Hypertension Research (2013) 36, 838–844

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REVIEW

Heart rate as a possible therapeutic guide for the prevention of cardiovascular disease

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Epidemiologic evidence indicates that an elevated heart rate (HR) is an independent predictor of all-cause and cardiovascular (CV) mortality. Ivabradine, a pure HR-lowering agent, reduces CV events in patients with coronary artery disease (CAD) and chronic heart failure, and indicate that an HR greater than 70 b.p.m. is hazardous. These findings demonstrate not only that an elevated HR is an epiphenomenon of CV risk status but also that an elevated HR itself should be a therapeutic target. In addition, recent epidemiologic evidence demonstrates that the in-treatment HR or HR change predicts subsequent all-cause and CV mortality, independent of the HR-lowering strategy. Characteristics of the in-treatment HR or HR change are also important as possible therapeutic guides for risk management. However, there have been concerns regarding deleterious effects on CV event prevention owing to β-blocker-derived pharmacologic HR reduction. The potential role of HR and its modulation should be considered in future guidance documents.
Hypertension Research (2013) **36,** 838–844; doi:10.1038/hr.2013.98; published online 22 August 2013

Keywords: β-blocker; cardiovascular disease; coronary artery disease; heart rate; mortality

INTRODUCTION

On the basis of extensive evidence from epidemiologic studies and clinical trials designed for other purposes, an elevated heart rate (HR; >70 b.p.m.) is an undesirable prognostic sign. The resting HR increases with an increase in temperature, fear, immobility and cardiometabolic risk, so physicians have considered an elevated HR to be an epiphenomenon representing 'poor conditioning'. The BEAUTIFUL (morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left-ventricULar dysfunction)[1] and SHIFT (systolic heart failure treatment with the If inhibitor ivabradine Trial)[2] studies, however, prospectively evaluated the prognostic significance of lowering HR and demonstrated that HR should be a therapeutic target in patients with coronary artery disease (CAD) and chronic heart failure. Apart from patients with acute coronary syndrome and congestive heart failure, there are no reports regarding the optimal level of the resting HR in guidelines for the chronic care of patients with hypertension or stable CAD, for example. The importance of an elevated HR is therefore still not generally accepted in actual clinical practice. In this context, we summarize the clinical importance of HR, especially from an epidemiologic point of view. Moreover, we discuss several of the clinical applications of in-treatment HR for improving patient prognosis.

EPIDEMIOLOGIC EVIDENCE DEMONSTRATING HR AS A PROGNOSTIC FACTOR

Numerous studies have demonstrated that the baseline HR is associated with all-cause and cardiovascular (CV) mortality for a wide spectrum of subjects among the general population, including patients with CV disease, such as hypertension, acute myocardial infarction and congestive heart failure.[3] Further support derives from studies of patients with type 2 diabetes[4] and individuals undergoing hemodialysis.[5–7] Iseki *et al.*[7] examined the relationship between pulse rate and survival based on a nationwide hemodialysis registry. The authors demonstrated that the adjusted odds ratio for 1-year all-cause mortality was 1.20 (40–49 b.p.m.), 1.06 (50–59 b.p.m.), 1.13 (70–79 b.p.m.), 1.46 (80–89 b.p.m.), 1.91 (90–99 b.p.m.), 2.61 (100–109 b.p.m.) and 2.43 (110–129 b.p.m.) compared with the reference pulse rate (60–69 b.p.m.) (Figure 1). A recent evaluation of 2608 stable CAD patients indicated that an elevated HR is associated with CV events in diabetic but not non-diabetic patients.[8]

Evidence of in-treatment HR as a prognostic factor

Recent studies indicated that the in-treatment HR provides prognostic information beyond the baseline HR (Table 1). The Nord-Trøndelag County Health Study[9] evaluated a general population of 29 325 people and reported that the hazard ratio of death from ischemic heart disease in participants with a baseline HR of less than 70 but more than 85 b.p.m. at follow-up was 1.8–1.9 times greater compared with those with a HR of less than 70 b.p.m. at both baseline and follow-up. The Paris Prospective Study 1[10] evaluated healthy male workers and demonstrated that an increase in the follow-up HR caused a 19% higher mortality risk (95% confidence interval (CI): 4–37%). Importantly, this study, but not the Nord-Trøndelag County Health Study, demonstrated that a decrease in the follow-up HR of at least 4 b.p.m. had a 14% lower mortality risk (relative risk: 0.86, 95%

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Received 7 January 2013; revised 3 April 2013; accepted 18 April 2013; published online 22 August 2013

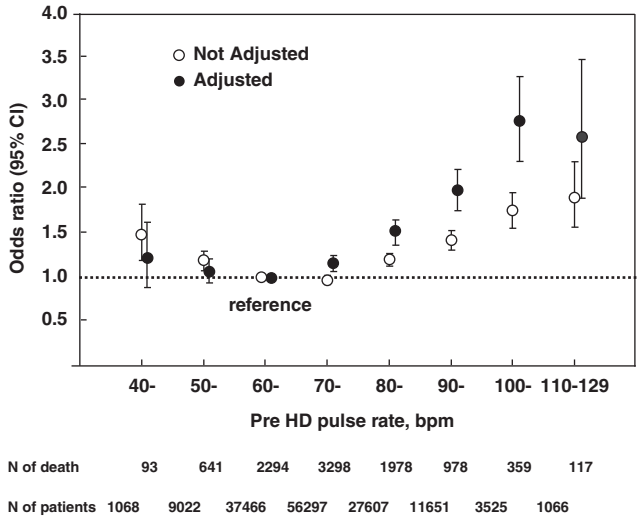


Figure 1 Odds ratio (95% CI) of death based on the pre-hemodialysis (HD) pulse rate. Patients with a pre-HD pulse rate of 60–69 b.p.m. were used for comparison (reference). Reprinted with permission from Iseki *et al.*[7]

CI: 0.74–1.00). Paul *et al.*[11] evaluated the relationship between HR change and all-cause and CV mortality risk in ~4000 hypertensive patients followed in the Glasgow Blood Pressure Clinic study. The authors demonstrated that a developing or persistent HR above 80 b.p.m. increases the risk of all-cause (hazard ratio: 1.78, 95% CI: 1.31–2.41) and CV (hazard ratio: 1.92, 95% CI: 1.24–2.99) mortality, even after adjusting for rate-limiting therapy. Moreover, patients whose HR increased at least 5 b.p.m. between baseline and their final clinic visit had a 51% higher all-cause mortality risk (hazard ratio: 1.51, 95% CI: 1.03–2.20). The LIFE study, in which CV and all-cause mortality were evaluated in hypertensive patients with ECG-confirmed left ventricular hypertrophy, yielded the same results.[12] A similar increase in risk associated with a higher in-treatment HR in both losartan- and atenolol-based treatment indicated that atenolol-treated patients did not have lower mortality. The association between the in-treatment HR and CV events was nearly the same as in other hypertensive studies, regardless of β-blocker use.[13,14] In patients with stable CAD, an increased CV event risk was apparent in patients with a mean in-treatment HR greater than 75 b.p.m., and a J-shape relation was observed regardless of the therapeutic strategy[15] (Figure 2). These results suggest that a serial assessment of HR can provide additional information about CV event risk.

Table 1 Studies demonstrating the association between in-treatment HR or serial HR change and adverse outcome

				HR		
Study name	*Patients*	*No.*	*Follow (years)*	*Baseline*	*In-treatment*	*Results*
Nord-Trøndelag County Health Study[9]	General population	29 325	12	NA	N/A	Total mortality >85 b.p.m. *vs.* <70 b.p.m.: hazard ratio 1.9, 95% CI 1.0–3.6 >85 b.p.m. *vs.* 70–85 b.p.m.: hazard ratio 1.8, 95% CI 1.2–2.8
Paris Prospective Study 1[10]	General population	5139	23	NA	N/A	Total mortality of HR decrease *vs.* no change: RR 0.86, 95% CI 0.74–1.00 Total mortality of HR increase *vs.* no change: RR 1.19, 95% CI 1.04–1.37
Glasgow BP Clinic study[11]	Outpatient HT	4065	2.5	77	74	Total mortality Persistent >80 b.p.m. *vs.* persistent <60 b.p.m.: hazard ratio 1.78, 95% CI 1.31–2.41 HR change at the end of follow-up >5 b.p.m. *vs.* <−10 b.p.m.: hazard ratio 1.51, 95% CI 1.03–2.20
LIFE[12]	HT	9190	4.8	At Los	−4.1 −0.5	Every 10 b.p.m. increment CV mortality: hazard ratio 1.16, 95% CI 1.06–1.27 Total mortality: hazard ratio 1.25, 95% CI 1.17–1.33 Developing or persist ⩾84 b.p.m. CV mortality; hazard ratio 1.55, 95% CI 1.16–2.05 Total mortality; hazard ratio 1.79, 95% CI 1.46–2.21
ASCOT-BPLA[13]	HT without CAD	12 759	3.8	At 73.8 Am 73.8	−12.0 −1.3	HR at 6 weeks was associated with the nonfatal MI and fatal CHD outcome.
ONTARGET/TRANSCEDENT[14]	High-risk HT	31 531	5	68.0	N/A	Every 10 b.p.m. increment Total mortality: hazard ratio 1.35, 95% CI 1.30–1.40 CV mortality: hazard ratio 1.36, 95% CI 1.32–1.45 MCE: hazard ratio 1.26, 95% CI 1.22–1.30 MI: hazard ratio 1.03, 95% CI 0.97–1.03 Stroke: hazard ratio 1.17, 95% CI 1.10–1.25
INVEST[15]	CAD with HT	22 576	2.7	75.7 75.7	69.2 72.8	No adverse outcome difference between the drugs. CV event risk was apparent in patients with HR >75 b.p.m. J-shape HR and events relation was observed.

Abbreviations: ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure-Lowering Arm; b.p.m., beats per minute; BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; HR, heart rate; HT, hypertension; INVEST, International Verapamil SR/Trandolapril Study; MI, myocardial infarction; MCE, major cardiovascular events; NA, not available; At, Atenorol; Los, Losaltan; Am, Amlodipine; ONTARGET, The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; TRANSCEDENT, The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease.

EVIDENCE DEMONSTRATING THE ASSOCIATION BETWEEN HR AND CV RISK AND TARGET ORGAN DAMAGE

Individuals with tachycardia often have characteristic features of insulin resistance syndrome, including high blood pressure, obesity, increased blood glucose and insulin levels, and an abnormal lipid profile.[16,17] An elevated HR not only coexists with these cardiometabolic risks but also can precede these cardiometabolic abnormalities,[18,19] indicating that HR is not merely an epiphenomenon of patient risk status. We examined the relationship between HR and cardiometabolic risk in ~10 000 healthy individuals and demonstrated that an elevated HR was independently associated with cardiometabolic risk clustering[17] and developing metabolic syndrome.[18] The elevated HR and sympathetic overactivation found in masked hypertension and white-coat hypertension are also consistent with this finding.[20,21] Multiple exaggerated spikes in postprandial blood glucose, free-fatty acids and triglycerides induced by the excessive intake of a high-calorie diet generate free radicals and trigger biochemical cascades of nitric oxide degeneration, inflammation, endothelial dysfunction, sympathoexcitation, parasympathetic depression and concurrent HR elevation.[22,23] These findings indicate that a lifestyle-induced increase in sympathetic drive may promote these cardiometabolic changes.

An elevated HR is also associated with target organ damage. In patients with high-risk hypertension, an elevated HR is an independent predictor of microalbuminuria.[24] We evaluated a total of 6759 healthy subjects and demonstrated that subjects with an elevated HR are likely to develop proteinuria in middle-aged or older.[25] Benetos *et al.*[26] found that an elevated HR is one of the most powerful predictors of the accelerated progression of arterial stiffness, as assessed by pulse-wave velocity.

EVIDENCE OF PHARMACOLOGIC HR LOWERING AND OUTCOME

Patients with chronic heart failure and acute myocardial infarction

Certain drug categories used for CV disease, for example, β-blockers and non-dihydropyridine calcium channel blockers, lower HR. Mortality reduction is evident with pharmacologic HR lowering in patients with chronic heart failure and acute myocardial infarction.[27,28] The reduction in HR is linearly related to mortality in this spectrum of subjects.

Ivabradine, which specifically acts on the sino-atrial node by inhibiting the I_f current of cardiac pacemaker cells, without affecting other cardiac ionic currents, recently became available. The I_f current, which goes through the I_f channel, is an important ionic current involved in the pacemaker activity of the sino-atrial node cells.[29] The degree of activation of the I_f channel determines the velocity of diastolic depolarization and thus determines the time at which the threshold for the initiation of an action potential is reached. Ivabradine specifically binds to the I_f channel and reduces the slope of spontaneous diastolic depolarization in these cells, without other hemodynamic effects.[30] This drug does not bind to calcium channels, muscarinic acetylcholine receptors, or β receptors. Studies using this characteristic drug reinforced the clinical significance of lowering HR. BEAUTIFUL[31] evaluated whether lowering HR with ivabradine reduced CV death and morbidity in CAD patients with left ventricular systolic dysfunction. Lowering HR, but not ivabradine use itself, improved the outcomes of CAD in a subgroup of patients with an HR of at least 70 b.p.m. (Figure 3). SHIFT[2] evaluated the effect of HR lowering on CV mortality and hospital admission for worsening heart failure in patients with symptomatic chronic heart failure with guideline-based heart failure therapy. The in-treatment HR was directly associated with the subsequent CV outcome. Patients with an HR lower than 60 b.p.m. on treatment had fewer CV events than patients with a higher HR. The effect of ivabradine is accounted for by the HR reduction (Figure 4). These results indicated that HR per se should be a therapeutic target.

Patients with stable CAD

Few clinical studies have demonstrated the effects of lowering HR in patients with stable CAD (Table 2). In the ASIST (Atenolol Silent Ischemia Study), atenolol reduced HR from 75 b.p.m. to 63 b.p.m., resulting in a reduction in CV events and other adverse events compared with placebo.[32] The BIP (Bezafibrate Infarction Prevention) study examined 2723 patients with diabetic CAD and demonstrated that β-blocker therapy is associated with a 42% reduction in total mortality (95% CI: 0.44–0.77) and a 34% reduction in cardiac mortality (95% CI: 0.46–0.96) compared with non-β blockers.[33] The TIBBS (Total Ischemic Burden Bisoprolol Study) compared the prognostic significance of bisoprolol and a sustained-release formulation of nifedipine and demonstrated that CV event rates were significantly lower in the

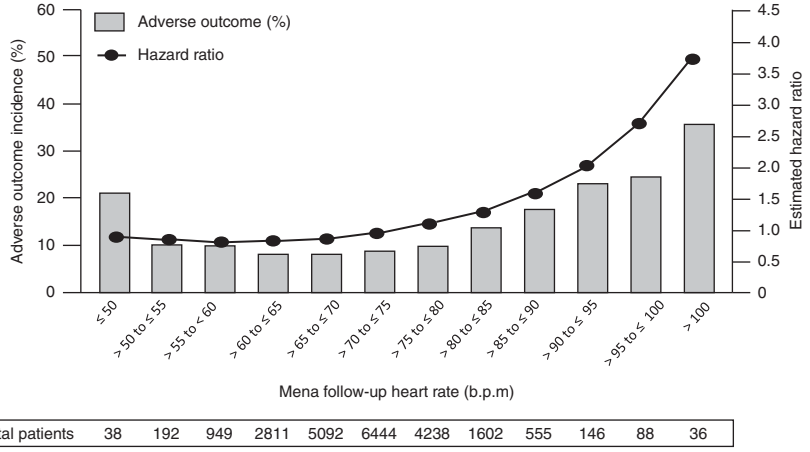
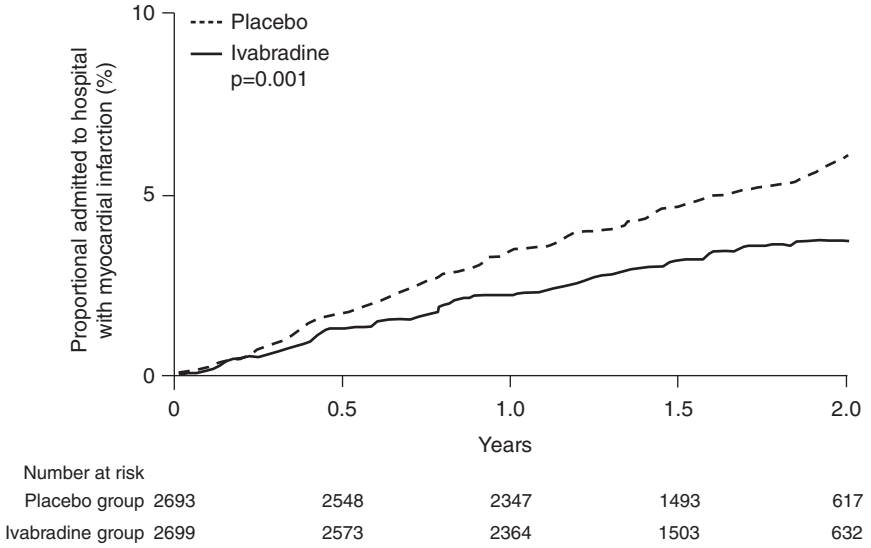


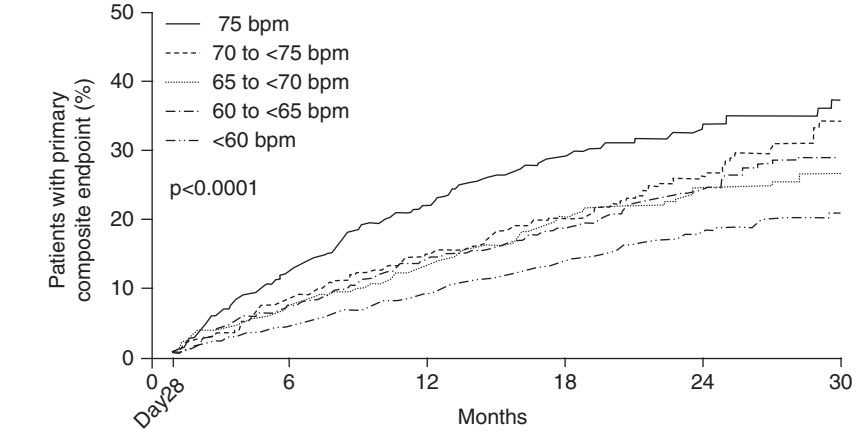
Figure 2 Relationship between in-treatment HR for INVEST (International Verapamil SR/Trandolapril Study) patients and incidence of adverse outcomes (left axis, bars) and risk (right axis -●-, hazard ratio) derived from a stepwise Cox proportional hazards model. The nadir for in-treatment HR was 59 b.p.m. Reprinted with permission from Kolloch *et al.*[15]



Number at risk

Placebo group	2693	2548	2347	1493	617
Ivabradine group	2699	2573	2364	1503	632

Figure 3 Kaplan–Meier time-to-event plots, by treatment group in a prespecified subgroup with HR of 70 b.p.m. or greater for secondary endpoints of admission to hospital for acute myocardial infarction in BEAUTIFUL. Reprinted with permission from Fox *et al.*[31]



Number at risk

75 bpm	527	451	376	291	141	47
70 to <75 bpm	344	314	276	221	116	41
65 to <70 bpm	444	404	358	287	149	62
60 to <65 bpm	605	556	488	407	176	59
<60 bpm	1192	1132	1004	842	414	162

Figure 4 Kaplan–Meier cumulative event curves for CV death or hospital admission for worsening heart failure in the ivabradine group, according to groups defined by HR achieved at 28 days in the SHIFT (Self-Harm Intervention, Family Therapy). Reprinted with permission from Bohm *et al.*[2]

bisoprolol group compared with the nifedipine group (22 *vs.* 31%, $P=0.033$).[34] The TIBET (Total Ischaemic Burden European Trial),[35] however, showed no advantage for atenolol other than a greater HR reduction, probably owing to the significant high withdrawal rate (27% for atenolol, 40% for nifedipine and 29% for combined use). The APSIS (Angina Prognosis Study in Stockholm)[36] and INVEST (International Verapamil SR/Trandolapril Study)[15] compared the prognostic effects of β-blockers (atenolol or metoprolol) and a HR-lowering calcium channel blocker (verapamil) and found no significant prognostic difference between the two therapeutic strategies. INVEST, however, reported that the in-treatment HR is associated with patient prognosis and increases in the mean follow-up resting HR from 70 to 80 b.p.m. are associated with a 31% increased risk of adverse outcomes.[15]

A real-world, large, contemporary database of stable CAD patients described an in-treatment HR of 68.3 b.p.m., and 75.1% of them were prescribed β-blockers.[37] Among the patients using β-blockers, 41.1% had a mean HR above 70 b.p.m., which was selected on the basis of the results of several studies to be an important prognostic threshold.[14,31,38]

Patients with uncomplicated hypertension

Hypertension is the leading cause of CVD, and blood pressure lowering is therefore the primary goal for patients with hypertension. There are several reports demonstrating that β-blockers do not improve the prognosis of patients with hypertension.[39,40] Bangalore *et al.*[41] demonstrated in their meta-regression analysis that HR

Table 2 Studies demonstrating the association between rate-limiting therapy using β-blocking agents and the prognosis of patients with stable CAD. The effect of risk reduction using β-blocking agents are shown in the table

					HR		
Study name	*Patients*	*No.*	*Follow (years)*	*Drug*	*Baseline*	*In-treatment*	*Results*
ASIST[32]	Silent ischemia	306	0.9	Ate Pla	75	63	All-cause death and CV events: RR 0.55, 95% CI 0.22–1.33
					75	75	Aggravation of angina: RR 0.35, 95% CI 0.17–0.72
							Adverse outcome: RR 0.44, 95% CI 0.26–0.75
BIP[33]	DM with CAD	2723	3	BB	70	N/A	Total mortality: RR 0.58, 95% CI 0.44–0.77
				Non BB	75	N/A	Cardiac mortality: RR 0.66, 95% CI 0.46–0.94
TIBBs[34]	Stable CAD	317	1	Bis	74.2	N/A	CV events rate:
				Nif	74.0	N/A	Bis 22.1% *vs.* Nif 33.1%, $P=0.033$
TIBET[35]	Stable CAD	682	2	Ate	N/A	−15.4	No difference in adverse outcome among the strategies
				Nif	N/A	+2.9	
				Com	N/A	−13.5	
APSIS[36]	Stable CAD	809	3.4	Met	N/A	N/A	All-cause death: OR 0.94, 95% CI 0.53–1.67
				Ver	N/A	N/A	All-cause death and CV events: OR 1.22, 95% CI 0.95–1.56
INVEST[15]	Stable CAD	22576	2.7	Ate	75.6	69.2	No adverse outcome difference between the drugs.
				Ver	75.5	72.8	CV event risk was apparent in patients with HR >75 b.p.m.
							J-shape HR and event relation were observed.

Abbreviations: ASIST, Atenolol Silent Ischemia Study; APSIS, Angina Prognosis Study in Stockholm; Ate, atenolol; BB, β-blocker; BIP, Bezafibrate Infarction Prevention; Bis, bisoprolol; CAD, coronary artery disease; CI, confidence interval; Com, combination; CV, cardiovascular; DM, diabetes mellitus; IHD, ischemic heart disease; INVEST, International Verapamil SR/Trandolapril Study; Met, metoprolol; MI, myocardial infarction; N/A, not available; Nif, nifedipine; NS, not significant; Pla, placebo; RR, relative risk; TIBET, Total Ischaemic Burden European Trial; TIBBs, Total Ischemic Burden Bisoprolol Study; Ver, verapamil.

lowering using a β-blocker increased the risk of a CV event in patients with hypertension. Their results, however, should be cautiously interpreted. The blood pressure of the β-blocker group was at most 9.2 mm Hg higher than that of most patients in the active control group. Accordingly, their result simply indicated that β-blockers are inferior to other drugs for blood pressure lowering. In the CAFÉ (Conduit Artery Functional Endpoint) study, an increase in central aortic pressure owing to HR lowering might have been the cause of increased CV events in a β-blocker-based strategy.[42] In the ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure-Lowering Arm) study, however, the SBP difference of 2.7 mm Hg between the β-blocker- and amlodipine-based regimens could explain the risk of stroke.[43] Moreover, the ASCOT-BPLA study demonstrated that the HR at 6 weeks was associated with nonfatal myocardial infarction and a fatal CHD outcome.[13]

HR AS A POSSIBLE THERAPEUTIC GUIDE

An elevated HR represents sympathetic overactivation and is comorbid with 'poor conditioning', such as cardiometabolic risks and target organ damage. It is logically plausible that in-treatment HR reduction leads to a better prognosis.[10,11] In fact, non-pharmacologic HR-lowering strategies, such as dietary supplementation with omega-3 fatty acids,[44] docosahexaenoic acid use,[45] exercise training,[46] body weight reduction[47,48] and lipid lowering by HMG-CoA (3-hydroxy-3-methyl coenzyme A) reductase inhibitors,[49] also reduce HR and lead to favorable outcomes. A serial assessment of HR in addition to the baseline HR may provide additional information about subsequent CV event risk. The in-treatment HR and decreases in HR can be used as possible therapeutic guides.

The resting HR is an established index for predicting the short- and medium-term prognoses of patients with acute coronary syndromes, and several risk scales have been developed.[50–54] Despite numerous epidemiologic studies, HR is not being used as an indicator of risk management in patients with hypertension and stable CAD who are often treated in actual medical practice. A resting HR of 70 b.p.m. is a critical prognostic threshold that is based on the results of several studies on patients with stable CAD.[14,31,38] In the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial,[55] optimal medical therapy included β-blockers and antiplatelet use in addition to a combined intensive reduction in blood pressure and serum lipid levels. Taking the 'optimal HR level' into account might be a therapeutic option and might contribute to reducing residual risk.[56]

HR is a ready-to-use, cost-effective biomarker. HR-guided patient care, in addition to the control of other cardiometabolic risk factors, contributes to a better prognosis for the prevention of CV events. Attention should be paid to the further evaluation of patients with a developing or persistent elevated HR during medication to identify possible underlying abnormalities.

CONCLUSION

HR is an independent predictor of all-cause and CV mortality. As HR is a target for the prevention of CV events, the clinical importance of HR as a therapeutic guide should be emphasized. HR-guided patient care allows for ready-to-use, cost-effective, CV risk reduction.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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