European Journal of Heart Failure Advance Access published August 7, 2013

European Journal of Heart Failure
doi:10.1093/eurjhf/hft129

Heart rate: a prognostic factor and therapeutic target in chronic heart failure. The distinct roles of drugs with heart rate-lowering properties

Daniela Dobre[1]*, Jeffrey S. Borer[2], Kim Fox[3], Karl Swedberg[4], Kirkwood F. Adams[5], John G.F. Cleland[6], Alain Cohen-Solal[7], Mihai Gheorghiade[8], Francois Gueyffier[9], Christopher M. O'Connor[10], Mona Fiuzat[10], Athul Patak[11], Ileana L. Piña[12], Giuseppe Rosano[13], Hani N. Sabbah[14], Luigi Tavazzi[15], and Faiez Zannad[1,16]

[1]INSERM, Center of Clinical Investigation 9501, Institut Lorrain du Coeur et des Vaisseaux, CHU Nancy, Université de Lorraine, Nancy, France; [2]State University of New York Downstate Medical Center, Brooklyn and New York, NY, USA; [3]NHLI, Imperial College, ICMS, Royal Brompton Hospital, London, UK; [4]Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [5]Division of Cardiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [6]Hull York Medical School, University of Hull, UK; [7]Cardiology Department and Research Medical Unit INSERM U-942, Hôpital Lariboisière, Université Paris VII Denis Diderot, Paris, France; [8]Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [9]Clinical Pharmacology and Therapeutic Trials, Hospices Civils de Lyon, France; [10]Duke University and Duke Clinical Research Institute, Durham, NC, USA; [11]Department of Clinical Pharmacology, Unité INSERM U 1048 and Faculty of Medicine, Toulouse, France; [12]Division of Cardiology, Albert Einstein College of Medicine, Montefiore Medical Center Bronx, NY, USA; [13]Cardiovascular Research Unit, IRCCS San Raffaele Roma, Rome, Italy; [14]Department of Medicine, Henry Ford Hospital, Detroit, MI, USA; [15]Maria Cecilia Hospital, GVM Care and Research, E.S. Health Science Foundation, Cotignola, Italy; and [16]INSERM U961, Université de Lorraine, Nancy, France

Received 18 January 2013; revised 16 April 2013; accepted 31 May 2013

Heart rate not only predicts outcome but may also be a therapeutic target in patients with chronic heart failure. Several classes of pharmacological agents can be used to modulate heart rate, including beta-blockers, ivabradine, digoxin, amiodarone, and verapamil. Choice of agent will depend on heart rhythm, co-morbidities, and disease phenotype. Beneficial and harmful interactions may also exist. The aim of this paper is to summarize the current body of knowledge regarding the relevance of heart rate as a prognostic factor (risk marker) and particularly as a therapeutic target (risk factor) in patients with chronic heart failure, with a special focus on ivabradine, a novel agent that is currently the only available purely bradycardic agent.

Keywords Heart rate • Heart rate-lowering drugs • Beta-blockers • Ivabradine • Digoxin • Amiodarone • Verapamil • Chronic heart failure

Introduction

Despite advances in medical and device therapy, prognosis remains poor for patients with chronic heart failure (HF), with a mortality rate of 75% at 7 years of follow-up.[1] Accordingly, there is a need to identify new therapeutic targets. In patients with chronic HF, heart rate (HR) can be measured easily and appears to be both a marker of risk and a target for therapy, i.e. a risk factor.

Beta-blockers reduce HR by blocking cardiac sympathetic activation[2] and have become a cornerstone of therapy for patients with chronic HF and reduced left ventricular ejection fraction (HF-rEF).[3] However, recommended target doses of beta-blockers are achieved in less than half of patients in daily practice.[4,5] Also, in some cases these agents cannot be tolerated or are contraindicated. Thus, HR may not be adequately controlled, and other drugs should be considered to control HR. These may include either the pure HR-lowering drug ivabradine or other drugs that lower HR in addition to other pharmacological effects, namely digoxin, amiodarone, or verapamil.

The aim of this paper is to summarize the current body of knowledge regarding the relevance of HR as a prognostic factor (risk marker) and particularly as a therapeutic target (risk factor) in patients with chronic HF, with a special focus on ivabradine. Part of the manuscript is based on presentations and discussions between basic and clinical scientists at the Global CardioVascular Clinical Trialists (CVCT) Forum in 2011.

* Corresponding author. INSERM, Center of Clinical Investigation 9501, Lorrain Institute of Heart and Vessels Louis Mathieu, University Hospital Nancy, 4, rue du Morvan, 54500 Vandoeuvre-Les-Nancy, France. Tel: +33 3 83 15 73 82, Fax: +33 3 83 15 73 24, Email: d.dobre@chu-nancy.fr

Heart rate as a prognostic factor: insights from epidemiology

Several large epidemiological studies have shown that resting HR is associated with risk of cardiovascular (CV) morbidity and mortality in healthy populations,[6] in patients with hypertension,[7] in those with CAD,[8] and in patients with LV systolic dysfunction (LVSD),[9] including those with chronic HF.[10,11] HR is associated with a number of CV risk factors. Nonetheless, in many multivariable analyses, the association of HR with CV morbidity and mortality was independent of traditional risk factors.[6,8,9,11,12]

Importantly, although the conventional definition of tachycardia is HR of 90–100 b.p.m.,[12] the risk of CV complications and death in patients with CAD and LVSD or those with chronic HF appears to increase progressively once HR exceeds 70 b.p.m. (*Figures 1* and *2*).[9,11] In patients with chronic HF in sinus rhythm, a steep rise in CV mortality is observed at an HR $\geq$ 80 b.p.m. (*Figure 2*), although this might not be the case for patients with AF.

Pathophysiological mechanism

Autonomic imbalance resulting from sympathetic overactivity and parasympathetic withdrawal is a characteristic feature of the HF syndrome and likely to be the underlying mechanism of HR increase in HF. The mechanism by which higher heart rates drive prognosis is less clear. A higher HR leads to greater myocardial oxygen consumption and decreased myocardial perfusion, the latter by shortening the duration of diastole.[12] High HR may also increase shear (pulsatile) stress that may trigger an inflammatory endothelial cell response.[13] Overall, HR may be, at least partially, a covariate of excessive sympathetic drive that may also explain the higher CV event rate associated with increasing HR.

Drugs with heart rate-lowering effects

The main mechanism of action and the indications of the drugs with HR-lowering properties are briefly presented in the *Table 1*. For each drug, the mechanism of HR reduction and studies showing the benefit of lowering this specific variable (if any) are described. To comply with the definition of a risk factor, HR should not only predict risk, but a reduction in HR by therapy should be associated with improved clinical outcomes. Some HR-lowering agents have met this criterion, although whether HR reduction is the sole mechanism of benefit is hard to demonstrate.

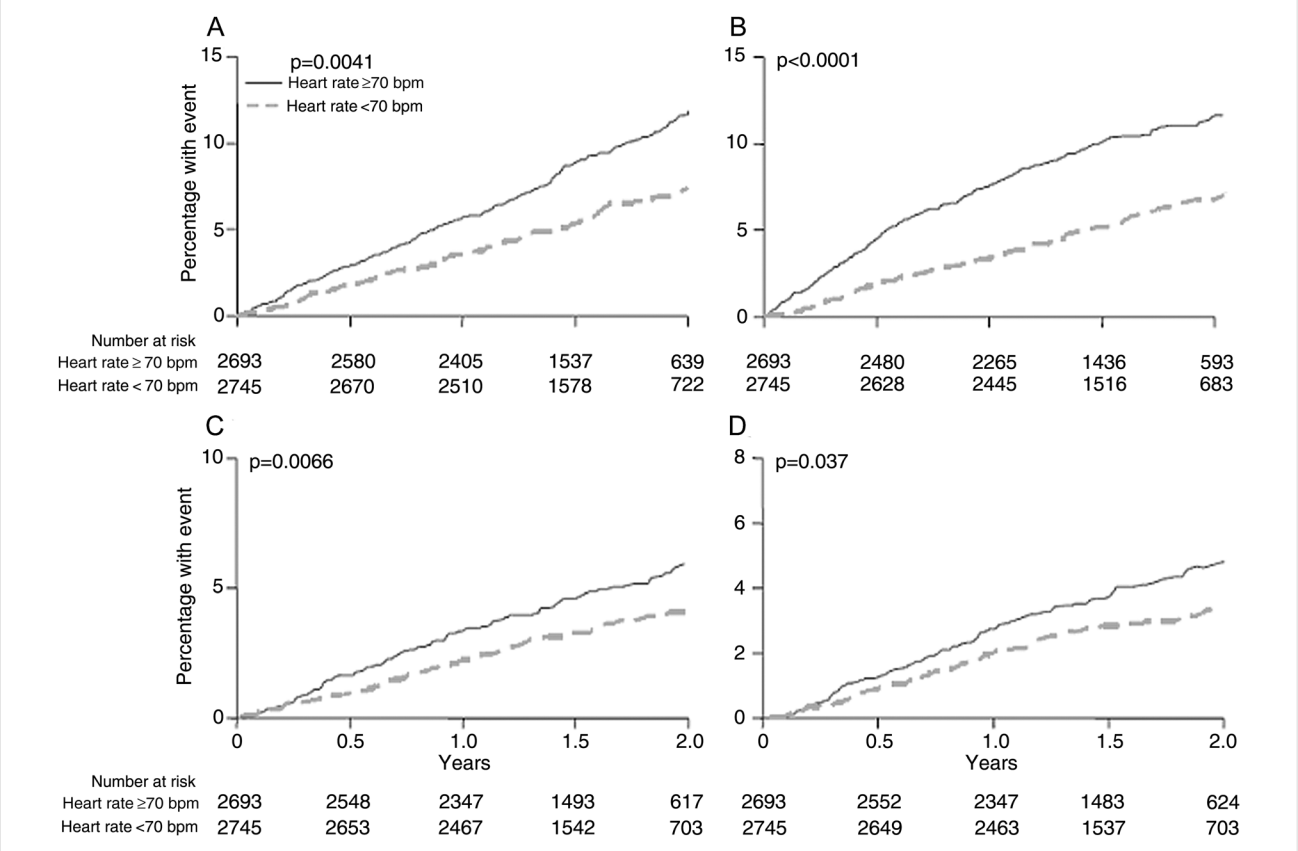

Figure 1 Relationship between resting heart rate at baseline and the risk of (*A*) cardiovascular death, (*B*) admission to hospital for heart failure, (*C*) admission to hospital for myocardial infarction, and (*D*) coronary revascularization, in patients with CAD and LV systolic dysfunction in sinus rhythm included in the placebo group of the BEAUTIfUL trial.[9]

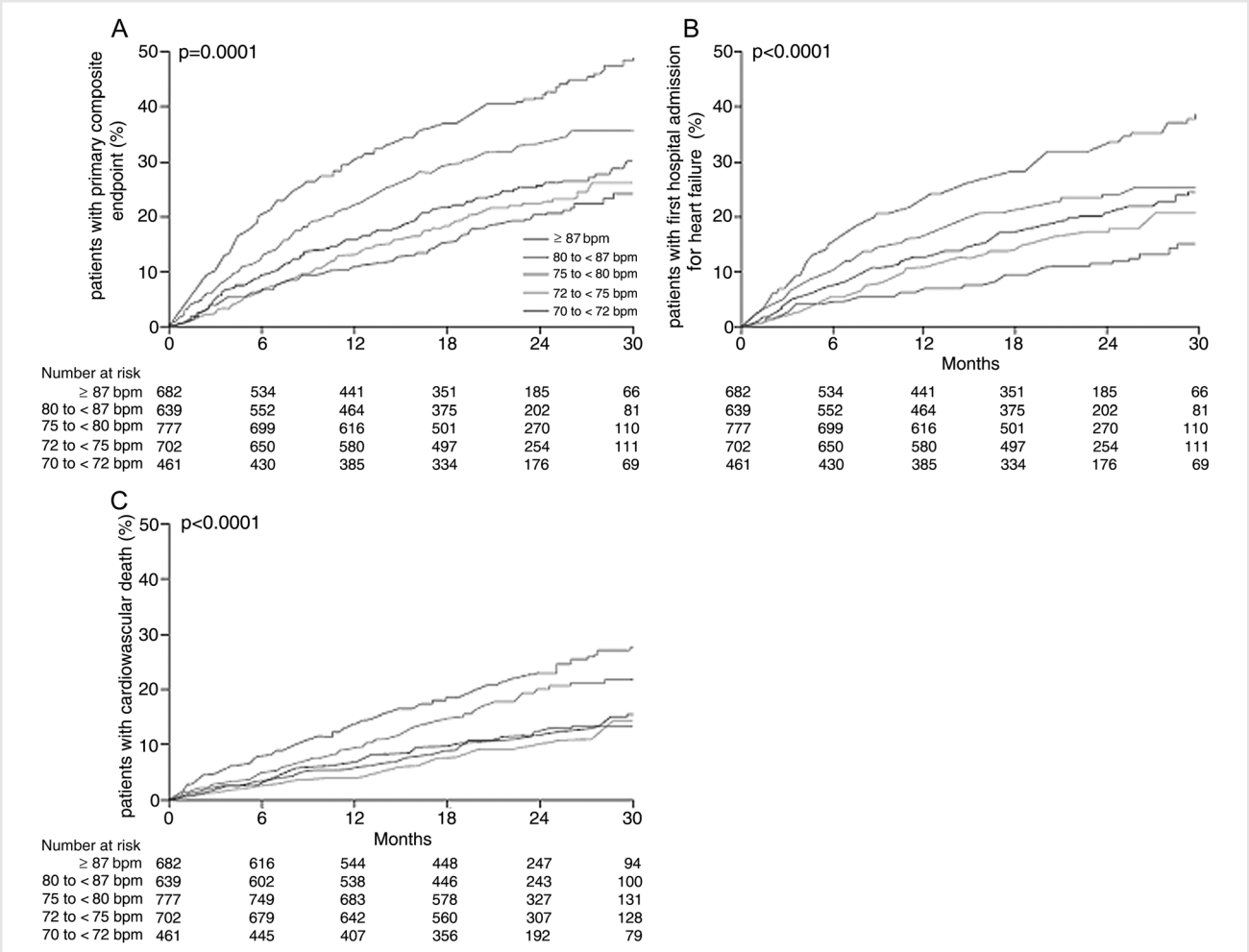

Figure 2 Relationship between resting heart rate at baseline and the risk of (*A*) cardiovascular (CV) mortality or hospital admission for HF, (*B*) first admission to hospital for heart failure, and (*C*) CV mortality, in patients with chronic HF in sinus rhythm included in the placebo group of the SHIFT trial.[11]

Beta-adrenergic blockers

Mechanism of action

The HR reduction action of this group of drugs is probably explained by its sympathetic inhibition only, though indirect actions, such as modulation of beta-receptor expression and/or of the renin–angiotensin system through the prevention of renal renin release, might also be involved.[2] Beta-blockers block the activity of endogenous catecholamines and therefore decrease the adrenergic tone/stimulation of the pacemaker cells in the sino-atrial node, thus slowing HR in sinus rhythm (negative chronotropic effect). The effect on the atrioventricular node slows the conduction at this level and is responsible for lowering the ventricular rate in supraventricular tachycardias, most notably in AF (negative dromotropic effect). Beta-blockers are first-line therapy in patients with HF-rEF as they have been shown to improve cardiac function and reduce CV hospitalizations, sudden death, and overall mortality. Beta-blockers reduce HR both at rest and during exercise, in both sinus rhythm and AF. Possible side effects of beta-blockers include symptomatic bradycardia, fatigue, worsening HF, and exacerbations of asthma.

Heart rate as a therapeutic target

There is good evidence that the beneficial effects of beta-blockers agents in HF-rEF are related, at least in part, to drug-mediated HR reduction. In a recent meta-regression of beta-blocker trials including 19 537 chronic HF patients with HF-rEF, the risk reduction in all-cause mortality was well correlated ($r^2 = 0.41$) with a reduction in HR.[14] A multivariate meta-regression of 23 beta-blocker trials has shown similar results; in a model including several clinical variables, beta-blocker dose, HR at baseline, and HR reduction, the latter was associated with the survival benefit of beta-blockers (18% risk reduction per 5 b.p.m. decrease), whereas the dose of beta-blocker was not.[15]

Table 1 The mechanism of action and indications of drugs with heart rate-lowering effects in chronic heart failure

Drug	Mechanism of action	HF indication
Beta-blockers	Blocks adrenergic activity; slows sinus rate and prolongs AV conduction.	HF-rEF with sinus rhythm or AF; HF-pEF with AF
Ivabradine	Selective inhibition of the pacemaker modulating 'f' current (I_f) in the sinoatrial node; slows sinus rate. No effect on AV node.	HF-rEF with sinus rhythm
Digoxin	Increases vagal tone; inhibits sympathetic nervous system activity; slows sinus rate and prolongs AV conduction.	HF-rEF with sinus rhythm or AF; HF-pEF with AF
Verapamil	Blocks high voltage calcium channels; slows sinus rate and prolongs AV conduction.	HF-pEF with sinus rhythm or AF
Amiodarone	Blocks potassium channels; antiadrenergic effects; slows sinus rate and prolongs AV conduction.	HF-rEF with AF

AV, atrioventricular; HF-pEF, heart failure with preserved ejection fraction; HF-rEF, heart failure with reduced ejection fraction.

Ivabradine (selective inhibitors of the sinoatrial pacemaker-modulating 'f' current)

Mechanism of action

The mode of action of this novel drug involves selective inhibition of a pacemaker-modulating current in the sinoatrial node, the so-called 'f-current' or I_f, a mixed sodium/potassium-, cyclic AMP-, and voltage-dependent current mediated by the 'f-channels' of the sinoatrial cell membrane.[16,17] The sinoatrial myocytes are characterized by the presence of 'slow' spontaneous depolarization during diastole; the I_f inhibition by ivabradine prolongs the slow depolarization phase, thereby slowing the HR.[18]

The beneficial effects of ivabradine are apparently associated only with the reduction of HR. At doses employed in clinical studies, the drug has no effect on myocardial contractility, impulse conduction, or blood pressure.[19] The drug exhibits a trend towards a plateau dose–response effect.[20] This finding relates to its 'use dependence', i.e. the drug can act only when the f-channels are open; the slower the HR, the less frequently f-channels are open. In addition, since the f-current is a modulator, rather than a generator, of the pacemaker current, the fundamental rate is mediated by several ion channels which are not affected by the drug. The selectivity of the drug for sinoatrial cells explains the lack of effect on ventricular rate in AF, in which the sinus node does not pace the heart.

Overall, ivabradine appears safe and well tolerated. The most commonly reported side effects are bradycardia and visual symptoms (phosphenes, or flashing scotomata).[19] Visual symptoms are usually temporary and disappear after the drug is stopped.

Heart rate as a therapeutic target

Patients with CAD and LVSD

In the 'morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left-ventricULar dysfunction' (BEAUTIfUL) trial, 10 917 patients with chronic stable CAD, LVEF $<40\%$, and resting HR >60 b.p.m. were randomized to receive ivabradine (target 7.5 mg twice daily), on top of usual medical care.[21] After a median follow-up of 19 months, treatment with ivabradine did not affect the primary endpoint of the study, a composite of CV death, acute myocardial infarction (MI), or new-onset HF. However, in a pre-specified subgroup of patients with HR ≥ 70 b.p.m., ivabradine did reduce the secondary endpoints, including admission to hospital for MI (36% risk reduction) and coronary revascularization (30% risk reduction).

Patients with chronic heart failure

In the 'Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial' (SHIFT), 6505 outpatients with chronic HF in sinus rhythm, with LVEF $\leq 35\%$ and HR ≥ 70 b.p.m., hospitalized for HF in the previous year, were randomized to a target dose of 7.5 mg ivabradine twice daily on top of conventional therapy.[8,11] A post-hoc analysis including 98% of patients revealed that at baseline 26.5% of patients received medium to high doses of beta-blockers, and 23% of patients received target or supratarget doses of beta-blockers.[22] Despite the difference in dose, HR was similar in these two categories (79.1 and 78.9 b.p.m.). The SHIFT trial may have selected patients relatively unresponsive to beta-blocker therapy, given the protocol requirement of optimized HF therapy and a baseline HR ≥ 70 b.p.m.

After a median follow-up of 22.9 months, treatment with ivabradine reduced the primary composite endpoint of CV death or worsening HF by 18% (*Table 2*). This effect was mostly due to a favourable effect on HF events (hospitalization or death). All-cause and CV mortality as well as sudden death were not significantly reduced by the drug. The incidence of AF increased slightly among patients assigned to ivabradine vs. placebo (9% vs. 8%), though this may have been a function of a prior history of AF in the patients so affected (unpublished observation).

Compared with placebo, ivabradine reduced HR by 11 b.p.m. at 28 days. After adjustment for both HR achieved at 28 days and HR at baseline, the effect of ivabradine became non-significant, suggesting that the beneficial effects were largely explained by HR change.[11]

Table 2 The effect of ivabradine on primary and secondary end-points in patients with chronic heart failure and left ventricular ejection fraction <35%, sinus rhythm, and heart rate ≥70 b.p.m.[10]

	Ivabradine group (n = 3241)	Placebo group (n = 3264)	HR (95% CI)	P-value
Primary endpoint				
CV death or hospital admission for HF	793 (24%)	937 (29%)	0.82 (0.75–0.90)	<0.0001
Mortality endpoints				
All-cause mortality	503 (16 %)	552 (17%)	0.90 (0.80–1.02)	0.092
CV mortality	449 (14 %)	491 (15%)	0.91 (0.80–1.03)	0.128
Death from HF	113 (3 %)	151 (5%)	0.74 (0.58–0.94)	0.014
Other endpoints				
All-cause hospital admission	1231 (38 %)	1356 (42 %)	0.89 (0.82–0.96)	0.003
Hospital admission for worsening HF	514 (16 %)	672 (21 %)	0.74 (0.66–0.83)	<0.0001
Any CV hospital admission	977 (30 %)	1122 (34 %)	0.85 (0.78–0.92)	0.0002
CV death, or hospital admission for worsening HF, or hospital admission for non-fatal MI	825 (25 %)	979 (30 %)	0.82 (0.74–0.89)	<0.0001

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio, MI, myocardial infarction.

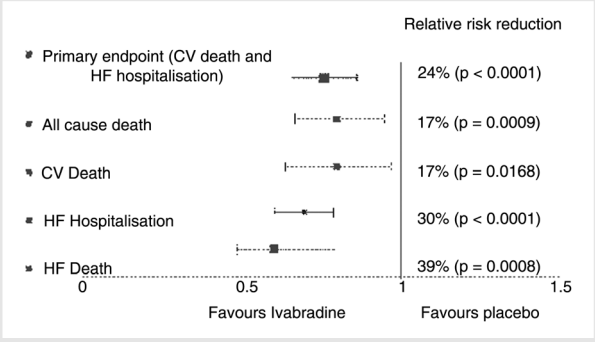

Figure 3 Subgroup analysis of the patients in the SHIFT trial with baseline heart rate ≥75 b.p.m. (n = 4150).[23] CV, cardiovascular; HF, heart failure.

HR at 28 days, HR at baseline, and, to a lesser extent, the dose of beta-blocker at baseline were related to the degree of HR reduction.[22]

In a subsequent analysis requested by the European Medicine Agency (EMA), in patients with baseline HR ≥ 75 b.p.m., all-cause mortality (not significantly reduced in the population with HR ≥ 70 b.p.m.) was decreased significantly by ivabradine (17% risk reduction), suggesting that the higher the baseline HR the greater the effect of the drug (*Figure 3*).[23] Based on this evidence, EMA recommends prescription of ivabradine for patients with chronic HF of NYHA classes II–IV, with systolic dysfunction, in sinus rhythm, and with HR ≥ 75 b.p.m., in combination with standard therapy including a beta-blocker or when beta-blocker therapy is contraindicated or not tolerated.

Digoxin (digitalis glycosides)

Mechanism of action

The primary pharmacological mechanism of digoxin is inhibition of membrane sodium–potassium ATPase, which promotes sodium–calcium exchange. The increase in intracellular calcium concentration mediates the positive inotropic effect of digoxin.[24,25] Digoxin is thought to reduce HR mainly by stimulating the central vagal nucleus and enhancing cardiac vagal tone. Additionally, digoxin may reduce HR by reducing sympathetic nervous system activity.[26] The drug slows conduction of both sinoatrial and atrioventricular node cells. Digoxin can reduce the ventricular rate in both sinus rhythm and AF.

In patients with HF-rEF in sinus rhythm, a beta-blocker is the first option to reduce HR because digoxin does not adequately control HR during exercise. In cases where HR is not controlled with beta-blocker therapy, digoxin may be added. However, for patients in sinus rhythm, the option of using digoxin is probably now overtaken by the use of ivabradine (when HR is ≥70 b.p.m.) given the evidence from the SHIFT. However, digoxin is still an option, particularly in symptomatic patients intolerant to beta-blockers.[3]

In patients with HF-rEF and AF, digoxin is the preferred second drug to control ventricular rate (ivabradine does not reduce HR in AF).[3] Indeed, the combination of beta-blocker and digoxin appears superior to beta-blocker or digoxin alone to improve LVEF and symptoms, and to control ventricular rate.[27] Finally, in patients with HF-pEF and AF, digoxin is also the preferred second drug to control HR, in combination with either a rate-limiting calcium channel blocker (CCB) or a beta-blocker.[3] Importantly, ~ 30% of patients with chronic HF have AF. The optimal ventricular rate in patients with chronic HF-rEF and AF is uncertain, but appears higher than for sinus rhythm.[28]

Heart rate as a therapeutic target

Evidence favouring the benefit of digoxin in patients with chronic HF and sinus rhythm comes from the DIG trial. In this study, 6800 patients with LVEF ≤ 45% were randomized to digoxin or placebo, on top of ACE inhibitors/diuretics.[29] Beta-blocker therapy was not reported, but presumably most patients were not taking a beta-blocker. After an average follow-up of 37 months, digoxin did not affect all-cause mortality, but it reduced the composite outcome of

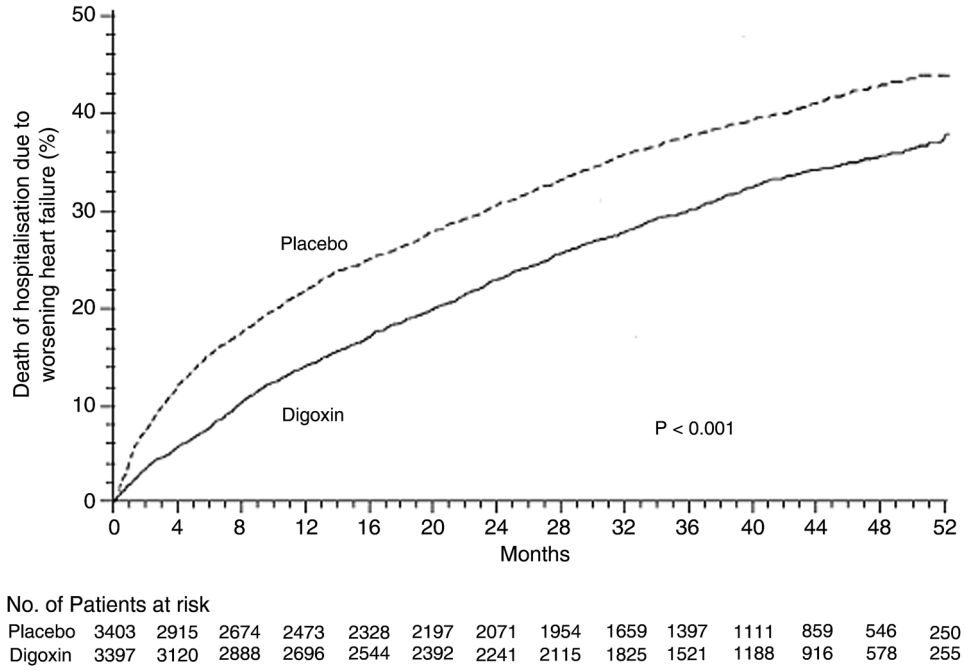

Figure 4 Incidence of death or hospitalization due to worsening heart failure in digoxin vs. placebo groups (DIG trial).[29]

HF death or hospitalization by 39%. This benefit occurred early after randomization and persisted throughout follow-up (*Figure 4*). A trend towards a similar benefit was observed in the subsample of patients with HF-pEF (LVEF >45%) included in the DIG trial.

The safety of digoxin has been much discussed since one post-hoc analysis of the DIG trial suggested that digoxin may increase all-cause mortality in women.[30] Nevertheless, subsequent analysis showed that an increase in mortality occurred only in women with a serum concentration >1.0 ng/mL.[31] Digoxin had beneficial effects on HF death and hospitalization in all age groups studied in the DIG trial.[32] Ahmed *et al*. described a decrease in all-cause mortality and hospitalization at low serum concentration of digoxin (0.5–0.9 ng/mL),[33] and a similar benefit at low concentration was described in elderly individuals.[34]

At baseline, the mean HR in the DIG trial was 79 b.p.m. (similar to HR in SHIFT), but the effects of digoxin on HR were not reported in this trial. Two other trials reported the change in HR with digoxin use. In the Dutch Ibopamine Multicenter trial, mean HR over 24 h was reduced by ~ 4 b.p.m. with digoxin vs. placebo.[35] In the RADIANCE trial, compared with continuation of digoxin, withdrawal of digoxin was associated with an increase in HR of 7 b.p.m. over 3 months from a baseline of 77 b.p.m.[36] No data are available that may allow elaboration on the interaction of digoxin with HR lowering in improving outcomes.

Verapamil (non-dihydropyradine calcium channel blocker)

Mechanism of action

The pharmacological action of CCBs (overall) involves blocking voltage-gated calcium channels in myocardial cells and in vessels. As a group, CCBs are divided into dihydropyridine and non-dihydropyridine subgroups, the latter being relatively selective for the myocardium and possessing HR-lowering effects. By blocking calcium channels during the plateau phase of the action potential, the non-dihydropyridine CCBs (verapamil and diltiazem) have a negative chronotropic effect that may slow the sinus rate, and an additional negative dromotropic effect at the atrioventricular node level, on the basis of which they could be recommended to control HR in patients with AF or with flutter.[3] The most common side effects of the non-dihydropyridine drugs include gastrointestinal symptoms and ankle oedema.

Heart rate as a therapeutic target in heart failure with preserved ejection fraction

Due to its negative inotropic effects, verapamil is contraindicated in HF-rEF, and uncertainties about the efficacy and safety of diltiazem and dyhydropyridine agents have prevented them gaining an established role.[37] However, verapamil might be beneficial in HF with preserved ejection fraction (HF-pEF), in both sinus rhythm and AF, particularly in hypertensive patients.[3] This indication is based on two small randomized controlled trials (<30 patients) suggesting that verapamil improves LV diastolic function and exercise capacity in patients with LVEF >45% and evidence of diastolic dysfunction. HR was decreased to a modest extent. Given the small size of these trials, more studies are needed to confirm their beneficial effects and safety, and to gain a better understanding of their pharmacological mechanisms in HF-pEF.

Amiodarone (class III antiarrhythmic)

Mechanism of action

Amiodarone has a variety of effects, including blocking potassium channels, thereby prolonging repolarization. In patients with HF,

amiodarone also has antiadrenergic effects and prolongs ventricular and atrial refractoriness.[38] Amiodarone suppresses supraventricular and ventricular arrhythmias, with a relatively low incidence of proarrhythmia. It is the only antiarrhythmic drug recommended in HF-rEF.[3] Other drugs from this class, including dronedarene, have similar electrophysiological effects but, as this agent increased mortality in trials of HF-rEF, it is contraindicated.[39]

In patients unable to tolerate or unresponsive to the combination of a beta-blocker and digoxin, substitution of digoxin with amiodarone may be considered to control ventricular rate in patients with HF-rEF and AF.[3] Amiodarone has numerous side effects, including gastrointestinal symptoms and thyroid dysfunction, which may limit its tolerability.[40] Importantly, there are no clinical trials indicating that a reduction in HR by amiodarone is associated with better clinical outcomes in HF-rEF.

Devices

There is a complex interaction between electrical devices used to treat HF and HR. Pacemakers, implantable cardiac defibrillators, and cardiac resynchronization devices all prevent excessive bradycardia, and this may be one of their mechanisms of benefit.[41] However, devices, especially standard pacemakers, are often programmed to maintain a higher HR than that which we now believe optimal for patients with HF, and this may have a detrimental effect on cardiac function.[42] Devices should be programmed to permit pharmacologically induced bradycardia. In a pilot study of patients with systolic HF and pacing, in which the pacing rate was set at either 55 or 75 b.p.m., pacing at 55 b.p.m. was associated with better cardiac function.[43] Failure to control HR adequately may detract from the benefits of devices, especially with conditions such as AF.[44] In the case of resynchronization therapy, HR may fall due to improved haemodynamics leading to reduction in sympathetic tone. One important reason for the failure to titrate a beta-blocker dose to target or to achieve HR control is the fear of excessive bradycardia. Implantation of a device with a pacing function generally increases the clinician's confidence in the safety of increasing the dosage of bradycardic agents, particularly beta-blockers. However, most of the published studies have addressed the issue of HR-lowering agents in HF patients without a device or with a device operational only for a limited portion of the day. The extent to which the same benefits could be expected in the presence of a constantly functioning device is unknown.

Discussion

Heart rate as a risk factor

A large body of evidence shows that HR is a risk marker of CV morbidity and mortality in several populations, including chronic HF. According to current data, HR lowering is the sole pharmacological basis of the CV benefits of ivabradine, and a scientific probe that supports HR as a therapeutic target (risk factor) in HF-rEF. Beta-blocker meta-regression studies also show an association between drug-mediated HR reduction and outcomes, supporting the relevance of HR as a therapeutic target. Similar analyses have not been yet performed for other interventions that may be used to modulate HR in chronic HF.

Ivabradine and the maximum-tolerated beta-blockers dose

A debated topic generated by SHIFT was the effect of the background beta-blocker dose employed during the study.[45] In the SHIFT, 56% of patients received $\geq$ 50% of target beta-blocker doses.[22] These doses were lower than the doses used in previous trials, e.g. in the CIBIS II and in MERIT trials 67% of patients received $\geq$ 50% of target dose.[46,47] Patients in SHIFT had a slightly lower systolic blood pressure than those in previous beta-blocker trials, and additionally they received aldosterone antagonists (60% of patients). This could have made a difference on beta-blocker titration. Doses of beta-blockers achieved in SHIFT were nevertheless similar to or higher than those generally achieved in the community.[5]

However, it is unclear whether target doses of beta-blockers are associated with better clinical outcomes. Only the MOCHA trial, which enrolled only 345 patients (with 25 deaths) treated for 6 months, has tested the dose-related effects of the beta-blocker carvedilol in patients with chronic HF.[48] Interestingly, the reduction in HR was minimally dose related. This could have been because 90% of patients were on background digoxin therapy. However, despite this non-proportional effect on HR, carvedilol produced a dose-related improvement in CV hospitalizations and survival. This observation is consistent with the results of a recent post-hoc analysis of the HF-ACTION trial which showed in patients with chronic HF that lower all-cause death or hospitalization was associated with the beta-blocker dose.[49] On the other hand, post-hoc analysis of MERIT-HF,[47] CIBIS-II,[46] and SENIORS trials[50] did not show a dose-related improvement in clinical outcomes. Meta-analysis studies also show that the magnitude of HR reduction and not the beta-blocker dose relates to better outcomes.[15] Other post-hoc studies have suggested that the HR achieved rather than the magnitude of reduction appears to be an even stronger indicator of benefit.[51] Admittedly, given the inherent limitations of the post-hoc studies, and the fact that beta-blocker dose and HR during follow-up were probably inadequately measured in most of the trials, a definite answer regarding the beta-blocker dose effect would require a randomized controlled trial.

Taking all these analyses together, it appears that the individual patient HR response to beta-blocker therapy is variable, and that a subset of patients could be poor responders to this therapy. This may be due to the severity of HF, heart rhythm, and the health of the sinus node, but the beta-adrenergic receptor polymorphism may also provide a genetic basis for this variability.[52] In such patients, ivabradine on top of beta-blocker therapy can decrease HR and improve outcome.

Ivabradine and digoxin put into perspective in heart failure patients in sinus rhythm

Recently, it was pointed out that digoxin may have been too easily dismissed as an HR-lowering agent in HF-rEF (and HF-pEF) patients in sinus rhythm.[53] Notably, 50–90% of patients included in the previous placebo-controlled beta-blocker trials were receiving background digoxin therapy, suggesting that beta-blockers may exert a positive effect on top of digoxin (and ACE inhibitor) therapy.[25] The latest European Society of Cardiology (ESC) guidelines on HF favour treatment with ivabradine rather than digoxin in HF-rEF (LVEF $\leq$ 35%)

patients in sinus rhythm, with a resting HR $\geq$ 70 b.p.m., and persisting symptoms despite treatment with guideline target (or maximally tolerated) dose of beta-blocker, given the fact that the SHIFT (as opposed to the DIG trial) was performed in patients on background beta-blocker therapy. However, if patients are intolerant of beta-blockers and have persisting symptoms despite treatment with an ACE inhibitor/ARB and a mineralocrticoid receptor antagonist (MRA), the evidence is in favour of digoxin rather than ivabradine.[3] The decision to prescribe one drug or another in HF-rEF patients in sinus rhythm may depend on clinical presentation. Ivabradine may have a better safety profile, and be more efficient to control HR at exercise, while digoxin has additional neurohormonal properties, which could make the drug more appropriate for patients with advanced disease, particularly those intolerant to beta-blockers. To clarify the effects of low-dose digoxin in HF, including patients on beta-blocker therapy, in sinus rhythm and in AF, a new trial is also needed.[54–56]

What is the target heart rate value to be achieved with therapy?

Based on the SHIFT data, for outpatients with chronic HF-rEF in sinus rhythm, a HR of 55–60 b.p.m. can be recommended as a target HR value.[11,23] Observational analyses also suggest a target HR of 55–65 b.p.m. to achieve the lowest event rate with beta-blocker therapy.[57] On the other hand, an HR of 55 b.p.m., if reached with therapy, would probably be a low HR limit accepted for safety purposes. From daily clinical observation, it is obvious that some patients may not tolerate such a low HR, while others may do well with lower HRs. Symptoms rather than an absolute target HR may guide therapy. In patients with chronic HF-rEF and AF, the optimum HR is still uncertain, but it is apparently higher than for patients in sinus rhythm. Also, the optimal ventricular rate in HF-pEF is uncertain whether the patient is in sinus rhythm or in AF. Reducing HR in patients with HF-pEF could be deleterious as it may cause a rise in atrial pressures and worsen congestion.

Conclusion

There is a substantial body of evidence that HR is a potential therapeutic target (risk factor) in patients with chronic HF and LVSD who are in sinus rhythm. Beta-blockers remain the first-line therapy to reduce HR and improve clinical outcomes in patients with HF-rEF. In patients with HF-rEF or those with CAD and LVSD in sinus rhythm with HR $\geq$ 70–75 b.p.m. despite beta-blockers, ivabradine appears a safe treatment to improve clinical outcomes. Several other classes of pharmacological agents can be used to modulate HR in chronic HF, and their choice would depend on heart rhythm, comorbidities, and disease phenotype. Digoxin is primarily an option to control ventricular rate when combined with a beta-blocker in patients with HF-rEF and AF, but the optimal ventricular rate has to be established. Digoxin at low doses may also be an option in symptomatic HF-rEF patients in sinus rhythm intolerant to beta-blockers. Amiodarone may be an alternative to digoxin in patients with HF-rEF and AF, and verapamil might be beneficial in patients with HF-pEF, though data in this area as yet are sparse. The ideal ventricular rate in patients with HF-pEF, regardless of heart rhythm, is uncertain, and it would be dangerous to assume that would be similar to that of patients with HF-rEF.

Conflicts of interests: K.F. has received research grants, fees, and honoraria from Servier. J.G.F.C. and K.S. have received honoraria and research support from Servier. H.N.S. received research grants and was a consultant to Servier. L.T. was a consultant or committee member for Medtronic, Servier, St. Jude Medical, Boston Scientific, Vifor Pharma, Brystol Meyers Squibb, and Cardiorentis. J.S.B. has received honoraria from Servier, the manufacturer of ivabradine, and from Biotronik, the manufacturer of biventricular pacing devices for CRT. A.C.-S. declares having received fees or having had contracts with Novartis, GE Health Care, Servier, Thermofischer, Roche Diagnostics, Abbott, Pfizer, Bayer, Amgen, Vifor, Alere, Menarini, and Actelion. F.Z. has received consultant or steering committee/scientific advisory honoraria from Servier, Biotronik, Bayer, Boston Scientific, Gambro, Janssen, Novartis, Pfizer, Resmed, Takeda. M.G. has received consultant or steering committee/scientific advisory honoraria from Abbott Laboratories, Astellas, AstraZeneca, Bayer Schering Pharma AG, Cardiorentis Ltd, CorThera, Cytokinetics, CytoPherx, Inc., DebioPharm S.A., Errekappa Terapeutici, GlaxoSmithKline, Ikaria, Intersection Medical, Inc., Johnson & Johnson, Medtronic, Merck, Novartis Pharma AG, Ono Parmaceuticals USA, Otsuka Pharmaceuticals, Palatin Technologies, Pericor Therapeutics, Protein Design Laboratories, Sanofi-Aventis, Sigma Tau, Solvay Pharmaceuticals, Sticares InterACT, Takeda Pharmaceuticals North America, Inc., and Trevena Therapeutics, and has received signficant (>US$10 000) support from Bayer Schering Pharma AG, DebioPharm S.A., Medtronic, Novartis Pharma AG, Otsuka Pharmaceuticals, Sigma Tau, Solvay Pharmaceuticals, Sticares InterACT, and Takeda Pharmaceuticals North America, Inc. All other authors have no conflicts to declare.

Acknowledgements

The authors would like to thank Alain Berdeaux, Michael Bristow, Henry Dargie, Michael Felker, Michael Lauer, Aldo Pietro Maggioni, Marc Pfeffer, Kurt Stoschitzky, and Xavier Jouven for their contribution to the panel discussion at the CVCT Forum 2011 on which this manuscript is partially based.

References

1. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y. Heart disease and stroke statistics–2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009;**119**:480–486.
2. Bristow MR. Beta-adrenergic receptor blockade in chronic heart failure. *Circulation* 2000;**101**:558–569.
3. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task

Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;**14**:803–869.
4. Dobre D, Haaijer-Ruskamp FM, Voors AA, van Veldhuisen DJ. Beta-adrenoceptor antagonists in elderly patients with heart failure: a critical review of their efficacy and tolerability. *Drugs Aging* 2007;**24**:1031–1044.
5. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Leiro MC, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors A, Nielsen OW, Zannad F, Tavazzi L. EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail* 2010;**12**:1076–1084.
6. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005;**352**:1951–1958.
7. Palatini P, Benetos A, Julius S. Impact of increased heart rate on clinical outcomes in hypertension: implications for antihypertensive drug therapy. *Drugs* 2006;**66**:133–144
8. Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. *Eur Heart J* 2005;**26**:967–974.
9. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. 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**:817–821.
10. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–885.
11. Bohm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet* 2010;**376**:886–894.
12. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, Steg PG, Tardif JC, Tavazzi L, Tendera M. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol* 2007;**50**:823–830.
13. Traub O, Berk BC. Laminar shear stress: mechanisms by which endothelial cells transduce an atheroprotective force. *Arterioscler Thromb Vasc Biol* 1998;**18**:677–685.
14. Flannery G, Gehrig-Mills R, Billah B, Krum H. 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.
15. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med* 2009;**150**:784–794.
16. DiFrancesco D, Camm JA. Heart rate lowering by specific and selective i(f) current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. *Drugs* 2004;**64**:1757–1765.
17. Perry CM. Ivabradine: n adults with chronic heart failure with reduced left ventricular ejection fraction. *Am J Cardiovasc Drugs* 2012;**12**:415–426.
18. DiFrancesco D. Funny channels in the control of cardiac rhythm and mode of action of selective blockers. *Pharmacol Res* 2006;**53**:399–406.
19. Savelieva I, Camm AJ. I f inhibition with ivabradine: electrophysiological effects and safety. *Drug Saf* 2008;**31**:95–107.
20. Thollon C, Bedut S, Villeneuve N, Coge F, Piffard L, Guillaumin JP, Brunel-Jacquemin C, Chomarat P, Boutin JA, Peglion JL, Vilaine JP. Use-dependent inhibition of hHCN4 by ivabradine and relationship with reduction in pacemaker activity. *Br J Pharmacol* 2007;**150**:37–46.
21. Fox K, Ford I, Steg PG, Tendera M, Ferrari R. 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.
22. Swedberg K, Komajda M, Bohm M, Borer J, Robertson M, Tavazzi L, Ford I. 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.
23. Bohm M, Borer J, Ford I, Gonzalez-Juanatey JR, Komajda M, Lopez-Sendon J, Reil JC, Swedberg K, Tavazzi L. 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.
24. Eichhorn EJ, Gheorghiade M. Digoxin. *Prog Cardiovasc Dis* 2002;**44**:251–266.
25. Gheorghiade M, van Veldhuisen DJ, Colucci WS. Contemporary use of digoxin in the management of cardiovascular disorders. *Circulation* 2006;**113**:2556–2564.
26. Wang W, Chen JS, Zucker IH. Carotid sinus baroreceptor sensitivity in experimental heart failure. *Circulation* 1990;**81**:1959–1966.
27. Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am Coll Cardiol* 2003;**42**:1944–1951.
28. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH, Kamp O, Tukkie R, Bosker HA, Van Veldhuisen DJ, Van den Berg MP. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med* 2010;**362**:1363–1373.
29. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Intervention Group. *N Engl J Med* 1997;**336**:525–533.
30. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med* 2002;**347**:1403–1411.
31. Adams KF Jr, Patterson JH, Gattis WA, O'Connor CM, Lee CR, Schwartz TA, Gheorghiade M. Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. *J Am Coll Cardiol* 2005;**46**:497–504.
32. Rich MW, McSherry F, Williford WO, Yusuf S. Effect of age on mortality, hospitalizations and response to digoxin in patients with heart failure: the DIG study. *J Am Coll Cardiol* 2001;**38**:806–813.
33. Ahmed A, Pitt B, Rahimtoola SH, Waagstein F, White M, Love TE, Braunwald E. Effects of digoxin at low serum concentrations on mortality and hospitalization in heart failure: a propensity-matched study of the DIG trial. *Int J Cardiol* 2008;**123**:138–146.
34. Ahmed A. Digoxin and reduction in mortality and hospitalization in geriatric heart failure: importance of low doses and low serum concentrations. *J Gerontol A Biol Sci Med Sci* 2007;**62**:323–329.
35. van Veldhuisen DJ, Brouwer J, Man in 't Veld AJ, Dunselman PH, Boomsma F, Lie KI. Progression of mild untreated heart failure during six months follow-up and clinical and neurohumoral effects of ibopamine and digoxin as monotherapy. DIMT study group. Dutch ibopamine multicenter trial. *Am J Cardiol* 1995;**75**:796–800.
36. Packer M, Gheorghiade M, Young JB, Costantini PJ, Adams KF, Cody RJ, Smith LK, Van Voorhees L, Gourley LA, Jolly MK. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. Radiance study. *N Engl J Med* 1993;**329**:1–7.
37. Goldstein RE, Boccuzzi SJ, Cruess D, Nattel S. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The adverse experience committee; and the multicenter diltiazem postinfarction research group. *Circulation* 1991;**83**:52–60.
38. Riggio DW, Peters RW, Feliciano Z, Gottlieb SS, Shorofsky SR, Gold MR. Acute electrophysiologic effects of amiodarone in patients with congestive heart failure. *Am J Cardiol* 1995;**75**:1158–1161.
39. Chatterjee S, Ghosh J, Lichstein E, Aikat S, Mukherjee D. Meta-analysis of cardiovascular outcomes with dronedarone in patients with atrial fibrillation or heart failure. *Am J Cardiol* 2012;**110**:607–613.
40. Piepoli M, Villani GQ, Ponikowski P, Wright A, Flather MD, Coats AJ. Overview and meta-analysis of randomised trials of amiodarone in chronic heart failure. *Int J Cardiol* 1998;**66**:1–10.
41. Cleland JG, Buga L. Device therapy: defibrillators—a shocking therapy for cardiomyopathy? *Nat Rev Cardiol* 2010;**7**:69–70.
42. Thackray SD, Ghosh JM, Wright GA, Witte KK, Nikitin NP, Kaye GC, Clark AL, Tweddel A, Cleland JG. The effect of altering heart rate on ventricular function in patients with heart failure treated with beta-blockers. *Am Heart J* 2006;**152**:713.e9–e13.
43. Logeart D, Gueffet JP, Rouzet F, Pousset F, Chavelas C, Solal AC, Jondeau G. Heart rate per se impacts cardiac function in patients with systolic heart failure and pacing: a pilot study. *Eur J Heart Fail* 2009;**11**:53–57.
44. Brignole M, Botto G, Mont L, Iacopino S, De Marchi G, Oddone D, Luzi M, Tolosana JM, Navazio A, Menozzi C. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. *Eur Heart J* 2011;**32**:2420–2429.
45. Teerlink JR. Ivabradine in heart failure—no paradigm shift . . . Yet. *Lancet* 2010;**376**:847–849.
46. Simon T, Mary-Krause M, Funck-Brentano C, Lechat P, Jaillon P. Bisoprolol dose–response relationship in patients with congestive heart failure: a subgroup analysis in the cardiac insufficiency bisoprolol study (CIBIS II). *Eur Heart J* 2003;**24**:552–559.
47. Wikstrand J, Hjalmarson A, Waagstein F, Fagerberg B, Goldstein S, Kjekshus J, Wedel H. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). *J Am Coll Cardiol* 2002;**40**:491–498.
48. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S, Shusterman N. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Mocha investigators. *Circulation* 1996;**94**:2807–2816.
49. Fiuzat M, Wojdyla D, Kitzman D, Fleg J, Keteyian SJ, Kraus WE, Pina IL, Whellan D, O'Connor CM. Relationship of beta-blocker dose with outcomes in ambulatory

heart failure patients with systolic dysfunction: results from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial. *J Am Coll Cardiol* 2012;**60**:208–215.
50. Dobre D, van Veldhuisen DJ, Mordenti G, Vintila M, Haaijer-Ruskamp FM, Coats AJ, Poole-Wilson PA, Flather MD. Tolerability and dose-related effects of nebivolol in elderly patients with heart failure: data from the study of the effects of nebivolol intervention on outcomes and rehospitalisation in seniors with heart failure (SENIORS) trial. *Am Heart J* 2007;**154**:109–115.
51. Metra M, Torp-Pedersen C, Swedberg K, Cleland JG, Di Lenarda A, Komajda M, Remme WJ, Lutiger B, Scherhag A, Lukas MA, Charlesworth A, Poole-Wilson PA. Influence of heart rate, blood pressure, and beta-blocker dose on outcome and the differences in outcome between carvedilol and metoprolol tartrate in patients with chronic heart failure: results from the COMET trial. *Eur Heart J* 2005;**26**: 2259–2268.
52. Terra SG, Pauly DF, Lee CR, Patterson JH, Adams KF, Schofield RS, Belgado BS, Hamilton KK, Aranda JM, Hill JA, Yarandi HN, Walker JR, Phillips MS, Gelfand CA, Johnson JA. Beta-adrenergic receptor polymorphisms and responses during titration of metoprolol controlled release/extended release in heart failure. *Clin Pharmacol Ther* 2005;**77**:127–137.
53. Castagno D, Petrie MC, Claggett B, McMurray J. Should we shift our thinking about digoxin? Observations on ivabradine and heart rate reduction in heart failure. *Eur Heart J* 2012;**33**:1137–1141.
54. van Veldhuisen DJ, Van Gelder IC, Ahmed A, Gheorghiade M. Digoxin for patients with atrial fibrillation and heart failure: paradise lost or not? *Eur Heart J* 2013;**34**:1468–1470.
55. Gheorghiade M, Fonarow GC, van Veldhuisen DJ, Cleland JG, Butler J, Epstein AE, Patel K, Aban IB, Aronow WS, Anker SD, Ahmed A. Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: findings from post hoc propensity-matched analysis of the AFFIRM trial. *Eur Heart J* 2013;**34**: 1489–1497.
56. Whitbeck MG, Charnigo RJ, Khairy P, Ziada K, Bailey AL, Zegarra MM, Shah J, Morales G, Macaulay T, Sorrell VL, Campbell CL, Gurley J, Anaya P, Nasr H, Bai R, Di Biase L, Booth DC, Jondeau G, Natale A, Roy D, Smyth S, Moliterno DJ, Elayi CS. Increased mortality among patients taking digoxin—analysis from the AFFIRM study. *Eur Heart J* 2013;**34**:1481–1488.
57. Cullington D, Goode KM, Clark AL, Cleland JG. Heart rate achieved or beta-blocker dose in patients with chronic heart failure: which is the better target? *Eur J Heart Fail* 2012;**14**:737–747.