European Heart Journal Supplements (2008) **10** (Supplement F), F17–F21
doi:10.1093/eurheartj/sun022

Heart rate management: a therapeutic goal throughout the cardiovascular continuum

Jose Luis Zamorano*

Hospital Clinico San Carlos, Plaza de Cristo Rey, 28040 Madrid, Spain

KEYWORDS
Heart rate;
Risk factors;
Cardiovascular disease continuum;
Coronary artery disease

A number of physiological pathways and risk factors leading to cardiovascular disease (CVD) are now well identified, although there are still aspects to be investigated. An interesting concept has been developed called the CVD continuum which frames CVD as a chain of events initiated by a number of risk factors leading to end stage of the disease with the hypothesis that any interruption along this chain of events may interrupt the pathological process thereby conferring cardiovascular prevention. In recent years, heart rate (HR), a simple and familiar clinical finding, has been shown to be an independent risk factor of mortality and morbidity in various populations including patients with CVDs. This review shows that high HRs intervene along the chain of events which constitutes the cardiovascular continuum promoting CVD. Experimental data and clinical observations that demonstrate the major role played by resting HR in the pathophysiology of atherosclerosis through the stress exerted on the vascular endothelium leading to atherosclerotic lesion formation and plaque rupture are reviewed. Therefore, HR reduction should lead to prevention of atherosclerosis and therefore to the reduction of cardiovascular events. Trials have been undertaken to answer this question and the results are expected in the near future.

Introduction

Cardiovascular disease (CVD) is common in the general population and represents an important public health problem. A number of physiological pathways leading to CVD have been identified, although there are still a number of processes which remain to be clarified. Dzau *et al.*[1] came out in 1991 with a concept called the CVD continuum which framed CVD as a chain of events initiated by a number of risk factors leading to end stage of the disease and hypothesized that any interruption along this chain of events may interrupt the pathological process thus conferring cardiovascular prevention.[2] In recent years, heart rate (HR), a simple and familiar clinical finding, has been shown to be an independent risk factor of mortality and morbidity in various populations including CVD.[3–6]

The aim of this paper is to show how high HR may intervene to promote CVD along the chain of events which constitute the cardiovascular continuum.

The cardiovascular disease continuum

Epidemiological studies have identified well-known risk factors such as dyslipidaemia, arterial hypertension, diabetes mellitus, smoking, and obesity, mainly visceral adiposity as part of the so-called metabolic syndrome.[7,8] These risk factors may promote atherosclerosis and/or left ventricular (LV) hypertrophy. The most common and life-threatening manifestation of atherosclerosis is coronary artery disease which has two major clinical presentations, i.e. stable angina pectoris related to myocardial ischaemia and acute myocardial infarction. Among the possible complications of myocardial infarction, ventricular arrhythmias with the risk of sudden cardiac death and loss in myocardial tissue inducing ventricular remodelling and ventricular

* Corresponding author. Tel: +34 91 3303290; fax: + 34 91 3303292.
E-mail address: jlzamorano@vodafone.es

enlargement leading to heart failure and end-stage heart disease are life-threatening (*Figure 1*). This review article aims to demonstrate how HR may intervene in the cascade of events that constitute the CVD continuum.[1]

Heart rate and cardiovascular mortality

Many clinical or epidemiological studies have shown that resting HR is an independent risk factor of total mortality and cardiovascular mortality. These studies have been analysed by Aboyans *et al*. and others.[9–12] Overall, they include 15 500 patients followed up for 8–36 years. For example, the 'Chicago Peoples Gas Company study' included 1233 men followed up for 15 years. Two other cohorts of patients belonging to the 'Chicago Western Electric Company' and to the 'Chicago Heart Association Detection Project' included 1899 and 5784 men followed up for 17 and 5 years, respectively.[3] A relation was found between HR and cardiovascular mortality and total mortality. Similarly, the Framingham study showed with a 30-year follow-up that a significant relationship exists in men as in women, between high resting HR and the increase in cardiovascular mortality, coronary heart disease, and sudden coronary death.[4] The MATISS Project included 2533 men aged 40–69 followed up for a total of 24 457 subject-years and showed that HR was an independent predictive factor for total mortality, cardiovascular mortality and non-cardiovascular mortality.[5] Jouven *et al*.[6] reported a French population of 5713 asymptomatic working men (between the ages of 42 and 53 years) with a 23-year follow-up and found that after adjustment for potential confounding variables resting HR was significantly associated with an increase in sudden death and non-sudden death from myocardial infarction. Wide variations of HR were analysed in these studies. Some compared HR of $\leq$60 bpm with HR above 90 or even 100 bpm Jouven *et al*.[6] compared those subjects with a resting HR above 75 bpm with those with a HR below 60 bpm and found that those with high HR had a relative risk of sudden death from a myocardial infarction of 3.92 (95% CI).

The question of the optimal HR often arises and faces the difficulty of the wide variation seen over a 24-h period with a circadian rhythm, the fact that HR decreases with age, that HR is generally higher in women than in men, and that it varies with the position (sitting vs. supine) in which it is measured.[10] Palatini *et al*.[13] recommend in a consensus that HR should be measured by pulse palpation over two periods of 30 s each after 5 min in a quiet room in a sitting position.

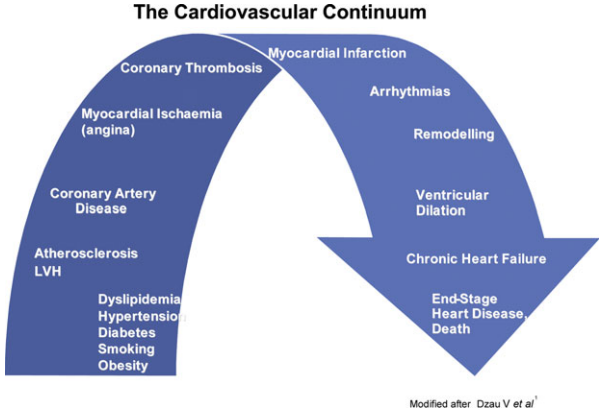

Figure 1 The cardiovascular disease continuum. Modified after Dzau *et al*.[1,2]

Cardiovascular disease and the pathophysiological continuum

The pathophysiological processes known to initiate CVD include oxidative stress, endothelial dysfunction, inflammation, and vascular remodelling (*Figure 1*). Knowledge gained in the understanding of these processes has promoted the development of new therapeutic strategies. These processes may lead to tissue damage characterizing atherosclerotic disease. Oxidative stress results in reduction in nitric oxide (NO) activity and endothelial dysfunction. The latter induces pathological vascular responses, e.g. vasoconstriction, inflammation, muscle cell proliferation, and thrombosis.[1,2] The renin–angiotensin–aldosterone system plays an important role in the CVD continuum. Inhibition of angiotensin-converting enzyme and angiotensin II through the AT1 receptors is used in the management of CVD, particularly the treatment of hypertension and of congestive heart failure (CHF). Other hormones such as atrial natriuretic peptide and brain natriuretic peptide, endothelin, prostacyclin, and prostaglandin E are also involved in the pathophysiology of CVD.[1] Inflammation is associated with endothelial injury and with the development of atherosclerosis to the point that C-reactive protein has become a marker of CVD risk. Vascular remodelling represents the structural transformation resulting from changes of haemodynamic conditions as seen in arterial hypertension. It is important to underline that several processes are taking place simultaneously to generate CVD.

Experimental evidence of the role of heart rate in the cardiovascular continuum

In order to understand the role of HR in endothelial dysfunction and atherosclerotic lesions, basic knowledge of local haemodynamic forces imposed on the arterial wall is necessary. These forces include flow-generated shear stress which is the tangential forces due to the friction of the blood flowing on the endocardial surface and blood-pressure-derived tensile stress, also called circumferential stress, which represent the blood-pressure-derived force imposed on the circumference of the arterial wall.[14] Low shear stress stimulates mechanoreceptors located on the surface of endothelial stress transducing them into biochemical signals (mechanicotransduction) which cannot be developed in detail here but which are well explained in the excellent review of Giannoglou *et al*.[14] Tensile stress is also sensed by mechanoreceptors which trigger a cascade of signalling molecules. Elevated tensile stress is thought to induce direct endothelial injury and to increase endothelial permeability to LDL

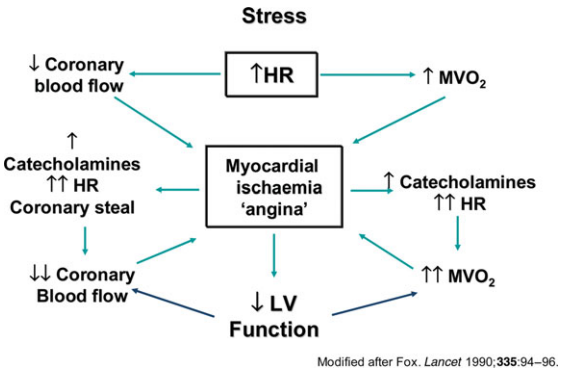

Figure 2 Mechanism of myocardial ischaemia as a mismatch between oxygen demand and oxygen supply by coronary blood flow.

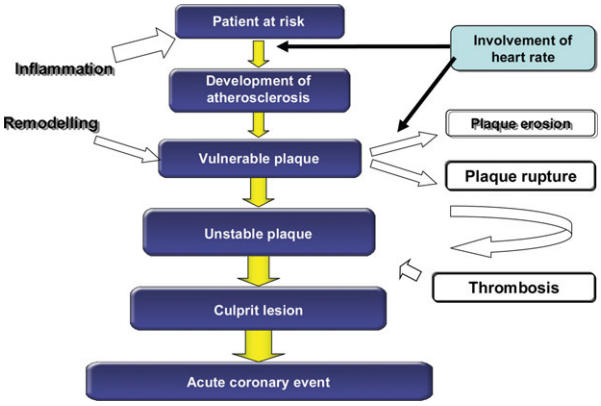

Figure 3 Role of heart rate in the development and progression of atherosclerosis (see text).

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 blood pressure and the tensile stress and may promote endothelial injury and wall stiffness.

The role of HR in myocardial ischaemia as seen in patients with stable angina and those who suffered a myocardial infarction is also well established (*Figure 2*). It is well known that increased HR is present in angina pectoris and myocardial ischaemia as a consequence of exercise or emotional stress. Several mechanisms may account for the increase in HR including catecholamine discharge. Kop *et al.*[15] analysed HR variability (HRV) 1 h before and after ischaemic events in 19 patients who underwent 24 h ambulatory recordings and assessed the role of exercise and mental stress on pre-ischaemic autonomic changes. Ischaemic events at high mental stress were preceded by depressed high frequency HRV levels compared with events at low mental activity, whereas the effects of mental activities were not observed during non-ischaemic control periods.

HR may be involved at different phases of the development of atherosclerosis, in plaque erosion, and plaque rupture resulting in thrombosis and in acute coronary event (*Figure 3*).

Experimental evidence supports the role of HR reduction in the progression of atherosclerosis. Beere *et al.*[16] investigated the role of HR reduction in six monkeys (*Macaca fascicularis*) fed with an atherogenic high cholesterol diet for 6 months. These animals underwent sinus node ablation and compared with eight animals which had the same operation without sinus node ablation. Coronary atherosclerosis was less than half in the group with low HR related to sino-atrial ablation when compared with the control group without sino-atrial ablation suggesting a protective effect of lower HR. Yamamoto *et al.*[17] in an isolated sino-atrial preparation in hypertensive rats showed that the increase in HR with cardiac pacing, therefore independent of sympathetic nerve activity, enhances cardiac oxidative stress and activates mitogen-activated protein kinases, which seem implicated in cardiac hypertrophy and cardiac remodelling. Guth *et al.*[18] evaluated the beneficial effect of intravenous atenolol on exercise-induced regional myocardial ischaemia and contractile dysfunction in conscious dogs with single-vessel coronary stenosis. The regional dysfunction was reduced with atenolol but the improvement is prevented if HR is kept constant with atrial pacing. Therefore, HR reduction may play an important role in the CVD continuum.

Heart rate reduction and cardiovascular risk reduction in man

Beta-blockers have been shown to reduce total mortality and sudden cardiac death after myocardial infarction. At least part of their beneficial effects has been ascribed to their effect on HR.[19] Furthermore, a recent meta-regression of randomized clinical trials of beta-blockers and calcium channel blockers in post-myocardial infarction patients strongly suggests that the beneficial effect of these agents is proportionally related to resting HR reduction.[20] A statistically significant relationship was found between resting HR reduction and reduction in cardiac death, all-cause death, sudden death, and non-fatal MI recurrence. Each 10 bpm reduction in the HR is estimated to reduce the relative risk of cardiac death by 30% (*Figure 4*). This meta-regression of the randomized clinical trials strongly suggests that resting HR reduction could be a major determinant of the clinical benefit in these trials. Recently, this hypothesis was tested within randomized controlled trials of beta-blockers in systolic CHF. There was a close relation between all-cause

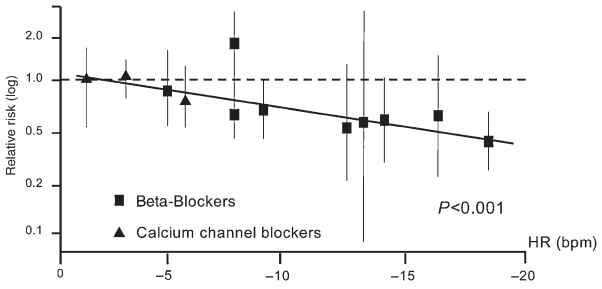

Figure 4 Heart rate lowering is associated with reduction in cardiac deaths in post-myocardial infarction patients. From Cucherat.[20]

annualized mortality rate and HR. A strong correlation between change in HR and change in LV ejection fraction was also observed.[21]

These data suggest that HR reduction is indeed a major component of the prognostic benefit in post-MI and CHF trials with beta-blockers and therefore should be an important therapeutic goal for the improvement of prognosis.

The mechanisms by which HR influences the outcome has not been completely unravelled. It is well known that exercise training is associated with lower resting HR. In fact, exercise capacity was found to be a strong predictor of mortality.[22] HR is also determined by the influence of the autonomic nervous system balance. The major effect of beta-blockers is HR reduction but other actions may operate. A significant proportion of patients with myocardial infarction or myocardial ischaemia do not receive beta-blockers, probably because the common occurrence of side effects or contraindication in patients with asthma, hypotension, and atrioventricular conduction disorders, together with their negative inotropic effect, limit their use. Therefore, there is a need for developing new agents to obtain HR reduction in vast majority of patients.

Ivabradine is a new medication that has HR-lowering properties without other direct cardiovascular effects. Ivabradine is the first of a new class of agents that act specifically on the sino-atrial node by inhibiting the I_f 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.[23]

Ivabradine has been investigated in patients with stable coronary artery disease. A double-blind, placebo-controlled study in patients with chronic stable angina showed that ivabradine produced dose-dependent improvements in exercise duration and time to development of exercise-induced ischaemia.[24] Ivabradine showed anti-anginal and anti-ischaemic efficacy compared with such well-established reference anti-anginal drugs, such as beta-blockers and calcium antagonists.[25,26] Ivabradine was also found to have beneficial effects on cardiac remodelling, capillary density, and LV dysfunction.[27,28] In a rat model of CHF, Mulder *et al*. showed that chronic administration of ivabradine induced a dose-dependent reduction in HR without modification in systemic haemodynamics. Cardiac output was preserved despite the decrease in HR because stroke volume is increased owing to a decrease in LV end-systolic diameter.[28] This improvement in LV function was attributed to a possible modification of LV structure and/or of myocyte properties. Therefore, patients with coronary artery disease and LV systolic dysfunction may derive benefit from additional HR reduction with ivabradine. Whether the use of ivabradine in patients with coronary artery disease or heart failure results in the reduction in cardiovascular morbidity-mortality remains to be demonstrated. This prompted the BEAUTIFUL study, a large, international, randomized, placebo-controlled mortality trial in a high-risk population of coronary artery disease patients with LV dysfunction.[29] The ongoing SHIFT trial was designed to assess the prognostic value of pure HR reduction in patients with heart failure.[30]

Conclusions

The concept of the CVD continuum based on the hypothesis that CVD is the result of a chain of events initiated by risk factors leading to end stage of the disease and that any interruption along this chain of events may interrupt the pathological process thus conferring cardiovascular prevention has been validated by large clinical trials. HR intervenes in different phases of the CVD continuum as supported by epidemiological studies, experimental data and clinical observations showing the role that HR plays in the pathophysiology of atherosclerosis and the stress exerted on the vascular endothelium leading to atherosclerotic lesion formation and plaque rupture. Therefore, HR reduction by the new HR-lowering agent ivabradine should lead to the prevention of atherosclerosis via reduction in endothelial dysfunction and result in the reduction in cardiovascular events. Trials have been undertaken to answer this question and the results are expected in the near future.

Conflict of interest: none declared.

References

1. Dzau VJ, Antman EM, Black HR, Hayes DL, Manson JE, Plitzky J, Popma JJ, Stevenson W. The cardiovascular disease continuum validated: clinical evidence of improved outcome. Part I. Pathophysiology and clinical trial evidence (Risk factors through stable coronary artery disease). *Circulation* 2006;**114**:2850–2870.
2. Dzau VJ, Antman EM, Black HR, Hayes DL, Manson JE, Plutzky J, Popma JJ, Stevenson W. The cardiovascular disease continuum validated: clinical evidence of improved outcome. Part II. Clinical trial evidence (Acute coronary syndromes through renal disease. *Circulation* 2006;**114**:2871–2891.
3. Dyer AR, Persky V, Stamler J, Paul O, Shekelle RB, Berkson DM, Lepper M, Schoenberger JA, Lindberg HA. Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies. *Am J Epidemiol* 1980;**112**:736–749.
4. Kannel WB, Kannel CE, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality in the Framingham study. *Am Heart J* 1987; **113**:1489–1494.
5. Seccareccia F, Pannozzo F, Dima F, Minoprio A, Menditto A, Lo Noce C, Giampaoli S; Malattie Cardiovascolari Aterosclerotiche Istituto Superiore di Sanita Project. Heart rate as a predictor of mortality: the MATISS project. *Am J Public Health* 2001;**91**:1258–1263.
6. Jouven X, Empana JP, Schwarz PJ, Desnos M, Courbon D, Ducimetière P. Heart rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005;**352**:1951–1958.
7. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, Wilson PW. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA* 2003;**290**:891–897.
8. Khot UN, Khot MB, Bajzer CT, Sapp SK, Ohman EM, Brener SJ, Ellis SG, Lincoff AM, Topol EJ. Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA* 2003;**290**:898–904.
9. Aboyans V, Criqui MH. Can we improve cardiovascular risk prediction beyond risk equations in the physician's office? *J Clin Epidemiol* 2006; **59**:547–558.
10. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, Steg PG, Tardif JC, Tavazzi L, Tendera M; Heart Rate Working Group. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol* 2007;**50**:823–830.
11. Lévy S, Guize L. Heart rate, a major prognostic factor of cardiovascular risk. *Therapie* 2006;**61**:115–119.
12. Palatini P. Heart rate as an independent risk factor for cardiovascular disease: current evidence and basic mechanisms. *Drugs* 2007; **67**(Suppl. 2):3–13.
13. Palatini P, Benetos A, Grassi G, Julius S, Kjeldsen SE, Mancia G, Narkiewicz K, Parati G, Pessina AC, Ruilope LM, Zanchetti A;

European Society of Hypertension. Identification and management of the hypertensive patient with elevated heart rate: statement of a European Society of Hypertension Consensus Meeting. *J Hypertens* 2006;**24**:603–610.
14. Giannoglou GD, Chatzizisis YS, Zamboulis C, Parcharidis GE, Mikhailidis DP, Louridas GE. Elevated heart rate and atherosclerosis: An overview of the pathogenetic mechanisms. *Int J Cardiol* 2008;**126**: 302–312.
15. Kop WJ, Verdino RJ, Gottdiener JS, O'Leary ST, Bairey Merz CN, Krantz DS. Changes in heart rate and heart rate variability before ambulatory ischemic events. *J Am Coll Cardiol* 2001;**38**:742–749.
16. Beere PA, Glagov S, Zarins CK. Retarding effect of lowered heart rate on coronary atherosclerosis. *Science* 1984;**226**:180–182.
17. Yamamoto E, Lai ZF, Yamashita T, Tanaka T, Kataoka K, Tokutomi Y, Ito T, Ogawa H, Kim-Mitsuyama S. Enhancement of cardiac oxidative stress by tachycardia and its critical role in cardiac hypertrophy and fibrosis. *J Hypertens* 2006;**24**:2057–2069.
18. Guth BD, Heusch G, Seitelberger R, Ross J Jr. Mechanism of beneficial effect of beta-adrenergic blockade on exercise-induced myocardial ischemia in conscious dogs. *Circ Res* 1987;**60**:738–746.
19. Kjekshus J. Importance of heart rate in determining beta-blocker efficacy in acute and long-term myocardial infarction intervention trials. *Am J Cardiol* 1986;**57**:43F–49F.
20. Cucherat M. Quantitative relationship between resting heart rate reduction and magnitude of clinical benefits in post-myocardial infarction: a meta-regression of randomized clinical trials. *Eur Heart J* 2007;**28**:3012–3019.
21. Flannery G, Gehrig-Mills R, Billah B, Krum H. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. *Am J Cardiol* 2008;**101**:865–869.
22. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002;**346**:793–801.
23. Di Francesco D, Camm AJ. Heart rate lowering by specific and selective I_f current inhibition with ivabradine. *Drugs* 2004;**64**:1757–1765.
24. Borer JS, Fox K, Jaillon P, Lerebours G, for the Ivabradine Investigators Group. Antianginal and antiischemic effects of ivabradine, an I_f inhibitor, in stable angina. A randomized, double blind, multicentered, placebo-controlled trial. *Circulation* 2003;**107**:817–823.
25. Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K for the INITIATIVE Investigators. Efficacy of ivabradine, a new selective If inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J* 2005;**26**:2529–2536.
26. Ruzyllo W, Tendera M, Ford I, Fox KM. Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial. *Drugs* 2007;**67**:393–405.
27. Manz M, Reuter M, Lauck G, Omran H, Jung W. A single intravenous dose of ivabradine, a novel I_f inhibitor, lowers heart rate but does not depress left ventricular function in patients with left ventricular dysfunction. *Cardiology* 2003;**100**:149–155.
28. Mulder P, Barbier S, Chagraoui A, Richard V, Henry JP, Lallemand F, Renet S, Lerebours G, Mahlberg-Gaudin F, Thuillez C. Long-term heart rate reduction induced by the selective I_f current inhibitor ivabradine improves left ventricular function and intrinsic myocardial structure in congestive heart failure. *Circulation* 2004;**109**: 1674–1679.
29. Fox K, Ferrari R, Tendera M, Steg PG, Ford I. Rationale and design of a randomized, double-blind, placebo-controlled trial of ivabradine in patients with stable coronary artery disease and left ventricular systolic dysfunction: the morBidity-mortality EvAlUaTion of the I(f) inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction (BEAUTIFUL) study. *Am Heart J* 2006;**152**:860–866.
30. Current controlled trials. ISRCTN70429960: effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction. A three-year randomised double-blind placebo-controlled international multicentre study. http://www.controlled-trials.com/ISRCTN70429960/ivabradine.