If Channel Inhibition - Ivabradine for the Treatment of Heart Failure

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Abstract

The novel first-in-class If channel antagonist, Ivabradine, is effective in improving clinical outcomes and functional capacity, in patients with HF, as well as demonstrating useful anti-anginal and protective anti-ischaemic effects. It can help improve heart rate control and can be usefully co-administered with beta blockers on HFrEF patients with residually elevated resting sinus rhythm heart rate. We review the clinical trial evidence for the benefits of Ivabradine in the treatment of heart failure.

Keywords: heart failure; ivabradine; clinical trial

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Introduction

Ivabradine is a selective antagonist of the If (funny) channels with anti-anginal and anti-ischaemic properties.[1-2] The drug provides pure heart rate reduction, reducing the diastolic depolarization slope, without altering other cardiac and haemodynamic parameters. Ivabradine is effective for the treatment of ischaemic heart disease, where it reduces episodes of both symptomatic angina pectoris and myocardial ischemia, and in heart failure where it has been shown to reduce mortality and morbidity.[3-13] At approved doses ivabradine also improves exercise performance and reduces heart rate.

Ivabradine selectively blocks the If-channels in the pace-maker cells of the sinus node by binding to a site in the channel and inhibits the ion flow through the channels.[1] Therefore, ivabradine reduces the If-current and the slope of the slow diastolic depolarisation phase of the action potential in the sinus node cells. This effect increases the time required to reach the voltage threshold for action potential initiation slowing the spontaneous firing of sino-atrial node cells and therefore reducing heart rate. At therapeutic doses, ivabradine does not affect any other cardiac ion currents (IK, ICaL or ICaT). Because of its mode of action it is only indicated for use in patients in sinus rhythm.

Ivabradine acts specifically on the sinus node and it has no effects on intra-atrial, atrio-ventricular or intra-ventricular conduction. It does not affect directly myocardial contractility, blood pressure

or ventricular repolarisation. The EU approved starting dose of ivabradine is 5 mg twice daily (b.i.d) and 2.5 mg b.i.d. for patients over 75 years of age. The dose can be increased to 7.5 mg twice daily depending on the therapeutic response.

Ivabradine has been initially approved for the treatment of angina pectoris on the basis of sound data showing its effectiveness in improving exercise capacity and ischaemic threshold significantly more than placebo, and with an effectiveness similar to that of atenolol.[3] Comparative data against atenolol show a greater effect of ivabradine in improving ischaemic threshold and exercise capacity.[4] Subsequent data have shown a greater effect of ivabradine when added to atenolol than atenolol alone and a significant reduction of mortality and morbidity in patients with heart failure.[5,8]

Subsequently, after the publication of the results of the SHIFT study, ivabradine was approved in Europe for the treatment of patients with chronic heart failure in New York Heart Association (NYHA) class II to IV with systolic dysfunction in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.

In patients with stable heart failure with a heart rate above 70 beats per minute (bpm) included in the SHIFT trial (Systolic Heart failure treatment with the If inhibitor ivabradine Trial), an elevated baseline resting heart rate was associated with an increased risk of cardiovascular death and heart failure hospitalizations,

Figure 1. Effect of Ivabradine on all-cause hospitalizations after a first hospital admission for HF. Adapted with permission from Komajda M et al. Eur J Heart Fail. 2016; doi: 10.1002/ehf.582

which translates into a 3% increase in risk for every 1-bpm increase from baseline heart rate and 15% increase in risk for every 5-bpm increase.[9] Heart rate reduction with ivabradine reduced the composite outcome of cardiovascular death and heart failure hospitalisation in patients with HFrEF with a heart rate above 70 bpm and cardiovascular death and total mortality in the subgroup of patients with a heart rate above 75 bpm. [10] Hospitalisations for heart failure were reduced by 26% with ivabradine and the effect appeared early and was constant throughout the study.

Furthermore the SHIFT study showed amongst the 1,186 patients a 34% reduction in second heart failure hospitalizations among those who were admitted once, and a 29% reduction among those who were admitted twice. All-cause and cardiovascular hospitalisations were similarly reduced by ivabradine and, in patients with more than one admission, ivabradine prolonged the time to a second admission, with a longer time out of hospital free of worsening heart failure. Indeed, the time from one admission to the subsequent one was prolonged by 17% by ivabradine, and significantly fewer patients with HFrEF who received ivabradine during the study suffered a second hospital admission.

Ivabradine is effective in preventing early re-admission in patients with HFrEF who had been hospitalised for heart failure. Indeed, among those patients who suffered a first hospitalization during the study, patients receiving ivabradine had a reduced occurrence of re-hospitalisation in the following 30 days (4.1%) compared to those receiving placebo (6.3%). These findings clearly show the benefit of ivabradine, on a background of beta-blockade, angiotensin-converting enzyme inhibitors, mineralocorticoid receptor antagonists, and diuretics in reducing early and later re-hospitalisations for heart failure.

After discharge from a heart failure-related hospitalization, relative under-treatment of patients with β -blockers and angiotensin-converting enzyme (ACE) inhibitors occurs often in patients with low blood pressure. A proportion ranging between 15% to 25% of patients discharged from hospital for an episode of de-compensation have low blood pressure (ie, <120 mm Hg), which reduces the likelihood of full implementation of guideline-directed medical therapy which consequentially puts these patients at an increased risk for poor outcomes. The combination

Figure 2. Benefit of IVABRADINE on Mortality in patients with heart rate $\geq$ 75bpm

of higher heart rates and low blood pressure further increases event rates in patients with heart failure. In this population of patients with heart failure ivabradine showed a consistent effect on the reduction of hospitalisations and events.[11] An early initiation of ivabradine in patients discharged after an episode of cardiac de-compensation leads to a higher proportion of patients receiving evidence-based treatment, and to a greater number of patients reaching target heart rate.

Clinical trials have demonstrated that ivabradine effectively improves functional capacity in HFrEF. The CARVIVA-HF (CARvedilol, IVABradine or their combination on exercise capacity in patients with Heart Failure) trial[12] found that ivabradine alone or in combination with carvedilol was more effective than carvedilol alone in improving exercise tolerance and quality of life in HF patients. In this study, patients receiving carvedilol and ivabradine in combination had a better exercise performance than those receiving carvedilol alone. The effects of ivabradine on exercise capacity were associated with an improvement in isokinetic strength compared to carvedilol, and with a significant decrease in the fatigue index. These data are in agreement with a sub-analysis of the SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine Trial) in 1944 patients, in which health-related quality of life was found to be inversely associated with clinical events.[18] Treatment with ivabradine was associated with improvements in quality of life scores and improved outcomes. This was due largely to improvements in exercise capacity and symptoms.

Therefore, ivabradine-beta-blocker therapy is associated with a better functional capacity than beta-blocker therapy alone and combination therapy provides better quality of life than beta-blocker monotherapy. Most of the effects of ivabradine on functional capacity are related to the haemodynamic improvements provided by ivabradine in HF and not only through heart rate reduction.[13-14] In fact ivabradine provides an anti-remodelling effect, improves left ventricular structure and function, and reduces N-terminal pro-brain natriuretic peptide levels. When compared to beta-blockers, ivabradine, for the same degree of heart rate reduction, does not impair the neuro-muscular junction thereby affecting skeletal muscular contraction.

Declarations of interest

The authors declare no conflict of interest.

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Conclusions

The novel first-in-class If channel antagonist, Ivabradine, is effective in improving clinical outcomes and functional capacity, in patients with HF, as well as demonstrating useful anti-anginal and protective anti-ischaemic effects. It can help improve heart rate control and can be usefully co-administered with beta blockers on HFrEF patients with residually elevated resting sinus rhythm heart rate. [15]

References

1. Sulfi S, Timmis AD. Ivabradine -- the first selective sinus node I(f) channel inhibitor in the treatment of stable angina. *Int J Clin Pract*. 2006;60(2):222-228.
2. DiFrancesco D. Funny channels in the control of cardiac rhythm and mode of action of selective blockers. *Pharmacol Res*. 2006;53(5):399-406.
3. Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K, Investigators I. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J*. 2005;26(23):2529-2536.
4. Tardif JC, Ponikowski P, Kahan T, Investigators AS. Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. *Eur Heart J*. 2009;30(5):540-548.
5. Fox K, Ford I, Steg PG, Tendera M, Ferrari R, Investigators B. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372(9641):807-816.
6. 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(19):2337-2345.
7. Steg P, Lopez-de-Sa E, Schiele F, et al. Safety of intravenous ivabradine in acute ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention: a randomized, placebo-controlled, double-blind, pilot study. *Eur Heart J Acute Cardiovasc Care*. 2013;2(3):270-279.
8. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376(9744):875-885.
9. Tardif JC, O'Meara E, Komajda M, et al. Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy. *Eur Heart J*. 2011;32(20):2507-2515.
10. Fox K, Komajda M, Ford I, et al. Effect of ivabradine in patients with left-ventricular systolic dysfunction: a pooled analysis of individual patient data from the BEAUTIFUL and SHIFT trials. *Eur Heart J*. 2013;34(29):2263-2270.
11. Borer JS, Böhm M, Ford I, et al. Effect of ivabradine on recurrent hospitalization for worsening heart failure in patients with chronic systolic heart failure: the SHIFT study. *Eur Heart J* 2012;33:2813-20.
11. Borer JS, Fox K, Jaillon P, Lerebours G, Ivabradine Investigators G. Antianginal and antiischemic effects of ivabradine, an I(f) inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. *Circulation*. 2003;107(6):817-823.
12. Volterrani M, Cice G, Caminiti G, et al. Effect of Carvedilol, Ivabradine or their combination on exercise capacity in patients with Heart Failure (the CARVIVA HF trial). *Int J Cardiol*. 2011;151(2):218-224.
13. Rosano GM, Vitale C, Volterrani M. Heart rate in ischemic heart disease. The innovation of ivabradine: more than pure heart rate reduction. *Adv Ther*. 2010;27(4):202-210.
14. Sarullo FM, Fazio G, Puccio D, et al. Impact of "Off-Label" Use of Ivabradine on Exercise Capacity, Gas Exchange, Functional Class, Quality of Life, and Neurohormonal Modulation in Patients with Ischemic Chronic Heart Failure. *J Cardiovasc Pharmacol Ther* 2010; 15:349-55.
15. Shewan LG, Coats AJS, Henein MY. Authors' Responsibilities and Ethical Publishing. *International Cardiovascular Forum Journal* 2018;13:3-4, DOI: 10.17987/icfj.v13i0.525"