NYHA] class III). In these patients, i.v. application of ivabradine was associated with a reduction of heart rate but accompanied by an unchanged cardiac index resulting from an increase in stroke volume.[48)] Given the negative inotropic

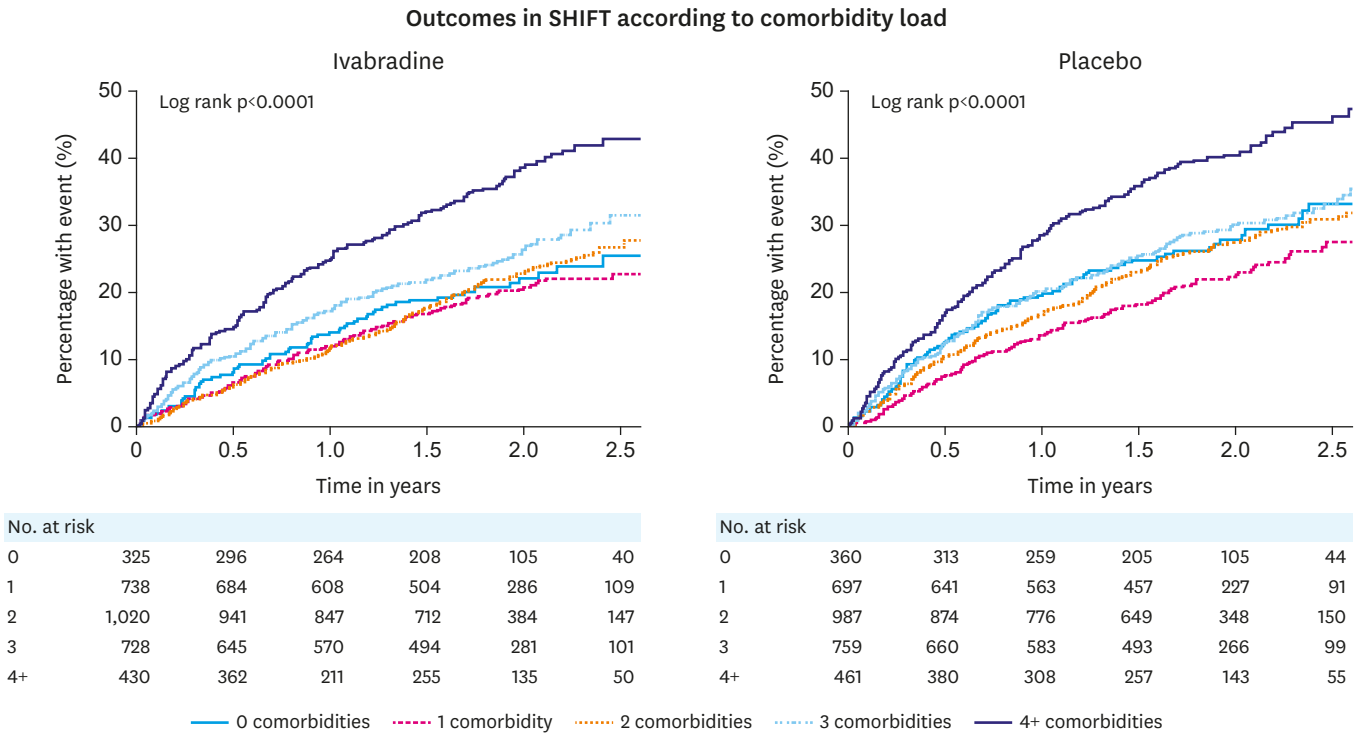

Figure 5. Outcomes according to comorbidities (comorbidities≥4) on the primary outcome (cardiovascular death or heart failure hospitalization) on ivabradine (left) or placebo (right). Data from the SHIFT study. Modified from 43.
SHIFT = Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial.

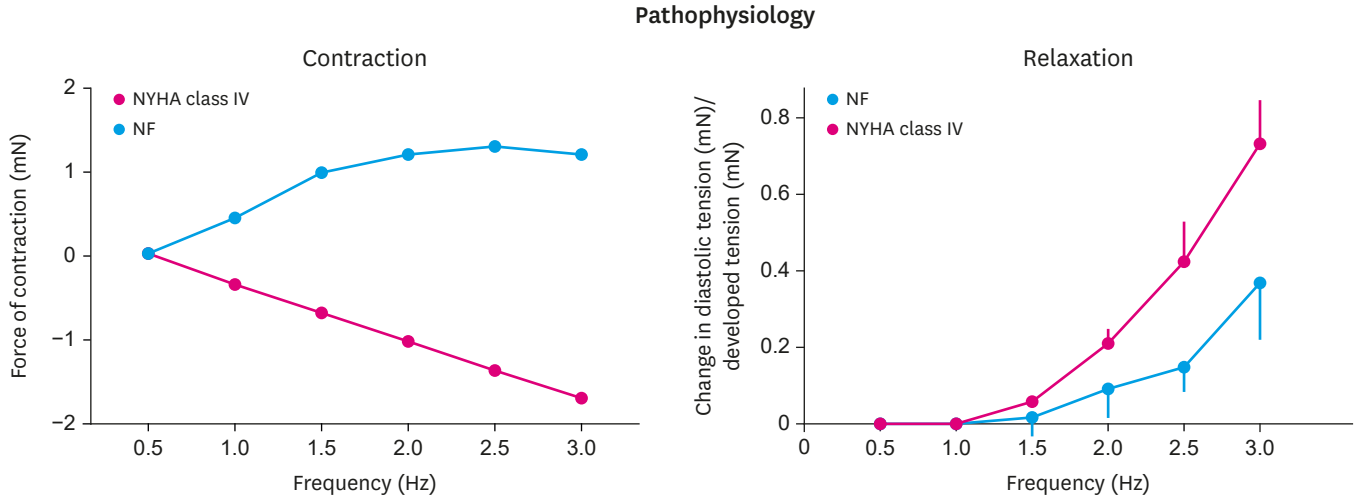

Figure 6. Isometric force of contraction (left) and change in diastolic tension (right) in isolated electrically driven cardiac preparations in vitro from patients with severe heart failure (NYHA class IV) or NF. Please note that the heart failure force of contraction declined (negative force-frequency relationship, on negative "Treppe") and relaxation deficit in NYHA class IV. Modified from 45.
NF = non-failing hearts; NYHA = New York Heart Association.

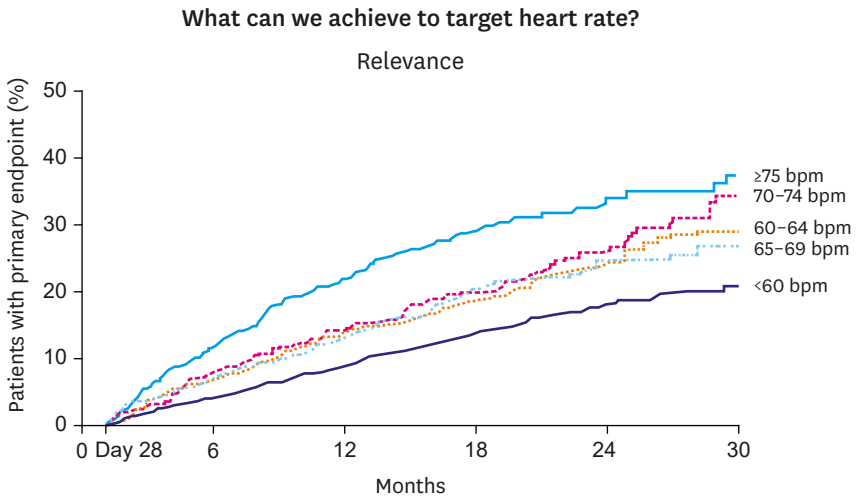

Figure 7. Kaplan Meier cumulative event curves for the primary composite endpoint (cardiovascular death or heart failure hospitalization) according to patient groups defined by quintiles of heart rate achieved at 28 days on treatment with ivabradine. Log rank p-values show the difference between the groups. Modified according to 7.

effect of beta-blockers with a drop in left ventricular ejection fraction and an increase in filling pressures after initiation of HF patients,[49] a reduction of RHR with ivabradine might at least in part antagonize these contractility-depressant effects. Indeed, co-application of carvedilol[49] and other beta blockers[50] have been shown to facilitate up-titration of beta-blockers with more rapidly achieving a lower RHR and more prominently increasing ejection fraction after co-administration of these drugs.[49][50] Therefore, a new concept might be the concomitant application of beta-blockers with ivabradine in chronic HF.

CONCLUSION

RHR reduction with ivabradine remains an important component of HF therapy in patients with a RHR in sinus rhythm above 70 bpm RHR. It was shown to reduce the cardiovascular death and HF hospitalization composite, which was primarily driven by HF hospitalization and has been classified with a class IIa recommendation in the HF Guidelines of the European Society of Cardiology.[51] Since RHR is an important modifiable risk factor with a doubling risk from a RHR of 70–72 bpm compared to 87 bpm at baseline, it should be pharmacologically adjusted with ivabradine on top of maximally tolerated doses of beta-blockers as suggested by the SHIFT trial.[7][10] Physicians should achieve an optimal RHR of 50–60 bpm on treatment at which RHR associated risk is maximally reduced[7] (**Figure 7**). Since high RHR remains a risk marker also in other cardiovascular and non-cardiovascular conditions, it might be important and worthwhile to initiate randomized controlled trials in conditions other than chronic HF like cancer, chronic disease like COPD and critical illness as well as neurological disease as an adjunctive therapy.[52]

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