Ivabradine added to guidelines-based therapy in systolic heart failure patients

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Background

Raised resting heart rate is a risk factor for morbidity and mortality in a patient with heart disease [1]. Several patients with heart failure show increased heart rate even if treated with beta-blockers. Furthermore, most patients are intolerant to these drugs. Ivabradine is a selective inhibitor of the I_f current in the sinoatrial node, resulting in heart rate reduction without affecting myocardial contractility and intracardiac conduction. This pure negative chronotropic effect was previously evaluated in patients with stable angina pectoris. Previously randomised clinical studies demonstrate that ivabradine reduces the heart rate and the risk of angina attacks, and improves exercise capacity, without affecting cardiovascular death and hospital admission for heart failure [2–4].

Summary

The SHIFT Trial [5] compared ivabradine with placebo in adjunct to standard therapy in patients with symptomatic heart failure with a left ventricular ejection fraction of 35% or

lower, who were in sinus rhythm, with a heart rate of 70 beats/min or higher. Three thousand two hundred and sixty eight patients were randomized to ivabradine (3,241 analyzed, mean age 60.7 years) and 3,290 to placebo (3,264 analyzed, mean age 60.1 years). Median follow-up was 22.9 months. The primary endpoint, consisting in cardiovascular death or hospital admission for worsening heart failure, occurred in 24% of patients in the ivabradine group and in 29% of those taking placebo (HR 0.82, 95% CI 0.75–0.90, $p < 0.0001$). This effect was mainly driven by hospital admissions for worsening heart failure (21 placebo vs. 16% ivabradine; HR 0.74, 95% CI 0.66–0.83, $p < 0.0001$). Considering the predefined subgroup of patients receiving at least 50% of the evidence-based target daily dose of beta-blockers, the primary composite endpoint and mortality were not significantly different between the ivabradine and placebo groups. Nevertheless, ivabradine reduced hospital admissions for worsening heart failure by 19% in this subgroup (HR 0.81, 95% CI 0.67–0.97, $p = 0.021$).

This drug was relatively well-tolerated: most common side effects were symptomatic bradycardia, which occurred in 5% of patients taking ivabradine as compared with 1% of patients taking placebo ($p < 0.0001$), and phosphenes, reported in 3% of patients on ivabradine and 1% on placebo ($p < 0.0001$).

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Strengths of the study

- The good pathophysiological rationale of the study: specific heart rate lowering drugs can reduce myocardial oxygen demand, without negative inotropic effects, thus preserving ventricular contractility. The SHIFT trial is the first study that evaluates a pure negative chronotropic agent in heart failure patients.

- The primary end point of mortality and hospitalization is clinically relevant: the reduction of hospital admissions observed in patients with advanced heart failure might improve their quality of life.

Weakness of the study

External validity: similar to previous studies on heart failure and as underlined by the authors, the population included in SHIFT study does not reflect the spectrum of patients with chronic heart failure usually met in common clinical practice as the mean age of included patients was about 60 years, with male gender predominance (76 in ivabradine and 77% in placebo groups) and the major cause of heart failure was ischemic in most of them (68%). In daily practice, heart failure epidemiology is different; with older patients and female gender more represented [6].

Question marks

- The number of patients who withdrew from the study is quite high (21 for ivabradine and 19% placebo groups). The authors underline that a lower incidence of serious adverse events was observed in ivabradine group; however, the reasons for loss to follow-up are not explained in detail.
- It would be interesting to know why more patients in the ivabradine group than in the placebo group developed atrial fibrillation (9 vs. 8%, $p = 0.012$). This aspect has not been commented upon in the manuscript.

Sponsorship

- The trial is sponsored by the ivabradine manufacturer, which was responsible for data management and final data analysis. However, all analyses were verified by an independent statistical center.

Clinical bottom line

- Ivabradine should be considered as an adjunctive drug for patients with systolic heart failure presenting with a high resting heart rate and who are truly intolerant to or on maximally tolerated dose of beta-blockers.
- For patients with ongoing therapy with optimal β -blockers dose, SHIFT trial results do not permit a definitive conclusion about ivabradine benefit.
- Patients should be carefully monitored for ivabradine dose titration and for symptomatic bradycardia development.

Conflict of interest None.

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