

# Heart rate control with adrenergic blockade: Clinical outcomes in cardiovascular medicine

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**Abstract:** The sympathetic nervous system is involved in regulating various cardiovascular parameters including heart rate (HR) and HR variability. Aberrant sympathetic nervous system expression may result in elevated HR or decreased HR variability, and both are independent risk factors for development of cardiovascular disease, including heart failure, myocardial infarction, and hypertension. Epidemiologic studies have established that impaired HR control is linked to increased cardiovascular morbidity and mortality. One successful way of decreasing HR and cardiovascular mortality has been by utilizing  $\beta$ -blockers, because their ability to alter cell signaling at the receptor level has been shown to mitigate the pathogenic effects of sympathetic nervous system hyperactivation. Numerous clinical studies have demonstrated that  $\beta$ -blocker-mediated HR control improvements are associated with decreased mortality in postinfarct and heart failure patients. Although improved HR control benefits have yet to be established in hypertension, both traditional and vasodilating  $\beta$ -blockers exert positive HR control effects in this patient population. However, differences exist between traditional and vasodilating  $\beta$ -blockers; the latter reduce peripheral vascular resistance and exert neutral or positive effects on important metabolic parameters. Clinical evidence suggests that attainment of HR control is an important treatment objective for patients with cardiovascular conditions, and vasodilating  $\beta$ -blocker efficacy may aid in accomplishing improved outcomes.

**Keywords:** adrenergic beta-antagonists, heart failure, hypertension, myocardial infarction

## Introduction

Numerous studies have reported that increased heart rate (HR) is a predictor of cardiovascular mortality in healthy people, those who have had a myocardial infarction (MI), and in patients with heart failure (HF).<sup>1</sup> Increased HR is recognized as a negative prognostic factor independent of other clinical parameters, including left ventricular function.<sup>1</sup> The increased mortality observed with an increased HR may be a consequence of the deleterious sympathovagal imbalance that can be characterized by sympathetic nervous system predominance, vagal depression, or the combined impact of this dysregulation on cardiovascular function.<sup>1,2</sup> Elevated HR increases cardiac output (short term) and myocardial oxygen consumption, while simultaneously reducing time of diastole and myocardial blood supply, conditions that favor the development of myocardial ischemia and arrhythmias in ischemic areas.<sup>1</sup>

Blockade of  $\beta$ -adrenergic receptors is part of the combined medical prevention of cardiovascular disease.<sup>3,4</sup>  $\beta$ -Blockers have been efficacious and beneficial in the treatment of various cardiovascular disease states, including angina, HF, MI, and ventricular arrhythmias.<sup>5</sup> Randomized controlled clinical studies consistently

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demonstrate that  $\beta$ -blockers reduce sudden cardiac death by 30% to 50% in patients with coronary artery disease and HF.<sup>6</sup> The clinical benefits of  $\beta$ -blockers have been attributed to their ability to antagonize  $\beta$ -adrenergic receptors in the heart and the periphery.<sup>7</sup> Traditional  $\beta$ -blockers (eg, atenolol and propranolol), which target either  $\beta_1$ - (cardioselective) or  $\beta_1$ - and  $\beta_2$ -adrenergic receptors (nonselective), decrease BP primarily via a reduction in HR and cardiac output, but do not appreciably affect peripheral vascular resistance.<sup>5</sup> Acutely, up-titration of  $\beta$ -blockers can decrease cardiac output and increase vascular tone, which may exert a detrimental effect on renal perfusion and decrease patient drug tolerability, while exacerbating glucose and lipid metabolism.<sup>8,9</sup> In addition, these metabolic perturbations may lead to further vascular complications by adversely affecting endothelial function and promoting the development or progression of diabetes.<sup>9,10</sup>

Vasodilatory  $\beta$ -blockers (eg, carvedilol, labetalol, and nebivolol) and those that provide more complete adrenergic blockade may, in part, mediate vasodilation via blockade of  $\alpha_1$ -adrenergic receptors or increased endothelium-derived nitric oxide release, which may lead to a reduction in total peripheral vascular resistance.<sup>9</sup> This review will examine the data, including recent analyses from the large cardiovascular trials, related to adrenergic blockade, HR control, and its impact on outcomes across the cardiovascular disease spectrum (ie, patients who have had a MI or who have HF or hypertension).

## Heart rate and heart rate variability

Heart rate is not a static hemodynamic parameter but instead changes over time in response to physical and mental demands. Heart rate is normally determined by spontaneous and periodic depolarizations of the sinoatrial node, the frequency of which is modulated by the sympathetic and parasympathetic divisions of the autonomic nervous system, the intrinsic cardiac nervous system, reflexes, and respiration. These neural systems also partially control cardiac contractility and conduction of electrical activity through the heart. As a result, HR (chronotropism), contractility (inotropism), and conduction (dromotropism) are adjusted to meet the changing needs of the body. Aberrant sympathetic activation has been implicated as part of the sequelae consistent with the development of HF, MI, and hypertension.<sup>11,12</sup> Profoundly elevated sympathetic activity for an extended period accompanied by parasympathetic withdrawal may result in chronically elevated HR, as well as neurohormonal stimulation, and is associated with a decreased

threshold for ventricular fibrillation. This upregulation of the sympathetic nervous system and increased adrenergic activation is also associated with pathologic remodeling, myocyte apoptosis, and a dysregulation of calcium handling that leads to myocardial ischemia, a decrement in contractile function, and an increased risk of ventricular arrhythmias.<sup>13,14</sup> Due to the correlative linkage of HR and sympathetic nervous system outflow, HR control may be used as a surrogate for sympathetic nervous system activity.

## Optimal heart rate

Heart rate varies between individuals, and in a resting individual HR may vary according to time of day, physical conditioning, environmental influences, and sympathetic nervous system vagal tone. However, recent reports suggest that HR should generally be maintained substantially below the traditionally defined tachycardia threshold of 90 to 100 beats/minute.<sup>15</sup> A continuous linear increase in cardiovascular risk has been noted in patients whose HR exceeds 60 beats/minute.<sup>16,17</sup> Results from the Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO-1) study suggest that an increased risk of cardiovascular disease may even exist when HR is <60 beats/minute.<sup>18</sup> Increases in HR exceeding 10 beats/minute are associated with a 14% increase in cardiovascular mortality and a 20% increase in total mortality in patients with hypertension.<sup>19</sup> In the general population, the mortality risk is increased three-fold in individuals with a HR of 90 to 99 beats/minute compared with individuals with a HR  $\leq$  60 beats/minute.<sup>20</sup>

## Heart rate and mortality

Numerous studies report that a significant association exists between resting HR and cardiovascular and all-cause mortality in the general population, as well as among patients with cardiovascular disease. Epidemiologic studies involving approximately 30,000 individuals over a period of five to 36 years revealed an inverse relationship between HR and survival in the general population.<sup>20–25</sup> The risk of coronary artery disease, stroke, death due to noncardiovascular diseases, and total mortality increased with higher HR. Among 5713 healthy male volunteers without known or suspected cardiovascular disease who were observed for an average of 23 years, cardiovascular and all-cause mortality from acute MI increased with progressive elevations in resting HR.<sup>17</sup> This independent variable remained significant after adjustment for exercise capacity, age, diabetes, systolic arterial pressure, body mass index, level of physical activity, and other factors. The relationship

was most apparent for sudden death (Figure 1).<sup>17</sup> In a study of 10,267 patients with acute coronary syndromes, mortality at 30 days and 10 months progressively increased with increasing HR ( $P < 0.001$ ).<sup>26</sup> Similarly, all-cause and cardiovascular mortality were directly related to resting HR at study entry in 24,913 patients with suspected or proven coronary artery disease who participated in the Coronary Artery Surgery Study (CASS) registry for a period of 15 years ( $P < 0.0001$ ; Figure 2).<sup>15,16</sup> The predictive capacity of HR was independent of concomitant hypertension, diabetes, smoking, left ventricular ejection fraction, and number of diseased coronary vessels.

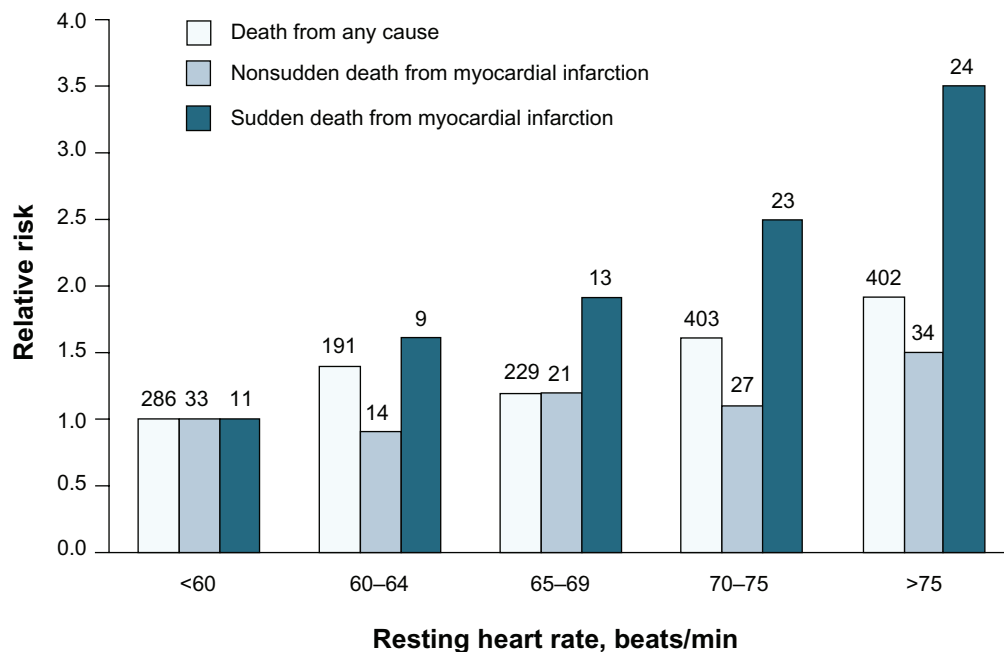
Because the association between HR and mortality is well known, resting HR is currently included in risk assessment indices for patients with acute coronary syndromes (eg, the Global Registry of Acute Coronary Events risk prediction score)<sup>27</sup> and acute MI (eg, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Prevenzione risk assessment model<sup>28</sup> and the Thrombolysis in Myocardial Infarction Risk Score<sup>29</sup>). However, HR is not included in some of the more widely used indices for cardiovascular risk assessment, including the Copenhagen Risk Score<sup>30</sup> and the European SCORE project,<sup>31</sup> which indicates that HR is not universally accepted as a prognostic factor and a potential therapeutic target in patients with cardiovascular disease.

## Heart rate variability

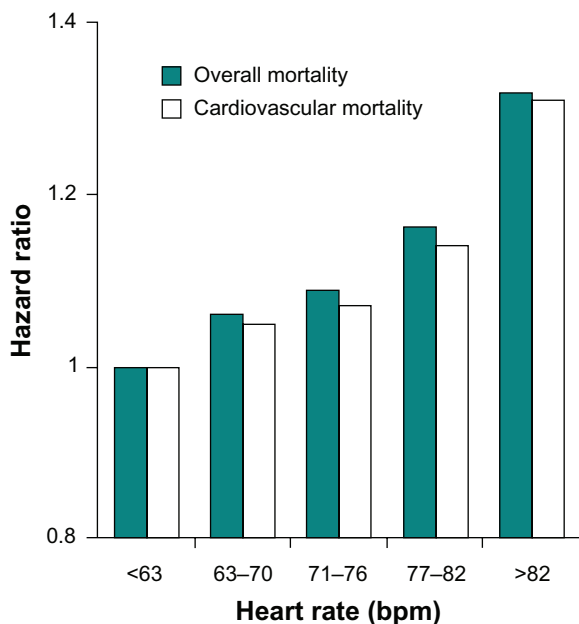
Heart rate variability (HRV) refers to the beat-to-beat difference or R-R interval change in the intrinsic rhythm of the heart.<sup>32</sup> Assessment of HRV may provide a surrogate measure of cardiac health, as defined by the degree of equilibrium between sympathetic and parasympathetic (vagus nerve) activity.<sup>33</sup> HRV can be assessed by time or frequency domain indices.<sup>32</sup> Time domain measures are based on the amount of time in milliseconds in the beat-to-beat intervals of the heart or on the differences between the normal beat-to-beat intervals.<sup>33</sup> Frequency domain measures of HRV provide information about the frequency distribution of the components of HRV using power spectral density analysis.<sup>33</sup> Nonlinear dynamic analysis (eg, Poincaré plots) may also be used to quantify HRV, but the clinical utility of this method has not been fully established.<sup>32</sup> As discussed in subsequent sections, numerous studies have demonstrated the positive prognostic power of reduced HRV to predict all-cause mortality, sudden cardiac death, and cardiac events in patients who have experienced an MI, as well as in patients who have HF or hypertension.

## Heart rate control in heart failure

HF is frequently associated with a decreased threshold for ventricular fibrillation, as well as an increased risk of other malignant arrhythmias and sudden cardiac death.



**Figure 1** Heart rate and mortality in healthy individuals: Relative risk of death from any cause, nonsudden death from myocardial infarction (MI), and sudden death from MI in 5713 people without known or suspected heart disease. Differences among quintiles with respect to risk of death from any cause,  $P < 0.001$ ; nonsudden death from cardiac causes,  $P = 0.02$ ; sudden death from cardiac causes,  $P < 0.001$ . Copyright © 2005, Massachusetts Medical Society. All rights reserved. Reprinted with permission from Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med.* 2005;352(19):1951-1958.



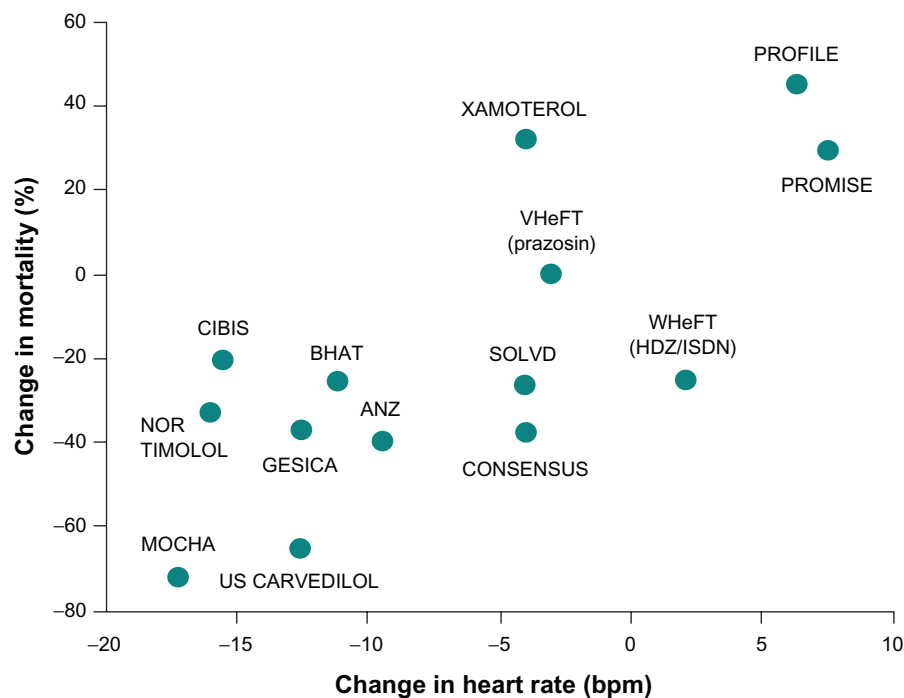
**Figure 2** Heart rate and mortality in coronary artery disease: Relationship between resting heart rate and all-cause and cardiovascular mortality in 24,913 patients with suspected or proven coronary artery disease. Based on data from Diaz et al.<sup>16</sup> Copyright © 2007. Reprinted with permission from Fox K, Borer JS, Camm AJ, et al. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol.* 2007;50(9):823–830. **Abbreviation:** bpm, beats per minute.

Increased HR (eg, atrial fibrillation with a rapid ventricular rate or multiple premature contractions) may contribute to the development of HF and is also associated with a poor prognosis in patients with HF.<sup>34</sup> In the normal heart, a stepwise increase in contractility develops as HR increases. Ninety percent of patients with HF die of cardiovascular causes.<sup>35</sup> Approximately half of these patients die from progressive, advanced disease and the remaining patients die suddenly, most frequently because of arrhythmia despite a perceivably stable clinical condition. Sudden cardiac death occurs most frequently in patients in New York Heart Association Functional Class II or III. Risk factors for sudden cardiac death include elevated resting HR, and reduced HRV and left ventricular ejection fraction.<sup>36</sup>

Numerous studies have established a relationship between reduction in HR and improved survival of patients with HF who are receiving  $\beta$ -blocker therapy (Figure 3).<sup>37</sup> In a recent meta-analysis of 35 studies of patients with chronic systolic HF (n = 22,926), a strong correlation was observed between HR and annualized all-cause mortality ( $P = 0.004$ ) and between change in HR and change in left ventricular ejection fraction ( $P < 0.001$ ).<sup>38</sup> As a result, it was suggested that the HR-lowering effect of  $\beta$ -blockers was a major contributor to the clinical benefit associated with these agents. In a study of 152 patients with HF who were receiving  $\beta$ -blocker therapy, greater reductions in HR were associated with better clinical outcomes

for patients overall, and higher  $\beta$ -blocker doses provided additional clinical benefits among patients with persistently elevated HR.<sup>39</sup> These results suggest that the magnitude of reduction in HR may be more important than achieving the target dose of  $\beta$ -blocker therapy in patients with HF.<sup>38,39</sup> In the Cardiac Insufficiency BIsoprolol Study (CIBIS), treatment of 557 patients with bisoprolol reduced HR by approximately 15 beats/minute relative to placebo ( $P < 0.001$ ), and HR change was the most powerful predictor of survival ( $P < 0.01$ ).<sup>40</sup> In the larger CIBIS II study (n = 2539), baseline HR and HR change were both significant predictors of mortality ( $P \leq 0.005$ ).<sup>41</sup> The most favorable prognosis occurred in patients with the lowest baseline HR and with the greatest HR reduction, conditions which were encountered more frequently in the bisoprolol group than in the placebo group.

The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial evaluated patients with left ventricular dysfunction or HF after a myocardial infarction (n = 1959),<sup>42</sup> whereas the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial enrolled only patients with severe HF (n = 2289).<sup>43</sup> The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) enrolled patients with New York Heart Association Class II–IV HF with an ejection fraction  $<40\%$  (n = 3991).<sup>44</sup> These trials each independently demonstrated benefits of  $\beta$ -blockade in patients with HF throughout a large spectrum of disease. Additionally, the Carvedilol or Metoprolol (tartrate) European Trial (COMET; n = 3029) may suggest that nonselective neurohumoral blockade has an additional benefit compared with selective  $\beta_1$ -blockade.<sup>45</sup> Consequently, adrenergic-receptor pathophysiology and thereafter specific signal transduction pathways may underlie the benefit of using specific  $\beta$ -blockers.<sup>46</sup> Although studies using one of the three  $\beta$ -blockers approved for HF in the US (carvedilol, metoprolol succinate, or bisoprolol) have demonstrated benefit in patients with HF, nebivolol has also received approval in Europe for the treatment of mild-to-moderate HF in patients  $\geq 70$  years of age.<sup>47</sup> Nebivolol is a  $\beta_1$ -selective  $\beta$ -blocker without  $\alpha_1$ -adrenergic receptor blocking activity. Nebivolol, which is approved for the treatment of hypertension in the US, has a neutral effect on metabolic parameters in patients with hypertension.<sup>48</sup> Nebivolol has been shown to reduce BP and HR to a similar extent as atenolol at one-tenth of the dose.<sup>49</sup> More importantly, the hemodynamic effect observed with nebivolol treatment better preserved cardiac output by decreasing peripheral vascular resistance and increasing stroke volume compared with atenolol.<sup>50</sup>



**Figure 3** Heart rate reduction and mortality in heart failure: Relationship between change in heart rate and mean change in mortality among patients with chronic heart failure who received  $\beta$ -blocker therapy. Copyright © 1999. Reprinted with permission from Kjekshus Kjekshus J, Gullestad L. Heart rate as a therapeutic target in heart failure. *Eur Heart J Suppl.* 1999;1(Suppl H):H64–H69.

Comparison of bisoprolol, carvedilol, and nebivolol in patients with HF demonstrated that each agent decreased HR to a similar extent.<sup>51</sup> Additionally, exercise capacity increases during  $\beta$ -blocker therapy. For example, among 16 healthy male volunteers, HR during exercise decreased by 14% in the bisoprolol group, 15% in the carvedilol group, and 13% in the nebivolol group ( $P < 0.05$ ).<sup>51</sup> Additionally, the effect of carvedilol and nebivolol on exercise capacity were compared in a 12-month study of patients with non-ischemic dilated cardiomyopathy.<sup>52</sup> Exercise duration improved significantly in both groups of patients ( $P = 0.01$ ), although patients treated with nebivolol experienced an initial decrease in exercise capacity over the first three months.<sup>52</sup> In patients with HF, reduction in peak  $VO_2$  is associated with left ventricular systolic dysfunction and increased neurohormonal response. Treatment with carvedilol improved left ventricular systolic function, exercise tolerance (at 12 months, exercise was prolonged by 143.9 sec;  $P = 0.001$ ), and peak oxygen consumption as well as significant reductions in brain natriuretic peptide, endothelin-1, and associated cytokines (ie, interleukin-6 and tumor necrosis factor- $\alpha$ ).<sup>53</sup> In a recent analysis of 47 randomized studies of HF, a significant increase in the six-minute walk test was observed in three of 17 studies that involved  $\beta$ -blocker therapy.<sup>54</sup> Similar to the results of exercise treadmill tests, patients who received  $\beta$ -blocker

therapy for more severe HF experienced greater improvements in the six-minute walk test compared with those having milder HF. Therefore, administration of  $\beta$ -blocker therapy to patients with HF is associated with improved HR control, improvement in clinical functioning, and reduction in mortality and hospitalization risk. The benefits of  $\beta$ -blocker therapy are clear, ie, mortality and HF hospital admissions are reduced by approximately one-third when eligible patients receive  $\beta$ -blocker therapy.<sup>55,56</sup>

## Chronotropic incompetence in heart failure

Patients with HF experience severe chronic exercise intolerance. Although the pathophysiology of exercise intolerance is not completely understood, chronotropic incompetence, defined as an impaired capacity to increase HR during exercise, and diastolic dysfunction are important determinants of this condition.<sup>57</sup> Chronotropic incompetence occurs in  $>70\%$  of patients with advanced HF and is believed to arise as a result of  $\beta$ -receptor desensitization and impaired norepinephrine release.<sup>58</sup> Risk factors for the development of chronotropic incompetence include increased left ventricular mass, enlarged cavity size, and depressed systolic function.<sup>59</sup> Chronotropic incompetence is predictive of mortality and coronary artery disease risk, even after adjusting



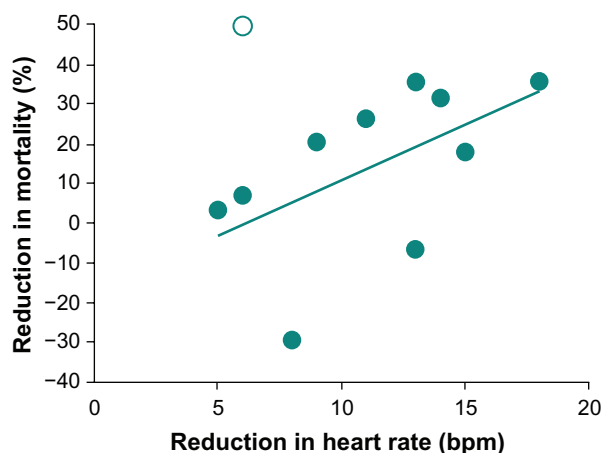
for age, physical fitness, and other standard cardiovascular risk factors.<sup>60</sup> Although some studies have reported that chronotropic incompetence was more common in patients taking  $\beta$ -blockers,<sup>61</sup>  $\beta$ -blockade has been reported to have a minimal effect on the association between chronotropic incompetence and cardiovascular mortality.<sup>62,63</sup> At doses <10 mg, nebivolol did not attenuate the exercise-induced increase in HR, thereby suggesting that nebivolol may mitigate the risk of chronotropic incompetence suggested to occur with  $\beta$ -blockade.<sup>64</sup> Similarly, carvedilol dose did not affect the HR dynamics during treadmill exercise testing among patients with HF who were stratified by resting HR ( $\leq 60$  beats/minute or  $>60$  beats/minute).<sup>65</sup> In a trial comparing the  $\beta_1$  effects of metoprolol succinate and carvedilol, carvedilol did not attenuate exercise-induced HR to the same degree as metoprolol.<sup>66</sup> Cardiac pacing may be required to restore chronotropic competence and exercise capacity in patients with persistent bradycardia, as well as allowing for continued  $\beta$ -blocker therapy.<sup>67</sup> There is a developing body of literature regarding the treatment of diastolic HF and chronotropic incompetence, but the clinical relevance of this information has yet to be determined.

## Heart rate control after myocardial infarction

Increased HR in patients with atherosclerosis may impair the stability of coronary plaques because of repetitive changes in BP that induce mechanical stress. Increased HR ( $>80$  beats/minute) is associated with more plaque ruptures compared with lower HR in patients with coronary artery disease ( $n = 106$ ).<sup>68</sup> HRs in patients following MI are higher than in patients who have not experienced an acute event.<sup>69</sup> Consequently, HR has been identified as an independent risk factor for the development of plaque rupture. In addition, HR but not HRV was identified as an independent prognostic indicator of mortality in a study of 366 patients after MI ( $P < 0.001$ ).<sup>70</sup> However, a subsequent study reported that decreased HRV and increased randomness of HR shortly after MI are independent risk factors for mortality in this patient population.<sup>71</sup> Similar to HF, increased HR or reduced HRV are associated with increased cardiovascular mortality in patients after MI.<sup>32</sup> A meta-analysis of the GISSI-2 and GISSI-3 trials that included approximately 20,000 patients demonstrated that inhospital mortality rates after MI increased from 3% for patients with HR  $<60$  beats/minute on admission to 10% for patients with HR  $>100$  beats/minute on admission.<sup>72</sup> Furthermore, higher HR at hospital discharge correlated with increased mortality rates after one year.<sup>69</sup>

Traditional  $\beta$ -blockers exert beneficial effects on HR and HRV and improve mortality rates in patients who have experienced an MI. Administration of  $\beta$ -blockers to 1427 patients within six hours of the onset of MI symptoms resulted in a mean reduction in infarct size that was directly proportional to the mean reduction in HR ( $P < 0.001$ ).<sup>73</sup> Furthermore, a significant association was reported between reduction in HR and reduction in mortality in 11 long-term  $\beta$ -blocker studies that involved more than 16,000 patients (Figure 4;  $r = 0.60$ ;  $P < 0.05$ ).<sup>73</sup> The Norwegian Timolol study reported similar results in that  $\beta$ -blocker-mediated HR reductions in patients who had experienced an MI were a significant predictor of overall mortality.<sup>74</sup> Compared with placebo, timolol treatment was associated with a 42% reduction in overall mortality compared with placebo ( $P < 0.001$ ); in logistic regression analysis, HR during follow-up remained predictive but treatment did not, suggesting that the beneficial effect of timolol on mortality could be ascribed to its effect on HR. HRV was also significantly improved among 28 patients who were treated with atenolol or metoprolol tartrate for six weeks after an acute MI ( $P \leq 0.01$ ); trends toward lower HR were also observed in both treatment groups.<sup>2</sup> Similarly, treatment of 30 patients who were stable following an MI with atenolol or metoprolol controlled-release (succinate) for six weeks decreased HR ( $P < 0.001$ ) and increased HRV.<sup>75</sup> Propranolol treatment was also associated with significantly greater improvements in HRV after an acute MI compared with placebo ( $P < 0.05$ ;  $n = 184$ ).<sup>76</sup>

Similar to the traditional  $\beta$ -blockers, vasodilating  $\beta$ -blockers exert beneficial effects on HR and HRV in



**Figure 4** Heart rate reduction and mortality after myocardial infarction: Relationship between mean reduction in heart rate and mean change in mortality relative to placebo in randomized, placebo-controlled studies of  $\beta$ -blockers after myocardial infarction ( $r = 0.60$ ;  $P < 0.05$ ). Copyright © 1986. Reprinted with permission from Kjekshus JK. Importance of heart rate in determining beta-blocker efficacy in acute and long-term acute myocardial infarction intervention trials. *Am J Cardiol.* 1986;57(12):43F–49F.

patients who have experienced an MI. Carvedilol produced reductions in HR relative to placebo in 151 patients with an acute MI ( $P < 0.0001$ ).<sup>77</sup> Labetalol, a nonselective  $\beta$ -blocker that targets  $\alpha_1$ -,  $\beta_1$ -, and  $\beta_2$ -adrenergic receptors, is used for the treatment of hypertension of all severities and during hypertensive emergencies.<sup>78,79</sup> When given acutely, labetalol decreases peripheral vascular resistance and BP but may have limited effects on HR and cardiac output.<sup>80</sup> In another study, administration of labetalol to 32 patients with sustained elevations in systemic arterial pressure after a recent MI resulted in significant reductions in HR relative to pretreatment levels ( $P < 0.01$ ).<sup>81</sup> Nebivolol and atenolol both decreased HR in patients who had ischemic heart disease and a previous MI ( $n = 40$ ); however, nebivolol maintained cardiac output and improved ejection fraction ( $P < 0.05$ ).<sup>82</sup> The relationship between improved HR control and decreased mortality has not been assessed among patients who have been treated with vasodilating  $\beta$ -blockers after MI.

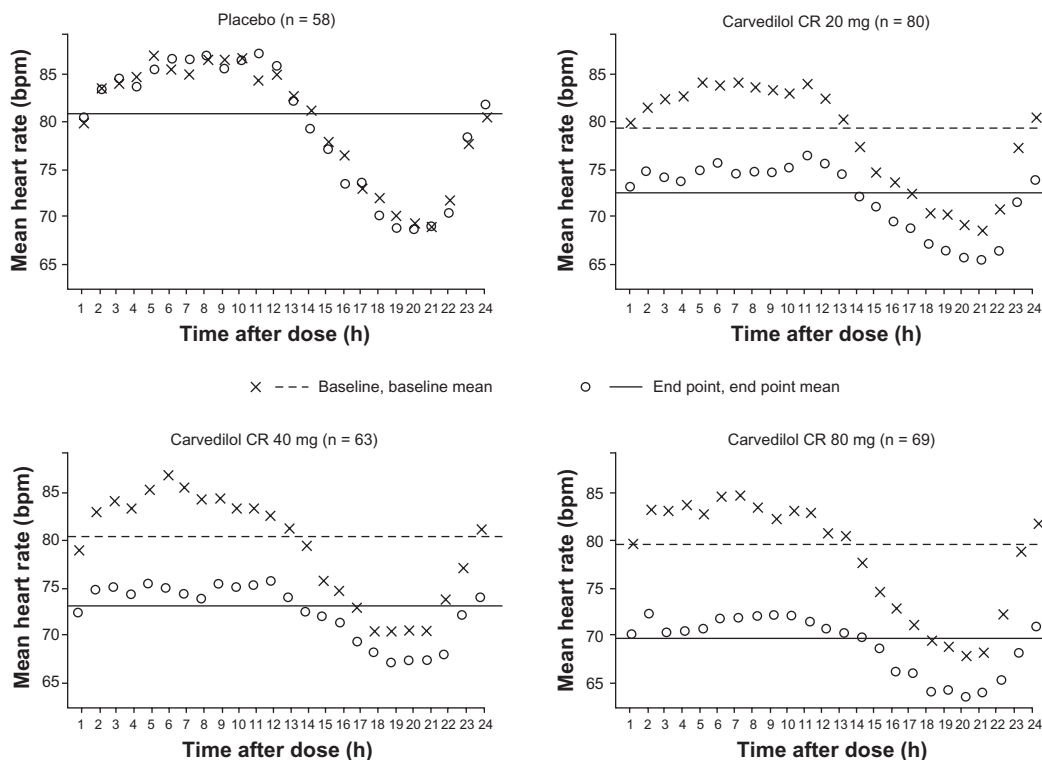
## Heart rate control in hypertension

In patients with hypertension, sympathetic nervous system overactivity increases HR, contributing to cardiac output and raised BP. The association between increased HR and the development of hypertension was demonstrated in the HARVEST (Hypertension and Ambulatory Recording Venetia Study) trial, which revealed a strong linkage between elevated HR and increases in BP among patients with Stage 1 hypertension.<sup>83</sup> Patients whose HR was persistently elevated during the six-year study period had a two-fold higher risk of developing hypertension compared with patients with normal HR ( $n = 796$ ). In patients with hypertension, normal sinus rhythm, and cardiovascular risk factors ( $n = 18,900$ ), increasing HR from 81 to 119 beats/minute was associated with an increasing proportion of patients with microalbuminuria (63% to 69%, respectively;  $P < 0.0001$ ).<sup>84</sup> Elevated HR is also an independent predictor of microalbuminuria, a predictor for cardiovascular events, and an indicator of renal impairment in patients with hypertension ( $n = 18,900$ ).<sup>84</sup> In addition, greater impairment of HRV responsiveness to autonomic challenge was observed in patients with hypertension compared with a normotensive group ( $n = 40$ ).<sup>85</sup> Increased HR generally results in a poor prognosis for patients with hypertension. The rate of complications caused by cardiovascular disease as well as total mortality in patients with hypertension increased two-fold when HR increased by 40 beats/minute ( $n = 4530$ ).<sup>86</sup>

The importance of lowering systemic vascular resistance and increasing tissue perfusion in patients with hypertension is well recognized, given that clinical evidence has established

an association between impairment of microcirculation and development of end organ damage.<sup>87,88</sup> Consequently, a goal of hypertension management is effective BP reduction while maintaining tissue perfusion. Traditional  $\beta$ -blockers reduce BP via decreased cardiac output but do not directly affect central aortic pressure or peripheral resistance, although a slight compensatory increase in peripheral resistance may occur.<sup>9</sup> Administration of the traditional  $\beta$ -blocker, atenolol, to patients with hypertension significantly reduced HRV compared with placebo or losartan ( $P < 0.05$ ).<sup>89,90</sup> HR and BP at rest and during exercise was decreased in 10 patients with mild to moderate hypertension who received atenolol therapy for five years; however, systemic vascular resistance was elevated and cardiac output remained depressed compared with pretreatment levels.<sup>91</sup> Similar results have also been reported using 10 different traditional  $\beta$ -blockers.<sup>9</sup> Therefore, although traditional  $\beta$ -blockers lower BP, they do not appear to normalize cardiac hemodynamics in patients with hypertension. In addition, traditional  $\beta$ -blockers are associated with an increased risk for the development of abnormalities in metabolic parameters (eg, diabetes or endothelial dysfunction) or stroke compared with other antihypertensive agents.<sup>92-94</sup>

Vasodilatory  $\beta$ -blockers reduce BP via the lowering of peripheral vascular resistance and only slightly decreased in cardiac output; decreases in central aortic pressure have also been observed with vasodilatory  $\beta$ -blockers.<sup>79,95</sup> In contrast with traditional  $\beta$ -blockers, carvedilol was shown to maintain cardiac output, decrease vascular resistance, and decrease HR to a lesser extent.<sup>96</sup> A once-daily formulation of the vasodilatory  $\beta$ -blocker carvedilol controlled-release was administered to 320 patients with hypertension, resulting in greater reductions in HR (Figure 5) and 24-hour diastolic BP compared with placebo ( $P \leq 0.001$ ).<sup>97</sup> In the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) study of 1235 patients with hypertension and Type 2 diabetes mellitus, reductions in diastolic BP were similar in the carvedilol and metoprolol tartrate treatment groups ( $10.0 \pm 0.4$  and  $10.3 \pm 0.3$  mmHg, respectively). At mean doses required to achieve target BP (carvedilol 35 mg/day; metoprolol 256 mg/day), both agents effectively reduced HR, although decreases were less among carvedilol- versus metoprolol-treated patients ( $6.7 \pm 0.4$  versus  $8.3 \pm 0.4$  beats/minute, respectively;  $P < 0.001$ ).<sup>98</sup> Of clinical importance, carvedilol demonstrated neutral or positive effects on glycemic control and lipid metabolism in analyses of the GEMINI study. After six weeks of treatment, once-daily nebivolol reduced HR by



**Figure 5** Twenty-four-hour heart rate in patients with hypertension at baseline and after six weeks of treatment with carvedilol controlled-release (CR) or placebo. Copyright © 2006. Reprinted with permission from Weber MA, Bakris GL, Tarka EA, Iyengar M, Fleck R, Sica DA. Efficacy of a once-daily formulation of carvedilol for the treatment of hypertension. *J Clin Hypertens (Greenwich)*. 2006;8(12):840–849.

10.6 ± 10.3 beats/minute, systolic BP by 29 ± 17 mmHg, and diastolic BP by 16 ± 10 mmHg in an observational study of 6376 patients with hypertension.<sup>99</sup> Patients with higher initial values experienced greater reductions in HR and BP compared with patients having moderately elevated initial values.<sup>99</sup> In other clinical trials, nebivolol reduced vascular resistance and improved endothelial function in patients with hypertension, and also lowered the levels of the inflammatory marker, high-sensitivity C-reactive protein, in healthy volunteers who smoked cigarettes.<sup>100,101</sup>

The clinical relevance of  $\beta$ -blocker-mediated HR control to long-term clinical outcomes is less clear in hypertension than in HF or after MI. However, it is clear that reducing peripheral vascular resistance with a vasodilatory  $\beta$ -blocker is a beneficial mechanism to patients with hypertension, ie, a state of inherently elevated peripheral vascular resistance. In addition, vasodilating  $\beta$ -blockers maintain cardiac output but decrease peripheral vascular resistance, which improves peripheral blood flow. Improved blood flow is a major contributing factor to the more favorable tolerability and metabolic profiles of vasodilating  $\beta$ -blockers compared with traditional  $\beta$ -blockers.<sup>48,98</sup>

Recently, the use of  $\beta$ -blockade in essential hypertension has been called into question. Bangalore et al report increased cardiac events in hypertensive patients being treated with

$\beta$ -blockade.<sup>102</sup> A lower HR achieved from  $\beta$ -blockade compared with other antihypertensives or placebo in a meta-analysis of over 34,000 patients with hypertension was associated with an increase in all-cause mortality, cardiovascular mortality, MI, stroke, and HF. One caveat to this study, however, is that 78% of those studied were prescribed atenolol, and it has been suggested that atenolol, and not  $\beta$ -blockade itself, was the cause. The results were certainly provocative, and clearly additional testing needs to be conducted to determine whether this is a class effect or an effect based on receptor specificity.<sup>46</sup>

## Conclusion

An elevated or invariant HR is associated with the development of complications or various cardiovascular diseases including HF, MI, and hypertension. Patients with impaired HR control are at increased risk for all-cause and cardiovascular mortality, especially sudden cardiac death. As a result, HR should be included among the major risk factors for cardiovascular disease and should be used to establish individual cardiovascular risk profiles. Epidemiologic studies have demonstrated that  $\beta$ -blockers improve HR control and decrease mortality in patients with cardiovascular disease. Clinical evidence has established a clear relationship between



improved HR control and decreased mortality in patients who have had an MI or who have HF. Although HR is an important contributor to the development of hypertension, a definite association between improved HR control and decreased mortality has yet to be established in this patient population. However, the importance of decreased peripheral vascular resistance while maintaining tissue perfusion is well recognized in patients with certain cardiovascular conditions, such as hypertension. Traditional  $\beta$ -blockers do not decrease but may in fact increase peripheral vascular resistance during long-term treatment. In contrast, vasodilating  $\beta$ -blockers reduce peripheral vascular resistance and maintain cardiac output. Consequently, vasodilating  $\beta$ -blockers are an appropriate treatment option for patients with cardiovascular disease who are at high risk of sudden cardiac death, HF, or coronary artery disease, and for those with concordant comorbidities, including diabetes and peripheral vascular disease.

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