VIA MEDICA

EDITORIAL

Cardiology Journal
2015, Vol. 22, No. 5, 482–484
DOI: 10.5603/CJ.2015.0068

ISSN 1897–5593

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

Giuseppe Cocco, Paul Jerie

Cardiology Office, Rheinfelden, Switzerland

Article p. 501

Ivabradine selectively reduces heart rate (HR) by inhibiting I*f* of the sinus node. The BEAUTIFUL 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).

Address for correspondence: Giuseppe Cocco, MD, Cardiology Office, Marktgasse 10A, CH-4310 Rheinfelden, Switzerland, tel: +00 41 61 831 45 55, fax: +00 41 61 833 97 56, e-mail: praxis@cocco.ch

Received: 05.07.2015 Accepted: 06.07.2015

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 undetected in patients with a pacemaker. Third, patients had a systolic EF < 35%. Many patients (data are unclearly offered) had a combination of CAD, hypertension and diabetes mellitus. Concomitant pathologies are 'real-life' facts in patients with severe congestive HF. The authors did not report necessary data, such as the clinical conditions and values of blood pressure and did not report any adverse events. It is difficult to assess the effect of ivabradine in a mixed-population.

We are left with the question how ivabradine should optimally be used in cardiological practice. Given that the primary cardiovascular effect of ivabradine is to reduce HR, in patients who have stable CAD without clinical HF, an elevated HR might only be a marker of risk, but not a modifiable determinant of outcomes. Elevated HR may be a sign of different pathophysiological mechanisms in patients with HF and in those with CAD. Perhaps ivabradine has no effect on outcomes in patients with stable CAD. At least from the SIGNIFY study, it might be assumed that there may be a J-shaped curve for the relationship between HR and cardiac outcomes. There is a signal for an increase in the risk of cardiovascular events among patients with angina of CCS class II or higher. In some patients ivabradine may decrease HR too much or induce 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

1. Fox K, Ford I, Gabriel Steg G et al.; on behalf of the BEAUTIFUL Investigators. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: A subgroup analysis of the randomized controlled BEAUTIFUL trial. Eur Heart J, 2009; 30: 2337–2345. doi: 10.1093/eurheartj/ehp358.
2. Swedberg K, Komajda M, Borer JS et al.; on behalf of the SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. Lancet, 2010; 376: 875–885.
3. Fox K, Ford I, Steg PG et al. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: A subgroup analysis of the randomized controlled BEAUTIFUL trial. Eur Heart J, 2009; 30: 2337–2345.
4. Böhm M, Swedberg K, Komajda M et al. Heart rate as a risk factor in chronic heart failure (SHIFT): The association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet, 2010; 376: 886–894.
5. Cocco G, Jerie P. Comparison between ivabradine and low-dose digoxin in the therapy of diastolic heart failure with preserved left ventricular systolic function. Clin Pract, 2013: 3: e29:7783. doi:4081/cp.2013.e29.
6. Fox K, Ford I, Steg PG et al.; for the SIGNIFY Investigators. Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure. N Engl J Med, 2014; 371: 1091–1099. doi: 10.1056/NEJMoa1406430.

7. Mc Murray J, McMurray JJ, Adamopoulos S et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J, 2012; 33: 1787–1747.
8. Montalescot G, Sechtem U, Achenbach S et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J, 2013; 34: 2949–2903.
9. Cocco G, Jerie P. Torsades de pointes induced by the concomitant use of ivabradine and azithromycin. An unexpected dangerous interaction. Cardiovasc Toxicity, doi: 10.1007/sI2012-014-9274-y.
10. Ordu S, Yildiz BS, Alihanoglu YI et al. Effects of ivabradine therapy on heart failure biomarkers. Cardiol J, 2015; 22: 501–509. doi: 10.5603/CJ.a2015.0012.
11. Damman K, Testani JM. The kidney in heart failure: an update. Eur Heart J, 2015; 36: 1437–44. doi: 10.10.109/eurHeartj/ehv010.
12. Shlipak MG, Sarnak MJ, Katz R et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med, 2005; 352: 49. doi: 10.1056/NEJMoa043161.
13. Faulkner D, Meldrum C. "Tumour markers". Australian Prescriber, 2012; 35: 125–128.
14. Cocco G, Jerie P. Assessing the benefits of natriuretic peptides-guided therapy in chronic heart failure. Cardiol J, 2015; 22: 1–11. doi:10.5603/CJ.a2014.0041.