The beat goes on: on the importance of heart rate in chronic heart failure

Karl Swedberg1* and Michel Komajda2

1Department of Emergency and Cardiovascular Medicine, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden; and 2Department of Cardiology, University Pierre et Marie Curie Paris VI, La Pitie-Salpêtrière Hospital, Paris, France

Resting heart rate is a modifiable risk factor both in the general population and in patients with cardiovascular (CV) disease.1 The reasons for this increased risk are not fully understood and may have several explanations. Elevated heart rate is associated with reduced myocardial function in experimental settings and various pathophysiological mechanisms exist for the development of CV and myocardial dysfunction by tachycardia.2 In heart failure and systolic dysfunction, the myocardium is energetically starving. Elevated heart rate has then added negative consequences, including progressive mechanical dyssynchrony and reduced inotropy.3 The importance of heart rate in chronic heart failure (CHF) was recently explored in SHIFT (The Systolic Heart failure Treatment with the If inhibitor Ivabradine Trial).

In SHIFT, eligible patients who had CHF and ejection fraction <35% were in sinus rhythm and on recommended therapy4,5 and were randomized to ivabradine or placebo. Heart rate at baseline was analysed in relation to various outcomes. When the placebo group was divided by quintiles based on baseline heart rate, the incidence of the primary composite endpoint (CV mortality or hospitalization for worsening heart failure) was reduced by 18% in the ivabradine group (P < 0.0001). Analysis with heart rate as a continuous variable showed that for every beat increase in heart rate at baseline, the risk of the primary composite endpoint event increased by 3% (P < 0.0001).

Treatment with a β-blocker will reduce heart rate, a reduction thought to be the important mechanism to account for why β-blockers exert their beneficial effects in systolic CHF. However, β-blockers have several effects on the CV system, which today are of unclear importance. Further support for the relationship between changes in heart rate and improved myocardial function after treatment with β-blockers and outcome has been presented by Flannery et al.6 in a meta-regression analysis of β-blocker trials. In 35 trials with a mean follow-up duration of 9.6 months, there was a close relation between all-cause annualized mortality rate and achieved heart rate (adjusted r = 0.51, P = 0.004). In a meta-analysis of 23 trials on β-blockers in heart failure that included 19 209 patients in which mortality was reported, McAlister et al. could present data on heart rate vs. other variables for outcome. In a multivariable analysis, the degree of heart rate reduction by β-blockers was the only significant variable remaining of prognostic importance.6,7 For every 5 b.p.m. reduction, the risk of death decreased by 18%. By contrast, the dose of the β-blocker treatment in 17 trials was not predictive of outcome.

Pure heart rate reduction

As stated above, heart rate reduction in association with a β-blocker seems to be related to improved outcomes. Ivabradine, which acts primarily only on the sinus node through a mechanism different from a β-blocker (i.e. If-current inhibition), reduces heart rate in patients in sinus rhythm. In SHIFT, eligible patients were randomized to placebo or ivabradine and followed for 23 months. Heart rate was reduced about 11 b.p.m. after correction for placebo effects. The primary composite endpoint (CV mortality or hospitalization for heart failure) was reduced by 18% in the ivabradine group (P < 0.0001). The effects were driven mainly by hospitalizations for worsening HF, which were reduced by 26% (P < 0.0001), and deaths that were due to HF (P = 0.014). Patients with the highest heart rate at baseline had the greatest benefit from ivabradine.

Digoxin and heart rate

Castagno et al.8 have addressed the problem of heart rate reduction by another more traditional approach, namely digoxin. By analysing
the effect of digoxin in the DIG trial on the same outcomes as those found beneficial in SHIFT, they observed a similar beneficial effect on the composite of CV death or hospitalization for worsening heart failure. However, heart rate in DIG was only measured at baseline and an assumed reduction in heart rate is extrapolated by the authors from other studies in which the effects of digoxin on sympathetic and vagal activity have been studied as well as changes in heart rate. From studies on withdrawal of digoxin as well as initiation of digoxin, it is reasonable to assume a modest reduction of 4–7 b.p.m. in heart rate from the baseline heart rate of 78 b.p.m. in DIG. The main difference with SHIFT in this context is that the background use of a β-blocker was probably very low and was not even recorded in DIG. The absolute risk of patients enrolled in SHIFT and DIG was also different. The rate of the composite made of CV death or heart failure hospitalization in the placebo arm was 29% in SHIFT vs. 49% in DIG over a follow-up of 23 in SHIFT and 37 months in DIG. These differences in event rates were true for the two components of this composite CV mortality (15 vs. 30%) and HF hospitalizations (21 vs. 35%). The findings are not surprising, in that the two trials were conducted at a 13-year interval with very different background heart failure therapies.

We therefore believe that Castagno’s observation strengthens the importance of heart rate reduction to improve outcomes in a historical population treated by diuretic agents and angiotensin-converting enzyme inhibitors and complements the more recent findings of β-blocker trials and SHIFT in this respect.

The major difference between digoxin and ivabradine in heart rate reduction is safety. Digoxin is associated with well-known CV toxicity and accompanying symptomatic side effects that include nausea and visual disturbances. In addition, there are reports of more serious side effects by digoxin with increased mortality. This risk can be reduced, however, if blood concentrations are controlled and kept under certain levels, particularly in women, implying regular and costly blood examinations. The therapeutic margins are narrow between efficacy and toxicity.

Finally, the cardiac toxicity of digoxin is more likely to occur when there is renal dysfunction, a common situation in the elderly heart failure patients. The cardiac toxicity occurs partly because digoxin is excreted via the kidney. In contrast, ivabradine is safe, inducing few adverse effects. The most common side effect is bradycardia, which, if symptomatic, may lead to dose reduction or withdrawal in a few situations.

Serious adverse events are rare in SHIFT and we observed an incidence of significant bradycardic events leading to treatment discontinuation in only 1% of the cases. The overall incidence of serious side effects was lower in the ivabradine arm than in the placebo arm. No monitoring of blood concentration is required.

Finally, initiation and titration of ivabradine are not associated with haemodynamic effects such as hypotension. When compared with carvedilol, no significant effects on blood pressure were observed for ivabradine, whereas carvedilol induced a significant reduction in systolic and diastolic blood pressure, as would be expected.

**Clinical perspective**

The clinical implications of our findings reflect the importance of heart rate as we have reported previously. When a resting heart rate (≥70 b.p.m.) is observed in patients with systolic heart failure in sinus rhythm, the background pharmacological treatment should be reviewed, with particular focus on β-blocker therapy. If an increase in the dose of the β-blocker can be achieved and results in lowering the heart rate to <70 b.p.m., therapy with β-blocker alone is warranted. If this goal is not achievable clinically, the addition of ivabradine may be considered in order to reduce the risk of future CV events. If ivabradine is not available or in the presence of atrial fibrillation or flutter, digoxin is a viable alternative to reduce heart rate. However, whether this approach can improve prognosis above and beyond what is achieved by treatment with a β-blocker is not known.

**Conflict of interest:** Both authors have received research grant and honoraria from Servier, sponsor of SHIFT.

**References**