R E V I E W

Advances in the management of heart failure: the role of ivabradine

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Abstract: A high resting heart rate ($\geq$70–75 b.p.m.) is a risk factor for patients with heart failure (HF) with reduced ejection fraction (EF), probably in the sense of accelerated athero-sclerosis, with an increased morbidity and mortality. Beta-blockers not only reduce heart rate but also have negative inotropic and blood pressure-lowering effects, and therefore, in many patients, they cannot be given in the recommended dose. Ivabradine specifically inhibits the pacemaker current (funny current, I_f) of the sinoatrial node cells, resulting in therapeutic heart rate lowering without any negative inotropic and blood pressure-lowering effect. According to the European Society of Cardiology guidelines, ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with a reduced left ventricular EF $\leq$35% and sinus rhythm $\geq$70 b.p.m. despite treatment with an evidence-based dose of beta-blocker or a dose below the recommended dose (recommendation class "IIa" = weight of evidence/opinion is in favor of usefulness/efficacy: "should be considered"; level of evidence "B" = data derived from a single randomized clinical trial or large nonrandomized studies). Using a heart rate cutoff of $\geq$ 75 b.p.m., as licensed by the European Medicines Agency, treatment with ivabradine 5–7.5 mg b.i.d. reduces cardiovascular mortality by 17%, HF mortality by 39% and HF hospitalization rate by 30%. A high resting heart rate is not only a risk factor in HF with reduced EF but also at least a risk marker in HF with preserved EF, in acute HF and also in special forms of HF. In this review, we discuss the proven role of ivabradine in the validated indication "HF with reduced EF" together with interesting preliminary findings, and the potential role of ivabradine in further, specific forms of HF.

Keywords: heart failure, endotoxin, I_f inhibitor, ivabradine, pacemaker current inhibitor, heart rate, heart rate variability

Introduction to the management issues in the treatment of heart failure (HF) – the role of ivabradine

During the past half-century, age-adjusted cardiovascular disease-related mortality has declined by about two-thirds in industrialized nations. However, HF is a notable exception with this respect: in the US, hospitalizations because of HF have risen steadily since 1975 up to one million discharges per year.[1] In Europe, 1–2% of the population suffer from HF, with the prevalence rising to $\geq$ 10% among the population aged $\geq$ 70 years; age-standardized death rate is about 30/100,000 population, with the mean age at death of 83 years.[2]

HF is not a homogenous entity (Table 1) but consists[3] of HF with reduced ejection fraction (HFrEF; LVEF < 40%; "systolic" HF), of HF with preserved ejection fraction

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Table 1 Types of heart failure with prognostic relevance of resting heart rate (sinus rhythm) and role of the pacemaker current inhibitor ivabradine

Role of heart rate/ ivabradine	HFrEF chronic stable	HFpEF chronic stable	Acute/ decompensated HF	Post-cardiac transplantation	Peripartum CM	Shock and MODS	ROSC after OHCA
Heart rate is prognostically relevant	Yes	Yes	Yes	?	Yes	Yes	Yes
Ivabradine reduces heart rate	Yes	Yes	Yes	Yes	Yes	Yes	?
Ivabradine improves prognosis	Yes	?	?	?	?	?	?
Ivabradine approved for use in EU/USA	Yes	No	No	No	No	No	No
Combination of ivabradine + beta-blocker feasible	Yes	Yes	Yes	?	Yes	?	?

Note: For patients with HFmrEF, no prospective trials with ivabradine are yet available.
Abbreviations: CM, cardiomyopathy; EU, European Union; HF, heart failure; HFmrEF, heart failure with mild-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MODS, multiple organ dysfunction syndrome; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation.

(HFpEF[4]; LVEF ≥ 50%; "diastolic" HF) and – according to the 2016 version of the ESC HF guideline[w] – HF with mid-range ejection fraction (HFmrEF; LVEF 40–49%) of either ischemic or nonischemic origin. All these forms can present as acute HF, as chronic stable HF or as decompensated chronic HF.

Evidence-based treatment of all these different forms of HF is shown in the European[3] and the American[5] HF guidelines.

For the pacemaker channel inhibitor ivabradine, the European HF guideline[3] gives the following recommendations for the treatment of HFrEF:

1. Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤ 35%, in sinus rhythm and a resting heart rate ≥ 70 b.p.m. despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), an ACE inhibitor (or ARB) and an MRA (or ARB) (IIa/B) (recommendation class "IIa" = weight of evidence/opinion is in favor of usefulness/efficacy: "should be considered"; level of evidence "B" = data derived from a single randomized clinical trial or large nonrandomized studies).

2. Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤ 35%, in sinus rhythm and with a resting heart rate ≥ 70 b.p.m. who are unable to tolerate or have contraindications for a beta-blocker. Patients should also receive an ACE inhibitor (or ARB) and an MRA (or ARB) (IIb/C) (recommendation class "IIb" = usefulness/ efficacy is less well established by evidence/opinion; level

of evidence "C" = consensus of the opinions of the experts and/or small studies, retrospective studies and registries).

In Germany, ivabradine (ivabradine hydrochloride as Procoralan® [Servier, Neuilly-sur-Seine, France]; 5 mg/7.5 mg film-coated tablets; starting dose 5 mg b.i.d., target dose 7.5 mg b.i.d.) is licensed for patients with chronic HF (NYHA II–IV) with systolic dysfunction who have sinus rhythm with a heart rate ≥ 75 b.p.m. It is used in combination with standard therapy including beta-blockers, or in patients who cannot be treated with beta-blockers.

The cardiovascular risk factor "resting heart rate"
Resting heart rate as a risk marker and risk factor

Among mammals, the number of heartbeats per lifetime is relatively constant ($7.3 \pm 5.6 \times 10^8$ heartbeats/lifetime) which is explained by the dependency of lifetime on the rules of energetics.[6] However, it was only when ivabradine, a selective heart rate-reducing agent, was launched in cardiovascular medicine that interest regained in the role of an inadequately high heart rate as a simple-to-measure risk marker of morbidity and mortality.[7]

Heart rate is an important determinant of the cardiac oxygen equilibrium, with high heart rates leading to increased myocardial oxygen demand and impaired oxygen supply by shortening of diastolic time during the cardiac cycle.[8] An elevated heart rate causes shortening of the duration of the whole cardiac cycle, predominantly at the cost of diastolic duration because systolic time remains fairly stable. The association of heart rate and diastolic duration is not linear,

showing disproportionate shortening of diastolic time with rising heart rate. In contrast, low heart rates induce prolongation of diastolic duration, thereby improving coronary blood flow and oxygen supply, as perfusion of coronary arteries occurs mainly in diastole.[9]

For the sake of reproducibility, resting heart rate in patients should be measured in a standardized manner, with a resting phase of 5 (to 10) min before measurement, with at least two pulse measurements in sitting position with a duration of at least 30 s.

Increased resting heart rate indeed is a risk factor, a sign of sympathetic hyperactivity and/or reduced parasympathetic tone, with many detrimental consequences of a disturbed autonomic balance:[7,10–17] acceleration of coronary atherosclerosis,[18] plaque rupture and coronary heart disease, impairment of arterial compliance and distensibility, increase in the risk of coronary thrombosis, subclinical inflammation and reactive oxygen species (ROS) generation, myocardial ischemia, induction of left ventricular (LV) dysfunction and life-threatening ventricular arrhythmias. The main connecting link between high heart rate and morbidity and mortality is supposed to be the endothelial damage and dysfunction triggered by high heart rate, representing some kind of accelerated atherosclerosis.[10,11,18]

Many of these heart rate-induced impairments of vessels and heart can be improved by treatment with the heart rate-reducing agent ivabradine.[10,11,13–17,19] Even life span prolongation in mice was reported by ivabradine-induced heart rate reduction.[20] Though a good correlation exists between ivabradine-reduced heart rate reduction and beneficial actions, findings for some heart rate-independent effects of ivabradine were also reported.[11,21–25]

Resting heart rate as a risk factor of HF

A high resting heart rate is of prognostic relevance not only in middle-aged and elderly men and women with no apparent heart disease[12] but also in a broad spectrum of cardiovascular diseases,[7] including chronic HFrEF[26–30] and acute/decompensated HFrEF[31] as well as chronic HFpEF[32–34] and acute/decompensated HFpEF.[31]

For the largest patient group, those with chronic HFrEF, Table 2 presents the prognostic relevance of a high resting heart rate (≥75/min vs. < 75/min) with respect to mortality and hospitalization because of HF, both in a large RCT (SHIFT study) and in a registry of ambulatory care.

In chronic HF patients of the CHARM study, baseline resting heart rate in those with sinus rhythm is associated with increased mortality, with every 10-b.p.m. increase associated with respective increases of 8% in all-cause mortality, in both HFrEF and HFpEF; however, this association was not observed in the 15% of patients with atrial fibrillation at baseline.[28,35]

A high heart rate also indicates an unfavorable prognosis in specific forms of acutely life-threatening disease states with impaired heart function (explained in the "Specific forms of HF" section and Table 1).

Ivabradine – mode of action and pharmacology

If as a target of beta-blockers and ivabradine

### HCN channels in the sinoatrial node

Target protein for physiological heart rate variation and pharmacologically induced therapeutic heart rate modification is the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel as tetramer in four isoforms. The HCN channels constitute the pacemaker current I_f in the sinoatrial node cells of the heart (Figure 1). In the human sinoatrial node, HCN1 (exclusively), HCN2 and HCN4 proteins are expressed.[37]

Table 2 Prognostic relevance of resting heart rate in chronic systolic heart failure in sinus rhythm

| Patients with sinus rhythm + NYHA II–IV + LVEF ≤ 35% | SHIFT study[27] | | Registry data[30] | |
	Placebo group: guideline therapy (without ivabradine), 2.5-year follow-up, 3,261 patients		Guideline therapy (without ivabradine), 5-year follow-up, 443 patients	
Heart rate	< 75/min	≥ 75/min	< 75/min	≥ 75/min
Patients (% of total)	35.7%	64.3%	47%	53%
Primary end point: death or hospital admission for worsening heart failure	21%	33%	12%	27%
	(RR 1.57; p < 0.0001)		(RR 2.25; p < 0.01)	
Secondary end point: mortality	11%	17%	2%	9%
	(RR 1.55; p = 0.0166)		(RR 4.5; p < 0.05)	

Notes: SHIFT study:[27] data are given from patients of the placebo group (sinus rhythm ≥ 70/min; LVEF ≤ 35%; NYHA II–IV) under standard heart failure treatment including beta-blocker and excluding ivabradine. Of the total patients, 64.3% had a resting heart rate ≥ 75/min, with a higher value of the primary end point and the secondary end point "mortality" than those with a resting heart rate < 75/min. Registry data:[30] data are given from patients from outpatient clinics (sinus rhythm; LVEF ≤ 35%; NYHA II–IV), with standard heart failure treatment including beta-blocker and excluding ivabradine. Of the total patients, 53% had a resting heart rate ≥ 75/min, with a higher value of the primary end point and the secondary end point "mortality" than those with a resting heart rate < 75/min.
Abbreviations: LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RR, relative risk.
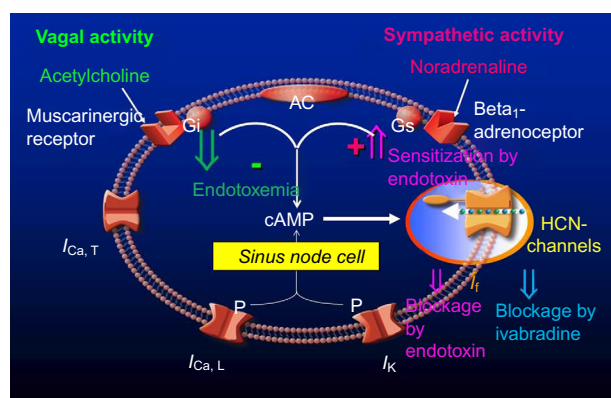
Figure 1 Effects of endotoxin on pacemaker current I_f (HCN channels) and adrenergic pacemaker current I_f stimulation in human atrial cardiomyocytes.
Notes: Endotoxin not only inhibits I_f but also intensifies beta-adrenoceptor-mediated stimulation of I_f.[36] I_f inhibition by endotoxin is not an unspecific effect, as the L-type calcium current is not inhibited by endotoxin. ⇑ indicates stimulation and ⇓ indicates inhibition.
Abbreviations: AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; Gi, inhibitory G protein; Gs, stimulatory G protein; HCN, hyperpolarization-activated cyclic nucleotide-gated; $I_{Ca,T}$, T-type calcium current; $I_{Ca,L}$, L-type calcium current; I_f, "funny" current; I_K, potassium current.

The pacemaker current I_f and regulation of cardiac automaticity

The pacemaker current I_f (Figure 1) generates spontaneous depolarizations toward the initiation threshold for an action potential in the sinoatrial node cells.[38] Velocity of this spontaneous depolarization can be enhanced by sympathetic activity, mediated by norepinephrine binding to the beta$_1$-adrenoceptors of these cells, thereby triggering a rise in intracellular cyclic adenosine monophosphate (cAMP) level. In contrast, velocity of this spontaneous depolarization can be slowed by the vagal activity, mediated by binding of acetylcholine to muscarinergic receptors. By binding to the beta$_1$-adrenoceptors of the sinoatrial node cells, beta-blockers attenuate the endogenous sympathetic chronotropic effect. However, beta-blockers of course do bind not only to the beta$_1$-adrenoceptors of the sinoatrial node cells but also to beta-adrenoceptors of many other cells. The consequence is that beta-blockers do have not only negative chronotropic but also negative inotropic effects on the heart, and they exert blockage of many well-known beta-adrenoceptor-mediated effects in various organs. Furthermore, beta-blockade may interact in an unwanted mode with alpha-adrenoceptor stimulation on the coronary circulation.[39]

However, it has to be mentioned that the I_f current mediated by HCN channels is not the only relevant determinant of cardiac rhythm generation.[38] It is now well established that other ion currents, for example, triggered by L- and T-type calcium channels,[40] and also by potassium channels, contribute to diastolic depolarization and action potential generation.[41] Apart from membrane voltage-gated ion channels ("membrane clock"), other mechanisms have been identified as important

components in rhythm control, namely, spontaneous rhythmic calcium release from the SR. This process activates a current generated by the sodium–calcium exchanger, which contributes to diastolic depolarization ("calcium clock"), ultimately triggering action potential firing.[42] Although there is debate whether one of these "clock" mechanisms is the key initiator of diastolic depolarization and cardiac pacemaking,[43] a close interplay between both concepts ("coupled clock") seems to be crucial for proper rhythm generation in pacemaker cells.[44]

Interestingly in this context, it has recently been shown that ivabradine not only selectively blocks I_f in sinoatrial nodal pacemaker cells but is also associated with other unspecific effects on the calcium-dependent components of the "coupled clock" pacemaker mechanisms, for example, reduced SR calcium loading and a prolongation of the period of spontaneous local calcium releases from SR stores. Thus, ivabradine indirectly suppresses intracellular calcium cycling, which also contributes to the bradycardic effects of the drug, indicating once more the relevance of a coordinated cross talk between the two pacemaking "clocks".[45,46]

Ivabradine and the pacemaker current I_f

In therapeutic concentrations (starting dose 5 mg b.i.d., target dose 7.5 mg b.i.d.), the I_f inhibitor ivabradine binds to HCN channel proteins in the sinoatrial node, thereby reducing the slope of I_f, with consecutive lowering of heart rate in patients with sinus rhythm. With respect to the heart, the action is specific for the sinoatrial node, with no other effects, either on intraatrial, atrioventricular (PQ interval) or intraventricular conduction time or on myocardial contractility or ventricular repolarization (QTc interval). Also, blood pressure is not altered.

Ivabradine and heart rate variability

HRV is considered as a measure of autonomic nervous system function, and a reduced HRV has been identified as an independent predictor of cardiac events and death in the general population without apparent heart disease,[47] and also in those with chronic cardiac disease such as systolic HF.[48] These results support the concept of autonomic imbalance with sympathetic overactivity as an important feature in HF.

Heart rate in general[49] and also selective heart rate reduction by ivabradine are inversely correlated to HRV, as shown in a study with conscious rats.[50] Improvement of HRV with ivabradine was blocked in this model by administration of the beta-blocker propranolol or the muscarinic antagonist atropine, indicating the critical importance of the two components of the autonomic nervous system.

Though acute administration of ivabradine in a short-term animal study was associated with a reflex increase of

sympathetic nerve activity,[51] there clearly seem to be beneficial long-term effects in clinical practice, as demonstrated by the 24-h Holter ECG substudy (n = 602 patients) of the SHIFT. A significant improvement in time domain HRV indices and various parameters of parasympathetic activity was demonstrated in the well-treated (including ACE inhibitors and beta-blockers) systolic HF patients after 8 months of additional treatment with ivabradine compared to placebo.[52] Possible explanations for these positive effects of ivabradine on HRV include the following: prolonged diastole with enhanced cardiac blood supply and ventricular filling; and positive effects on structural ventricular remodeling and reduced sympathetic influence with concomitantly enhanced vagal tone, resulting in an improvement of the autonomic imbalance in sympatho-vagal regulation. These findings could be confirmed in a smaller patient cohort (n = 48) with nonischemic dilated cardiomyopathy, also demonstrating beneficial effects on a number of HRV indices with additional ivabradine treatment for 8 weeks.[53]

Pharmacology of ivabradine

Treatment should be started with 5 mg ivabradine b.i.d. (in patients > 75 years: 2.5 mg b.i.d.). After 3–4 weeks, dosage can be increased in the still symptomatic patients to the maximum dose of 7.5 mg b.i.d. In case of lowering of the heart rate < 50 b.p.m. or in case of symptomatic bradycardia under treatment, dosage should be reduced down to a minimum of 2.5 mg b.i.d. Treatment must be stopped if – despite dose reduction – heart rate remains < 50 b.p.m. or symptomatic bradycardia persists.

The enteral absorption of ivabradine hydrochloride taken as Procoralan tablet after oral ingestion is quick and nearly complete. In the fastened state, highest plasma levels will be achieved after 1 h. Bioavailability is about 40% (first-pass effect). Seventy percent of ivabradine in blood is bound to plasma proteins. The drug has an effective half-time of 11 h and is given twice daily. In patients under daily oral treatment with 5 mg b.i.d., peak concentration of 20 ng/mL and steady-state concentration of 10 ng/mL of ivabradine can be measured.[54–56]

The intravenous route[57,58] is still experimental and not approved for clinical use.

HCN channels and inflammation

Endotoxin directly blocks I_f and indirectly sensitizes I_f to beta-adrenoceptor agonists

Several diseases involving the heart show an inflammatory component due to systemic inflammation, such as septic shock and multiorgan dysfunction syndrome (MODS). Further on, also bacterial and endotoxin translocation from the gut into the systemic circulation due to hypotension and low cardiac output – as in severe HF and cardiogenic shock – can aggravate cardiac impairment by cardiodepressive and antiarrhythmic effects of endotoxin (lipopolysaccharide) and inflammatory mediators. And indeed, in cardiogenic shock complicating myocardial infarction, the proinflammatory cytokine interleukin-6 is a better predictor of unfavorable outcome than BNP.[59]

Though cardiodepression is in the focus of cardiac impairment, endotoxin also interferes with the rhythm: in human atrial cardiomyocytes which also bear HCN channels as do sinoatrial node cells, endotoxin was found to significantly impair I_f by suppressing the current at membrane potentials positive to –80 mV and slowing down current activation, but without effecting maximal current conductance. In a model of a spontaneously active sinoatrial cell, endotoxin-induced I_f impairment reduced the responsiveness of the model cell to fluctuations of autonomic input, thereby reducing heart rate variability between 38% and 62%.[36] This endotoxin effect is not mediated by any of the intracellular modulatory pathways affecting HCN channels, but is instead due to a direct interaction with the channel.[60–62] In addition to this direct inhibitory effect of endotoxin on I_f, endotoxin in human atrial cardiomyocytes also sensitizes I_f to beta-adrenergic stimulation, thereby increasing heart rate.[36] In mice in vivo, endotoxin does not lower but increase heart rate,[63] as can also be seen in humans. However, when autonomous nervous system in these mice is blocked by propranolol and atropine, endotoxin induces a significant reduction of heart rate.[63] Thus, both effects can be demonstrated in the mice, while under in vivo conditions, the positive chronotropic effect of endotoxin by sensitization of I_f to the positive chronotropic beta-adrenoceptor stimulation prevails the direct negative chronotropic effect on I_f.

Ivabradine blocks I_f even in the presence of endotoxin

Even in the presence of endotoxin, ivabradine can further decelerate pacemaker activity of human atrial cardiomyocytes and thereby effectively reduce heart rate.[64]

Clinical efficacy, safety and tolerability of ivabradine in HF

Ivabradine is approved for treatment of patients with chronic HFrEF, based on the data of the SHIFT study.[16] All other forms of HF remain potential indications for the future.[65]

Needless to say that therapy with the pacemaker channel inhibitor ivabradine is restricted to patients with sinus rhythm. This is an important limitation, as atrial fibrillation is frequent

in patients with HFrEF, ranging from 5% in mild to 10–26% in moderate and up to 50% in severe HF.[66,67]

Chronic HFrEF

The SHIFT

The SHIFT ("Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial)[16] is the landmark trial for ivabradine treatment of patients with chronic HFrEF: 6,558 patients with stable (≥4 weeks), chronic symptomatic HF under standard medication, an ejection fraction of ≤ 35%, a previous admission to hospital for worsening HF within the previous 12 months and sinus rhythm ≥ 70 b.p.m. were additionally treated using standard regimen with either placebo or ivabradine. Ivabradine regimen was started with 5 mg b.i.d., and the dose was either maintained if resting heart rate was between 50 b.p.m. and 60 b.p.m. or increased to 7.5 mg b.i.d. unless the resting heart rate was 60 b.p.m. or lower. Demographic data were as follows: mean age 60 years, 77% male; mean heart rate 80 b.p.m.; mean RR_{syst} 122 mm Hg; mean LVEF 19%, NYHA II/III 49%/50%, ischemic origin 68%; treatment with beta-blockers 90%, ACE inhibitors 79%, ARB 14%, diuretics 84%, MRAs 61% and cardiac glycosides 14%. Excluded were patients with HF due to congenital heart disease or primary severe valvular disease. After a median follow-up for analysis of 22.9 months (interquartile range 18–28 months) with a mean ivabradine dosage of 6.4 ± 1.6 mg b.i.d. at day 28 and 6.5 ± 1.6 mg b.i.d. at 1 year, the primary end point – composite of cardiovascular death or hospital admission for worsening HF – was achieved in 29% in the placebo group, but only in 24% in the ivabradine group, representing a significant relative reduction of 18% (HR 0.82; 95% CI 0.75–0.90; $p < 0.0001$). The effects were driven mainly by hospital admissions for worsening HF (21% vs. 16%; HR 0.74; 95% CI 0.66–0.83; $p < 00001$), while cardiovascular death was not significantly different (15% vs. 14%; HR 0.91; 95% CI 0.80–1.03; $p = 0.128$). However, deaths from HF were significantly reduced (5% vs. 3%; HR 0.74; 95% CI 0.58–0.94; $p = 0.014$). Five percent of ivabradine patients had symptomatic bradycardia compared with 1% of the placebo group ($p < 0.0001$). Visual side effects (phosphenes) occurred in 3% of patients on ivabradine and in 1% of patients on placebo ($p < 0.0001$).

In view of the positive SHIFT data, the neutral data of the BEAUTIFUL trial[29,68] with 10,917 patients are a bit surprising. No beneficial effect of ivabradine in these patients with stable coronary artery disease and LV dysfunction (mean LVEF 32%) was seen with respect to cardiovascular death and to admission to hospital for acute myocardial infarction, and for new onset or worsening HF, either in the total population

(heart rate ≥60 b.p.m.) or in the prespecified subpopulation (49%) with a heart rate ≥70. In the SHIFT, 100% of the patients had symptomatic HF (NYHA II: 49%; NYHA III: 50%; NYHA IV: 2%), and in the BEAUTIFUL trial, 84% had symptomatic HF (NYHA I: 15%; NYHA II: 61%; NYHA III: 23%). From this comparison, it becomes evident that patients in the SHIFT had more severe symptomatic HF than those in the BEAUTIFUL trial. Also, another aspect might add to the discrepancy: in view of the SHIFT analysis, one could also speculate that patients with nonischemic HF might benefit even more (primary composite end point: HR 0.72; 95% CI 0.60–0.85) than patients with ischemic HF (HR 0.87; 95% CI 0.78–0.97; test for interaction, $p = 0.59$).

And finally, a word of caution may be allowed, though concerning patients without HF. In patients with stable coronary artery disease and sinus rhythm ≥70 b.p.m., but without clinical HF, ivabradine is of symptomatic but not of prognostic value, as shown in the SIGNIFY trial.[19] In the prespecified SIGNIFY subgroup of patients with angina Canadian Cardiovascular Society grade ≥2, even a higher incidence of the primary end point – cardiovascular death or nonfatal myocardial infarction – was observed (HR 1.18; 95% CI 1.03–1.35; $p = 0.02$).

The EMA decision for a cutoff of ≥ 75 b.p.m.

Based on the positive data of the SHIFT, the European Medicines Agency (EMA) approved ivabradine for treatment of chronic heart failure. Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction in patients in sinus rhythm and whose heart rate is >/= 75 b.p.m., in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated. Therapy approval is given for patients with sinus rhythm ≥ 75 b.p.m. This – at a first glance – was a bit surprising, as the beneficial effects of SHIFT have been obtained in patients with a heart rate ≥ 70 b.p.m. This decision by the EMA is based on a retrospective analysis from the SHIFT study.[27] When analyzing the benefit of ivabradine medication in SHIFT in patients with an initial heart rate ≥ 75 b.p.m., it becomes evident (Table 3) that those patients had not only a reduced rate of HF hospitalizations (30%) and deaths from HF (39%) but also a significant reduction of cardiovascular death rate by 17%. In contrast, the SHIFT patients with an initial heart rate < 75 b.p.m. did not benefit significantly regarding outcomes.[27]

The INTENSIFY study: proof of concept in daily clinical practice

The INTENSIFY study is a prospective, open-label, multicenter, nonintervention study.[69] A group of 1,956 HFrEF patients with an initial sinus rhythm (85 ± 11 b.p.m.) were

Table 3 Therapeutic effects of heart rate reduction by ivabradine in heart failure patients with systolic dysfunction and sinus rhythm ≥ 75/min – data from the SHIFT

In patients with systolic heart failure (sinus rhythm; NYHA II–IV; EF < 35%; *f* >/= 75/min; follow-up 2.5 years)	
Ivabradine treatment achieves	
Heart failure hospitalization	↓ 30% (p < 0.0001)
Cardiovascular mortality	↓ 17% (p = 0.0166)
Heart failure mortality	↓ 39% (p < 0.0006)
Best effect	
f < 60/min or heart rate reduction > 10/min after 28 days	

Note: Data from the SHIFT study.[27]
Abbreviations: EF, ejection fraction; *f*, heart rate; NYHA, New York Heart Association.

treated in German outpatient clinics with ivabradine (44.1% of patients received 5 mg b.i.d., 52.4% received 7.5 mg b.i.d. and 3.5% received 2.5 mg b.i.d.).

After 4 months of treatment, heart rate has fallen down to 67 ± 8.9 b.p.m. In parallel with this heart rate reduction, the proportion of patients with signs of decompensation fell from 22.7% initially to 5.4%, and the proportion of BNP levels > 400 pg/mL dropped from 53.9% to 26.7%. This coincided with a reduction in NYHA class from 9.6% (I), 51.1% (II), 37.2% (III) and 2.1% (IV) initially to 24.0% (I), 60.5% (II), 14.8% (III) and 0.7% (IV), respectively.

After 4 months, the physicians rated the effectiveness of ivabradine as very good in 54.9% of patients and good in 41.5%. Tolerability was rated by the physicians as very good in 68.2% and good in 31.0%. At least one adverse event occurred in 2.9% of patients treated with ivabradine, with 1.4% being cardiac events, 0.5% related to the nervous system and 0.5% being eye events. Bradycardia (0.3%) was mainly seen in patients with an initial heart rate < 75 b.p.m. In 4.4% of the patients, the study drug was discontinued for different reasons (patient's request: 50%, insufficient efficacy: 14.1%, intolerance: 20.5%, lack of compliance: 15.4%, other reasons: 29.5%). During this 4-month period, 0.3% of patients died, reflecting a low-risk chronic systolic heart failure outpatient cohort. In summary, the INTENSIFY study documented over a 4-month period of treatment that ivabradine – in 77.8% given in addition to a beta-blocker – can effectively reduce heart rate and symptoms in patients with HFrEF under daily clinical practice.[69] A similar heart rate reduction and safety profile of ivabradine were also reported in the ADDITIONS study[70] on 2,330 patients with stable angina pectoris. Needless to say that nonintervention trials such as the INTENSIFY study as well as the ADDITIONS study have well-known limitations: they were not blinded, they were not placebo controlled and both studies had a relatively short follow-up of 4 months.

Table 4 Hemodynamic effects of intravenously applied ivabradine in patients with advanced heart failure

Variable	Baseline	1 h	4 h	24 h	*p*
HR	93 ± 8	81 ± 7	68 ± 9	82 ± 11	<0.01
CI	2.2 ± 0.6	2.3 ± 0.5	2.5 ± 0.5	2.5 ± 0.5	0.149
SV	44 ± 11	51 ± 12	66 ± 17	53 ± 12	< 0.01
LVSW	39 ± 13	43 ± 14	58 ± 20	45 ± 17	< 0.01
RVSW	12 ± 5	13 ± 7	17 ± 9	14 ± 8	< 0.01
SAP	103 ± 7	101 ± 9	103 ± 12	100 ± 11	0.848
DAP	71 ± 6	65 ± 4	64 ± 10	63 ± 6	< 0.01
MAP	82 ± 6	78 ± 6	77 ± 11	76 ± 9	0.098
PASP	36 ± 11	37 ± 11	44 ± 15	40 ± 13	< 0.01
PADP	21 ± 7	20 ± 7	20 ± 8	20 ± 8	0.92
PAMP	27 ± 8	27 ± 8	29 ± 10	29 ± 9	0.18
PAWP	19 ± 4	18 ± 5	18 ± 5	18 ± 6	0.8
RAP	7 ± 5	8 ± 6	9 ± 5	9 ± 5	< 0.01
SVR	1,576 ± 374	1,426 ± 334	1,334 ± 420	1,340 ± 381	0.176
TPVR	571 ± 222	539 ± 195	566 ± 297	548 ± 195	0.663

Note: The *p* values are for the prespecified contrasts between baseline and 3, 4, 6, 8, and 24 h of Table 2 of De Ferrari GM, Mazzuero A, Agnesina L, et al. Favourable effects of heart rate reduction with intravenous administration of ivabradine in patients with advanced heart failure. *Eur J Heart Fail.* 2008;10(6):550–555.[57]
Abbreviations: CI, cardiac index (L ×min⁻¹×m⁻²); DAP, diastolic arterial pressure (mm Hg); HR, heart rate (min⁻¹); LVSW, left ventricular systolic work (g); MAP, mean arterial pressure (mm Hg); PADP, pulmonary arterial diastolic pressure (mm Hg); PAMP, pulmonary arterial mean pressure (mm Hg); PASP, pulmonary arterial systolic pressure (mm Hg); PAWP, pulmonary artery wedge pressure (mm Hg); RAP, right atrial pressure (mm Hg); RVSW, right ventricular systolic work (g); SAP, systolic arterial pressure (mm Hg); SV, stroke volume (mL); SVR, systemic vascular resistance (dyn×s×cm⁻⁵); TPVR, total pulmonary vascular resistance (dyn×s×cm⁻⁵); h, hours.

Intravenous ivabradine in advanced systolic HF

De Ferrari et al[57] looked for the hemodynamic effects (Table 4) of intravenously given ivabradine in ten NYHA class III patients (50 ± 12 years) with advanced HFrEF (mean LVEF 21 ± 7%) and sinus rhythm with a mean heart rate of 93 ± 8 b.p.m. Ivabradine regimen was started by an infusion of 0.1 mg/kg over 90 min, followed by 0.05–0.075 mg/kg in the subsequent 90 min. At 4 h, the time point of largest hemodynamic changes achieved, ivabradine significantly had reduced heart rate at the maximum of 27% (24% and 30% among patients treated (n = 6) and not treated (n = 4) with beta-blockers, respectively), without decreasing cardiac index, but leading to a significant increase in SV and LV systolic work. Heart rate remained significantly reduced up to 24 h, when heart rate was still significantly 11 b.p.m. lower than baseline. No significant effect of ivabradine was found on PR, QRS or QT intervals or on laboratory findings.[57]

Chronic HFpEF
Prognosis
Despite somewhat lower than that of HFrEF, mortality of HFpEF ranges from 10% to 30% annually.[71] The majority of deaths in HFpEF are of cardiovascular origin (sudden death and HF), comprising 51–60% of deaths in epidemiological

studies and ~70% in clinical trials. Non-cardiovascular deaths constitute a higher proportion of deaths in HFpEF than in HFrEF.[71] HFpEF with atrial fibrillation represents a more advanced disease than HFpEF with sinus rhythm.[72]

Relevance of resting heart rate
Relevant for morbidity and mortality
Also in HFpEF, a high heart rate indicates unfavorable morbidity (HF hospitalization rates[33]) and also unfavorable all-cause, cardiovascular and HF mortality.[32,34]

Heart rate as a therapeutic target
In HFpEF, neither for ACE-inhibitors/ARB[4] or beta-blockers[3,73–77] nor for MRAs,[3,78–80] a beneficial therapeutic effect has been shown. A positive exception could be effective treatment by beta-blockers of HFpEF risk factors such as hypertension, thereby delaying the progression of HFpEF.[81]

With respect to ivabradine, no RCT with a primary composite end point "cardiovascular death or hospital admission for worsening HF" does exist for HFpEF patients.[4]

Ivabradine and exercise tolerance in HFpEF
Patients with HFpEF suffer from exertional dyspnea and exercise intolerance. Ivabradine seems to be able to improve exercise-induced symptoms. Seventy-one patients with HFpEF (NYHA II/III; EF ≥50%; age 67 ± 9 years; 55% under beta-blocker treatment) in sinus rhythm (resting heart rate 72 ± 7 b.p.m.), reduced exercise capacity (< 80% of normal range) and increased LV filling pressure during exertion were treated for 7 days with either 5 mg ivabradine twice daily or placebo.[82] After 7 days, only the ivabradine group demonstrated a significant reduction in resting heart rate (62 ± 8 b.p.m. compared to baseline heart rate of 72 ± 7 b.p.m; $p = 0.001$), combined with a significant improvement in exercise capacity (from 4.2 ± 1.8 METs at baseline to 5.7 ± 1.9 METs, $p = 0.001$) as well as in peak oxygen uptake (from 14.0 ± 6.1 mL/min/kg to 17.0 ± 3.3 mL/min/kg; $p = 0.001$). The change in METs was greater in the treated patients than in controls (Δ 1.5 ± 1.2 METs vs. Δ 0.4 ± 1.2 METs, $p = 0.001$) as was the change in peak volume of oxygen uptake (Δ 3.0 ± 3.6 mL/min/kg vs. Δ 0.4 ± 2.7 mL/min/kg, $p = 0.003$). In parallel, the ivabradine group showed an improvement in resting LV lusitropic function, while the placebo group did not, with the intergroup difference being significant ($p = 0.01$). During exercise, LV filling pressure was reduced by ivabradine.

These positive short-time (7 days) effects of the randomized study[82] have been extended to 12 months by an observational study[83] with 48 HFpEF patients (NYHA II/III; 55 ± 10 years), treated with ivabradine (5 mg twice daily; in case if heart rate did not decrease < 75 b.p.m., 7.5 mg twice daily). After 1 month, resting heart rate had fallen from 85 ± 5 b.p.m. to 68 ± 4 b.p.m., exercise duration had increased from 6.1 ± 1.9 min to 7.1 ± 1.3 min, in parallel with an increase in peak oxygen uptake from 16 mL/min/kg to 18 mL/min/kg, and an improvement in diastolic dysfunction. These improvements remained stable thereafter for the full observation period of 12 months.

Very similar positive findings of ivabradine in HFpEF patients were described up to 36 months by several groups.[84–86] Switching from beta-blockers to ivabradine in patients with coronary artery disease and elevated LV filling pressure (E/e′ > 8) may cause a reduction in LV filling pressure and an improved SV response to exercise.[84] On the other hand, Pal et al[87] did not see these positive effects in a randomized, crossover study. They compared selective heart rate reduction by ivabradine (7.5 mg twice daily) with placebo for 2 weeks each in 22 symptomatic patients with HFpEF who had objective evidence of exercise limitation (peak oxygen consumption at maximal exercise < 80% of normal range) in comparison with 22 similarly treated matched asymptomatic hypertensive volunteers. Ivabradine selectively reduced peak heart rate compared with placebo in the HFpEF (107 b.p.m. vs. 129 b.p.m.; $p < 0.0001$) and hypertensive (127 b.p.m. vs. 145 b.p.m.; $p = 0.003$) cohorts. However, submaximal exercise capacity was not enhanced but reduced by ivabradine vs. placebo, and the same was true for the change in peak oxygen consumption (–2.1 mL/min/kg vs. 0.9 mL/min/kg). The authors[87] state that the reasons underlying the discrepant results of their own and those of Kosmala et al[82] are unclear, but may be due to the different age of the study patients – 74.6 ± 5.9 years[87] vs. 66.5 ± 8.5 years.[82] Older patients have an advanced chronotropic incompetence and a diminished SV reserve (a largely fixed SV) and are therefore more sensitive to heart rate reduction. The larger mean resting heart rate reduction from 77 b.p.m. to 57 b.p.m. achieved with 7.5 mg ivabradine twice daily in these older patients[87] in comparison to the reduction of only 10 b.p.m. by ivabradine 5 mg twice daily in the younger patient group[82] might support this hypothesis.

Taken together, there is some evidence that ivabradine can improve exercise capacity and attenuate diastolic dysfunction in HFpEF patients, but further supporting evidence is needed.[88,89]

Acute/decompensated chronic HF
Limited study results
Also in patients with acute/decompensated HF,[90–92] ivabradine has been applied by oral route.[93,94] Sargento et al[94] studied ten consecutive patients with acute/decompensated HFrEF under

full standard treatment, an LVEF < 40% (mean 31.2 ± 9.2%), RR_{syst} > 90 mm Hg and sinus rhythm > 70 b.p.m. (admission: mean 88.3 ± 11.1 b.p.m.; immediately before ivabradine addition: 82.8 ± 13.9 b.p.m.). Ivabradine was given orally (5 mg b.i.d.; in patients > 75 years, a lower dose of 2.5 mg b.i.d. could be considered), with 60% of patients having started this therapy by the second day. Preexisting mean serum creatinine was 1.48 ± 0.6 mg/dL, and mean GFR_{MDRD} was 62.9 ± 29.8 mL/min/1.73 m². The mean dose of ivabradine at discharge was 9.5 ± 2.8 mg/day. Ivabradine treatment resulted in a reduction in heart rate by 10.7 ± 7.2 b.p.m. 24 h after starting treatment and by 16.3 ± 8.2 b.p.m. at discharge. RR_{syst} was significantly decreased 24 h after initiation of ivabradine (from 113.2 ± 17.4 mm Hg to 105.6 ± 13.6 mm Hg; $p = 0.008$), but diastolic and mean blood pressure were not. The surrogate marker Nt-ProBNP at baseline and heart rate correlated significantly ($p = 0.013$). At discharge, the NYHA class had fallen by one and two levels in 70% and 30% of patients, respectively. The subgroup whose NYHA class fell by two levels had lower heart rate values at discharge (69.7 ± 7.6 b.p.m. vs. 59.0 ± 3.6 b.p.m.; $p = 0.033$). None of the patients suspended ivabradine. There were no reports of hemodynamic deterioration because of symptomatic bradycardia or other adverse events.[94]

Lowering catecholamine-induced tachycardia by ivabradine

In those patients with acute/decompensated heart necessitating inotropes according to guidelines recommendations,[3] ivabradine via the oral route has effectively been tried to attenuate a detrimental heart rate increase triggered by inotropes used such as dobutamine.[95,96]

Specific forms of HF

Sinus tachycardia in cardiac transplant patients

Cardiac transplant patients often have a relatively high resting heart rate (> 90 b.p.m.) due to graft denervation. Several studies described an effective heart rate reduction in cardiac transplant patients with a beta-blocker, with diltiazem or with ivabradine.[97–99] However, there is no clear consensus about what the normal range of heart rate should be following heart transplantation and whether therapeutic heart rate reduction might be of prognostic relevance.[99]

Chronic or prolonged severe tachycardia in cardiac transplant patients – especially in combination with reduced pump function – can trigger cardiac decompensation and shock. Beta-blockers for control of tachycardia are only helpful when contractility of the heart is not severely impaired; otherwise, they bear the risk of further deterioration of heart function. In this situation, ivabradine might be helpful to control sinus tachycardia. Zwicker et al[100] report successful treatment with ivabradine of a heart transplant patient who developed cardiogenic shock due to long-acting tachycardia (sinus tachycardia of 120/min), with further deterioration of cardiac function after administration of the short-acting beta-blocker esmolol under invasive hemodynamic monitoring. Heart rate control by administration of increasing doses of ivabradine supported recovery from cardiogenic shock and led to an improvement in the patient's clinical condition as well as LV function during follow-up.[100]

Acute peripartum cardiomyopathy (PPCM)

High initial resting heart rate in a patient with PPCM indicates poor prognosis.[101] The proposed therapeutic strategy consists of treatment with standard HF medication.[102] In the absence of complete recovery and when beta-blocker uptitration is not possible and sinus rhythm is > 75 b.p.m., ivabradine can be given. Ivabradine should be tapered, when beta-blocker uptitration is possible and/or heart rate is < 60 b.p.m. After complete and sustained recovery of LV structure and function, ivabradine medication should be continued when sinus rhythm is > 75 b.p.m. despite beta-blocker uptitration.[102] An impressive improvement of clinical symptoms and cardiac function by additional ivabradine treatment has been described in 20 patients in a substudy of the PPCM registry.[103]

Tachycardia in cardiogenic shock complicating myocardial infarction

Patients with cardiogenic shock complicating myocardial infarction (post-AMI CS) usually show a high heart rate, often aggravated by catecholamine therapy. A case report[104] and a small randomized trial[105] documented the heart rate-lowering effect of ivabradine in post-AMI CS patients and also reported some beneficial therapeutic effects.

In the prospective randomized trial,[105] 58 patients with post-AMI CS in sinus rhythm and after primary percutaneous coronary intervention were treated either with standard medical treatment (28 patients) or with standard medical treatment plus ivabradine (30 patients; starting with 2.5 mg b.i.d.) given orally or – in mechanically ventilated patients – by nasogastric route. Heart rate in the ivabradine group fell from 97.2 ± 6.8 b.p.m. initially to 86.9 ± 4.8 b.p.m. after 1 week, to 79.8 ± 5.5 b.p.m. after 4 weeks and to 65.7 ± 9.8 b.p.m. after 6 months. In the control group, the respective values were 94.6 ± 6.0 b.p.m. initially (intergroup difference: not significant), 90.5 ± 4.6 b.p.m. after 1 week (intergroup difference: not significant), 87.0 ± 6.9 b.p.m. after 4 weeks (intergroup difference: $p < 0.005$) and 81.9 ± 7.5 b.p.m. after 6 months

(intergroup difference: $p < 0.001$). Better improvement in the ivabradine group occurred with respect to blood pressure stabilization, LVEF, LV diastolic dysfunction and NT-ProBNP. Two patients died in the ivabradine group, and four patients died in the control group. Patients in the ivabradine group did not experience adverse events.

Septic shock and multiple organ dysfunction syndrome (MODS)

Heart rate as a risk marker

An inadequately high resting heart rate – as a component of autonomic dysfunction – is a well-known phenomenon in patients with septic shock[106] and in critically ill patients with MODS[107] in general. High heart rate in MODS patients is of prognostic relevance: in a study with 89 patients with MODS of septic and of non-septic origin[108] (APACHE II score $\geq$ 20), median baseline heart rate was 83 b.p.m. in 28-day survivors and 92 b.p.m. in 28-day non-survivors ($p = 0.048$; aHR 2.3 for initial heart rate $\geq$ 90/< 90 b.p.m.).

Heart rate reduction by the short-acting beta-blocker esmolol

In a trial by Morelli et al,[109] 154 patients with septic shock and a heart rate of at least 95 b.p.m. were randomized either to a 96-h infusion with esmolol (25–2,000 mg/h) or to placebo. Esmolol reduced heart rate by 28 b.p.m. (control: –6 b.p.m.), and all esmolol patients did achieve the prespecified heart rate corridor of 80–94 b.p.m., which was the primary end point. In the control group, 28-day mortality was 80.5%, and in the esmolol group, 49.4% (aHR 0.39; 95% CI 0.26–0.59; $p < 0.001$).

Heart rate reduction by ivabradine

In the MODIFY trial (protocol[110]), we prospectively randomized 70 patients with MODS (APACHE II score $\geq$ 20) of septic and non-septic origin with an elevated heart rate $\geq$90 b.p.m. to either a standard therapy or a standard therapy plus a 4-day treatment with ivabradine given by the enteral route (up to 7.5 mg b.i.d.). Primary end point was proportion of patients with a reduction of heart rate by at least 10 b.p.m. In the ivabradine group, initial heart rate fell after the 4-day treatment from an initial value of > 100 b.p.m. to < 90 b.p.m.; 28-day mortality was not significantly different in both groups (Werdan et al, in preparation).

Heart rate, a risk marker or risk factor?

Future trials should answer the question whether the high heart rate as a component of septic cardiomyopathy[106] and

MODS[108] is indeed a risk factor and not only a risk marker, and whether lowering of a high resting heart rate can indeed lower mortality in these patients.

Bradycardia in out-of-hospital cardiac arrest (OHCA) patients indicates favorable prognosis

Bradycardia during targeted temperature management (TTM) of patients with Return-Of-Spontaneous-Circulation (ROSC) is a physiologic response to lower body temperature and has been associated with favorable outcome in smaller observational studies. This finding was confirmed in a large multicenter cohort of comatose ROSC patients with OHCA treated with TTM at 33°C (n = 447) and at 36°C (n = 430).[111] These findings therefore define spontaneous bradycardia during TTM as a novel, early marker in ROSC patients after OHCA. Whether active heart rate reduction, for example, by beta-blocker or ivabradine, might improve prognosis remains to be tested.

Beta-blocker and ivabradine in combination

The SHIFT was designed to demonstrate prognostic effects of ivabradine in already well-treated HF patients on standard medication (including beta-blockers), but 11% of the study cohort did not receive beta-blockers due to intolerance or contraindications. Subgroup analyses revealed that ivabradine treatment without concomitant beta-blockers in these patients achieved a significant outcome benefit with a relative reduction of the primary end point of 32%, compared to placebo.[112] Nevertheless, the drug is often used in combination with beta-blockers due to complementarity of action, which is described in the following paragraphs. Ivabradine has only little interactions with other cardiovascular drugs and can therefore be given together with the guideline-recommended standard medication for HF such as ACE inhibitors, beta-blockers, ARBs, MRAs, diuretics and cardiac glycosides.

Ivabradine fills the beta-blocker gap

In the attempt to achieve therapeutic heart rate reduction in HFrEF patients, a synergistic approach of beta-blocker and ivabradine is often necessary: many patients do tolerate only suboptimal but not the recommended full doses of a beta-blocker because of objective or subjective side effects. Therefore, an additional heart rate-reducing agent is necessary to achieve the goal. In the SHIFT,[112] 89% of the patients had beta-blockers, but only 26% of them were at the target dose, and only 56% had at least $\geq$ 50% of the target dose, irrespective of the specific beta-blocker used in this trial (46% carvedilol, 25% bisoprolol, 14% metoprolol

succinate, 10% metoprolol tartrate, 3% nebivolol, 2% other). The reasons for this suboptimal beta-blocker dosing were hypotension (44%), fatigue (32%), dyspnea (24%), dizziness (13%), bradycardia (6%) and others (9%). The reasons for nonprescription of beta-blocker in the 11% of the SHIFT patients despite strong guideline recommendation were COPD (37%), hypotension (17%), asthma (10%), cardiac decompensation (7%), dizziness or bradycardia (7%), fatigue (5%), Raynaud syndrome or peripheral arterial disease (5%) and others (13%). It is interesting to see that these absolute and relative contraindications to achieve full beta-blocker dosing are seen not only in the SHIFT with chronic HF patients[16] but also in other large ivabradine RCTs testing patients with stable coronary artery disease with LV dysfunction (BEAUTIFUL trial)[68] and without clinical HF (SIGNIFY trial).[19] These beta-blocker contraindications are also prohibiting "real-life" noninterventional ivabradine trials with patients with HFrEF[69] as well with chronic coronary artery disease.[70] Therefore, there is a clear gap in achieving full therapeutic heart rate reduction with beta-blockers alone in many HF patients. This gap can be filled by combination with ivabradine, a drug with a remarkably low side-effect profile. In the SHIFT,[16] significantly higher adverse event rates in the ivabradine group in comparison to the control group were only seen for symptomatic bradycardia (5% vs. 1%, drug withdrawal in 1% vs. < 0.02%), asymptomatic bradycardia (6% vs. 1%, drug withdrawal in 1% vs. < 1%), atrial fibrillation (9% vs. 8%, drug withdrawal in 4% vs. 3%, n.s.), phosphenes (3% vs. 1%, drug withdrawal in < 1% vs. < 1%, n.s.) and blurred vision (1% vs. < 1%, drug withdrawal in < 1% vs. 1%, n.s.). In the noninterventional INTENSIFY study[69] with addition of ivabradine for 4 months to standard HF medication, 2.9% of the 1,956 HFrEF patients reported at least one adverse event, most commonly affecting the heart (1.4%), the nervous system (0.5%) and the eyes (0.5%); bradycardia was detected in this study in 0.3% of patients (n = 5), and seen more common in the group with the baseline heart rate < 75 b.p.m.

Role of beta-blocker dose
It has been known for many years that the reduction in mortality of HFrEF patients by beta-blocker treatment shows stronger correlation with the achieved heart rate reduction than with the beta-blocker dosage used. The SHIFT study has now confirmed and extended this correlation in HFrEF patients with sinus rhythm ≥ 70 b.p.m. for ivabradine as well as for the combination of beta-blocker and ivabradine. The magnitude of heart rate reduction achieved by beta-blocker

plus ivabradine, rather than beta-blocker background dose, determines subsequent effect on outcome.[112] The effect of ivabradine on the primary composite end point of cardiovascular death or HF hospitalization is independent from the type of beta-blocker given.[113] Patients prescribed a combination of carvedilol – the most often used beta-blocker in the SHIFT study – and ivabradine had lower rates of primary composite end point (HR 0.80; 95% CI 0.68–0.94), HF hospitalization (HR 0.73; 95% CI 0.6–0.86) and cardiovascular hospitalization (HR 0.80; 95% CI 0.69–0.92) than patients under carvedilol and placebo.[113] The dose of carvedilol had no detectable effect, and there were no unexpected safety issues.[113]

Exercise tolerance: the CARVIVA trial
Not only prognosis but also exercise tolerance can be improved by the combination of beta-blocker and ivabradine in comparison to beta-blocker alone: in the CARVIVA HF trial[114] with 131 HF patients (NYHA II/II, LVEF 27 ± 4.9%), ivabradine as well as the combination of carvedilol plus ivabradine after 12 weeks of treatment improved exercise tolerance and QoL, but carvedilol alone did not, though in all three patient groups, heart rate was reduced, which was strongest in the combination group.

This can be explained by dominant negative effects of an increasing blockade of $beta_1$-adrenoceptors with higher doses of $beta_1$-selective beta-blockers. Such effects prevent upregulation of heart rate and cardiac output during physical exercise and result in reduced exercise capacity, which is additionally impaired by negative inotropic properties of beta-blockers. In contrast, treatment with ivabradine alone or in combination with low- or medium-dose beta-blockers allows adequate rise in heart rate with increasing sympathetic activation (induced by physical exercise), as ivabradine lacks any inhibitory effects on $beta_1$-adrenoceptors and maintains cardiac conduction and contractility.[115] Combination therapy therefore enables additive heart rate reduction without the negative effects that would be generated by high doses of an equivalent beta-blocker monotherapy.

"The heart rate goal"
The findings presented argue for a reduction of heart rate to < 60/min or at least for a reduction of 10 b.p.m. in patients with HFrEF and sinus rhythm of ≥ 75 b.p.m., either by beta-blocker alone or by the combination of beta-blocker plus ivabradine. For treatment, the lower heart rate limit is either 50 b.p.m. or symptomatic bradycardia. As many HFrEF patients under beta-blocker have a heart rate ≥ 75 b.p.m.,

there is a need for a combination therapy of beta-blocker plus ivabradine in these patients. For patients with chronic stable angina pectoris, a combination preparation (Implicor®) is now on the market for use, with a fixed combination of metoprolol tartrate and ivabradine (25/5 mg, 50/5 mg, 25/7.5 mg, 50/7.5 mg). In the opinion of the authors, similarly, a combination product of beta-blocker and ivabradine would also be desirable for the indication of chronic systolic HF.

Patient focus perspectives: quality of life (QoL)
QoL: a stepchild of HF therapy!
Reduction in mortality is important in chronic HF, but it is only a poor reflection of how HF patients experience their situation and what impact treatment may have on a patient's day-to-day life.[116] QoL – as reflected by symptoms and the impact of disease on social, emotional and occupational function – may be even more important than longevity. HF as a chronic disease impairs patients' QoL[117] to a similar extent as end-stage renal disease in a patient on chronic dialysis.[118] Table 5 shows representative QoL data from elderly HF patients (Table 5, A) in comparison to community-dwelling elderly (Table 5, B).[117]

Guideline-recommended HF medication is clearly focused on prolongation of life, but much less on improving QoL:[119,120] ACE inhibitors and ARBs,[120] beta-blockers[114,119–121] and also the aldosterone antagonist eplerenone[122] are neutral, or only modestly improve or at best delay the progressive worsening of QoL.

QoL improvement by ivabradine
Ivabradine, on the other hand, seems clearly to improve health-related QoL. In SHIFT, low health-related QoL is associated with an increased rate of cardiovascular death or hospital admission for HF.[116] Reduction of heart rate with ivabradine is associated with improved health-related QoL, as assessed by the Kansas City Cardiomyopathy Questionnaire. The magnitude of heart rate reduction is related to the extent of improvement in health-related QoL.[116] And also in the nonintervention INTENSIFY study, the mean value of the European quality of life-5 dimensions QOL index increased from 0.64 ± 0.28 to 0.79 ± 0.21 after a 4-month period of additional ivabradine treatment with standard HF treatment including beta-blockers.[69]

QoL: beta-blockers and ivabradine in comparison
A direct comparison of the effect of treatment with beta-blocker vs. ivabradine on QoL is presented in the APULIA study with 221 patients with typical symptoms and signs of HFrEF (< 50%) (NHYA II–IV; mean LVEF: $44 \pm 5\%$ in ivabradine group and $43 \pm 6\%$ in beta-blocker group; initial heart rate 72 ± 5 b.p.m. in ivabradine group and 72 ± 4 b.p.m. in beta-blocker group).[119] According to the new HF classification of the ESC,[3] these patients would now be classified as patients with HFmrEF. In addition to HF standard treatment without beta-blockers, 110 patients with contraindications to beta-blocker treatment received for 1 month ivabradine 5 mg b.i.d., and 111 patients received beta-blockers (50 patients bisoprolol 1.25 m b.i.d.; 51 patients carvedilol 6.25 mg b.i.d.). Ivabradine treatment as well as beta-blocker treatment (Table 5, C–F) was associated with a significant improvement of physical functioning (p 0.001 vs. p 0.01), physical role (p 0.001 vs. p 0.01), general health (p 0.001 vs. p 0.03) and mental health (p 0.001 vs. p 0.01). But only ivabradine, not beta-blockers achieved a significant improvement in body pain (p 0.001 vs. p 0.5), vitality (p 0.01 vs. p 0.44), social functioning (p 0.01 vs. p 0.92), emotional role (p 0.01 vs. p 0.85), physical component summaries (p 0.01 vs. p 0.52) and mental component summaries (p 0.01 vs. p 0.80) (Table 5, C–F). Thus, an improvement in global physical and in global mental activity was only achieved by ivabradine treatment, but not by beta-blocker treatment. With respect to improvement of health-related QoL, the sum of data clearly favors ivabradine over beta-blockers.

Ivabradine in the old patients
HF is a syndrome that predominantly affects the elderly (> 65 years), the old (> 75 years) and also the very old (> 85 years) patients. In these patient groups, drug efficacy and drug safety may be influenced by altered drug metabolism, by polypharmacy with drug interactions and by lower drug adherence. In view of this, the low side-effect profile of ivabradine proven in RCTs as well as in clinical practice (explained in the "Ivabradine fills the beta-blocker gap" section) is a great advantage.

The elderly patients in the SHIFT
In the SHIFT, an age group analysis was carried out with 6,505 patients, categorized into the age groups "< 53 years" (n = 1,522), "53 to < 60 years" (n = 1,521), "60 to < 69 years" (n = 1,750) and "≥ 69 years" (n = 1,712).[123] With advancing age, the percentage of women increased from 16% to 34%, as did the percentage of NYHA II/III from 45% to 59%, as well as the incidence of comorbidity, and creatinine clearance fell from 87 mL/min/1.73 m^2 to 63 mL/min/1.73 m^2. RR_{syst} rose with age from 118 mm Hg to 124 mm Hg, but heart rate fell from 81 b.p.m. to 79 b.p.m. The use of HF

Table 5 Health-related quality of life in elderly heart failure patients (A) in comparison to community-dwelling elderly (B), and impact of heart failure medication – ivabradine (C, D) vs. beta-blocker (E, F) – on health-related quality of life

Medical outcome	A: heart failure patients (n = 781), mean ± SD	B: community-dwelling elderly (n = 781), mean ± SD	p value: A vs. B	Medical outcome	C: IVA (n = 110), T0 mean	D: IVA (n = 110), T1 mean	p value: C vs. D	E: beta-blockers (n = 111), T0 mean	F: beta-blockers (n = 111), T1 mean	p value: E vs. F
Physical functioning	35 ± 26	67 ± 27	< 0.001	Physical functioning	63.5	77.2	0.001	64.5	72.3	0.01
Role limitations physical	19 ± 34	66 ± 41	< 0.001	Physical role	63.8	78.9	0.001	65.2	74.2	0.01
Bodily pain	66 ± 33	79 ± 22	< 0.001	**Body pain**	65.4	77.6	0.001	64.7	64.5	0.5
General health perceptions	44 ± 18	60 ± 19	< 0.001	General health	57.2	69.6	0.001	59.1	63.2	0.03
Vitality	40 ± 24	64 ± 19	< 0.001	**Vitality**	58.2	66.5	0.01	58.4	62.1	0.44
Social functioning	54 ± 31	79 ± 24	< 0.001	**Social functioning**	56.3	64.2	0.01	59.2	60.5	0.92
Role limitations emotional	51 ± 45	77 ± 37	< 0.001	**Emotional role**	55.8	65.3	0.01	59.4	59.8	0.85
Mental health	66 ± 23	75 ± 17	< 0.001	Mental health	55.2	61.3	0.001	55.7	57.1	0.01
Perceived health change	26 ± 24	46 ± 18	< 0.001	**Physical component summaries**	44.5	49.2	0.01	43.2	45.2	0.52
Well-being	**6.3 ± 1.8**	**7.2 ± 1.4**	**< 0.001**	**Mental component summaries**	49.7	53.5	0.01	49.9	50.1	0.80
Depression				Heart rate (b.p.m.)	72	63	0.001	72	67	0.01
Depressive symptoms[a]	39%	21%	< 0.001							
Depression scale[b]	15 ± 10	10 ± 9	< 0.001							

Notes: Columns 1–4: comparison of quality of life – as assessed by the Medical Outcome. Study 36-item General Health Survey (RAND-36) – in 781 patients with heart failure with 781 community-dwelling elderly. Modified from Lesman-Leegte et al.[117] Columns 5–11: quality of life improvement – as documented by the SF-36 questionnaire – by ivabradine and beta-blockers in comparison in heart failure patients. [a]Center for Epidemiological Studies-Depression scale ≥ 16.[117] [b]Center for Epidemiological Studies-Depression scale.[117] The bolding is to show those medical outcomes with a significant improvement by ivabradine, but no significant improvement by beta-blocker. Data in columns 1–4 are from Lesman-Lesman-Leegte I, Jaarsma T, Coyne JC, Hillege HL, van Veldhuisen DJ, Sanderman R. Quality of life and depressive symptoms in the elderly: a comparison between patients with heart failure and age- and gender-matched community controls. *J Card Fail.* 2009;15(1):17–23.[117] and columns 5–11 are from Riccioni G, Masciocco L, Benvenuto A, et al. Ivabradine improves quality of life in subjects with chronic heart failure compared to treatment with β-blockers: results of a multicentric observational APULIA study. *Pharmacology.* 2013;92(5–6):276–280.[119]
Abbreviations: IVA, ivabradine; SD, standard deviation.

medications declined with increasing age for beta-blockers from 93% to 85% and for those with the beta-blocker target dose from 27% to 18%, for MRAs from 68% to 54% and for cardiac glycosides from 30% to 17%, while the use of ACE inhibitors (~ 80%) and ARB (~ 15 %) remained fairly constant.

As expected, both age and heart rate separately contributed significantly to outcome. For each b.p.m. increase in heart rate, the relative risk of the primary end point (cardiovascular death and HF hospitalization) increased in the groups by 3.6%, 3.1%, 3.2% and 2.2%, respectively. Ivabradine uptitration reduced heart rate similarly in all age groups, by 11 b.p.m.

The primary end point was reduced by ivabradine in all age groups, ranging from 38% (HR 0.62; 95% CI 0.50–0.78; $p < 0.001$) in the youngest patients < 53 years to 16% (HR 0.84; 95% CI 0.71–0.99; $p = 0.035$) in the oldest. Adverse events as bradycardia and phosphenes did not increase with increasing age, and in the Holter substudy, there were no episodes of severe bradycardia and no clinically relevant pauses with ivabradine in any age group.

The elderly patients in the INTENSIFY nonintervention study

The results of the INTENSIFY study (explained in the "The INTENSIFY study: proof of concept in daily clinical practice" section) confirm the efficacy and safety of ivabradine across the age spectrum of patients with chronic HFrEF in daily practice:[69] the mean age of the INTENSIFY patients was 67 ± 11.7 years, with 750 patients being < 65 years, 967 being between 65 years and 80 years and 224 being > 80 years. Comparable effectiveness (alterations in NYHA classification and signs of decompensation), improvement in health-related QoL and tolerability were seen in all three age groups in this study.[69]

In the sum of data, ivabradine sustains its efficacy, low side-effect profile and patient adherence also in the old patients with HFrEF, and it is also safe when taking the comorbidity of the old patients into account.

Conclusion: the place of ivabradine in HF therapy

Especially in the elderly patients, HF is only one of a number of disease entities present. Therefore, medication for HF has to be considered within the scope of the total approach of disease management in the individual elderly patients. Cardiac drugs used should not interfere with other drugs and should not further impair but even improve health-related QoL which often is reduced because of comorbidities.

In the patients with HF, the ten most common conditions other than hypertension and ischemic heart disease are anemia, arrhythmias, cognitive dysfunction, depression, diabetes, musculoskeletal disorders, renal dysfunction, respiratory diseases, sleep disorders and thyroid disease.[124]

A multidisciplinary position statement identified five key steps (ARISE-HF) that could potentially improve clinical outcomes if applied in a systematic manner:[124]

1. Acknowledge multimorbidity as a clinical syndrome that is associated with poor health outcomes
2. Routinely profile (using a standardized protocol – adapted to the local health care system) all patients hospitalized with HF to determine the extent of concurrent multimorbidity
3. Identify individualized priorities and person-centered goals on the extent of concurrent multimorbidity
4. Support individualized, home-based, multidisciplinary, case management to supplement standard HF management, and
5. Evaluate health outcomes well beyond acute hospitalization and encompass all-cause events and a person-centered perspective in affected individuals.

With respect to our patients with HF, this means that our medication should not only prevent HF-related death and hospitalization but also improve QoL, which often is severely impaired due to the symptoms of HF. Further, our medication should not further deteriorate QoL by severe adverse events. And, we should know which target – symptomatic and/or prognostic? – we have to achieve.

Having this in mind, ivabradine is a good candidate for a HF drug: its QoL profile is above average, and its side-effect profile is below average. Many HFrEF patients under standard medical treatment inclusive of beta-blocker have a resting heart rate of ≥75 b.p.m. (Table 2) and therefore might benefit from additional ivabradine treatment (Table 3). In these patients, a reduction of heart rate should be achieved by additional ivabradine to ≤ 60 b.p.m. or at least a reduction by > 10 b.p.m. within 4 weeks. If this goal can be achieved, then we can tell the patient that his cardiovascular mortality risk within the next 2.5 years will be lowered by 17%, his HF mortality risk will be lowered by 39%, his HF hospitalization risk will be lowered by 30% and his health-related QoL will probably improve.

Disclosure

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