Heart failure (HF) affects ≈2% to 3% of the population in many industrialized countries and is a major cause of mortality. Although widely used treatments such as β-blockers and renin-angiotensin system antagonists have largely improved outcomes in the past 2 decades, prognosis remains poor. Accumulating data collected in >200,000 individuals in various epidemiological studies support that an elevated heart rate (HR) is a risk marker for future cardiovascular outcomes (including sudden cardiac death) in the general population, in patients with risk factors for coronary artery disease (CAD), and in those with established CAD (both stable and unstable), as well as an established risk factor in those with HF, as discussed below. HR reduction is particularly beneficial in chronic HF, and novel therapeutic approaches that selectively target HR have been recently proposed and raise new hopes for the treatment of HF.

HR generation relies on different molecular mechanisms, including the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (Figure 1). The HCN family of channels is involved in numerous physiological functions in the central nervous system and heart where they are responsible for the If current in the sinoatrial node (SAN). HCN channels have been shown to be involved in the pathophysiology of neurological disorders, including epilepsy (reviewed by Lewis and Chetkovich) and chronic pain, as well as in retinal physiology (see Table 1 for a summary of HCN functions in extracardiac pathophysiology). HCN channels have also emerged as interesting targets for the development of drugs that lower HR. A unique mechanism among vertebrate voltage-gated ion channels involves the permeability of Na+ and K+ (higher permeability to K+ ions than to Na+ ions). During diastole, the inward current is carried mainly by Na+ and K+, with a permeability ratio of 1:4, leading to a slow depolarization phase, i.e., the pacemaker activity. Although K+ is the most easily conducted ion, followed by Na+, a small passage of Ca2+ ions also seems possible, whereas the inward current is blocked by Cs+. However, despite the preference for K+ conductance, under physiological conditions, HCN channels carry mainly an inward Na+ current. HCN channel isoforms differ from each other in their voltage dependency, activation kinetics, and response to cAMP.

The HCN Channel Family

HCN channels belong to the superfamily of voltage-gated pore-loop cation channels. Four isoforms (HCN1–HCN4) with a high homology have been cloned and share common biophysical properties. They have a reverse voltage dependence leading to activation on hyperpolarization, a
Expression Patterns of HCN Channels

There are 4 isoforms of HCN channels, and the expression of all of them has been reported in the myocardium, albeit at low levels for HCN3. The relative expression profiles of HCN channel isoforms show regional differences.

HCN expression is highly regulated during embryonic development. In the mouse heart, the transcription profiles of the 4 HCN genes from embryonic stage to postnatal day 120 vary significantly. The consistently low HCN transcription in adult myocardium may be required to prevent atrial and ventricular arrhythmogenesis. HCN N-glycosylation has been observed in the embryonic heart and could be involved in membrane localization.

In the adult SAN, HCN4 seems to be the major isoform found at the mRNA level in rabbits, mice, and humans. In mice, HCN2 mRNA is expressed in the SAN and myocardium, whereas HCN1 is found only in the SAN and atrioventricular node at lower levels. HCN3 is only weakly detected. HCN expression patterns were also studied in rats by laser capture microdissection of the inferior nodal extension, a specific area located in the atrioventricular junction area. HCN4 mRNA expression was high in the inferior nodal extension, atrioventricular node, and SAN, with low expression levels observed in Purkinje fibres. Although the expression of HCN1 was low in the rat heart, it was observed in the inferior nodal extension, atrioventricular node, and SAN. HCN2 was expressed at higher levels in working myocytes than in nodal tissues.

Aging also affects the expression of HCN genes in the SAN. In rats, an age-dependent decrease in HCN1, HCN2, and HCN4 transcription has been observed. The effect of Cs+ on pacemaker activity was consistently reduced with age. Because aging is associated with deteriorating SAN function, the transcription and relative function of HCN channels may contribute to the decline of function in aged rats. In humans, higher expression of HCN4 and HCN1 mRNAs was observed in the SAN compared with the right atrium.

Regulation of HCN Channel Function

HCN channels are involved in the regulatory pathways of SAN activity. HCN channels are regulated by many pathways, and complex models have been used to describe their gating. Modulation by cAMP appears to be a common mechanism because the cyclic nucleotide-binding domain region is conserved in all 4 HCN channels (schematically presented in Figure 2). cAMP (or cGMP) accelerates the opening kinetics by binding to the C terminus of HCN4 and HCN2 isoforms and shifts their open probability toward more depolarized voltages, whereas HCN1 and HCN3 are almost unaffected. Regulation by cAMP can be influenced by the composition of the milieu or the parameters of the experimental conditions.

Table 1. HCN Channels in Noncardiac Physiology or Pathophysiology: Central Nervous System and Retina

<table>
<thead>
<tr>
<th>Findings</th>
<th>Potential Clinical Interest</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior</td>
<td>Rewarding effects of ethanol targeting HCN genes expressed in dopaminergic neurons</td>
<td>Fight alcohol abuse and addiction</td>
</tr>
<tr>
<td>Pain</td>
<td>Neuropathic pain is initiated by HCN2-driven action potential firing in Na(V) 1.8-expressing nociceptors</td>
<td>New medications</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Genetic HCN variants could predispose to sudden death in epilepsy</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>HCN2-deficient mice exhibit spontaneous absence seizures and sinus dysrhythmia</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Dendritic HCN1 subunit facilitates epileptogenesis</td>
<td>13</td>
</tr>
<tr>
<td>Febrile seizure</td>
<td>Febrile seizures modulate the expression of different HCN genes, thus altering the neuronal HCN phenotype; seizure-induced augmentation of HCN2 expression</td>
<td>14</td>
</tr>
<tr>
<td>Retina</td>
<td>HCN channels are involved in retinal physiology because they could modulate the function of photoreceptors</td>
<td>9</td>
</tr>
<tr>
<td>Retina</td>
<td>Phosphophine and troubled vision</td>
<td>Limiting side effects</td>
</tr>
</tbody>
</table>

HCN indicates hyperpolarization-activated cyclic nucleotide-gated.
and muscarinic M2 receptors, respectively). Because cAMP concentration determines the open probability of the HCN channel, sympathetic/parasympathetic control of intracellular cAMP is able to induce an increase/decrease of the net inward current during diastolic depolarization and thereby an increase/decrease of firing rate. HR regulation through cAMP levels could be mediated rapidly by direct binding of cAMP to the β2-adrenergic receptors (β2-ARs) and membrane caveolae is of great importance in HR control.36

Both β1 and β2 subtypes of β-ARs are expressed in the heart; β1-ARs are abundant in the whole heart, whereas β2-ARs are highly expressed in the SAN and localized in caveolae.36–38 Furthermore, the β2-ARs have been shown to colocalize and form protein complexes with the HCN channels.39 The β2-AR–binding site was identified at a proximal region of the N-terminal tail of HCN4, and a synthetic peptide derived from the β2-AR–binding domain of HCN4 was shown to disrupt this interaction. From a therapeutic point of view, the interest of β-blockers in HF could rely at least in part on their action on HCN channels.

Other molecules that can regulate HCN function include locally interacting proteins, phosphatidylinositol-4,5-bisphosphate (PIP2),40 protons,41 and chloride42 (Figure 2). PIP2-induced potentiation was localized to the transmembrane domain.43 The HCN channels are regulated by a local pool of PIP2 that may be enhanced after receptor-mediated activation of phospholipase C.44 The high variability of PIP2 content could explain large variations of HCN channel physiology, especially in different regions of the heart.

Table 2. Involvement of Different HCN Channels in Cardiac Pathophysiology

<table>
<thead>
<tr>
<th>Isoform</th>
<th>Expression in the Heart</th>
<th>Knockout Mouse Phenotype</th>
<th>Additional Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCN1</td>
<td>Conduction system</td>
<td>Neuronal dysfunction; no cardiac phenotype described</td>
<td>Decreased in old rats</td>
</tr>
<tr>
<td>HCN2</td>
<td>Ubiquitous, mainly in SAN</td>
<td>Sinus arrhythmia</td>
<td></td>
</tr>
<tr>
<td>HCN3</td>
<td>Left ventricle</td>
<td>Defects in ventricular late repolarization</td>
<td></td>
</tr>
<tr>
<td>HCN4</td>
<td>Ubiquitous, the isofrom most expressed in SAN but also present in AVN (and His-Purkinje fibers)</td>
<td>Varying (mild to marked) effects on cardiac automaticity; embryonic lethality</td>
<td>Main HCN channel involved in the generation of sinus rhythm</td>
</tr>
</tbody>
</table>

AVN indicates atrioventricular node; HCN, hyperpolarization-activated cyclic nucleotide-gated; and SAN sinoatrial node.
HCN Channels: Heart Failure and Arrhythmia

Roubbie and Tardif

Both extracellular and intracellular protons regulate HCN channel function. Intracellular acidosis seems to inhibit HCN activation, which is important during cardiac ischemia and HF, whereas extracellular acidosis activates the channel. Numerous auxiliary proteins have been shown to regulate HCN function by controlling the fine electrophysiological regulation or the subcellular compartment trafficking: K⁺ channel regulator-1, Tamalin, c-Src, scaffold proteins such as Mint2 and synaptic scaffolding molecule (which positively regulates cell-membrane localization), caveolin-3 (which could provide a pathway for β2-AR regulation of HCN by clustering HCN4 in caveolae), and potassium voltage-gated channel subfamily E member-2 (also known as MinK-related protein). Posttranslational modifications such as phosphorylation were shown to account for the function of HCN channels in specific cells. All these interacting proteins and modifications affect HCN function, as well as the abundance of HCN channels in the membrane (the number of functional pores) and their subcellular localization.

HCN Function and Disease

Genetic mice models are available for all 4 HCN channels. Constitutive cardiac deletion of HCN4 results in embryonic lethality, highlighting the role of HCN4 for SAN action potential formation. In some nonconstitutive knockout models, only mild effects on cardiac automaticity were observed with no alterations of HR control. Ablation of HCN4 in an isolated SAN cell from rabbit using patch clamp technique revealed strong effects (Table 2). HCN mutations in humans lead to detectable changes in HCN function (reviewed elsewhere). The search for human channelopathies related to HCN mutations confirmed that HCN4 is crucial in normal physiology. Four loss-of-function mutations of HCN4 have been described and were all associated with idiopathic sinus bradycardia, accompanied in 1 case by more complex arrhythmias.

Electrophysiological remodeling has been described for many channels, including the HCN channels, in humans and in a canine model of ventricular tachypacing. In the canine model of tachypacing-induced HF, HCN4 was the dominant subunit in the SAN and right atrium; downregulation of HCN4 and HCN2 expression contributed to HF-induced sinus node dysfunction, whereas upregulation of atrial HCN4 was proposed to promote atrial arrhythmia formation. In contrast, analysis in human hearts showed that the expression of both HCN2 and HCN4 was significantly increased in failing ventricles. Studies have suggested that HCN upregulation may play a role in serious ventricular arrhythmias.

HCN Channel Inhibition With Ivabradine

Although some nonspecific compounds can block the function of HCN channels, specific inhibitors have emerged; currently, only ivabradine (3-(3-[[((7R,8S)-3-benzazepin-2-one hydrochloride]-3-benzazepin-2-one hydrochloride]-3-benzazepin-2-one hydrochloride]-(7S)-3-benzazepin-2-one hydrochloride]-3-benzazepin-2-one hydrochloride]) is available for clinical use and represents a new approach in selective HR reduction (Figures 2 and 3). Ivabradine contains 2 moieties (benzazepine and benzoclobutane) linked by an azapentane chain. The N-demethylated metabolite of ivabradine has also shown HR reduction activity in animals and humans.

The pharmacokinetic properties of ivabradine have previously been described. It is rapidly absorbed (tmax=0.75–1.5 hours) with a bioavailability of 37% to 49%. Ivabradine has extensive tissue distribution with 70% protein binding. It is extensively metabolized by the cytochrome P450 3A4 into several metabolites, including the N-demethylated derivate, which is the major active metabolite. The elimination process occurs by both fecal and urinary pathways. The main half-life of ivabradine is 2 hours, whereas that of its N-demethylated metabolite is 13 hours.

In vitro, ivabradine reduces the spontaneous beating rate in an isolated SAN cell from rabbit using patch clamp technique (see Figure 3). In patch-clamp experiments, ivabradine has been shown to block the pacemaker current of isolated SAN cells of rabbits in the low-micromolar range, with minimal or no effects on other potassium and calcium currents. In a study of healthy volunteers assessing the correlation between bradycardic activity and plasma levels of the parent compound and its metabolite, ivabradine was found to exert a dose-dependent HR-reducing effect, partly through its N-demethylated metabolite. The maximal reductions of HR during exercise were 11±4% (10 mg) and 18±6% (20 mg) after single oral doses and 18±4% (10 mg twice daily) and 27±6% (20 mg twice daily) after repeated doses. Maximal reduction of the diastolic depolarization slope by blocking the If current, leading to selective heart rate reduction. Reproduced from DiFrancesco and Camm with permission from the publisher. Copyright © 2004, Springer Science+Media BV.

Figure 3. Spontaneous action potential in rabbit sinoatrial node in the absence (control, gray) or presence (orange) of ivabradine 0.3 μmol/L. Ivabradine slows the diastolic depolarization slope by blocking the If current, leading to selective heart rate reduction.
resting HR was 16±18% after the single 10-mg oral dose and 24±16% after the 10-mg twice-daily repeated dose.

In patch-clamp experiments, ivabradine induced a use-dependent inhibition of heterologously expressed HCN4 with an IC50 of 0.5 μmol/L; the development of the progressive blocking action on the current was related on channel openings during the activating pulses rather than time itself.26 This property results from the fact that ivabradine is an open channel blocker and exhibits a current-dependent release of block,66,68 rendering its action sensitive to the number of pulses and the voltage at which HCN channels are activated.

Additionally, the use dependence of ivabradine may be at the origin of the frequency dependency that is observed in vitro in SAN preparations from different species.77 Such a frequency-dependent property could, at least partly, explain its increased effectiveness in species with rapid SAN pacemaker activity and supports its greater impact in patients with elevated HR. In contrast, patients with low HR are less responsive, reducing the risk of clinically significant bradycardia.

Importantly, ivabradine has been shown to bind only weakly to other ionic channels.65 In a patch-clamp model in rabbit cells, a high concentration of ivabradine (10 μmol/L) had no detectable effect on T-type calcium current and slightly decreased L-type calcium current. Furthermore, ivabradine did not affect the delayed outward potassium current (Ito) at a concentration of 3 μmol/L and slightly decreased the current amplitude only at high concentrations (16.3±1.2% decrease at 10 μmol/L).65

Effects on cardiac Na+ channels69 and on Kv1.5 potassium channels70 were reported only in vitro at very high concentrations (30–100 μmol/L), so these nonspecific effects seem unlikely to arise at therapeutically relevant concentrations, as in clinical practice. The electrophysiological effects of a single intravenous administration of ivabradine were studied in patients with normal baseline electrophysiology.71 An intravenous dose of ivabradine does not prolong the corrected QT interval or modify the conductivity and refractoriness of the atria, atrophicventricular node, His-Purkinje system, and ventricles. Ivabradine also does not cause detrimental effects on coronary vasomotion.72

The clinical effects of ivabradine appear to be mediated by HR reduction. An analysis of the Systolic Heart Failure Treatment With Ii, Inhibitor Ivabradine Trial (SHIFT) study underlined that HR reduction by itself explains the positive impact of ivabradine in HF.73 Other beneficial effects of ivabradine on endothelial function,74 oxidative stress, and atherosclerosis severity in mice are also probably mediated through HR reduction.75 There is no other known pharmacological target for the effect of ivabradine. In patients with stable CAD, ivabradine was shown in the phase 3 INternational TrIAl on the Treatment of angina with IVabradinE vs. atenolol (INITIATIVE) trial (n=939) not to be inferior to the β-blocker atenolol in terms of its antiangiinal and anti-ischemic effects.76 Furthermore, ivabradine (5 mg twice daily for 2 months followed by 7.5 mg twice daily for 2 additional months) provided additional antiangiinal and anti-ischemic efficacy in patients with residual symptoms despite β-blocker treatment, as demonstrated in the evaluation of the Antiangiinal efficacy and Safety of the aSSociation Of the If Current Inhibitor ivAbradine with a beTa-blockEr (ASSOCIATE) study (n=889).77

HCN Channels and HF

HCN Blockade in Animal Models

The efficacy of ivabradine in HF has been shown in various animal models. In a rat model of myocardial infarction leading to HF, ivabradine significantly reduced left ventricular (LV) end-systolic but not end-diastolic diameter, which preserved cardiac output.78 Ivabradine also reduced LV diastolic dysfunction and both atrial and ventricular fibrosis in hypercholesterolemic rabbits.79 Angiotensin II and aldosterone levels after treatment with ivabradine were correlated with HR in that study. This beneficial impact of ivabradine on diastolic dysfunction was recently corroborated in another model.80 In a mouse model of angiotensin II–induced HF,81 both ivabradine and metoprolol led to a similar reduction in HR, but only ivabradine led to a significant improvement in LV systolic and diastolic function. This effect was associated with reductions in cardiac hypertrophy, fibrosis, inflammation, and apoptosis. Colin et al82 investigated the effects of ivabradine and atenolol on LV isovolumetric relaxation at rest and during treadmill exercise in chronically instrumented dogs. For a similar reduction in HR at rest and during exercise, ivabradine, in contrast to atenolol, did not exert any negative lusitropic effects.

In a rat myocardial infarction model, metoprolol (250 mg·kg−1·d−1) and ivabradine (10 mg·kg−1·d−1) had similar effects on HR reduction, and both treatments partially prevented deterioration of LV ejection fraction and reduced LV wall stress.53 Metoprolol partially prevented LV dilation, whereas ivabradine potentiated LV hypertrophy. However, in another study in severe post–myocardial infarction chronic HF in rats,84 ivabradine prevented the worsening of LV dysfunction and remodeling, and this was associated with a down-regulation of cardiac renin-angiotensin-aldosterone system transcripts. Ivabradine has also been shown to induce reverse electrophysiological remodeling in a myocardial infarction model of HF in rats, underlining the importance of transcriptional and posttranscriptional mechanisms.85 The increase in Ihi after myocardial infarction was attenuated by ivabradine, and reduced HCN4 expression was associated with increases in both the microRNAs miR-1 and miR-133, which regulate the HCN2 and HCN4 genes.85 Finally, in a dog model of coronary stenosis and exercise leading to myocardial stunning, ivabradine reduced ineffective postsystolic LV wall thickening and modified it into ejectional thickening, thereby improving ventricular efficiency.86

HCN Blockade in Patients With HF

The effect of a single intravenous dose of ivabradine on LV function was studied in patients with systolic dysfunction with echocardiography.57 The LV ejection fraction did not significantly decrease with ivabradine (0.2%) compared with placebo (1.7%). Other echocardiographic parameters such as fractional shortening and stroke volume were also unchanged after the intravenous administration of ivabradine. In a small study of 10 patients with advanced HF and severe LV systolic dysfunction (mean ejection fraction, 21%), intravenous administration of ivabradine reduced HR by 27%, increased stroke volume, and preserved cardiac output.88
The first large trial of ivabradine dedicated to patients with LV systolic dysfunction and HF was the SHIFT study.89 This randomized, double-blind, placebo-controlled study included 6558 patients with symptomatic HF (equally distributed between classes II and III), with an LV ejection fraction ≤35% (mean ejection fraction at baseline, 29%), and in sinus rhythm with an HR of 70 bpm. These patients were admitted to hospital for HF within the previous year and were on stable contemporary background treatment, including a β-blocker if tolerated (89% were actually treated with a β-blocker).

The placebo-corrected reduction in HR with ivabradine was 9.1 bpm at 1 year. Over a median follow-up of 22.9 months (interquartile range, 18–28 months), ivabradine led to an 18% relative risk reduction in the primary composite end point of cardiovascular death or hospitalization for worsening of heart failure (HR = 0.82, 95% CI 0.75–0.90, p<0.0001); 793 patients (24%) in the ivabradine group and 937 patients (29%) in the placebo group indeed experienced a primary clinical event during the study (Figure 4A).

Ivabradine was associated with relative risk reductions of 26% for both hospitalizations for worsening HF (HR = 0.74, 95% CI 0.58–0.94, p=0.014) and deaths caused by HF (HR = 0.74, 95% CI 0.58–0.94; p=0.014; see Figure 4C). The reduction in cardiovascular deaths with ivabradine did not reach statistical significance (see Figure 4D).

In the placebo group of SHIFT, the risk of suffering a primary composite end point event increased by 3% with every beat increase in baseline HR.73 In the ivabradine group, there was a direct association between HR achieved at 28 days and subsequent cardiovascular outcomes. Patients with HR <60 bpm at 28 days on treatment had fewer primary events during the study (event rate, 17.4%) than did patients with higher HR. The benefit of ivabradine was accounted for by the HR reduction, as shown by the neutralization of the treatment effect after adjustment for change in HR.

The effects of ivabradine on quality of life were evaluated in a subset of 1944 patients with HF in SHIFT.90 The reduction in HR with ivabradine was associated with improved health-related quality of life. Furthermore, the magnitude of HR reduction was related to the extent of improvement of quality of life. An echocardiographic substudy was also conducted in 411 patients with HF in SHIFT.91 Ivabradine improved both LV end-systolic and end-diastolic volume indexes compared with placebo by −5.8 and −5.5 mL/m² (P<0.001 and P=0.002, respectively) from baseline to the 8-month follow-up, which translate into placebo-corrected reductions of 11 mL in both nonindexed LV end-systolic and end-diastolic volumes (Figure 5A and 5B). Ivabradine also improved LV ejection fraction by a mean of 2.7% when corrected for placebo (P<0.001). Thus, ivabradine induces reverse LV remodeling in patients with HF and LV systolic dysfunction.
Clinical Use and Side Effects of Ivabradine

The results mentioned above have been taken into consideration in the new European Society of Cardiology guidelines on HF, leading to a recommendation for ivabradine in patients in sinus rhythm with an LVEF ≤35%, an HR ≥70 bpm, and persisting symptoms (New York Heart Association class II–IV) despite treatment with an evidence-based dose of a β-blocker (or a maximally tolerated dose), an angiotensin-converting enzyme inhibitor (or angiotensin receptor blocker), and a mineralocorticoid receptor antagonist to reduce the risk of HF hospitalization (Class IIa, Level B).

Ivabradine is not indicated to slow HR in patients with chronic atrial fibrillation because it acts on the SAN, not the atroventricular node. Of note, the incidence of atrial fibrillation was 9% with ivabradine and 8% with placebo in the SHIFT trial (P=0.012). The concomitant use of ivabradine with strong cytochrome P450 3A4 inhibitors such as azole antifungals, macrolide antibiotics, HIV protease inhibitors, and nefazodone is contraindicated. Ivabradine should be avoided in patients with a prolonged QT interval because QT prolongation may be exacerbated by HR reduction (although the corrected QT interval has not been shown to be modified with ivabradine). Concomitant use of ivabradine with HR-reducing calcium channel blockers such as verapamil or diltiazem is not recommended. No pharmacokinetic changes have been observed with ivabradine between elderly (≥65 years of age) or very elderly (≥75 years of age) patients and the overall population. In patients with HF ≥75 years of age, a lower starting dose should be considered (2.5 mg twice daily) with further titration if necessary. No dose adjustment is required in patients with creatinine clearance >15 mL/min; however, there are no data available in patients with creatinine clearance <15 mL/min; therefore, ivabradine is not recommended in these patients.

Bradyarrhythmias and phosphenes (transient enhanced brightness in a limited region of the visual field) are the most common side effects associated with the pharmacological action of ivabradine. The cardiac safety of ivabradine was specifically evaluated in the Holter substudy of morBidity-mortality EvAlUaTion of the IF inhibitor ivabradine in patients with CAD and left ventricular dysfunction (BEAUTIFUL), which included 840 patients. Although 93% of patients receiving concomitant β-blockers, the incidence of episodes of HR <30 bpm during waking hours or during sleep was ≤1% in the ivabradine and placebo groups. No between-group difference in episode severity was observed, despite the fact that there were more patients with HR <40 or <50 bpm with ivabradine than with placebo (eg, asleep, 22% versus 5% for <40 bpm and 77% versus 50% for <50 bpm, respectively). Furthermore, there was no increase in the incidence of conduction or rhythm disturbances.

Phosphenes are related to the effect of ivabradine on related h channels in the retina. These visual symptoms are transient, do not interfere with quality of life, and have led to few withdrawals (24 of 2545 patients [<1%] in a safety study). These visual side effects have been shown typically to resolve during treatment, as previously reported. In the BEAUTIFUL study of 10917 patients, <1% of patients discontinued the treatment because of visual symptoms. Eosinophilia has been reported by the European Medicines Agency to occur uncommonly with ivabradine. In the large SHIFT study in 6558 HF patients, fewer serious adverse events occurred in the ivabradine group than in the placebo group. The total number of serious adverse events, including cardiac and noncardiac serious events, was 3388 in the ivabradine group and 3847 in the placebo group (P=0.025). Symptomatic bradycardia occurred in 150 patients (5%) in the ivabradine group and 32 patients (1%) in the placebo group (P<0.0001). Bradycardia led to permanent withdrawal from

Figure 5. Ivabradine reverses cardiac remodeling in patients with heart failure and left ventricular systolic dysfunction. Main results of the Systolic Heart Failure Treatment With I, Inhibitor Ivabradine Trial (SHIFT) echocardiography substudy as reported by Tardif et al. A total of 411 patients with chronic heart failure and systolic dysfunction (left ventricular ejection fraction [LVEF] ≤35%) who were in sinus rhythm and had resting heart rate ≥70 bpm were randomly allocated to ivabradine or placebo. Complete echocardiographic data at baseline and 8 months are presented. A, Treatment with ivabradine reduced left ventricular end-systolic volume index (primary substudy end point) vs placebo (−7.0±16.3 vs −0.9±17.1 mL/m²; difference, −5.8 mL/m²; SE, 1.6 mL/m²; 95% confidence interval, −8.8 to −2.7; P<0.001). B, Left ventricular end-diastolic volume index was improved in the ivabradine group vs placebo (−7.9±18.9 vs −1.8±19.0 mL/m²; P=0.002). Ivabradine also increased LVEF (2.4±7.7% vs −0.1±8.0%; P<0.001; not shown).
HCN Channels and Arrhythmias

Human genetic and animal studies have highlighted the involvement of HCN channels in the pathophysiology of arrhythmias. In a canine model, upregulation of atrial HCN4 has been shown to promote atrial arrhythmias. Furthermore, overexpression of the human mineralocorticoid receptor in embryonic stem cells resulted in increased expression of HCN4 and other ion channels. In dogs undergoing atrial tachypacing and with evidence of impaired sinoatrial function, SAN HCN2 and HCN4 mRNA expression and HCN-related current densities were reduced (perhaps because of a lack of need owing to pacing).

HCN modulation could be of interest for therapeutic purposes when HCN channels are either upregulated (mainly in HF, as previously detailed, or in inappropriate sinus tachycardia) or downregulated (mainly in SAN disease). The best example of restoring HCN channel activity to treat an arrhythmia is provided by research on bioartificial pacemakers, which underline several important factors involved in arrhythmias, including the HCN channels, the ratio between \( I_{Ks} \) and \( I_{K1} \) currents, and the distribution of different HCN subtypes among the cells. Strategies to restore biological activity of a deficient pacemaker involve either fusion of cells expressing large amounts of HCN1 or HCN gene-based therapy. In terms of gene therapy, overexpression of an engineered HCN construct via somatic gene transfer has been used to fine-tune cardiac pacing in vivo. Focal transduction of this construct, a shortened S3–S4 linker to favor channel opening, in the left atrium of animals with sick sinus syndrome reproducibly induced a stable, catecholamine-responsive in vivo bioartificial node.

On the other hand, the best example of a therapeutic decrease in HCN channel activity (ie, blocking the \( I_{Ks} \) current) for the treatment of an arrhythmia is the management of the inappropriate sinus tachycardia syndrome. Many case reports have suggested the efficacy and tolerability of the treatment of inappropriate sinus tachycardia with ivabradine. In addition, a study of 18 patients with a typical history of inappropriate sinus tachycardia showed that HR was significantly reduced by ivabradine and that tolerance to physical activity was increased, with a progressive rise in maximal load reached. Ivabradine has also been suggested to alleviate symptoms related to the postural orthostatic tachycardia syndrome. In a retrospective study of 18 patients, 8 patients reported reduced tachycardia and fatigue, 4 patients reported only reduced tachycardia, and 6 patients did not experience benefits.

The safety of ivabradine in terms of its effects on arrhythmias was evaluated in the BEAUTIFUL study, a randomized, placebo-controlled trial of 10917 patients with stable CAD and an LV ejection fraction <40%. The primary composite end point in BEAUTIFUL was not affected significantly, although a hypothesis-generating analysis revealed that patients with a resting HR of ≥70 bpm at baseline appeared to benefit from ivabradine. The Holter substudy in BEAUTIFUL involved 840 patients who underwent 24-hour ambulatory ECG monitoring at baseline and 1 and 6 months. There was no increase in the incidence of conduction and rhythm disturbances with ivabradine.

Finally, HCN channels could be considered a common point between \( \beta \)-blockers and ivabradine. Ivabradine is a selective HCN channel antagonist, providing pure HR reduction, hence its usefulness in cardiovascular disease, including HF. The use of \( \beta \)-blockers is associated with side effects because of their actions on the neurohormonal system or effects on other targets. On the other hand, the impact of \( \beta \)-blockers on neurohormonal imbalance remains of interest against ventricular arrhythmias. \( \beta \)-Blockers are likely to be more effective in treating ventricular arrhythmias (eg, generated in areas of myocardial scarring) compared with HCN blockade, the effect of which is focused on the SAN. Therefore, \( \beta \)-blockers and ivabradine can be considered complementary drugs.

Conclusions

HR is a prognostic marker in a wide spectrum of individuals, including patients with HF, in whom it has been shown to be a risk factor for future cardiovascular clinical events. HCN channels play a significant role in cardiac pacemaker activity in animals and humans, and ivabradine is the only drug currently available clinically that specifically blocks HCN channels. HR reduction with the HCN channel blocker ivabradine reduces hospital admissions for worsening HF and deaths resulting from HF in patients with an LV ejection fraction <35%, HF, and an HR of at least 70 bpm (in sinus rhythm). Ivabradine has gained approval for the treatment of HF and angina in several regions of the world. The Study assessing the morbidity–mortality benefits of the If inhibitor ivabradine in patients with coronary artery disease (SIGNIFY) trial (n=19000) is currently testing whether the HCN channel blocker ivabradine will also improve clinical outcomes of patients with stable CAD, without HF, and with a resting HR of ≥70 bpm.

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**Key Words:** arrhythmias, HCN channels, heart failure, heart rate, ivabradine
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