Left ventricular remodelling in systolic heart failure using ivabradine. Slower is smaller is better?

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This commentary refers to ‘Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiographic substudy’¹, by J.-C. Tardif et al., on page 2507

Tardif and co-workers have published the echocardiographic substudy of the SHIFT trial.¹ This pre-defined substudy included 611 out of 6505 patients from SHIFT, or, in other words, 9.3% of the entire cohort studied in SHIFT.² The authors report that of these 611 patients, 96 ivabradine- and 104 placebo-treated patients had to be excluded, mainly due to incomplete or unreadable echo recordings, which left 208 patients in the ivabradine group and 203 in the placebo group for analysis. The echoes were analysed centrally and the investigations were done at baseline and after 8 months, with the primary endpoint of change of left ventricular systolic volume index (LVESVI) at 8 months. This well-treated population [92% were on beta-blockers, with 56% taking 50% of the recommended dose, and 94% were treated with a renin–angiotensin system (RAS) antagonist] was not different from the entire SHIFT cohort, except for a lower rate of hypertension and a higher rate of use of mineralocorticoid receptor antagonists.

Eight months of ivabradine treatment resulted in a 7 mL/m² reduction of LVESVI, as compared with 0.9 mL/m² in the placebo group, and an increase in left ventricular ejection fraction (LVEF; a secondary endpoint) of 2.4%, whereas there was no change in the placebo group at all.

What can we learn from this study? What are the merits?

First of all, there was a huge amount of work done finalizing this substudy which is comparable with the REVERSE trial studying 684 patients.³ ⁴ Looking at substudies of the other class of heart failure drugs slowing heart rate—the beta-blockers—one is amazed at how few patients were investigated there. For example, the CAPRICORN echo study investigated 127 patients, in SENIORS 112 patients were investigated (but only 43 with an LVEF of 35%), and the MERIT-HF substudy looking at anti-remodelling effects investigated only 41 patients (although this was a magnetic resonance, not an echo study).⁵ ⁶ ⁷ In other words, 6.5% of the CAPRICORN cohort, 2% of the SENIORS cohort, and 1% of the MERIT-HF cohort served as a basis to investigate the anti-remodelling effect of these three beta-blockers in systolic heart failure. Keeping in mind that 9.3% of the SHIFT cohort took part in the echo study, the data should not leave much uncertainty.

Secondly, the data show that despite good treatment of heart failure, there is still the possibility to improve ventricular geometry by adding ivabradine to standard therapy. A total of 38% of patients on ivabradine had a decrease of LVESVI of at least 15% after 8 months and 36% had an increase of LVEF of at least 5% (corresponding to 25% and 23% for the placebo group, respectively).

Thirdly, a more detailed analysis of the placebo group according to median baseline LVESVI showed that those with LVESVI above the median more often reached the primary endpoint of the study, mainly driven by heart failure hospitalization. In other words, larger ventricles are prone to more frequent heart failure hospitalization.

All that glitters is not gold

Despite all the progress made in the last years, there are still too many patients that do not respond well enough to modern heart failure treatment with a reduction in heart failure hospitalizations.⁸ The SHIFT echo study supports this painful knowledge. Nearly 50% of these well-treated patients taking additional ivabradine or placebo did not respond with a relevant change in LVESVI.

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(± 15%) or in LVEF (± 5%) after 8 months of treatment. This is truly disillusioning.

Furthermore, the mean reduction of LVESVI of 7 mL/m² after 8 months of treatment is quite acceptable, but other types of treatment can do even more. Specifically, cardiac resynchronization in patients with mild heart failure leads to a reduction of LVESVI of 19 mL/m² after 12 months of stimulation\(^3,4\) and an increase of 4.6% in LVEF (compared with a 2.4% LVEF increase in SHIFT). In the recent largest echocardiographic substudy with CRT, reverse remodelling was even more pronounced.\(^9\)

Finally, ivabradine only works in patients with sinus rhythm. Luckily, the majority of heart failure patients are in sinus rhythm. However, between 23% and 35% of heart failure patients have current atrial fibrillation (AF) and up to 44% of patients have a history of AF; the sicker patients more often.\(^10,11\) These patients cannot enjoy the anti-remodelling effect of ivabradine.

### How do these findings fit into the picture?

Reversing ventricular remodelling is undoubtedly important. We can treat patients with all the neurohumoral blockers of the RAS and sympathico-adrenergic system. Although they improve ventricular geometry and survival, there is now a further possibility to do so by adding ivabradine to these drugs. In contrast to cardiac resynchronization this treatment can be started by every heart failure physician without great expense. However, as mentioned above, it works only in patients with sinus rhythm and, at least in this substudy, in a third of them.

Also, it is unclear if the anti-remodelling effects of ivabradine were similar if more patients were on target doses of beta-blockers. Direct inhibition of \(I_f\) channels by ivabradine in ventricular cardiomyocytes, which are upregulated in heart failure, may also play a role in reverse remodelling. In consequence, this large echocardiographic substudy shows that reverse remodelling can be induced by ivabradine, and that smaller ventricles were associated with better outcomes. Time will tell whether ivabradine will keep all its promises.

### Conflict of interest: none declared.

### References

3. Linde C, Abraham WT, Gold MR, St. John Sutton M, Ghio S, Daubert C, on behalf of the SHIFT-Investigators. Effects of selective heart rate reduction with ivabradine in patients with mild heart failure leads to a reduction of LVESVI of 15% or in LVEF (± 5%) after 8 months of stimulation\(^3,4\) and an increase of 4.6% in LVEF (compared with a 2.4% LVEF increase in SHIFT). In the recent largest echocardiographic substudy with CRT, reverse remodelling was even more pronounced.\(^9\)