Heart-rate-lowering drug ivabradine reduces death when added to treatments in heart failure patients

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The heart-rate-lowering drug ivabradine significantly reduces the risk of cardiovascular death and hospitalisation for worsening heart failure when added to standard treatment in patients with heart failure and a high heart rate, according to the first of two Articles published Online First in The *Lancet*, and being presented at the European Society of Cardiology Annual Congress in Stockholm. A second Article concludes that a high heart rate is an independent risk factor for heart failure and that lowering of heart rates is an important treatment target for patients with heart failure.

The Systolic Heart Failure treatment with the If inhibitor ivabradine Trial (SHIFT) investigated whether lowering heart rate with ivabradine reduces cardiovascular death and admission to hospital with worsening heart failure among patients with chronic heart failure, systolic dysfunction, and a high heart rate (70 beats per minute [bpm] or higher), over a median of 22.9 months' follow-up. 6505 patients from 37 countries were randomly assigned to ivabradine (starting dose 5 mg adjusted to a maximum of 7.5 mg twice daily; 3241) or placebo (3264) in addition to standard heart failure treatments.

Overall, treatment with ivabradine significantly reduced the risk of major heart failure outcomes by 18% compared to placebo. 16% of patients taking ivabradine were admitted to hospital with worsening heart failure compared to 21% in the placebo group, and 3% of patients

in the ivabradine group died due to heart failure compared to 5% in the placebo group. Additionally, treatment with ivabradine was associated with an average reduction in heart rate of 15 bpm.

Ivabradine was safe and generally well tolerated with serious side effects occurring more frequently in the placebo group (3847 events) than in the ivabradine group (3388 events).

They conclude: "Our results support the importance of heart-rate reduction with ivabradine for improvement of clinical outcomes in heart failure and confirm that heart-rate modulation can interfere with progression of disease."

To further evaluate these findings, Michael Böhm from the Universitätsklinikum des Saarlandes in Germany, together with the SHIFT authors, examined whether raised resting heart rate at the start of the study was a risk factor for subsequent cardiovascular events. Analysing data from the SHIFT study, they calculated the likelihood of cardiovascular death and hospitalisation for worsening heart failure in patients with highest (≥87 bpm) and the lowest (70-72 bpm) pretreatment heart rates, and after 28 days of treatment with ivabradine.

Overall, placebo-treated patients with the highest heart rates were more than twice as likely to die or experience a cardiovascular event. For every increase of 5 bpm from the start of the study, there was a 16% increased risk of cardiovascular death or hospitalisation.

Additionally, there was a direct association between heart rate at 28 days after treatment with ivabradine and cardiac outcomes. Patients with heart rates lower than 60 bpm at 28 days had fewer events (17.4%) during the study compared to patients with heart rates of 75 bpm or higher (32.4%).

The authors say: "There is a continuous direct association between baseline heart rate and outcomes. The risk is modified and significantly decreased by ivabradine. The effect of ivabradine on heart rate is most pronounced in patients with high baseline values and correspondingly high reductions in heart rate due to ivabradine treatment."

They conclude: "The lowest heart rates achieved on treatment are associated with the best outcomes, and because the incremental benefit of ivabradine was obtained by titration of the drug to heart rates lower than 60 bpm, we estimate that this target, when tolerated, should be pursued by patients with chronic heart failure."

In a Comment, John Teerlink from the University of California, San Francisco, USA, says: "Ivabradine therapy might reduce heart-failure hospitalisations when added to contemporary heart-failure therapies. However, whether ivabradine can improve outcomes in addition to optimally managed heart failure therapies or its benefits relative to other therapies, especially beta blockers, remains unknown. The results from SHIFT provide the basis for additional trials to test these important and clinically relevant questions... Until these questions are answered, the place of ivabradine in heart failure therapies remains unclear."

More information: www.thelancet.com/journals/lan … (10)61198-1/abstract

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