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Role of ivabradine in management of stable angina in patients with different clinical profiles

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ABSTRACT

In chronic stable angina, elevated heart rate contributes to the development of symptoms and signs of myocardial ischaemia by increasing myocardial oxygen demand and reducing diastolic perfusion time. Accordingly, heart rate reduction is a well-known strategy for improving both symptoms of myocardial ischaemia and quality of life (QOL). The heart rate-reducing agent ivabradine, a direct and selective inhibitor of the I_f current, decreases myocardial oxygen consumption while increasing diastolic time, without affecting myocardial contractility or coronary vasomotor tone. Ivabradine is indicated for treatment of stable angina and chronic heart failure (HF). This review examines available evidence regarding the efficacy and safety of ivabradine in stable angina, when used as monotherapy or in combination with beta-blockers, in particular angina subgroups and in patients with stable angina with left ventricular systolic dysfunction (LVSD) or HF. Trials involving more than 45 000 patients receiving treatment with ivabradine have shown that this agent has antianginal and anti-ischaemic effects, regardless of age, sex, severity of angina, revascularisation status or comorbidities. This heart rate-lowering agent might also improve prognosis, reduce hospitalisation rates and improve QOL in angina patients with chronic HF and LVSD.

INTRODUCTION

Heart rate is one of the main determinants of myocardial oxygen consumption and, under normal circumstances, an increase in heart rate is mirrored by a parallel increase in coronary blood flow.[1] Elevated heart rate shortens the length of each cardiac cycle, reducing diastolic perfusion time and thus oxygen supply.[1] Elevated heart rate may also enhance the development of atherosclerosis, according to animal data, by increasing the exposure of the endothelium to shear stress.[2]

The pathogenesis of chronic stable angina is complex but basically implies an imbalance between myocardial oxygen supply and demand. An elevated heart rate plays an important role in the development of myocardial ischaemia and angina as a result of increased myocardial oxygen demand and a reduction in diastolic perfusion time, the latter being of particular importance considering that 90% of coronary flow occurs in diastole. In patients with elevated heart rates, shortened diastolic duration and impaired collateral flow lead to reduced tissue perfusion in myocardial regions downstream of stenoses.[3 4] In these regions, myocardial blood flow and contractility are impaired.[4–6]

This review article will focus on the use of ivabradine, a drug that selectively reduces heart rate for the treatment of stable angina pectoris in different clinical conditions, including patients with preserved or impaired left ventricular (LV) function. By reducing heart rate without affecting myocardial inotropic function or coronary vasomotor tone, ivabradine reduces oxygen demand and maintains diastolic time.[7] Longer diastole and higher collateral pressure enhance coronary flow and contractility in ischaemic myocardium.[8–11] This review explores existing evidence from both randomised clinical trials and real-world clinical data regarding the role of ivabradine for management of stable angina pectoris in patients with and without LV dysfunction and other comorbidities. Although important for clinical decision making, we do not—in the present manuscript—discuss reimbursement status or cost effectiveness, given the limited data available on the topic.

IVABRADINE: CLINICAL PHARMACOLOGY

Pharmacokinetic properties

Under physiological conditions, ivabradine is rapidly released from tablets and quickly and almost completely absorbed after oral administration. Under fasting conditions, it reaches peak plasma levels in approximately 1 hour. Taking ivabradine during meals reduces intraindividual variability in absorption time. Ivabradine is metabolised by both the liver and the gut by oxidation through cytochrome P450 3A4 (CYP3A4). This agent

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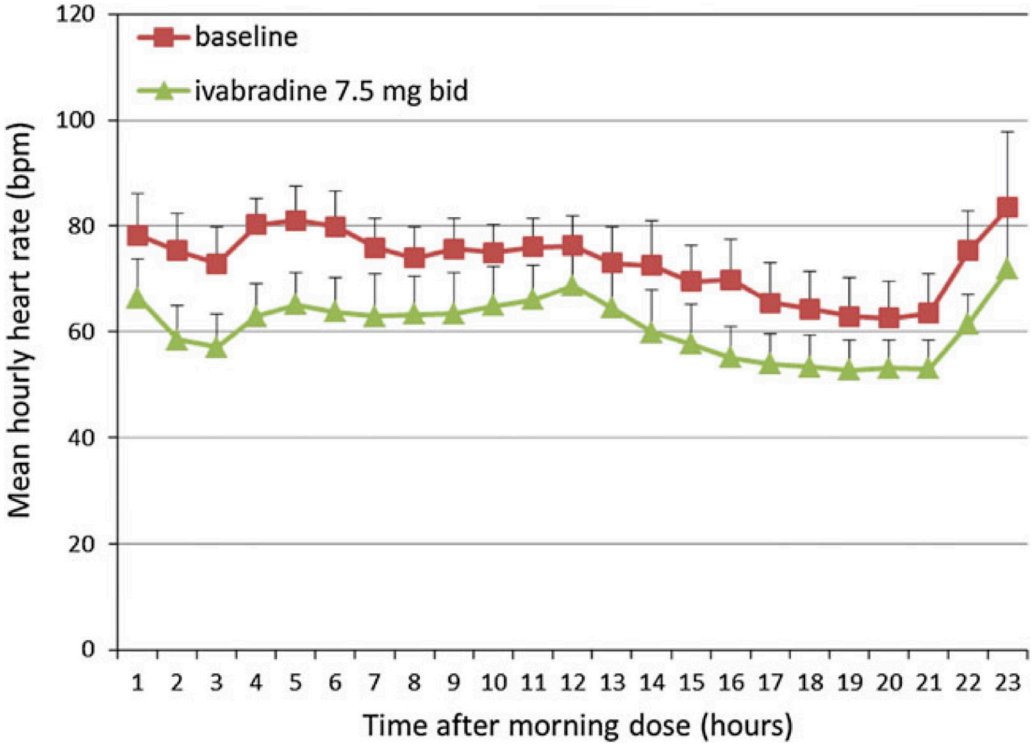


Figure 1 Change from baseline in mean heart rate over 24 hours after treatment with ivabradine 7.5 mg twice daily in volunteers. Clinical data from the Institut de Recherches Internationales Servier (IRIS) database. EudraCT record 2011-001665-40 (data on file). bid, twice a day; bpm, beats per minute. Copied from reference: Deedwania 2013.[12]

has low affinity for CYP3A4 and does not seem to modify CYP3A4 substrate metabolism or plasma concentrations. Potent inhibitors and inducers of CYP3A4, however, may affect the plasma levels of ivabradine. It is for this reason that ivabradine must not be coprescribed with strong or moderate CYP3A4 inhibitors, such as diltiazem and verapamil. Ivabradine's main half-life is approximately 2 hours (70%–75% of the AUC) and its effective half-life around 11 hours. Of clinical importance, ivabradine can be safely combined with first-line pharmacological agents commonly used to improve outcome in the management of cardiovascular disease such as aspirin, statins, beta-blockers and renin–angiotensin–aldosterone system inhibitors, as well as antidiabetic agents, proton pump inhibitors and antidepressant agents.

Pharmacodynamic effects

In humans, at the currently recommended doses, heart rate reduction—the main pharmacodynamic property of ivabradine—is approximately 10 bpm both at rest and during exercise. A study in 23 healthy volunteers (aged 19–63 years) using ivabradine 7.5 mg twice daily demonstrated a significant reduction in heart rate over 24 hours, without affecting circadian heart rate patterns (figure 1).[12]

Of major importance in clinical practice and particularly in subjects with comorbidities, ivabradine does not influence intracardiac conduction, contractility or ventricular repolarisation nor does it affect central aortic pressure (or LV afterload).[13] Studies have reported no effects of ivabradine on atrioventricular or intraventricular conduction times or corrected QT interval.[14]

Mechanisms of action

Under physiological circumstances, heart rate is determined by the rate of spontaneous diastolic depolarisation in the sinoatrial node.[15] Spontaneous diastolic depolarisation is influenced by a mixed sodium–potassium current (I_f) across f-channels. I_f is directly and selectively inhibited by ivabradine, which results in reduced diastolic depolarisation rates and the slowing of heart rate (figure 2).[16–19] Ivabradine enters—and blocks—the f-channel from the cytoplasmic side of the cell membrane and does it mainly when the channel is in the open state.[17] It has been reported that this blocking action reduces the rate of pacemaker activity of the heart, which is more intense at a higher firing rate, as suggested by different groups of investigators.[17 20 21] Ivabradine, therefore, is a specific heart rate-reducing drug. Indeed, its specificity for the I_f current guarantees that this compound has no direct effects on myocardial function, ventricular repolarisation or cardiac conduction.[22 23] Of importance, ivabradine's specific mode of action limits its use to patients with sinus rhythm and excludes patients in atrial fibrillation or atrial flutter.

Many studies in humans—including both healthy volunteers and patients[24–26]—have shown that heart rate reduction with ivabradine largely depends on the dose used and the individual's baseline heart rate. In a 6-month Holter substudy of the morBidity-mortality EvAlUaTion

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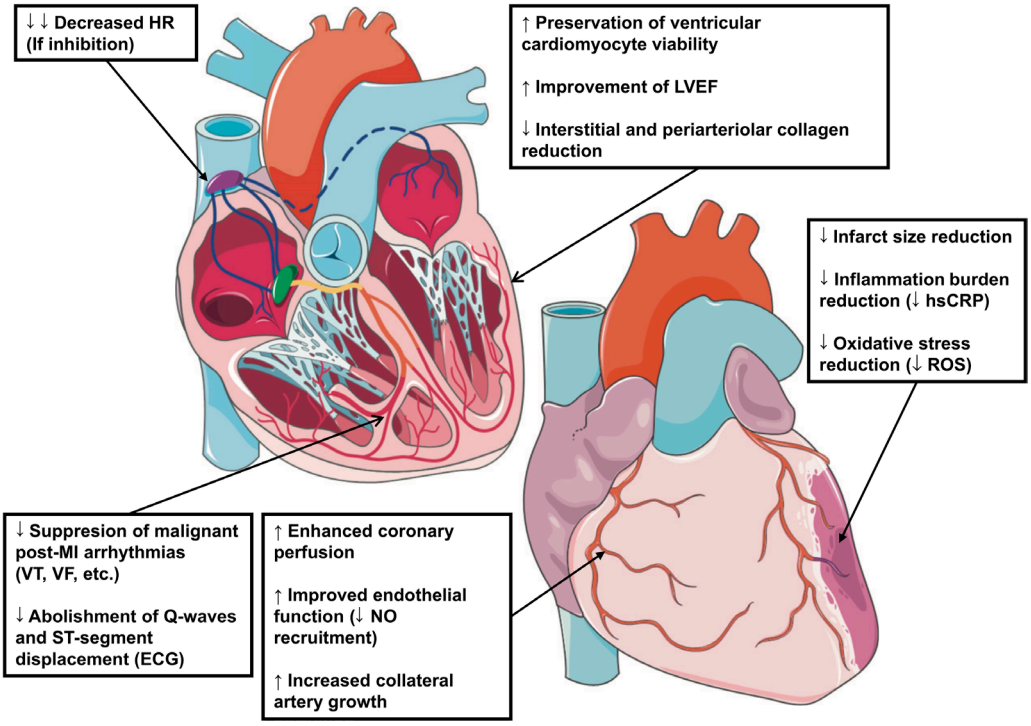


Figure 2 Cardioprotective effects of ivabradine administration in the setting of acute coronary syndromes and myocardial infarction. HR, heart rate; hsCRP, high sensitivity C reactive protein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NO, nitric oxide; ROS, reactive oxygen species; VF, ventricular fibrillation; VT, ventricular tachycardia. Copied from reference: Niccoli *et al*.[19]

of the I_f inhibitor ivabradine in patients with coronary disease and left-ventricULar dysfunction (BEAUTIFUL) trial, involving patients with stable coronary artery disease (CAD) and left ventricular systolic dysfunction (LVSD),[27] treatment with ivabradine reduced 24 hours heart rate by 6.3±9.5 beats per minute (bpm) compared with no demonstrable changes in patients receiving placebo (0.4±7.2 bpm, P<0.001). Of interest, this study showed that heart rate reduction during waking hours in patients receiving treatment with ivabradine was greater than the heart rate reduction achieved during night sleep (6.8±10.4 vs 5.2±8.9 bpm). Ivabradine per se rarely triggers severe bradycardia when used at the recommended doses.

INternatIonal TrIal of the AnTi-anginal effects of IVabradinE (INITIATIVE compared with atenolol), involving 939 patients with stable angina, showed that ivabradine reduced heart rate both at rest and at peak exercise.[28] In a randomised, double-blind study in 386 patients with stable angina receiving treatment with ivabradine (5 mg or 7.5 mg twice daily) for 1 year,[29] heart rate reduction with this agent was shown to be sustained over time. Another study showed that heart rate reduction triggered by ivabradine is greatest in those patients with the highest pretreatment baseline heart rate.[30] Investigations on the role of ivabradine in cardiovascular medicine have shown that this agent has beneficial effects on blood vessels, coronary disease progression and the myocardium (figure 2).[19] These effects are likely to be related to the heart rate-reducing actions of this drug, although ivabradine may have pleiotropic effects unrelated to its actions on heart rate.

IVABRADINE IN TREATMENT OF STABLE ANGINA PECTORIS

Improving both symptoms of myocardial ischaemia and quality of life (QOL) are major goals in the treatment of stable angina pectoris.[31] A large body of evidence on the efficacy and safety of ivabradine for the symptomatic therapy of stable angina has accumulated over the past years (table 1).[11 12 24 26 28 29 32–50] Nearly 5000 patients with angina have been included in randomised clinical trials and nearly 11 000 angina patients have been included in open, observational studies assessing the antianginal efficacy of ivabradine.

Ivabradine as monotherapy in angina

In a placebo-controlled, randomised, dose-ranging study in 360 patients with stable CAD and chronic stable angina, Borer *et al*[24] showed that ivabradine improved—in a dose-dependent fashion—exercise stress testing variables. In this study, ivabradine given twice daily improved the time to 1 mm ST-segment depression compared with placebo (P=0.016) and other important variables in a dose-dependent manner.[24] In an open-label extension phase spanning over 2–3 months in this study, ivabradine-reduced angina attacks from 4.14 to 0.95 attacks per week (P<0.001) and the use of short-acting nitrates from 2.28 to 0.50 units per week (P<0.001).[24]

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Table 1 Summary of the clinical data on ivabradine in patients with stable angina with or without left ventricular systolic dysfunction or heart failure

Effects of ivabradine on symptoms/myocardial ischaemia in patients with stable angina

Publication	Study summary
Stable angina – monotherapy	
Borer *et al*[24] (n=360)	Randomised, double-blind, placebo-controlled, multicentre study in patients with chronic SA (n=360). Duration: 2 wks double-blind+2–3 months open-label. Efficacy: TST and TLA. At 2 wks, TST increased by 32.0 and 44.1 s with ivabradine 2.5 mg and 5 mg twice daily versus 9.0 s with placebo (P=0.016 for 5 mg twice daily dose vs placebo). TLA increased by 22.5 s and 27.2 s with ivabradine 2.5 and 5 mg twice daily versus 12.7 s with placebo. Resting HR and exercise HR decreased significantly with ivabradine 2.5 mg and 5 mg twice daily (both P<0.05 vs placebo).
INITIATIVE, 2005[28] (n=939)	Randomised, double-blind, parallel-group, multicentre study in patients with SA. Duration: 16 wks. Efficacy: TED during ETT. Change in TED at trough: +86.8 s with ivabradine 7.5 mg twice daily versus +78.8 s with atenolol 50–100 mg/day (mean difference 10.3 s; P<0.001 for non-inferiority). Change in the number of angina attacks/wk at 16 wks: −2.2 for ivabradine 7.5 mg twice daily versus −2.7 mg for atenolol. Change in resting HR: −14.3 bpm for ivabradine 7.5 mg twice daily versus −15.6 bpm for atenolol.
Ruzyllo *et al*[32] (n=1195)	Randomised, double-blind, parallel-group, multicentre study in patients with chronic SA. Duration: 3 months. Efficacy: TED during ETT. Change in TED at trough: +27.6 s with ivabradine 7.5 mg twice daily versus +31.2 s with amlodipine 10 mg od (mean difference 1.8 s; P<0.001 for non-inferiority). Change in the number of angina attacks/wk: −3.0 for ivabradine 7.5 mg twice daily versus −3.0 for amlodipine.
Skalidis *et al*[33] (n=21)	Prospective, open single-centre study in patients with stable CAD of one or two vessels, who were eligible for PCI. Duration: 1 wk. Efficacy: ivabradine 5 mg twice daily improved hyperaemic coronary flow velocity and reserve in patients with stable CAD. Resting-APV (17.0±5.5 vs 19.7±7.6, P=0.003) and augmentation of hyperaemia-APV (57.9±17.8 vs 53.5±21.4, P=0.009) led to improvement in CFR (3.51±0.81 vs 2.78±0.61, P<0.001).
Tagliamonte *et al*[34] (n=59)	Prospective, randomised, double-blind trial in patients with stable CAD. Duration: 1 month. Efficacy: coronary flow velocity reserve increased significantly with ivabradine 2.5–7.5 mg twice daily (3.52±0.64 vs 2.67±0.55, P<0.001) and bisoprolol 2.5–10 mg od (3.35±0.70 vs 2.72±0.55, P<0.001), but it was significantly greater with ivabradine. HR decreased similarly (63±7 vs 61±6 bpm; P=NS).
Gloekler *et al*[11] (n=46)	Prospective, randomised, placebo-controlled, monocentre, proof-of-concept trial in 46 patients with chronic stable CAD, 23 of whom received placebo and 23 ivabradine for 6 months. HR changed by +0.2 bpm with placebo and −8.1 bpm with ivabradine (P=0.0089). With placebo, collateral flow index decreased from 0.140 at baseline to 0.109 at follow-up (P=0.12), while it increased from 0.107 to 0.152 with ivabradine (P=0.0461).
Maranta *et al*[35] (n=15)	An open-label, proof-of-concept study in 15 patients with exercise-inducible ischaemia. Stress echocardiography was done at baseline after washout and repeated after 2 wks of ivabradine 7.5 mg twice daily at the same workload. Ivabradine reduced both acute LV dysfunction and stunning in CAD patients with exercise-induced ischaemia.
REDUCTION 2009[36] (n=4954)	Multicentre, open-label, observational study in patients with SA pectoris. Duration: 4 months. Ivabradine 2.5–7.5 mg twice daily+BB. Change in resting HR: −12.4 bpm (P<0.0001 vs baseline). Change in the number of angina attacks/wk: 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).
Stable angina – in combination	
ASSOCIATE, 2009[37] (n=889)	Randomised, double-blind, placebo-controlled, multicentre study in patients with chronic SA. Duration: 4 months. Ivabradine 5–7.5 mg twice daily+atenolol 50 mg od versus placebo+atenolol 50 mg od. Efficacy: TED during ETT. Change in TED at trough: +24.3 s versus +7.7 s (P<0.001). Change in TLA: +26.0 s versus +9.4 s (P<0.001). Change in TAO:+49.1 s versus +22.7 s (P<0.001). Change in TST: +45.7 s versus +15.4 s (P<0.001).
ADDITIONS 2012[38] (n=2330)	Multicentre, open-label, observational study in patients with SA. Duration: 4 months. Ivabradine 2.5–7.5 mg twice daily+BB. Change in resting HR: from 85.0 bpm to 65.6 bpm (P<0.0001 vs baseline). Change in the number of angina attacks/wk: −1.4 (P<0.0001 vs baseline). Change in the consumption of nitrates: −1.9 U (P<0.0001 vs baseline).

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Table 1 Continued

Effects of ivabradine on symptoms/myocardial ischaemia in patients with stable angina	
Publication	**Study summary**
López-Bescós *et al*[29] (n=386)	Randomised, double-blind, parallel-group, multicentre study in patients with chronic SA on concomitant therapy (excluding BBs). Duration: 12 months. Ivabradine 5 mg or 7.5 mg twice daily. Change in resting HR: −9.7 and −12.3 bpm. Change in the number of angina attacks/wk: −1.9 and −1.2. Change in the consumption of nitrates: −1.2 U and −1.7 U.
Pooled analysis by Werdan[39] (n=8555)	Pooled data from three observational clinical studies in 8555 patients with SA received 2.5 mg, 5 mg or 7.5 mg twice daily of ivabradine for 4 months. Therapy with ivabradine was associated with a significant reduction in the frequency of angina attacks and consumption of short-acting nitrates of 87%. Ivabradine is effective and safe in all subpopulations of angina patients seen in clinical practice, independent of age, comorbidities and use of BBs.
Panhellenic study, 2015[40] (n=2403)	Observational, prospective, open-label study in 2403 patients with chronic SA receiving ivabradine 5–7.5 mg twice daily for 4 months in combination with BBs. Ivabradine reduced resting HR from 81.5±9.7 bpm to 63.9±6.0 bpm (P<−0.001), mean number of anginal attacks decreased from 2.0±2.0 times/wk to 0.2±0.6 times/wk (P<0.001) and nitroglycerin consumption decreased from 1.4±2.0 times/wk to 0.1±0.4 times/wk (P<0.001). The percentage of patients with CCS angina class I increased from approximately 38% (baseline) to 84% (study completion; P<0.001). The mean EQ-5D visual analogue scale index increased by 16.1 points (P<0.001), and compliance with treatment was high throughout the trial (96%).
Stable angina – special populations	
Elderly – REDUCTION, 2011[42] (n=382)	Multicentre, open-label, observational study in elderly patients (≥80 years old) with SA. Duration: 4 months. Ivabradine 2.5–7.5 mg twice daily+BBs. Change in resting HR: −12.0 bpm (P<0.0001 vs baseline). Change in the number of angina attacks/wk: from 3.0 to 0.8 (P<0.0001 vs baseline). Change in the consumption of short-acting nitrates: from 4.2 U to 1.2 U (P<0.0001 vs baseline).
Elderly – ADDITIONS, 2014[43] (n=479)	Retrospective analysis of observational, multicentre, prospective, open-label ADDITIONS study investigating ivabradine twice daily+BB in SA patients ≥75 years. Duration: 4 months. Efficacy: HR fell by 19.2±11.6 bpm to 65.4±8.3 bpm. Frequency of angina attacks diminished by 1.6±1.8/wk to 0.4±1.3/wk and consumption of short-acting nitrates fell by 2.2±3.2 units/wk to 0.6±1.8 units/wk (both P<0.0001). Severity of angina, according to CCS grade, decreased and QOL improved (P<0.0001).
Pooled analysis from RCTs, 2009[26] (n=2425)	Pooled analysis of five randomised, double-blind, parallel-group studies in patients with SA. Duration: 3–4 months. Ivabradine ≥5 mg twice daily. 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/wk: −59.4% in all patients; reduction of 51%–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/wk in subpopulations.
Diabetes, 2010[44] (n=2907)	Pooled analysis of eight multicentre, randomised, double-blind studies in patients with SA. Duration: 2 wks–1 year. Change in resting HR: −11.3 bpm in patients without diabetes mellitus versus −11.6 bpm in patients with diabetes mellitus. Change in the number of angina attacks/wk: −2.2 in patients without diabetes mellitus versus −2.0 in patients with diabetes mellitus.
Postrevascularisation – post hoc analysis from ADDITIONS, 2015[45] (n=1193)	Observational, multicentre prospective study in patients with SA on BBs treated with ivabradine at standard doses. Duration: 4 months. In post-PCI patients, ivabradine decreased HR from 83.1 to 64.4 bpm (P<0.0001). Number of angina attacks decreased from 1.9/wk to 0.5/wk. Frequency of nitroglycerin fell from 2.7 times/wk to 1.0 times/wk.
Postrevascularisation – post hoc analysis of the Panhellenic study, 2017[46] (n=926)	Post hoc analysis of postrevascularisation patients in a prospective, observational study of 2403 patients with SA with CAD taking optimised BB therapy. Duration: 4 months. Treatment with ivabradine reduced angina attacks from 2.2/wk to 0.3/wk (P<0.001) and nitroglycerin consumption from 1.5 times/wk to 0.1 times/wk (P<0.001). QOL improved versus baseline (P<0.001).
Postrevascularisation – RIVENDEL study, 2017[47] (n=70)	Prospective, randomised controlled, open-label study examining the addition of ivabradine (up to 7.5 mg twice daily) to standard medical therapy in CAD patients >30 days after PCI. Duration: 8 wks. Addition of ivabradine to standard therapy reduced HR from 68.0 bpm to 62.2 bpm (P<0.001), improved flow-mediated dilation from 8.7 to 15.0 (P<0.001) and enhanced nitroglycerin-mediated dilation from 12.7 to 17.7 (P<0.001).

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Table 1 Continued

Effects of ivabradine on symptoms/myocardial ischaemia in patients with stable angina	
Publication	**Study summary**
Effects of ivabradine on outcomes in patients with stable CAD	
SIGNIFY, 2014[48] (n=19 102)	Randomised, double-blind, placebo-controlled trial of ivabradine, added to standard therapy, in patients with stable CAD without clinical HF and HR ≥70 bpm. Ivabradine up to 10 mg twice daily versus placebo. Duration: 27.8 months (median). Efficacy: no difference in the incidence of the primary endpoint (a composite of death from CV causes or non-fatal MI) between the ivabradine and placebo groups (6.8% and 6.4%, respectively; HR: 1.08; 95% CI 0.96 to 1.20; P=0.20).
Effects of ivabradine in patients with LVSD with and without HF	
Amosova *et al*[49] (n=29)	Randomised, parallel-group, single-blind study in patients with SA and moderate LVSD. Duration: 2 months. Ivabradine 5–7.5 mg twice daily+bisoprolol 5 mg od versus bisoprolol 5–10 mg od. Change in mean resting HR: from 76.6 bpm to 59.3 bpm (P<0.001 vs baseline) versus from 75.9 bpm to 60.5 bpm (P=0.002 vs baseline). Change in 6 min walking test distance: from 388 m to 446 m (P<0.001 vs baseline) versus from 386 m to 400 m (P=NS). Angina attacks were reduced from 3.3±1.1 to 1.7±0.6 in the ivabradine group and from 3.2±1.0 to 2.5±0.9 in the bisoprolol-alone group (intergroup P=0.041).
Angina subgroup analysis from BEAUTIFUL, 2009[50] (n=1507)	Post hoc analysis in patients with SA and LVEF <40% from a randomised, double-blind, placebo-controlled, multicentre study. Duration: 19 months (median). Ivabradine 5–7.5 mg twice daily versus 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). Hospitalisation for MI: 42% RRR (P=0.021). In patients with HR ≥70 bpm: hospitalisation for MI: 73% RRR (P=0.002); coronary revascularisation: 59% RRR.
Angina subgroup analysis from SHIFT, 2017[56] (n=2220)	Post hoc analysis in patients with SA and chronic HF (LVEF ≤35%) from a randomised, double-blind, placebo-controlled, multicentre study in adults in sinus rhythm with stable. Duration: 22.9 months (median). Ivabradine up to 7.5 mg twice daily versus placebo. Efficacy: composite endpoint of CV death or non-fatal MI reduced by 8% versus placebo (P=NS) compared with 11% and 11% in patients without angina and in the overall population, respectively.

Modified from reference: Deedwania.[12]
ADDITIONS, prActical Daily efficacy and safety of procoralan In combinaTION with beta blockerS; APV, time-averaged peak flow velocity; ASSOCIATE, evaluation of the Antianginal efficacy and Safety of the aSsociation Of the I_f Current Inhibitor ivAbradine with a beTa-blockEr; BB, beta-blocker; bid, twice daily; bpm, beats per minute; BEAUTIFUL, morBidity-mortality EvAlUaTion of the *If* inhibitor ivabradine in patients with coronary disease and left-ventricULar dysfunction; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CFR, coronary flow reserve; CV, cardiovascular; EQ-5D, EuroQol five dimensions questionnaire; ETT, exercise tolerance test; HF, heart failure; HR, heart rate;INITIATIVE; INternatIonal TrIal of the AnTi-anginal effects of IVabradinE; LV, left ventricular; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; NS, not significant; od, once daily; PCI, percutaneous coronary intervention; QOL, quality of life; REDUCTION, Reduction of ischemic events by reduction of heart rate in the treatment of stable angina with ivabradine; RIVENDEL, Heart Rate reduction by IVabradine for improvement of ENDothELial function in patients with coronary artery disease; RRR, relative risk reduction; SA, stable angina; SIGNIFY, Study assessInG the morbidity-mortality beNefits of the *If* inhibitor ivabradine in patients with coronarY artery disease; SHIFT, Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial; TAO, time to angina onset; TED, total exercise duration; TLA, time to limiting angina; TST, time to 1 mm ST-segment depression; wk, week.

The anti-ischaemic effects of ivabradine were compared with those of the beta-blocker atenolol in the INITIATIVE study.[28] The study revealed that after 16 weeks of treatment, patients in the ivabradine group (receiving 7.5 mg twice daily) and those receiving atenolol (100 mg/day) had similar beneficial effects on total exercise duration and the number of angina attacks per week (−2.2±4.3 vs −2.7±12.3).[28] In addition to ivabradine's non-inferiority in this study, data at 4 months of follow-up showed that all stress test variables, including time to limiting angina, time to angina onset and time to 1 mm ST-segment depression, showed a tendency to a larger improvement with ivabradine compared with atenolol. Ivabradine reduced heart rate by 14.3 bpm compared with a 15.6 bpm reduction achieved with atenolol.[28]

Ivabradine's anti-ischaemic effects were also compared with those of amlodipine (10 mg once daily) in a multicentre, double-blind, randomised, parallel-group trial involving 1195 patients with stable angina pectoris.[32] In this study, ivabradine was non-inferior to amlodipine regarding exercise capacity, time to onset of angina, time to limiting angina, time to 1 mm ST-segment depression, on stress testing and prevention of daily life angina attacks or nitrate use. Ivabradine administration resulted in a larger reduction in heart rate–blood pressure product, a marker for myocardial oxygen consumption, than amlodipine.[32]

Whether ivabradine (5 mg twice daily) can improve coronary flow reserve (CFR) was assessed by Skalidis *et al*[33] in 21 patients with stable angina. Coronary blood

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flow was assessed using an intracoronary Doppler technique at both baseline and after 1 week of treatment with ivabradine. The study showed that ivabradine improved both hyperaemic and resting coronary flow velocity and CFR after 1 week of treatment. These results were confirmed by Tagliamonte *et al*[34] in a more recent randomised controlled study in 59 stable angina patients. They compared the effects of bisoprolol and ivabradine on CFR and found that after 1 month of treatment, both the ivabradine and bisoprolol patient groups showed an increase in CFR, although the increment was larger in the ivabradine group than in the bisoprolol group (3.52±0.64 vs 3.35±0.70, respectively; P<0.01), despite that these agents caused a similar reduction in heart rate.

In what could be considered a 'proof-of-concept' study, Gloekler *et al*[11] assessed the effect of reducing heart rate with ivabradine on coronary collateral function. In this small-sized, randomised, placebo-controlled study in 46 patients with stable CAD, mean heart rate a 6-month follow-up remained practically unchanged in the placebo groupm, that is, +0.2 bpm, whereas it dropped by 8.1 bpm in the ivabradine group. Coronary collateral function was assessed invasively using a collateral flow index (CFI). CFI was similar at baseline and after treatment in the placebo group but increased from 0.107±0.077 at baseline to 0.152±0.090 at 6 months in the ivabradine group (P=0.04). In another small 'proof of concept' study, Maranta *et al*[35] showed that in patients with exercise-induced myocardial ischaemia treatment with ivabradine reduced the intensity and duration of postischaemic stunning.

In another large trial in patients with stable angina, the REDUCTION (Reduction of ischemic events by reduction of heart rate in the treatment of stable angina with ivabradine) study[36] (n=4954), ivabradine was well tolerated and improved angina symptoms. Symptom improvement was associated with a reduction of heart rate (from 82.9 bpm to 70.4 bpm) (P<0.0001). Daily life angina attacks were reduced by ivabradine from 2.4/week to 0.4/week (P<0.0001). As a result, use of short-acting nitrates in the ivabradine group decreased from 3.3 to 0.6 units/week.

Ivabradine in combination therapy in angina

Additional anti-ischaemic benefits have been observed with ivabradine in patients who were already receiving standard therapy with beta-blockers.[37 38 48] Evaluation of the Antianginal efficacy and Safety of the aSsociation Of the I_f Current Inhibitor ivAbradine with a beTablockEr (ASSOCIATE)—a double-blind, randomised, multicentre, placebo-controlled trial—study enrolled 889 patients with stable angina[37] and a positive exercise stress test despite treatment with atenolol 50 mg once daily. ASSOCIATE study randomised patients to receive placebo (n=440) or ivabradine (n=449) 5 mg twice daily for 2 months, which was then increased to 7.5 mg twice daily for two further months. Patients underwent exercise testing at 2 months and 4 months of follow-up. 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 daily. Patients in the ivabradine group showed a significant increase in total exercise time and 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 patients receiving placebo (figure 2).[37] This improvement was dose dependent with greater beneficial effects observed in patients receiving 7.5 mg twice daily compared with those on 5 mg twice daily. Ivabradine was well tolerated, and 90% of patients were uptitrated to 7.5 mg twice daily after the first 2 months. This study demonstrated that in patients with stable angina receiving anti-ischaemic therapy with the beta-blocker atenolol the addition of ivabradine resulted in a significant long-term improvement in exercise induced myocardial ischaemia.

Another large, multicentre, open-label study assessed the effects of combined therapy with ivabradine and beta-blockers over a 4-month period. The prActical Daily efficacy anD safety of procoralan In combinaTION with beta blockerS (ADDITIONS) trial recruited 2330 patients with stable angina pectoris who were receiving beta-blockers and initiated treatment with ivabradine 5 mg or 7.5 mg twice daily.[38] ADDITIONS showed that combined therapy with ivabradine and a beta-blocking agent reduced heart rate (from 85 bpm to 65.6 bpm), angina attacks per week (from 1.7 to 0.3) and nitrate consumption from 2.3 to 0.4 per week (all P<0.0001).[38] The addition of ivabradine was associated with improved QOL, as assessed by EQ-5D index scores (P<0.0001).[38]

In 2007, López-Bescós *et al* assessed 386 patients with chronic stable angina receiving concomitant therapy with antianginal therapies such as long-acting nitrates, molsidomine, nicorandil, trimetazidine or dihydropyridine calcium channel blockers.[29] The efficacy and tolerability of different dosages of ivabradine was assessed in this study that demonstrated that ivabradine was well tolerated, and treatment efficacy was maintained for over 12 months. Both the 5 mg and 7.5 mg ivabradine doses reduced resting heart rate (from 72.4 to 62.7 bpm and from 71.8 to 59.4 bpm, respectively), and the number of angina attacks per week (P<0.001), with >80% of patients having just one or no angina after 12 months of ivabradine therapy, compared with 58% of patients at study onset.[29]

A recent analysis[39] of pooled data from three observational clinical studies in 8555 patients with stable angina who received 2.5 mg, 5 mg or 7.5 mg twice daily of ivabradine for 4 months showed that therapy with ivabradine was associated with a significant reduction in the frequency of angina attacks and a significant (87%) reduction in the use of short-acting nitrates (P<0.0001). An interesting finding in the study was that compared with data at baseline—when only 27% of patients were in Canadian Cardiovascular Society (CCS) class I—67% were in class I at the end of the study 4 months later. Furthermore, the proportion of patients in higher class severity was reduced from 53% at baseline to 29% for

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class II and from 20% to 4% in class III/IV. Ivabradine had a good safety profile in this study.

In another observational prospective study in 2403 patients with stable angina, Zarifis *et al* showed that 4-month therapy with ivabradine (5 mg uptitrated to 7.5 mg twice daily reduced resting heart rate from 81.5 bpm to 63.9 bpm (P<0.001), mean number of anginal attacks from 2.0 to 0.2 per week (P<0.001) and sublingual nitroglycerin use from 1.4 to 0.1 per week (P<0.001).[40] As in other studies mentioned above, drug compliance was high (96%), and the percentage of patients in CCS class I angina increased from approximately 38% to 84% (P<0.001). Quality of life also improved significantly (P<0.001).[40]

Based on the above antianginal and anti-ischaemic efficacy of ivabradine, this agent has been approved for treatment of stable angina pectoris for patients in sinus rhythm and a heart rate ≥70 bpm whose symptoms are inadequately controlled by optimal doses of beta-blockers, cannot tolerate beta-blockers or have contraindications for the use of beta-blockers.

Ivabradine was shown to be as effective as traditionally used antianginals, such as beta-blockers or calcium channel blockers, as shown in two randomised clinical trials including ~2000 patients.[28 32] The efficacy of ivabradine was also shown in patients receiving combination therapy,[37] which is usually needed for the majority of patients. A recently published consensus[41] highlighted that currently available antianginal treatments have similar levels of efficacy, and therefore choice of therapy in the individual patient should be based on patient comorbidities and the mechanisms underlying angina in a given individual. Tolerability and other pharmacological properties should be taken into account together with the patient's comorbidities.

Effects of ivabradine in special angina patient subgroups

Elderly patients with angina

Elderly patients with angina represent a growing population of stable angina patients and pose major challenges to treatment. These patients have a higher prevalence of comorbidities and frequently develop undesirable side effects with the use of antianginal agents or intolerance to certain compounds. Ivabradine has been shown to have beneficial antianginal effects in elderly patients,[42 43] patients with comorbidities[26] (eg, diabetes[44]) and postrevascularisation angina patients.[45–47] In patients over 80 years of age, the REDUCTION study showed that ivabradine was effective.[42] This was an open-label, multicentre, non-interventional subanalysis of 382 patients with stable angina pectoris taking ivabradine that showed that ivabradine therapy over 4 months significantly reduced angina pectoris episodes, heart rate and the use of nitrates (all P<0.0001 vs baseline).[42] This was a relatively small size study, and its results require confirmation in larger, double blind, placebo-controlled studies.

The effect of ivabradine (mean study dose 11.61±3.18 mg per day) on angina symptoms and QOL was assessed in 479 patients ≥75 years of age in the ADDITIONS trial. The study also evaluated the tolerability of ivabradine when combined with beta-blockers.[43] After 4 months of treatment, the administration of ivabradine was associated with a reduced heart rate and a reduction of both the number of angina attacks per week and the use of short-acting nitrates in this elderly population. CCS grade distribution and quality of life also improved significantly (P<0.0001). Tolerability of treatment with ivabradine in the elderly population was rated as very good by 72% and as 'good' by 28% of physicians.[43]

Patiens with comorbidities

Ivabradine has been shown to be effective in patients with stable angina and various concomitant diseases.[26] Pooled data from five randomised studies in patients with angina (n=2425) and comorbidities showed that ivabradine had antianginal effects irrespective of age, gender or angina severity. The efficacy of ivabradine was confirmed in the presence of comorbidities including asthma, chronic obstructive pulmonary disease, diabetes mellitus and peripheral vascular disease.[26] Similar results were obtained in a pooled analysis of observational studies in 8555 patients.[39] Ivabradine had comparable antianginal efficacy in the elderly, in women, in patients with diabetes and in patients with other comorbidities. In different randomised controlled trials,[44] a total of 535 patients with stable angina and diabetes, ivabradine improved exercise capacity to a similar extent as that in patients without diabetes and was not associated with adverse effects on glucose metabolism.[44] Data derived from observational study, although important, require further confirmation by controlled trials.

Patients with angina after myocardial revascularisation

Ivabradine was effective in patients with angina who had undergone coronary revascularisation.[45–47] In a post hoc analysis from ADDITIONS[45] in 1193 patients with angina and history of PCI treated with ivabradine 5.0 mg or 7.5 mg twice daily for 4 months, the number of angina attacks was reduced from 1.9±2.4 per week to 0.5±1.5 per week and the frequency of nitrate consumption fell from 2.7±3.7 per week to 1.0±1.9 per week (P<0.0001). Moreover, a post hoc analysis from the Panhellenic study[46] involving 926 stable angina patients with a history of coronary revascularisation who received treatment with ivabradine for 4 months showed that this pharmacological agent reduced the number of anginal attacks from 2.2±2.3 per week to 0.3±0.6 per week (P<0.001), nitroglycerin consumption from 1.5±2.2 per week to 0.1±0.4 per week (P<0.001) and improved QOL, compared with baseline (P<0.001).

Heart Rate reduction by IVabradine for improvement of ENDothELial function in patients with coronary artery disease (RIVENDEL), a relatively small size prospective, randomised, controlled open-label study,[47] in 70 patients who underwent successful PCI assessed the effect of ivabradine on brachial artery reactivity, as assessed by

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flow-mediated dilatation (FMD) and nitroglycerin-mediated dilatation (NMD). A significant reduction was observed in the ivabradine group at both 4 weeks and 8 weeks, respectively, in heart rate (65.2±5.9 bpm and 62.2±5.7 bpm; P<0.001), associated with improvement of FMD (12.2%±6.2% and 15.0%±7.7%; P<0.001) and enhancement of NMD (16.6%±10.4% and 17.7±10.8; P<0.001) compared with standard therapy.[47]

Data derived from post hoc analysis, or using surrogate endpoints, although reflecting important findings in real life medical practice, need to be interpreted with caution.

Ivabradine in stable CAD without heart failure

In addition to the assessment of antianginal efficacy, the role of ivabradine in prevention of cardiovascular events was evaluated in the Study assessInG the morbidity-mortality beNefits of the *If* inhibitor ivabradine in patients with coronarY artery disease (SIGNIFY) trial.

SIGNIFY trial assessed whether heart rate reduction with ivabradine would improve clinical outcomes in patients with stable CAD.[48] SIGNIFY was a randomised, double-blind, placebo-controlled trial of ivabradine given on top of standard antianginal therapy, involving 19 102 patients without clinically apparent heart failure, and a baseline heart rate ≥70 bpm. The study also included 12 049 patients with effort-limiting angina (CCS class ≥II)). Patients were randomised to placebo or ivabradine (up to 10 mg twice daily to achieve a target heart rate of 55–60 bpm). A composite of death from cardiovascular causes or non-fatal myocardial infarction was the primary endpoint. At 3 months, the mean (±SD) heart rate in the ivabradine group was 60.7±9.0 bpm versus 70.6±10.1 bpm in the placebo group. After 27.8 months (median follow-up), there was no significant difference in the primary endpoint (6.8% and 6.4%, respectively; HR 1.08; 95% CI 0.96 to 1.20; P=0.20) as well as no significant difference in the incidence of death from cardiovascular causes or non-fatal myocardial infarction. As reported by the SIGNIFY investigators, the main finding in the study was that 'among patients who had stable CAD without clinical heart failure, the addition of ivabradine to standard background therapy to reduce the heart rate did not improve clinical outcomes'.[48]

There was also a significant interaction between the effects of ivabradine and the presence of angina (CCS class ≥II) at baseline. In that subgroup, ivabradine increased the absolute risk of the primary composite endpoint of death from cardiovascular causes or non-fatal myocardial infarction by 1.1%.[48] These unexpected findings were most likely the result of the use of larger than recommended ivabradine dosages and combination therapy with other heart rate-lowering drugs such as verapamil. Following intense data analysis and scrutiny, the European Medicines Agency concluded that the risk/benefit ratio of ivabradine for reducing the symptoms of angina remained positive, provided that ivabradine is administered at the usual dosage of 5 mg twice daily and uptitrated to 7.5 mg twice daily, it is not given in combination with verapamil or diltiazem and it is used in angina patients in sinus rhythm with a heart rate ≥70 bpm who remain symptomatic despite antianginal therapy.[51]

Ivabradine in stable angina with LVSD

In 2011, Amosova *et al* assessed in 29 patients with stable angina and moderate LV dysfunction the effects and tolerability of the combined use of ivabradine and bisoprolol compared with a strategy that involved uptitrating the dose of bisoprolol alone. Ivabradine (7.5 mg twice daily) in combination with the beta-blocker bisoprolol (5 mg once daily) showed greater efficacy and tolerability than the uptitration of bisoprolol from 5 mg/day to 10 mg/day.[49] After 2 months of treatment, resting heart rate decreased similarly in both patient groups. However, patients in whom ivabradine was added to bisoprolol showed greater improvement in exercise capacity, that is, the 6 min walking test (from 388 m to 446 m (P<0.001) vs from 386 m to 400 m (P=0.216)) and exercise stress testing. Of importance, workload increased significantly with ivabradine, from 5.9 to 7.0 metabolic equivalents (P=0.004), but not with bisoprolol uptitration (from 5.7 to 6.2 metabolic equivalents; P=0.141). These results, which suggest that the combination of ivabradine and a beta-blocker is preferable to beta-blocker uptitration in patients with stable angina,[49] should be interpreted with caution given the small study size. The findings should be deemed hypothesis generating.

The randomised, double-blind, placebo-controlled BEAUTIFUL study assessed the effects of ivabradine—given in addition to standard antianginal treatment—in 10 917 patients with CAD and LV ejection fraction (LVEF) <40%.[52 53] Patients were randomised to receive ivabradine 5.0–7.5 mg twice daily or placebo on top of non-prespecified guideline-recommended cardiovascular treatment. The primary endpoint was a composite of cardiovascular death, hospitalisation for acute myocardial infarction or new-onset or worsening heart failure. This incidence of the primary endpoint did not differ in the ivabradine group compared with the placebo group. A post hoc analysis of the BEAUTIFUL trial, however, in patients whose limiting symptom at baseline was angina (n=1507) showed that ivabradine reduced the primary composite endpoint by 24% (HR 0.76; 95% CI 0.58 to 1.00; P=0.05) and the rate of hospitalisation for myocardial infarction by 42% (HR 0.58; 95% CI 0.37 to 0.92; P=0.021).[50]

In 6558 patients with symptomatic chronic heart failure (CHF), LV systolic dysfunction (LVEF ≤35%) and a heart rate of 70 bpm or higher, Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT) was carried out to assess the effect of ivabradine on clinical outcomes in this patient population. As reported by Swedberg *et al*, SHIFT was a 'randomized, double-blind, parallel-group, multicentre, placebo-controlled study that 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'.[54 55] The primary endpoint of SHIFT was a composite of cardiovascular

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mortality or hospitalisation for worsening heart failure, and the median follow-up was 22.9 months. Ivabradine significantly reduced the risk of cardiovascular death and hospitalisation due to worsening heart failure by 18% (29% vs 24%; HR 0.82; 95% CI 0.75 to 0.90; P<0.0001), compared with placebo.[55 56] A post hoc analysis of SHIFT carried out in 2220 stable angina patients with CHF showed that ivabradine improved cardiovascular outcomes in the angina subgroup.[51] Ivabradine also reduced the composite endpoint of CV death and heart failure hospitalisation by 15%, 20% and 18% in the respective subgroups (P for interaction=0.52).[56]

FIXED-DOSE COMBINED THERAPY: NEW PERSPECTIVES

As discussed in previous sections in the present manuscript, several studies in patients with stable angina have demonstrated the antianginal efficacy of the I_f inhibitor ivabradine when given as monotherapy and also in combination with beta-blockers, particularly with metoprolol or carvedilol.[38 40 57–59] The combination of ivabradine and beta-blockers is well tolerated, and the addition of ivabradine does not affect the dosage of beta-blockers that can be used. Ivabradine combined with metoprolol significantly decreased angina symptoms and the use of sublingual nitroglycerin in patients with stable angina and CAD leading to improved QOL.[57 58]

In 1376 patients with angina treated with ivabradine and metoprolol, this combination reduced weekly angina attacks and nitrate consumption and improved QOL. The EQ-5D index and visual analogue scale scores rose from 0.68±0.27 mm to 0.84±0.20 mm and from 58.1±18.4 mm to 72.2±15.5 mm, respectively).[57] The combined use of ivabradine and metoprolol was well tolerated. In terms of safety, there was a low rate of reported adverse events, with only one patient experiencing the presence of phosphenes and only one experiencing symptomatic bradycardia with palpitations. About a third (30.3%) of previously uncontrolled patients attained a heart rate of 55–60 bpm.

In a different study,[58 59] ivabradine added to metoprolol was shown to improve angina symptoms and QOL in 636 patients with stable angina. Angina attacks were reduced from 2.0/week to 0.2/week (P<0.001) and sublingual nitroglycerin use reduced from 1.4 times/week to 0.1 times/week (P<0.001). In this study, percentage of patients in CCS angina class III or IV decreased from 15.4% to 1.9% (P<0.001). The improvement of symptoms and angina class led to a significant 14.7-point increase in EQ-5D questionnaire score (P<0.001). Adherence to treatment was high (98%) throughout the duration of the study.

Results such as those described above with the use of both ivabradine and beta-blockers provided the rationale for the development of fixed-dose combination tablets. Two different formulations of ivabradine and beta-blockers are currently available in clinical practice, that is, Implicor (ivabradine and metoprolol) and Carivalan, a combination of ivabradine and carvedilol is now available in clinical practice. These types of formulation are likely to improve adherence to treatment.

Indeed, the recent European Society of Cardiology guidelines on heart failure recommend ivabradine as the antianginal of choice together with beta-blockers, in this setting.[60] The use of fixed-dose combination treatments is known to be associated with significant reduction in the risk of non-adherence when compared with non-fixed combination regimens.[61] Fixed-dose combinations improve treatment adherence over the long term compared with individual treatments taken separately.[62] Of interest, an analysis of SHIFT data demonstrated that 2596 patients receiving treatment with carvedilol with ivabradine had lower rates of the primary composite study endpoint, that is, CV death or hospitalisation for heart failure (HR 0.80; 95% CI 0.68 to 0.94), heart failure hospitalisation (HR 0.73; 95% CI 0.61 to 0.88) and cardiovascular hospitalisation (HR 0.80; P=0.002).[63] Hence, the combination of these two agents may prove useful in heart failure.

THERAPEUTIC INDICATIONS, DOSES AND SIDE EFFECTS

Ivabradine has been assessed in numerous clinical trials involving over 45 000 participants and is currently indicated for the symptomatic treatment of chronic stable angina pectoris in adults who are in sinus rhythm and with a baseline heart rate ≥70 bpm (box 1). Ivabradine is also indicated in adults with angina pectoris who cannot take beta-blockers and in individuals whose symptoms are inadequately controlled by optimal dose beta-blocker therapy.[64] The mechanism of action, dosages (starting, maintenance and uptitration), discontinuation, common side effects, precautions and contraindications of ivabradine are also summarised in box 1.

Treatment with ivabradine may be particularly beneficial in angina patients with concomitant CHF. Ivabradine is also indicated for treatment of New York Heart Association class II–IV CHF with systolic dysfunction, in patients in sinus rhythm with a heart rate ≥75 bpm, in combination with standard therapy (including beta-blocker therapy) or when beta-blocker therapy is contraindicated or not tolerated.

Undesirable effects

The most common ivabradine-related adverse reactions include phosphenes (luminous visual phenomena) and bradycardia, both of which are dose dependent and related to the pharmacological actions of this agent (box 1).[64] Phosphenes—usually of mild to moderate intensity—have been reported in 14.5% of patients and are usually triggered by sudden variations in light intensity. They generally occur within 2 months of treatment initiation, after which they may occur repeatedly. However, symptoms have very rarely led to patient withdrawal in trials. In a middle-term randomised clinical trial,[37] phosphenes were reported by 2% of patients. In

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Box 1 Treatment with ivabradine in chronic stable angina

Use of ivabradine in chronic stable angina
Indication

Symptomatic treatment of chronic stable angina pectoris in adult patients:
- with normal sinus rhythm
- with heart rate ≥70 bpm
- in combination with beta-blockers in patients inadequately controlled with optimal beta-blocker therapy or in patients with a beta-blocker intolerance or contraindication.

Mechanism of action
Selective and specific inhibition of the cardiac pacemaker I_f current that controls the spontaneous diastolic depolarisation in the sinus node and regulates heart rate.

Starting dosage
- <75 years: 5 mg twice daily
- ≥75 years: 2.5 mg twice daily
- renal impairment: no dose adjustment with renal insufficiency or creatinine clearance>15 mL/min
- hepatic impairment: mild (no dose adjustment), moderate (caution) and severe (contraindicated).

Uptitration
Uptitration to next highest dose is possible after 3–4 weeks if:
- initial dose is well tolerated
- symptoms persist
- Heart rate >60 bpm.

Maintenance dose
- ≤7.5 mg twice daily.

Discontinuation
- no symptomatic response within 3 months
- persistent bradycardia (heart rate <50 bpm) or bradycardic symptoms (ie, dizziness, fatigue or hypotension) after dose reduction.

Common side effects
Visual
- phosphenes: usually mild/moderate intensity
- blurred vision.

Cardiovascular
- bradycardia
- atrioventricular block (first degree)
- atrial fibrillation
- ventricular extrasystole
- uncontrolled blood pressure.

Other
- Headache: during first month of treatment.

Precautions
- hypotension
- atrial fibrillation – cardiac arrhythmias
- congenital QT syndrome/QT-prolonging medicines
- antihypertensive treatment changes in hypertensive patients
- galactose intolerance/Lapp lactase deficiency/glucose-galactose malabsorption.

Contraindications
- hypersensitivity to active ingredient or excipients
- pretreatment resting heart rate <70 bpm
- cardiogenic shock
- acute myocardial infarction
- severe hypotension (<90/50 mm Hg)
- severe hepatic insufficiency
- sick sinus syndrome
- sinoatrial block
- unstable/acute heart failure
- pacemaker dependence
- unstable angina
- atrioventricular block (third degree)
- concomitant treatment with strong CYP3A4 inhibitors (eg, azoles, macrolide antibiotics, HIV protease inhibitors and nefazodone)
- concomitant use of calcium channel blockers that reduce heart rate (ie, verapamil, diltiazem) that moderately inhibit CYP3A4
- pregnancy/lactation/women of childbearing potential not using contraceptive measures.

bpm, beats per minute.

a long-term study in patients with stable CAD,[52] the use of ivabradine in 5477 patients (8893 patient years) was associated with visual disorders in 2% of patients (1.29 patient years). In this study, only 0.3% of patients withdrew because of symptoms, and symptoms disappeared after discontinuation of the treatment.

Severe bradycardia was reported by 3.3% of patients, particularly during the first 2–3 months of treatment. Severe bradycardia (≤40 bpm) was reported by approximately 0.5% of patients. In SIGNIFY,[48] atrial fibrillation was observed in 5.3% of patients taking ivabradine compared with 3.8% in the placebo group. In a pooled analysis of more than 40 000 patients from all the phase 2/3 double-blind controlled clinical trials with a duration ≥3 months, the incidence of atrial fibrillation was 4.86% in ivabradine-treated patients versus 4.08% in controls, corresponding to a HR of 1.26% and 95% CI of 1.15 to 1.39.

CONCLUSION

In many clinical trials in patients with angina, ivabradine, given as monotherapy or in combination with beta-blockers, has been shown to have antianginal and anti-ischaemic effects and to improve QOL. Evidence from the large development programme in angina and data from observational studies in daily practice show that ivabradine improves angina symptoms regardless of age, gender, severity of angina, revascularisation status, history of previous myocardial infarction, peripheral vascular disease or diabetes. In angina patients with CHF and LVSD, the use of ivabradine improves prognosis, reduces recurrent hospitalisations and improves QOL. Taken together, the beneficial effects of ivabradine on myocardial ischaemia and ventricular function, as summarised in this manuscript, suggest that ivabradine represents a

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useful agent for the symptomatic treatment of patients with angina pectoris, especially those with CHF.

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