

Böhm, M., Komajda, M., Borer, J. S., Ford, I. , Maack, C., Tavazzi, L., Moyne, A. and Swedberg, K. (2018) Duration of chronic heart failure affects outcomes with preserved effects of heart rate reduction with ivabradine: findings from SHIFT. *European Journal of Heart Failure*, 20(2), pp. 373-381. (doi:[10.1002/ejhf.1021](https://doi.org/10.1002/ejhf.1021))

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

This is the peer-reviewed version of the following article: Böhm, M., Komajda, M., Borer, J. S., Ford, I. , Maack, C., Tavazzi, L., Moyne, A. and Swedberg, K. (2018) Duration of chronic heart failure affects outcomes with preserved effects of heart rate reduction with ivabradine: findings from SHIFT. *European Journal of Heart Failure*, 20(2), pp. 373-381, which has been published in final form at [10.1002/ejhf.1021](https://doi.org/10.1002/ejhf.1021). This article may be used for non-commercial purposes in accordance with [Wiley Terms and Conditions for Self-Archiving](#).

<http://eprints.gla.ac.uk/150049/>

Deposited on 18 October 2017

03.08.2017

# **DURATION OF CHRONIC HEART FAILURE AFFECTS OUTCOMES WITH PRESERVED EFFECTS OF HEART RATE REDUCTION WITH IVABRADINE: FINDINGS FROM SHIFT**

Michael Böhm, MD<sup>a</sup>, Michel Komajda, MD<sup>b</sup>, Jeffrey S Borer, MD<sup>c</sup>, Ian Ford, PhD<sup>d</sup>,  
Christoph Maack, MD<sup>a</sup>, Luigi Tavazzi, MD<sup>e</sup>, Aurélie Moyne, PhD<sup>f</sup>, and Karl  
Swedberg, MD<sup>g</sup> on behalf of the SHIFT Investigators

<sup>a</sup>Universitätsklinikum des Saarlandes, Universität des Saarlandes, Klinik für Innere Medizin III, Homburg/Saar, Germany

<sup>b</sup>Department of Cardiology, Université Pierre et Marie Curie Paris VI, La Pitié-Salpêtrière Hospital, Paris, France

<sup>c</sup>Howard Gilman and Schiavone Institutes, State University of New York Downstate Medical Center, Brooklyn and New York, NY, USA

<sup>d</sup>Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK

<sup>e</sup>Maria Cecilia Hospital—GVM Care and Research, Ettore Sansavini Health Science Foundation, Cotignola, Italy

<sup>f</sup>Institut de Recherches Internationales Servier, Suresnes, France

<sup>g</sup>Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden and National Heart and Lung Institute, Imperial College, London, UK

Funding Sources: SHIFT was supported by Servier, France.

## **Address for correspondence:**

Michael Böhm, MD  
Universitätsklinikum des Saarlandes, Klinik für Innere Medizin III  
Kardiologie, Angiologie und Internistische Intensivmedizin  
Kirrberger Str. 1  
66421 Homburg/Saar  
Germany  
Tel.: (+49)-6841-16-15031  
Fax: (+49)-6841-16-15032  
E-mail: michael.boehm@uks.eu

**Word Count:** 2672

## ABSTRACT

**AIMS** In heart failure (HF) with reduced ejection fraction and sinus rhythm, heart rate (HR) reduction with ivabradine reduces the composite of cardiovascular death and heart failure hospitalization.

**METHODS AND RESULTS** It is unclear whether the duration of HF prior to therapy independently affects outcomes and whether it modifies the effect of HR reduction. In SHIFT, 6505 patients with chronic HF (LVEF  $\leq 35\%$ ), in sinus rhythm, HR  $\geq 70$  bpm, treated with guideline-recommended therapies were randomized to placebo or ivabradine. We examined outcomes and the treatment effect of ivabradine in patients with different HF durations. Prior to randomization, 1416 (ivabradine) and 1459 (placebo) patients had HF duration  $\geq 4$  weeks -  $<1.5$  years; 836 and 806 patients 1.5 to  $<4$  years, and 989 and 999 patients had HF duration 4 years or longer on ivabradine and placebo, respectively. Patients with longer duration were older (62.5 years vs 59.0 years,  $p < 0.0001$ ), had greater severity (NYHA III/IV in 56% vs 44.9%,  $p < 0.0001$ ), more comorbidities (myocardial infarction: 62.9% vs 49.4%,  $p < 0.0001$ ; renal dysfunction: 31.5% vs 21.5%,  $p < 0.0001$ ; peripheral artery disease: 7% vs 4.8%,  $p < 0.0001$  compared with patients with a more recent diagnosis. After adjustments, longer HF duration was independently associated with poorer outcome. Effects of ivabradine were independent of HF duration.

**CONCLUSIONS** Duration of HF predicts outcome independently of risk indicators like higher age, greater severity and more comorbidities. HR reduction with ivabradine improved outcomes independently of HF duration. Thus, HF treatments should be initiated early and HF chronicity is important to characterize HF populations in future trials.

### Clinical Trial Registration

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 multi-centre study; ISRCTN70429960

**Key words:** chronic heart failure – chronicity of heart failure - heart rate – comorbidities – age - ivabradine

**Running Title:** Heart failure duration modifies outcomes in HFREF

## INTRODUCTION

Chronic heart failure (CHF) is a clinical syndrome frequently accompanied by a high load of comorbidities and characterized by poor outcome despite optimal medical guideline-directed treatments (1). In stable heart failure (HF) with reduced ejection fraction (HFrEF), it is not known whether the duration from the time of onset of signs or symptoms until full treatment initiation has an effect on clinical outcomes. Interestingly, mortality rates are different between acute *de novo* and acutely decompensated CHF patients (2,3). Cardiac resynchronization therapy initiated early after emerging HF symptoms improved clinical outcomes more than applied later after development of clinical symptoms (4). In patients requiring mechanical circulatory support, outcome was better in acute or sub-acute HF than in patients with worsening of CHF and longstanding symptoms (5). Whether these associations apply also to patients with stable CHF of different chronicity is not well examined. High resting heart rates are related to poor outcome in HFrEF in the general population (6), in patients with high risk for vascular disease (7) and stable HF (8). Consistently, heart rate reduction in patients in sinus rhythm above a resting heart rate of 70 bpm reduced the composite of cardiovascular death and hospitalization for HF (9) and in a population  $\geq 75$  bpm all secondary endpoints including all-cause death and cardiovascular death (10). This study addresses the two objectives of whether the duration of HF symptoms influences outcomes and whether the treatment effect of heart rate reduction with ivabradine is modified by the duration of CHF.

## METHODS

**Study Design and Participants.** The SHIFT study (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; SHIFT (ISRCTN70429960) was a randomised double-blind placebo-controlled clinical trial in patients with moderate to severe HF and left ventricular dysfunction ( $LVEF \leq 35\%$ ) with the diagnoses of heart failure at least  $\geq 4$  weeks before randomization. Patients had to be in sinus rhythm, age  $\geq 18$  years with a heart rate at rest  $\geq 70$  bpm at two consecutive visits. Patients were either assigned to ivabradine or placebo. Ivabradine was started at 5 mg bid and adjusted according to heart rate achieved to either 7.5 mg or 2.5 mg bid. SHIFT randomized patients on optimal guideline-directed medications at maximally tolerated doses for CHF including  $\beta$ -blockers. The design (5) and the main results (9,10) of the SHIFT trial have been published previously. The primary endpoint was a composite of cardiovascular death or hospital admissions for worsening of HF. All endpoints were adjudicated by an independent endpoint committee (9,10). The SHIFT study showed that heart rate reduction with ivabradine reduced the composite of cardiovascular death and HF hospitalization with the lowest event rates occurring when heart rate on achieved treatment was below 60 bpm (8).

**Follow-up and outcomes.** The duration of HF symptoms was captured in the case report forms in each patient by the investigators. HF duration at baseline was separated into groups of practical time frames  $\geq 4$  weeks -  $<1.5$  year ( $n=2875$ ),  $1.5-<4$  years ( $n = 1642$ ) and  $\geq 4$  years ( $n=1988$ ) which roughly represented tertiles of HF duration. In these groups, baseline characteristics as well as accompanying treatments were reported. The eight most prominent comorbidities (chronic obstructive pulmonary disease (COPD), diabetes mellitus, anemia, stroke, impaired renal function (glomerular filtration rate  $\leq 60$  ml/min), myocardial infarction, hypertension and peripheral artery disease) were reported and evaluated herein. The composite primary endpoint consisting of cardiovascular death and hospitalization for

worsening of HF was explored according to duration of HF in patients on placebo or on ivabradine.

**Statistical analysis.** Descriptive statistics are presented as means  $\pm$  standard deviation (SD) for continuous variables, and as numbers and percentages for categorical variables. For baseline characteristics, the pooled placebo and ivabradine groups were divided into groups with different HF duration at baseline (<1.5 years, 1.5-<4 years and  $\geq$ 4 years). Baseline characteristics were compared between the duration of HF groups using a Kruskal–Wallis test for continuous variables and a chi-square test for categorical variables. In addition, we present the distribution of the number of comorbidities in patients on each treatment arm according to duration of HF groups. The association between risk and disease duration was tested in a Cox proportional hazards model, with disease duration as a continuous variable (1, 2, 3, 5 or 10-year increase), adjusted for prognostic factors at baseline ( $\beta$ -blocker intake at randomization, heart rate, NYHA class, LVEF, ischaemic aetiology, systolic blood pressure, and estimated glomerular filtration rate), and hazard ratios (HRs), 95% confidence intervals (CIs), and p-value were calculated. All time-to-first-event regression analyses were based on Cox proportional hazard models. Hazard ratios for ivabradine treatment relative to placebo were provided with 95% confidence intervals, and p-values calculated from the Wald statistics. The treatment effect of ivabradine vs placebo was estimated in the duration of HF groups separately, from a Cox model adjusted for prognostic factors at baseline ( $\beta$ -blocker intake at randomization, NYHA class (III or IV/II), left ventricular ejection fraction (LVEF), ischemic heart failure (yes/no), age, systolic blood pressure, heart rate at baseline and creatinine estimated glomerular filtration rate (eGFR)). Sensitivity analyses were also performed with other adjustments (age + comorbidities, cf. supplement tab1). P-

values for interaction between randomized treatments and duration of HF groups were also provided by addition of treatment by subgroup interaction to the model. The outcomes analyzed were the primary endpoint (composite of cardiovascular death or hospital admission for worsening of HF) as well as all-cause mortality and HF mortality. Time-to-event curves for each treatment arm according to duration of HF groups were estimated using the Kaplan-Meier method. SAS version 9.2 was used for all statistical analyses.

## RESULTS

**Baseline characteristics.** In SHIFT, 6558 patients were randomized into the treatment arms (3268 ivabradine, 3290 placebo). 6505 patients had available data on duration of heart failure. Baseline characteristics of all patients according to HF duration at baseline are depicted in Table 1. 2875 patients had a HF duration of  $\geq 4$  weeks -  $<1.5$  years, 1642 patients of  $1.5$ - $<4$  years and 1988 patients  $\geq 4$  years. Patients with longer HF duration tended to be older with a higher body mass index, a lower eGFR and a higher systolic and diastolic blood pressure. Moreover, they were more likely to have a previous myocardial infarction, diabetes, stroke or lower eGFR. There was also heterogeneity between the HF functional classes (NYHA), but all patients had similar treatment intensities with ACE-inhibitors, ARBs and mineralocorticoid antagonists, with a higher rate of device utilization in those with longer HF duration. Prevalence of beta blocker pre-treatment was similar, but there were more patients on higher doses with longer duration.

**Comorbidities.** In order to investigate whether there is a different prevalence of single comorbidities in the groups of duration of HF observed at baseline, we investigated the total comorbidity load (i.e. numbers of comorbidities) in these 3 groups. Figure 1 shows the distribution of the number of comorbidities by HF duration in the SHIFT population. In the group of short HF duration, more patients had 0 or 1 comorbidities compared to HF durations  $\geq 1.5$  years. In patients with a HF duration  $\geq 4$  years, 3 or 4 comorbidities were more prominent than in those patients with a shorter HF duration.

**Outcomes.** Figure 2 shows the effect of HF duration on the primary composite endpoint on placebo (A) or ivabradine (B). For the primary endpoint there was a significantly higher event rate, when patients had a longer duration compared to an intermediate or shorter HF duration irrespective of whether they were on ivabradine (Figure 2A) or on placebo (Figure 2B) (log rank  $p < 0.0001$ ). Similar results were observed for cardiovascular death regardless whether patients were on placebo (Figure 2C, log rank  $p < 0.0001$ ) or ivabradine (Figure 2D, log rank  $p < 0.0001$ ). Similar results were obtained for worsening of HF (log rank  $p < 0.0001$ ) for placebo (Figure 2E) and ivabradine (Figure 2F). To account for the high variability of disease durations, the associations were also evaluated in a statistical model with HF duration in a continuous manner. Figure 3 shows that with longer disease duration risk is higher. The disease duration is a risk indicator for cardiovascular outcomes in the SHIFT population.

The treatment effects of ivabradine according to HF duration are summarized in Figure 4. Presented hazard ratios with 95% confidence interval are adjusted for prognostic factors at baseline ( $\beta$ -blocker intake at randomization, NYHA class, LVEF,



ischemic heart failure, age, systolic blood pressure, heart rate at baseline and creatinine clearance). There was a significant reduction of the primary composite endpoint and hospitalization for the worsening of HF irrespective of HF duration. There was a nominal decrease of cardiovascular mortality and all-cause mortality, which was not statistically significant, but a 40% decrease of HF mortality was observed in the subgroup of patients with a HF duration  $\geq 4$  years. We performed the same analyses with other adjustments. The effects of treatment were not affected by comorbidities or risk indicators (Suppl. Table 1). In order to exclude a threshold of HF duration for the effect of ivabradine, an adjusted cox model on prognostic factors for the primary endpoint was performed on patients having an HF duration  $\geq$  threshold value which varied from 0.5 years to 8 years. There was no threshold detectable (Figure 5). There was no significant heterogeneity of the treatment effects of ivabradine between the HF duration groups or defined endpoints. Neither the effect of HF duration on outcomes nor the effects of treatment were affected by comorbidities or risk indicators (Suppl. Table 1). The drop in HR after up-titration of ivabradine at 28 days was similar between the groups ( $>4$  weeks – 1.5 years:  $16.6 \pm 10.9$  bpm; 1.5 - 4 years:  $14.6 \pm 10.8$  bpm;  $>4$  years:  $15.8 \pm 10.4$  bpm).

## DISCUSSION

We demonstrated in this post-hoc analysis from the SHIFT study that the duration of HF was associated with morbidity and mortality. Although higher chronicity of HF was accompanied by a higher prevalence of single cardiac and non-cardiac comorbidities and a higher cumulative load of comorbid conditions, poor outcome was independent of comorbidities and risk indicators. The treatment effect of heart rate lowering with ivabradine was maintained across all groups with different HF durations.

Herein, we report a remarkable increase of all cardiovascular outcomes according to the duration of HF independent of comorbidities and risk indicators. This is to the best of our knowledge the first study to explore the impact of HF duration on outcomes in stable CHF. These data are in line with several studies on acute HF showing that mortality is higher in acute on chronic HF decompensation rather than on *de novo* HF decompensation (2,3). Furthermore, patients receiving a mechanical circulatory support system earlier in the course of CHF provide better outcomes than those with longstanding CHF before implantation (5). Finally, in patients with a shorter duration of CHF, a lower rate of cardiovascular death and HF hospitalization was observed after CRT implantation than in patients with longstanding symptoms (4). Recently, the ASCEND-HF investigators reported that patients with longer duration of the heart failure syndrome presenting with acute decompensation, had a higher 180-day mortality (11). The hazard ratios were between 1.82-2.02 between 1-12 month and > 60 months being quite similar between the groups indicating that there was no gradual worsening of outcomes. Similarly, patients with longer duration of heart failure appeared to be more difficult to stabilize reflected by more persistent dyspnea at 24 hours (11). Therefore, pathophysiological changes driven by acute decompensation might modify the risk-duration relationship in solely chronic heart failure described herein.

CHF is a long-term condition accompanied by cardiovascular remodeling, which is progressive over time (12). Therefore, it is likely that progressive maladaptive cardiac remodeling involving cardiac hypertrophy, defects in calcium handling and  $\beta$ -adrenergic signal transduction in response to neuroendocrine activation (13,14) are involved, inducing continuous deterioration of cardiac function. Finally, it is very likely that recovery in terms of adaptive deremodeling is impaired in long-standing heart

failure compared to individuals with a more recent onset contributing to poorer outcomes. Patients with longer HF duration also differ concerning their baseline characteristic. Patients with longer duration of symptoms were older and had more previous myocardial infarctions, diabetes, stroke, atrial fibrillation, renal failure, chronic obstructive pulmonary disease and peripheral artery disease. The association of HF duration to outcome was robust to adjustment for comorbidities or risk indicators. Comorbidities were associated with higher hospitalizations and morbidity (15,16,17), which are in turn related to higher age (18). Therefore, ageing, comorbidities and factors directly acting on the pathophysiology of cardiac remodeling or impairing cardiac recovery in HF (12) might further contribute to higher event rates according to the chronicity of CHF. Finally, sub-clinical decompensations below the threshold for hospitalizations in the outpatient setting might also be predictive, if not mechanistically involved, in death and hospitalization as shown recently (19). Patients with no or a remote decompensation, although having a somewhat lower risk, had a 22% incidence of cardiovascular death or heart failure hospitalization at follow-up in PARADIGM indicating that despite stability over a longer period of time, novel therapies should be introduced (20).

Heart rate predicts outcome in CHF (10) and heart rate reduction reduces cardiovascular outcomes as shown in the SHIFT trial (9). The effect of heart rate reduction with ivabradine was unchanged within the groups of different HF durations. Heart rate reduction with ivabradine reduces progressive remodeling of the left ventricle (21). Relative risk reduction in the different HF duration groups was similar. This implies that a higher absolute event rate reduction might be attained in higher risk groups with longer HF duration. Therefore, early introduction of heart failure therapies as well as timely introduction of cardiac resynchronization devices (4) or, in

most severe HF, mechanical support systems (5) could provide higher absolute event rate reductions. In addition, the present findings show that the risk increase by HF duration is independent, however, accompanied by increased comorbidity loads. In many of these comorbid conditions heart rate also predicts risk, although an effect of heart rate reduction as CHF has not been shown yet. However, recent findings suggest that the effects of ivabradine in single-comorbid conditions like impaired renal function (22), chronic obstructive pulmonary disease (23), ageing (24) or high cumulative comorbidity load (17) is maintained. An outcome predictor of HF is low systolic blood pressure (25), in particular in association with high heart rate (26). However, herein, blood pressure was not different in patients with longstanding HF duration compared with lower chronicity, indicating that the age-associated increase in blood pressure overrides the HF associated decreases in blood pressure. Since heart rate is also associated with outcomes in conditions which are prominent comorbidities in HF, like chronic obstructive pulmonary disease, critical care disease, cancer (27,28) and endothelial function (29), the unaffected efficacy of heart rate reduction is not surprising.

These findings might have also implications for future trial designs. Since patients with long HF duration differ considerably from those with shorter duration of HF, it is surprising that this parameter is neither reported in baseline characteristics of HF trials nor is part of the randomization stratification. It could further be used to enrich heart failure populations towards higher event rates, although in the overall population this could limit the generalizability of trial results. Nevertheless, this parameter should be taken into consideration of defining heterogeneity of HF populations and for power calculations of future trials.

Some limitations of this analysis need to be acknowledged. This is a retrospective analysis and the treatment groups in the sub-groups of HF duration are not subject to randomization. Therefore, this analysis is, by nature, hypothesis-generating.

## CONCLUSIONS

These results from the SHIFT study show that the duration of CHF independently predicts poor outcome in patients with long HF duration and might be related to longstanding remodeling and poorer capacity to recover and deremodeling of the failing heart. It is however, accompanied by higher age and a higher prevalence of non-cardiac and cardiac comorbidities in these patients. This concept is summarized in Figure 6. There is no signal of heterogeneity in the treatment effect of heart rate reduction with ivabradine linked to the HF disease duration. A medical history of longer HF duration is a risk indicator and should, therefore, be introduced into randomization strategies and risk evaluation of heart failure populations in future clinical trials.

**Funding:** SHIFT was funded by Les Laboratoires Serviers (Suresness, France)

**Conflicts of interest:** All authors received speaker's honoraria from Servier or are consultants for Servier. A.M. is an employee of Servier. MK has consulting activities for Servier and Novartis and received speaker's honoraria from Servier, Novartis, Merck Sharpe Dohme, Sanofi, Novo Nordisk, Bristol Myers Squibb. KS has received research grants from Servier, Novartis and Amgen and is a consultant for AstraZeneca and Roche. MB has received speaker's honoraria from Boehringer Ingelheim, Medtronic, Novartis, St. Jude and Vifor and is on the scientific advisor board of Servier. JB is a consultant for Servier, is a member of Executive

Committee of the SHIFT study, sponsored by Servier and has received consultation fees and honoraria for services on the SHIFT Executive Committee. He also consults for Takeda USA, Amgen, Novartis, AstraZeneca, Pfizer, Gilead and GlaxoSmithKline. CM received speaker's honoraria from Servier, Novartis, Bayer, Pfizer, Boehringer Ingelheim and is a consultant to Servier. AM is an employee of Servier. LT is a member of Executive Committee of the SHIFT study and the QUALIFY registry, and country responsible of the ATPCI trial sponsored by Servier, and member of trial committees for Saint Jude. IF has received honoraria from Servier and AMGEN.

## REFERENCES

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891-975.
2. AlHabib KF, Kashour T, Elasfar AA, Alfaleh H, Hersi A, Alshamiri M, Alshaer F, Mimish L, Almasood A, AlHabeeb W, AlGhamdi S, Ghabashi A, Asfina K, Altaradi H, Alnobani O, Alkamel N, Thalib L. Long-Term Mortality Rates in Acute De Novo Versus Acute-on-Chronic Heart Failure: From the Heart Function Assessment Registry Trial in Saudi Arabia. *Angiology* 2015;**66**:837-44.
3. Lassus JP, Siirilä-Waris K, Nieminen MS, Tolonen J, Tarvasmäki T, Peuhkurinen K, Melin J, Pulkki K, Harjola VP; FINN-AKVA study group. Long-term survival after hospitalization for acute heart failure--differences in prognosis of acutely decompensated chronic and new-onset acute heart failure. *Int J Cardiol* 2013;**168**:458-62.
4. Verbrugge FH, Dupont M, Vercammen J, Jacobs L, Verhaert D, Vandervoort P, Tang WH, Mullens W. Time from emerging heart failure symptoms to cardiac resynchronisation therapy: impact on clinical response. *Heart* 2013;**99**:314-9.
5. Loyaga-Rendon RY, Acharya D, Pamboukian SV, Tallaj JA, Cantor R, Starling RC, Naftel DC, Kirklin JK. Duration of heart failure is an important predictor of outcomes after mechanical circulatory support. *Circ Heart Fail* 2015;**8**:953-9.
6. Custodis F, Roggenbuck U, Lehmann N, Moebus S, Laufs U, Mahabadi AA, Heusch G, Mann K, Jöckel KH, Erbel R, Böhm M, Möhlenkamp S. Resting heart rate is an independent predictor of all-cause mortality in the middle aged general population. *Clin Res Cardiol* 2016;**105**:601-12.
7. Lonn EM, Rambihar S, Gao P, Custodis FF, Sliwa K, Teo KK, Yusuf S, Böhm M. Heart rate is associated with increased risk of major cardiovascular events, cardiovascular and all-cause death in patients with stable chronic cardiovascular disease: an analysis of ONTARGET/TRANSCEND. *Clin Res Cardiol* 2014;**103**:149-59.

8. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L; SHIFT Investigators. 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.
9. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875-85.
10. Böhm M, Borer J, Ford I, Gonzalez-Juanatey JR, Komajda M, Lopez-Sendon J, Reil JC, Swedberg K, Tavazzi L. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. *Clin Res Cardiol* 2013;**102**:11-22.
11. Greene SJ, Hernandez AF, Dunning A, Ambrosy AP, Armstrong PW, Butler J, Cerbin LP, Coles A, Ezekowitz JA, Metra M, Starling RC, Teerlink JR, Voors AA, O'Connor CM, Mentz RJ. Hospitalization for recently diagnosed versus worsening chronic heart failure: from the ASCEND-HF Trial. *J Am Coll Cardiol* 2017;**69**:3029-39.
12. Heusch G, Libby P, Gersh B, Yellon D, Böhm M, Lopaschuk G, Opie L. Cardiovascular remodelling in coronary artery disease and heart failure. *Lancet* 2014;**383**:1933-43.
13. Hasenfuss G, Reinecke H, Studer R, Meyer M, Pieske B, Holtz J, Holubarsch C, Posival H, Just H, Drexler H. Relation between myocardial function and expression of sarcoplasmic reticulum Ca(2+)-ATPase in failing and nonfailing human myocardium. *Circ Res* 1994;**75**:434-42.
14. Böhm M, Gierschik P, Jakobs KH, Pieske B, Schnabel P, Ungerer M, Erdmann E. Increase of Gi alpha in human hearts with dilated but not ischemic cardiomyopathy. *Circulation* 1990;**82**:1249-65.
15. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA* 2005;**294**:716-24.
16. Braunstein JB, Anderson GF, Gerstenblith G, Weller W, Niefeld M, Herbert R, Wu AW. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol* 2003;**42**:1226-33.
17. Böhm M, Robertson M, Ford I, Borer JS, Komajda M, Kindermann I, Maack C, Lainscak M, Swedberg K, Tavazzi L. Influence of cardiovascular and noncardiovascular co-morbidities on outcomes and treatment effect of heart rate



reduction with ivabradine in stable heart failure (from the SHIFT Trial). *Am J Cardiol* 2015;**116**:1890-7.

18. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002;**347**:1397-402.

19. Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC1, Swedberg K, Zile MR, Solomon SD, Packer M, McMurray JJ; PARADIGM-HF Investigators and Committees\*.Importance of Clinical Worsening of Heart Failure Treated in the Outpatient Setting: Evidence From the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF). *Circulation* 2016;**133**:2254-62.

20. Solomon SD, Claggett B, Packer M, Desai A, Zile MR, Swedberg K, Rouleau J, Shi V, Lefkowitz M, McMurray JJ. Efficacy of Sacubitril/Valsartan Relative to a Prior Decompensation: The PARADIGM-HF Trial. *JACC Heart Fail* 2016;**4**:816-22.

21. Tardif JC, O'Meara E, Komajda M, Böhm M, Borer JS, Ford I, Tavazzi L, Swedberg K; SHIFT Investigators. Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy. *Eur Heart J* 2011;**32**:2507-15.

22. Voors AA, van Veldhuisen DJ, Robertson M, Ford I, Borer JS, Böhm M, Komajda M, Swedberg K, Tavazzi L; SHIFT investigators. The effect of heart rate reduction with ivabradine on renal function in patients with chronic heart failure: an analysis from SHIFT. *Eur J Heart Fail* 2014;**16**:426-34.

23. Tavazzi L, Swedberg K, Komajda M, Böhm M, Borer JS, Lainscak M, Robertson M, Ford I; SHIFT Investigators. Clinical profiles and outcomes in patients with chronic heart failure and chronic obstructive pulmonary disease: an efficacy and safety analysis of SHIFT study. *Int J Cardiol* 2013;**170**:182-8.

24. Tavazzi L, Swedberg K, Komajda M, Böhm M, Borer JS, Lainscak M, Ford I; SHIFT Investigators. Efficacy and safety of ivabradine in chronic heart failure across the age spectrum: insights from the SHIFT study. *Eur J Heart Fail* 2013;**15**:1296-303.

25. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, Stough WG, Yancy CW, Young JB, Fonarow GC; OPTIMIZE-HF Investigators and Coordinators. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA* 2006;**296**:2217-26.

26. Komajda M, Böhm M, Borer JS, Ford I, Robertson M, Manolis AJ, Tavazzi L, Swedberg K; SHIFT Investigators. Efficacy and safety of ivabradine in patients with

chronic systolic heart failure according to blood pressure level in SHIFT. *Eur J Heart Fail* 2014;**16**:810-6.

27. Böhm M, Reil JC, Deedwania P, Kim JB<sup>4</sup>, Borer JS. Resting heart rate: risk indicator and emerging risk factor in cardiovascular disease. *Am J Med* 2015;**128**:219-28.

28. Böhm M. Heart rate: from heart failure to chronic diseases and cancer. Is there a role for supportive care by heart rate reduction? *Eur J Heart Fail* 2017;**19**:250-252.

29. Mangiacapra F, Colaïori I, Ricottini E, Balducci F, Creta A, Demartini C, Minotti G, Di Sciascio G. Heart Rate reduction by IVabradine for improvement of ENDothELial function in patients with coronary artery disease: the RIVENDEL study. *Clin Res Cardiol* 2017;**106**:69-75.

## LEGENDS TO FIGURES

### Figure 1

Distribution of the number of comorbidities in patients on placebo (left) or ivabradine (right) according to duration of HF (<1.5 year, 1.5-<4 years, ≥4 years).

The percentages (%) were calculated in each class of disease duration.

The HF durations were for the comorbidity groups (mean ± SD): 0: 2.33 +/-3.37 years (n=685); 1: 2.95+/-3.83 years (n=1437); 2: 3.72+/-4.57 years (n=2008); 3: 3.87+/-4.2; >=4: 4.17+/-4.38 (n=890).

### Figure 2

Kaplan-Meier event curves for the primary endpoint (A,B), cardiovascular death (C,D) and hospitalization for worsening HF (E,F), patients on placebo (A,C,E) or ivabradine (B,C,D) according to duration of HF (<1.5 year, 1.5-<4 years, ≥4 years). Log rank p-values are given. Numbers at risk are depicted below Kaplan-Meier events curves.

### Figure 3

Effect of a 1, 2, 3, 5 and 10-year increase using time as a continuous variable for the primary endpoint, hospitalization for worsening HF (WHF), cardiovascular (CV) death and all-cause death. Hazard ratios (95% CI) from a Cox model adjusted for prognostic factors.

### Figure 4

Effect of ivabradine treatment in different duration of HF. Hazard ratios for the primary endpoint, cardiovascular mortality, all-cause mortality and heart failure mortality according to the duration of HF (<1.5 year, 1.5-<4 years, ≥4 years).

<sup>a</sup> Number of patients in the placebo group: <1.5 years, n=1459; 1.5 to <4 years, n=806 ; and ≥4 years, n=999. Number of patients in the ivabradine group: <1.5 years, n=1416; 1.5 to <4 years, n=836; and ≥ 4 years, n=989. %PY=annual incidence rate

<sup>b</sup> Adjusted for prognostic factors (β-blocker intake at randomisation, NYHA (III or IV / II), LVEF (%), ischaemic HF (yes/no), age (years), systolic blood pressure (mmHg), heart rate (bpm), creatinine clearance).

<sup>c</sup> P-value for interaction between randomized treatment and HF duration group.

<sup>d</sup> Composite of cardiovascular mortality and hospitalization for worsening HF.

### Figure 5

Effect of ivabradine treatment for the primary endpoint from a Cox model adjusted for prognostic factors according to HF disease duration.

For each value of the threshold (from 0.5 to 8 years by a 0.5 year step), the model was performed on the patients having a HF disease duration ≥ threshold value.

### Figure 6

Interaction of duration of heart failure with progressive maladaptive responses, impaired recovery and comorbidities and prognosis.

This figure shows the concept of the impact on progressive remodeling, impaired deremodeling and recovery increasing loads of comorbidities and maladaptive responses according to the duration of heart failure. Early treatment might significantly slow the course of deterioration with evidence based treatments including heart rate reduction.

Arrows depict heart failure decompensation without optimal treatment (blue area) or optimal treatment (green area). Comorbidities (red graph) and maladaptive remodeling (red shaded area) progress over time.

**Table 1 – Baseline demographics and clinical characteristics of the total SHIFT population according to Heart failure duration at baseline**

	Heart failure duration at baseline			P value
	≥4 weeks to <1.5 years n=2875	1.5 to <4 years n=1642	≥4 years n=1988	
<b>Disease duration</b>				
Mean, years (SD)	0.60 ± 0.38	2.64 ± 0.71	8.40 ± 4.51	
Median, years (Q1; Q3)	0.52 (0.26; 0.88)	2.61 (2.03; 3.21)	7.09 (5.24; 10.13)	
<b>Demographic characteristics</b>				
Mean age, years	58.96 ± 11.88	60.45 ± 11.03	62.45 ± 10.60	<.0001
Male, %	77	77	75	0.4879
Body mass index, kg/m <sup>2</sup>	27.53 ± 5.02	28.27 ± 5.01	28.43 ± 5.09	<.0001
<b>Cardiac parameters</b>				
Heart rate, bpm	80.21 ± 9.94	79.56 ± 9.28	79.70 ± 9.42	0.1392
SBP, mmHg	121.05 ± 16.29	122.00 ± 15.65	122.27 ± 15.70	0.0092
DBP, mmHg	75.42 ± 9.58	76.08 ± 9.29	75.67 ± 9.49	0.0498
LVEF, %	29.07 ± 5.10	29.16 ± 5.13	28.77 ± 5.24	0.0463
<b>Medical history</b>				
NYHA Class II, %	55.03	43.91	43.56	<.0001
NYHA Class III, %	43.58	54.38	54.18	
NYHA Class IV, %	1.32	1.71	2.26	
Duration of CHF, years	0.6	2.64	8.4	<.0001
Ischaemic HF, %	62.61	73.26	71.18	<.0001
Myocardial infarction, %	49.36	60.66	62.93	<.0001
Hypertention, %	59.86	71.62	71.28	<.0001
Diabetes, %	27.79	31.12	33.65	<.0001
Stroke, %	6.30	8.53	10.16	<.0001
AF and, or flutter, %	7.03	8.65	8.95	0.0291
Renal failure, %	4.97	7.31	7.90	<.0001
eGFR <60ml/min, %	21.46	27.22	31.54	<.0001
Chronic obstructive pulmonary disease, %	10.23	12.24	11.82	0.071
Peripheral artery disease, %	4.83	7.73	6.99	0.0001
Anemia, %	7.90	7.61	7.04	0.5401
<b>Treatment at randomization</b>				
Beta-blockers, %	89.77	89.77	88.78	0.4882
Beta-blockers dose ≥50% of target, %	51.30	58.82	59.47	<.0001
Beta-blockers dose ≥100% of target, %	22.28	28.58	29.45	<.0001
ACE inhibitor, %	77.84	79.42	79.18	0.3656
ARB, %	13.88	13.52	15.39	0.2056
ACE inhibitor and/or ARB, %	90.02	90.93	92.66	0.0064
MRA, %	61.01	59.74	59.71	0.5753
Diuretics, %	82.12	84.10	84.10	0.1044
At least one device, %	2.61	3.17	5.89	<.0001
Randomised to ivabradine, %	49.25	50.91	49.75	0.5598

Figure 1

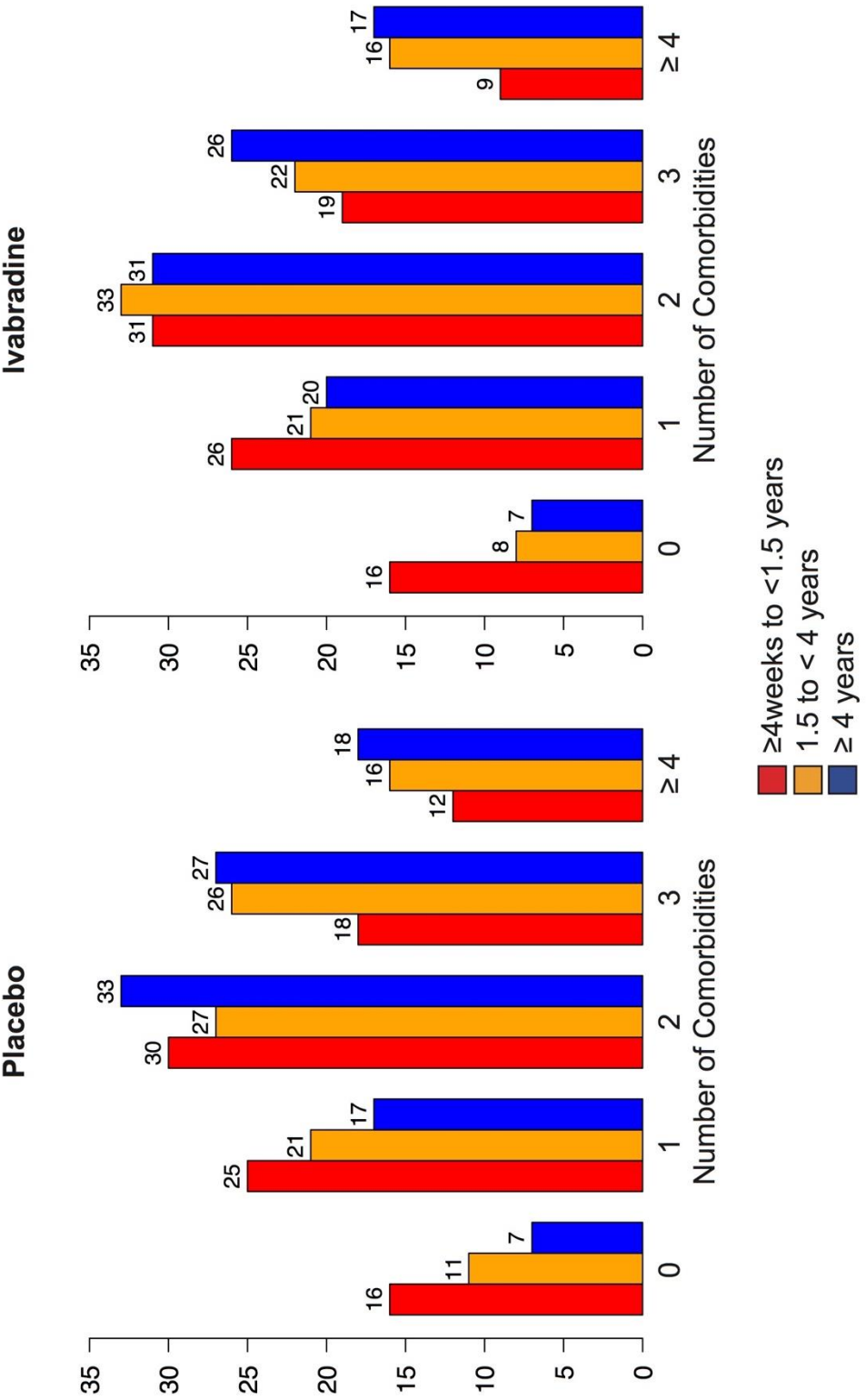


Figure 2

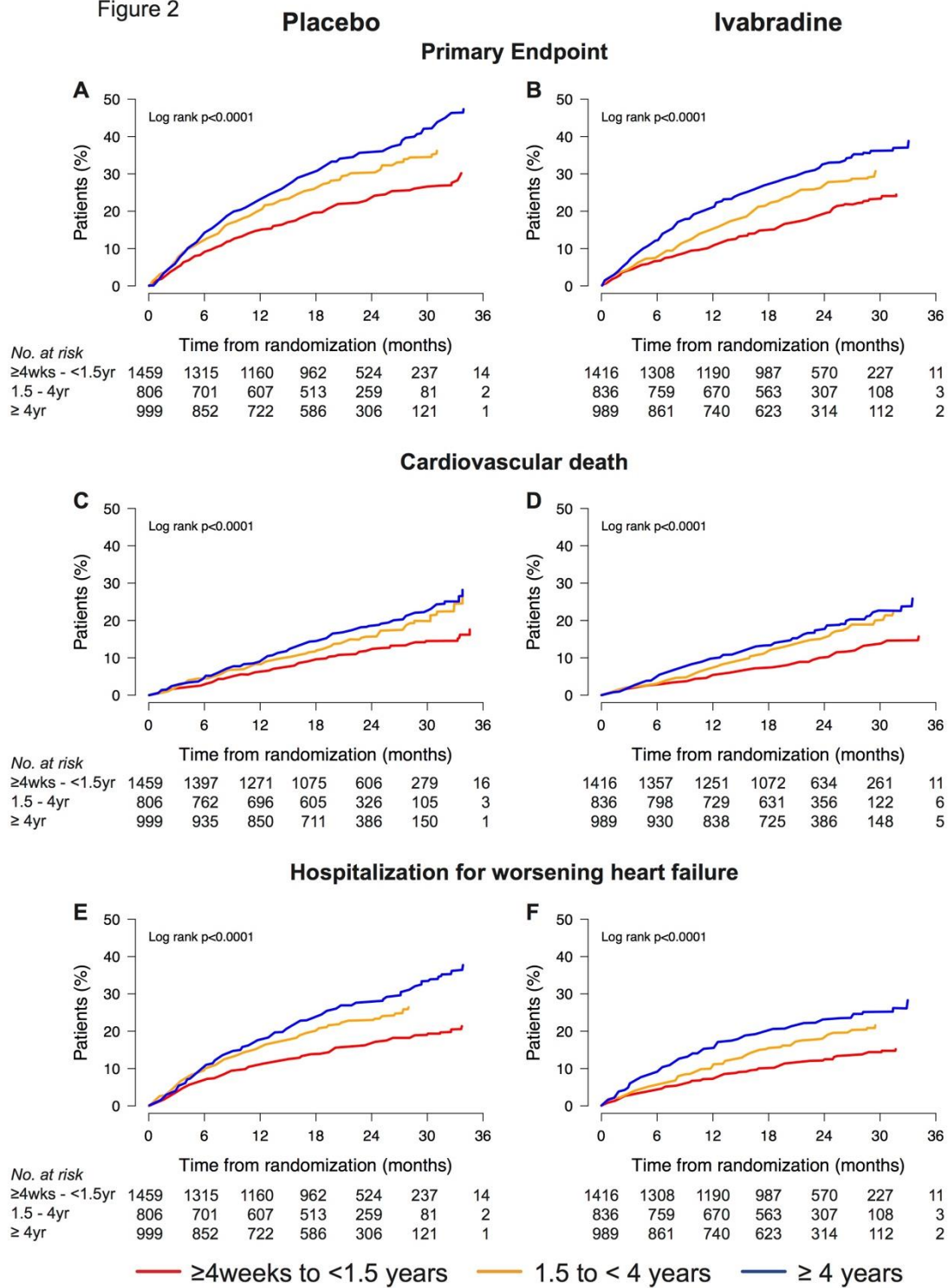


Figure 3

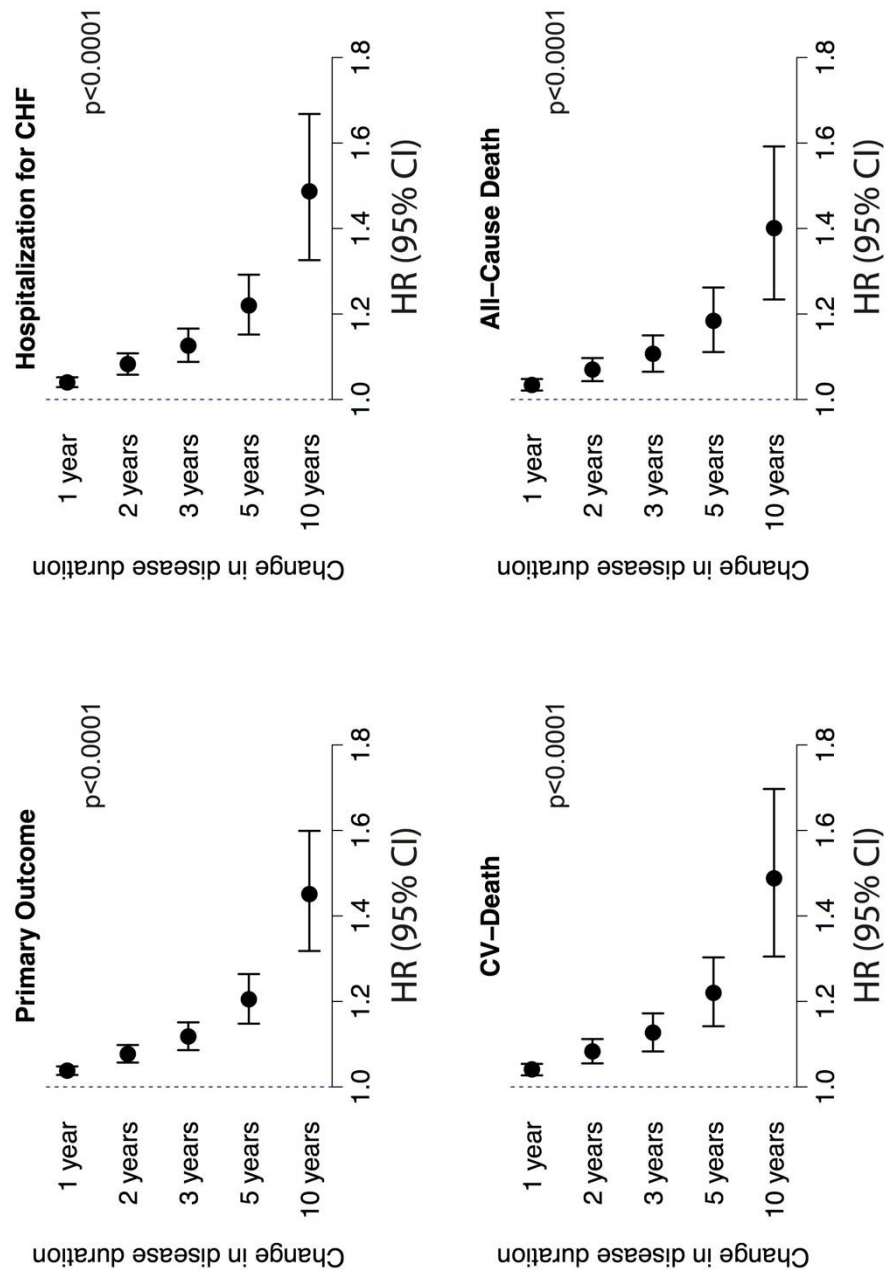




Figure 4

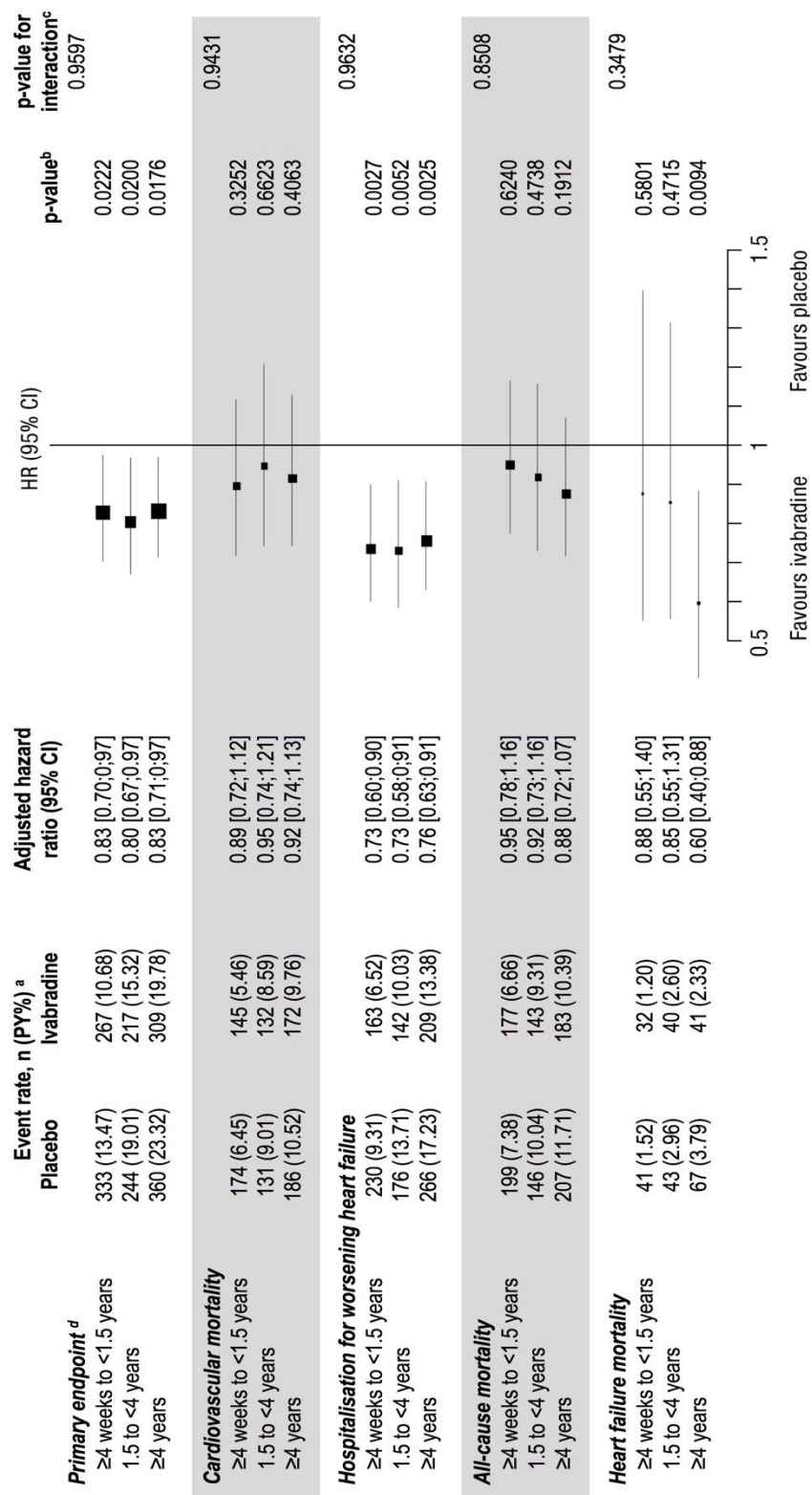


Figure 5 Treatment Effect of Ivabradine on Cardiovascular Mortality or Heart Failure Hospitalization

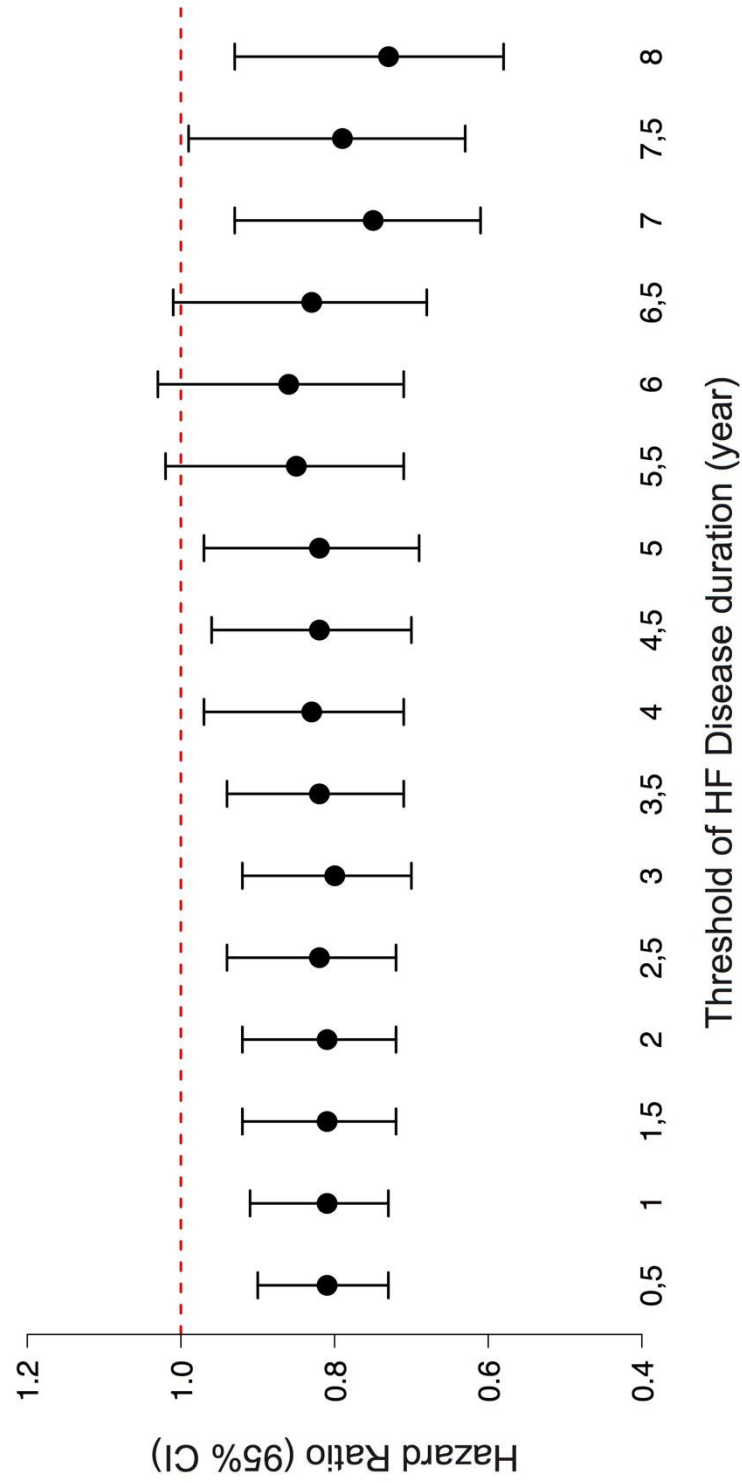


Figure 6

