Can ivabradine reduce NT-proBNP and improve outcomes in systolic heart failure?

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Ivabradine selectively reduces heart rate (HR) by inhibiting If of the sinus node. The BEAUTI-FUL trial has shown that ivabradine is ‘beneficial’ in patients who suffered from coronary artery disease (CAD) with systolic heart failure (HF) (ejection fraction [EF] 32%) without evidence of overt HF. Added to standard therapy ivabradine did not significantly the primary composite endpoint (admission to hospital for new onset or worsening HF, admission to hospital for acute myocardial infarction or cardiovascular death); however, in a subgroup of patients with baseline HR > 70 bpm (mean 79 bpm) ivabradine significantly decreased (–36%) the risk for fatal and non-fatal acute myocardial infarction, and (–30%) the risk of coronary revascularization [1].

In the SHIFT trial patients with systolic HF (EF < 35%), mainly class New York Heart Association (NYHA) II–III and HR > 70 bpm, and who received optimized background therapy according to guideline recommendations were treated with ivabradine or placebo. A higher HR ≥ 75 bpm at entry, there was a significant reduction in the cardiovascular death and all-cause mortality endpoints [2]. Patients on ivabradine with an HR reduction (11 bpm) had an 18% decrease of composite endpoint; this result was primarily driven by a reduction (−26%) in hospital admissions for worsening HF [3, 4].

In patients with HF, due to ischemic etiology with left ventricular diastolic dysfunction and preserved systolic function ivabradine is poorly effective [5].

Importantly, in the SIGNIFY trial, in patients who had stable CAD (Canadian Cardiovascular Society [CCS] class ≥ 2) without clinical HF, and who were treated with guideline-recommended medical therapy, the addiction of ivabradine did not improve the outcome; furthermore, adverse events occurred statistically (p < 0.001 for all class comparisons) more frequently with ivabradine than with placebo [6]. Adverse events led to study-drug withdrawal in 13.2% of the ivabradine-group and in 7.4% of the placebo group (p < 0.001) [2]. Ivabradine significantly increased the frequency of symptomatic bradycardia, atrial fibrillation and phosphenes.

Ivabradine is generally considered to be safe [7, 8]. However, in patients with stable CAD, when added to other drugs such as beta-blockers, the drug may induce severe bradycardia and increase the occurrence of atrial fibrillation [6]. Furthermore, at least in patients with a long QT ivabradine has the potential for the occurrence for the occurrence of torsades de pointes [9].

In the present issue of the journal, Ordu et al. [10] report the findings of a prospective, open-label study in 98 outpatients with stable systolic HF (LVEF < 35%). The study had a two-arm design. Patients received optimized background therapy according to guideline recommendations. Ivabradine (average dose 10 ± 3 mg/day) or placebo was added for 6 months. Ivabradine significantly decreased the NYHA class and HR from 84 ± 8.8 to 68 ± 8.3 bpm. The authors assessed the effect of ivabradine on cystatin C, CA-125 and N-terminal of the prohormone B-type natriuretic peptide (NT-proBNP). The three biomarkers decreased significantly (p = 0.001 in comparison with placebo).
Cystatin C decreased from 2.1 ± 0.7 to 1.5 ± 0.4 ml/L. It is established that renal dysfunction is frequent in HF and, when present, is associated with higher mortality and morbidity [11]. The decrease of cystatin C might be interpreted as evidence that renal dysfunction decreased, thus improving cardiovascular outcomes. Unfortunately, the values at the end of the study were still elevated (1.5 ± 0.4 mg/L) and, as well demonstrated by Shlipak et al. [12], the risk for all cause of death remained very high.

Ordu et al. [10] also measured CA-125, which decreased from 31 ± 21 to 13 ± 8 U/L. CA-125 is not a ‘cardiac’ marker: it has limited specificity for ovarian cancer, may be elevated in a number of conditions, and in the presence of any inflammatory condition in the abdominal area as well as in cirrhosis and diabetes mellitus [13]. The ‘normal’ level for CA-125 is considered to be up to 35 U/mL. CA-125 values were normal before and after ivabradine. Even if the decrease was statistically significant, one cannot explain how the observed minor decrease might interact with cardiac outcomes.

NT-proBNP is a well-known cardiac marker which has been extensively used to assess the benefits of BNP-guided therapy in chronic HF [14]. In the study by Ordu et al. [10] NT-proBNP significantly decreased from 1.353 ± 1.454 to 718 ± 835 pg/L. However, standard deviation is greater than the mean value and the detected changes might be within the well-known spontaneous fluctuations observed in patients with severe congestive HF [14]. Perhaps ivabradine decreased NT-proBNP, at least in some patients. Nonetheless, the end-values are still much higher than the levels regarded as necessary to consider if medical therapy is adequate [14].

Several caveats also limit the authors’ findings. First, the data result from a single center, the duration of therapy was short and the number of patients is too small to detect adverse effects and assess the effect on cardiac outcomes. Second, 16% of patients had cardiac pacemakers. Ivabradine, especially combined with beta-blockers, may induce severe bradycardia, but this adverse effect can be monitored to avoid the occurrence of severe bradycardia and to be properly treated if atrial fibrillation.

When patients who have HF due to ischemic etiology are treated with ivabradine, they should be monitored to avoid the occurrence of severe bradycardia and to be properly treated if atrial fibrillation occurs.

Conflict of interest: None declared

References

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