Received Date : 18-Feb-2014

Revised Date : 07-May-2014

Accepted Date : 08-May-2014

Article type : Unsolicited Review

# Is there a role for ivabradine beyond its conventional use?

Ivano Bonadei MD, Enrico Vizzardi MD, Edoardo Sciatti MD, Valentina Carubelli MD, Carlo M Lombardi MD, Antonio D'Aloia MD, Marco Metra MD

Section of Cardiovascular Diseases, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Study of Brescia

**Corresponding Author:**

Enrico Vizzardi, MD

P. le Spedali Civili 1

Section of cardiovascular diseases

University of Study of Brescia

25123 Brescia

Tel.: +39303995679;

Fax: +390303995061

Mail: enrico.vizzardi@tin.it

**Abstract**

Results of recent clinical trials in patients with stable angina and chronic heart failure have successfully demonstrated a beneficial role of use of ivabradine in addition to the conventional therapy. Based on the results of these trials, the aim of our review is to give an

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1111/1755-5922.12080

overview of the literature about the use of ivabradine in clinical settings outside its usual purpose.

**Introduction**

There has been increasing evidence that resting heart rate (HR) might be a marker of risk, or even a risk factor for cardiovascular morbidity and mortality. HR is a powerful predictor of mortality in normal individuals (1, 2) as well as in patients with hypertension (3), myocardial infarction (MI) (4), stable coronary artery disease (CAD) (5) and chronic heart failure (HF) (6). HR is a major determinant of myocardial oxygen consumption and energy use; in addition, an increase in HR reduces the diastolic coronary perfusion time. In effect, reducing HR decreases myocardial oxygen demand and improves endocardial blood supply.

At the time, existing therapies capable of reducing HR — that is, beta-blockers and some calcium antagonists — had a number of potential adverse effects, such as negative inotropism and arterial hypotension as well as undesirable effects, which led to problems achieving target doses, treating patients with comorbidities and minimizing drug Interactions. The novel aspect of ivabradine relates to selectivity and specificity for If channels (7).ivabradine Moreover, it does not affect myocardial contractility, preserves cardiac output, and significantly enhances stroke volume and systolic stroke work (8). Recent multicentre, prospective, randomised and controlled trials have demonstrated both a significant reduction in non-fatal myocardial infarction (9) and a decrease of hospitalisation rate from HF (10) in patients with left ventricular (LV) systolic dysfunction treated with ivabradine; in those patients, ivabradine still improves LV reverse remodelling (11), quality of life (12) and exercise capacity (13).

Since the reduction in HR may be prognostically favourable in several diseases in which β blockers or calcium antagonists are contraindicated, the aim of our review is to describe the effects of ivabradine beyond its conventional clinical use.

**Acute myocardial infarction**

Tachycardia is common in the acute stage of ST-elevation myocardial infarction (STEMI), whether related to the sympathetic nervous system activation caused by pain or as a compensatory phenomenon to acute HF complicating STEMI.

The VIVIFY (eValuation of the IntraVenous If inhibitor ivabradine after ST segment elevation mYocardial infarction) trial showed that intravenous ivabradine (over 8 hours) after percutaneous coronary intervention (PCI) for STEMI produced a rapid and sustained

reduction in HR, which was safe and well tolerated. Specifically, the HR reduction produced by ivabradine was not associated with any impact on blood pressure and hemodynamics but was associated with lower left ventricular volumes (14).

Fasullo et al. (15) have investigated the feasibility, tolerability, and the effects of ivabradine versus metoprolol in early phases of anterior STEMI reperfused by PCI. Even if in this randomised trial, the Ivabradine group was not given beta-blockers and ivabradine was delivered late after angioplasty (i.e. 12 hours), results suggested that oral ivabradine may be administered early to patients with successful PCI for anterior STEMI with impaired left ventricular function, high HR and sinus rhythm. Furthermore, Gerbaund et al. have demonstrated that in successfully reperfused STEMI patients, early administration of ivabradine (1-3 hours after PCI) may improve LV remodelling when added to current guideline-based therapy (16).

**Acute decompensated systolic heart failure**

Increased HR is usual in acute decompensated HF, and may act as a compensatory mechanism or be because of vasopressor use or a contributing factor for clinical deterioration. Ivabradine, improving ventricular-arterial interaction caused by HR reduction, seems to contribute to the increase in stroke volume and improved cardiac efficiency thereby preserving cardiac output ivabradine(17).

Based on these features, Sargento et al, have recently published the results of a pilot study about the safety of ivabradine in 10 patients with acute decompensated systolic HF and HR >70 bpm. They noted a significant reduction in HR after the introduction of oral ivabradine, correlated with the reduction of NT-proBNP values and NYHA class. These results suggested that the addition of oral ivabradine before in that population - might be safe and efficient (18).

**Inappropriate sinus tachycardia**

Initially ivabradine was reported for its off-label efficacy in cases of inappropriate sinus tachycardia (IST) and postural orthostatic tachycardia syndrome (POTS) (19-21). Calò et al. in a case series that included 18 IST patients demonstrated the effects of ivabradine in reducing HR at the Holter recordings and to increasing the exercise tolerance in stress tests (22). Still, in another case series comparing the effect of Metoprolol and ivabradine on

resting HR and during exercise in IST patients, ivabradine was more effective in relieving symptoms during exercise or daily activity and was better tolerated (23).

Cappato et al. investigated the role of ivabradine in the treatment of symptomatic IST using a double blind, placebo-controlled, crossover design. They evidenced that ivabradine significantly improved symptoms associated with IST and eliminated them in approximately half of the patients (24).

More recently, a clinical benefit and quality of life improvement during 1 year of treatment with ivabradine has been demonstrated in a series of IST patients (25). Moreover, in a case series of 22 patients with POTS, McDonald et al. demonstrated that ivabradine could reduce the symptoms and patient perceived tachycardia in 55% of cases, an efficacy comparable with other therapies (26, 27).Still, Sutton et al. reported that 72% of 25 patients with vaso-vagal syncope, who demonstrated sinus tachycardia before collapse on tilt testing, reported a marked benefit or complete resolution of symptoms (28).

Even if the results of these studies are encouraging but not conclusive, ivabradine appears to control POTS and IST-related symptoms with an efficacy similar to conventional treatment; thus further systematic collection of objective data or controls are needed to establish the true efficacy of ivabradine over placebo and pharmacological agents used in the management of these autonomic disorders.

**Microvascular angina pectoris**

Microvascular angina pectoris (MVA) is usually suspected, by exclusion, in patients with sufficiently typical chest pain in whom, despite abnormalities of the ECG and/or stress test results indicative of myocardial ischemia, arteriography surprisingly fails to show fixed or dynamic obstructions in the epicardial coronary arteries (29). Although several epidemiological studies have consistently shown that the prognosis of stable MVA is excellent, from 20% to 30%, MVA patients have progressive worsening of symptoms, with angina attacks becoming more frequent and prolonged over time and induced by only mild effort or even appearing at rest, which significantly impairs quality of life (30). Classical anti-ischemic medications, particularly β blockers, are the mainstream of the therapy (31). Villano et al. have demonstrated a beneficial effect of ivabradine on angina symptoms and quality of life in 16 MVA patients, independently from many major direct effects on systemic vascular and coronary microvascular function (32).

**Chronic obstructive pulmonary diseases**

Cardiovascular diseases, including coronary artery diseases and HF, are major comorbidities in chronic obstructive pulmonary diseases (COPD) (33, 34). COPD patients with CAD generally have elevated HR and beta-blockers are known to improve the survival of patients with CHF or CAD (35, 36). Previous studies have shown that patients with CAD and coexisting COPD generally failed to receive optimal therapy or appropriate drug dosages of β blockers for HR reduction. In a recent study, 54% of patients suffered from HF in a population with CAD and COPD, and only 52.8% of these patients were receiving β blocker therapy. In addition, in the majority of these patients the daily dosages of beta-blockers were not at target dose, which could be explained by the physicians' hesitation to prescribe them due to possible adverse pulmonary effects (37). So far, smaller studies have suggested that ivabradine does not affect pulmonary function and may be safe in both asthma and COPD (38).

Tavazzi et al. evaluated data from SHIFT regarding the effectiveness and safety of Ivabradine in patients with HF and COPD, focusing on hard clinical endpoints during long-term follow-up in a reasonably large sample of patients (n = 730). Ivabradine was equally safe and effective in reducing the primary endpoint in patients with and without COPD when added to standard therapy. This effect seems to be independent of β blocker use although this was not properly tested. Thus, when the maximally tolerated β blocker dose is achieved and HR remains elevated, ivabradine can be safely added in HF patients also suffering from COPD just like in the other HF patients (39).

**Other possible uses and perspectives**

- *HF with preserved ejection fraction (HFpEF) and right ventricular HF*

  In the early stages of HFpEF, while the primary problem relates to impaired LV relaxation, high HR during exercise may be particularly detrimental by reducing time for diastolic filling and promoting increased LV filling pressure and exercise intolerance. Therapeutic measures prolonging the LV filling phase may optimize transmitral flow, thereby reducing increased filling pressures and the resultant dyspnoea. Kosmala et al. have demonstrated that short-term treatment with ivabradine increased exercise capacity, with a contribution from improved left ventricular filling pressure response to exercise as reflected by the ratio of peak early diastolic mitral

flow velocity to peak early diastolic mitral annular velocity (40). It may be explained by ivabradine properties to decrease arterial elastance through enhancement of arterial compliance and reduction in HR (17), and through the improvement in endothelial function (41).

•*Pericarditis and myocarditis*

It has been proposed that HR could be at least partly associated with inflammation, providing a vicious circle, supporting the value of HR-lowering drugs for controlling symptoms linked to tachycardia and, above all, inflammation worsened by tachycardia (42). Roubille et al. have proposed a possible role of ivabradine in that setting (43).

•*Pre–treatment before coronary CT angiography*

Several authors have proposed pre-treatment with ivabradine before coronary CT angiography both in patients that were taking a β blocker or a calcium channel antagonist (44) and in patients that were not taking anything (45,46). Results of those studies demonstrated that ivabradine is safe and effective in increasing the rate of patients at the target HR before coronary TC angiography and in reducing the need for additional IV β blockade in patients referred for the exam. In particular, ivabradine 7.5 mg is more effective than ivabradine 5 mg (47).

• *Sepsis or multi-organ dysfunction syndrome (MODS)*

Uncontrolled tachycardia in systemic inflammatory response syndrome and sepsis deprives the heart muscle of oxygen. As it progresses, insufficient heart muscle nutrition eventually leads to myocardial dysfunction. It can also present as systolic and/or diastolic HF. In acute coronary syndromes, β blockers are used to control HR. However, in MODS, it cannot be used due to hemodynamic instability and worsened myocardial function (48). In that setting ivabradine could be safe and to test this hypothesis the MODIFY trial was designed (49).

•*Heart transplant*

The clinical evidence regarding ivabradine treatment in heart transplant (HTx) recipients remains limited. Zhang et al. during a 12-week follow-up of patients with

HTx and chronic tachycardia demonstrated a significant reduction in HR (22%) after ivabradine treatment (50). These results were confirmed during a long follow-up (51).

**Conclusions**

Because of its peculiar and unique mechanism of action, ivabradine is a fascinating agent and the exploration of its potential use is very interesting. Despite its indication in chronic HF and stable angina patients, ivabradine may be safe and effective in several other clinical settings. This finding needs to be confirmed by further studies.

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