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Ivabradine in practice

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Ivabradine is an innovation in the cardiovascular fraternity with specific heart rate-lowering property, which expresses selective action on pacemaker activity in the sinoatrial node of the heart, resulting into important clinical benefits for improvement in coronary perfusion and pump efficiency. Ivabradine demonstrated substantial antianginal and anti-ischemic efficacy, improvement in exercise capacity and in quality of life in monotherapy or in combination with beta-blockers. The analysis of pooled data from ivabradine angina development programme assessing the antianginal efficacy of ivabradine across several different subgroups provided clinical evidence that ivabradine diminishes angina in all types of patients, whatever their age, sex, severity of angina, and revascularization status, history of previous myocardial infarction, peripheral vascular disease, or diabetes. These clinical benefits make ivabradine an important agent for symptomatic treatment of patients with angina pectoris. The important role of ivabradine in the management of patients with chronic heart failure (HF) is well established and supported by its benefits in prevention of morbidity and mortality demonstrated in SHIFT trial. Efficacy and tolerability of ivabradine in patients with HF, including those with different clinical profiles (elderly; severe disease; low blood pressure; comorbidities, including renal dysfunction, diabetes, chronic obstructive pulmonary disease), make ivabradine particularly pertinent for achievement of all targets in the treatment of HF, including improvement of symptoms and well-being, as well as outcomes. The available wealth of evidence supports the important place of ivabradine as an essential therapeutic modality to enhance the management of patients with angina or chronic HF.

Ivabradine is an innovation in the cardiovascular (CV) fraternity with specific heart rate (HR)-lowering property, which expresses selective action on pacemaker activity in the sinoatrial node of the heart, resulting into important differences compared with non-selective HR-reducing agents such as beta-blockade.[1] By inhibiting I_f, an ionic current that modulates pacemaking activity, ivabradine lowers HR without directly affecting myocardial contractility (or relaxation), ventricular repolarization, or intracardiac conduction.[2] The specific nature of the HR lowering action of ivabradine offers additional benefits resulting to a realization of full benefits of HR reduction for improved coronary perfusion and pump efficiency. The available wealth of scientific evidences supports the important place of ivabradine in clinical practice as an essential therapeutic modality to enhance management of patients with angina or chronic heart failure (HF).

Symptomatic treatment in patients with stable angina pectoris

The optimal management of coronary artery disease (CAD) is based on achieving the following goals: reduce myocardial ischaemia, improve quality of life, and prevent CV events. However, the SIGNIFY (Study assessInG the morbidity–mortality beNefits of the If inhibitor ivabradine in patients with coronarY artery disease) trial which evaluated the efficacy of ivabradine in patients without HF and left ventricular systolic dysfunction (LVSD),[3] revealed surprising neutral effects of ivabradine in preventing CV events [CV deaths and non-fatal myocardial infarctions (MIs)]. Since then, the European Medicines Agency (EMA) through its evaluation has concluded that there were no

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favourable effects observed with ivabradine on clinical outcomes and prognosis in patients with stable CAD.[4] However, it was also pointed out that this is also true for other drugs such as beta-blockers or calcium antagonists used for the symptomatic treatment of CAD recommended by the European Cardiology Society (ECS) guidelines.[5] Hence the agency concluded that there are clinically relevant benefits to the symptomatic treatment of angina pectoris with ivabradine with specific product information amendments for its clinical use, including initiation of treatment in patients with HR $\geq$70 b.p.m., recommendation not to exceed the authorized posology and contraindication of concomitant treatment with moderate CYP3A4 inhibitors with HR-reducing properties such as diltiazem or verapamil.

Throughout ivabradine's development programme, it has been proved to be effective in reducing angina attacks and improving the quality of life for angina patients. Ivabradine substantially reduced the frequency of angina attacks and the consumption of short-acting nitrates compared with placebo,[6] standard antinational therapies such as beta-blocker or calcium channel blocker[7,8] in the short-term (2 to 3 months) and maintained antianginal efficacy in long-term (1 year) therapy without development of pharmacological tolerance.[9] Ivabradine also showed significant anti-ischaemic efficacy and improvement of exercise capacity, which are important clinically for angina. Ivabradine demonstrated improvements in time to 1-mm ST-segment depression, to angina onset, and to limiting angina in monotherapy[6,7] or in patients receiving beta-blocker therapy.[10] In clinical practice, these data suggest ivabradine with beta-blockers as the best evidence-based combination therapies for angina patients. Moreover, the importance of increases of HR during daily activity due to physical or emotional stress as a trigger of myocardial ischaemia is well established and explained the crucial need to prevent the excessive increases of HR.[11]

In addition, the clinical use of ivabradine is also confirmed in day-to-day practice when added to beta-blockers with a significant reduction of angina attacks and short-acting nitrate consumption.[12] In line with reduction in angina attacks, ivabradine improved quality of life assessed by EQ-5D questionnaire (both EQ-AD index as well as visual analogue scale) throughout of 4 months of therapy with ivabradine.

These data have important clinical implication showing that symptomatic patients with stable angina with HR above 70 b.p.m. will have a significant reduction in angina attacks, and improvement in exercise capacity and in quality of life with the addition of ivabradine. The difference in the clinical benefits rendered by ivabradine when compared with other HR-lowering agents can be partly explained by its significant increase in coronary flow reserve after short-term treatment.[13] The improvement of coronary flow reserve may have profound clinical implications taking into account that it has a direct impact to address ischaemia.[14]

There are few sources of contemporary information on the current clinical presentation and management of outpatients with CAD: from randomized clinical trials or large registries. Among the latest source of data CLARIFY registry examined a large cohort of 33 438 outpatients with stable CAD from 45 countries in Europe, the Americas, Africa, Middle East, and Asia/Pacific.[15] Among patients with angina, the majority comprised men (72%), with a mean age of 63 years. Majority of patients had percutaneous coronary intervention or coronary artery bypass graft in history (38 and 20%, respectively), myocardial infarction in history (52%), and diabetes (33%). Data from another registry Euro Herat Survey in patients with angina indicated that patient characteristics and the presence of a coexisting illness may have an impact on the management of stable angina.[16,17]

The analysis of pooled data from ivabradine angina development programme assessing the antianginal efficacy of ivabradine is similar across several different subgroups of patients with stable angina selected on the basis of pre-therapy characteristics or co-morbidities.[18] These results provide clinical evidence that ivabradine diminishes or prevents angina in all types of patients, independent of their baseline characteristics including age, sex, severity of angina, and revascularization status, as well as other features such as previous myocardial infarction, peripheral vascular disease, or diabetes. A reduction in HR of 11 b.p.m. was associated with an almost 60% reduction in the frequency of angina attacks and SAN consumption across all groups. Ivabradine also had a good safety and tolerability profile in all the subpopulations analysed.

Clinical benefits with ivabradine in chronic heart failure patients

The effect of ivabradine in improvement of prognosis in HF has been successfully tested in the SHIFT trial (Heart failure treatment with If inhibitor ivabradine Trial), randomized, placebo-controlled, clinical trial in 6558 patients with moderate to severe chronic HF and LVSD [LV ejection fraction (LVEF) $<$35%], resting HR is $\geq$70 b.p.m., receiving guidelines recommended therapies.[19] The primary composite endpoint (CV death or hospital admission for worsening HF) was significantly reduced by 18% ($P < 0.0001$). Results were consistent across all subgroups. On the strength of the absolute risk reduction of the primary endpoint, 26 patients would need to be treated for 1 year to prevent one CV death or HF-related hospital admission. Ivabradine significantly reduced HF death [regular rate and rhythm (RRR), 26%; $P = 0.014$] and hospitalization for HF (RRR, 26%; $P < 0.0001$).

Despite current intensive multidrug therapies, readmission rates following HF remain very high, with readmission to hospital of up to 50% of patients within 6 months of discharge. Moreover, the recent analysis showed that data on mortality and hospitalization rates have trended in opposite directions.[20] The SHIFT analysis shows that ivabradine substantially reduces the total number of HF hospitalizations by 25% ($P = 0.0002$). Over 2 years of follow-up, ivabradine substantially reduced the risk of recurrent HF hospitalization: 34% ($P < 0.001$) reduction in risk of second hospitalization, 29% ($P < 0.012$) reduction in risk of third hospitalization.[21] Ivabradine also reduces hospitalizations for any cause (by 15%, $P = 0.001$) and CV hospitalizations (by 16%, $P = 0.002$).

This analysis confirms that ivabradine reduces the risk of clinical deterioration in patients with HF, reducing substantially the risk of hospitalization (one or more times), with a similar or greater effect on recurrent events. These

findings are very important for clinical practice as hospital admissions are not only distressing for patients and their families, but they are also harbingers of accelerated disease progression (manifest by increased risk of re-admission and death) and the major driver of the economic burden of HF.

Additional analysis from SHIFT in patients with placebo has showed a direct correlation between increased CV risk and elevated HR in patients with CHF.[22] The results of this analysis show that in patients with baseline HR $\geq$75 b.p.m., ivabradine significantly reduces all clinical outcomes, all-cause death by 17% ($P = 0.0109$), and CV death by 17% ($P = 0.0166$).

In parallel, symptoms and well-being are other important targets for therapy together with improvement of outcomes. The SHIFT trial found that ivabradine significantly improved the NYHA class and patient-reported global assessment in overall SHIFT population.[19] Furthermore, a sub-study of SHIFT trial in 1944 patients demonstrated that in parallel to a reduction of outcomes in SHIFT trial ivabradine improved quality of life (HQoL) in patients with HF, assessed by specific Kansas City Cardiomyopathy Questionnaire (KCCQ).[23] These data demonstrate that ivabradine-associated reduction in the severity of HF, as reflected by reduced hospital admissions and improved NYHA functional class, also translates into a favourable impact on HQoL. These evidence place ivabradine as a particularly pertinent treatment to achieve all targets of treatment of HF patients—to improve symptoms and well-being together with improvement of outcomes. Other therapies which improves prognosis such as beta-blockers or angiotensin-converting enzyme inhibitors (ACEIs) did not demonstrated improvement of QoL in patients with HF.

Combination of ivabradine with beta-blocker was demonstrated to be more effective in improvement of exercise capacity and QoL compared with beta-blocker alone. Based on a randomized, open-blinded endpoint study (CARVIVA) which assessed the effect of HR reduction with carvedilol (25 mg b.i.d.), ivabradine (7.5 mg b.i.d.), and their combination (12.5/7.5 mg b.i.d.) on exercise capacity and QoL in 121 HF patients receiving maximal dose of ACEI.[24] After 3 months of therapy, NYHA class improved significantly more in patients receiving ivabradine and combination therapy compared with those allocated to carvedilol. The results of such studies suggested that the addition of ivabradine to a beta-blocker increases exercise capacity in patients with CHF compared with beta-blocker alone.

The results of the recent INTENSIFY study confirmed clinical efficacy of ivabradine in daily practice over a 4-month period in 1956 patients with CHF.[25] After 4 months, ivabradine had reduced HR by 18.1 $\pm$ 12.3 to 67.1 $\pm$ 8.9 b.p.m., accompanied by symptomatic improvement with a shift in NYHA classification of patients towards lower grading and a reduction in signs of decompensation from 23 to 5% of patients.

Reversing of LV remodelling has important clinical implications since cardiac remodelling is a central feature of the progression of HF and is an established prognostic factor in patients with HF. An echo-substudy in 611 patients from SHIFT demonstrated that 8 months of therapy with ivabradine resulted in a significant reduction in LV end-systolic and end-diastolic volumes as well as in increase in LVEF.[26] Moreover, these results occurred despite treatment with beta-blockers and renin–angiotensin–aldosterone system antagonists, each used in more than 90% of patients. Further analysis from SHIFT demonstrated that HR reduction with ivabradine without changes in LV contractility resulted into increase in stroke volume and maintaining cardiac output.[27] The beneficial impact of ivabradine on LV remodelling and function may contribute to the reduction in cardiac morbidity and mortality found in patients with HF with ivabradine.

Patients with HF are characterized by the presence of multiple co-morbidities or conditions such as old age, low systolic blood pressure which not only complicate treatment strategies, but also increases the risk of side effects and worsens prognosis. This make important to analyse efficacy and tolerability of medications in patients with HF with different clinical profiles.

Several additional analyses from SHIFT assessed efficacy and tolerability of ivabradine across different clinical profiles. The results indicated that the effect of ivabradine in reducing outcomes is consistent in these populations:

- The effect of ivabradine on HF-related outcomes was maintained in patients with severe and less severe HF, with no significant statistical interaction between the results in the two groups.[28]
- The use of ivabradine was associated with a reduction in HF outcomes in patients both with and without renal dysfunction at baseline, and tolerability of ivabradine was comparable between the two groups.[29] No differences were found in changes in renal function over time between ivabradine- and placebo-treated patients.
- Ivabradine was similarly effective and safe in chronic HF patients with or without chronic obstructive pulmonary disease.[30]
- The efficacy and safety of ivabradine was similar whatever the baseline SBP, including patients with in the low SBP group ($<$115 mmHg).[31]
- The recently published data demonstrated the similar benefits of ivabradine in patients with and without diabetes.[32]
- Another analysis demonstrated that age does not limit the benefits of ivabradine with the comparable safety and efficacy across all age groups.[33]

The pharmacological and clinical properties of ivabradine make it an important treatment option for patients with angina or chronic HF. The ability of ivabradine to affect angina symptoms or myocardial ischaemia makes it an important agent for symptomatic treatment for the management of patients with angina pectoris. SHIFT results significantly extended the range of clinical benefits of ivabradine, making it an important approach in the management of patients with CHF. These data support the important place of ivabradine as an essential therapeutic modality to enhance the management of patients with angina or CHF.

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