The therapeutic role of ivabradine in heart failure

Ther Adv Chronic Dis
2018, Vol. 9(11) 199–207
DOI: 10.1177/2040622318784556

Charles Badu-Boateng, Robert Jennings and Daniel Hammersley

Abstract: Heart failure represents a major global cause of morbidity and mortality. Ivabradine is a selective funny current (I_f) inhibitor, which acts on the sinoatrial node, resulting in a reduction in heart rate. Ivabradine is currently licensed for use in patients with symptomatic heart failure with reduced ejection fraction and a heart rate persistently at least 70 beats per minute in spite of otherwise optimal prognostic heart failure pharmacotherapy. In this review article, we examine the mechanism of action of ivabradine, evaluate the clinical trials underpinning its application in heart failure and discuss its current recommended clinical use in this capacity.

Keywords: drug therapy, heart failure, ivabradine

Received: 3 February 2018; accepted in revised form: 30 May 2018.

Introduction

Heart failure (HF) is a clinical syndrome identified by a combination of characteristic symptoms (such as dyspnoea, ankle swelling and fatigue) and clinical signs (including raised jugular venous pressure, pulmonary crackles and peripheral oedema). These clinical signs and symptoms may be secondary to an abnormality in cardiac structure or function resulting in reduced cardiac output, which may lead to elevated intracardiac pressures at rest or during stress.[1] Although prevalence is dependent on definition applied, it is estimated at approximately 1–2% of the adult population in developed countries.[2] In the UK, 900,000 patients have HF and over 60,000 are thought to develop the condition per year. Overall, it is estimated that HF accounts for 2% of the total NHS budget in the United Kingdom, the majority of which relates to repeated hospitalization.[3] The prevalence of HF in the United States of America is estimated at 5.8 million; worldwide it is thought to be in the order of 23 million.[4]

The prevalence of HF increases with age. Hence, with an ageing population, improved survival from ischaemic heart disease and more effective treatments, HF prevalence is expected to rise. HF prognosis has improved over the past 10 years, principally as a result of the improved understanding and utility of prognostic HF pharmacotherapy, yet in spite of this, the overall prognosis remains poor.[5,6]

Current international guidelines advocate the classification of HF based on left ventricular systolic function, as estimated by left ventricular ejection fraction (EF). Using this classification, HF is divided into three categories: HF with preserved EF (HFpEF; EF $\geq$ 50%), HF with mid-range EF (HFmrEF; EF 40–49%) and HF with reduced EF (HFrEF; EF $<$ 40%). This differentiation is clinically important due to different therapeutic responses of many prognostic HF medications based on underlying EF, with most clinical trials showing a reduction in both morbidity and mortality only in patients with HFrEF.[1] The therapeutic goals of drug therapies in HF are to improve patients' symptoms, prevent hospital admissions and reduce mortality. In HFrEF, standard pharmacotherapy is centred around three neurohumeral antagonists: angiotensin converting enzyme (ACE) inhibitors (ACEi) or angiotensin receptor blockers (ARBs), β blockers and mineralocorticoid receptor antagonists (MRAs). In patients with symptomatic HFrEF and a high resting heart rate (heart rate >70) in spite of optimal medical therapy, ivabradine is indicated. In this article, the mechanism of action of ivabradine is examined, the evidence base for its use in

Correspondence to:
Daniel Hammersley
Department of Cardiology, Kings College Hospital NHS Foundation Trust, Denmark Hill, London SE5 9RS, UK
djhammersley@gmail.com

Charles Badu-Boateng
Robert Jennings
Department of Medicine, Frimley Park Hospital, Frimley, Camberley, UK

patients with HF is explored and this is applied to its current role within the available armamentarium of drug treatments for HF. Ivabradine is additionally used in clinical practice as a primary antianginal therapy; its use in this capacity is beyond the scope of this article and thus not discussed in detail.

The significance of heart rate in patients with HF

Elevated resting heart rate is an independent predictor of cardiovascular morbidity and mortality in both the general population and in patients with HF, irrespective of underlying ejection fraction.[7–11] The pathophysiology of this observation is multifaceted, relating to the creation of a mismatch between myocardial oxygen supply and demand at higher heart rates, with increased vascular oxidative stress, endothelial dysfunction, acceleration of atherogenesis and coronary plaque instability.[12] Patients with HF in particular are prone to higher resting heart rates due to compensatory neurohumeral activation resulting in increased sympathetic activity.[13] This drives an increase in oxygen demand, reduced ventricular efficiency and consequently worsens HF.[14] Multicentre studies have demonstrated an association between higher admission heart rates with worse outcomes, including mortality, in patients admitted to hospital with HF.[15] Additionally, higher discharge heart rates in patients with HF are associated with increased mortality and hospital readmission.[16]

The association of β-blocker use with improved mortality in patients with HFrEF is well established.[17] An area of controversy had related to whether the beneficial effects of β blockers in this patient group are derived directly from the reduction in heart rate itself, or from a more complex pathway relating to their effect of adrenergic inhibition. A meta-analysis of patients with HFrEF treated with β blockers demonstrated that the degree of heart rate reduction correlated with improved mortality.[18,19] These findings indicated that there may be a possible role for additional heart rate reducing therapies in the treatment of HF, either with greater β receptor or I_f channel inhibition. This is particularly pertinent as optimal heart rate control is sometimes not achieved in patients with HF. Some patients may be unable to tolerate β blockers, or titration to optimal doses, due to their well established side-effect profile or pre-existing contraindications. A meta-analysis of patients with HF indicated that for every 5 beats per minute (bpm) reduction in heart rate achieved, an 18% reduction in all-cause mortality is observed.[19]

Ivabradine

Ivabradine (Procoralan, Servier Laborataories Ltd, France and Corlanor, Amgen Inc., USA) is a selective I_f ('funny') channel inhibiting drug. The sinoatrial (pacemaker) nodal cells of the cardiac myocytes are responsible for generating a spontaneous diastolic depolarization current that determines the heart rate, by allowing the threshold for action potentials to be reached. This is achieved through the use of the I_f channels, located in the sinoatrial node, which control the slope of the diastolic depolarization.[20,21] This is known as the I_f current and can be activated by voltage changes, cyclic nucleotides and nitric oxide. Direct binding of cyclic adenosine monophosphate (c-AMP) molecules increases the opening probability of the channel, making it possible for the channel's activity to be altered by both sympathetic and parasympathetic stimulations.[22–24] Ivabradine reduces the heart rate by selectively and specifically inhibiting the I_f channels in a concentration-dependent manner.[25] Experimental studies of ivabradine have demonstrated independent reduction of heart rate without any effects on blood pressure, myocardial contractility and relaxation, ventricular repolarization or myocardial conduction.[26–28]

Ivabradine enters the I_f channel and binds to its intracellular side, subsequently disrupting the mixed sodium and potassium ion current flow through the channel. This prolongs the slow spontaneous phase of diastolic depolarization, and thereby reduces HR. The activity of ivabradine is therefore dependent on the opening (during repolarization) and closing (in depolarization) of the I_f channels, with greater potency seen with faster heart rates. At higher concentrations, the activity of ivabradine saturates, preventing adverse reductions in the HR.[23,29]

It has long been recognized that diseased, hypertrophied hearts are predisposed to malignant arrhythmia, and the discovery that I_f currents are also increasingly seen in such states raised the possibility that blocking this channel may be beneficial.[30–33]

I_f current is carried through a series of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, which are present in large numbers *in*

vitro, but decline thereafter such that in healthy adults they are only present in pacemaker cells such as the sinoatrial node. Its activity is mediated both by the sympathetic nervous system in response to β-adrenergic and muscarinic receptor activation but also by nitric oxide stimulated cGMP and calcium intracellular pathways.[34–36]

However, in animal models and human hearts with severe ischaemic cardiomyopathy, HCN channels reappear in greater numbers and increasing amplitude in ventricular myocytes, and appear, in mouse models at least to be associated with enhanced likelihood of automaticity and the development of malignant action potentials which may give rise to arrhythmia, independent of sympathetic mediated tachycardia.[32,34–36]

There is as yet little direct evidence in humans that this increased HCN expression in ventricular myocytes is linked to malignant arrhythmia, or that by blocking these channels leads to a reduction in rates of sudden cardiac death, although currently reported randomized controlled trials were not designed to look at this particular endpoint, and it remains a potential area of focus for future research.[31,36–39]

Ivabradine is administered in an oral tablet preparation. Under fasting conditions, it reaches peak concentrations at 1 h. Oral bioavailability is approximately 40%; ingestion with food is recommended as this increases systemic absorption by 20–30%. The main half life of ivabradine is 2 h with an effective half life of 11 h. About 70% of the drug is bound to plasma on absorption.[40]

Ivabradine undergoes extensive oxidation in the gut, and along with its metabolite, N-desmethylated derivative, by cytochrome P450 (CYP) 3A4 enzymes in the liver. Inhibitors of CYP 3A4 may affect ivabradine plasma concentration due to its low affinity for the enzyme, and it is recommended to avoid concurrent administration. Metabolites are excreted equally in faeces and urine.[23,40]

Fundamental clinical trials: ivabradine in patients with HFrEF

Large multicentre, randomized controlled trials have played a significant part in our understanding of the role ivabradine has in the pharmacotherapy of patients with HFrEF. The first of these was the Morbidity–Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients with Coronary Disease and Left-ventricular Dysfunction (BEAUTIFUL) trial.[41] The BEAUTIFUL trial was a multicentre, randomized, double-blinded, placebo-controlled study of 10,917 patients to assess the mortality–morbidity benefits of ivabradine use in patients with coronary artery disease (CAD) and left ventricular systolic dysfunction. A total of 5479 patients were randomized into a group receiving 5 mg ivabradine (uptitrating to 7.5 mg twice per day), and 5438 to the placebo group and followed up for 12–35 months (median 19 months). Both groups also received medical therapy, including aspirin, ACEi and β blockers. The trial included patients over the age of 55 with stable CAD, in sinus rhythm with resting HR at least 60 bpm, HFrEF with EF less than 40%, clinically stable for at least 3 months in regards to angina and HF symptoms, and on appropriate cardiovascular medication for 1 month. The results demonstrated no difference in the primary endpoint of composite of cardiovascular death, admission for myocardial infarction (MI) and admission for HF for those receiving ivabradine compared with placebo [22.5% *versus* 22.8%; hazard ratio (HR) 1.00; 95% confidence interval (95% CI) 0.91–1.1; $p = 0.94$] and no differences in any prespecified subgroup. There was an average of 6 bpm reduction in HR with ivabradine use. There were eight secondary endpoints ranging from all-cause mortality to admission for HF or MI. There were no differences in the secondary endpoints in the overall population. However, a subgroup analysis of those patients with HR at least 70 bpm (5392 patients), ivabradine appeared to reduce admission for acute MI by 36% (fatal and nonfatal; $p = 0.001$); reduce composite admission for acute MI or unstable angina by 22% ($p = 0.023$); and additionally to reduce coronary revascularization by 30% ($p = 0.016$). It should be noted, however, that these endpoints were only prespecified in the overall population and conclusions therefore should be interpreted with caution.[41]

Of note, some of the larger effects of ivabradine in the higher-HR subgroup in the BEAUTIFUL study could be attributed to the higher dosage of β blockers in patients with HR less than 70 bpm. The BEAUTIFUL study was successful in highlighting an important therapeutic target, which led to trials for assessing the true effects of ivabradine in the subgroup of patients with HFrEF and HR at least 70 bpm, the SHIFT trial.[42]

The SHIFT trial (Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial)

was a randomized, double-blinded, multicentre placebo-controlled trial of 6558 patients with stable symptomatic chronic HF of New York Heart Association (NYHA) class II–IV, with severe left ventricular systolic dysfunction (EF ⩽ 35%) of both ischaemic and nonischaemic aetiology. Patients were in sinus rhythm, with a resting heart rate of 70 bpm or higher (mean HR 79.9 bpm). Patients enrolled had had a HF-related hospitalization in the preceding 12 months and were already established on HF pharmacotherapy, with 89% taking a β blocker if tolerated, 91% taking ACEi or ARB and 60% taking an MRA. Patients were randomized to receive either ivabradine or placebo. The ivabradine dose was titrated over the first month of the study to achieve a heart rate less than 70 bpm. The trial assessed the outcome of HR reduction by ivabradine as an adjunct to standard HFrEF therapy, with median follow up of 22.9 months. The trials demonstrated that ivabradine use was associated with a reduction in the primary endpoint of the composite of cardiovascular death or hospitalization for worsening HF symptoms (HR 0.82, 95% CI 0.75–0.90, $p < 0.0001$). These findings were principally driven by hospital admissions for worsening HF (21% in the placebo group *versus* 16% in the ivabradine group; HR 0.74, 95% CI 0.66–0.83, $p < 0.0001$). For the secondary end points, there was no difference in the all-cause or CV mortality (HR 0.90, $p = 0.092$ and HR 0.91, $p = 0.128$ respectively). Ivabradine was associated with a reduction in all-cause hospitalization (HR 0.89, $p = 0.003$). There was a nonstatistically significant trend towards reduced benefit of ivabradine with concomitant baseline β-blocker use. Patients with the highest preintervention heart rate (HR > 87) were observed to have the greatest reduction in HR with ivabradine and also the largest reduction in clinical primary end points (HR 0.75, 95% CI 0.67–0.85). Subgroup analysis identified that ivabradine did not significantly reduce end points in patients with baseline HR less than 75 bpm. Ninety percent of patients in the SHIFT trial were on β blockers but only 26% of these were at target doses. Further subgroup analysis assessed the impact of baseline β-blocker dose on the efficacy of ivabradine at reducing composite endpoint, identifying only a statistically significant reduction in patients taking less than 50% of the target β-blocker dose. It is likely that patients receiving lower doses of β blockers had higher resting heart rates and thus are more likely to benefit from ivabradine therapy.[43]

Post hoc analysis of the SHIFT trial assessed the influence of comorbidities on the effects of ivabradine, and on the mortality and morbidity on the SHIFT patient population. Increasing comorbidities were associated with increased rate of CV death or HF hospitalization ($p < 0.0001$), with most events occurring in patients with more than three comorbidities (in both ivabradine and control groups). The rate of hospitalization was however lower in the ivabradine group.[44]

There is some evidence to suggest that ivabradine may have other, less quantifiable and more subjective beneficial effects for patients. In a prespecified substudy analysis from the SHIFT trial, 1994 patients were assessed for patient-reported quality of life metrics using the Kansas City Cardiomyopathy Questionnaire (KCCQ) at baseline, 4 and 12 months. The study found that ivabradine was associated with improved quality of life as measured with the KCCQ by 1.8 for Clinical Summary Scores (CSS) and 2.4 for Overall Summary Scores (OSS) (placebo corrected, $p=0.02$ and $p < 0.01$, respectively). What was noteworthy from the same study was that the larger the reduction in heart rate the greater the improvements seen in quality-of-life scoring ($p < 0.001$), although it must be acknowledged that the study population included a greater number of patients with less severe symptoms of NYHA class II than the overall population, allowing for a potential source of bias.[45] These improvements in quality-of-life scores seen with ivabradine have been replicated elsewhere, such as in a small randomized single-blinded Italian trial of 60 patients in which there was a greater improvement in the Minnesota Living with Heart Failure Questionnaire scoring in the group taking ivabradine compared with baseline at 3 months ($37.5 + 1.9$; $p < 0.0001$).[46]

Clinical applications of ivabradine in HF

The European Society of Cardiology (ESC) recommend the use of ivabradine to reduce risk of HF hospitalization or cardiovascular death in symptomatic patients (NYHA category II–IV) with severe left ventricular systolic impairment (EF ⩽ 35%), in sinus rhythm with resting heart rate at least 70 bpm, in spite of treatment with an evidence-based dose of a β blocker (or maximally tolerated dose below that), ACEi (or ARB) and an MRA. The guidance also recommends the use of ivabradine in patients with symptomatic

HFrEF who are unable to tolerate, or have contraindications, to β blockers, again in conjunction with an ACEi (or ARB) and an MRA. The European Medicines Agency (EMA) approved ivabradine for use in Europe for patients with HFrEF and EF up to 35%, in sinus rhythm with a resting HR at least 75 bpm, as this group conferred a survival benefit.[47] Due to its action as an antianginal medication, the ESC guidance also recommends the use of ivabradine as an antianginal drug in suitable patients with HFrEF (sinus rhythm with HR at least 70 bpm) with symptomatic stable angina pectoris.

The UK-based National Institute for Health and Care Excellence HF guidelines are similar, recommending the use of ivabradine as a treatment option for chronic HF for patients with severe left ventricular systolic impairment (EF ⩽ 35%), who are NYHA category II–IV, in sinus rhythm with resting heart rate ⩾75 bpm, and are already stabilized on optimal HF therapy (including ACE inhibitors, β blockers and MRA) for a period of at least 4 weeks. The guideline recommends the medication be initiated by a HF specialist with access to a multidisciplinary HF team and that dose titration be carried out.[6,48,49]

The US Food and Drug Administration (FDA) approved the use of ivabradine as an agent to reduce the risk of hospitalization in patients with worsening HFrEF. The 2017 American College of Cardiology/American Heart Association/Heart Failure Society of America updated guideline on the management of HF stipulates that ivabradine can be beneficial for reducing HF related hospitalization for patients with symptomatic (NYHA I–II) stable chronic HFrEF (EF ⩽ 35%) who are receiving guideline-directed medical therapy, including a β blocker at maximum dose, and who are in sinus rhythm with a resting heart rate of at least 70 bpm.[50]

More recently, there has been growing interest in assessing the use of ivabradine in other types of HF. The Preserved Left Ventricular Ejection Fraction Chronic Heart Failure with Ivabradine Study (EDIFY) was a randomized, double-blind, placebo-controlled study that assessed ivabradine use in 179 patients with HFpEF. Inclusion criteria were NYHA class II–III, sinus rhythm, HR at least 70 bpm, EF at least 45% and N-terminal pro B-type natriuretic peptide (NT-proBNP) at least 220 pg/ml (BNP ⩾ 80 pg/ml).[51] Over the 8-month treatment period, ivabradine in comparison to placebo did not confer any significant improvements in any of the three coprimary end points of cardiac filling pressure (E/e'), exercise capacity and reduction in NT-proBNP concentration, in patients with chronic stable HFpEF. Thus, at present, ivabradine therapy is not recommended for treatment of HFpEF or patients with HFmrEF.

Dosage and safety of ivabradine

Where indicated in clinical practice, a 2-week initial trial of 5 mg ivabradine twice per day is recommended as a starting dose. Thereafter, the dose can be uptitrated to 7.5 mg twice per day if the target heart rate is not met. If, after initiation, there is an observed resting HR less than 60 bpm, the dose is decreased to 2.5 mg twice per day. Treatment should be discontinued if HR remains persistently less than 50 bpm despite dose reduction or if the patient develops symptomatic bradycardia.[49] The starting dose may be decreased (2.5 mg, twice per day) instead of 5 mg twice per day for patients with a history of conduction defects or in whom bradycardia may result in haemodynamic compromise.

In patients with mild or moderate hepatic impairment (Child Pugh A or B), no dose adjustments are required. Ivabradine use is contraindicated in those with severe (Child Pugh C) hepatic impairment. No dose adjustment is required for renal impairment where the creatinine clearance (CrCl) is between 15 and 60 ml/min. There are currently no data available for use in patients with CrCl less than 15 ml/min.

The most common adverse effect of ivabradine (⩾1/10) reported is luminous phenomena, also known as phosphenes (14.5% of patients). Seventy-five percent of the reported phosphenes resolved during treatment, and 100% resolved after treatment. In the SHIFT trial there were 89 cases (3%) of phosphene occurrence amongst the ivabradine cohort compared with 17 (1%) in the placebo group ($p < 0.0001$) and in the BEAUTIFUL trial 37 patients (0.3%) withdrew from the trial due to visual disturbance, including phosphene occurrence.

Common (⩾1/100 to <1/10) side effects include bradycardia (reported in 3.3% of patients, usually within the first 3 months of initiation), headache and atrial fibrillation (AF). In both the BEAUTIFUL and SHIFT trials, withdrawal

from the study was reported due to symptomatic bradycardia, with 13% taking ivabradine reporting bradycardia in BEAUTIFUL and 11% in SHIFT (compared with 2% of the placebo group in both trials) ($p < 0.0001$). Indeed the authors of the BEAUTIFUL trial blamed higher rates of bradycardia among the ivabradine group for the markedly increased rates of medication discontinuation seen in the same group compared with placebo (28% compared with 16%).

In the Study Assessing the Morbidity–Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY), the morbidity and mortality benefits of ivabradine were assessed in patients with stable CAD without clinical HF. It was a large, multicentre, placebo-controlled, randomized controlled trial which reported a higher incidence of bradycardia in the ivabradine group (17.9% *versus* 2.1% in placebo group; $p = 0.001$).[52] AF was also higher in the ivabradine group (5.3%) compared with the placebo group (3.8%).[52] Using data from phase II/III double-blind trials, pooled analysis of over 40,000 patients given ivabradine for at least 3 months showed the incidence of AF to be 5.34%, with a 24% relative risk increase due to ivabradine compared with the placebo group (4.56% incidence).[53] This increased incidence of AF was seen to a lesser degree in the SHIFT trial, in which 9% of the ivabradine group developed AF compared with 8% in the placebo cohort ($p = 0.012$). However, a 2014 meta-analysis of 21,171 patients from 11 studies, including all the patients from both the BEAUTIFUL and SHIFT trials, found an increased relative risk of AF with ivabradine of approximately 15% compared with placebo (95% CI 1.07–1.24, $p = 0.0027$).[54] The ESC HF guidelines include a warning that ivabradine may increase the risk of AF.[1]

Overall adverse effect rates were similar between the ivabradine and control groups in the BEAUTIFUL trial (23% *versus* 23%; $p = 0.70$). Ivabradine was well tolerated in the SHIFT trial in combination with other HR-lowering drugs with a lower rate of adverse effects than seen in the placebo group (3388 *versus* 3847, $p = 0.025$) and only a 1% reported overall population medication discontinuation rate. In the EDIFY study there were no statistically significant differences between the ivabradine and placebo groups in the incidence of adverse effects ($p = 0.633$) or in rates of discontinuation ($p = 0.261$).[52]

Clinical uptake of ivabradine

Since ivabradine obtained its FDA licence for use in HF in 2015 and EMA approval in 2012, it remains a third-line therapy in HF. Epidemiological studies including the UK National Heart Failure audit do not routinely measure ivabradine prescribing rates as they do not form part of the key performance indicators and it now appears to be facing increased pressure from new medications such as valsartan/sacubitril which will further squeeze its market share.[55]

The main reason for ivabradine's lack of success is likely due to concerns generated from the SIGNIFY trial. The study exposed increased levels of symptomatic bradycardia and a statistically significant increase in combined risk of cardiovascular death or nonfatal heart attack in a subgroup of patients who had symptomatic angina (3.4% *versus* 2.9% yearly incidence rates); results that then prompted an EMA review of the medication which almost certainly impacted on its prescribing levels.[56]

Another potential stumbling block for ivabradine prescribing may include a smaller than anticipated target group, with one study suggesting that only 9.3% of patients with chronic HF and systolic impairment were suitable for ivabradine at 12-month follow up, once disease had been suitably optimized with β blockers and ACEi.[57]

Conclusion

Ivabradine is a drug that reduces heart rate by inhibiting the cardiac I_f channels in their open state. At present, it has been approved for use in clinical practice as an adjunct in the treatment of select patients with symptomatic HFrEF, specifically to reduce the risk of HF hospitalization or cardiovascular death in patients with severe left ventricular systolic impairment (EF $\leqslant$ 35%), who are in sinus rhythm with resting heart rate of at least 70 bpm, in spite of treatment with an evidence-based dose of a β blocker (or maximally tolerated dose below that), ACEi (or ARB) and an MRA. There is also a role for ivabradine in the treatment of patients with HFrEF who are unable to tolerate β-blocker therapy, in combination with other prognostic HF medication. In addition to its role as a therapeutic agent reducing HF-associated morbidity and mortality, the research allied to elucidating its role in HF therapy has proved a useful insight into the underlying role of elevated heart rate in the pathophysiology of HF.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Ponikowski P, Voors A, Anker S, *et al*. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016; 37: 2129–2200.
2. Mosterd A and Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007; 93: 1137–1146.
3. Drug and Therapeutics Bulletins. Ivabradine for chronic heart failure? *DTB* 2012; 50: 117–120.
4. Kenworthy W, Guha K and Sharma R. The patient with left ventricular systolic dysfunction now and in the future. *Br J Hosp Med (Lond)* 2016; 77: 516–522.
5. Mozzafarian D, Benjamin EJ, Go AS, *et al*. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation* 2016; 133: e38–e360.
6. National Institute for Health and Care Excellence. *Chronic heart failure in adults: management*, https://www.nice.org.uk/guidance/cg108/resources/chronic-heart-failure-in-adults-management-pdf-35109335688901 (2010, accessed 14 January 2018)
7. Kannel WB, Kannel C, Paffenbarger RS Jr, *et al*. Heart rate and cardiovascular mortality: the Framingham Study. *Am Heart J* 1987; 113: 1489–1494.
8. Palatini P and Julius S. Association of tachycardia with morbidity and mortality: pathophysiological considerations. *J Hum Hypertens* 1997; 11: 19–27.
9. Cook S, Togni M, Schaub MC, *et al*. High heart rate: a cardiovascular risk factor? *Eur Heart J* 2006; 27: 2387–2393.
10. Fox K, Borer JS, Camm AJ, *et al*. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol* 2007; 50: 823–830.
11. Reil JC and Bohm M. The role of heart rate in the development of cardiovascular disease. *Clin Res Cardiol* 2007; 96: 585–592.
12. Custodis F, Schirmer SH, Baumhakel M, *et al*. Vascular pathophysiology in response to increased heart rate. *J Am Coll Cardiol* 2010; 56: 1973–1983.
13. Kaye DM, Lefkovits J, Jennings GL, *et al*. Adverse consequences of high sympathetic nervous activity in the failing human heart. *J Am Coll Cardiol* 1995; 26: 1257–1263.
14. Custodis F, Reil JC, Laufs U, *et al*. Heart rate: a global target for cardiovascular disease and therapy along the cardiovascular continuum. *J Cardiol* 2013; 62: 183–187.
15. Bui AL, Grau-Sepulveda MV, Hernandez AF, *et al*. Admission heart rate and in-hospital outcomes in patients hospitalized for heart failure in sinus rhythm and in atrial fibrillation. *Am Heart J* 2013; 165: 567–574.
16. Laskey WK, Alomari I, Cox M, *et al*. AHA get with the guidelines®-heart failure program. Heart rate at hospital discharge in patients with heart failure is associated with mortality and rehospitalization. *J Am Heart Assoc* 2015; 22: e001626.
17. Lechat P, Hulot JS, Escolano S, *et al*. Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II Trial. *Circulation* 2001; 103: 1428–1433.
18. Flannery G, Gehrig-Mills R, Billah B, *et al*. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. *Am J Cardiol* 2008; 101: 865–869.
19. McAlister FA, Wiebe N, Ezekowitz JA, *et al*. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med* 2009; 150: 784–794.
20. DiFrancesco D. Pacemaker mechanisms in cardiac tissue. *Annu Rev Physiol* 1993; 55: 455–472.
21. DiFrancesco D and Camm JA. Heart rate lowering by specific and selective If current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. *Drugs* 2004; 64: 1757–1765.
22. Brown HF, DiFrancesco D and Noble SJ. How does adrenaline accelerate the heart? *Nature* 1979; 280: 235–236.
23. DiFrancesco D. Funny channels in the control of cardiac rhythm and mode of action of selective blockers. *Pharm Resear* 2006; 53: 399–406.
24. Musialek P, Lei M, Brown HF, *et al*. Nitric oxide can increase heart rate by stimulating the hyperpolarization-activated inward current, If. *Circ Res* 1997; 81: 60–68.

25. Deedwania P. Selective and specific inhibition of If with ivabradine for the treatment of coronary artery disease or heart failure. *Drugs* 2013; 73: 1569–1586.

26. Du XJ, Feng X, Gao XM, *et al*. If channel inhibitor ivabradine lowers heart rate in mice with enhanced sympathoadrenergic activities. *Br J Pharmacol* 2004; 142: 107–112.

27. Tardif JC, Ford I, Tendera M, *et al*. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J* 2005; 26: 2529–2536.

28. Vilaine JP. The discovery of the selective If current inhibitor ivabradine. A new therapeutic approach to ischemic heart disease. *Pharmacol Res* 2006; 53: 424–434.

29. Bucchi A, Baruscotti M and DiFrancesco D. Current-dependent block of rabbit sino-atrial node If channels by Ivabradine. *J Gen Physiol* 2002; 120: 1–13.

30. Cerbai E, Pino R, Porciatti F, *et al*. Characterization of the hyperpolarization-activated current, If, in ventricular myocytes from human failing heart. *Circulation* 1997; 95: 568–571.

31. Cerbai E, Laura Sartiani L, DePaoli P, *et al*. The properties of the pacemaker current IF in human ventricular myocytes are modulated by cardiac disease. *J Mol Cell Cardiol* 2001; 33: 441–448.

32. Stillitano F, Lonardo G, Zicha S, *et al*. Molecular basis of funny current (If) in normal and failing human heart. *J Mol Cell Cardiol* 2008; 45: 289–299.

33. Kjekshus J. Arrhythmias and mortality in congestive heart failure. *Am J Cardiol* 1990; 22: 42–48.

34. Kuwabara Y, Kuwahara K, Takano M, *et al*. Increased expression of HCN channels in the ventricular myocardium contributes to enhanced arrhythmicity in mouse failing hearts. *J Am Heart Assoc* 2013; 2: e000150.

35. Plotnikov AN, Bucchi A, Shlapakova I, *et al*. HCN212-channel biological pacemakers manifesting ventricular tachyarrhythmias are responsive to treatment with If blockade. *Heart Rhythm* 2008; 5: 282–288.

36. Musialek P. If current inhibition and mortality reduction in heart failure: more than just a 'pure' effect of lowering heart rate. *Kardiol Pol* 2013; 71: 764–767.

37. Mert KU, Mert GÖ, Morrad B, *et al*. Effects of ivabradine and β blocker therapy on dobutamine-induced ventricular arrhythmias in heart failure. *Kardiol Pol* 2017; 75: 786–793.

38. Musialek P. Drug action(s), drug marketing, and clinical medicine. Suppression of ventricular arrhythmogenicity with If blockade in human heart failure: emerging clinical evidence for ivabradine treatment benefit beyond heart rate control. *Kardiol Pol* 2017; 75: 1368–1371.

39. Dias P and Terracciano CM. Hyperpolarization-activated cyclic nucleotide-gated channels and ventricular arrhythmias in heart failure: a novel target for therapy? *J Am Heart Assoc* 2013; 2: e000287.

40. Servier. *Procoralan® summary of product characteristics*, http://www.medicines.org.uk/emc/medicine/17188/SPC/ (2016, accessed 14 January 2018).

41. Fox K, Ford I, Steg PG, *et al*. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; 372: 807–816.

42. Fox K, Ford I, Steg PG, *et al*. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet* 2008; 372: 817–822.

43. Swedberg K, Komajda M, Böhm M, *et al*. Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: is there an influence of beta-blocker dose?: findings from the SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial) study. *J Am Coll Cardiol* 2012; 59: 1938–1945.

44. Böhm M, Robertson M, Ford I, *et al*. Influence of cardiovascular and noncardiovascular co-morbidities on outcomes and treatment effect of heart rate reduction with ivabradine in stable heart failure (from the shift trial). *Am J Cardiol* 2015; 116: 1890–1897.

45. Ekman I, Chassany O, Komajda M, *et al*. Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: results from the SHIFT study. *Eur Heart J* 2011; 32: 2395–2404.

46. Sarullo F, Fazio G, Puccio D, *et al*. Impact of ''off-label'' use of ivabradine on exercise capacity, gas exchange, functional class, quality of life, and neurohormonal modulation in patients with ischemic chronic heart failure. *J Cardiovasc Pharmacol Ther* 2010; 15: 349–355.

47. Bohm M, Borer J, Ford I, *et al*. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. *Clin Res Cardiol* 2013; 102: 11–22.

48. Swedberg K, Komajda M, Böhm M, *et al*. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010; 376: 875–885.

49. National Institute for Health and Care Excellence. *Ivabradine for treating chronic heart failure*, https://www.nice.org.uk/guidance/ta267/documents/heart-failure-chronic-ivabradine-final-appraisal-determination3 (2012, accessed 14 January 2018)

50. Yancy CW, Jessup M, Bozkurt B, *et al*. ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart failure society of America. *Circulation* 2017; 136: e137–e161.

51. Komadja M, Isnard R, Cohen-Solal A, *et al*. Effect of ivabradine in patients with heart failure with preserved ejection fraction: the EDIFY randomized placebo-controlled trial. *Eur J Heart Fail* 2017; 19: 1495–1503.

52. Fox K, Ford I, Steg PG, *et al*. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med* 2014; 371: 1091–1099.

53. Tanboğa İH, Topçu S, Aksakal E, *et al*. The risk of atrial fibrillation with ivabradine treatment: a meta-analysis with trial sequential analysis of more than 40000 patients. *Clin Cardiol* 2016; 39: 615–620.

54. Martin RIR, Pogoryelova O, Santibáñez Koref M, *et al*. Atrial fibrillation associated with ivabradine treatment: meta-analysis of randomised controlled trials. *Heart* 2014; 100: 1506–1510.

55. Donkor A, McDonagh T and Hardman S. *National heart failure audit April 2015 to March 2016*. London: National Institute for Cardiovascular Outcomes Research (NICOR), 2017.

56. European Medicines Agency. *Corlentor and procoralan*, http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Corlentor_and_Procoralan/human_referral_prac_000044.jsp&mid=WC0b01ac05805c516f (2014, accessed 30 April 2018).

57. Cullington D, Goode KM, Cleland JG, *et al*. Limited role for ivabradine in the treatment of chronic heart failure. *Heart* 2011; 97: 1961–1966.