Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

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Summary

Background
Chronic heart failure is associated with high mortality and morbidity. Raised resting heart rate is a risk factor for adverse outcomes. We aimed to assess the effect of heart-rate reduction by the selective sinus-node inhibitor ivabradine on outcomes in heart failure.

Methods
Patients were eligible for participation in this randomised, double-blind, placebo-controlled, parallel-group study if they had symptomatic heart failure and a left-ventricular ejection fraction of 35% or lower, were in sinus rhythm with heart rate 70 beats per min or higher, had been admitted to hospital for heart failure within the previous year, and were on stable background treatment including a β blocker if tolerated. Patients were randomly assigned by computer-generated allocation schedule to ivabradine titrated to a maximum of 7·5 mg twice daily or matching placebo. Patients and investigators were masked to treatment allocation. The primary endpoint was the composite of cardiovascular death or hospital admission for worsening heart failure. Analysis was by intention to treat. This trial is registered, number ISRCTN70429960.

Findings
6558 patients were randomly assigned to treatment groups (3268 ivabradine, 3290 placebo). Data were available for analysis for 3241 patients in the ivabradine group and 3264 patients allocated placebo. Median follow-up was 22·9 (IQR 18–28) months. 793 (24%) patients in the ivabradine group and 937 (29%) of those taking placebo had a primary endpoint event (HR 0·82, 95% CI 0·75–0·90, p<0·0001). The effects were driven mainly by hospital admissions for worsening heart failure (672 [21%] placebo vs 514 [16%] ivabradine; HR 0·74, 0·66–0·83; p<0·0001) and deaths due to heart failure (151 [5%] vs 113 [3%; HR 0·74, 0·58–0·94, p=0·014). Fewer serious adverse events occurred in the ivabradine group (3388 events) than in the placebo group (3847; p=0·025). 150 (5%) of ivabradine patients had symptomatic bradycardia compared with 32 (1%) of the placebo group (p<0·0001). Visual side-effects (phosphenes) were reported by 89 (3%) of patients on ivabradine and 17 (1%) on placebo (p<0·0001).

Interpretation
Our results support the importance of heart-rate reduction with ivabradine for improvement of clinical outcomes in heart failure and confirm the important role of heart rate in the pathophysiology of this disorder.

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