

## Review Article

# Elevated heart rate across cardiovascular continuum and its management

Ashok Punjabi<sup>1,2\*</sup>, Sheeba George<sup>3</sup>, Peyush Khara<sup>4</sup>, Sameer Srivastava<sup>5</sup>

<sup>1</sup>Krishna Cardiac Care Centre, Dadar, Mumbai, Maharashtra, India

<sup>2</sup>Lilavati Hospital and Research Centre, Bandra, Mumbai, Maharashtra, India

<sup>3</sup>Sree Mookambika Institute of Medical Sciences at Kulasekharam, Trivandrum, Kerala, India

<sup>4</sup>Nishat Hospital, Lucknow, Uttar Pradesh, India

<sup>5</sup>Department of Non-Invasive Cardiology, Fortis Escorts Heart Institute, New Delhi, India

**Received:** 05 July 2021

**Revised:** 06 September 2021

**Accepted:** 07 September 2021

**\*Correspondence:**

Dr. Ashok Punjabi,

E-mail: drpunjabi1956@gmail.com

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

## ABSTRACT

Elevated heart rate in both healthy individuals and patients with coronary artery disease (CAD), acute myocardial infarction (AMI) and heart failure poses a major risk factor for morbidity and mortality. This fact has further been supported by several studies pointing out to elevated resting heart rate as an important marker for this catastrophe necessitating a prompt therapeutic action plan, consisting of early detection and treatment of the risk factors, to achieve ideal heart rates (approximately 60 beats/minute) in patients which could stop or prevent the progression of the cardiovascular disease (CVD) continuum. Lowering heart rate by therapeutic interventions has shown favorable results, but most of the data so far is retrospective and limited to AMI and heart failure with beta-blocker treatment. Addition of newer drugs into the cardiac armamentarium, like ivabradine, a sinus node inhibitor acting by selective heart rate reduction, has shown several beneficial effects in a variety of conditions spanning from stable angina to heart failure. A consensus meeting was held at the national level wherein experts from various parts of the country discussed and reviewed the importance of heart rate lowering across CV continuum and addition of ivabradine for patients with chronic heart failure and chronic stable angina.

**Keywords:** Cardiovascular disease, Acute myocardial infarction, Chronic stable angina, Heart failure, Ivabradine

## INTRODUCTION

Heart rate (HR) is an indirect marker of metabolic rate. As there is limited energy available, each living organism competes for its share. The organism that utilizes the energy quickly is supposed to have a shorter life span<sup>1</sup>. Hence, there is an inverse semi-logarithmic relation between HR and life expectancy. For example, a Galapagos tortoise with an HR of just six beats per min (bpm) is expected to live about 177 years compared to the tiny arthropod *Daphnia* with an HR of ~180 bpm which is expected to live for only 30 days. These observations on life expectancy after slowing down the HR speculate

whether similar observations can be extrapolated to humans. Indeed, in an experimental set-up in humans, it was observed that decrease in HR from 70 to 60 bpm would increase life expectancy from 80 to 93.3 years, but still there has been a limited understanding as to how modern humans have stretched the boundaries of biology to increase life expectancy.<sup>2</sup>

National level consensus meeting was held in October 2018. Eight eminent experts (cardiologists) from different regions of the country attended the panel meeting and reviewed the various therapeutic options for the importance of HR lowering across the cardiovascular (CV)

continuum and addition of ivabradine in patients with chronic heart failure and chronic stable angina. The article reviews the discussion held during these meetings and provides a consensus roadmap for the treatment of elevated HR across the CV continuum.

## HEART RATE AS A MODIFIABLE RISK FACTOR

HR is a potent predictor of CV and all-cause morbidity and mortality in the general population and in patients with cardiovascular disease (CVD). The prognosis of increased HR is validated in the general population and across the CVD continuum from hypertension, atherosclerosis, myocardial infarction (MI) to heart failure (HF). It exists irrespective of age, CV risk factors, or comorbidities.<sup>3</sup> Increase in HR will result in a decrease in diastolic time and an increase in systolic time (increase in systolic time is proportionally less than the decrease in diastolic time); these changes result in decreased myocardial perfusion and increased left ventricular work that in the long run may result in left ventricular hypertrophy (LVH), myocardial damage, and congestive heart failure (CHF). Increased HR may also be associated with endothelial damage, oxidative stress, inflammation, and stiff vessels, all of which may contribute to aging, development of atherosclerosis, arterial hypertension, and a stiff aorta. A stiff aorta results in an increase in pulse wave velocity (PWV) and reflected wave velocity that result in systolic hypertension, decreased myocardial blood flow, and organ damage. All these effects of a fast HR on the CV system may contribute to the development of CVD and increase CV morbidity and mortality.<sup>4</sup>

HR should be viewed in the same light as other risk factors, such as elevated blood pressure (BP) or cholesterol, smoking, cardiac dysfunction, or diabetes. This integral association of HR with CV events has been documented in several epidemiological studies.<sup>5</sup> A consensus meeting of the European Society of Hypertension in 2005 identified 43 publications describing 39 population studies in the literature demonstrating the association between increased HR and all-cause mortality.<sup>6</sup> The national FINRISK study demonstrated a strong, graded relationship of elevated HR with incident CVD, which was stronger for fatal than nonfatal events. The relationship was independent of age, gender, total cholesterol, physical activity, systolic blood pressure (SBP), body mass index (BMI), and high-density lipoprotein cholesterol (HDL-C).<sup>7</sup> The incident HF increased by 11% with each 10 bpm increase in resting HR above the reference range.<sup>8</sup> Some studies examined the relationship between baseline resting HR and outcome in subjects with hypertension and showed increased CV and overall mortality after adjusting for BP and other relevant factors.<sup>9-13</sup> Evidences from the Framingham study demonstrated that coronary events increase with antecedent HR. It is also seen that resting HR >90 bpm increases risk for CVD mortality by two-fold in men and three-fold in women.<sup>7</sup> Increased resting HR represents an independent predictor of CV mortality in men, independent of age and the presence of hypertension.<sup>10</sup>

Even in patients with changing HR during antihypertensive treatment, development of HR  $\geq 84$  bpm was associated with a 55% greater risk of CV death and a 79% greater adjusted risk of all-cause mortality. This increase in mortality was independent of treatment modality and BP lowering.<sup>14</sup>

### Expert opinion

HR is a potent predictor of CV and all-cause mortality in the general population and CVD patients. The impact of increased HR on the prognosis is validated across the CVD continuum. Sudden death increased strikingly with HR in men of 35–64 years of age. Sudden cardiac death is more common in younger patients with increased HR. Women are at increased risk compared to men.

## PATHOPHYSIOLOGICAL ASPECTS

Under the normal conditions, it is the sinoatrial (SA) node that regulates the heart rhythm, and HR is regulated by sympathetic and parasympathetic input to the SA node. The accelerans nerve provides sympathetic input to the heart by releasing norepinephrine onto the cells of the SA node, and the vagus nerve provides parasympathetic input to the heart by releasing acetylcholine (ACh) onto SA node cells. Release of norepinephrine at the neuromuscular junction of the cardiac nerves shortens the repolarization period, thus speeding the rate of depolarization and contraction, which results in an increased HR. Parasympathetic stimulation originates from the cardio-inhibitory region with impulses traveling via the vagus nerve (cranial nerve X) and releases the neurotransmitter ACh at the neuromuscular junction. ACh slows HR by opening chemical-or ligand-gated potassium ion channels to slow the rate of spontaneous depolarization, which extends repolarization and increases the time before the next spontaneous depolarization occurs. Thus, stimulus to increase in HR is brought about by accelerans nerve and the stimulus to vagus nerve decreases it. During rest, both centers provide slight stimulation to the heart, contributing to autonomic tone. Without any nervous stimulation, the SA node would establish a sinus rhythm of approximately 100 bpm. Since resting rates are considerably less than this, it becomes evident that parasympathetic stimulation normally slows HR.<sup>15</sup>

Increased heart rate promotes various pathophysiological mechanisms like development of atherosclerosis, progression of heart failure, imbalance of oxygen supply, and demand along with obstruction in coronary flow resulting into increased incidences of myocardial ischemia or myocardial infarction; this explains the relation between heart rate and different cardiovascular conditions across the continuum.<sup>16</sup>

### Heart rate in atherosclerosis

Elevated HR contributes to the pathogenesis of vascular disease; this action is independent of the underlying

trigger. Early experiments on cynomolgus monkeys helped in identifying the link between elevated HR and atherosclerotic plaque development.<sup>1</sup> Further, it was also noticed that accelerated HR was associated with vascular oxidative stress, endothelial dysfunction, acceleration of atherogenesis, and vascular stiffness.<sup>3</sup>

In order to understand the role of HR in endothelial dysfunction and atherosclerotic lesions, basic knowledge of local hemodynamic forces imposed on the arterial wall is necessary. These forces include flow-generated shear stress and BP-derived tensile stress, also called as circumferential stress. Shear stress is the tangential forces due to the friction of the blood flowing on the endocardial surface, whereas tensile stress represents the BP-derived force imposed on the circumference of the arterial wall. Both stresses are sensed by endothelial mechanoreceptors but shear stress induces endothelial gene expression (stimulating constitutive nitric oxide synthase [cNOS], which produces nitric oxide) and tensile stress triggers a cascade of signaling molecules. Elevated tensile stress is thought to induce direct endothelial injury and to increase endothelial permeability to low-density lipoprotein (LDL) and to circulating inflammatory mediators. Very high HR (>120 bpm) by reducing the diastolic phase reduces the stroke volume and the cardiac output. Moderate tachycardia (close to 100 bpm) increases BP and the tensile stress and may promote endothelial injury and wall stiffness.<sup>17</sup>

### ***Heart rate and hypertension***

Hypertension is a known independent risk factor for CVD. Hypertensive patients generally have an elevated HR; this elevation is associated with development of hypertension in such patients. In the HARVEST study, 15% of hypertensive patients had a resting HR >85 bpm, and approximately 27% had a HR >80 bpm. Additionally, sustained elevations in HR over the course of the study were a strong predictor of developing hypertension necessitating pharmacologic therapy. Hence, HR should always be considered before selecting antihypertensive medications. Apart from high BP, HR also contributes for other CV risk factors and has increased risk of incident diabetes, even when controlled for BMI and physical activity. However, the relationship between HR and BP is more complicated when both central and peripheral BP is considered. The relationship between HR and BP is location-dependent. HR has a direct relationship with peripheral BP. However, an inverse relationship is reported between HR and central BP. These varying relationships may have important therapeutic implications when considering antihypertensive medications that affect HR.<sup>18</sup>

### ***Heart rate and myocardial infarction***

HR is the primary determinant of myocardial oxygen demand, and it also controls myocardial oxygen supply. Oxygen is thus utilized for production of energy. So, a

reduction in HR would lead to a significant reduction in oxygen demand at the cellular level, and in coronary artery disease (CAD), lack of oxygen is a critical pathogenetic factor.<sup>1</sup> High resting HR reflects an imbalance of the autonomic nervous system with increased sympathetic activity and/or reduced vagal activity. HR is a major determinant of myocardial oxygen consumption and energy utilization; furthermore, an increase in HR reduces the diastolic coronary perfusion time. By way of these two mechanisms, an increase in HR may trigger ischemic events. An increase in sympathetic activity and/or lowering of vagal activity are known to increase the risk of ventricular fibrillation in experimental studies on myocardial ischemia. It is well known that psychosocial stress-associated increases in HR can trigger the onset of AMI, in addition to sudden cardiac death.<sup>19</sup>

### ***Heart rate and heart failure***

Patients with HF are noticed to have an accelerated resting HR. The increased sympathetic activity, which is associated with a positive chronotropic stimulation in HF patients, leads to accelerated resting HR. HR may directly affect myocardial performance by alteration of oxygen consumption, reduction of diastolic filling and coronary perfusion by impairment of relaxation, and finally by pro-arrhythmic effects. Furthermore, high HR per se can cause HF. Retrospective data from sub-analyses of several HF trials demonstrated the importance of HR on mortality in patients with advanced systolic HF. The general trend of these trials clearly demonstrates that high HR at rest contributes to poor survival and represents a negative prognostic predictor. In the cardiac insufficiency bisoprolol study (CIBIS) and CIBIS II trials, HR and HR change both were significant predictors of mortality.<sup>3</sup> In patients with HF, mortality can be reduced by lowering HR. It improves left ventricular filling, favorably affecting the imbalance between myocardial oxygen supply and demand. It should also be noted that a few patients with HF continue to have persistently high HR despite treatment.<sup>20</sup>

### ***Heart rate and neurological outcomes***

Unlike the association between HR and CV mortality and morbidity in the general population and patients with CVD, there is no association known for HR and neurological disease and ischemic stroke. As a consequence of a broad range of experimental data demonstrating a close link between HR and vascular function and phenotype, recent studies focused on the effects of HR reduction on cerebral vasculature and circulation. Inspired by these findings, a post hoc analysis of the prevention regimen for effectively avoiding second stroke (PROFESS) trial was performed, wherein patients after a first stroke and a baseline HR  $\geq$ 76 bpm were found to have a higher risk of total death, vascular death, and non-vascular death. No significant association was found with recurrent stroke, MI, and new onset or worsening CHF. A striking finding was a significant association

between HR and functional neurological outcomes after a recurrent stroke. Although preliminary and hypothesis-generating, these results identify HR as a mediator of cerebrovascular effects and may suggest HR as a potential novel target for intervention to improve cerebrovascular function after ischemic events.<sup>3</sup>

**ASSESSMENT OF HEART RATE**

In order to maintain the basal metabolic rate, HR keeps on changing and adjusting in response to the body. A number of different metrics are used to describe HR, such as resting HR, maximum HR (highest HR an individual can achieve), and HR reserve (difference between a person's measured or predicted maximum HR and resting HR)

The basal or resting HR is defined as the HR when a person is awake, in a neutrally temperate environment, and has not been a subject to any recent exertion or stimulation, such as stress or surprise. Resting HR is central to cardiac output and is influenced by changes occurring in numerous diseases. It predicts longevity and CVD, including HF.<sup>21</sup> Resting HR is an easily measurable CV parameter, but is subject to high variability. According to the consensus panel of the European Society of Hypertension, studies focusing on HR should be taken into account for all possible sources of variability as shown in Table 1.

**Table 1: Sources of variability in resting heart rate.**

Source	Specifications
Resting period before measurement	At least five minutes to achieve a stable hemodynamic condition
Environmental conditions	-
Method of measurement	Pulse palpation versus electrocardiogram (ECG)
Number of readings	Minimum of two measurements required
Duration of measurement	15 seconds to one minute
Position of the body	Sitting or half supine
Nature of the observer	

To minimize the effects of these confounding factors, the measurement of this clinical variable should be strictly standardized. Exercise, alcohol, nicotine, and coffee should be avoided in the hours preceding measurement. Electrocardiography, pulse oximetry, or other monitoring methods are used for measurement of HR. The simplest and most common method is pulse palpitation. Arteries like carotid, subclavian, and femoral are already identified as sites for pulse palpitation, but the most commonly used is radial artery.<sup>22</sup> Pulse counting for 60 seconds is recommended, but in clinical setting 60 is uncommon and hence a reading of 15 or 30 seconds is generally extrapolated.<sup>23</sup> However, a palpable delay, from the radial to the femoral pulse, suggests coarctation of the aorta or at

least an aortic obstruction below the take-off of the left subclavian artery.<sup>24</sup> Little is known about the predictive value of out-of-office HR measurement. HR recorded with ambulatory monitoring or self-measured at home may provide useful information.<sup>22</sup>

**Correlation of different cardiac conditions and heart rate**

Resting HR is an independent predictor of CAD, stroke, sudden death, and non-CVD over all of the studies combined. HR causes myocardial oxygen consumption. Slowing of HR would lead to a significant reduction in oxygen demand and thus in CAD. It is also observed that high HR shortens diastole and hence reduces coronary flow, even in the absence of coronary lesions. Elevated HR is also associated with an accelerated progression of arterial stiffness in normotensive and hypertensive subjects. Elevated HR favors coronary atherosclerosis. In patients with HF, elevated HR increases myocardial load and oxygen consumption, thus being potentially pro-ischemic.<sup>1</sup> Every 1 bpm increase in resting HR, increases the risk for HF by 4%.<sup>25</sup> Resting HR of more than 80 bpm could cause myocardial dysfunction, which further deteriorates HF.<sup>26</sup>

In existing CVD, a higher HR has been associated with worse clinical outcomes. Risk is continuous with increase in resting HR above 60 bpm. This has been linked to premature mortality through a multitude of actions, including its detrimental effects on progression of coronary atherosclerosis, on occurrence of myocardial ischemia and ventricular arrhythmia, on LVEF, and on circulating levels of inflammatory markers.<sup>27</sup>

The prognostic importance of resting HR for morbidity and mortality in patients without CVD also applies to populations with established CAD and after MI. Studies such as the coronary artery surgery study (CASS) and the morbidity-mortality evaluation of the I<sub>f</sub> inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) study demonstrated a positive association between increased resting HR and CV mortality. In the CASS registry, which included 24, 913 men and women with suspected or proven CAD with a median follow-up time of 14.7 years, resting HR was found to be a predictor of overall and CV mortality. In BEAUTIFUL, patients with CAD and left ventricular systolic dysfunction and a resting HR >70 bpm displayed increased CV mortality as well as an increased risk for hospitalization due to HF, MI, or need for coronary revascularization. Moreover, increased resting HR was associated with coronary vascular events. This finding may be explained by increased occurrence of coronary plaque disruption given that HR is a predictor for instability of coronary plaque.<sup>3,4</sup>

**Expert opinions**

Increased HR at the time of presentation of (acute coronary syndrome (ACS) is very critical in determining the risk

associated. Higher HR at the time of acute myocardial infarction (AMI) increases chances of mortality at 3-and 6-months post MI.

### ACHIEVING OPTIMAL HEART RATE

Table 2 summarizes the various benefits of achieving optimal heart rate.<sup>28-38</sup> HR is not only of prognostic importance, but is also an established therapeutic target. Pharmacological therapies that reduce HR are associated with improved coronary perfusion, reduced myocardial oxygen consumption, enhanced left ventricular function, and beneficial left ventricular remodeling. These functional changes translate into improvements in exercise capacity, cardiac function, angina, and quality of life.<sup>39</sup>

**Table 2: Benefits of achieving optimal heart rate.**

Effect	Reference
<b>Reduction of vascular oxidative stress</b>	28
<b>Restoration of endothelial function</b>	28, 29
<b>Restoration of erectile function</b>	28-30
<b>Reduction of vascular wall stress</b>	31
<b>Inhibition of atherogenesis</b>	28, 30, 32, 33
<b>Stimulation of angiogenesis</b>	34, 35
<b>Reduction of myocardial ischemia</b>	36-38

Certain therapeutic considerations in patients with an underlying disease and having fast HR can be mild-to-moderate regular aerobic exercise, good knowledge about the condition, and common sense. Apparently in healthy individuals, lifestyle modification includes regular aerobic exercise (avoid excessive exercise), maintaining normal body weight, regular follow-ups with doctors and avoiding stimulants such as caffeine, alcohol, tobacco, and others.<sup>4</sup>

### Pharmacotherapy

Reduction in HR can be brought by several agents such as beta-blockers, calcium channel blockers (CCB), and selective I<sub>f</sub> channel inhibitors such as ivabradine.<sup>40</sup> Beta-blockers play a vital role in the management of CVD, including hypertension and chronic HF. They vary with regards to several pharmacologic properties, including  $\beta$ 1/ $\beta$ 2 selectivity, intrinsic sympathomimetic activity (ISA), and vasodilation. The three generations of beta-blockers differ with respect to their selectivity of blocking receptors and CV protective effects.<sup>41</sup> Once beta-blockers bind to the  $\beta$ 1 and  $\beta$ 2 receptors, they block the effects of catecholamines, epinephrine, and norepinephrine. Therefore, the chronotropic and inotropic effects on the heart undergo inhibition, and as a result HR slows down. Beta-blockers also decrease BP via decreased renin and reduced cardiac output. Beta-blocker use also improves angina by decreasing the oxygen demand, which is due to the negative chronotropic and inotropic effects. They also prolong the atrial refractory periods and have a potent antiarrhythmic effect.<sup>42</sup> A meta-analysis of 18 randomized,

long-term, placebo-controlled hypertension trials in almost 19,000 patients found that treatment with beta-blockers was associated with a reduction in the risk of stroke, coronary heart disease, and HF by 29%, 7%, and 42%, respectively.<sup>41</sup> There are differences in their pharmacokinetic, pharmacodynamic, and side-effect profiles, which will have important effects on tolerability and the maximum prescribed dose.<sup>43</sup> Evidence suggests that  $\beta$ 1-selective agents may be more effective than nonselective agents.<sup>41</sup> Atenolol seems inferior to other antihypertensive drugs in reducing stroke and total mortality.<sup>43</sup>

As beta receptors are found all over the body and induce a broad range of physiologic effects, blockage of these receptors with beta-blocker medications can lead to adverse effects. Bradycardia and hypotension are common. Fatigue, dizziness, nausea, and constipation are also widely reported. Some patients report sexual dysfunction and erectile dysfunction. Beta-blockers, especially in patients with cardiac risk factors, carry a risk of heart block.<sup>42</sup> Another major concern with the use of beta-blockers is failure to reach target dose. In a study including 1919 outpatients with HF of New York Heart Association (NYHA) classes II-IV and left ventricular ejection fraction (LVEF) <40%, it was observed that target doses were reached in only 18% of beta-blocker users. It was also noted that only 47% of patients were able to reach 50% of the target dose.<sup>44</sup> In the organized program to initiate lifesaving treatment in hospitalized patients with heart failure (OPTIMIZE-HF) trial that enrolled 5791 patients with HF, it was noted that in the initial 60–90 days post discharge, more than 65% of patients had no change in their beta-blocker doses.<sup>45</sup>

Efforts are needed to help understand and overcome this beta-blocker titration gap. Combination therapy with other antihypertensive agents may be useful. The benefits of combination therapy in comparison with monotherapy include a synergistic enhancement of antihypertensive effects of each drug and a potential reduction of side-effects if each drug is used at a lower dose. Beta-blockers have been used in combination with short-acting dihydropyridine CCBs to reduce tachycardia, whereas non-dihydropyridine CCBs like verapamil, diuretic agents, and angiotensin-converting enzyme inhibitor should be avoided in the combination. However, adding an alpha-blocker to a beta-blocker is an effective combination.<sup>46</sup>

Ivabradine has HR-lowering properties without other direct CV effects. It acts specifically on the SA node by inhibiting the I<sub>f</sub> current of cardiac pacemaker cells without affecting other cardiac ionic currents. Ivabradine has a unique pharmacodynamic profile, as HR reduction is not associated with negative inotropic effects or vasodilation. Ivabradine showed anti-anginal and anti-ischemic efficacy compared with beta-blockers and CCBs. It was also found to have beneficial effects on cardiac remodeling, capillary density, and LV dysfunction.<sup>17</sup>

The use of combination therapy needs to be judicious and guided by the results of clinical trials rather than clinical trial and error. The results of the recently published antianginal efficacy and safety of the association of the  $I_f$  current inhibitor ivabradine with a betablocker (ASSOCIATE) trial conducted in over 880 patients demonstrated that the addition of ivabradine 7.5 mg twice daily to atenolol at the commonly used dosage in clinical practice in patients with chronic stable angina pectoris produced additional HR reduction. The average HR reduction of 9 bpm was significant, allowing the patients to reach the recommended HR level of less than 60 bpm. This HR reduction was associated with a significant further improvement on all exercise testing parameters, with no untoward effects on safety or tolerability.<sup>40</sup> In patients whose HR was  $>70$  bpm, addition of ivabradine to beta-blockers was found to be favorable. In the early therapy with ivabradine in patients with congestive acute heart failure (ETHIC-AHF) trial, early co-administration of ivabradine and beta-blockers was found to be beneficial. At 1 year, HR remained significantly lower (i.e.  $<70$  bpm) in the interventional group than in the control group.<sup>47</sup>

#### ***Role of ivabradine in patients with stable angina and heart failure***

Angina has a significant negative effect on quality of life, including physical activity, emotional well-being, and personal and sexual relationships. In patients with stable angina, HR control is of prime importance to achieve symptomatic control. Beta-blockers are used preferably aiming for an HR of  $<60$  bpm.<sup>48</sup> However, ivabradine was also found to be an effective treatment option in patients with stable angina pectoris. The REDUCTION study evaluated the efficacy and safety of ivabradine in 4954 patients with stable angina pectoris. Four months of ivabradine treatment significantly reduced the HR by 12.4 (12.2) bpm from 82.9 (15.3) to 70.4 (9.2) bpm ( $p<0.0001$ ). Significant reduction was also noted in angina pectoris attacks and in consumption of short-acting nitrates.<sup>49</sup> In BEAUTIFUL study, in patients with limiting angina and HR  $\geq 70$  bpm, ivabradine had positive coronary outcomes, and the treatment was associated with substantial reductions in hospitalization for fatal and non-fatal MI and coronary revascularization.<sup>50</sup>

Ivabradine also does not affect other cardiac ionic currents resulting in lack of hemodynamic effects such as reduction of BP, cardiac contractility, or atrioventricular conduction, which is often a limitation with beta-blockers.<sup>20</sup> Ivabradine has demonstrated efficacy in reducing re-hospitalizations and mortality in HF and in improving exercise tolerance and reducing angina attacks in patients with CAD. In systolic heart failure treatment with the  $I_f$  inhibitor ivabradine trial (SHIFT), a placebo-corrected average of 8.1 bpm reduction at study end on ivabradine was associated with an 18% reduction of CV death or HF hospitalization. Reduction in HR with ivabradine improved outcomes independently of HF duration. When HR is  $\geq 70$  bpm, reduction of HR with ivabradine will

provide additional clinical benefits regardless of the beta-blocker dose. The magnitude of HR reduction with ivabradine was beyond that achieved by beta-blockers. Ivabradine effectively reduced the HR in patients with HF who were previously on beta-blocker therapy.<sup>51</sup>

In patients whose HR was  $>70$  bpm, addition of ivabradine to the beta-blocker was favorable. In the ETHIC-AHF trial, early co-administration of ivabradine and beta-blockers was found to be beneficial. At one year, HR remained significantly lower (i.e.  $<70$  bpm) in the interventional group than the control group.<sup>47</sup>

#### **CONCLUSION**

Elevated HR is a potent predictor of all-cause morbidity and mortality in the general population and also assumes prognostic importance in patients across the CVD continuum. Several pharmacological therapies that reduce heart rate are known to be associated with improvement in hemodynamics like increased coronary perfusion, reduction in myocardial oxygen consumption, enhancement in the left ventricular functionality, and beneficial left ventricular remodeling, which comprehensively translate to anginal relief, improvements in exercise capacity, cardiac function, and quality of life. Cardioselective beta-blockers, either used singly or in combination, have no doubt shown to reduce tachycardia, but are associated with some challenges like dose titration, which might affect cardiovascular outcomes. Ivabradine, which acts specifically on the SA node by inhibiting the  $I_f$  current has heart rate-lowering properties. With its unique pharmacodynamic profile, ivabradine has shown HR reduction with no associated negative inotropic effects, anti-anginal and anti-ischemic efficacy compared with beta-blockers and CCBs. The additional beneficial effects on cardiac remodeling, capillary density, and LV dysfunction have as well placed ivabradine in the armamentarium of cardiac therapy.

#### **ACKNOWLEDGEMENTS**

Authors would like to gratefully acknowledge the contribution of experts across India who gave their expert opinion in conceptualization and finalization of this manuscript in advisory board meetings: Dr. Viveka Kumar, Dr. Ashwini Mehta, Dr. N. C. Krishnamany, Dr. G. S. Gupta, Dr. Rajeev Bansal, Dr. Mukesh Joon, Dr. Subash Saini, Dr. Sunil Maheshwari, Dr. Gautam Singh, Dr. Arun Mohanty, Dr. Saket Bhardwaj, Dr. C. K. Ponde, Dr. Dhiren Shah, Dr. Mukesh Parikh, Dr. Jitesh Desai, Dr. Manoj Mashru, Dr. Badresh Shah, Dr. Kaustub Vaidya, Dr. Akbarul Haq, Dr. S. Hansara, Dr. S. Ambardekar, Dr. Sushil Tripathi.

*Funding: The study was funded by Abbott Healthcare Pvt. Ltd.*

*Conflict of interest: None declared*

*Ethical approval: Not required*

## REFERENCES

- Ferrari R. Heart rate in the management of cardiovascular patients: it's time to act. *Medicographia.* 2012;34:379-86.
- Levine HJ. Rest heart rate and life expectancy. *J Am Coll Cardiol.* 1997;30:1104-6.
- Custodis F, Reil JC, Laufs U, Böhm M. Heart rate: A global target for cardiovascular disease and therapy along the cardiovascular disease continuum. *J Cardiol.* 2013;62:183-7.
- Boudoulas KD, Borer JS, Boudoulas H. Heart rate, life expectancy and the cardiovascular system: Therapeutic considerations. *Cardiology.* 2015;132:199-212.
- Singh BN. Increased heart rate as a risk factor for cardiovascular disease. *Eur Heart J Suppl.* 2003;5:3-9.
- Palatini P, Benetos A, Grassi G, Julius S, Kjeldsen SE, Mancia G, et al. Identification and management of the hypertensive patient with elevated heart rate: statement of a European Society of Hypertension Consensus Meeting. *J Hypertens.* 2006;24:603-10.
- Cooney MT, Vartiainen E, Laatikainen T, Juolevi A, Dudina A, Graham IM. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. *Am Heart J.* 2010;159:612-9.
- Pfister R, Michels G, Sharp SJ, Luben R, Wareham NJ, Khaw KT. Resting heart rate and incident heart failure in apparently healthy men and women in the EPIC-Norfolk study. *Eur J Heart Fail.* 2012;14:1163-70.
- Gillman MW, Kannel WB, Belanger A, D'Agostino RB. Influence of heart rate on mortality among persons with hypertension: the Framingham Study. *Am Heart J.* 1993;125:1148-54.
- Benetos A, Rudnichi A, Thomas F, Safar M, Guize L. Influence of heart rate on mortality in a French population: role of age, gender, and blood pressure. *Hypertension.* 1999;33:44-52.
- Farinaro E, Stranges S, Guglielmucci G, Iermano P, Celentano E, Cajafa A, et al. Heart rate as a risk factor in hypertensive individuals. The Italian Tensio Pulse Study. *Nutr Metab Cardiovasc Dis.* 1999;9:196-202.
- Thomas F, Rudnichi A, Bacri AM, Bean K, Guize L, Benetos A. Cardiovascular mortality in hypertensive men according to presence of associated risk factors. *Hypertension.* 2001;37:1256-61.
- Palatini P, Thijs L, Staessen JA, Fagard RH, Bulpitt CJ, Clement DL, et al. Predictive value of clinic and ambulatory heart rate for mortality in elderly subjects with systolic hypertension. *Arch Intern Med.* 2002;162:2313-21.
- Okin PM, Kjeldsen SE, Julius S, Hille DA, Dahlöf B, Edelman JM, et al. All-cause and cardiovascular mortality in relation to changing heart rate during treatment of hypertensive patients with electrocardiographic left ventricular hypertrophy. *Eur Heart J.* 2010;31:2271-9.
- Gordon R, Gwathmey JK, Xie L. Autonomic and endocrine control of cardiovascular function. *World J Cardiol.* 2015;7:204-14.
- Arnold JM, Fitchett DH, Howlett JG, et al. Resting heart rate: A modifiable prognostic indicator of cardiovascular risk and outcomes? *Can J Cardiol.* 2008;24:3-8.
- Zamorano JL. Heart rate management: a therapeutic goal throughout the cardiovascular continuum. *Eur Heart J.* 2008;10:17-21.
- Reule S, Drawz PE. Heart rate and blood pressure: Any possible implications for management of hypertension? *Curr Hypertens Rep.* 2012;14:478-84.
- Hjalmarson A. Heart rate: an independent risk factor in cardiovascular disease. *Eur Heart J.* 2007;9:3-7.
- Raja DC, Kapoor A, Sinha A, Kashyap S, Khanna R, Kumar S, et al. Heart rate manipulation in dilated cardiomyopathy: assessing the role of ivabradine. *Indian Heart J.* 2018;70:246-51.
- Böhm M, Reil JC, Deedwania P, Kim JB, Borer JS. Resting heart rate: risk indicator and emerging risk factor in cardiovascular disease. *Am J Med.* 2015;128:219-28.
- Palatini P. Recommendations on how to measure resting heart rate. *Medicographia.* 2009;31:414-9.
- Kobayashi H. Effect of measurement duration on accuracy of pulse counting. *Ergonomics.* 2013;56:1940-4.
- Hill RD, Smith RB. Examination of the extremities: pulses, bruits, and phlebitis. Walker HK, Hall WD, Hurst JW, Editors. *Clinical Methods: The History, Physical, and Laboratory Examinations.* 3rd edition. Boston: Butterworths. 1990;30.
- Opdahl A, Venkatesh BA, Fernandes VRS, Wu CO, Nasir K, Choi EY, et al. Resting heart rate as predictor for left ventricular dysfunction and heart failure: The multi-ethnic study of atherosclerosis. *J Am Coll Cardiol.* 2014;63:1182-9.
- Hori M, Okamoto H. Heart rate as a target of treatment of chronic heart failure. *J Cardiol.* 2012;60:86-90.
- Zhang D, Shen X, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. *CMAJ.* 2016;188:53-63.
- Custodis F, Baumhäkel M, Schlimmer N, List F, Gensch C, Böhm M, et al. Heart rate reduction by ivabradine reduces oxidative stress, improves endothelial function, and prevents atherosclerosis in apolipoprotein E-deficient mice. *Circulation.* 2008;117:2377-87.
- Drouin A, Gendron ME, Thorin E, Gillis MA, Mahlberg-Gaudin F, Tardif JC, et al. Chronic heart rate reduction by ivabradine prevents endothelial dysfunction in dyslipidaemic mice. *Br J Pharmacol.* 2008;154:749-57.
- Baumhäkel M, Custodis F, Schlimmer N, Laufs U, Böhm M. Heart rate reduction with ivabradine improves erectile dysfunction in parallel to decrease in atherosclerotic plaque load in ApoE-knockout mice. *Atherosclerosis.* 2010;212:55-62.

31. Albaladejo P, Carusi A, Apartian A, Lacolley P, Safar ME, Bénétos A. Effect of chronic heart rate reduction with ivabradine on carotid and aortic structure and function in normotensive and hypertensive rats. *J Vasc Res.* 2003;40:320-8.
32. Beere PA, Glagov S, Zarins CK. Retarding effect of lowered heart rate on coronary atherosclerosis. *Science.* 1984;226:180-2.
33. Beere PA, Glagov S, Zarins CK. Experimental atherosclerosis at the carotid bifurcation of the cynomolgus monkey. Localization, compensatory enlargement, and the sparing effect of lowered heart rate. *Arterioscler Thromb.* 1992;12:1245-53.
34. Zheng W, Brown MD, Brock TA, Bjercke RJ, Tomanek RJ. Bradycardia-induced coronary angiogenesis is dependent on vascular endothelial growth factor. *Circ Res.* 1999;85:192-8.
35. Li J, Hampton T, Morgan JP, Simons M. Stretch-induced VEGF expression in the heart. *J Clin Invest.* 1997;100:18-24.
36. Heusch G, Skyschally A, Gres P, van Caster P, Schilawa D, Schulz R. Improvement of regional myocardial blood flow and function and reduction of infarct size with ivabradine: protection beyond heart rate reduction. *Eur Heart J.* 2008;29:2265-75.
37. Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J.* 2005;26:2529-36.
38. Borer JS, Fox K, Jaillon P, Lerebours G. Antianginal and antiischemic effects of ivabradine, an I(f) inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. *Circulation.* 2003;107:817-23.
39. Westenbrink BD, van Gilst WH. Why should we consider heart rate in patients with cardiovascular disease? *Medicographia.* 2012;34:421-5.
40. Daly C. Is heart rate optimally controlled in patients with coronary artery disease in clinical practice? *Medicographia.* 2009;31:364-70.
41. Weber MA. The role of the new-blockers in treating cardiovascular disease. *Am J Hypertens.* 2005;18:169-76.
42. Farzam K, Jan A. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK532906/>. Accessed on 05 May 2021.
43. Ong HT.  $\beta$  blockers in hypertension and cardiovascular disease. *BMJ.* 2007;334:946-9.
44. de Groote P, Isnard R, Assyag P, Clerson P, Ducardonnet A, Galinier M, et al. Is the gap between guidelines and clinical practice in heart failure treatment being filled? Insights from the IMPACT RECO survey. *Eur J Heart Fail.* 2007;9:1205-11.
45. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiadu M, Greenberg BH, et al. Dosing of beta-blocker therapy before, during, and after hospitalization for heart failure (from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure). *Am J Cardiol.* 2008;102:1524-9.
46. Richards TR, Tobe SW. Combining other antihypertensive drugs with  $\beta$ -blockers in hypertension: a focus on safety and tolerability. *Can J Cardiol.* 2014;30:42-6.
47. Hidalgo FJ, Carrasco F, Castillo JC, Rodríguez S, Pardo L, Durán E, et al. Early therapy with beta blockers plus ivabradine versus beta blockers alone in patients hospitalised with heart failure and reduced ejection fraction (ETHIC-AHF Study): Results at one-year follow-up. *Int J Clin Cardiol.* 2017;4:093.
48. Arden C. Available at: <https://www.guidelinesinpractice.co.uk/cardiovascular/controlling-heart-rate-is-key-when-managing-stable-angina/311313.article>. Accessed on 05 May 2021.
49. Köster R, Kaehler J, Meinertz T. Treatment of stable angina pectoris by ivabradine in every day practice: the REDUCTION study. *Am Heart J.* 2009;158:51-7.
50. Ferrari R. Ivabradine in the management of coronary artery disease with or without left ventricular dysfunction or heart failure. *Eur Heart J.* 2015;17:24-9.
51. Kaski JC, Gloekler S, Ferrari R, Fox K, Levy BI, Komajda M, et al. Role of ivabradine in management of stable angina in patients with different clinical profiles. *Open Heart.* 2018;5:e000725.

**Cite this article as:** Punjabi A, George S, Khera P, Srivastava S. Elevated heart rate across cardiovascular continuum and its management. *Int J Adv Med* 2021;8:1784-91.