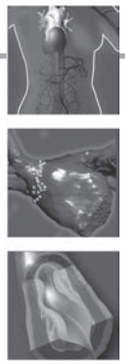

Ivabradine: the start of a SHIFT in heart failure treatment

Epidemiological studies and clinical trials clearly demonstrate a strong association between heart rate and risk in patients with a wide spectrum of cardiac diseases. The beneficial effects of β-blockers in heart failure and in acute myocardial infarction have long been thought to be related, at least in part, to heart rate lowering. Ivabradine is a selective inhibitor of the I_f ion channel found in cardiac pacemaker cells of the sinoatrial node. The drug reduces heart rate at rest and during exercise in patients in sinus rhythm while maintaining myocardial contractility and atrioventricular conduction. The development of this drug has helped to tease out the effect of heart rate lowering *per se*. The SHIFT study reported a 10 beats per minute reduction in heart rate on top of optimal therapy, associated with an 18% relative risk reduction for cardiovascular death and hospital admission for worsening heart failure ($p < 0.0001$), in patients with systolic heart failure, sinus rhythm and a heart rate of 70 beats per minute or above. Measuring and recording heart rate is essential in monitoring heart failure: it conveys important prognostic information. Further studies and analyses may identify a specific 'target' resting heart rate for such patients, and establish the effect of heart rate lowering in other groups of patients, including heart failure with normal ejection fraction, acute heart failure, and those with coronary disease, but normal left ventricular function.

KEYWORDS: β-blocker ▪ heart failure ▪ heart rate ▪ ivabradine ▪ SHIFT

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Heart rate as a marker of risk

Epidemiological studies and clinical trials have provided considerable evidence that an elevated resting heart rate is associated with increased cardiovascular morbidity and mortality, both in the general population and in patients with cardiovascular disease. This increased risk is independent of other established cardiovascular risk factors.

In the general population, 30-year follow-up of the Framingham epidemiological study reported that an increased resting heart rate was associated with an increase in all-cause mortality and cardiovascular mortality at all ages in both men and women [1].

More recently, three observational studies in subjects initially free of known cardiovascular disease reported adverse outcomes associated with increased resting heart rate. The Paris Prospective Study showed that an increase of 4 beats per minute (bpm) or more in resting heart rate over a 5-year period was associated with a 19% (95% CI: 4–37%; $p < 0.012$) increase in all-cause mortality [2]. A national population-based observational study in Finland (the FINRISK study) showed increased risk of cardiovascular disease with increasing heart rate [3], and in Norway the Nord-Trondelag County Health study reported that an increase in resting heart rate over a 10-year period was associated with increased risk of death from ischemic heart disease and also increased all-cause mortality compared with participants whose heart rate remained relatively stable over that decade [4].

Raised heart rate has also been shown to be an important marker of risk in patients with heart failure, coronary artery disease and hypertension.

■ Heart failure

In heart failure, the placebo groups in the landmark β-blocker trials provide data on the prognostic importance of resting heart rate, showing evidence of increased mortality with increasing baseline heart rate [5,6].

Earlier this year, a new *post hoc* analysis of data from the CHARM program, evaluating the angiotensin receptor blocker (ARB), candesartan, in chronic heart failure confirmed the predictive value of resting heart rate in patients with heart failure and sinus rhythm. Resting heart rate was an important independent predictor of outcome (with a 10 bpm increase in heart rate associated with a 6% [95% CI: 2–10%] increase in risk of death during the follow-up period), regardless of left ventricular ejection fraction or use of β-blockers [7]. The association was observed in both heart failure with systolic dysfunction and heart failure with normal ejection fraction

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(HFNEF). In contrast to sinus rhythm, in patients with atrial fibrillation at baseline, heart rate had no predictive value.

Further data on heart rate as a risk marker in heart failure come from the placebo arm of the SHIFT study in patients with chronic heart failure [8]. This study showed a continuous association between baseline heart rate and outcomes, across the whole follow-up period. The primary composite end point in this trial was cardiovascular death or first hospital admission for worsening heart failure. In the placebo group, patients in the highest quintile of resting heart rate (≥87 bpm) were at more than twofold higher risk for this end point than patients with the lowest heart rates (70 to <72 bpm; hazard ratio [HR]: 2.34; p < 0·0001). The risk of the combined end point increased by 16% for every 5 bpm increase from baseline heart rate (Figure 1).

■ Coronary artery disease

A similar association is seen in other cardiovascular diseases. In the CASS registry of patients with suspected or proven stable coronary artery disease [9], high resting heart rate was a predictor for total mortality and cardiovascular mortality, independent of other risk factors in a *post hoc* analysis. Patients with a resting heart rate of ≥83 bpm at baseline had a significantly higher risk of total mortality (HR: 1.32; p < 0.0001) and cardiovascular mortality (HR: 1.31; p < 0.0001) compared with those with a baseline resting heart rate of ≤62 bpm.

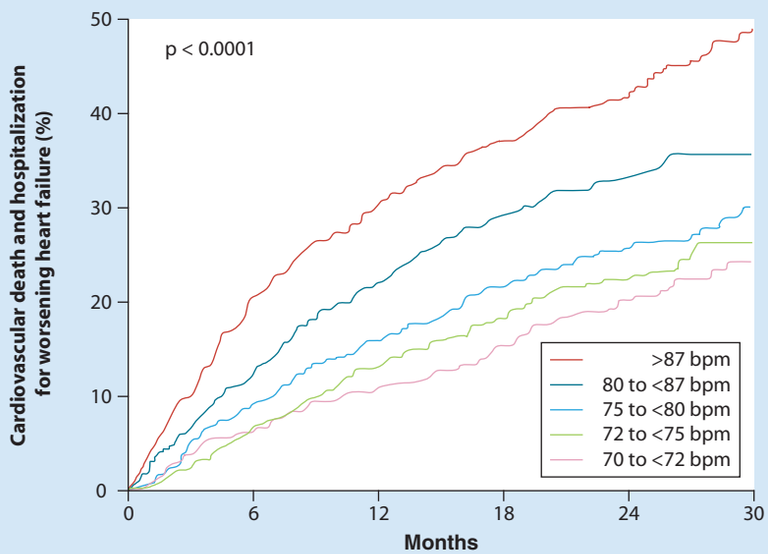
Likewise, *post hoc* analysis of the TNT trial involving well-treated patients with stable coronary artery disease found a linear relation between resting heart rate and cardiovascular outcomes. A heart rate of ≥70 bpm was an independent risk factor for all-cause mortality and a strong predictor of heart failure hospitalization compared with a heart rate of <70 bpm. With median follow-up of 4.9 years, the rate of major cardiovascular events was 11.9% in those with a baseline heart rate of ≥70 bpm and 8.8% in those with a baseline heart rate of <70 bpm (HR: 1.38 [95% CI: 1.19–1.59]; p<0.0001) [10].

The placebo group in the BEAUTIFUL trial of heart rate lowering in patients with stable coronary artery disease and left ventricular dysfunction (but not heart failure) confirms the association of heart rate with prognosis. Patients in this trial were on good background therapy [11]. Outcomes in patients with baseline heart rate ≥70 bpm were compared with those with heart rate <70 bpm in a prespecified analysis. Patients with the higher heart rates had increased risk of cardiovascular death (34%; p = 0.0041), admission to hospital for heart failure (53%; p < 0.0001), admission to hospital for myocardial infarction (46%; p = 0.0066) and coronary revascularization (38%; p = 0.037), after adjustment for other predictors of outcomes. For every increase of 5 bpm, there were increases in cardiovascular death (8%; p = 0.0005), admission to hospital for heart failure (16%; p < 0.0001), admission to hospital for myocardial infarction (7%; p = 0.052), and coronary revascularization (8%; p = 0.034).

In acute coronary syndromes, in-hospital mortality has been reported to increase with increasing admission heart rate [12,13], while 6-month [13] and 1-year [12] mortality have been reported to be related to heart rate at discharge. The Global Registry of Acute Coronary Events (GRACE Registry) reported that heart rate has independent prognostic value for in-hospital mortality in patients with acute coronary syndrome, with an odds ratio of 1.3 (95% CI: 1.16–1.48) per 30 bpm increase [14].

■ Hypertension & other cardiovascular disease

The prognostic importance of resting heart rate in hypertension was shown in the Framingham



Number at risk

>87 bpm	682	534	441	351	185	66
80 to <87 bpm	639	552	464	375	202	81
75 to <80 bpm	777	699	616	501	270	110
72 to <75 bpm	702	650	580	497	254	111
70 to <72 bpm	461	430	385	334	176	69

Figure 1. Association between resting heart rate (by quintiles) at baseline and the cumulative risk of the primary end point of cardiovascular death or heart failure hospitalization in the placebo arm of the SHIFT Study.
bpm: Beats per minute.
Reproduced with permission from [8].

study [15], as well as in several more contemporary studies [16–19]. For example, in the placebo arm of the SYST-EUR trial of older patients with systolic hypertension, heart rate >79 bpm was a significant predictor of all-cause, cardiovascular and noncardiovascular mortality [17]. In the INVEST study of elderly hypertensive patients with coronary artery disease, higher baseline and, in particular, follow-up resting heart rate were both associated with adverse outcomes [18].

In the UK, the Glasgow Blood Pressure Clinic study investigated the relationship between resting heart rate and outcomes in 4065 patients with mild-to-severe hypertension [19]. With mean follow-up of 897 days, heart rate was an independent predictor of all-cause, cardiovascular and ischemic heart disease mortality. Change in heart rate during follow-up was a better predictor of risk than baseline or final heart rate, with the highest risk seen in patients who increased their heart rate by ≥5 bpm during the follow-up period.

The Framingham Study reported that resting heart rate was associated with the risk of developing heart failure in a 38-year follow-up of those with coronary artery disease, hypertension or valvular heart disease [20]. The odds ratio for developing heart failure, adjusted for other covariates, over a 4-year period, was 1.15 (95% CI: 1.05–1.27; p = 0.002) for men and 1.10 (95% CI: 0.99–1.21; p = 0.07) for women.

Pathophysiological mechanisms

The precise pathophysiological mechanisms linking heart rate and cardiovascular outcomes are still uncertain. However, experimental studies show that raised heart rate is associated with vascular oxidative stress, endothelial dysfunction and acceleration of atherogenesis (**Figure 2**) [21,22].

Increased heart rate is associated with increased oxygen demand, reduced ventricular efficiency and reduced ventricular relaxation [23]. Mechanisms proposed to explain the association between raised heart rate and poorer outcomes in heart failure include induction of myocardial ischemia, precipitation of rhythm disturbances, acceleration of atherosclerosis and changes in the force-frequency relationship in heart failure, where force generation by the myocyte decreases as heart rate increases (unlike in the normal heart where force generation increases as heart rate increases) [24]. Heart rate reduction decreases energy expenditure, increases blood supply by prolonging diastole, improves force-frequency associations and reduces ventricular loading [24].

The evidence for clinical benefit of heart rate lowering

Raised heart rate is not only a marker of risk. There is increasing evidence that it is also a modifiable risk factor – that lowering a raised heart rate is associated with improved outcomes – particularly in heart failure and, most likely, also in coronary artery disease.

The beneficial effects of β-blockers in heart failure and in acute myocardial infarction have long been thought to be related, at least in part, to heart rate lowering. However, until recently, the specific effect of heart rate lowering has been unclear because β-blockers have multiple pharmacological effects and so it has not been possible to differentiate their effect on heart rate from other potential protective mechanisms, such as antiarrhythmic effects.

The development of the specific heart rate-lowering drug ivabradine has helped to tease out the effect of heart rate lowering *per se*. Ivabradine is a selective inhibitor of the I_f ion channel found in cardiac pacemaker cells of the sinoatrial node. The drug reduces heart rate at rest and during exercise in patients in sinus rhythm while maintaining myocardial contractility and atrioventricular conduction. Pleiotropic effects have been reported in some animal models, including reducing myocardial infarct size in ischemia and improved endothelium-dependent vasodilatation, but these effects have not clearly been demonstrated in humans [25].

The first major randomized controlled trial of ivabradine was the BEAUTIFUL trial in 11,000 patients with stable coronary artery disease and left ventricular dysfunction [26]. 87% of patients were receiving background β-blockers. In the overall trial population, ivabradine treatment did not significantly affect the primary composite end point (cardiovascular death, admission to hospital for acute myocardial infarction and admission to hospital for new onset or worsening heart failure). However, in a subgroup of patients with a baseline heart rate of 70 bpm or higher, while the primary end point was not met, treatment did reduce the risk of fatal and nonfatal myocardial infarction (a secondary end point) by 36% (p = 0.001), suggesting that lowering a raised heart rate may indeed be associated with improved outcomes. Importantly, it also showed the combination of a β-blocker and ivabradine to be well tolerated.

Meta-analysis of postmyocardial infarction β-blocker trials indicates that reduction in resting heart rate is an important determinant of clinical benefit [27,28]. In a meta-regression of randomized

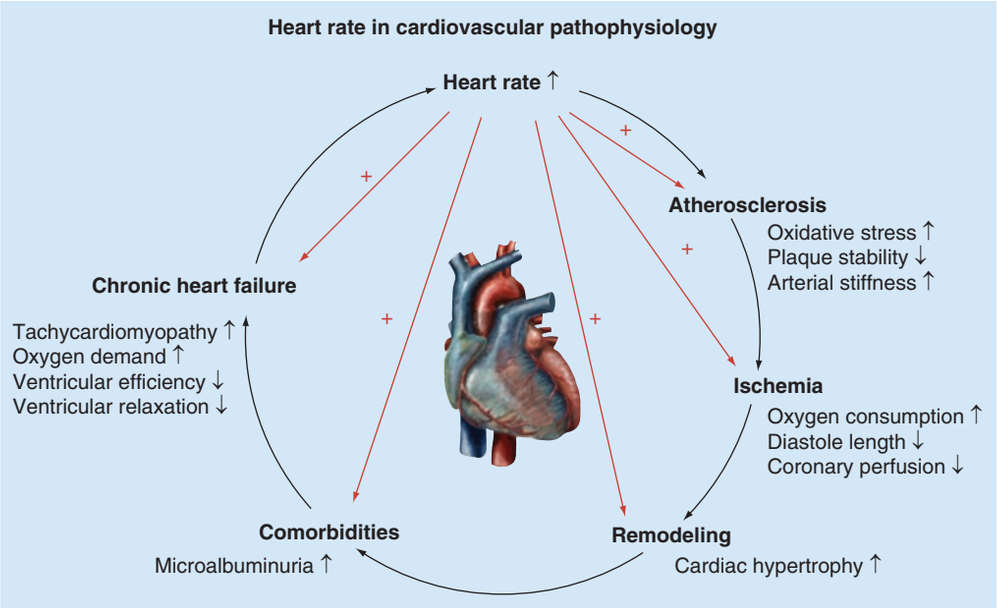


Figure 2. Potential pathophysiological effects of increased heart rate.
Reproduced with permission from [23].

trials, the beneficial effect of β-blockers and calcium channel blockers on mortality and nonfatal reinfarction in postmyocardial infarction patients was shown to be proportionally related to resting heart rate reduction [28]. Each 10 bpm reduction in resting heart rate was estimated to reduce the relative risk of cardiac death by about 30% ($p < 0.001$).

There are as yet no data suggesting that reducing heart rate is associated with improved outcome in hypertension.

■ Heart failure

Heart rate reduction has also been shown to contribute, certainly in part, to the clinical benefits of β-blockers in heart failure. Analysis of major trials showed that heart rate reduction with β-blockers (or other drugs) was associated with reduced mortality, while treatments that increased heart rate tended to increase mortality [29].

Multivariate *post hoc* analysis of the CIBIS II trial of bisoprolol in chronic heart failure [5] showed that patients in sinus rhythm in the lowest tertile of heart rate at baseline and with a heart rate reduction in the highest tertile at 2 months had the best prognosis (survival and reduction in hospital admissions). However, the survival benefit of β-blockade was similar at any level of heart rate at baseline and heart rate change, indicating that heart rate reduction is not the only mechanism responsible for β-blocker benefit in heart failure.

Further evidence of heart rate lowering as a major contributor to the clinical benefit of β-blockade in heart failure with systolic dysfunction comes from meta-analyses of clinical trials. An analysis of 35 trials of β-blockade in heart failure, involving around 23,000 patients, showed a close relationship between all-cause annualized mortality rate and heart rate and a strong correlation between change in heart rate and change in ejection fraction [30]. These data suggest that the magnitude of heart rate reduction may be more important than achieving a so-called 'target' dose of β-blocker (Figure 3).

A subsequent analysis of heart failure trials also showed a statistically significant association between the magnitude of heart rate reduction and survival benefit. For every 5 bpm reduction in heart rate, the relative risk of death decreased by 18% (95% CI: 6–29%). Survival benefit was not associated with β-blocker dosage [31].

Such observations appear to hold true in routine clinical practice also. A recent observational study on 654 patients with heart failure due to systolic dysfunction in sinus rhythm treated in a UK community heart failure clinic reported that the use of β-blocker, and resting heart rate (after attempted uptitration of β-blockers), were both independently associated with prognosis, but the actual maximal dose of β-blocker tolerated was not [32].

A study with the pure heart rate-lowering drug ivabradine has provided more definitive evidence on the benefit of heart rate lowering. The SHIFT randomized placebo-controlled trial investigated the use of ivabradine in 6558 patients with symptomatic heart failure and an ejection fraction of

≤35%, in sinus rhythm, and with a resting heart rate of at least 70 bpm [33]. Patients were on stable background therapy, including a β-blocker (if tolerated). Heart rate was reduced by 10.1 bpm after correction for placebo effects. The primary end point was a composite of cardiovascular death or hospital admission for worsening heart failure and over a median follow-up of 23 months there was an 18% relative risk reduction for this end point ($p < 0.0001$). This effect was mainly driven by hospital admissions for worsening heart failure, which were reduced by 26% ($p < 0.0001$), and deaths due to heart failure (relative risk reduction 26%; $p = 0.014$). Treatment benefit was related to heart rate reduction, with a direct association between heart rate achieved at 28 days and subsequent cardiac outcomes [8]. The greatest benefit of treatment was seen in patients with the highest heart rate at baseline.

SHIFT confirms the importance of heart rate in the pathophysiology and clinical course of heart failure. Treatment was generally well tolerated, with fewer serious adverse events in the ivabradine group than in the placebo group. The most common side effect of the drug was bradycardia, which led to drug withdrawal in 1.5% of patients compared with 0.3% of patients treated with placebo. The drug was initiated at 5 mg twice daily (b.i.d.), and could be up- or down-titrated to 7.5 mg b.i.d. or 2.5 mg b.i.d., respectively depending on heart rate response and side effects. At 1 year, the mean dose in the patients randomized to ivabradine was 6.5 mg b.i.d.

SHIFT substudies have added to our understanding of ivabradine's properties and the beneficial effects of heart rate lowering. An echocardiography substudy evaluated the effects of ivabradine on left ventricular remodeling, a feature of heart failure progression. Echocardiographic data at baseline and 8 months were available for 411 patients (ivabradine 208 patients; placebo 203 patients). Heart rate reduction was associated with reversal of cardiac remodeling, as shown by a significant reduction in left ventricular volumes and an increase in left ventricular ejection fraction [34].

Heart failure can have a major impact on health-related quality of life (health-related QoL) – perhaps more than most other chronic conditions. This will fluctuate depending on the stability of the heart failure syndrome, intercurrent illness, drug therapy, and social and psychological factors. Until recently, little attention was focused on trying to describe the impact of therapeutic interventions on health-related QoL in heart failure. Few data are available on the impact of, for example, angiotensin converting enzyme (ACE) inhibitors or β-blockers. More recent clinical trials of both drugs and devices have attempted to assess the effects of therapy on symptoms, functional level and health-related QoL, and to include the patient's own perspective in these assessments.

The effect of ivabradine on symptoms, functional class, and health-related QoL was evaluated in 1944 patients in a patient-reported outcomes substudy [35]. Interestingly, those with the lowest health-related QoL at baseline had the highest risk of a poor outcome. Ivabradine improved the score on the Kansas City Cardiomyopathy Questionnaire by 1.8 for the clinical summary score, and 2.4 for the overall summary score (placebo-corrected

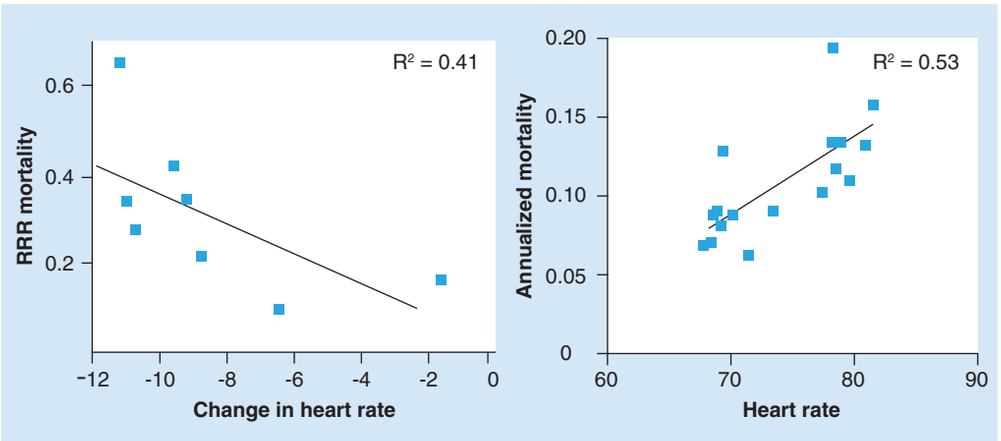


Figure 3. The association between heart rate and mortality, and between change in heart rate and relative risk reduction in mortality in a meta-analysis of trials of β-blockade in heart failure.
RRR: Relative risk reduction.
Reproduced with permission from [30].

p = 0.02 and p < 0.01, respectively). It was found that the greater the drop in heart rate, the greater the improvement in health-related QoL (Figure 4). These changes in health-related QoL were reflected in the improvement of physician-assessed New York Heart Association class, with data from the last (postbaseline) visit showing that 29.0% of ivabradine patients had improved New York Heart Association class compared with 24.2% in the placebo group (p = 0.016). Also, the patient-reported 'global' assessment improved in 65.9% of ivabradine patients compared with 61.3% of placebo patients (p = 0.034).

Such assessments provide a broader and, arguably, a more person-centered perspective on the effects of a therapy. This is particularly important when the primary goals of treatment include symptom relief, optimization of the activities of daily living, and minimization of the effect of the disease on an individual's sense of wellbeing.

Further evidence supporting the importance of heart rate reduction comes from a secondary *post hoc* analysis of the SHIFT data, [36] which showed that the effect of ivabradine was not significantly altered by background β-blocker dose: the data indicated that it was the amount of heart rate reduction by β-blocker plus ivabradine, rather than background β-blocker dose, that primarily determined the effect on outcomes.

Since the publication of SHIFT, Castagno and colleagues have suggested that the potential beneficial effects of digoxin in heart failure patients in sinus rhythm might, at least partially, be due to its heart rate-lowering effect: they cite evidence that the vagotonic effects of digoxin may lower heart rate in sinus rhythm by 4–7 bpm [37]. The principal trial supporting the use of digoxin in sinus rhythm in heart failure is the DIG trial, conducted at a time when β-blockers were considered contraindicated in heart failure [38].

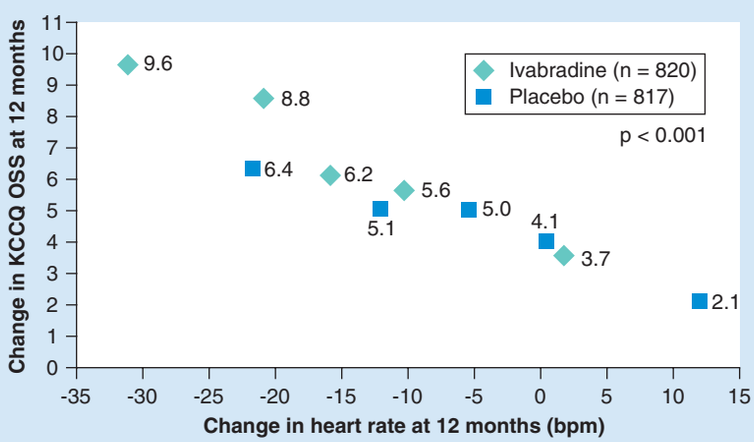


Figure 4. The association between change in heart rate from baseline to 12 months and improvement in health-related quality of life (as assessed by the overall summary score of the Kansas City Cardiomyopathy Questionnaire) in the placebo and ivabradine arms of the SHIFT Trial.
bpm: Beats per minute; KCCQ OOS: Kansas City Cardiomyopathy Questionnaire Overall Summary Score.
Reproduced with permission from [35].

Where we are now: reducing heart rate in systolic heart failure

Treatment of heart failure due to left ventricular systolic dysfunction has improved enormously in the past two decades. There is now a large evidence base for the use of neurohormonal antagonists – ACE inhibitors, ARBs, aldosterone antagonists and β-blockers – to improve both symptoms and prognosis. Device therapy (cardiac resynchronization therapy to improve efficiency of pumping and implantable cardioverter defibrillators to treat life-threatening arrhythmia) is also important in specific clinical situations. However, while modern therapy has certainly led to improved outcomes, heart failure remains a serious condition with a large impact on quality of life and life expectancy.

Only 5 years ago, a state-of-the-art article on heart rate in cardiovascular disease by Fox and colleagues noted that the importance of resting heart rate as a prognostic factor and potential therapeutic target had not been formally explored and so, despite suggestive evidence, was not generally accepted [39]. For heart failure, that is no longer the case. There are plenty of data now to suggest that heart rate – an easily measured variable – should be used in risk stratification. In addition, and particularly in light of the ivabradine data, heart rate can now be seen, not only as a prognostic marker, but also as a modifiable risk factor and treatment target, presenting clinicians with new opportunities to improve heart failure treatment.

The latest (2012) guidelines on heart failure management from the European Society of Cardiology include recommendation on the use of ivabradine [40]. In line with the SHIFT entry criteria, the European Society of Cardiology recommends ivabradine, added to standard therapy, to reduce the risk of heart failure hospitalization in patients in sinus rhythm with an ejection fraction ≤35%, a heart rate remaining ≥70 bpm, and persisting symptoms (New York Heart Association class II–IV) despite treatment with an evidence-based dose of β-blocker (or maximum tolerated

dose below that) or when patients are unable to tolerate a β-blocker.

Ivabradine is also included in the latest Australian and New Zealand heart failure guidelines which recommends the drug, as per the SHIFT entry criteria, when heart rate remains ≥70 bpm despite efforts to maximize dosage of background β-blockers [41]. Ivabradine is not yet marketed in the USA or Canada, but a 2011 update to the Canadian heart failure guideline notes that the results of SHIFT support its clinical use once approved [42].

In Europe, the regulatory authority, EMA, has approved ivabradine for use in heart failure patients with a heart rate ≥75 bpm in combination with standard therapy including β-blocker therapy or when β-blockade is contraindicated or not tolerated. This regulatory approval is in line with *post hoc* subgroup analysis of the SHIFT trial which showed statistically significant all-cause mortality benefit from ivabradine in patients with baseline heart rate ≥75 bpm [43]. In the overall SHIFT trial, there was no significant reduction in all-cause or cardiovascular mortality with ivabradine but in patients with heart rate ≥75 bpm, treatment significantly reduced both the primary composite end point (cardiovascular death or hospital admission for heart failure) and the secondary end points of all-cause death, cardiovascular death and death from heart failure. Risk reduction was related to the effect on heart rate after 28 days, with the best results in patients with heart rate <60 bpm or reductions >10 bpm.

β-blockers undoubtedly remain the first-choice drugs for reducing heart rate in patients with heart failure. Since the volte-face in the late 1990s when it was realized that, far from being dangerous, β-blockers have marked benefit in heart failure if used carefully, vast experience has accumulated with these drugs. Also, while heart rate lowering appears to be the predominant pharmacological effect in heart failure, other properties of β-blockers, beyond heart rate lowering, cannot be discounted as contributing to the drugs' beneficial clinical effects.

National and international guidelines [40,44,101] recommend β-blockers for all patients with heart failure due to left ventricular systolic dysfunction who do not have an absolute contraindication, with uptitration to the evidence-based doses that were used in the landmark clinical trials.

The intention of the SHIFT study was that all patients would be taking guideline doses of background β-blocker, if tolerated. In the event, only about one-quarter of patients reached the recommended European Society of Cardiology target dose, and about 50% achieved at least 50% of the target dose [33]. This usage of β-blocker closely mirrors clinical practice. One estimate, from trial data and registries, is that perhaps only 20–40% of patients in contemporary clinical practice – who are likely to be receiving more background therapy than in the original β-blocker trials – can be titrated to target β-blocker doses [36]. Another factor is that in clinical practice patients are often older and have more comorbidities than the selected patients in clinical trials.

In SHIFT, the most frequent reasons for not giving a β-blocker, or not achieving target dose, were chronic obstructive pulmonary disease, hypotension, fatigue, dyspnea, asthma, dizziness, cardiac decompensation and excessive bradycardia [36].

More important than the specific dose taken, if patients are not receiving adequate β-blockade there is a risk that they are not achieving good heart rate control and European registry data show this to be the case. Recent heart failure registries show that more than 50% of patients have heart rates of 70 bpm or higher, and around one-third of patients have heart rates of >75 bpm.

In 'real-life' heart failure populations, suboptimal heart rate control (heart rate ≥70 bpm) was found in around one-third of patients with heart failure due to systolic dysfunction in sinus rhythm, despite aggressive optimization of β-blocker therapy [45]. Another study, from a tertiary referral center, showed that 53% of patients who had been uptitrated to their maximum tolerated β-blocker dose (or were intolerant of β-blockers) had a heart rate of >70 bpm and 20% had a heart rate of >80 bpm [46].

There is, therefore, clearly scope for additional heart rate lowering with ivabradine for patients in sinus rhythm who are receiving their maximum dose of β-blocker but still have a heart rate of 70 bpm or more. The new drug also usefully extends heart rate-lowering treatment to patients who cannot take optimal β-blockers.

Ivabradine is easier to use than β-blockers and is better tolerated. Some clinicians might like the idea of initiating ivabradine in preference to β-blockade but there is no evidence for this and, though clearly important, heart rate lowering is unlikely to be the only beneficial effect of β-blockers in heart failure. Further trials will be needed before first-line use can be considered, except in patients who have an absolute contraindication to β-blockade.

The side-effect profile of ivabradine was reported in the SHIFT trial [29]. Bradycardia was more common in those on ivabradine than on placebo (10 vs 3%; p < 0.0001), although drug withdrawal was only necessary in 48 out of 3232 (1.5%) patients for this reason: 20 patients for symptomatic bradycardia and 28 patients for asymptomatic bradycardia (p = 0.002 and p < 0.0001 compared with placebo, respectively). The development of atrial fibrillation was more common in those on ivabradine (9 vs 8%; p = 0.012), as was phosphenes (3 vs 1% p < 0.0001), although withdrawal due to phosphenes was only necessary in seven out of 3232 (<1%) patients on ivabradine compared with three out of 3260 (<1%) patients on placebo (p = 0.224).

Conclusion

Heart rate is easily assessed in clinical practice. There is strong evidence that it is a marker of risk in the general population and in those with cardiovascular disease. There is now robust evidence in systolic heart failure that heart rate is not only a risk factor, but a risk marker, with intervention to reduce elevated heart rate translating into clinical benefit. The treatment of heart failure has improved markedly in recent years but the condition is still associated with considerable morbidity and mortality. The SHIFT trial with ivabradine has helped to establish the importance of heart rate lowering in heart failure. β-blockers remain the first-line drugs for reducing heart rate in systolic heart failure, with current guidelines recommending the titration of β-blocker dosage to the target doses used in the heart failure clinical trials for those without an absolute contraindication. There is growing evidence that it may be more important to target therapy to a specific heart rate, which may require the addition of ivabradine to optimally tolerated β-blockade in many patients. If a patient is unable to tolerate a β-blocker then ivabradine is likely to be of benefit in virtually all patients, if tolerated.

Future perspective

■ Target heart rate

As discussed, there is now considerable evidence for the concept of heart rate lowering as an important treatment for systolic heart failure. The emerging clinical data indicate that the way we view the use of β-blockers may have been over-simplistic.

Heart rate is currently not the determining factor when uptitrating β-blockers in heart failure. As recommended in the international guidelines, the emphasis has been on trying to achieve the target doses used in the major clinical trials. In these trials, β-blocker dose was not determined by clinical response or by heart-rate effects, but by a prespecified 'target' dose.

In view of the increasing data indicating that the heart rate achieved is more important than the actual dose of β-blocker [31,32,36], rather than concentrating on only attempting to reach the evidence-based β-blocker dosages, it is probably more logical to titrate treatment to a specific heart rate. This could be achieved with β-blockade, with the addition of ivabradine if the heart rate was still above this target.

It may be that clinical practice will move towards having a heart rate threshold for intervention and also a specified heart rate treatment target. Further work is needed to define a heart rate target, but it has been suggested that 55–65 bpm might be the target for many patients with systolic heart failure in sinus rhythm [32].

■ Heart failure with normal ejection fraction

HFNEF, or diastolic heart failure, is common – maybe 50% of patients have HFNEF – but the evidence base for treatment is much smaller than for heart failure with systolic dysfunction. Large trials of ACE inhibitors and ARBs in HFNEF were not conclusive. Most patients currently receive a diuretic, ACE inhibitor (or ARB) together with β-blocker or rate-limiting calcium channel blocker to reduce heart rate and increase time for ventricular filling to slow the heart, but there is no large randomized trial evidence base for this.

It will be important to investigate heart rate lowering in patients with HFNEF, especially in light of the new data [7] indicating that, in terms of prognostic value, heart rate is just as relevant in HFNEF as in systolic heart failure. There are currently no data on the use of ivabradine in HFNEF, although increased ventricular filling time should be of symptomatic benefit.

■ Acute heart failure

Most of the advances in heart failure care in recent years relate to chronic heart failure and there is a pressing need to improve the treatment of acute heart failure. β-blockers are used after stabilization in patients with acute heart failure; whether there is an advantage from additional heart rate reduction, or whether ivabradine might be useful in this situation for patients

who are unable to take β-blockers remains to be established. Acute heart failure is currently a contraindication to ivabradine therapy.

■ Prevention of cardiovascular disease

Raised heart rate has been shown to be a marker of risk in healthy individuals. At present, measurement of resting heart rate is recommended as part of the routine physical examination when assessing cardiovascular risk but there has been no trial of heart rate lowering *per se* for cardiovascular disease prevention in a healthy population and so guidelines do not recommend pharmacological lowering of heart rate in primary prevention [47].

Financial & competing interests disclosure

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Executive summary

- Increased heart rate is associated with increased cardiovascular risk in the general population, and in those with coronary artery disease, hypertension or heart failure.
- The mechanisms linking heart rate and cardiovascular outcomes are uncertain, but may include vascular oxidative stress, endothelial dysfunction, acceleration of atherosclerosis, induction of ischemia, precipitation of arrhythmia and changes in the force-frequency relationship in those with heart failure.
- There is good evidence that the benefit of β-blockade after myocardial infarction, and in heart failure, is proportional to the resting heart rate reduction on therapy.
- Ivabradine reduces heart rate by acting on the sinus node, and can be used with or without a β-blocker. The SHIFT study demonstrated a 10 beats per minute reduction in heart rate on top of optimal therapy, and was associated with an 18% relative risk reduction for cardiovascular death and hospital admission for worsening heart failure ($p < 0.0001$) in patients with systolic heart failure, sinus rhythm and a heart rate of 70 beats per minute or above.
- International clinical guidelines increasingly recommend the use of ivabradine for patients with systolic heart failure, sinus rhythm and a heart rate of 70 beats per minute or higher, despite optimal therapy with an angiotensin-converting enzyme inhibitor, β-blocker and aldosterone antagonist.
- Measuring and recording heart rate is essential in monitoring heart failure. The clinician should recognize that heart rate conveys important prognostic information and consider how best to reduce this risk factor for adverse outcomes. In the future, there may be a specific 'target' resting heart rate.

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