Heart rate decrease: A new paradigm in the treatment of heart failure. Insights from the SHIFT study

Réduction de la fréquence cardiaque : un nouveau paradigme dans le traitement de l’insuffisance cardiaque. Implications de l’étude SHIFT

Heart rate is recognized as a strong predictor of mortality and morbidity in the general population as well as in a broad spectrum of cardiovascular disorders including hypertension, myocardial infarction, coronary artery disease and chronic heart failure with reduced ejection fraction as well as heart failure with preserved ejection fraction[1—6]. The underlying mechanism of the deleterious effect of elevated heart rate remains partially unknown. However, beyond an increase in myocardial oxygen consumption, elevated heart rate is associated in experimental models with vascular oxidative stress, endothelial dysfunction, acceleration of atherogenesis and coronary plaque instability[7].

In heart failure, beta-blocker therapy is associated with a marked improvement in outcomes, which seems proportional to the magnitude of heart rate reduction and might involve a reverse remodelling effect [8,9]. However, since beta-blockers have multiple mechanisms of action, it was not known until the recent publication of the Systolic heart failure treatment with If inhibitor ivabradine trial (SHIFT) whether a pure heart rate reduction obtained by a brady-cardiac agent devoid of any other significant pharmacological properties — the If channel blocker ivabradine — would be beneficial in this condition.

Key lessons from SHIFT

In a population of 6558 chronic heart failure patients with reduced ejection fraction, in sinus rhythm and elevated heart rate greater or equal to 70 beats per minute (bpm), the addition of ivabradine 5 mg to 7.5 mg bid on top of the best possible recommended therapy brings additional benefit and reduces significantly the occurrence of the primary composite, cardiovascular mortality or heart failure hospitalizations, by 18%. This effect is driven mainly by a significant reduction in heart failure hospitalizations (—26%) and heart failure deaths (−26%) [10].

Heart rate is not only a risk marker but also a risk factor in heart failure: the risk of cardiovascular outcomes increases with heart rate and every 5 bpm increase in baseline heart rate is associated with a 16% increase in the risk of the primary outcome in the placebo arm. The beneficial effect of ivabradine is solely accounted for by heart rate reduction since the adjustment for change in heart rate at 28 days in the active arm neutralizes the effect of the drug for subsequent outcomes [11].

The minimal risk is observed in patients who reach a target heart rate less than 60 bpm at 28 days.
Implications and questions

SHIFT suggests that a greater attention should be paid to a simple biomarker, resting heart rate, which is a powerful predictor of outcomes in chronic heart failure. Indeed, epidemiological studies suggest that despite the dissemination of beta-blocker therapy, heart rate remains elevated (>70 bpm) in a substantial proportion of patients [12,13]. This is at least partially the result of under dosage of this therapy as a result of poor tolerance or lack of awareness of the recommended target dose in real-life conditions.

It might be tempting then to substitute beta-blocker therapy by ivabradine given the overall good tolerability of this drug. However, SHIFT provides no insight on this question since an overwhelming majority of patients included in this trial were on beta-blocker therapy (90%). Therefore, the only scientifically valid conclusion that can be drawn from SHIFT is that in chronic heart failure patients treated with beta-blockers who remain with an elevated heart rate for any reason, ivabradine should be considered on top of their existing therapy in order to improve outcomes and particularly heart failure events.

Of note, the magnitude of the effect was similar in the small subgroup not receiving a beta-blocker to that observed in the rest of the population, suggesting that in chronic heart failure patients intolerant to beta-blockers, reducing heart rate by ivabradine brings a similar benefit to that observed in other patients and could be considered as an alternative.

Would co-prescription of beta-blockers at low/medium dose with ivabradine be preferable to an up-titration of beta-blockers?

There is no clear answer to this important practical question from the SHIFT results since more than 50% of the patients enrolled in this trial were taking at least half of the target recommended dose and 26% were at target dose. The investigators were repeatedly encouraged by the executive committee to provide the best possible therapy to their patients including beta-blocker target dose. The SHIFT results should therefore be interpreted as heart rate reduction by ivabradine bringing an incremental benefit in patients with elevated heart rate who are unlikely to tolerate maximal doses of beta-blockers, as frequently observed in daily practice.

Can the results be generalized to the overall heart failure population?

Patients included in SHIFT were selected on the basis of high resting heart rate, sinus rhythm and reduced ejection fraction. In addition, the proportion of elderly patients was limited. The effects of ivabradine cannot therefore be generalized to the overall heart failure population and in particular to patients in atrial fibrillation or with heart failure and preserved ejection fraction.

Is there an optimal heart rate in chronic heart failure?

Since the analysis of the relationship between heart rate reduction achieved at 28 days with ivabradine and subsequent outcomes suggests that patients with the lowest risk reached a heart rate less than 60 bpm, it is reasonable to recommend this target in daily practice, when tolerated. There is no information available on the potential benefit/harm of lowering further heart rate although it should be reminded that cardiac output is the product of heart rate and stroke volume so that very low heart rates result in a significant decrease in cardiac output and therefore in reduced oxygen delivery to the body.

What is the underlying mechanism for the benefit observed with heart rate reduction?

Some beta-blocker studies suggest that one possible mechanism underlying the benefit of heart rate reduction is reverse remodelling with improvement in cardiac function [9]. Whether this applies to ivabradine is addressed in a specific cardiac function echo-Doppler substudy, which is currently being analysed.

Conclusion

SHIFT, a large outcome trial, brings new insight into the role of heart rate as a risk factor in chronic heart failure and on the importance of heart rate reduction — when elevated — in order to improve outcomes in heart failure in sinus rhythm and with reduced ejection fraction. The addition of a pure bradycardic agent, ivabradine, to the best possible recommended therapy provides a significant improvement in cardiovascular outcomes in this population and should be considered to reduce further the burden of chronic heart failure and the risk related to this disorder.

Conflict of interest statement

Michel Komajda is the co-primary investigator of the SHIFT trial and has received consulting and speaker fees from Servier as well as from other pharmaceutical companies.

References

Heart rate decrease and the SHIFT study


