Is selective heart rate reduction a new therapeutic principle in heart failure?

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Summary

In industrialised countries, chronic heart failure affects 2–3% of the general population. It is an increasingly recognised cause of morbidity and mortality. In the past decades, a successful launch of new therapeutic means has led to improved outcomes, but the prognosis remains fairly poor. In patients with heart failure, high heart rates are a negative prognostic predictor and can cause heart failure *per se*. A direct association between heart rate and cardiovascular outcomes has been observed, in beta-blocker trials in particular.

Ivabradine, the bencyclobutane derivate S16257, is a highly selective heart-rate-lowering agent that acts by inhibiting the pacemaker ionic current I_f in sinoatrial node cells. Since the development of ivabradine, a drug with no apparent cardiovascular effects other than heart rate slowing, it has become possible to selectively explore the effects of heart rate lowering separate from other cardiovascular effects (e.g., negative inotropism among others). Furthermore, it has become possible to test the hypothesis of whether therapeutic heart rate modulation reduces morbidity and mortality in heart failure patients. This hypothesis was tested in the recently published **S**ystolic **H**eart failure treatment with the **IF** inhibitor ivabradine **T**rial (SHIFT).

Key words: ivabradine; S16257; heart failure; heart rate; clinical trial

Introduction

Heart rate is an important parameter of cardiovascular physiology. It is a primary determinant of cardiac output and of myocardial oxygen utilisation. Decades ago, heart rate slowing was first recognised as a useful strategy for preventing angina pectoris in subjects whose myocardial oxygen supply was limited due to coronary artery disease. Accordingly, this principle has become part of current clinical guidelines for the management of stable angina [1]. Moreover, more than 60 years ago, a retrospective study of the records of more than 22 000 US army officers serving during World War II suggested a direct relationship between heart rate and the likelihood of leaving the service for health reasons [2]. When tachycardia was persistent, survival was negatively impacted [3]. These officers had no evidence of heart disease, albeit inferred from relatively insensitive screening techniques available at that time. More recently, data from cross-sectional analyses of drug trials for secondary prevention suggested a benefit of heart rate slowing after acute myocardial infarction [4] and heart failure [5]. This suggested that heart rate is related, in a fundamental manner, to processes that determine survival, as an index of deleterious variations in vital status and/or, perhaps, as part of the pathologic process itself. If the latter would be the case, then therapeutic heart rate modulation may be useful in mitigating such processes and improving survival. These considerations are of paramount scientific and clinical interest, since with the development of ivabradine, a drug with no apparent cardiovascular effects other than heart rate slowing, it became possible to explore the effects of heart rate slowing independent of other cardiovascular effects of currently available drugs such as beta-blockers.

Heart rate as a risk factor for cardiovascular disease

A lot of evidence from epidemiological data has been published, demonstrating a strong predictive power of heart rate for cardiovascular morbidity and mortality, and indicating that the measurement of heart rate should be an important component of clinical examination and cardiovascular disease risk assessment (fig. 1) [6]. In spite of this evidence, accepted screening strategies for preventing cardiovascular diseases do not include routine assessment of resting heart rate. In the past decades, several large-scale clinical trials have

No financial support and no other potential conflict of interest relevant to this article was reported.

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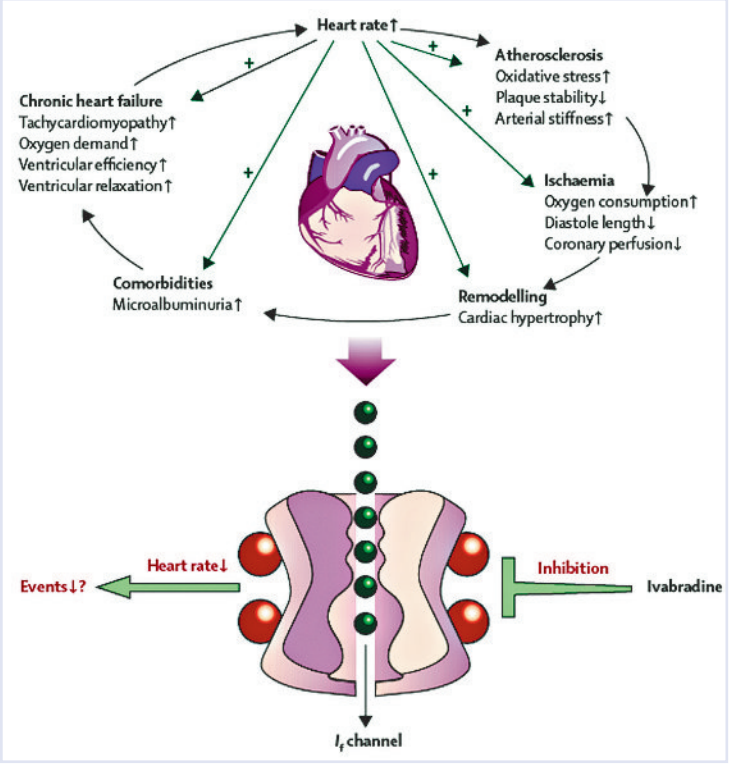
Figure 1
Potential role of heart rate in cardiovascular pathology.
High heart rate is a risk factor for the development of atherosclerosis. High heart rate leads to ischaemia, remodelling of heart and vessels, and contributes to co-morbidities in hypertension and in chronic heart failure. The figure shows potential mechanisms with experimental or clinical evidence. I_f channels are exclusively located in the sinoatrial node and are responsible for an inwardly directed current, which accelerates diastolic depolarisation of the sinus node and thus its pacemaker function. The I_f channel can be inhibited by ivabradine. Green dots = I_f current. Reprinted from Reil et al. [59], with permission from Elsevier.



shown that heart rate lowering with beta-adrenoreceptor antagonists significantly reduces future vascular events after myocardial infarction [7]. Unfortunately, the mechanisms involved have remained elusive as beta-blockers not only lower heart rate, but also exert negative inotropic and dromotropic effects in the heart [8] and alter peripheral vascular resistance as well as renin release [9]. Furthermore, data for patients with non-cardiac disease are lacking.

While studying the relationship between transient tachycardia and the development of hypertension, sixty years ago, Levy et al. were able to demonstrate that the prognostic power of high heart rate for the development of hypertension was equal to that of high blood pressure itself [2]. Many years later, these results were confirmed by Dyer et al. [10] in the Chicago cohort, and by Kannel et al. [11] in the Framingham study. In those studies, baseline heart rate showed an even stronger relationship with the level of blood pressure measured in subsequent years than bodyweight. Importantly, in several studies, the impact of heart rate on cardiovascular mortality persisted after excluding deaths occurring during the first years of follow-up, ruling out the hypothesis that heart rate was just an indicator of underlying chronic disease [7, 12]. A thorough review of the literature showed that over 30 articles confirmed the prognostic significance of heart rate for cardiovascular and/or all-cause mortality in individuals who were free of disease [6, 7]. However, the association between high heart rate and mortality appeared to be weaker in women, especially in the general population. However, it should be pointed out that in over half of those studies, a significant association between heart rate and total or cardiovascular mortality was also found among women [13].

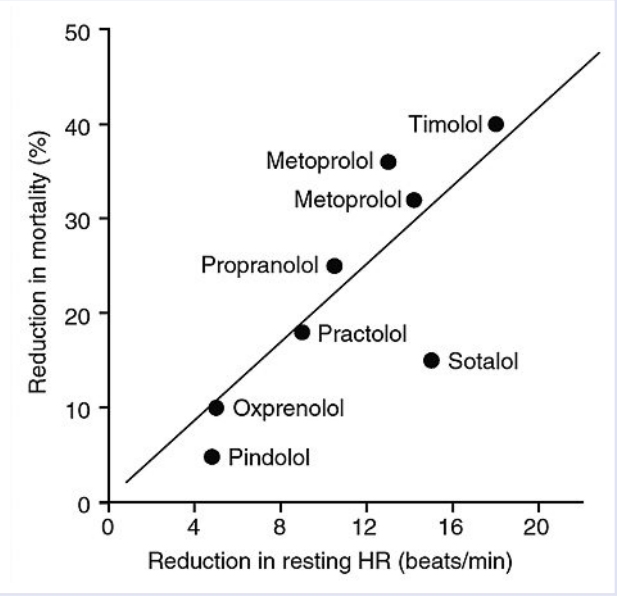
Role of heart rate in chronic heart failure

Chronic heart failure, affecting 2–3% of the general population in industrialised countries, is usually recognised as a serious and disabling disease [14]. The development of treatment options during the last decades has lead to improved outcomes, but the prognosis remains fairly poor [15, 16].

Neuroendocrine mechanisms, such as activation of the renin-angiotensin-aldosterone system as well as the sympathetic nervous system, are important in heart failure and contribute to the progression of ventricular dysfunction and remodelling. Indeed, a direct association between heart rate and cardiovascular outcomes has been observed [17, 18], in beta-blocker trials [5] in particular (fig. 2). Furthermore, epidemiological studies suggest that the risk of developing heart failure and sudden cardiac death increases with increasing heart rate [19, 20]. Hence, in patients with heart failure, high heart rate is a negative prognostic predictor and can cause heart failure *per se* [21]. In patients with tachycardia-induced heart failure, effective control of ventricular rate can improve left ventricular dysfunction within weeks [21].

The normal heart is able to enhance the cardiac output by an accelerated heart rate or by an increase in myocardial performance. Bowditch first described this so-called force–frequency relationship in 1871 [22]. This force–frequency relationship (strength–interval relationship or Treppe [staircase] phenomenon) was initially observed in isolated frog hearts [22]. However, more recent studies have demonstrated the presence of the force–frequency relationship also in isolated myocardium of non-failing human hearts [23]. The term force–frequency relationship usually describes the relationship between the stimulation rate and the developed force of the myocardium, which represents the amplitude between diastolic force and peak systolic force *in vitro* [23]. Therefore, alterations in the force–frequency relationship, as observed in the failing myocardium, may result from an altered systolic and/or diastolic function (fig. 3) [23]. In the failing human heart, the force–frequency relationship is flattened or inversed (fig. 3) [23–25]. A disturbed frequency-depend-

Figure 2
The relationship between mortality and resting heart rate with different beta-blocking drugs. A reduction in resting heart rate is associated with a reduction in mortality in patients with myocardial infarction (with permission from Böhm and Reil) [26].



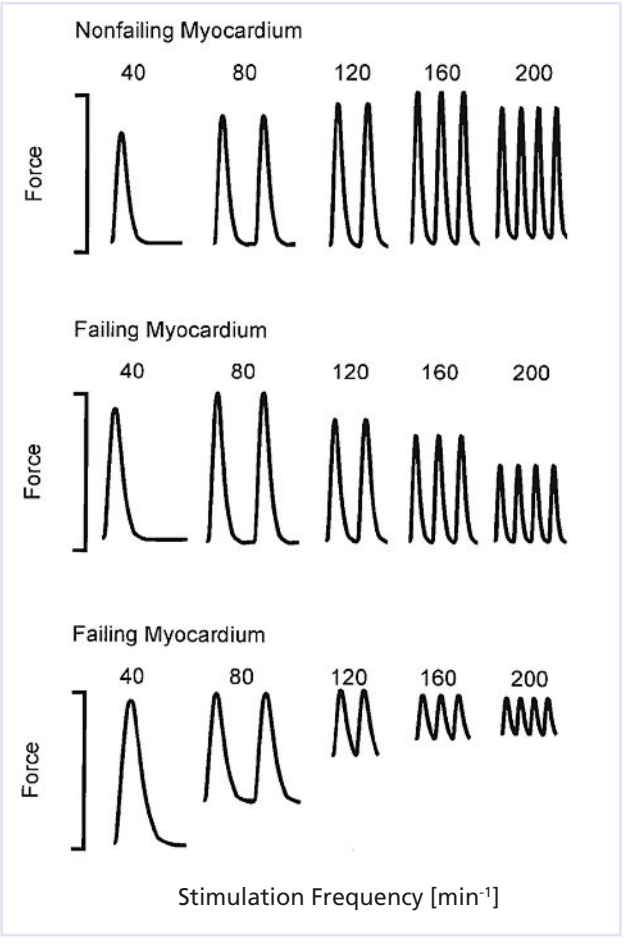
ent regulation of calcium transients or a disturbed calcium sensitivity may lead to this pathological force–frequency relationship [23]. While in the non-failing myocardium a frequency-dependent increase in isometric force and a corresponding increase in intracellular calcium transients are observed, the inversion of the force–frequency relationship is associated with a decline of the calcium transients [23]. This may indicate a decreased calcium release from the sarcoplasmatic reticulum at higher stimulation rates in the failing myocardium [23]. Moreover, in chronic heart failure, heart rate reduction attenuates the effect of energy starvation of the myocardium [14, 27].

These data are in line with findings from clinical trials using beta-blocking drugs. A meta-analysis by McAlister and colleagues including more than 19 000 patients in 23 beta-blocker trials revealed a 18% (Confidence interval [CI], 6–29%) relative reduction in the risk of death for every 5 beats/minute reduction of heart rate [28]. In daily clinical practice, however, uptitration of a beta-blocker to reduce a persistently elevated heart rate may lead to substantial adverse reactions [29, 30], which in turn limit beta-blocker therapy, leading to a significant number of patients without adequate heart rate reduction [31].

Ivabradine: a selective heart-rate-lowering drug

Ivabradine, the bencyclobutane derivate S16257, is a highly selective heart-rate-lowering agent that acts by inhibiting the pacemaker ionic current I_f in sinoatrial node cells (fig. 1). Although the I_f channel is predominately expressed in atrial cardiac tissue, the channel is

Figure 3
Force–frequency relationship in electrically stimulated myocardial trabeculae from a non-failing heart (upper panel) and two failing human hearts (middle and lower panels). Inversion of the force–frequency relationship can result from a frequency dependent decrease in systolic force (middle panel) or a frequency-dependent increase in diastolic force (lower panel), or from both mechanisms (with kind permission from Springer Science + Business Media and from Schillinger et al.) [23].

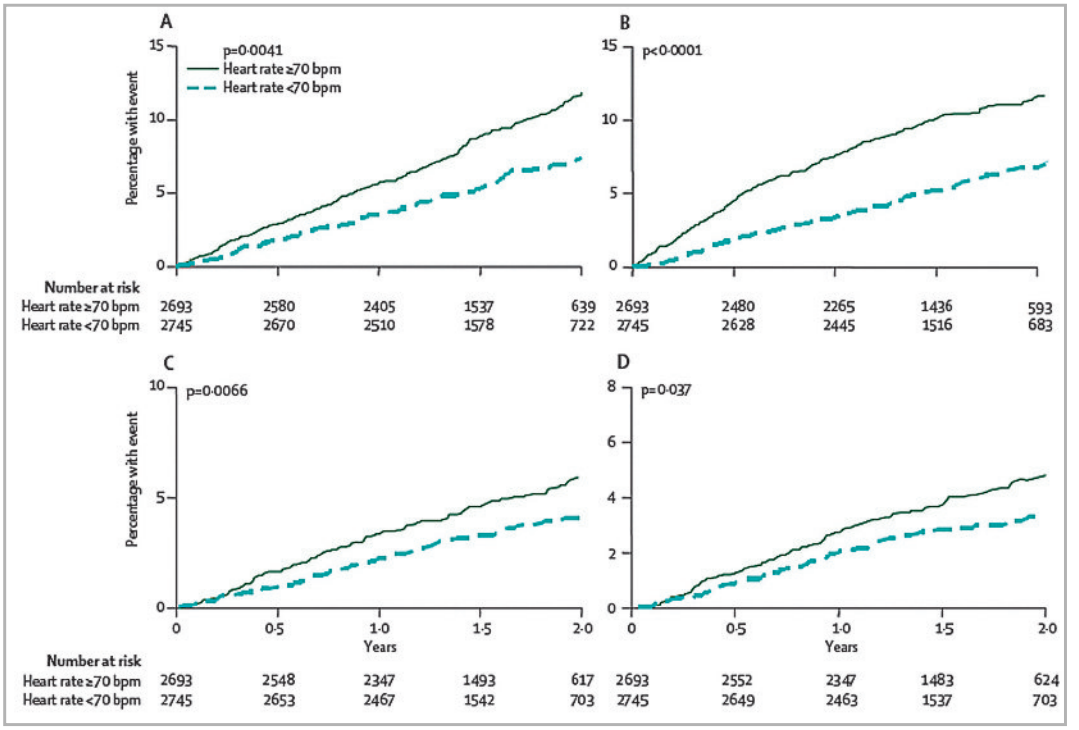


up-regulated in the human failing ventricular myocardium [32]. I_f channels are known to contribute to calcium overload in cardiac myocytes, leading to myocyte injury and adverse cardiac remodelling [33, 34]. At therapeutic concentrations, ivabradine has no effect on other cardiac ion channels or receptors, and it does not act via changing cAMP levels in cardiac cells [35–38]. Ivabradine, unlike conventional heart-rate-lowering agents including non-dihydropyridine calcium channel blockers and beta-blockers [1], has no direct effect on myocardial contractility, ventricular repolarisation, and intracardial conduction [39, 40]. Ivabradine does not reduce the left-ventricular ejection fraction in patients with impaired left-ventricular systolic function [41] and the drug has been shown to produce dose-dependent improvements, relative to a placebo, in exercise tolerance and time to development of exercise-induced ischemia in patients with chronic stable angina [42]. In another study, ivabradine was found to be non-

inferior to atenolol in terms of improvements in total exercise duration, time to limiting angina, and time to myocardial ischemia during exercise tolerance testing in stable angina pectoris [43]. The results of these trials set the stage for the BEAUTIFUL study (morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction), which was designed to compare ivabradine with placebo in patients with stable coronary artery disease and left-ventricular systolic dysfunction receiving optimal medical therapy. Hence, BEAUTIFUL was the first major outcome trial of a selective heart-rate-lowering agent [44]. Despite the decrease in heart rate through ivabradine, the primary endpoint (composite of cardiovascular death, admission to hospital for acute myocardial infarction, and admission to hospital for new-onset or worsening heart failure) did not differ between ivabradine and placebo, and analyses of the pre-specified subgroups did not reveal any differences between groups. However, patients with a heart rate <70 beats per minute (bpm) were significantly less admitted to hospital for myocardial infarction (Hazard ratio [HR] 0.64, 95% CI = 0.49–0.84, p = 0.001) or admitted to hospital for myocardial infarction or unstable angina (HR 0.78, 95% CI = 0.62–0.97, p = 0.023) and underwent fewer coronary revascularisations (HR 0.70, 95% CI = 0.52–0.93, p = 0.016) [45]. Most importantly, these benefits were recorded even though 84% of patients in this subset were already treated with beta-blockers. These data are in line with the observations from previous studies showing a relationship between resting heart rate and the risk of cardiovascular disease in patients with stable coronary heart disease with and without hypertension, as outlined above [11, 46]. Hence, this sets the stage for the analysis of cardiovascular outcomes in patients with a heart rate ≥70 bpm compared to those with a heart rate <70 bpm. To test the hypothesis that elevated resting heart rate at baseline is a marker for subsequent cardiovascular morbidity and mortality, an analysis was performed using the Cox proportional hazard models in the patients in the placebo group of the BEAUTIFUL study [47]. Patients with a heart rate of 70 bpm or greater were younger and had a lower left-ventricular ejection fraction and a higher systolic blood pressure than those with a heart rate of less than 70 bpm, and were more likely to have a higher NYHA functional class, to be smokers or diabetics, and less likely to be treated with beta-blockers [47].

In this analysis, a baseline heart rate of ≥70 bpm versus <70 bpm was associated with an increase in risk for all outcomes assessed (fig. 4). There was a 34% increase in the adjusted relative risk of cardiovascular death (p = 0.0041), a 53% increase in adjusted relative risk for admission to hospital for heart failure (p <0.0001), a 46% increase in risk of admission to hospital for fatal and non-fatal myocardial infarction (p = 0.0066), and a 38% increase in risk of coronary revas-

Figure 4
Kaplan-Meier time-to-event plots split by heart rate for **(A)** cardiovascular death, **(B)** admission to hospital for heart failure, **(C)** admission to hospital for myocardial infarction, and **(D)** coronary revascularisation. Reprinted from Fox et al. [47], with permission from Elseuier.



cularisation ($p = 0.037$) [47]. Analyses of heart rate as a continuous variable revealed that for every increase of 5 bpm, there was an 8% increase in cardiovascular death ($p = 0.0005$), a 16% increase in admission to hospital for heart failure ($p = 0.0001$), a 7% increase in admission to hospital for fatal and non-fatal myocardial infarction ($p = 0.052$), and an 8% increase in coronary revascularisation ($p = 0.034$) [47].

The question of whether patients with more severe impaired left-ventricular systolic function, symptomatic heart failure (NYHA II–IV) and all aetiologies of heart failure would benefit from heart-rate-lowering was investigated in a recent study named SHIFT (**S**ystolic **H**eart failure treatment with the **IF** inhibitor ivarbradine **T**rial) [14].

Results of SHIFT

SHIFT was designed as a multinational, event-driven, randomised, double-blind, placebo-controlled, parallel-group clinical trial including patients with moderate to severe heart failure and left-ventricular systolic dysfunction [14]. A total of 6558 adults with stable but symptomatic chronic heart failure (left-ventricular ejection fraction [LVEF] ≤35%), a resting heart rate ≥70 bpm in sinus-rhythm, and admission to hospital for decompensated heart failure within the previous 12 months were included and randomised. Main exclusion criteria were recent (<2 month) myocardial infarction, ventricular or atrioventricular pacing of more than 40% per day, and congenital or primary severe valvular heart disease [48]. Patients had to have been on stable heart failure therapy for at least four weeks. However, concomitant treatment with non-dihydropyridine calcium-channel blockers, class I anti-arrhythmics, and strong inhibitors of cytochrome P450 3A4 was not allowed. Eligible study patients were randomised to receive ivabradine in an adjusted-to-heart rate dose or a placebo on top of current standard therapy. The primary composite endpoint was cardiovascular death or hospitalisation for worsening heart failure. The prespecified, first secondary endpoint was the composite of cardiovascular death or hospital admission for worsening heart failure in patients receiving at least 50% of the target daily dose of a beta-blocker (as defined by the European Society of Cardiology guidelines) at randomisation [14, 48]. Further secondary endpoints were all-cause death, any cardiovascular death, hospital admission for worsening heart failure, all-cause admission to hospital, any cardiovascular admission and death from heart failure, and the composite of cardiovascular death, hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction [14, 48].

A total of 6558 patients were randomised and 6505 patients were analysed after a mean follow-up of 23 months. The mean age was 60.4 ± 11.4 years and 772 patients (11%) were ≥75 years old. Most patients were male (76%) and were of Caucasian origin (89%). Mean heart rate at inclusion was 79.9 ± 9.6 bpm and mean left-ventricular ejection fraction was 29 ± 5.1% [14]. Most of the patients suffered from ischemic heart disease (68%), however, most of the patients were in NYHA functional class II (49%) or III (50%). Concomitant medication included ACE inhibitors or angiotensin receptor blockers in 91% of the patients, beta-blockers in 89% and diuretics in 84%. However, only 26% of all patients achieved their beta-blocker target dose, but 56% of the patients received ≥50% of their target dose [14]. A total of 11% of the patients did not receive any

Table 1
Effects on the primary and major secondary endpoints in SHIFT. The data are the number of first events (%), hazard ratio (HR; 95% CI), and *p* values. Adapted from Swedberg et al. [14], reprinted with permission from Elsevier.

	Ivabradine group (n = 3241)	Placebo group (n = 3264)	HR (95% CI)	*p* value
Primary endpoint				
Cardiovascular death or hospital admission for worsening heart failure	793 (24%)	937 (29%)	0.82 (0.75–0.90)	<0.0001
Mortality endpoints				
All-cause mortality	503 (16%)	552 (17%)	0.90 (0.80–1.02)	0.092
Cardiovascular mortality	449 (14%)	491 (15%)	0.91 (0.80–1.03)	0.128
Death from heart failure	113 (3%)	151 (5%)	0.74 (0.58–0.94)	0.014
Other endpoints				
All-cause hospital admission	1231 (28%)	1356 (42%)	0.89 (0.82–0.96)	0.003
Hospital admission for worsening heart failure	514 (16%)	672 (21%)	0.74 (0.66–0.83)	<0.0001
Any cardiovascular hospital admission	977 (30%)	1122 (34%)	0.85 (0.78–0.92)	0.0002
Cardiovascular death, following hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction	825 (25%)	979 (30%)	0.82 (0.74–0.89)	<0.0001

beta-blocker. The main reasons for not receiving a beta-blocker were chronic obstructive lung disease, hypotension or asthma.

After 12 months of treatment, placebo-corrected heart rate was reduced by 9.1 (95% CI 8.5–9.7) bpm, with a mean dosage of 6.5 ± 1.6 mg BID. At the end of the study, the mean difference in heart rate was 8.1 (95% CI 7.5–8.7) bpm.

With this degree of heart rate slowing, a statistically significant reduction of the primary endpoint from 29% in the placebo group and 24% in the ivabradine group could be achieved (HR, 0.82; 95% CI 0.75–0.90; p <0.0001, table 1). This reduction of the primary endpoint was mainly driven by a reduction in hospital readmissions for worsening heart failure (16% in the ivabradine group vs 21% in the placebo groups, respectively, HR 0.74, 95% CI 0.58–0.94, p = 0.014, table 1) [14]. While death from a cardiovascular aetiology was not reduced significantly in the verum group (p = 0.128), death due to heart failure was significantly reduced in patients randomised to ivabradine (HR 0.74, 95% CI 0.58–0.94, table 1) [14]. Despite a reduction in heart rate of 15.5 ± 10.7 bpm in the subgroup of patients receiving at least 50% of the evidence-based target daily dose of a beta-blocker, the primary endpoint was not achieved (HR 0.90, 95% CI 0.77–1.04, p = 0.155). However, ivabradine reduced hospital admissions for heart failure significantly by 19% (HR 0.81, 95% CI 0.67–0.97, p = 0.021) [14]. Overall, fewer serious adverse events occurred in the ivabradine group (45% vs 48% in the placebo group, respectively, p = 0.025). However, bradycardia leading to permanent study withdrawal occurred in 48 patients (1%) taking ivabradine, compared to 10 patients (<1%) receiving placebo [14]. The occurrence of visual disturbances due to phosphenes is a well-known side effect of ivabradine [45]. However, in SHIFT, visual disturbances occurred in 89 patients (3%) randomised to ivabradine versus 17 patients (<1%) receiving placebo [14].

Discussion

In patients with heart failure, SHIFT demonstrated that ivabradine, if given on top of current standard heart failure therapy, is able to reduce major risks associated with heart failure. This improvement in outcome was mainly driven by a reduction in heart failure hospitalisations [14].

How should the results of this landmark clinical trial be translated into daily clinical practice?

Based on the findings of the previously published BEAUTIFUL study in patients with coronary artery disease [47] and the results of SHIFT [49], heart rate reduction can now be considered not only a marker of successful beta-blocker therapy in heart failure, but also a target for further therapy. Hence, an elevated heart rate is a marker of future morbidity and mortality in heart failure patients and a reduction of heart rate does improve the prognosis in these patients [49]. Indeed, an improved survival of patients with congestive heart failure (CHF) has been demonstrated in several large-scale beta-blocker trials with bisoprolol [50], carvedilol [51, 52] and metoprolol [53]. However, the question remains regarding what heart rate target should be reached. A retrospective analysis of COMET [54] revealed that a heart rate more than 68 bpm after four months of treatment predicts increased mortality (relative risk [RR] 1.333, 95% CI 1.152–1.542, p <0.0001) [55]. A *post hoc* analysis of the placebo group of MERIT-HF found an increased risk for total mortality (RR 1.51, 95% CI 1.12–2.05, p = 0.0047) and all-cause hospitalisations (RR 1.40, 95% CI 1.18–1.68, p = 0.001) in patients with heart rates more than 90 bpm [56]. However, the investigators found that the risk reduction after therapy with metoprolol was independent of baseline heart rate and independent of heart rate reduction or achieved heart rate after therapy [56]. These findings are in contrast to data from the Coronary Artery Surgery Study (CASS) [57]. This registry included 24 913 patients with suspected or proven coronary artery disease (CAD) and a median follow-up of 14.7 years. The investigators found an increase in all-cause mortality (hazard ratio [HR] 1.32, CI 1.19–1.47, p <0.0001) and cardiovascular mortality (HR 1.31, CI 1.15–1.48, p <0.0001) in patients with a heart rate more than 83 bpm at baseline [46]. In CASS, patients with a heart rate ≤62 bpm had a reduced risk for cardiovascular rehospitalisations [46].

The patient population in SHIFT suffered from advanced systolic heart failure, mainly in NYHA functional class II and III and was treated with optimal standard medical therapy, consisting of inhibitors of the renin-angiotensin-aldosterone system and a beta-blocker. However, only 26% of the patients received the target-dose of a beta-blocker and only 56% of the patients received at least 50% of the target-dose. In accordance with clinical experience, the main reason for the failure to adequately up-titrate a beta-blocker was hypotension. The mean blood pressure at enrolment in SHIFT averaged 122/76 mm Hg, which is comparable to the entry blood pressure in contemporary beta-blocker trials (table 2) [58]. Moreover, the mean heart rate at inclusion was 79.9 ± 9.6 bpm, a value comparable to that seen in beta-blocker-naïve patients in beta-blocker trials (table 2) [58]. It is therefore questionable, if the patients were already on maximal tolerated beta-blocker dosages. Although the results of contemporary beta-blocker trials included >1000 patients, ivabradine had no statistically significant effect on all-cause mortality (HR 0.90, CI 0.80–1.02, p = 0.092) (table 2).

It is of note that all patients presenting with heart failure symptoms need a careful diagnostic work-up including echocardiography to rule out a potential

Table 2
Baseline demographics in selected beta-blocker trials and in SHIFT. Adapted from Teerlink [58]. All-cause mortality assessed at different times between the trials. SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; bpm = beats per minute; LVEF = left-ventricular ejection fraction; NS = not statistically significant; * = metoprolol succinate; † = bisoprolol; ‡ = carvedilol; § = metoprolol tartrate; ¶ = ivabradine.

	Number of patients	Age (years)	Male (%)	SBP (mm Hg)	DBP (mm Hg)	HR (bpm)	LVEF (%)	All-cause mortality		
								Placebo or comparator	β-blocker	*p*
MERIT-HF	3991	64	77	130	78	83	28	11.0	7.2*	0.006
CIBIS-1	641	60	86	127	79	83	25	20.9	16.6†	NS
CIBIS-2	2647	61	80	130	80	80	28	17.3	11.8†	<0.0001
ANZ	415	67	80	–	–	–	29	12.5	9.7‡	NS
US Carvedilol	1094	58	77	116	73	84	23	7.8	3.2‡	<0.001
COPERNICUS	2289	63	79	123	76	83	20	18.5	11.4‡	0.001
COMET	3029	62	80	126	77	81	26	10.0§	8.3	0.002
SHIFT	6505	60	77	122	76	80	29	17.0	16.0¶	NS

reversible cause of heart failure, such as primary valvular disease.

The lack of benefit on all-cause mortality is certainly disappointing. Surprisingly, a very low use of device therapy in heart failure patients was noted. According to clinical guidelines, all patients in SHIFT would have qualified for an implantable cardioverter defibrillator (ICD), but in fact only 3% of the patients received such a device and only 1% received cardiac resynchronisation therapy [14]. This is likely to be related to the recruitment strategy in SHIFT: Two thirds of the patients were recruited in eastern Europe (66%) with no centres in the USA, and only 14% of the patients originated from western Europe [14]. However, SHIFT was not designed to show an improvement in all-cause mortality, since the study was powered for the composite primary endpoint of cardiovascular death or hospitalisation for worsening heart failure. In patients receiving at least 50% of the target beta-blocker dosage, there was no significant effect on the primary endpoint, although a modest reduction in heart failure hospitalisations was noted. These data are in line with the results of BEAUTIFUL, in that ivabradine in patients with stable coronary artery disease and a left-ventricular ejection fraction <40% showed no beneficial effects in terms of the composite primary endpoint consisting of cardiovascular death, hospital admission for acute myocardial infarction and hospital admission for new onset or worsening of heart failure. However, ivabradine reduced the coronary endpoints (admission to hospital for fatal and non-fatal myocardial infarction (HR 0.64, 95% CI 0.49–0.84, $p = 0.001$) and coronary revascularisation (0.70, 95% CI 0.52–0.93, $p = 0.016$), in patients with a heart rate of more than 70 bpm [45].

Since the majority of the patients in SHIFT were in NYHA functional class II (49%) or III (50%), the results of SHIFT are questionable in patients in NYHA functional class I or IV.

SHIFT has confirmed data from BEAUTIFUL, underscoring the importance of elevated heart rate as a risk factor in cardiovascular disease and heart failure in particular. Based on these results, clinicians should try to identify chronic heart failure patients with an elevated heart rate. Whether a strategy aiming for heart rate reduction provides direct haemodynamic benefit or reduces metabolic demand (or both) still remains elusive. Given the overwhelming data on beneficial clinical outcomes (all-cause mortality) in heart failure patients in particular, clinicians should primarily aim to up-titrate beta-blockers. Heart failure patients intolerant to adequate dosages of beta-blocking drugs due to hypotension and other side effects of these agents, with a persistently elevated heart rate, may benefit from additional therapy with ivabradine.

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