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REVIEW ARTICLE

Selective and Specific Inhibition of I_f with Ivabradine for the Treatment of Coronary Artery Disease or Heart Failure

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Abstract Heart rate is an important contributor in the pathophysiology of both coronary artery disease (CAD) and heart failure (HF). Ivabradine is an anti-anginal and anti-ischaemic agent, which selectively and specifically inhibits the I_f current in the sino-atrial node and provides pure heart rate reduction without altering other cardiac parameters, including conduction, and without directly affecting other haemodynamic parameters. It is approved for the treatment of CAD and HF. This article summarises the pharmacological properties, pharmacokinetics, clinical efficacy and tolerability of ivabradine in the treatment of CAD and HF, and presents evidence demonstrating that the pharmacological and clinical properties and clinical efficacy of ivabradine make it an important therapeutic choice for patients with stable CAD or HF. The positive effect of ivabradine on angina pectoris symptoms and its ability to reduce myocardial ischemia make it an important agent in the management of patients with stable CAD or chronic HF. Further studies are underway to add to the already robust evidence of ivabradine for the prevention of cardiovascular events in patients with CAD but without clinical HF. The SIGNIFY (Study assessInG the morbidity–mortality beNefits of the I_f inhibitor ivabradine in patients with coronarY artery disease) trial includes patients with stable CAD and an LVEF above 40 %, with no clinical sign of HF, and is investigating the long-term effects (over a period of 48 months) of ivabradine in a large study population. So far, this study has included more than 19,000 patients from 51 countries.

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1 Introduction

Although considerable progress has been made in the management and outcome of patients with cardiovascular disease, important challenges remain. Coronary artery disease (CAD) and heart failure (HF) are leading causes of death and disability despite advances in the prevention and treatment of these diseases. Cardiovascular disease, including CAD and HF, represents a huge public health problem globally. Over the next several decades, the prevalence of both CAD and HF is expected to increase, mostly because of an aging population and better survival after acute coronary events [1].

Heart rate is an important contributor in the pathophysiology of both CAD and HF and is being increasingly recognised as a modifiable risk factor in patients with cardiovascular disease [2–5]. There are many mechanisms through which an elevated heart rate might directly affect cardiovascular risk, including increased myocardial oxygen demand, energy depletion, accelerated atherosclerosis, and increased risk of plaque rupture [6]. This makes reduction of heart rate an important therapeutic target in patients with CAD and/or HF. Ivabradine is the first member of a new group of drugs, the specific heart rate-lowering agents, to be introduced into clinical use. Ivabradine acts by selectively inhibiting the ionic current I_f, which modulates pacemaker activity in the sino-atrial node, providing pure heart rate reduction [7].

This article summarises the pharmacological properties, pharmacokinetics, clinical efficacy and tolerability of ivabradine in the treatment of CAD and HF.

2 Mechanism of Action

Heart rate is normally determined by the rate of spontaneous diastolic depolarization of myocytes in the sino-atrial node [8]. The spontaneous slow diastolic depolarization drives membrane potential towards a threshold that triggers an action potential. The rate of spontaneous diastolic depolarization is significantly influenced by I_f, a mixed sodium–potassium current involving ion movement across so-called f-channels, which are activated by hyperpolarization, and the opening of which is dependent on the intracellular availability of cyclic adenosine monophosphate [8].

Ivabradine directly and selectively inhibits the I_f current, reducing diastolic depolarization rate and heart rate (Fig. 1) [9–11]. Ivabradine enters and blocks the channel from the cytoplasmic side of the membrane, preferentially when the channel is in the open state [10]. As a result of this use-dependent inhibition, the reduction in the rate of pacemaker activity induced by ivabradine must be more important at a higher firing rate, as has already been suggested [10, 12, 13].

The selective binding of ivabradine to I_f channels makes it a pure heart-rate–reducing agent. The specificity of ivabradine for the I_f current ensures that ivabradine has no direct effects on myocardial contractility (or relaxation), ventricular repolarization or intracardiac conduction [14, 15]. The mode of action of ivabradine allows the drug's effect to be enhanced when necessary in clinical practice without affecting other aspects of cardiac function and with only a minor risk (1–4 %) of excessive bradycardia. Some, but not all, computational models show that ivabradine doses sufficient to cause near-complete I_f inhibition can reduce heart rate substantially without abolishing spontaneous diastolic depolarization and associated action potentials [16–18]. In vitro studies have confirmed that full I_f block cannot occur in a clinical setting with ivabradine, because at therapeutic concentrations, I_f block is less than 50 % [9, 10].

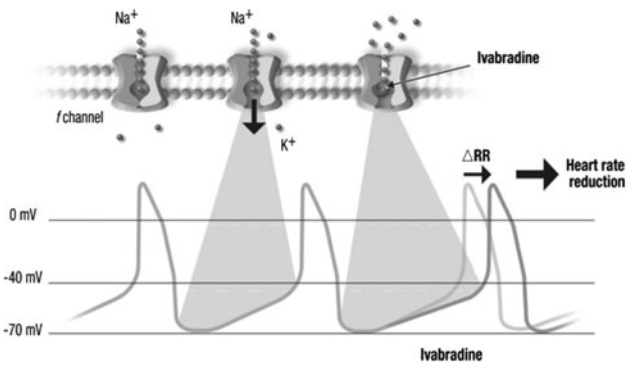

Fig. 1 Mode of action of ivabradine: by inhibiting ion flow though the f-channel, ivabradine reduces the slow diastolic depolarization phase of the action potential of sino-atrial node cells, thereby reducing heart rate. Reproduced with permission from Canet et al. [11]

3 Pharmacodynamic Properties

3.1 Effect on Heart Rate

The reduction of heart rate by ivabradine has been characterised in several human studies involving healthy volunteers and patients, and in several pooled analyses of data from multiple studies [19–21]. These studies have shown that the heart rate reduction with ivabradine is dependent on dose and baseline heart rate.

Treatment with ivabradine was associated with a decrease in 24-h heart rate of 6.3 ± 9.5 beats per minute (bpm) at last assessment versus no change with placebo (0.4 ± 7.2 bpm, $p < 0.001$) in a 6-month Holter substudy of the BEAUTIFUL (morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left-ventricULar dysfunction) trial, which examined the cardiac safety of ivabradine in patients with stable CAD and left ventricular systolic dysfunction (LVSD) [22]. The decrease in waking heart rate with ivabradine was greater than the decrease in heart rate during sleep (6.8 ± 10.4 versus 5.2 ± 8.9 bpm at last visit).

Another recent study in 23 healthy volunteers (aged 19–63 years) evaluated the effect of ivabradine 7.5 mg twice daily on heart rate over 24 h and demonstrated a significant reduction in heart rate through 24 h, while maintaining the circadian heart rate pattern (Clinical data from IRIS, EudraCT number: 2011-001665-40; data on file) (Fig. 2). The INITIATIVE (INternatIonal TrIal of the AnTi-anginal effects of IVabradinE compared to atenolol) trial, involving 939 patients with stable angina, showed that ivabradine significantly reduced heart rate after 1 and 4 months of treatment, at rest and at peak exercise [23]. At rest, heart rate was reduced by 14.3 bpm in the ivabradine 7.5 mg twice daily group compared with 15.6 bpm in the atenolol 100 mg once daily group.

Heart rate reduction with ivabradine in stable angina patients was maintained with long-term treatment in a randomized, double-blind study in 386 patients treated with ivabradine (either 5 or 7.5 mg twice daily) for 1 year [24]. Both doses of ivabradine were associated with a substantial reduction in resting heart rate: 10 bpm with ivabradine 5 mg twice daily (from 71 to 62 bpm) and

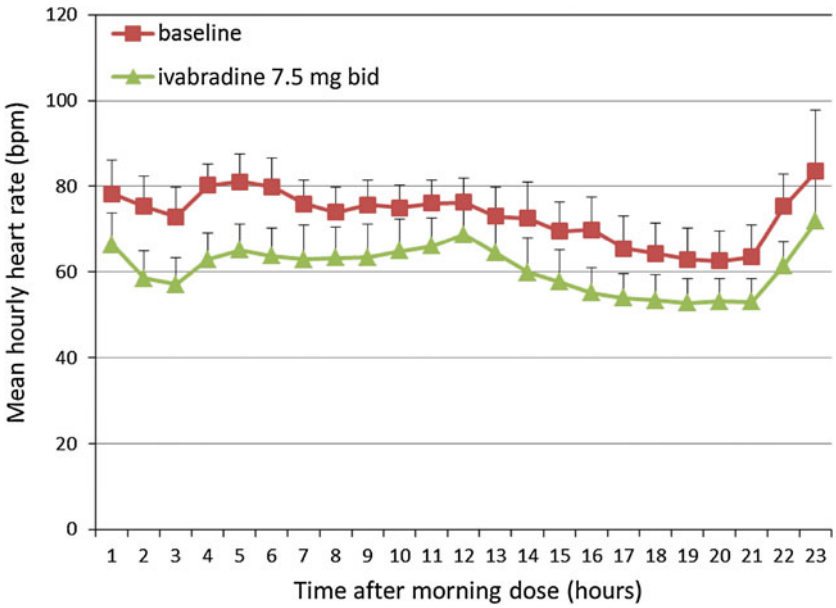

Fig. 2 Change from baseline in mean heart rate over 24 h after treatment with ivabradine 7.5 mg twice daily in volunteers. *bpm* beats per minute. Clinical data from the IRIS trial. EudraCT record 2011-001665-40 (data on file)

12 bpm with ivabradine 7.5 mg twice daily (from 71 to 59 bpm) [24].

The dependence of I_f inhibition with ivabradine on baseline heart rate suggests that heart rate slowing should be greatest in patients with the highest pre-treatment heart rate. This was corroborated by data in 2,351 patients, which showed that the magnitude of heart rate reduction was directly related to baseline heart rate, for each dose of ivabradine [16].

3.2 Anti-Ischaemic Effect

By reducing heart rate, ivabradine reduces myocardial oxygen demand. It also maximizes oxygen supply and myocardial perfusion by prolonging diastolic time and by enabling coronary vasodilation during exercise [25, 26]. In contrast, β-blockers tend to prolong systole because of their negative effect on myocardial contractility. In consequence, diastole is shorter with β-blockers than with ivabradine at rest and during exercise for a similar heart rate reduction [25, 26].

Adequate relaxation of left ventricular (LV) myocardium after systolic contraction is important in facilitating diastolic LV filling, particularly during exercise. Though it caused similar reductions in heart rate at rest and during exercise to those achieved by atenolol in an animal model, ivabradine did not alter the relaxation time constant at rest or during exercise, and gave results similar to the saline control [27]. Furthermore, despite a similar effect on heart rate, β-blockade resulted in constriction of large and small coronary arteries during exercise, while vasodilation was not affected by ivabradine [28]. Ivabradine also significantly reduces cardiac energy consumption and preserves redox potentials during ischaemia by reducing heart rate [29].

In a preclinical setting, ivabradine has been shown to improve regional ischaemia to a greater extent than the β-blocker propranolol. In an animal model simulating stable angina pectoris, ivabradine and propranolol (both at doses producing similar reductions in heart rate) reduced exercise-associated ST-segment shift in the ischaemic region by approximately 80 %, but ivabradine preserved systolic shortening to a significantly greater degree than propranolol ($p < 0.05$) [30].

Ivabradine has been shown to improve myocardial stunning in dogs [31, 32]. When therapy was administered before the ischaemic insult, atenolol and ivabradine both reduced post-ischaemic stunning compared with saline control, by reducing the degree of exercise-induced ischaemia [32]. However, when administered soon after the ischaemic insult with part of the myocardium in the stunned state, ivabradine improved myocardial contractility, but because of its negative inotropic action, atenolol significantly exacerbated contractile dysfunction [32].

The effect of ivabradine in acute myocardial infarction (MI) has also been explored [33]. Acute MI was modelled by hypoperfusing the myocardial region supplied by the left anterior descending coronary artery for 90 min and then reperfusing for 120 min. Intravenous ivabradine 0.6 mg/kg, administered before the ischemic episode, reduced the size of the resulting infarct from 35 % of the area at risk in saline controls to 19 %. Ivabradine also reduced infarct size when given after the onset of ischemia or just before reperfusion. When given 15–20 min after the onset of ischemia, ivabradine also improved regional blood flow and systolic wall thickening [33].

3.3 Effects on Ventricular Function and Structure

Several studies have investigated the longer-term effects of ivabradine on myocardial structure and function in models of HF after induction of experimental MI [34–36]. These studies have highlighted the potential of ivabradine to prevent negative cardiac effects following MI. Ivabradine, given 7 days after MI in a rat model, decreased heart rate over 90 days without any other haemodynamic effects [36]. Cardiac output was preserved because of increased stroke volume. In addition, ivabradine improved cardiac function by significantly decreasing left ventricular systolic diameter and increasing fractional shortening [36]. Similar cardiac benefits were also observed when ivabradine was given immediately after MI [34] or 2 months after MI [35].

Assessment of the effects of ivabradine on the global cardiac remodelling process in HF showed that it had beneficial effects on LV remodelling [37, 38]. Non-clinical data showed that ivabradine reduced fibrosis in surviving myocardium, and decreased circulating, as well as local, renin–angiotensin–aldosterone system (RAAS) stimulation [34]. In another study in a model of severe HF in rats, treatment with ivabradine for 3 months improved left ventricular ejection fraction (LVEF) and end-diastolic pressure, and reduced interstitial fibrosis in the non-infarcted LV region [35]. Another study comparing ivabradine and metoprolol for the prevention of experimental HF in hypertensive mice found that treatment with ivabradine led to a significant improvement in systolic and diastolic LV function, which was associated with less cardiac hypertrophy, fibrosis, inflammation and cardiac apoptosis [39]. Although both drugs reduced heart rate similarly and only metoprolol reduced systolic blood pressure, metoprolol did not prevent deterioration in cardiac function and adverse remodelling, despite a reduction of the inflammatory stress response [39].

3.4 Vascular Effects

Endothelial dysfunction has been demonstrated in various cardiovascular diseases, including CAD and congestive HF. In experimental studies, ivabradine has been shown to protect endothelial function. Treatment with ivabradine for 3 months prevented deterioration of endothelium-dependent vasodilation in the renal and cerebral arteries in dyslipidaemic mice [40]. The protective effect seen with ivabradine was not fully reproduced in mice receiving metoprolol, despite a similar heart rate reduction. This was possibly due to inhibition of β-adrenoceptor-mediated activation of endothelial nitric oxide synthase [40].

Ivabradine also reduced atherosclerotic plaque formation in transgenic mice models of atherosclerosis. In transgenic mice with severe hypercholesterolaemia and atherosclerotic plaques, ivabradine reduced the atherosclerotic plaque area in the aortic root (by >40 %) and ascending aorta (by >70 %) [41].

Aortic compliance was preserved in apolipoprotein E-deficient mice treated with ivabradine for 6 weeks [42]. This improvement could be due to an effect on the local RAAS system, attenuation of oxidative stress or modulation of inflammatory cytokine expression [42]. Irregular shear and mechanical stress, which are associated with elevated heart rate, might damage vascular endothelium, leading to dysfunction and atherogenesis [43].

4 Pharmacokinetic Properties

Ivabradine exhibits linear pharmacokinetics over an oral dose range of 0.5–24 mg, with rapid absorption after administration of a single oral dose [44]. In fasting conditions, the time to peak drug concentration is approximately 1 h, with an absolute bioavailability of the film-coated tablets of around 40 % following gastrointestinal and hepatic first-pass metabolism [44]. In fed conditions, the time to peak plasma drug concentration is prolonged by approximately 1 h and the plasma concentration of ivabradine is increased by 20–30 %.

Approximately 70 % of ivabradine is plasma protein bound. At steady state, after multiple doses of 5 mg twice daily, the maximum plasma concentration of ivabradine is 22 ng/mL and the mean plasma concentration is 10 ng/mL. Ivabradine has a half-life of 2 h in plasma and an effective half-life of 11 h. Renal clearance of ivabradine is 70 mL/min, and the total clearance is 400 mL/min. After oral administration, approximately 4 % of the ivabradine dose is excreted unchanged in urine.

Compared with younger individuals, no appreciable differences in the pharmacokinetic profile of ivabradine were observed in the elderly (aged ≥65 years) or very elderly (≥75 years). Renal impairment (creatinine clearance 15–60 mL/min) has a minimal effect on the pharmacokinetics of both ivabradine and its main metabolite, as renal clearance accounts for a small part (20 %) of the elimination of both products.

As regards hepatic impairment and ivabradine, patients with mild hepatic impairment require no dose adjustment. Caution is advocated when treating patients with moderate hepatic impairment, and ivabradine is contraindicated in patients with severe hepatic insufficiency (as a substantial increase in systemic exposure is predicted) [44].

Ivabradine is extensively metabolised by the cytochrome P450 (CYP) enzyme CYP3A4. It is a very weak inhibitor of this enzyme and has no apparent influence on the metabolism and plasma concentrations of other CYP3A4 substrates. Conversely, CYP3A4 inhibitors and

agonists have been shown to affect ivabradine plasma concentrations, so the concomitant use of strong CYP3A4 inhibitors with ivabradine is contraindicated. Proton pump inhibitors, sildenafil, 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, dihydropyridine calcium-channel blockers, digoxin and warfarin have not demonstrated any clinically significant effect on the pharmacokinetics and pharmacodynamics of ivabradine in drug–drug interaction studies [44].

5 Efficacy of Ivabradine in Coronary Artery Disease

5.1 Anti-Anginal and Anti-Ischaemic Efficacy

The anti-anginal and anti-ischemic efficacy of ivabradine has been confirmed in patients with stable angina in clinical studies comparing it either with placebo or with standard anti-anginal agents (Table 1).

5.1.1 Monotherapy

In a placebo-controlled, randomized, dose-ranging study conducted in 360 patients with stable CAD and chronic stable angina, Borer et al. [19] showed that ivabradine produced dose-dependent improvements in exercise tolerance parameters. At 2 weeks, ivabradine 5 and 10 mg twice daily significantly improved the time to 1-mm ST-segment depression compared with placebo (by 44.1 and 46.2 vs 9.0 s, $p = 0.016$). This reduction in angina and ischemia was associated with significant reductions in rate-pressure product at peak exercise ($p = 0.011$) and increases in total work performed in an exercise tolerance test [ETT] ($p = 0.019$) among ivabradine-treated patients; both changes showed significant dose-dependence ($p = 0.002$ for both) [19]. Furthermore, in the open-label extension phase (2–3 months) of this study, ivabradine reduced angina attacks from 4.14 to 0.95 attacks per week ($p < 0.001$) and consumption of short-acting nitrates from 2.28 to 0.50 U per week ($p < 0.001$) [19].

Ivabradine was compared directly with the β-blocker atenolol in INITIATIVE, a randomized, double-blind, parallel-group trial involving 939 patients [23]. After 16 weeks of treatment, patients receiving ivabradine 7.5 or 10 mg twice daily or atenolol 100 mg/day had similar increases in total exercise duration at trough (+86.8 and +91.7 vs 78.8 s, $p < 0.001$ for non-inferiority) and the number of angina attacks per week (−2.2 and −2.3 vs −2.7 attacks per week) [23]. Even though ivabradine was non-inferior, after 4 months of treatment, all ETT parameters (time to limiting angina, time to angina onset, and time to 1-mm ST-segment depression) tended to have improved more with ivabradine than with atenolol, resulting in a significantly greater increase in exercise capacity per beat reduction in heart rate with ivabradine than with atenolol. Heart rate was reduced by 14.3 and 14.3 bpm with ivabradine 7.5 and 10 mg twice daily, versus 15.6 bpm with atenolol [23].

The anti-anginal and anti-ischemic efficacy of ivabradine (7.5 and 10 mg twice daily) has been compared with amlodipine 10 mg daily in a large multicentre, international, double-blind, randomized, parallel-group trial in 1,195 patients with stable angina [45]. In this study, ivabradine was not inferior to amlodipine in improving exercise tolerance as well as increasing time to angina onset, time to limiting angina and time to 1-mm ST-segment depression. Similarly, ivabradine was not inferior to amlodipine in preventing angina attacks and limiting nitrate use; however, ivabradine produced a greater reduction of rate-pressure product (a surrogate for myocardial oxygen consumption) than amlodipine.

Skalidis et al. [46] assessed the effect of ivabradine (5 mg twice daily) on coronary blood flow velocity and coronary flow reserve (CFR) in patients with stable CAD ($n = 21$). Coronary blood flow was assessed invasively using intracoronary Doppler measurements at baseline and after 1 week of ivabradine treatment. This study showed that ivabradine significantly reduced heart rate and improved hyperaemic and resting coronary flow velocity and CFR in these patients after 1 week of treatment. These results suggested that in addition to ivabradine having anti-ischaemic effects in patients with CAD (as previously shown), it may also have an impact on ischaemic events, as CFR predicts adverse cardiovascular long-term outcomes [47].

5.1.2 Combination Therapy

Ivabradine has been shown to provide additional anti-ischaemic efficacy in patients who are already receiving standard therapy with β-blockers [48–50]. The double-blind, randomized, multicentre, placebo-controlled ASSOCIATE (evaluation of the Antianginal efficacy and Safety of the aSsociation Of the I_f Current Inhibitor ivAbradine with a beTa-blockEr) trial was conducted in 889 patients with stable angina already receiving atenolol [48]. All included patients had a positive symptom-limited exercise test while receiving atenolol 50 mg once daily. These patients were randomized to receive either ivabradine 5 mg twice daily for 2 months, which was then increased to 7.5 mg twice daily for an additional 2 months (449 patients), or placebo (440 patients) and underwent exercise testing at the trough of drug activity at 2 and 4 months. In the ivabradine group, heart rate decreased by 7 bpm during the first 2 months of treatment with 5 mg twice daily and by 9 bpm with ivabradine 7.5 mg twice

Table 1 Summary of the principal results of the main publications of ivabradine in coronary artery disease

Publication	Study summary
CAD: monotherapy	
Borer et al., 2003 [19] (n = 360)	Randomised, double-blind, placebo-controlled, multicentre study in patients with stable CAD and chronic stable angina (n = 360). Duration: 2 weeks double-blind + 2–3 months open-label. Efficacy: TST and TLA. At 2 weeks, TST increased by 32.0, 44.1 and 46.2 s with ivabradine 2.5, 5 and 10 mg bid vs 9.0 s with placebo (p = 0.016 for 5 and 10 mg bid dose vs placebo). TLA increased by 22.5, 27.2 and 40.8 s with ivabradine 2.5, 5 and 10 mg bid vs 12.7 s with placebo (p = 0.049 for 10 mg bid dose vs placebo). Resting HR and exercise HR decreased significantly with ivabradine 2.5, 5 and 10 mg bid (all $p < 0.05$ vs placebo)
INITIATIVE [23] (n = 939)	Randomised, double-blind, active-controlled, parallel-group, multicentre study in patients with CAD and stable angina. Duration: 16 weeks. Efficacy: TED during ETT. Change in TED at trough: +86.8 and +91.7 s with ivabradine 7.5 and 10 mg bid vs +78.8 s with atenolol 50–100 mg/day (mean difference 10.3 and 15.7 s; $p < 0.001$ for non-inferiority). Change in the number of angina attacks per week at 16 weeks: −2.2 and −2.3 for ivabradine 7.5 and 10 mg bid vs −2.7 for atenolol. Change in resting HR: −14.3 and −14.31 bpm for ivabradine 7.5 and 10 mg bid vs −15.6 bpm for atenolol
Ruzyllo et al., 2007 [45] (n = 1195)	Randomised, double-blind, parallel-group, multicentre study in patients with chronic stable angina. Duration: 3 months. Efficacy: TED during ETT. Change in TED at trough: +27.6 and +21.7 s with ivabradine 7.5 and 10 mg bid vs +31.2 s with amlodipine 10 mg od (mean difference 1.8 and 6.6 s; $p < 0.001$ for non-inferiority). Change in the number of angina attacks per week: −3.0 and −3.2 for ivabradine 7.5 and 10 mg bid vs −3.0 for amlodipine
CAD: combination therapy	
ASSOCIATE [48] (n = 889)	Randomised, double-blind, placebo-controlled, multicentre study in patients with chronic stable angina. Duration: 4 months. Ivabradine 5–7.5 mg bid + atenolol 50 mg od vs placebo + atenolol 50 mg od. Efficacy: TED during ETT. Change in TED at trough: +24.3 s vs +7.7 s ($p < 0.001$). Change in TLA: +26.0 s vs +9.4 s ($p < 0.001$). Change in TAO: +49.1 s vs +22.7 s ($p < 0.001$). Change in TST: +45.7 s vs +15.4 s ($p < 0.001$)
Amosova et al., 2011 [49] (n = 29)	Randomised, parallel-group, single-blind study in patients with MI and moderate left ventricular systolic dysfunction. Duration: 2 months. Ivabradine 5–7.5 mg bid + bisoprolol 5 mg od versus bisoprolol 5–10 mg od. Change in mean resting HR: from 76.6 to 59.3 bpm ($p < 0.001$ vs baseline) vs from 75.9 to 60.5 bpm (p = 0.002 vs baseline). Change in 6-min walking test distance: from 388 to 446 m ($p < 0.001$ vs baseline) vs from 386 to 400 m (p = NS)
ADDITIONS [50] (n = 2330)	Multicentre, open-label, observational study in patients with stable angina pectoris. Duration: 4 months. Ivabradine 2.5–7.5 mg bid + β-blocker. Change in resting HR: from 85.0 to 65.6 bpm ($p < 0.0001$ vs baseline). Change in the number of angina attacks per week: −1.4 ($p < 0.0001$ vs baseline). Change in the consumption of nitrates: −1.9 U ($p < 0.0001$ vs baseline)
REDUCTION [58] (n = 4,954)	Multicentre, open-label, observational study in patients with stable angina pectoris. Duration: 4 months. Ivabradine 2.5–7.5 mg bid + β-blocker. Change in resting HR: −12.4 bpm ($p < 0.0001$ vs baseline). Change in the number of angina attacks per week: from 2.8 to 0.5 ($p < 0.0001$ vs baseline). Change in the consumption of nitrates: from 3.7 to 0.7 U ($p < 0.0001$ vs baseline)
López-Bescós et al., 2007 [24] (n = 386)	Randomised, double-blind, parallel-group, multicentre study in patients with chronic stable angina on concomitant therapy (excluding β-blockers). Duration: 12 months. Ivabradine 5 or 7.5 mg bid. Change in resting HR: −9.7 and −12.3 bpm. Change in the number of angina attacks per week: −1.9 and −1.2. Change in the consumption of nitrates: −1.2 and −1.7 U
Skalidis et al., 2011 [46] (n = 21)	Prospective study in patients with stable CAD. Duration: 1 week. Ivabradine 5 mg bid plus current medication. HR: from 78 to 65 bpm ($p < 0.01$). Hyperaemia CFV: from 53.5 to 57.9 cm/s ($p < 0.01$). Resting CFV: from 19.7 to 17.0 cm/s ($p < 0.01$). Coronary flow reserve: from 2.78 to 3.51 ($p < 0.01$)
CAD: special populations	
Elderly [56] (n = 382)	Multicentre, open-label, observational study in elderly patients (>80 years old) with stable angina pectoris. Duration: 4 months. Ivabradine 2.5–7.5 mg bid + β-blocker. Change in resting HR: −12.0 bpm ($p < 0.0001$ vs baseline). Change in the number of angina attacks per week: from 3.0 to 0.8 ($p < 0.0001$ vs baseline). Change in the consumption of nitrates: from 4.2 to 1.2 U ($p < 0.0001$ vs baseline)
Subpopulations [21] (n = 2,425)	Pooled analysis of five randomised, double-blind, parallel-group studies in patients with angina pectoris. Duration: 3–4 months. Ivabradine 5–10 mg bid. Change in resting HR: −14.5 % (11.3 bpm) in all patients; reduction of 12.4–16.3 % in subpopulations (no difference between groups). Change in the number of angina attacks per week: −59.4 % in all patients; reduction of 51 % to 70 % in subpopulations (no difference between groups). Change in the consumption of nitrates: −53.7 % in all patients; reduction of 0.4 to 3.4 U/week in subpopulations

Table 1 continued

Publication	Study summary
Diabetes [57] (n = 2,907)	Pooled analysis of eight multicentre, randomised, double-blind studies in patients with stable angina. Duration: 2 weeks to 1 year. Ivabradine 2.5–20 mg bid. Change in resting HR: −11.3 bpm in patients without diabetes mellitus vs −11.6 bpm in patients with diabetes mellitus. Change in the number of angina attacks per week: −2.2 in patients without diabetes mellitus vs −2.0 in patients with diabetes mellitus
CAD: with left ventricular dysfunction (BEAUTIFUL)	
Main results [59] (n = 10,917)	Randomised, double-blind, placebo-controlled, multicentre study in patients with CAD and LVEF of <40 % also receiving conventional CV therapy. Duration: 19 months (median). Ivabradine 5–7.5 mg bid vs placebo. Efficacy: composite endpoint of CV death, admission to hospital for acute MI and admission to hospital for new-onset or worsening HF. Primary endpoint: 15.4 % vs 15.3 % of patients (p = 0.94). Pre-specified analysis in patients with heart rate ≥70 bpm (n = 5,392): hospitalization for MI, 36 % RRR (p = 0.001); coronary revascularization, 30 % RRR (p = 0.016)
Angina subgroup [61] (n = 1,507)	*Post hoc* analysis of the BEAUTIFUL trial in patients with stable angina. Duration: 18 months (median). Ivabradine 5–7.5 mg bid vs placebo. Efficacy: composite endpoint of CV death, admission to hospital for acute MI and admission to hospital for new-onset or worsening HF. Primary endpoint: 24 % RRR (p = 0.05). Hospitalization for MI: 42 % RRR (p = 0.021). In patients with heart rate ≥70 bpm: hospitalization for MI, 73 % RRR (p = 0.002); coronary revascularization, 59 % RRR
ECHO substudy [62] (n = 590)	Echocardiographic substudy of BEAUTIFUL. Duration: 3–12 months. Ivabradine 5–7.5 mg bid vs placebo. Efficacy: LVEDVI. Change in LVEDVI: −1.48 vs +1.85 mL/m^2 (p = 0.018). Change in LVEF: 2.00 vs 0.01 % (p = 0.009)
Holter substudy [22] (n = 840)	Holter substudy of the BEAUTIFUL trial. Duration: 6 months. Ivabradine 5–7.5 mg bid vs placebo. Efficacy: 24-h HR reduction. HR reduction: 6.3 vs 0.4 bpm ($p < 0.001$). In ivabradine group, waking vs sleeping HR reduction was 6.8 vs 5.2 bpm. Incidence of severe bradycardic episodes (<30 bpm) during waking or sleep was ≤1 % in both groups. More ivabradine patients than placebo patients had HR <40 or <50 bpm, but there was no between-group difference in episode severity

bid twice daily, *bpm* beats per minute, *CAD* coronary artery disease, *CFV* coronary flow velocity, *CV* cardiovascular, *ETT* exercise tolerance test, *HF* heart failure, *HR* heart rate, *LVEDVI* left ventricular end-diastolic volume index, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *NS* not significant, *od* once daily, *RRR* relative risk reduction, *TAO* time to angina onset, *TED* total exercise duration, *TLA* time to limiting angina, *TST* time to 1-mm ST-segment depression

daily. Ivabradine significantly increased the total exercise duration as well as all other exercise test criteria such as time to limiting angina, time to angina onset and time to 1 mm ST-segment depression ($p < 0.001$) compared with placebo (Fig. 3) [48]. Significant improvements were seen with ivabradine 5 mg twice daily after 2 months of treatment but were more pronounced after up-titration to 7.5 mg twice daily. The treatment with ivabradine was well tolerated, and 90 % of patients were up-titrated to 7.5 mg twice daily after the first 2 months. This study clearly demonstrated that ivabradine treatment in patients with stable angina receiving the β-blocker atenolol resulted in a significant long-term improvement in total exercise duration in standardized Bruce protocol exercise testing. A recent analysis of this study extended these findings and demonstrated that ivabradine treatment resulted in improvements in all ETT criteria relative to placebo in patients with stable angina pectoris with resting heart rates above and below 65 bpm [51].

A pilot study compared the anti-anginal and anti-ischemic efficacy and tolerability of ivabradine (7.5 mg twice daily) in combination with the β-blocker bisoprolol (5 mg once daily) versus bisoprolol 10 mg/day in 29 patients with stable angina [49]. After 2 months of therapy, the mean resting heart rate decreased similarly in both groups (from 76.6 to 59.3 bpm [$p < 0.001$] vs from 75.9 to 60.5 bpm [p = 0.002]). However, addition of ivabradine was more efficient for improvement of exercise capacity, as shown by the results of the 6-min walking test (from 388 to 446 m [$p < 0.001$] vs from 386 to 400 m) and an ETT (workload increased from 5.9 to 7.0 metabolic equivalents with ivabradine + bisoprolol, p = 0.004, vs 5.7 to 6.2 metabolic equivalents with bisoprolol alone, p = 0.141). Because of the small size of the study, its results should be viewed with caution and as hypothesis generating in nature. Nevertheless, they do suggest that the combination of ivabradine and a β-blocker is preferable to treatment with a β-blocker alone in patients with stable angina [49].

The non-interventional, multicentre, open-label ADDITIONS (prActical Daily efficacy anD safety of procoralan In combinaTION with beta blockerS) trial followed 2,330 German patients with stable angina pectoris receiving β-blockers who initiated treatment with ivabradine 5–7.5 mg twice daily [50]. This study demonstrated that adding ivabradine to standard therapy with a β-blocker significantly reduced heart rate (from 85 to 65.6 bpm after

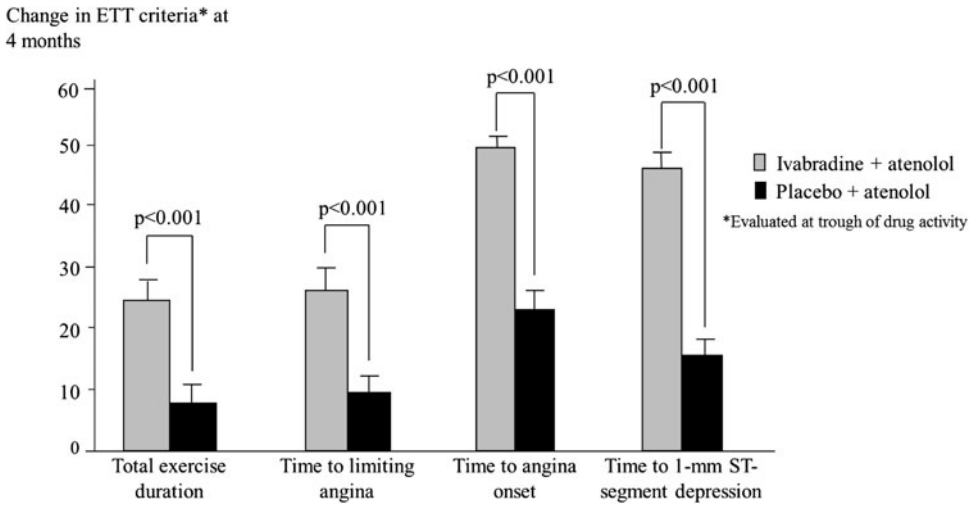

Fig. 3 Results of the ASSOCIATE study showing the effects of ivabradine on exercise tolerance testing (ETT) after 4 months of treatment in patients with chronic stable angina who received the β-blocker atenolol. Adapted from Tardif et al. [48]

4 months), the number of angina attacks per week (from 1.7 attacks to 0.3 attacks per week) and nitrate consumption (from 2.3 to 0.4 U per week) over 4 months of treatment (all $p < 0.0001$) [50].

Finally, the results of a long-term trial investigating the efficacy and tolerability of add-on ivabradine demonstrated that the initial efficacy observed with ivabradine is maintained over a longer period of time (12 months) in patients with chronic stable angina receiving concomitant therapy with anti-anginal therapies such as long-acting nitrates, molsidomine, nicorandil, trimetazidine or dihydropyridine calcium-channel blockers [24]. In both ivabradine treatment groups, there was a significant reduction in resting heart rate (from 72.4 to 62.7 bpm and from 71.8 to 59.4 bpm with ivabradine 5 and 7.5 mg twice daily). Furthermore, the mean number of angina attacks per week decreased significantly by more than 50 % after 12 months' treatment with ivabradine ($p < 0.001$), and more than 80 % of patients had no attacks or only one angina attack per week after 12 month of therapy (compared with 58 % of patients at baseline) [24].

Combination therapy is widely used in clinical practice in order to achieve adequate control of angina, and the majority of patients receive two or more anti-anginal drugs. However, clinical trials evaluating combination therapy have yielded inconsistent results [52–55]. Most studies have been small, and many have not shown significant benefits with combinations as opposed to single-drug therapy. The ASSOCIATE study has demonstrated that addition of ivabradine to β-blockers provides further clinical benefits, and this might be considered one of the best evidence-based combination therapies for angina patients. Furthermore, the ADDITIONS study confirmed that combining ivabradine with β-blocker therapy was efficient and well tolerated in everyday clinical practice.

The proven anti-anginal and anti-ischemic efficacy of ivabradine has led to its approval for the treatment of patients with stable angina pectoris in normal sinus rhythm with a heart rate >60 bpm who are inadequately controlled with an optimal dose of β-blocker or who are unable to tolerate β-blockers, or for whom the use of β-blockers is contraindicated.

5.1.3 Special Populations

Ivabradine provides anti-anginal efficacy in a wide range of patients, including elderly patients [56] or those with concomitant diseases [21] such as diabetes [57]. An analysis of the REDUCTION (Reduction of ischaemic Events by reDUCtion of hearT rate In the treatment Of stable aNgina with ivabradine) study showed that ivabradine was effective in patients older than 80 years of age [56]. This open-label, multicentre, non-interventional subanalysis of 382 patients with stable angina pectoris receiving ivabradine showed that ivabradine therapy over 4 months significantly reduced angina pectoris episodes (from 3.0 to 0.8 per week), heart rate (from 83.0 to 71.0 bpm) and the consumption of short-acting nitrates (from 4.2 to 1.2 U per week) [all $p < 0.0001$ vs baseline] [56, 58].

Furthermore, ivabradine is effective in subpopulations of patients with stable angina pectoris and various concomitant diseases [21]. In a pooled analysis of five randomized studies investigating the efficacy of ivabradine in patients with angina (n = 2,425), the anti-anginal efficacy of ivabradine was similar across a range of subpopulations (51–70 % reduction in the frequency of angina attacks in subpopulations, divided by age, gender, angina severity, disease characteristics and comorbidities). The efficacy of ivabradine was maintained in the presence of different comorbidities: no difference in efficacy was observed in

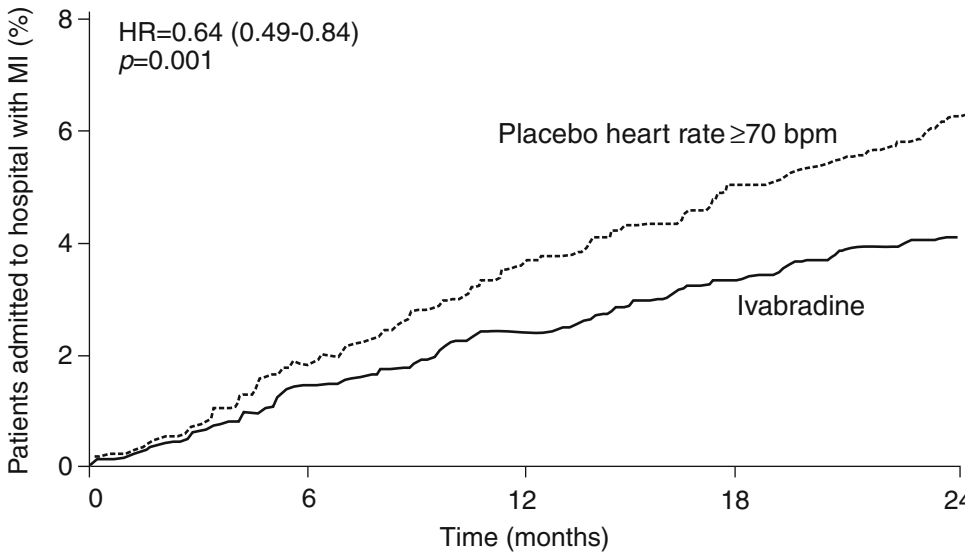

Fig. 4 Effect of ivabradine on risk of hospitalization for myocardial infarction (MI) in patients with coronary artery disease with left ventricular systolic dysfunction and a heart rate ≥70 beats per minute (bpm) in the BEAUTIFUL trial. *HR* hazard ratio. Adapted from Fox et al. [59]

patients with asthma or chronic obstructive pulmonary disease, diabetes mellitus or peripheral vascular disease.

These findings are further supported by an analysis of the effect of ivabradine in 535 patients with stable angina and diabetes [57]. The heart rate reduction and anti-ischaemic and anti-anginal effects seen with ivabradine, as evaluated by ETTs, were similar in patients with and without diabetes mellitus [57]. Ivabradine treatment was not associated with adverse effects on glucose metabolism.

5.2 Prevention of Coronary Events

The BEAUTIFUL study investigated the prognostic effects of adding ivabradine to standard treatment [59, 60]. This randomized, double-blind, placebo-controlled study was conducted in patients with CAD and an LVEF of <40 % (n = 10,917) randomized to receive ivabradine 5–7.5 mg twice daily or placebo on top of conventional cardiovascular treatment as recommended by guidelines. In BEAUTIFUL, the composite primary endpoint of cardiovascular death, admission to hospital for acute MI and admission to hospital for new-onset or worsening HF in the ivabradine group was similar to that in the placebo group. In discussing the BEAUTIFUL results, the investigators underlined that heart rate in the total population was low at baseline (72 bpm), leading to insufficient heart rate reduction with ivabradine (5.6 bpm of reduction corrected for placebo) and therefore limiting the impact of ivabradine on the primary composite endpoint. However, in a pre-specified subgroup of patients with an elevated heart rate (≥70 bpm), ivabradine reduced the rate of admission to hospital for fatal or non-fatal MI by 36 % (hazard ratio [HR] 0.64, 95 % confidence interval [CI] 0.49–0.84, p = 0.001; Fig. 4) and coronary revascularization by 30 % (HR 0.70, 95 % CI 0.52–0.93, p = 0.016) [59].

A post hoc analysis of the trial in patients whose limiting symptom at baseline was angina (n = 1,507) showed that ivabradine reduced the primary composite endpoint by 24 % (HR 0.76, 95 % CI 0.58–1.00, p = 0.05) and reduced the rates of hospitalization for MI by 42 % (HR 0.58, 95 % CI 0.37–0.92, p = 0.021) [61].

The echo cardiographic substudy of the BEAUTIFUL trial in 590 patients showed that 12 months of therapy with ivabradine significantly improved LV end-systolic volume index [LVESVI] (−1.48 vs +1.85 mL/m^2 with placebo, p = 0.018) and LVEF (+2 % vs no change, p = 0.009). This reduction in LVESVI was related to the degree of heart rate reduction with ivabradine [62].

5.3 Effect on Health-Related Quality of Life

The non-interventional, multicentre, open-label ADDITIONS trial also investigated the effects of adding ivabradine to standard therapy with β-blockers on quality of life [50]. The results of this study highlighted that not only did the addition of ivabradine have significant anti-anginal and anti-ischaemic efficacy (as previously discussed) but it was also associated with an improvement in quality of life, as assessed using EQ-5D index scores (+0.17, $p < 0.001$) [50]. This improvement in EQ-5D index scores correlated well with the results of the EQ-5D visual analogue scale (VAS), for which the general health status throughout the 4 months of treatment improved with ivabradine (VAS 57.4 ± 18.3 points at visit 1, 65.6 ± 16.0 points at visit 2 and 72.7 ± 15.4 at visit 3).

5.4 Efficacy of Ivabradine in Heart Failure

In the first quarter of 2012, ivabradine was approved by the European Medicines Agency for the treatment of chronic

Table 2 Summary of the principal results in SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial) and its main publications[a]

Endpoint	Ivabradine 5–7.5 mg bid	Placebo	Hazard ratio	*p*-value
SHIFT main results: Swedberg et al. [65]	$n = 3,268$	$n = 3,290$		
Primary composite endpoint[b]	24 %	29 %	0.82	<0.0001
All-cause hospitalization	38 %	42 %	0.89	0.003
Hospitalization for worsening heart failure	16 %	21 %	0.74	<0.0001
Cardiovascular hospitalization	30 %	34 %	0.85	0.0002
All-cause death	16 %	17 %	0.90	0.092
Cardiovascular death	14 %	15 %	0.91	0.13
Heart failure death	3 %	5 %	0.74	0.014
Analysis in patients with heart rate ≥75 bpm: Böhm et al. [66]	$n = 2,052$	$n = 2,098$		
Primary composite endpoint[b]	27 %	33 %	0.76	<0.0001
All-cause hospitalization	39 %	44 %	0.82	<0.0001
Hospitalization for worsening heart failure	18 %	24 %	0.70	<0.0001
Cardiovascular hospitalization	31 %	37 %	0.79	<0.0001
All-cause death	17 %	19 %	0.83	0.0109
Cardiovascular death	15 %	17 %	0.83	0.0166
Heart failure death	4 %	6 %	0.61	0.0006
Post hoc analysis of MRA status ($n = 6,505$): Komajda et al. [68]				
Primary composite endpoint in patients with MRA ($n = 3,922$)	28 %	33 %	0.82(0.78–0.95)[f]	
Hospitalization for worsening heart failure	19 %	23 %	0.77(0.67–0.89)[f]	
Cardiovascular death	16 %	18 %	0.88(0.76–0.94)[f]	
Rehospitalization analysis: Borer et al. [69]	$n = 3,241$	$n = 3,264$		
First hospitalization	16 %	21 %	0.75	<0.001
Second hospitalization	6 %	9 %	0.66	<0.001
Third hospitalization	3 %	4 %	0.71	<0.012
Echocardiographic substudy: Tardif et al. [70][c]	$n = 304$	$n = 307$		
LVESV index (mL/m^2)[d]	−7.0	−0.9		<0.001
LVESV (mL)	−13.0	−1.3		<0.001
LVEDV index (mL/m^2)	−7.9	−1.8		0.002
LVEDV (mL)	−14.7	−2.9		0.001
LVEF (%)	2.4 %	−0.1 %		<0.001
Health-related quality-of-life analysis: Ekman et al. [73][e]	$n = 968$	$n = 976$		
Heart rate (bpm)	−14.8	−4.9		<0.0001
KCCQ				
Overall summary score	6.7	4.3		<0.001
Clinical summary score	5.0	3.3		0.018

bid twice daily, *bpm* beats per minute, *KCCQ* Kansas City Cardiomyopathy Questionnaire, *LVEDV* left ventricular end-diastolic volume, *LVEF* left ventricular ejection fraction, *LVESV* left ventricular end-systolic volume, *MRA* mineralocorticoid receptor antagonist

[a] Values are expressed as percentages or means

[b] Cardiovascular death or hospitalization for worsening heart failure

[c] Change from baseline to 8 months

[d] Primary endpoint of substudy

[e] Change from baseline to 12 months

[f] 95 % confidence intervals are shown in brackets

HF, on the basis of the results of the Systolic Heart failure treatment with I_f inhibitor ivabradine Trial (SHIFT). Furthermore, the updated European Society of Cardiology (ESC) guidelines for the treatment of chronic HF recommend ivabradine for patients with sinus rhythm, LVEF ≤ 35 % and heart rate ≥70 bpm who remain symptomatic despite recommended therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin

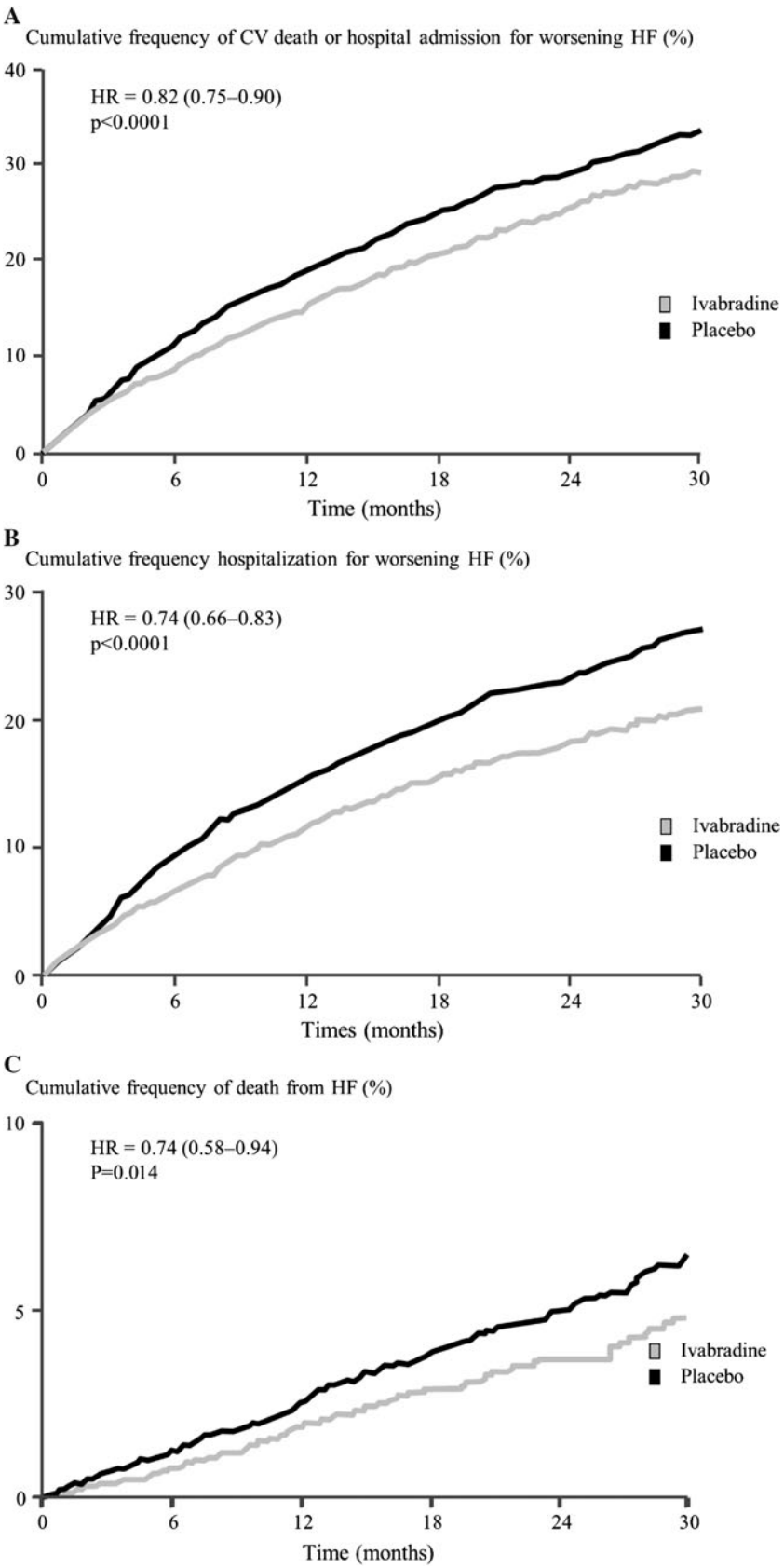

Fig. 5 Results of the SHIFT study in patients with chronic heart failure (HF), showing the effects of ivabradine on the cumulative event curves for (**a**) the primary composite endpoint of cardiovascular (CV) death or hospital admission for worsening HF, (**b**) hospital admission for worsening HF, and (**c**) death from HF. *HR* hazard ratio. Adapted from Swedberg et al. [65]

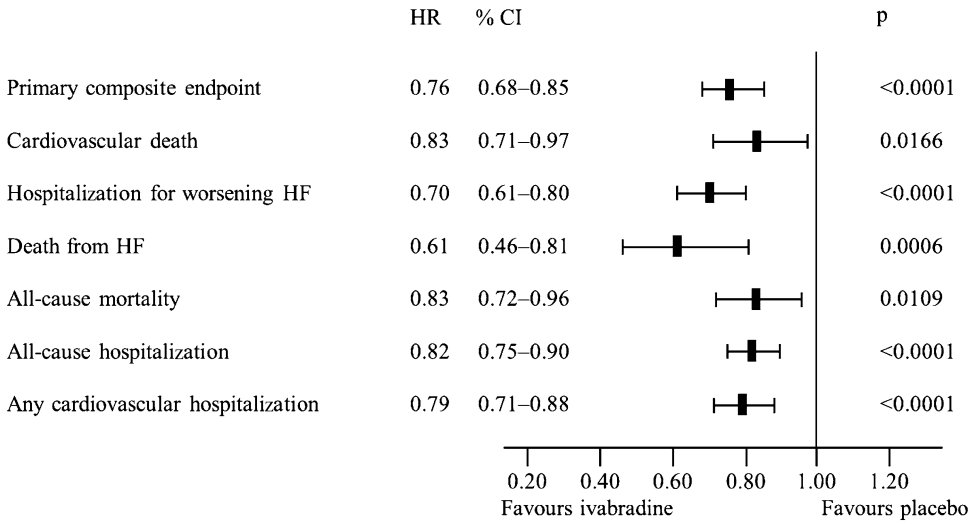

Fig. 6 Effects of ivabradine on cardiovascular outcomes in patients with chronic heart failure (HF) and a baseline heart rate ≥75 beats per minute: subanalysis of the SHIFT study. The primary composite endpoint of this study was cardiovascular death or hospital admission for worsening HF. *CI* confidence interval, *HR* hazard ratio. Adapted from Böhm et al. [66]

receptor blockers, β-blockers, or mineralocorticoid receptor antagonists [63]. The key results of the SHIFT trial are summarised in Table 2.

5.5 Improvement of Clinical Outcomes

SHIFT was a randomized, double-blind, parallel-group, multicentre, placebo-controlled study, which investigated the effects of ivabradine (initiated at 5 mg twice daily and titrated to a maximum of 7.5 mg twice daily) when added to current guideline-based therapy in 6,558 patients with symptomatic chronic HF, LV systolic dysfunction (LVEF ≤ 35 %) and heart rate of 70 bpm or higher [64]. The primary endpoint of SHIFT was a composite of cardiovascular mortality or hospitalization for worsening HF, and the median follow-up was 22.9 months.

SHIFT showed that ivabradine significantly reduced the risk of cardiovascular death and hospitalization due to worsening HF, compared with placebo, by 18 % (937 [29 %] vs 793 [24 %], HR 0.82, 95 % CI 0.75–0.90, $p < 0.0001$; Fig. 5) [65]. The number needed to treat for 1 year to prevent one primary endpoint was 26. Furthermore, ivabradine reduced the risk of hospitalization for worsening HF, compared with placebo, by 26 % (672 [21 %] vs 514 [16 %], HR 0.74, 95 % CI 0.66–0.83, $p < 0.001$) and the risk of death related to HF by 26 % (151 [5 %] vs 113 [3 %], HR 0.74, 95 % 0.58–0.94, $p = 0.014$) [65]. Importantly, the favourable effect of ivabradine on HF events became apparent within 3 months of initiation of treatment, and the benefits were maintained through the course of the trial. The effect was consistent across all pre-specified subgroups (elderly, β-blocker intake, cause of HF, diabetes mellitus and hypertension status, and baseline heart rate) [65].

An increase in heart rate is associated with a high risk of cardiovascular events, and so patients with higher heart rate are expected to benefit the most from preventive therapy. This was shown in an analysis of patients enrolled in SHIFT whose heart rate was ≥75 bpm [66]. In these patients, ivabradine significantly reduced the primary composite endpoint, all-cause mortality, cardiovascular mortality, HF death and HF hospitalization (Fig. 6). Risk reduction depended on heart rate after 28 days, with the best protection for heart rates <60 bpm or reductions >10 bpm.

Another post-hoc analysis of SHIFT assessed the impact of background β-blockers on the response to ivabradine [67]. This analysis demonstrated that there was no evidence of an influence of β-blocker dose on the placebo-corrected change of heart rate with ivabradine. However, there was evidence of a clear effect of baseline heart rate on heart rate reduction ($p < 0.0001$), with the greatest changes in heart rate being observed in patients with the highest baseline heart rates [67]. After adjustment for the previously identified interaction between baseline heart rate and the effect of treatment with ivabradine, there was no evidence of a trend across the four dose categories, even in the analysis adjusting only for baseline heart rate ($p = 0.135$ for the primary endpoint, $p = 0.19$ for hospital admission for worsening heart failure and $p = 0.30$ for cardiovascular death). This analysis indicated that the magnitude of heart rate reduction by ivabradine beyond what is achieved by a β-blocker, rather than the background β-blocker therapy itself, primarily determines subsequent outcome. The additional heart rate reduction achieved by adding ivabradine to the treatment regimen of patients whose heart rate was ≥70 bpm despite β-blockade (as well as those who could not tolerate β-blockers) was shown to be beneficial [67].

Another post-hoc analysis of SHIFT assessed the impact of background mineralocorticoid receptor antagonists (MRAs) on the response to ivabradine. This analysis

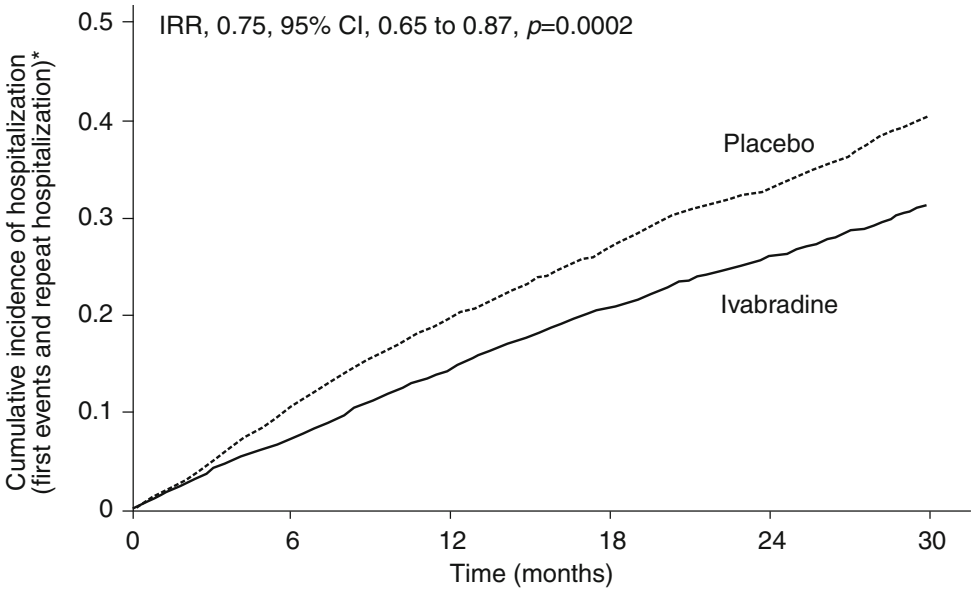

Fig. 7 Cumulative incidence of hospitalization for worsening heart failure (mean number of events per patient) in the SHIFT study. *CI* confidence interval, *IRR* incidence rate ratio. *Estimate of rate of hospitalization over time (corrected for the competing risk of death). Adapted from Borer et al. [69]

showed that the beneficial effect of ivabradine observed in the patients with chronic HF enrolled in the SHIFT study was similar in patients who were receiving MRAs at baseline and those who were not. This shows that ivabradine improves outcomes in patients receiving multiple neurohormonal modulation treatments (ACE inhibitor or angiotensin receptor blocker, β-blocker and/or MRA) and should be considered in patients receiving these treatments whose heart rate is ≥70 bpm [68].

Finally, an analysis of the SHIFT trial investigated the effect of ivabradine on recurrent hospitalizations for worsening HF in patients with chronic systolic HF receiving guideline-based background therapy [69]. This analysis showed that ivabradine significantly reduced the likelihood of recurrent hospitalizations for worsening HF. During the study (median follow-up 22.9 months), ivabradine was associated with a 25 % reduction of the total number of hospitalizations for worsening of HF (902 vs 1,211 events with placebo, $p = 0.0002$; Fig. 7). Ivabradine-treated patients also had a lower risk of a second or third HF hospitalization (HR 0.66, 95 % CI 0.55–0.79, $p < 0.001$; and HR 0.71, 95 % CI 0.54–0.93, $p = 0.012$, respectively). Reduction of recurrent hospitalization for worsening HF is extremely important, as HF admissions are not only distressing for patients and their families, but also significantly affect patients' quality of life and are the major driver of the economic burden of heart failure. In addition, hospitalization itself may not only be the consequence of worse prognosis but may contribute to worse outcome. Consequently, it is important to quantify the influence of treatment on these recurrent, non-fatal events because the true benefit of treatment should be determined by its effect on all events (including repeat events) and not just first events.

5.6 Effect on Left Ventricular Remodelling

The echocardiography substudy of the SHIFT trial showed that ivabradine has a beneficial effect on LV remodelling and function in patients with chronic HF [70]. This pre-planned substudy investigated the effects of ivabradine on the LVESVI and cardiac dimensions in 411 patients who underwent echocardiography at baseline and after 8 months of treatment. At 8 months, ivabradine treatment had significantly improved the LVESVI compared with placebo (−7.0 vs −0.9 mL/m^2, difference −5.8, 95 % CI −8.8 to −2.7, $p < 0.001$). Compared with placebo, ivabradine also significantly reduced LV end-systolic volume ($p < 0.001$), LV end-diastolic volume index ($p = 0.002$) and LV end-diastolic volume ($p = 0.001$) and increased LVEF ($p < 0.001$) after 8 months. These results indicate a reversal of cardiac remodelling with ivabradine. All changes in LV volumes and LVEF were consistent in all pre-specified subgroups regardless of the disease aetiology, baseline LVEF or β-blocker use. The beneficial effect of ivabradine was observed despite the fact that more than 90 % of the patients were receiving treatment with β-blockers and RAAS antagonists. As cardiac remodelling is a central feature of the progression of HF, these results have important clinical implications.

5.7 Effect on Exercise Capacity and Clinical Symptoms

Ivabradine improves exercise capacity in patients with HF. The CARVIVA HF (effect of CARVedilol, IVAbradine or their combination on exercise capacity in patients with Heart Failure) study investigated the effects of ivabradine (up to 7.5 mg twice daily) and the β-blocker carvedilol (up

to 25 mg twice daily) or their combination (5/12.5 mg twice daily) on exercise capacity in 121 patients with HF receiving a maximal dose of an angiotensin-converting enzyme (ACE) inhibitor [71]. This prospective, randomized, open, blinded endpoint study showed that compared with carvedilol, ivabradine alone and in combination over 12 weeks improved 6-min walk distance (from 346.7 to 474.8 m and from 358.2 to 453.1 m with ivabradine alone or in combination with carvedilol, respectively, vs from 379.0 to 435.7 m with carvedilol alone, $p < 0.01$ and $p < 0.02$) and exercise capacity, as assessed with a mixed venous oxygen saturation (MVO_2) test. Significant improvements in peak maximal oxygen consumption (VO_2) and the ventilatory anaerobic threshold (VAT) were also observed with ivabradine alone and in combination with carvedilol when compared with carvedilol alone ($p < 0.01$ and $p < 0.03$, respectively). The New York Heart Association (NYHA) functional class improved significantly more in patients receiving ivabradine alone or in combination than in those allocated to carvedilol alone.

The effects of ivabradine on exercise capacity, gas exchange, functional class, quality of life, and neurohormonal modulation in patients with ischaemic congestive HF were demonstrated in a study by Sarullo et al. [72]. This randomized, placebo-controlled study showed that ivabradine had a positive effect on exercise capacity and clinical symptoms in the 60 patients who were enrolled. The exercise capacity increased from 14.8 to 28.2 min ($p < 0.0001$), and the peak oxygen consumption improved from 13.5 to 17.9 mL/kg per minute ($p < 0.0001$) in the ivabradine group. NTproBNP levels decreased from 2,356 to 1,434 pg/mL ($p = 0.045$).

5.8 Effect on Health-Related Quality of Life

Ivabradine has also been shown to improve quality of life in patients with chronic HF [71–73]. Firstly, patient-reported global assessment in patients in the SHIFT trial showed significant improvement in 2,118 patients (72 %) in the ivabradine group compared with 2,017 (68 %) in the placebo group ($p = 0.0005$). There was also significant improvement in NYHA class at the last recorded value in 887 patients (28 %) on ivabradine versus 776 patients (24 %) on placebo ($p = 0.001$) [65]. The Patient-Reported Outcomes substudy of the SHIFT trial showed that a reduction in heart rate with ivabradine improved health-related quality-of-life parameters, as assessed by the disease-specific Kansas City Cardiomyopathy Questionnaire (KCCQ) [73]. After 12 months of ivabradine therapy, significant improvements in health-related quality of life were shown across all eight dimensions of the KCCQ, compared with placebo, in patients with chronic HF ($n = 1,944$). These changes were observed after 4 months of treatment and were maintained until the last post-baseline visit (24 months). Moreover, the improvement in KCCQ scores seen at 12 months was associated with the magnitude of the observed heart rate reduction seen with ivabradine, and this benefit was maintained at 24 months. An improvement of 5 or more points on the KCCQ is considered to be clinically meaningful, so this analysis shows that ivabradine is associated with clinically meaningful improvements in health-related quality of life [73].

The CARVIVA HF study showed that patients receiving ivabradine alone or in combination with carvedilol had a better quality of life than those receiving carvedilol alone [71]. Quality of life was assessed in this study using both a VAS and the MacNew Quality of Life after Myocardial Infarction (QLMI) questionnaire. Ivabradine and combination therapy significantly improved the overall assessment of quality of life from baseline (from 4.3 to 6.7 [$p < 0.01$] and from 4.7 to 6.1 [$p < 0.02$], respectively). In contrast, quality-of-life scores did not improve with carvedilol (from 4.6 to 4.1) [71]. These findings are further supported by another study by Sarullo et al. [72], which also demonstrated that ivabradine improved quality of life. Compared with placebo, ivabradine significantly improved Minnesota Living with Heart Failure Questionnaire scores after 3 months of treatment.

5.9 Effect on Cardiovascular Events in a Pooled Analysis

Individual trial data from SHIFT and BEAUTIFUL were pooled to determine the effect of ivabradine on outcomes in a wide range of patients with LVSD, heart rate ≥70 bpm, and CAD and/or HF [74]. The pooled population ($n = 11,897$, baseline age 62.3 ± 10.4 years, heart rate 79.6 ± 9.2 bpm, and LVEF 30.3 ± 5.6 %) was well treated according to current recommendations (87 % received β-blockers, 90 % received RAAS inhibitors). Median follow-up was 21 months. Treatment with ivabradine led to a significant 13 % reduction in the relative risk of the SHIFT primary composite endpoint [cardiovascular mortality or hospitalization for worsening heart failure] versus placebo ($p < 0.001$), and a 15 % reduction in the relative risk of the BEAUTIFUL primary composite endpoint [cardiovascular death, admission to hospital for acute MI, or admission to hospital for new-onset or worsening heart failure] ($p < 0.001$). The relative risk reduction of the SHIFT composite endpoint was driven by a 13 % relative risk reduction in hospitalization for worsening heart failure, while that of the BEAUTIFUL composite endpoint was driven by 10 % relative risk reductions in cardiovascular death and hospital admission for MI. Treatment with ivabradine also led to significant reductions in a range of heart failure outcomes in patients with heart rate ≥75 bpm

(n = 7,632 [64 %]) compared with placebo. Cardiovascular mortality or hospitalization for worsening heart failure ($p < 0.0001$), cardiovascular mortality ($p = 0.049$), hospitalization for worsening heart failure ($p < 0.0001$) and all-cause mortality ($p = 0.048$) were all reduced with ivabradine in these patients. This analysis also confirmed the safety of ivabradine in a large population with LVSD, particularly with regard to bradycardia. It also showed that regardless of clinical presentation or profile, ivabradine has an important role in the treatment of patients with LVSD and elevated heart rate ≥70 bpm.

6 Safety and Tolerability

Ivabradine has a favourable tolerability profile, as observed during its clinical development [44, 75]. It is safe and well tolerated when administered as a monotherapy [19, 23, 45] or when administered in combination with atenolol [48], bisoprolol [49], other β-blockers [50, 58] or other cardiovascular therapies [24]. Ivabradine was well tolerated in a range of patient populations, including those with stable angina, CAD or HF [22, 65].

Ivabradine is also well tolerated in patients with comorbidities including asthma and chronic obstructive pulmonary disease [21, 57] or in patients with diabetes mellitus, without any particular safety concerns or adverse effects on glucose metabolism [57]. Another important advantage of ivabradine is that it can be safely used in the presence of low blood pressure because it has no effect on blood pressure or other haemodynamic parameters.

The two most common adverse events associated with the recommended doses of ivabradine are bradycardia and visual symptoms [75]. Bradycardia is an expected adverse event of any heart rate-reducing treatment. However, in the clinical programme of ivabradine, only 3–4 % of patients receiving therapeutic doses of ivabradine (5 or 7.5 mg twice daily) experienced symptomatic bradycardia. Furthermore, there were very low rates of discontinuation in these studies due to this adverse event [23, 59, 65]. For example in the SHIFT trial, bradycardia led to permanent withdrawal from the study of 48 patients (1 %) on ivabradine versus 10 (<1 %) of those in the placebo group [59]. A Holter substudy of the BEAUTIFUL trial investigated the cardiac safety of ivabradine in patients with stable CAD and LV systolic dysfunction also receiving β-blockers [22]. In this study, 840 patients who were enrolled in the BEAUTIFUL trial also underwent 24-h digital ambulatory ECG recording at baseline and after 1 and 6 months of treatment. There was no increase in the incidence of conduction and rhythm disturbances with ivabradine compared with placebo [22]. This study showed that ivabradine significantly lowers heart rate without affecting cardiac safety.

The visual symptoms associated with ivabradine are due to the action of ivabradine on retinal ion channels (I_h current), which belong to the same family as those responsible for the I_f current in the sino-atrial node. In the clinical trials of ivabradine, visual symptoms (mainly phosphenes) were reported in a small proportion of patients. These symptoms were generally mild and resolved spontaneously during or after treatment. Fewer than 1 % of patients receiving ivabradine in clinical trials discontinued treatment because of visual symptoms [19, 23, 24, 45, 48–50, 58, 65].

7 Dosage and Administration

Ivabradine is available in 5 mg and 7.5 mg film-coated tablets. For the treatment of CAD, the recommended starting dose of ivabradine is 5 mg twice daily, which can be up-titrated to 7.5 mg twice daily after 3 or 4 weeks if the resting heart rate is still above 60 bpm. The dose of ivabradine can be reduced to 2.5 mg twice daily if the resting heart rate goes below 50 bpm or if the patient experiences symptoms related to bradycardia, such as dizziness, fatigue or hypotension, during treatment with the recommended daily dose of ivabradine.

For the treatment of chronic HF, the recommended starting dose of ivabradine is 5 mg twice daily, which can be titrated up to 7.5 mg twice daily after 2 weeks if the resting heart rate is still above 60 bpm [44]. If the resting heart rate is below 50 bpm or if the patient experiences symptoms related to bradycardia, ivabradine can be reduced to 2.5 mg twice daily.

A lower starting dose (2.5 mg twice daily) is recommended in patients aged 75 years or older. No dose adjustment is required in patients with renal insufficiency and creatinine clearance above 15 mL/min, or in patients with mild hepatic impairment.

8 Conclusions and Future Perspectives

The pharmacologic properties and clinical efficacy of ivabradine make it an important therapeutic choice for patients with stable CAD or HF. The positive effect of ivabradine on angina pectoris symptoms and myocardial ischaemia, and its ability to reduce myocardial ischemia, make it an important agent in the management of patients with stable CAD.

Following the results of SHIFT, ivabradine has also been approved for the treatment of patients with chronic HF and LVSD who remain symptomatic and therefore are

still at risk of high mortality despite therapy with conventional agents such as RAAS blockers or β-blockers. The use of ivabradine improves prognosis, reduces recurrent hospitalizations and improves quality of life in patients with chronic heart failure with LVSD.

Further studies are evaluating the efficacy of ivabradine for prevention of cardiovascular events in patients with CAD but without clinical HF. The SIGNIFY (Study assessInG the morbidity–mortality beNefits of the I_f inhibitor ivabradine in patients with coronarY artery disease) trial includes patients with stable CAD and an LVEF above 40 %, with no clinical sign of HF, and is investigating the long-term effects (over a period of 48 months) of ivabradine in a large study population [76]. So far, this study has included more than 19,000 patients from 51 countries. The results of SIGNIFY will undoubtedly provide further insights into the role of ivabradine in CAD patients.

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