Association of heart rate and outcomes in a broad spectrum of patients with chronic heart failure: results from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) program.

UNIVERSITÀ DEGLI STUDI DI TORINO

[Association of heart rate and outcomes in a broad spectrum of patients with chronic heart failure: results from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) program. J Am Coll Cardiol 2012; 59 (20): 1785-95. doi: 10.1016/j.jacc.2011.12.044.]

Association of Heart Rate and Outcomes in a Broad Spectrum of Patients with Chronic Heart Failure. Results from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) Program.

Running title: Heart rate and outcomes in the CHARM Program.

Authors: Davide Castagno, MD *†;

Hicham Skali, MD, MSc *;

Madoka Takeuchi, MS *;

Karl Swedberg, MD, PhD ‡;

Salim Yusuf, MBBS, DPhil §;

Christopher B. Granger, MD ||;

Eric L. Michelson, MD ¶;

Marc A. Pfeffer, MD, PhD *;

John J.V. McMurray, MD*#;

Scott D. Solomon, MD*;

for the CHARM Investigators.

Affiliations: * Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; † Division of Cardiology, Department of Internal Medicine, University of Turin, Turin, Italy; ‡ Department of Emergency and Cardiovascular Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; § Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada; || Duke University Medical Center, Durham, NC, USA; ¶ AstraZeneca LP, Wilmington, DE, USA; # BHF Glasgow Cardiovascular Research Centre, Faculty of Medicine, University of Glasgow, Glasgow, United Kingdom.

Correspondence: Dr. Scott D. Solomon

Cardiovascular Division

Brigham and Women's Hospital

75 Francis Street

Boston, MA 02115, USA

Tel: +1 857 307 1960

Fax: +1 857 307 1944

ssolomon@rics.bwh.harvard.edu

Word count: Abstract = 256

Text (including references) = 4491

Relationship with industry: Davide Castagno, Hicham Skali, Madoka Takeuchi and Scott D. Solomon have no relationship with industry to disclose in connection with this article. Karl Swedberg, Salim Yusuf, Christopher B. Granger, Marc A. Pfeffer and John J.V. McMurray have received research grants, honoraria for lectures and/or consulting fees from AstraZeneca. Karl Swedberg has received research grants, honoraria or consulting fees from Servier. Marc A. Pfeffer has received consulting fees from Servier. Eric L. Michelson is an employee of AstraZeneca, sponsor of the CHARM Program.

Financial disclosure: The CHARM Program was sponsored by AstraZeneca. No extramural funding was used to support this work.

Abstract

Objective

To explore the relationship between baseline resting heart rate and outcomes in patients with chronic heart failure (HF) according to baseline left ventricular ejection fraction (LVEF) and cardiac rhythm.

Background

Elevated resting heart rate is associated with worse outcomes in patients with HF and reduced LVEF. Whether this association is also found in patients with HF and preserved LVEF is uncertain, as is the predictive value of heart rate in patients in atrial fibrillation (AF).

Methods

Patients enrolled in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Program were divided into groups by tertiles of baseline heart rate. Cox proportional hazard models were used to investigate the association between heart rate and pre-specified outcomes in the overall population as well as in subgroups defined according to LVEF (≤40% vs. >40%) and presence (or absence) of AF at baseline.

Results

After adjusting for predictors of poor prognosis, patients in the highest heart rate tertile had worse outcomes when compared with those in the lowest heart rate group (e.g. for the composite of cardiovascular death or HF hospitalization HR=1.23, 95% CI 1.11-1.36, p<0.001). The relationship between heart rate and outcomes was similar across LVEF categories and was not influenced by beta-blocker use (p value for interaction >0.10 for both

endpoints). However, amongst patients in AF at baseline, heart rate had no predictive value (p value for interaction <0.001).

Conclusions

Resting heart rate is an important predictor of outcome in patients with stable chronic HF without AF, regardless of LVEF or beta-blocker use.

Key words

Heart rate

Heart failure

Ejection fraction

Atrial fibrillation

Prognosis

Abbreviations list

ACE-I = angiotensin-converting enzyme inhibitor

AF = atrial fibrillation

BMI = body mass index

BMP = beats per minute

DBP = diastolic blood pressure

ECG = electrocardiogram

HF = heart failure

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

T = tertile

Introduction

Elevated resting heart rate is an established risk factor for cardiovascular mortality and morbidity in a variety of cardiovascular diseases (1). In patients with reduced left ventricular ejection fraction (LVEF), with or without signs or symptoms of heart failure (HF), high heart rate has been associated with worse outcomes, independently of other known risk factors (2-6). Several pathophysiologic mechanisms including blunting of the force-frequency relationship, the induction of myocardial ischemia, precipitation of rhythm disturbances and acceleration of atherosclerosis have been proposed to explain the association between higher heart rate and worse outcomes in patients with HF (1,7). Higher heart rate may also be a marker of greater neurohumoral activation. The recent findings of the Systolic Heart failure treatment with the I*f* inhibitor ivabradine Trial (SHIFT), have confirmed the importance of heart rate in the pathophysiology of HF with reduced LVEF and have suggested heart rate reduction *per se* as a mechanism responsible for improvement of clinical outcomes (8).

Whether higher resting heart rate also has prognostic importance in patients with HF and preserved LVEF, representing a third to a half of the patients with HF (9,10), is less well documented. Furthermore, little is known about the relationship between heart rate and outcomes in patients with atrial fibrillation (AF), the prevalence of which increases in parallel with the severity of HF (11). The Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) Program, enrolled 7599 patients with a clinical diagnosis of HF, irrespective of LVEF, and assessed the effect of the angiotensin receptor blocker candesartan on cardiovascular mortality and morbidity (12). The main aims of this analysis were to examine the relationship between resting heart rate at baseline and fatal and

nonfatal cardiovascular outcomes and all-cause mortality in a broad spectrum of patients with HF, and to determine whether the relationship between heart rate and outcomes was influenced by LVEF or underlying cardiac rhythm.

Methods

The CHARM Program

The design, baseline findings and overall results of the CHARM Program have been previously reported in detail (12-14). In brief, 7599 patients with at least 4 weeks duration of symptomatic HF [New York Heart Association (NYHA) class II-IV] receiving standard therapy, were enrolled into one of three component clinical trials according to LVEF and angiotensin converting enzyme inhibitor (ACE-I) treatment: CHARM-Alternative (n=2028, LVEF ≤40% and not receiving an ACE-I due to previous intolerance), CHARM-Added (n=2548, LVEF ≤40% receiving ACE-I treatment) and CHARM-Preserved (n=3023, LVEF >40%) (15-17). Important exclusion criteria were serum creatinine 3mg/dL (265 µmol/L) or more, serum potassium 5.5 mmol/L or more, known bilateral renal artery stenosis, symptomatic hypotension, critical aortic or mitral stenosis, or recent (in the previous 4 weeks) myocardial infarction, stroke, or heart surgery. Within each of the component trials, patients were randomly allocated to candesartan or matching placebo, initiated at 4 mg or 8 mg (at the investigator's discretion) once daily at the enrollment visit. The dose was increased towards the target dose (32 mg once daily) in a stepwise fashion as tolerated, but not faster than every 2 weeks. Because the rate of recruitment varied between the CHARM trials, follow-up

ranged from a median of 34 months in CHARM-Alternative and 37 months in CHARM-Preserved to 41 months in CHARM-Added (38 months in the overall CHARM Program).

Baseline heart rate measurement and outcomes evaluated

In accordance with the protocol and standard operating procedures, all patients enrolled in the CHARM Program had baseline heart rate measured by the site investigator at the randomization visit. After a resting period of 5 minutes, heart rate was either assessed by palpation for at least 30 seconds or from auscultation of the heart or from electrocardiogram (ECG). In addition, a 12-lead ECG was recorded in all patients and interpreted by investigators at each participating center using a structured report taking into account, amongst others, the presence or absence of atrial fibrillation. In patients for whom both pieces of information were available, we examined the association between baseline resting heart rate, heart rhythm (determined by the baseline ECG) and all-cause death (the primary outcome of the entire CHARM Program) and the composite outcome of cardiovascular death or hospitalization for the management of worsening HF (the primary outcome of each component trial). All endpoints were adjudicated in a blinded fashion. Deaths were considered to be cardiovascular unless another clear cause was apparent. Treatment in hospital for worsening HF was defined as an unplanned admission that was necessitated by HF and required intravenous diuretics.

Statistical analysis

To illustrate the relationship between resting heart rate and baseline characteristics, we divided patients into groups by tertiles of heart rate. Tertiles were chosen according to the resting heart rate distribution at baseline. Each of these heart rate bands was centered round a multiple of 10, because we observed a substantial "digit preference" for investigator reported heart rate. Differences in baseline characteristics across tertiles of baseline heart rate were assessed with a test for trend by means of variance weighted least square regression for continuous variables and with a nonparametric test for trend (18) for categorical variables in the overall CHARM population, as well as in subgroups defined according to LVEF (i.e. reduced *vs.* preserved) and heart rhythm (presence or absence of AF). Kaplan-Meier survival analysis stratified according to tertiles of baseline heart rate for death from any cause and for the composite of cardiovascular death or hospitalization for worsening heart failure were determined and presented as event curves, compared by means of log-rank test. Incidence rates were calculated per 100 person-years. The association between baseline heart rate and risk was assessed with either univariate and multivariable Cox proportional-hazard models, fitting heart rate both as a continuous variable (hazard ratio for each 10-beats per minute [bpm] change in heart rate) and as a categorical (hazard ratio calculated for the lowest tertile as reference). Multivariable analysis adjusted for the 10 strongest predictors of outcome, as expressed by decreasing χ^2 statistic, previously identified in the CHARM program (19): age (years), LVEF, diabetes, previous HF hospitalization, NYHA class, body mass index (BMI), diastolic blood pressure (DBP), gender, radiologic cardiomegaly (defined as a cardiothoracic ratio ≥ 0.5 at chest X-ray) and candesartan treatment. In addition, beta-blocker use at baseline was added into the model because of the direct heart rate-lowering effect of beta-blockers and because of their

beneficial effect on morbidity and mortality in patients with HF. The proportional hazards assumption was checked both graphically and by means of scaled Schoenfeld residuals. Interaction testing was used to assess whether the relation between baseline heart rate and outcome was modified by LVEF (modeled either as a continuous variable or categorized ≤40% *vs.* >40%) and beta-blocker use at randomization. Formal interaction testing was also used to ascertain whether the relation between baseline heart rate and outcomes differed in specific subgroups: patients with and without AF, diabetic and non diabetic patients, current smokers and non smokers. Continuous variables were expressed as medians and interquartile ranges (IQR) and categorical variables as counts and percentages. All p-values were two sided, and $p<0.05$ was used to determine statistical significance, except for tests for interaction for which $p<0.10$ was used. Analyses were all based on intention-to-treat and were performed with STATA, version 11.2 (StataCorp LP, College Station, TX, USA).

Results

Baseline characteristics

Information about baseline resting heart rate and rhythm were available for 7597 (99.9%) participants in the CHARM Program and the median heart rate overall was 72 bpm (IQR 64, 80). Baseline demographic and clinical characteristics in the overall CHARM population grouped by tertiles of baseline heart rate are shown in Table 1. Patients with a higher heart rate were younger and more often female, diabetic or a current smoker. A higher resting

heart rate was also associated with lower LVEF and with higher DBP and NYHA class. More patients in the highest heart rate tertile had been previously admitted to hospital because of HF decompensation, compared with patients in the two lower heart rate tertiles. By contrast, patients in the highest heart rate group were less likely to have suffered from myocardial infarction compared with patients in the other groups. The proportion of patients treated with a beta-blocker decreased as heart rate increased, whereas, the use of a diuretic, spironolactone and digoxin increased with increasing heart rate. In patients with reduced and preserved LVEF, as well as in those without AF at baseline, the distribution of baseline characteristics across tertiles of heart rate was similar to what was observed in the overall population (Table 2 and 3). However, some of the differences between heart rate tertiles seen in these other subgroups were not present in patients with AF (Table 3). In particular, there was no gradient in LVEF, NYHA class or history of diabetes. There was also no gradient in history of hospitalization for HF or in use of diuretics or digoxin, although the frequency of each of these was higher in patients with AF (irrespective of heart rate) than in patients without AF (Table 3).

Baseline heart rate and all-cause mortality

In the overall CHARM population, during a median follow-up of 37.7 months, 1831 patients (24.1%) died. Individuals with a higher heart rate at baseline had a greater risk of death from any cause compared with those with a lower heart rate (overall log-rank test p value <0.001, Figure 1A). Beta-blocker use at randomization was associated with a lower risk of death but did not change the association between heart rate and mortality (p for interaction = 0.55, Figure 2A). The relationship between heart rate and mortality (and cardiovascular death or

HF hospitalization) was also observed when beta-blocker dose was taken into consideration (higher heart rate was associated with worse outcomes whether or not patients were taking ≥50% of recommended dose or ≥median dose). The absolute death rate/100 patient-years of follow up in patients with reduced LVEF was approximately double that in patients with preserved LVEF but a concordant increment in death rates was seen with increasing heart rate in each of the two LVEF categories (Table 4 and Figure 3A). Similarly, the unadjusted risk of death showed a concordant increase across tertiles of heart rate irrespective of LVEF (p for interaction with continuous LVEF = 0.80; with categorical LVEF = 0.68; Figure 4A); the findings were similar if LVEF was dichotomized at 50% rather than 40% in the categorical analysis (and this was also true for the outcome of cardiovascular death or HF hospitalization). The association between higher heart rate and the risk of death remained significant in a multivariable model that adjusted for the covariates listed in the Methods in both LVEF subgroups (Table 4); adding baseline treatment including ACE-inhibitors, beta-blockers, diuretics, spironolactone and digitalis glycosides to the multivariable model did not change this finding. Treating baseline heart rate as a linear continuous variable, for each additional 10-beat increase there was a 6% and 5% adjusted risk accrual in patients with reduced and preserved LVEF, respectively (Table 4).

When heart rhythm at randomization was taken into account, the association between higher heart rate and the risk of death was confirmed in patients without AF but not in those with AF at baseline (p for interaction <0.001; Table 4 and Figure 5A). Modeling heart rate as a linear continuous variable, a 10-beat increase in heart rate was associated with a 8% increase in the risk of death in patients without AF but no significant increase in risk was observed in patients with AF (Table 4). The association between a higher baseline heart rate and a higher risk of death was observed regardless of diabetic and smoking status (p for

interaction between heart rate and diabetes = 0.47; p for interaction between heart rate and smoking status = 0.33).

Baseline heart rate and cardiovascular death or hospitalization for worsening heart failure

Patients with a higher heart rate at baseline had a higher incidence of the composite outcome of cardiovascular death or HF hospitalization (overall Log-rank test p value <0.001, Figure 1B). The association between higher heart rate and the risk of the composite outcome was observed independently of beta-blocker use at baseline (p for interaction = 0.77, Figure 2B). A similar pattern of increase in event rate across heart rate tertiles was seen in both the reduced and preserved LVEF groups (Table 4 and Figure 3B). This finding was confirmed in the univariate and multivariable analysis, where an increase in the risk of cardiovascular death or HF hospitalization was observed with increasing heart rate regardless of baseline LVEF (p for interaction with continuous LVEF = 0.88; with categorical LVEF = 0.96, Figure 4B, Table 4). Adding baseline treatment including ACE-inhibitors, beta-blockers, diuretics, spironolactone and digitalis glycosides to the multivariable model did not change this finding. Using baseline heart rate as a continuous variable, a 10-beat increase in heart rate was associated with a 7% and with a 6% increase in the risk of the composite endpoint in patients with reduced and preserved LVEF, respectively (Table 4).

The prognostic importance of heart rate was confirmed in patients without AF at baseline either modeling heart rate as a categorical (adjusted HR 1.28, CI 1.14 – 1.44 for patients in the highest heart rate tertile of heart rate) or as a continuous variable (adjusted HR 1.10, CI 1.06 – 1.13 for each 10-beat increase in heart rate). By contrast, in patients with AF at baseline, there was no association between heart rate and the risk of the composite

outcome (p value for interaction between heart rate and the presence of AF <0.001; Table 4 and Figure 5B). This conclusion was not altered by adding digoxin to the multivariable model. Although higher event rates were observed with increasing heart rate, the association between a higher heart rate and a higher risk of cardiovascular death or HF hospitalization seemed stronger in nondiabetics than in diabetics (p for interaction between heart rate and diabetes = 0.01) A possible interaction between heart rate and current smoking was also observed (p = 0.07).

Effect of candesartan and baseline heart rate

Although candesartan did not reduce mortality overall in the CHARM Program, there was a nominally significant interaction between heart rate at baseline and the effect of candesartan on all-cause mortality (p value for interaction = 0.04), with an apparent reduction in mortality only in patients in the highest heart rate-tertile (data not shown). This interaction was not seen for the composite of cardiovascular death or heart failure hospitalization (p=0.24) for which there were many more events and which was reduced, overall, by candesartan.

Discussion

The CHARM dataset provided a unique opportunity to examine the relationship between baseline resting heart rate and outcomes in a large cohort of patients with a wide range of LVEF and receiving contemporary management for symptomatic HF. Our analysis confirmed

the predictive value of resting heart rate in patients with HF and sinus rhythm, for both the composite outcome of cardiovascular death or heart failure hospitalization and all-cause mortality. The greater risk of events in patients with higher heart rate was observed across the full spectrum of LVEF and persisted even after adjustment for other recognized predictors of mortality and morbidity. Moreover, the relationship between heart rate and outcomes in patients with sinus rhythm was not modified by the use of beta-blockers at baseline. Interestingly, however, higher heart rate was not related to outcome in patients with AF.

Heart rate as a risk marker in patients with HF

Certain variables previously reported to be associated with worse outcomes in HF (e.g. diabetes, higher NYHA class, lower LVEF and a history of HF hospitalization) were more frequent in patients with a higher heart rate at baseline, but other variables associated with a better outcome were also more common in patients with a higher heart rate (e.g. younger age, female sex and lower frequency of prior myocardial infarction). The baseline use of beta-blockers was also lower in patients with higher heart rate, possibly because these individuals had worse overall clinical status or less indications for beta-blockers. In addition, higher heart rate may also reflect unmeasured variance such as neuroendocrine activity, particularly sympathetic activity (or sympathetic-parasympathetic imbalance). However, heart rate remained an independent predictor of outcome in a multivariable analysis taking into account these imbalances and no interaction between baseline heart rate and beta-blocker use was observed.

Association between heart rate and outcomes across the continuum of LVEF

We found no interaction between resting heart rate and LVEF, indicating that the value of elevated heart rate in predicting worse outcomes was independent of baseline left ventricular systolic function in patients with HF. Despite the epidemiologic importance of HF with preserved LVEF, only two other studies have examined the association between baseline heart rate and outcomes in this sub-group of patients. In a *post hoc* analysis of the Digitalis Investigation Group (DIG) Trial, a higher heart rate was associated with a greater risk of HF hospitalization both in patients with reduced and preserved LVEF. However, an association between higher heart rate and higher mortality was only seen in patients with a reduced LVEF (20). The discrepancy between these findings and ours warrants further investigations but may be due to differences between the studies. Beta-blockers were not used to treat HF at the time of DIG and patients in that trial had a LVEF greater than 45% (compared with 40% in CHARM). Perhaps, most importantly, the DIG preserved LVEF ancillary trial was a much smaller that CHARM-Preserved, resulting in considerably fewer deaths in this subset of patients in DIG (i.e. 231 versus 364 in CHARM-Preserved), and greater statistical power in CHARM-Preserved. Nevertheless, further examination of the relationship between heart rate and outcomes in HF with preserved LVEF is needed before any definitive conclusion can be drawn. Recently, Kapoor et al. reported that high resting heart rate was associated with worse survival among 685 consecutive patients with preserved systolic function (with 278 deaths overall) (21). This cohort was, however, unusual in that 97% of the patients were male.

The prognostic value of heart rate according to baseline cardiac rhythm

An interesting finding of our analysis was the lack of predictive value of higher heart rate in patients with AF at baseline. Although the number of patients and events was much smaller in the AF subgroup, the highly significant interaction between heart rhythm and the relationship between heart rate and outcomes suggests that this finding is a true one. Moreover, a similar observation was made in a cohort of patients with acute heart failure, in which a higher heart rate was associated with a significantly lower all-cause and cardiovascular mortality in those with AF (22). In another study of patients with moderate to severe chronic HF and concomitant AF, a lower heart rate at baseline was associated with a worse prognosis (23). The explanation for this apparently paradoxical finding in patients with AF (compared with those in sinus rhythm) is uncertain. Whilst in patients with HF and in sinus rhythm a higher heart rate could be a marker of greater neurohumoral activation (24) or significant autonomic impairment (25) this may not be so in those with AF. Furthermore, systematic underestimation of the ventricular rate may have occurred in patients with AF when the rate was assessed by palpation or auscultation. Conversely, a true low ventricular rate may indicate conducting system disease, itself a poor prognostic feature. In patients with AF, a higher ventricular rate may be a compensatory response to the reduction in cardiac output due to loss of effective atrial contraction (26).

The prognostic value of heart rate according to diabetic and smoking status

Although both diabetic and nondiabetic patients showed increasing event rates with increasing heart rate, the association between a high heart rate and the risk of the primary composite outcome (cardiovascular death or HF hospitalization) appeared to be stronger in

nondiabetic than in diabetic patients. For the same outcome, a similar figure was observed in nonsmokers as compared with current smokers. The imbalance between sympathetic/parasympathetic systems associated with cardiac autonomic neuropathy in diabetics and the increased sympathetic outflow induced by smoking are possible explanations for these findings (27,28). However, multiple interaction tests were conducted with the possibility of a nominally significant interaction occurring by chance alone (29).

Strengths and limitations

One of the main strengths of the present study is the wide spectrum of LVEF across which the prognostic impact of heart rate was investigated. In addition, the modern HF treatment used in the CHARM Program, especially beta-blockers, in more than half of the patients, makes our results more generalizable to real clinical practice, compared with previous reports (5,20). Some limitations of the present analysis should also be acknowledged. We relied on investigator-reported baseline heart rate, which was probably measured in different ways, at different times of day and under different circumstances. Estimation of the average ventricular rate in patients with atrial fibrillation was probably less reliable than measurement of heart rate in those in sinus rhythm. Similarly, patients were classified as having AF or no AF according to the investigator interpretation of their baseline ECG. In addition, we did not use serial assessments of heart rate over time for the prediction of risk.

Conclusions

In patients with stable chronic symptomatic HF and without AF, resting heart rate is a powerful predictor of mortality and cardiovascular outcomes, irrespective of LVEF,

treatment with beta-blockers and other important prognostic factors. This easily measured clinical variable could be used in the risk stratification of these patients in everyday clinical practice.

References

1. Fox K, Borer JS, Camm AJ, *et al.* for the Heart Rate Working Group. Resting heart rate in cardiovascular disease. J Am Coll Cardiol 2007;50:823-30.

2. Lechat P, Hulot JS, Escolano S, *et al.* Heart rate and cardiac rhythm relationship with bisoprolol benefit in chronic Heart failure in CIBIS II trial. Circulation 2001;103:1428-33.

3. Fox K, Ford I, Steg PG, *et al.* on behalf of the BEAUTIFUL Investigators. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. Lancet 2008;372:817-21.

4. Ahmadi-Kashani M, Kessler DJ, Day J, *et al.* for the INTRINSIC RV Study Investigators. Heart rate predicts outcomes in an implantable cardioverter-defibrillator population. Circulation 2009;120:2040-5.

5. Fosbøl EL, Seibaek M, Brendorp B, *et al.* for the Danish Investigations and Arrhythmia ON Dofetilide Study Group. Long-term prognostic importance of resting heart rate in patients with left ventricular dysfunction in connection with either heart failure or myocardial infarction: the DIAMOND study. Int J Cardiol 2010;140:279-86.

6. Böhm M, Swedberg K, Komajda M, *et al.* Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet 2010;376:886-94.

7. Mulieri LA, Hasenfuss G, Leavitt B, Allen PD, Alpert NR. Altered myocardial force-frequency relation in human heart failure. Circulation 1992;85:1743-50.

8. Swedberg K, Komajda M, Böhm M, *et al.* on behalf of the SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010;376:875-85.

9. Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. Eur Heart J 2008;29:2388-42.

10. Hunt SA, Abraham WT, Chin MH, *et al*. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009;119:e391-479.

11. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003;91:2D-8D.

12. Pfeffer MA, Swedberg K, Granger CB, *et al.* for the CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362:759-66.

13. Swedberg K, Pfeffer MA, Granger CB, *et al.* for the CHARM-Programme Investigators. Candesartan in heart failure—assessment of reduction in mortality and morbidity (CHARM): rationale and design. J Card Fail 1999;5:276–82.

14. McMurray JJ, Ostergren J, Pfeffer MA, *et al.* for the CHARM Investigators and Committees. Clinical features and contemporary management of patients with low and preserved ejection fraction heart failure: baseline characteristics of patients in the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) programme. Eur J Heart Fail 2003;5:261–70.

15. Granger CB, McMurray JJ, Yusuf S, *et al.* for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362:772–6.

16. McMurray JJ, Ostergren J, Swedberg K, *et al.* for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362:767–71.

17. Yusuf S, Pfeffer MA, Swedberg K, *et al.* for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left ventricular systolic function: the CHARM-Preserved trial. Lancet 2003;362:777-81.

18. Cuzick J., A Wilcoxon-type test for trend. Stat Med 1985;4:87-90.

19. Pocock SJ, Wang D, Pfeffer MA, *et al.* on behalf of the CHARM investigators. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J 2006;27:65-75.

20. Maeder MT, Kaye DM. Differential impact of heart rate and blood pressure on outcome in patients with heart failure with reduced versus preserved left ventricular ejection fraction. Int J Cardiol 2010;Oct 27 [Epub ahead of print], doi:10.1016/j.ijcard.2010.10.007.

21. Kapoor JR, Heidenreich PA. Heart rate predicts mortality in patients with heart failure and preserved systolic function. J Card Fail 2010;16:806-11.

22. Bertomeu-González V, Núñez J, Núñez E, *et al.* Heart rate in acute heart failure, lower is not always better. Int J Cardiol 2010;145:592-3.

23. Rienstra M, Van Gelder IC, Van den Berg MP, *et al.* A comparison of low versus high heart rate in patients with atrial fibrillation and advanced chronic heart failure: effects on clinical profile, neurohormones and survival. Int J Cardiol 2006;109:95-100.

24. Cohn JN, Levine TB, Olivari MT, *et al.* Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984;311:819-21.

25. Binkley PF, Nunziata E, Haas GJ, Nelson SD, Cody RJ. Parasympathetic withdrawal is an integral component of autonomic imbalance in congestive heart failure: demonstration in human subjects and verification in a paced canine model of ventricular failure. J Am Coll Cardiol 1991;18:464-72.

26. Atwood JE, Myers J, Sullivan M, *et al.* Maximal exercise testing and gas exchange in patients with chronic atrial fibrillation. J Am Coll Cardiol 1988;11:508-13.

27. Pop-Busui R. Cardiac autonomic neuropathy in diabetes: a clinical perspective. Diabetes Care 2010;33:434-41.

28. Narkiewicz K, van de Borne PJ, Hausberg M, *et al.* Cigarette smoking increases sympathetic outflow in humans. Circulation 1998;98:528-34.

29. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine--reporting of subgroup analyses in clinical trials. N Engl J Med 2007;357:2189-94.

Figure Legends

Figure 1. Kaplan-Meier survival analysis according to baseline heart rate.

Event curves for all-cause mortality [A] and for the composite outcome of cardiovascular (CV) death or hospitalization for worsening heart failure (WHFH) [B] according to tertiles of baseline heart rate in the overall CHARM population. T = tertile.

Figure 2. Kaplan-Meier survival analysis according to baseline heart rate, stratified by beta-blocker use at baseline.

Event curves for all-cause mortality [A] and for the composite outcome of cardiovascular (CV) death or hospitalization for worsening heart failure (WHFH) [B] according to tertiles of baseline heart rate, stratified by beta-blocker use at baseline (dashed line = no beta-blocker use at randomization, continuous line = beta blocker use at randomization) in the overall CHARM population. P value refers to the test for interaction between baseline heart rate and beta-blocker use at baseline. T = tertile.

Figure 3. Event rates in patients with preserved and reduced LVEF according to baseline heart rate.

All-cause mortality [A] and cardiovascular (CV) death or hospitalization for worsening heart failure (WHFH) [B] event rates (per 100-patient years) according to tertiles of baseline heart rate in patients with preserved (blue) and reduced (red) left ventricular ejection fraction. LVEF = left ventricular ejection fraction; T = tertile.

Figure 4. Association between baseline heart rate and outcomes by subgroups of LVEF.

Unadjusted hazard ratios and 95% confidence intervals for all-cause mortality [A] and for cardiovascular death or hospitalization for worsening heart failure [B] across tertiles of baseline heart rate; p values for interaction between heart rate and left ventricular ejection fraction treated as linear continuous variables are shown. CI = confidence interval; HR = hazard ratio; T = tertile.

Figure 5. Association between baseline heart rate and outcomes by baseline cardiac rhythm. Unadjusted hazard ratios and 95% confidence intervals for all-cause mortality [A] and for cardiovascular death or hospitalization for worsening heart failure [B] across tertiles of baseline heart rate; p values for interaction between heart rate treated as a linear continuous variable and baseline rhythm (sinus rhythm vs. atrial fibrillation) are shown. CI = confidence interval; HR = hazard ratio; T = tertile.

Table 1. Baseline characteristics of the overall CHARM population according to group defined by tertiles of baseline heart rate

	Heart rate group at baseline (bmp)			
	T1	**T2**	**T3**	
	N = 2553	**N = 2689**	**N = 2355**	
	(33.6%)	**(35.4%)**	**(31.0%)**	**p-value**
Median heart rate (IQR)	**60 (57, 64)**	**72 (70, 75)**	**85 (80, 91)**	**for trend**
Patient's characteristics				
Median age(IQR)	67 (59, 74)	67 (58, 74)	65 (57, 73)	<0.001
≥75 years	609 (23.9)	625 (23.2)	503 (21.4)	0.04
Female	692 (27.1)	905 (33.7)	802 (34.1)	<0.001
LVEF (%)	38 (30, 50)	37 (28, 50)	35 (25, 47)	<0.001
NYHA class				
II	1260 (49.4)	1202 (44.7)	953 (40.5)	
III/IV	1293 (50.7)	1487 (55.3)	1402 (59.5)	<0.001
Atrial fibrillation on ECG	283 (11.1)	398 (14.8)	467 (19.8)	<0.001
Blood pressure (mmHg)				
Systolic	130 (118, 142)	130 (120, 142)	130 (118, 144)	0.22
Diastolic	75 (70, 80)	80 (70, 84)	80 (70, 85)	<0.001
Medical history				
Current smoking	305 (11.9)	378 (14.1)	431 (18.3)	0.008
Diabetes mellitus	601 (23.5)	789 (29.3)	772 (32.8)	<0.001
Hypertension	1365 (53.5)	1529 (56.9)	1290 (54.8)	0.33
Hospital admission for HF	1691 (66.2)	1945 (72.3)	1789 (76.0)	<0.001

Myocardial infarction	1510 (59.2)	1433 (53.3)	1059 (45.0)	<0.001
Stroke	238 (9.3)	238 (8.9)	187 (7.9)	0.09
History of atrial fibrillation	673 (26.4)	746 (27.7)	664 (28.2)	0.15
Medical treatment				
ACE inhibitors	1054 (41.3)	1098 (40.8)	973 (41.3)	0.99
B-blockers	1769 (69.3)	1445 (53.7)	988 (42.0)	<0.001
Diuretics	2031 (79.6)	2202 (81.9)	2051 (87.1)	<0.001
Spironolactone	369 (14.5)	432 (16.1)	470 (20.0)	<0.001
Digoxin/digitalis glycosides	962 (37.7)	1156 (43.0)	1136 (48.2)	<0.001

ACE = angiotensin converting enzyme; BMP = beats per minute; HF = heart failure; IQR = interquartile range; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; T = tertile.

Table 2. Baseline characteristics according to group defined by tertiles of baseline heart rate in patients with reduced and preserved LVEF.

	Reduced LVEF				Preserved LVEF			
	T1	**T2**	**T3**		**T1**	**T2**	**T3**	
	N = 1414	**N = 1617**	**N = 1545**		**N = 1060**	**N = 1037**	**N = 924**	
	(30.9%)	**(35.3%)**	**(33.8%)**	**p-value**	**(35.1%)**	**(34.3%)**	**(30.6%)**	**p-value**
Median heart rate (IQR)	**60 (58, 64)**	**72 (70, 76)**	**86 (80, 92)**	**for trend**	**60 (56, 63)**	**71 (68, 74)**	**84 (80, 90)**	**for trend**
Patient's characteristics								
Median age(IQR)	66 (58, 74)	67 (58, 73)	65 (56, 72)	<0.001	68 (61, 75)	68 (59, 75)	68 (58, 75)	0.03
≥75 years	311 (22.0)	329 (20.4)	290 (18.8)	0.03	281 (26.5)	275 (26.5)	251 (27.2)	0.75
Female	303 (21.4)	447 (27.6)	438 (28.4)	<0.001	360 (34.0)	429 (41.4)	422 (45.7)	<0.001
LVEF (%)	30 (25, 35)	30 (24, 35)	29 (22, 35)	<0.001	53 (46, 60)	52 (46, 60)	53 (46, 60)	0.73
NYHA class								
II	536 (37.9)	561 (34.7)	483 (31.3)		672 (63.4)	630 (60.8)	533 (57.7)	
III/IV	878 (62.1)	1056 (65.3)	1062 (68.7)	<0.001	388 (36.6)	407 (39.3)	391 (42.3)	0.01
Blood pressure (mmHg)								
Systolic	125 (110, 140)	126 (114, 140)	128 (113, 140)	0.09	135 (120, 150)	135 (120, 150)	140 (124, 150)	0.007
Diastolic	75 (68, 80)	77 (70, 80)	80 (70, 85)	<0.001	78 (70, 82)	80 (70, 86)	80 (70, 88)	<0.001

Medical history								
Current smoking	171 (12.1)	230 (14.2)	304 (19.7)	0.01	127 (12.0)	139 (13.4)	143 (15.5)	0.72
Diabetes mellitus	311 (22.0)	486 (30.1)	509 (32.9)	<0.001	269 (25.4)	297 (28.6)	290 (31.4)	0.003
Hypertension	650 (46.0)	812 (50.2)	781 (50.6)	0.01	660 (62.3)	690 (66.5)	591 (64.0)	0.39
Hospital admission for HF	981 (69.4)	1186 (73.4)	1183 (76.6)	<0.001	651 (61.4)	736 (71.0)	688 (74.5)	<0.001
Myocardial infarction	917 (64.9)	968 (59.9)	779 (50.4)	<0.001	555 (52.4)	459 (44.3)	324 (35.1)	<0.001
Stroke	130 (9.2)	141 (8.7)	124 (8.0)	0.26	98 (9.3)	93 (9.0)	77 (8.3)	0.48
History of atrial fibrillation	366 (25.9)	444 (27.5)	393 (25.4)	0.76	286 (27.0)	292 (28.2)	302 (32.7)	0.006
Medical treatment								
ACE inhibitors	808 (57.1)	903 (55.8)	838 (54.2)	0.11	226 (21.3)	192 (18.5)	158 (17.1)	0.02
B-blockers	984 (69.6)	868 (53.7)	667 (43.2)	<0.001	736 (69.4)	578 (55.7)	369 (39.9)	<0.001
Diuretics	1206 (85.3)	1411 (87.3)	1410 (91.3)	<0.001	764 (72.1)	760 (73.3)	733 (79.3)	<0.001
Spironolactone	247 (17.5)	303 (18.7)	370 (24.0)	<0.001	112 (10.6)	126 (12.2)	113 (12.2)	0.24
Digoxin/digitalis glycosides	699 (49.4)	845 (52.3)	868 (56.2)	<0.001	241 (22.7)	293 (28.3)	308 (33.3)	<0.001

ACE = angiotensin converting enzyme; BMP = beats per minute; HF = heart failure; IQR = interquartile range; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; T = tertile.

Table 3. Baseline characteristics according to group defined by tertiles of baseline heart rate in patients without and with atrial fibrillation.

	No Atrial fibrillation at randomization				Atrial fibrillation at randomization			
	T1	**T2**	**T3**		**T1**	**T2**	**T3**	
	N = 2270	**N = 2058**	**N = 2121**		**N = 453**	**N = 352**	**N = 343**	
	(35.2%)	**(31.9%)**	**(32.9%)**	**p-value**	**(39.5%)**	**(30.7%)**	**(29.9%)**	**p-value**
Median heart rate (IQR)	**60 (57, 64)**	**72 (70, 74)**	**84 (80, 90)**	**for trend**	**64 (60, 68)**	**76 (72, 80)**	**90 (86, 100)**	**for trend**
Patient's characteristics								
Median age(IQR)	67 (59, 74)	67 (57, 73)	65 (56, 72)	<0.001	70 (64, 76)	70 (63, 77)	69 (61, 75)	0.009
≥75 years	519 (22.9)	429 (20.9)	414 (19.5)	0.007	149 (32.9)	125 (35.5)	101 (29.5)	0.36
Female	636 (28.0)	684 (33.2)	731 (34.5)	<0.001	109 (24.1)	127 (36.1)	112 (32.7)	0.005
LVEF (%)	38 (30, 50)	37 (28, 50)	35 (25, 46)	<0.001	37 (28, 50)	38 (29, 51)	38 (29, 50)	0.94
NYHA class								
II	1151 (50.7)	949 (46.1)	853 (40.2)		174 (38.4)	136 (38.6)	152 (44.3)	
III/IV	1119 (49.3)	1109 (53.9)	1268 (59.8)	<0.001	279 (61.6)	216 (61.4)	191 (55.7)	0.11
Blood pressure (mmHg)								
Systolic	130 (120, 142)	130 (120, 142)	130 (118, 144)	0.57	130 (112, 140)	130 (120, 145)	130 (120, 145)	0.005
Diastolic	75 (70, 80)	80 (70, 84)	80 (70, 85)	<0.001	75 (70, 82)	80 (70, 85)	80 (70, 90)	<0.001

Medical history								
Current smoking	276 (12.2)	310 (15.1)	390 (18.4)	0.001	44 (9.7)	38 (10.8)	56 (16.3)	0.93
Diabetes mellitus	531 (23.4)	613 (29.8)	732 (34.5)	<0.001	112 (24.7)	91 (25.9)	83 (24.2)	0.90
Hypertension	1217 (53.6)	1153 (56.0)	1174 (55.4)	0.24	247 (54.5)	201 (57.1)	192 (56.0)	0.65
Hospital admission for HF	1466 (64.6)	1458 (70.9)	1572 (74.1)	<0.001	358 (79.0)	291 (82.7)	280 (81.6)	0.32
Myocardial infarction	1393 (61.4)	1176 (57.1)	1024 (48.3)	<0.001	183 (40.4)	109 (31.0)	117 (34.1)	0.05
Stroke	211 (9.3)	165 (8.0)	166 (7.8)	0.08	49 (10.8)	37 (10.5)	35 (10.2)	0.78
History of atrial fibrillation	406 (17.9)	328 (15.9)	252 (11.9)	<0.001	432 (95.4)	335 (95.2)	330 (96.2)	0.59
Medical treatment								
ACE inhibitors	911 (40.1)	829 (40.3)	911 (43.0)	0.06	227 (50.1)	128 (36.4)	119 (34.7)	<0.001
B-blockers	1627 (71.7)	1143 (55.5)	884 (41.7)	<0.001	229 (50.6)	156 (44.3)	163 (47.5)	0.34
Diuretics	1764 (77.7)	1638 (79.6)	1820 (85.8)	<0.001	422 (93.2)	324 (92.1)	316 (92.1)	0.57
Spironolactone	311 (13.7)	297 (14.4)	405 (19.1)	<0.001	105 (23.2)	83 (23.6)	70 (20.4)	0.38
Digoxin/digitalis glycosides	754 (33.2)	773 (37.6)	881 (41.5)	<0.001	330 (72.9)	265 (75.3)	251 (73.2)	0.87

ACE = angiotensin converting enzyme; BMP = beats per minute; HF = heart failure; IQR = interquartile range; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; T = tertile.

Table 4. Event rates, adjusted hazard ratios across tertiles of heart rate and adjusted hazard ratios for each 10-beat increase in baseline heart rate for all-cause mortality and for cardiovascular death or hospitalization for worsening heart failure

	All-cause mortality			CV-death or hospitalization for HF		
	Event rates and 95% CI per 100 patient-years	**HR and 95% CI***	**HR and 95% CI per 10 bpm increase***	**Event rates and 95% CI per 100 patient-years**	**HR and 95% CI***	**HR and 95% CI per 10 bpm increase***
Overall						
T1	7.2 (6.6 – 7.8)	1.00		10.3 (9.5 – 11.1)	1.00	
T2	8.3 (7.7 – 9.0)	1.07 (0.95 – 1.20)		12.8 (12.0 – 13.7)	1.11 (1.01 – 1.23)	
T3	10.2 (9.4 – 11.0)	1.27 (1.13 – 1.43)		15.3 (14.3 – 16.4)	1.23 (1.11 – 1.36)	
All patients	-	-	1.06 (1.02 – 1.10)	-	-	1.07 (1.04 – 1.10)
Reduced LVEF						
T1	8.9 (8.0 – 9.8)	1.00		12.5 (11.5 – 13.7)	1.00	
T2	10.5 (9.6 – 11.5)	1.10 (0.96 – 1.27)		15.8 (14.6 – 17.1)	1.15 (1.01 – 1.30)	
T3	12.2 (11.2 – 13.3)	1.26 (1.09 – 1.45)		18.4 (17.0 – 19.8)	1.25 (1.11 – 1.42)	
All patients	-	-	1.06 (1.02 – 1.10)	-	-	1.07 (1.03 – 1.10)

Preserved LVEF						
T1	5.0 (4.3 – 5.8)	1.00		7.4 (6.5 – 8.4)	1.00	
T2	5.2 (4.4 – 6.1)	1.05 (0.84 – 1.32)		8.9 (7.8 – 10.0)	1.14 (0.94 – 1.37)	
T3	6.3 (5.4 – 7.3)	1.25 (0.99 – 1.58)		9.8 (8.6 – 11.1)	1.14 (0.93 – 1.38)	
All patients	-	-	1.05 (0.98 – 1.12)	-	-	1.06 (1.00 – 1.12)
No Atrial fibrillation						
T1	6.7 (6.1 – 7.4)	1.00		9.4 (8.7 – 10.2)	1.00	
T2	7.7 (7.0 – 8.5)	1.08 (0.94 – 1.23)		12.0 (11.1 – 13.0)	1.14 (1.02 – 1.28)	
T3	9.5 (8.8 – 10.4)	1.26 (1.10 – 1.43)		15.0 (14.0 – 16.1)	1.28 (1.14 – 1.44)	
All patients	-	-	1.08 (1.04 – 1.12)	-	-	1.10 (1.06 – 1.13)
Atrial fibrillation						
T1	11.6 (9.8 – 13.6)	1.00		18.3 (15.9 – 21.1)	1.00	
T2	13.0 (10.9 – 15.5)	1.15 (0.90 – 1.48)		17.5 (14.9 – 20.6)	0.97 (0.78 – 1.21)	
T3	10.3 (8.4 – 12.5)	0.97 (0.75 – 1.26)		14.3 (12.0 – 17.1)	0.85 (0.67 – 1.07)	
All patients	-	-	0.97 (0.90 – 1-05)	-	-	0.95 (0.89 – 1.02)

bpm = beats per minute; CI = confidence interval; LVEF = left ventricular ejection fraction; HF = Heart Failure; HR = hazard ratio; T = tertile.

* Model is adjusted for age, LVEF, diabetes, BMI, previous HF hospitalization, gender, NYHA class, radiologic cardiomegaly, diastolic blood pressure, randomized treatment and beta-blocker use at baseline.

Figure 1.

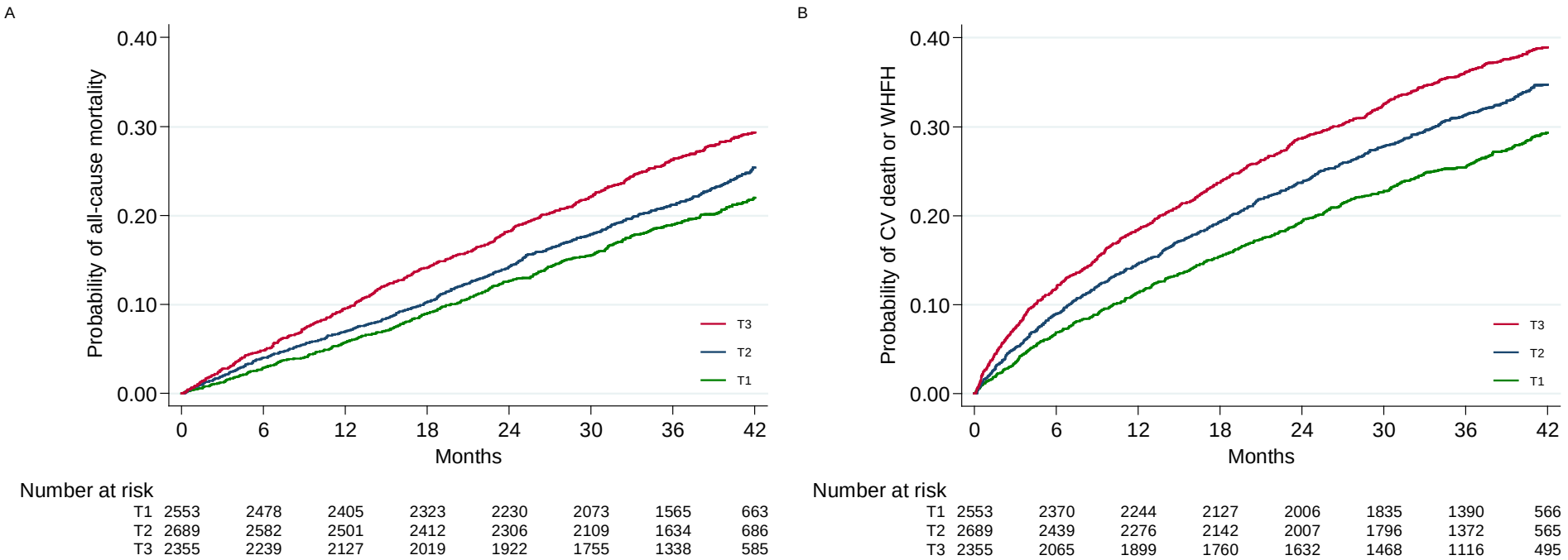

A
Probability of all-cause mortality
0.00
0.10
0.20
0.30
0.40
0
6
12
18
24
30
36
42
Months
T3
T2
T1
Number at risk
T1 2553 2478 2405 2323 2230 2073 1565 663
T2 2689 2582 2501 2412 2306 2109 1634 686
T3 2355 2239 2127 2019 1922 1755 1338 585
B
Probability of CV death or WHFH
0.00
0.10
0.20
0.30
0.40
0
6
12
18
24
30
36
42
Months
T3
T2
T1
Number at risk
T1 2553 2370 2244 2127 2006 1835 1390 566
T2 2689 2439 2276 2142 2007 1796 1372 565
T3 2355 2065 1899 1760 1632 1468 1116 495

Figure 2.

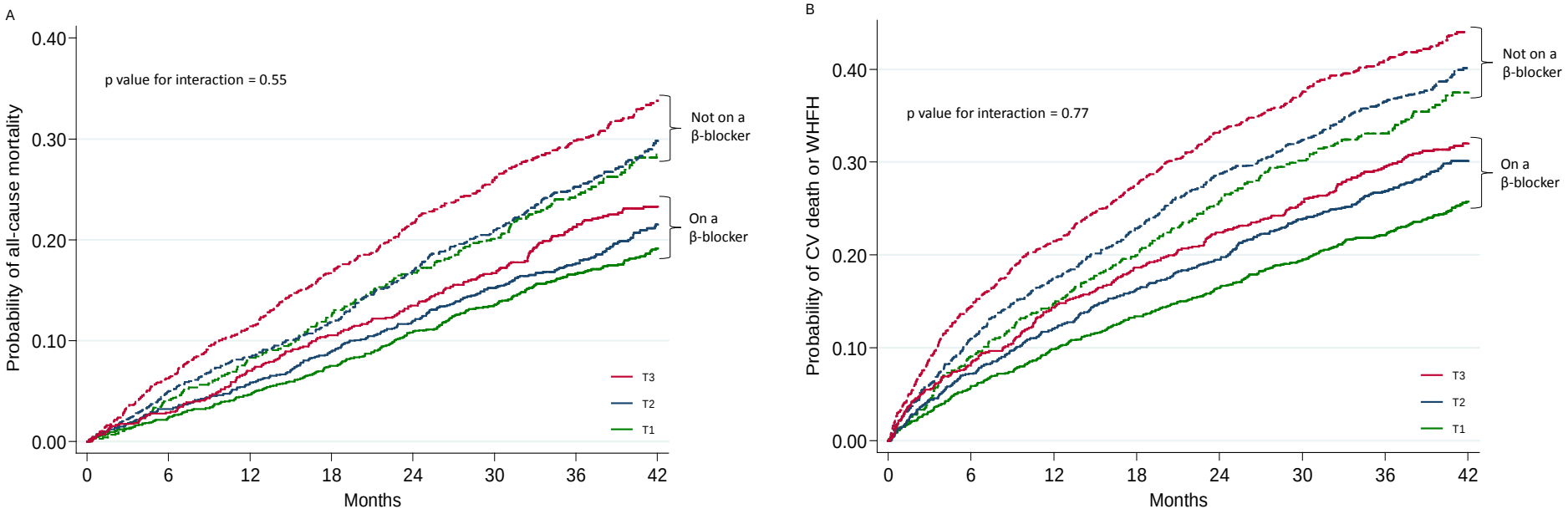
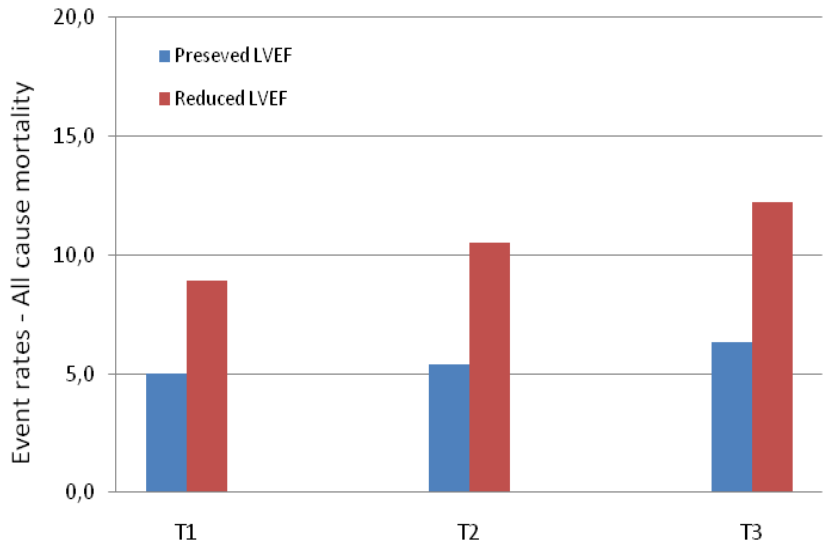

A
Probability of all-cause mortality
0.00
0.10
0.20
0.30
0.40
p value for interaction = 0.55
Not on a β-blocker
On a β-blocker
T3
T2
T1
0
6
12
18
24
30
36
42
Months
B
Probability of CV death or WHFH
0.00
0.10
0.20
0.30
0.40
p value for interaction = 0.77
Not on a β-blocker
On a β-blocker
T3
T2
T1
0
6
12
18
24
30
36
42
Months

Figure 3.

A


20,0
15,0
10,0
5,0
0,0
Preseved LVEF
Reduced LVEF
Event rates - All cause mortality
T1
T2
T3

B

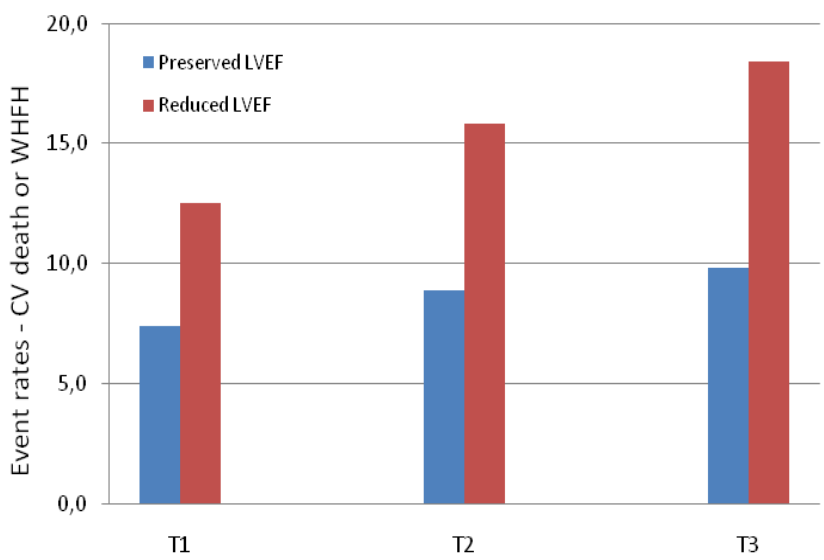
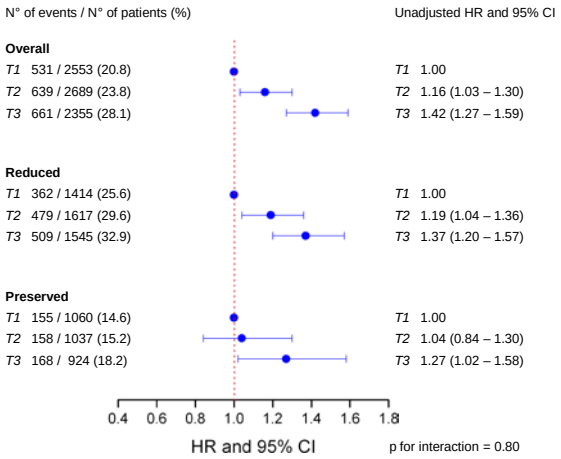

20,0
15,0
10,0
5,0
0,0
Preserved LVEF
Reduced LVEF
Event rates - CV death or WHFH
T1
T2
T3

Figure 4.

A



B

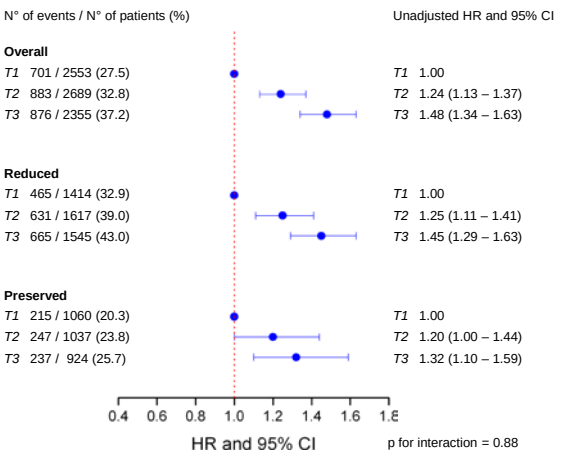
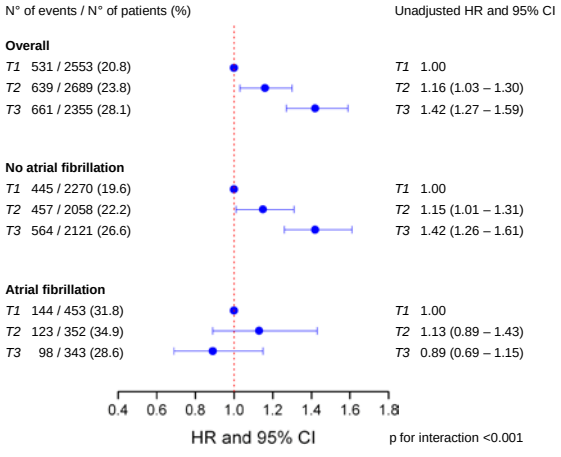


Figure 5.

A



B