The role of heart rate reduction in angina management and beyond

This article highlights the significance of heart rate as an independent risk factor and prognostic marker for cardiovascular disease and examines the pharmacological measures available that lead to effective heart rate reduction.

Several large-scale epidemiological studies have shown that resting heart rate is a predictor of cardiovascular and all-cause mortality. An association between high heart rate and cardiovascular disease had been reported as early as the 1940s (Levy et al, 1945).

A sustained increase in resting heart rate is a strong predictor of death not only in patients with established vascular disease, diabetes and hypertension, but also in the general population (Diaz et al, 2005). It has been reported that a graded increase in risk of cardiovascular events occurs in heart rate above approximately 60 beats per minute (Fujiura et al, 2001). Hypothetically, a modest reduction in resting heart rate may substantially prolong life span. The mean resting heart rate in humans is 70 beats per minute, with a life expectancy of 80 years. It has been theorized that lowering heart rate from 70 beats per minute to 60 beats per minute may increase life expectancy to 93.3 years (Ferrari, 2003a), although such a hypothesis would need to be rigorously tested in large-scale human clinical trials, before any claim that life span may be prolonged by lowering heart rate in the non-cardiac patient could be made.

The total number of heart beats per lifetime remains strikingly constant among all mammals despite a 40-fold difference in life span. The Galapagos tortoise has a heart rate of 6 beats per minute with a life expectancy of 177 years and a total number of heart beats of about 5.6 x 10^8 in a lifetime. This figure is remarkably close to that obtained for a rat (6.3 x10^8) with a typical heart rate of 240 beats per minute and a life expectancy of only 5 years (Ferrari, 2003a). The inverse relationship between resting heart rate and life expectancy holds true across different species and is likely to represent an epiphenomenon in which heart rate is a marker of metabolic rate (Ferrari, 2003b). Generally, smaller mammals have higher heart rates and shorter life spans than larger members of their class (Ferrari, 2003b).

Adverse consequences of a high heart rate

There is mounting evidence from numerous epidemiological studies that implicates high resting heart rate as a risk marker and low heart rate variability as an independent risk factor in vascular disease (Dyer et al, 1980; Wilhelmsen et al, 1986; Kannel et al, 1987; Gillum, 1988; Gillum et al, 1991; Ferrari, 2003a; Singh, 2003). Many long-term follow-up studies suggest that elevated heart rate increases all-cause mortality and cardiovascular disease and it has also been associated with sudden cardiac death in patients with known or suspected coronary heart disease, survivors of myocardial infarction and those with hypertension (Singh, 2003; Shattock and Camm, 2006).

The heart rate profile during exercise and recovery has been shown to be a predictor of sudden death. In the Paris Prospective Study I (Jouven et al, 2005), 5713 asymptomatic working men between 42 and 53 years of age, none of whom had clinically detectable cardiovascular disease, underwent graded exercise testing. Data on increase in heart rate from rest to peak exercise and decrease in heart rate from peak exercise to 1 minute after exercise termination were recorded. During a 23-year follow-up period, the risk of sudden death from myocardial infarction was increased in individuals with a resting heart rate that was more than 75 beats per minute, in subjects with an increase in heart rate during exercise that was less than 89 beats per minute and in subjects with a decrease in heart rate of less than 25 beats per minute after termination of exercise.

High heart rate is associated with the metabolic disturbances that lead to hypertension and atherosclerosis (Ferrari, 2003a). In general, hypertensive patients have a higher heart rate than normotensive individuals (Gillum, 1988). A total of 4350 hypertensive persons (blood pressure >140/90 mmHg) between the ages of 35 and 74 years from the Framingham study were followed by Gillman et al (1993) for a period of 36 years. The investigators concluded that for those individuals who had an increase in heart rate in excess of 40 beats per minute, there was a 70% increase in the age, and systolic blood pressure, adjusted relative risk for cardiovascular mortality over the follow-up period. The increase in heart rate observed was not related to any other pre-existing conditions and was an independent risk factor for cardiovascular death. The extensive and prolonged follow up of the study individuals indicates that the adverse relationship of high heart rate and car-

Dr Lena Marie Izzat *is Associate Specialist Cardiologist in the Cardiology Department, Prince Philip Hospital, Llanelli SA14 8DR*

diovascular mortality was not caused by an underlying disease process resulting in tachycardia. Evidence shows similar associations between high heart rate and cardiovascular mortality in hypertensive individuals, particularly men (Palatini et al, 2006a).

The association between resting heart rate and mortality has also been observed in patients with the metabolic syndrome, the elderly, and in patients who have undergone coronary artery bypass surgery (Palatini et al, 1997, 2002; Fillinger et al, 2002; Di Francesco and Camm, 2004). Therefore, extensive data from epidemiological trials link high heart rate to a number of cardiovascular risk factors such as hypertension, insulin resistance, dyslipidaemia and obesity. This begs the question as to whether high heart rate is truly an independent risk factor for cardiovascular events. Most studies performed in disease-free individuals confirmed a significant association between high heart rate and total and cardiovascular mortality after adjusting for all possible confounding factors, including all traditional risk factor for atherosclerosis (Palatini et al, 2006a).

In patients with coronary heart disease, symptoms strongly correlate with high resting heart rate. The explanation is logical; an increase in heart rate increases myocardial oxygen demand and reduces myocardial perfusion by reducing diastolic perfusion time during the cardiac cycle. Myocardial ischaemia results from an imbalance between myocardial oxygen demand and blood supply, which is notable with increased heart rate.

In a post-hoc analysis of 24 913 patients with suspected or proven coronary heart disease from the Coronary Artery Surgery Study Registry, with a median follow up of 14.7 years, all-cause and cardiovascular mortality in addition to cardiovascular re-hospitalizations were significantly increased with increasing heart rates ($P<0.0001$). Importantly this was independent of other known risk factors such as hypertension, diabetes, smoking, left ventricular function and the number of diseased coronary vessels (Diaz et al, 2005).

How is resting heart rate determined?

A characteristic feature of the mammalian heart is its ability to maintain rhythmic contractions without the presence of external stimuli (Di Francesco and Camm, 2004). This spontaneous activity is initiated by pacemaker activity within the sinoatrial node which determines the overall heart rate. The natural pacemaker cells generate spontaneous, slow, diastolic depolarization that drives the membrane voltage away from a hyperpolarized level reached at the completion of one action potential towards the threshold level for initiation of a subsequent action potential. This generates rhythmic action potentials that propagate through the myocardium triggering contractions.

The I_f current is one of the most important ionic currents that control the sinoatrial node. It is characterized by the unusual property of being activated on hyperpolarization thus determining the diastolic depolarization slope which in turn controls heart rate. Agents which increase I_f current accelerate the heart rate and those that inhibit I_f slow the heart rate (Di Francesco and Camm, 2004).

The prospect of selective I_f current inhibition is very attractive in view of the often debilitating side effects seen with conventional heart rate-lowering drugs that target the atrioventricular node. Beta-blockers, for example, do reduce heart rate but also have negative inotropic effects, which limit their use in acute left ventricular failure, in addition to non-cardiovascular metabolic side effects and their contraindication in asthma and bronchospastic airways disease. The atrioventricular-blocking action itself may be undesirable in certain patients with a potential for variable degrees of atrioventricular block.

The benefits of heart rate reduction

The evidence linking increased heart rate to adverse clinical outcome suggests that heart rate reduction may be a valuable therapeutic option for patients with established coronary heart disease. Patients with angina pectoris experience worsening ischaemic symptoms in circumstances that lead to an increase in heart rate, such as effort and emotion. Most episodes of silent ischaemia are often preceded by a period of increased heart rate and the success of different medications in preventing these episodes is often related to their efficacy in reducing heart rate (Di Francesco and Camm, 2004; Diaz et al, 2005).

Increased heart rate has also been associated with the progression of atherosclerosis and coronary plaque instability, which may both result in adverse clinical outcomes. This relationship has been shown in young male post-myocardial infarction patients (Perski et al, 1988). Experimental and clinical evidence suggests that a slower heart rate might improve both these important pathophysiological determinants.

The success of heart rate-limiting pharmacological agents in the management of patients with cardiovascular disease has highlighted the importance of targeting heart rate. Beta-blockers, at doses that significantly reduce heart rate, have proven invaluable in improving the symptoms, quality of life and functional classification of patients with chronic stable angina. The majority of the beneficial effect of beta-blockers in stable angina stems from lowering heart rate and they have been classed as first-line therapy in the absence of contraindications (Fox et al, 2006). Despite their important symptomatic and clinical benefit in chronic stable angina, beta-blockers have not been shown to alter prognosis in this group of patients (Fox et al, 2006) unless there is a history of previous myocardial infarction or heart failure.

In post-myocardial infarction patients, increased heart rate during hospitalization and at discharge is predictive

of mortality from discharge to 1 year, even in absent to mild heart failure (Hjalmarson et al, 1990). The risk of cardiovascular death and re-infarction in post-myocardial infarction patients is consistently reduced with beta-blockers by about 30% (Ferrari, 2003b). They reduce both the resting heart rate and the heart rate response to exercise. Rate-limiting calcium-channel blockers such as diltiazem and verapamil also have a favourable effect in the post-myocardial infarction population, but short-acting dihydropyridines, which can increase heart rate, have no favourable effect and could even lead to a worse prognosis in some cases (Furberg et al, 1995), adding further weight to the evidence that heart rate reduction is an important factor in the post-myocardial infarction patient.

Retrospective studies have shown a beneficial effect of heart rate-lowering agents such as beta-blockers and non-dihydropyridine calcium-channel blockers in hypertensive patients, particularly those with coronary heart disease. However, to date there are no prospective randomized controlled trials specifically designed to demonstrate the benefit of pharmacological reduction of heart rate on cardiovascular outcomes in hypertensive individuals free from overt coronary heart disease (Palatini et al, 2006b; Grassi, 2007).

Unlike the marked beneficial effect seen with beta-blockade in the ischaemic heart disease or post-myocardial infarction patient, the results obtained for beta-blockers in uncomplicated hypertension have been lower than expected (Dahlöf et al, 2002). The valuable benefits likely to be achieved with lower heart rate may be counterbalanced by adverse metabolic consequences, with a significant increase in new onset diabetes (Gillum et al, 1993). In the absence of outcome trials, the use of antihypertensive agents with bradycardia-inducing effects has been advocated only when tachycardia is symptomatic to the patient and have also stressed the role of aerobic exercise for controlling both the heart rate and blood pressure (Palatini et al, 2006a).

Heart failure deserves particular attention in view of its generally poor prognosis, especially in the post-myocardial infarction patient. Numerous clinical trials of heart failure have demonstrated a negative correlation between heart rate and life expectancy. This has been observed regardless of whether patients are treated with beta-blockers (Tavazzi, 2003). It is often difficult to decide whether the increased heart rate observed in heart failure patients is a marker of a compensatory mechanism related to the disease process and resultant renin–angiotensin and sympathetic nervous system stimulation, or an actual contributor to the disease.

Analysis of some of the major angiotensin-converting enzyme inhibitor trials have indicated that the beneficial effects of neurohormonal modulation were most marked in patients with heart failure and higher heart rates (Swedberg et al, 1990). Therefore heart rate reduction has emerged as an important therapeutic target in heart failure. Trials of beta-blocker treatment in heart failure have demonstrated consistent reductions in mortality in the order of approximately 35% and these effects have been associated with a reduction in heart rate of 10–15 beats per minute, providing supportive evidence that heart rate may be one of the important targets in the management of heart failure (Tavazzi, 2003).

However, data from CIBIS II indicate that the mortality reduction achieved with bisoprolol compared with placebo was similar at all levels of heart rate reduction and at all levels of baseline heart rate. These data show that heart rate reduction is not the sole mechanism of beta-blocker induced benefit in heart failure patients and numerous alternative mechanisms have been proposed (Lechat et al, 2001). It is notable, however, that the best survival results overall were obtained within the beta-blocker group when heart rate reduction was at its highest (>10 beats per minute), regardless of baseline, as long as this was not associated with a marked fall in systolic blood pressure (Lechat et al, 2001).

The concept of pure heart rate reduction in angina

Chronic stable angina is a common medical condition affecting 30 000–40 000 per million of the population in Europe and the USA (Tardif, 2005). Statistics from the British Heart Foundation show that there are 338 000 new cases of angina every year and the current UK prevalence of angina in those over 75 years of age is 1.2 million (British Heart Foundation, 2004).

Management of symptoms and improving quality of life are major goals in the management of angina. The major drug classes used in the management of anginal symptoms include beta-blockers, calcium-channel blockers, nitrates and potassium-channel openers (Gibbons et al, 1999; Fox et al, 2006). Antiplatelet agent, statins and angiotensin-converting enzyme inhibitors are used for secondary prevention of cardiac events in these patients (Fox et al, 2006). Current guidelines suggest that patients should be managed with a trial of medical therapy before consideration of percutaneous or surgical revascularization (Fox et al, 2006). Moreover, revascularization is not always practical in patients with significant co-morbidity.

Beta-blockers and non-dihydropyridine calcium-channel blockers reduce heart rate which is fundamental in controlling anginal symptoms. Beta-blockers are the preferred first line in chronic stable angina in the absence of contraindications (Fox et al, 2006). They have a good overall safety and efficacy track record. However, patient compliance can be limited because of the numerous side effects of this class of drugs such as fatigue, depression, erectile dysfunction, cold peripheries and hypotension (Ko et al, 2002). In addition the metabolic adverse consequences can be significant (Krone and Nagele, 1988). Beta-blockers can exacerbate vasospastic angina and their

negative inotropic effect may exacerbate heart failure in some patients with impaired left ventricular function (Bortone et al, 1990). Up to one fifth of patients with stable angina fail to respond adequately to beta-blockers (Gillum, 1988).

Calcium-channel blockers such as diltiazem and verapamil can lower the heart rate by 6–7 beats per minute and have been shown to reduce the risk of death and non-fatal re-infarction in acute myocardial infarction survivors, with no evidence of clinical heart failure or impaired left ventricular function (The Multicenter Diltiazem Post-Infarction Trial Research Group, 1988; The Danish Study Group on Verapamil in Myocardial Infarction, 1990; Ferrari, 2003b). Therefore overt heart failure is a contraindication for the use of most calcium antagonists, with the exception of new vasoselective dihydropiridines.

Many side effects have been reported with these agents, particularly hypotension, worsening heart failure, peripheral oedema, constipation, headache and flushing (The Multicenter Diltiazem Post-Infarction Trial Research Group, 1988). These side effects often limit patient compliance. Moreover, the use of conventional therapies often fails to optimally manage and prevent anginal episodes and hence a true unmet need exists in the medical management of this common medical problem.

The recent addition of the selective sinus node inhibitor ivabradine is likely to play a key role in the armamentarium in patients with angina, where beta-blockers are contraindicated or not tolerated. Ivabradine binds specifically to I_f channels in the sinoatrial node, inhibiting the I_f current, thus reducing the slope of the diastolic depolarization curve, with a consequent reduction in heart rate. This drug provides dose-dependant negative chronotropic effects both at rest and during exercise and has proven anti-anginal and anti-ischaemic efficacy, which has been demonstrated in a number of clinical trials (Gillum, 1988; Lopez-Bescos et al, 2004; Ruzyllo et al, 2004; Tardif et al, 2005). The beneficial effects of ivabradine are at least equivalent to those of atenolol during exercise testing of patients with stable angina (Tardif et al, 2005). This benefit is maintained in patients over the age of 65 years (Fox et al, 2005). Similar non-inferiority of ivabradine has been demonstrated in comparison to amlodipine in the prevention of angina and ischaemic symptoms (Ruzyllo et al, 2004).

The highly selective reduction in heart rate achieved with ivabradine means that it can offer pure slowing of heart rate without other cardiovascular consequences; in particular the lack of a negative inotropic effect makes it an attractive potential contender for the management of ischaemia in patients with heart failure. The BEAUTIFUL trial, a major morbidity and mortality trial, is underway to assess the role of ivabradine in patients with coronary heart disease and left ventricular systolic dysfunction (Gillum, 1988).

Ivabradine appears to be well tolerated with very little in the way of adverse events in its clinical trial programme (Lopez-Bescos et al, 2004). Ivabradine has not shown any evidence of rebound tachycardia and angina upon its withdrawal, unlike the phenomenon observed upon abrupt withdrawal of short-acting beta-blockers (Lewis and Lofthouse, 1993). Despite the selectivity of ivabradine to I_f channels, it may also interact with the structurally similar I_h channels in the retina. Transient visual symptoms with abrupt changes in light intensity (phosphenes) have been reported in approximately 2% of patients treated with the commonly used 5 mg twice daily dose with less than 1% withdrawal rate (Gillum, 1988). The use of ivabradine has been advocated for consideration by the updated guidance from the European Society of Cardiology for the management of stable angina in cases of beta-blocker intolerance or contraindication (Fox et al, 2006).

Conclusions

A wealth of clinical and epidemiological data indicate that a sustained increased heart rate is an independent risk factor for mortality in patients with established coronary artery disease, previous myocardial infarction, hypertension, heart failure and the elderly. Sudden cardiac death has been shown to be associated with an increased heart rate. Accordingly, heart rate reduction has become increasingly recognized as a therapeutic target to improve the outcome in patients with ischaemic heart disease.

Beta-blockers have been classed traditionally as first-line treatment for patients with ischaemic heart disease and angina, but their role is often limited by contraindications and side effects. The survival benefit associated with beta-blockers has been proven in post-myocardial infarction patients and in those with heart failure, earning them an integral role in the management of these conditions. However, to date, improved survival end points have not been documented in patients with chronic stable angina treated with beta-blockers, despite the favourable effect on symptoms and quality of life. A significant proportion of the favourable effect achieved

KEY POINTS

- Heart rate is an important risk factor and prognostic marker for cardiovascular disease.
- Epidemiological studies suggest an inverse relationship between resting heart rate and life expectancy regardless of clinically detectable coronary disease.
- The established beneficial role of beta-blockers in coronary disease, myocardial infarction and heart failure may be attributable to heart rate reduction.
- Heart rate reduction with beta-blockers and rate-limiting calcium antagonists is limited by numerous side effects and contraindications.
- Pure heart rate reduction by sinoatrial node inhibition with ivabradine is a good treatment choice in patients with stable angina where a beta-blocker is contraindicated or poorly tolerated.

with beta-blockers in angina is attributable to their heart rate-lowering efficacy. Therefore a pure heart rate-limiting agent such as ivabradine, devoid of negative inotropic effects and effects on coronary vasomotion, may prove to be a key player in the management of stable angina in those with contraindications or intolerance to beta-blockers. **BJHM**

Conflict of interest: Dr Izzat has served on advisory boards and delivered lectures sponsored by AstraZeneca, MSD, Novartis and Servier Laboratories.

Bortone AS, Hess OM, Gaglione A et al (1990) Effect of intravenous propranolol on coronary vasomotion at rest and during dynamic exercise in patients with coronary artery disease. *Circulation* **81:** 1225–35

British Heart Foundation (2004) *Statistics Factsheet.* British Heart Foundation Health Promotion Research Group, Department of Public Health, University of Oxford

Dahlöf B, Devereux RB, Kjeldsen SE et al (2002) Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* **359:** 996–1003

Diaz A, Bourassa MG, Guertin M-C, Tardif J-C (2005) Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. *Eur Heart J* **26:** 967–74

Di Francesco D, Camm J (2004) Heart rate lowering by specific and selective I_f current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. *Drugs* **64**(16): 1757–65

Dyer A, Persky V, Stamler J et al (1980) Heart rate as a prognostic factor for coronary heart disease and mortality: Findings in three Chicago epidemiologic studies. *Am J Epidemiol* **112:** 736–49

Ferrari R (2003a) Prognostic benefits of heart rate reduction in cardiovascular disease. *Eur Heart J* **5**(Suppl G): G10–G4

Ferrari R (2003b) Editorial: Heart Rate. *Eur Heart J* **5**(Suppl G): G1–G2

Fillinger MP, Surgenor SD, Hartman GS et al (2002) The association between heart rate and in-hospital mortality after coronary artery bypass graft surgery. *Anaesth Analg* **95**(6): 1483

Fox KM, Tardif JC, Ford M, Tendera M on behalf of the INITIATIVE study investigators (2005) Anti-anginal and anti-ischemic efficacy of ivabradine - a selective and specific sinus node If current inhibitor - compared to atenolol in elderly patients with chronic stable angina. *Heart* **91**(Suppl 1): A69

Fox K, Garcia MA, Ardissino D et al (2006) Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur Heart J* **27:** 1341–81

Fujiura Y, Adachi H, Tsuruta M, Jacobs DRJ, Hirai Y, Imaizumi T (2001) Heart rate and mortality in a Japanese general population. An 18-year follow-up study. *J Clin Epidemiol* **54:** 495–500

Furberg CD, Psaty BM, Meyer JV (1995) Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. *Circulation* **92:** 1326–31

Gibbons RJ, Chatterjee K, Daley J et al (1999) ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* **33:** 2092–219

Gillman M, Kannel W, Belanger A, D'Agostino R (1993) Influence of heart rate on mortality among persons with hypertension: The Framingham study. *Am Heart J* **125:** 1148–54

Gillum R (1988) The epidemiology of resting heart rate in a national sample of men and women: association with hypertension, coronary heart disease, blood pressure, and other cardiovascular risk factors. *Am Heart J* **116:** 163–74

Gillum R, Makuc D, Feldman J (1991) Pulse rate, coronary heart disease, and death: The NHANES I epidemiologic follow-up study. *Am Heart J* **121:** 172–7

Grassi G (2007) Heart rate as a marker of cardiovascular risk: Lights and shadows. *E journal of Cardiology Practice* **5**(21) (www.escardio.org/knowledge/cardiology_practice/ejournal_vol5/vol5n21.htm accessed 25 March 2008)

Hjalmarson A, Gilpin EA, Kjekshus J et al (1990) Influence of heart rate on mortality after acute myocardial infarction. *Am J Cardiol* **65**(9): 547–53

Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetière P (2005) Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* **352:** 1951–8

Kannel C, Paffenbarger R, Cupples A (1987) Heart rate and cardiovascular mortality: The Framingham study. *Am Heart J* **113:** 1489–94

Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM (2002) Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA* **288:** 351–7

Krone W, Nagele H (1988) Effects of antihypertensives on plasma lipids and lipoprotein metabolism. *Am Heart J* **116:** 1729–34

Lechat P, Hulot JS, Escolano S et al (2001) Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II Trial. *Circulation* **103:** 1428–33

Levy RL, White PD, Stroud WD, Hillman CC (1945) Transient tachycardia: prognostic significance alone and in association with transient hypertension. *JAMA* **129:** 585–8

Lewis RV, Lofthouse C (1993) Adverse reactions with beta-adrenergic blocking drugs: an update. *Drug Safety* **9:** 272–9

Lopez-Bescos L, Filipova S, Martos R et al (2004) Long-term safety and antianginal efficacy of the If current inhibitor ivabradine in patients with chronic stable angina. A one-year randomized, double-blind, multicentre trial. *Eur Heart J* **25:** 876

Palatini P, Casiglia E, Pauletto P et al (1997) Relationship of tachycardia with high blood pressure and metabolic abnormalities: a study with mixture analysis in three populations. *Hypertension* **30:** 1267–73

Palatini P, Thijs L, Staessen JA et al (2002) Predictive value of clinic and ambulatory heart rate for mortality in elderly subjects with systolic hypertension. *Arch Intern Med* **162:** 2313–21

Palatini P, Benetos A, Grassi G et al (2006a) Identification and management of the hypertensive patient with elevated heart rate: statement of a European Society of Hypertension Consensus Meeting. *J Hypertens* **24:** 603–10

Palatini P, Benetos A, Julius S (2006b) Impact of increased heart rate on clinical outcomes in hypertension. Implications for antihypertensive drug therapy. *Drugs* **66**(2): 133–44

Perski A, Hamsten A, Lindvall K, Theorell T (1988) Heart rate correlates with severity of coronary atherosclerosis in young postinfarction patients. *Am Heart J* **116**(5 Pt 1): 1369–73

Ruzyllo W, Ford I, Tendera M et al (2004) Antianginal and anti-ischemic effects of the If curent inhibitor ivabradine compared to amlodipine as monotherapy in patients with chronic stable angina: a 3-month randomized, controlled, double-blind, multicenter trial. *Eur Heart J* **25**(Suppl): 878

Shattock M, Camm J (2006) Pure heart rate reduction: the I_f channels from discovery to therapeutic target. *Br J Cardiol* **13:** 27–35

Singh BN (2003) Increased heart rate as a risk factor for cardiovascular disease. *Eur Heart J* **5**(Suppl G): G3–G9

Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L (1990) Hormone regulation of cardiovascular function in patients with severe congestive heart failure and their relation to mortality. *Circulation* **82:** 1730–7

Tardif J-C (2005) Ivabradine in clinical practice: benefits of If inhibition. *Eur Heart J* **7**(Suppl): H29–H32

Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K, INITIATIVE Investigators (2005) Efficacy of ivabradine, a new selective If inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J* **26:** 2529–36

Tavazzi L (2003) Heart rate as a therapeutic target in heart failure? *Eur Heart J* **5**(suppl G): G15–G18

The Danish Study group on Verapamil in Myocardial Infarction (1990) Secondary prevention with verapamil after myocardial infarction. *Am J Cardiol* **66**(21): 33I–40I

The Multicenter Diltiazem Post-Infarction Trial Research Group (1988) The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* **319:** 385–91

Wilhelmsen L, Berglund G, Elmfeldt D et al (1986) The multifactor primary prevention trial in Göteborg, Sweden. *Eur Heart J* **7:** 279–88