Chronic exposure to ivabradine reduces readmissions in the vulnerable phase after hospitalisation for worsening systolic heart failure: a post hoc analysis of SHIFT

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Target journal: *Eur J Heart Fail* (IF 6.526).

Manuscript statistics: 3854 words; 35 references; 2 tables + 2 figures.

Abstract (228 words)

Background:

During the post discharge phase following a heart failure hospitalisation (HFH), patients are at high risk of early readmission despite standard of care therapy. We examined the impact of chronic exposure to ivabradine on early readmissions in patients hospitalised for heart failure during the course of the SHIFT study (Systolic Heart Failure treatment with the I_f inhibitor ivabradine Trial).

Methods and results:

1186 of the 6505 randomised patients experienced at least one HFH during the study, and were more severe than those without HFH. Of these 1186 patients, 334 patients (28%) were rehospitalised within 3 months for any reason, mostly for cardiovascular causes (86%), including HFH (61%). Ivabradine was associated with fewer all-cause hospitalisations at one month (incidence rate ratio (IRR): 0.70, 95% CI 0.50 to 1.00 p<0.05), 2 months (IRR 0.75, 95% CI 0.58 to 0.98, p=0.03), and 3 months (IRR 0.79, 95% CI 0.63 to 0.99, p=0.04). A trend for a reduction in cardiovascular and HF hospitalisations was also observed in ivabradine-treated patients.

Conclusion:

We demonstrate in this post hoc analysis that chronic exposure to ivabradine reduces the incidence of all cause hospitalisations during the vulnerable phase after a HFH. Further studies are needed to investigate if in-hospital or early post discharge initiation of ivabradine could be useful to improve early outcomes in patients hospitalised for HF.

Keywords: Ivabradine; hospitalisations; heart failure; outcomes; vulnerable phase.

Introduction

The number of hospitalisations for heart failure remains high in many European countries, representing 1-2% of all hospital admissions.[1] In comparison to outpatients with chronic heart failure, patients hospitalised for heart failure have high rates of readmission. A recent European registry reports a rate of 1-year hospitalisation as high as 44% after discharge, versus 32% in outpatients.[2] These alarming figures have a considerable impact on both healthcare cost and prognosis. Patients hospitalised for heart failure are particularly at risk for death or rehospitalisation in the first weeks following discharge, while risk decreases significantly after 3 to 6 months.[3-5] In Europe, 3 months after discharge, a quarter of patients had been rehospitalised, and 13.5% had died.[6] This immediate post discharge period has been referred as the "vulnerable phase".[7]

Patients with heart failure often present with multiple comorbidities, which put them at a higher risk for recurrent hospitalisations, whatever the cause.[8] The need for an effective treatment reducing the global burden of rehospitalisation -whether of cardiac or non-cardiac causes- is crucial. In SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial), heart rate reduction with ivabradine was associated with a 26% risk reduction of first heart failure hospitalisation, and 11% risk reduction of first all-cause hospitalisation.[9]

Since reducing the burden of rehospitalisations during the vulnerable phase is of critical clinical importance, we analyse here the effect of chronic exposure to ivabradine versus placebo on all-cause recurrent hospitalisations occurring up to 3 months after a hospitalisation for worsening heart failure in the SHIFT trial.

Methods

The complete design and results of the SHIFT trial have been previously reported.[9,10] Briefly, SHIFT was a randomised, double-blind, placebo-controlled trial in outpatients with symptomatic and stable heart failure (≥4 weeks), systolic dysfunction (left ventricular ejection fraction ≤35%), heart rate ≥70 bpm, and in sinus rhythm. All subjects had been hospitalised for worsening heart failure in the year before inclusion. In total, 6505 patients treated with guideline-recommended therapy were randomised to placebo or ivabradine (starting dose 5 mg bid, titrated to 7.5 mg or 2.5 mg bid, according to heart rate and tolerability). The primary study endpoint was a composite of cardiovascular mortality or hospitalisation for worsening heart failure. Secondary endpoints included both individual components of the composite endpoint, all-cause mortality, heart failure mortality, and all-cause hospitalisation, among others. All hospitalisations were adjudicated by an endpoint validation committee. Diagnosis of heart failure as a main reason for hospitalisation had to be confirmed.

In the present study, we identified SHIFT patients who had had at least one heart failure hospitalisation during the trial, and analysed events subsequent to that hospitalisation during the vulnerable phase. This vulnerable phase was defined as the 3 months after the date of admission for a first hospitalisation due to worsening heart failure, and, thus, includes the period of hospitalisation. In this population, the median duration of hospitalisation was 8 days. We considered the total number of events that occurred during a selected timeframe (1, 2, and 3 months) after the first admission for worsening heart failure. Readmissions after a heart failure hospitalisation are known to be driven by both cardiac and non-cardiac causes.[4] Thus our analysis focuses on all-cause rehospitalisations. Hospitalisations due to cardiovascular cause or due to heart failure are also described.

This study is a post hoc analysis of SHIFT data. Therefore, statistical methods and analysed population were selected a posteriori. Disposition of the population was described by counting the number of patients with a recurring event during the vulnerable phase for each treatment group. Baseline characteristics are shown as means±standard deviations (SD) for continuous variables, and numbers and percentages for categorical variables. Baseline characteristics of patients with at least one heart failure hospitalisation during the study were compared with those of patients who had no heart failure hospitalisation. Comparison was done in the pooled treatment groups, using a Kruskal-Wallis test for continuous variables and χ^2 test for categorical variables. In addition, we present the baseline characteristics of patients rehospitalised for any cause within 3 months after the first heart failure hospitalisation. Treatment effect between ivabradine and placebo groups was measured as the incidence rate ratio (IRR) for recurrent hospitalisations during the vulnerable phase (all-cause, due to cardiovascular cause, or due to heart failure). Each IRR was calculated using a Poisson regression model (with correction for overdispersion), with censoring time at 1, 2, and 3 months after the first hospital admission for worsening heart failure. In addition, IRRs were adjusted for the following prognostic factors at baseline: beta-blocker intake (also used as a stratification factor for randomisation); New York Heart Association (NYHA) class; ischaemic cause of heart failure; age; systolic blood pressure; heart rate; left ventricular ejection fraction; and glomerular filtration rate, estimated using the Modification in Diet in Renal Disease equation.[11] Associated 95% confidence intervals (CI) and p values (two-sided test) are presented, with a p value <0.05 considered as significant. The cumulative incidence rate of all-cause rehospitalisations was plotted across time for each treatment group, using the Nelson-Aalen's estimator. Death rates were calculated at 1, 2 and 3 months after the first hospital admission for worsening heart failure in both ivabradine and placebo groups. SAS (statistical analysis system) version 9.1 and R version 2.14.0 were used for analyses.

Results

In total, 1186 of the 6505 randomised patients experienced at least one hospitalisation for heart failure during the study. The breakdown of participants and events in this population is presented in **Figure 1**. A total of 334 patients (28%) were rehospitalised within 3 months for any reason (131 [25%] in the ivabradine group, and 203 [30%] in placebo). The reasons for rehospitalisations were cardiovascular for 286 (86%) patients (109 [83%] ivabradine, 177 [87%] placebo), and worsening heart failure for 204 (61%) patients (78 [60%] ivabradine, 126 [62%] placebo). A total of 85 patients experienced at least two recurrent hospitalisations for any cause after the first heart failure hospitalisation during the study (27 ivabradine, 58 placebo). Of these, 53 had at least two recurrent hospitalisations due to cardiovascular cause (16 ivabradine, 37 placebo), and 27 due to heart failure cause (7 ivabradine, 20 placebo).

Baseline characteristics of patients who had at least one hospitalisation for heart failure during the study were compared with those who had no heart failure hospitalisation (**Table 1)**. Overall, the two groups of patients differed significantly in many respects. As compared with patients with no heart failure readmission, those who had at least one heart failure hospitalisation were more likely to be older, to have a higher heart rate, a lower blood pressure, a lower left ventricular ejection fraction, a lower glomerular filtration rate , and were more likely to be in NYHA class III or IV. As regards their medical history, hospitalised patients had a longer duration of heart failure, and were more likely to have renal failure, diabetes, atrial fibrillation and/or flutter, and to have had a history of stroke. Both groups of patients also differed in terms of their concomitant treatments: patients hospitalised for heart failure during the study were more likely to be treated with mineralocorticoid receptor antagonists, other diuretics, and digitalis at baseline as compared with patients who had no

heart failure rehospitalisation. On the other hand, patients hospitalised for heart failure during the study were less likely to be prescribed beta-blockers or angiotensin-converting enzyme (ACE) inhibitors at baseline, and fewer patients were receiving ≥50% of target dose of beta-blocker as compared with patients who had no heart failure admission.

The 334 patients rehospitalised for any cause within 3 months after the first heart failure hospitalisation had similar baseline characteristics as compared with all patients who had an hospitalisation for heart failure during the study, with the exception of the dose of beta-blockers at randomisation: fewer (39%) patients rehospitalised within 3 months were receiving ≥50% of target dose, versus 47% of all patients hospitalised for heart failure (**Table 1**).

Cumulative incidence of all-cause hospitalisations was lower in the ivabradine group as compared with the placebo group over the 3 months after a first hospital admission for worsening heart failure (**Figure 2**). Accordingly, ivabradine was associated with fewer total all-cause hospitalisations as compared with placebo at 1 month (54 events with ivabradine versus 102 events with placebo, IRR 0.70, 95% CI 0.50 to 1.00, $p<0.05$), 2 months (115 versus 201 events, IRR 0.75, 95% CI 0.58 to 0.98, p=0.03), and 3 months (166 versus 278 events, IRR 0.79, 95% CI 0.63 to 0.99, p=0.04) after the first heart failure hospitalisation.

As regards the other endpoints, there was a trend towards reduction in the recurrence of hospitalisations due to cardiovascular causes in the ivabradine group as compared with placebo at 1 month (38 versus 76 events, IRR 0.66, 95% CI 0.44 to 1.01, p=0.05), 2 months (90 versus 155 events, IRR 0.77, 95% CI 0.57 to 1.02, p=0.07) and 3 months (131 versus 221 events, IRR 0.79, 95% CI 0.62 to 1.01, p=0.06) after the first heart failure hospital admission

event (**Table 2**). A similar pattern of effect was identified for rehospitalisations due to heart failure at 1 month (21 versus 42 events, IRR 0.67, 95% CI 0.40 to 1.13, p=0.13), 2 months (56 versus 97 events, IRR 0.77, 95% CI 0.55 to 1.09, p=0.14), and 3 months (86 versus 148 events, IRR 0.78, 95% CI 0.59 to 1.02, p=0.07). Death rates were similar in both treatment groups at 1 month (8% with ivabradine versus 9% with placebo), 2 months (11% versus 12%), and 3 months (13% versus 14%) after the first heart failure hospitalisation.

Discussion

Our analysis showed that patients hospitalised for heart failure during the study were more severe as compared with their counterparts who had no heart failure hospitalisation with respect to clinical status, cardiac function, and comorbidities. In line with the more severe HF profile, these patients had more concomitant treatment with diuretics, digitalis, and mineralocorticoid receptor antagonists. Moreover, patients hospitalised for heart failure who had been randomised to ivabradine had a lower incidence of early recurrent hospitalisations following a first heart failure hospitalisation during the trial than those on placebo. This reduction of risk was significant when considering all-cause rehospitalisations, and ranged from 21% to 30% within the first 3 months after a first event of heart failure hospitalisation. A consistent trend for reduction in the same range of magnitude (from 21% to 34%) was observed for both cardiovascular and heart failure rehospitalisations. The favourable effect of ivabradine on early readmissions was unlikely to be influenced by a difference in death rates, as these were similar between the two groups.

Some data support the importance of early initiation of recommended heart failure therapies. One trial compared the effect of an in-hospital initiation of carvedilol with a later initiation of carvedilol performed in an outpatient setting.[12] This trial was not powered to

assess the impact of the timing of beta-blockers initiation on outcome. However, it demonstrated that in-hospital initiation of carvedilol was associated with its higher use 90 days after discharge, supporting importance of early introduction of heart failure recommended therapies. Data from a registry similarly suggest that use of beta-blockers at hospital discharge was associated with better prognosis.[13] A propensity score analysis suggested that discharge use of ACE inhibitor was associated with improvement of prognosis.[14] A recent post hoc analysis from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial demonstrated that eplerenone prevents readmission when initiated soon after a cardiovascular hospitalisation in patients with systolic heart failure and mild symptoms.[15] Only a few randomised clinical trials have explored the effect of treatment during the vulnerable phase after hospitalised heart failure, by analysing outcomes early post discharge.[16-20] In a randomised phase 2 clinical trial, tolvaptan did not demonstrate differences in worsening heart failure at 60 days compared with placebo.[16] However, in a post hoc analysis, 60 day mortality was lower in tolvaptan-treated patients with renal dysfunction or severe systemic congestion. In the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, nesiritide had no effect on rehospitalisation or death within 30 days compared with placebo.[17] Treatment of acute heart failure with the intravenous vasodilator serelaxin was associated with fewer deaths at day 180 although this was a post hoc analysis.[19] Finally, the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) demonstrated that in hospitalized patients with heart failure, the initiation of the direct renin inhibitor aliskiren in addition to standard therapy did not reduce cardiovascular death or heart failure hospitalisation at 6 and 12 month after discharge.[20]

We acknowledge the fact that our current analysis included patients who were chronically exposed to ivabradine from the time of randomisation and who experienced a first heart failure admission. In a previous analysis, we demonstrated that ivabradine reduced the total burden of heart failure hospitalisations by 25% during the full duration of the study (22.9 months).[21] We here further extend our analysis by showing that this beneficial effect is observed during the high risk early post discharge vulnerable phase and applies to all-cause hospitalisations.

Prescription of standard heart failure treatment at discharge could help to mitigate immediate post discharge outcomes. This is supported by data of heart failure cohorts, where use of beta-blockers, ACE inhibitors, and angiotensin receptor blockers (ARBs) were associated with a lower rate of readmission and/or mortality up to 90 days after discharge.[22-24] Accordingly, ESC guidelines recommend the initiation of evidence-based therapy as soon as patients are stabilised after a hospitalisation for heart failure.[25] The early introduction of treatments is critical, as patients not optimally managed at the time of discharge are often left untreated at a later stage. However, despite these recommendations, prescription rates of beta-blockers, ACE inhibitors and ARBs remain insufficient, especially in patients at highest risk.[26] This is in line with the results of our analysis, which showed that patients with a more severe profile had a lower prescription rate of beta-blockers and ACE inhibitors than less severe patients. One of the obstacles limiting the early prescription or uptitration of standard care therapy after a heart failure hospitalisation is linked to the adverse effects of these drugs on blood pressure, in a period during which the haemodynamic status of patients is still unstable. Unlike beta-blockers, ivabradine is devoid of a negative inotropic effect. In addition, ivabradine does not share the blood pressure–lowering effects of beta-blockers, ACE inhibitors, and ARBs. This suggests that ivabradine might be a relatively manageable

treatment without undesired incremental collateral effects in the days or weeks following a heart failure hospitalisation. This is in line with the observations of a recent pilot trial in patients with decompensated heart failure in whom ivabradine appeared to be well tolerated with no haemodynamic deterioration when used in acutely ill patients.[27]

The exact mechanism underlying the beneficial effects of ivabradine suggested by our analysis during the vulnerable period after an episode of worsening heart failure remains to be elucidated. At discharge, elevated heart rate occurs in a large proportion of patients,[28] and is associated with an increased risk of death and rehospitalisation in the early post discharge period.[29-31] In a cohort study of heart failure patients with heart rate ≥75 bpm at discharge, each 10-bpm increment was associated with an increase of 30% in risk of all-cause death, and 13% in risk of rehospitalisations during the 30-day period following hospital discharge.[30] Outside this window, the correlation between high heart rate at discharge and worse outcome was lessened (16% increased risk for all-cause death per 10-bpm increment; and no increase in risk for all-cause rehospitalisations). These data are in agreement with the favourable effect of heart rate reduction with ivabradine on early outcomes observed in our study. Decreasing heart rate with ivabradine at discharge may improve myocardial energetics and oxygen consumption, and reduce total afterload,[32] thereby lessening the risk of relapse after hospital discharge. Recent data from the OPTIMIZE-HF (Organized Program To Initiate lifesaving treatMent In hospitaliZed patients with heart failure) registry found that a large proportion of heart failure patients (71%) had a heart rate ≥70 bpm at hospital discharge, despite being treated with beta-blockers. Overall, the authors estimated that approximately 40% of hospitalised patients for heart failure could qualify for initiation of ivabradine at time of discharge.[28]

The reduction in readmissions in the ivabradine group was observed as early as 1 month after first hospitalisation. This early effect is in line with the immediate improvement in haemodynamic parameters (increase in stroke volume with maintained cardiac output) observed after an acute administration of ivabradine in heart failure patients with severely depressed left ventricular function.[33] This rapid stabilising effect is further supported by the short-term reduction in N-terminal pro-brain natriuretic peptide and improvement in NYHA class provided by ivabradine, which were achieved after only 3 months of treatment on top of standard care in heart failure patients.[34] Similar findings were reported in a separate study after just 4 months of treatment with ivabradine.[35] Altogether, these data suggest that patients chronically treated with ivabradine could rapidly stabilise patients after a hospitalisation for heart failure, by preventing degradation of left ventricular function and clinical status.

However our current analysis does not provide information on the potential benefit of in-hospital or early post discharge initiation of ivabradine since patients were exposed to the drug from the randomisation.

There are some limitations to our analysis. The present data are based on a post hoc analysis of a trial including chronic, stable heart failure patients, and the original study was not designed to investigate the effect of treatment in patients hospitalised for heart failure. Therefore, we cannot assess the respective role of exposure to ivabradine before versus after hospitalisation in the observed effects on early readmissions. IRR were adjusted using prognostic factors which may no longer be representative of the patient's risk, as they were collected at the time of inclusion in the SHIFT study, and not at the time of the first HF hospitalisation during the study. On the other hand, this is the first analysis that describes the effect of a treatment on repeated hospitalisation during the critical 3 month-period after a hospitalisation for heart failure. Our analysis is based on the date of hospitalisation for heart

failure, which, in contrast to the date of discharge, was adjudicated in SHIFT, and thus more reliable. However, the statistical method does not take into account the treatment effect on the first heart failure hospitalisation, which had been shown to be reduced by ivabradine.[9] This might have produced an imbalance between the placebo and ivabradine groups, and does not preserve the randomisation planned in the original design. Although a beneficial trend in favour of ivabradine was observed on heart failure and on cardiovascular rehospitalisations, this did not reach a significant threshold. This may be due to the limited number of events observed here and therefore a lack of power. It should however be noticed that the vast majority (86%) of all-cause rehospitalisations during the vulnerable phase was due to cardiovascular cause, and 61% were due to heart failure.

Conclusion

Development of new therapeutic strategies to prevent early recurrent hospitalisations is a major goal for heart failure management. Here, we demonstrated that chronic exposure to ivabradine is associated with a decrease in all-cause hospitalisation during the critical 3 months after a hospitalisation for heart failure. Further studies are needed to investigate if in hospital or early post discharge initiation of ivabradine could be useful to improve early outcomes in hospitalised heart failure patients.

Funding:

The SHIFT trial was sponsored by Servier, France. No other funding was provided to the co-authors for the current analysis.

Acknowledgements:

The authors would like to thank all participating investigators for their contributions to the SHIFT study. We thank Julie Salzmann, PhD, who provided medical writing assistance on behalf of Servier, France.

Conflict of interest:

M.K. reports fees for board membership for Astra-Zeneca, BMS, Menarini, and Novartis, consultancy fees from Amgen and Servier and speaker's bureau for BMS, AstraZeneca, Menarini, MSD, Novartis, Sanofi, Servier and Menarini. L.T. reports personal fees from Servier, Boston Scientific, St Jude Medical, Medtronic, CVIE Therapeutics, and Cardiorentis while conducting the study, outside the submitted work. K.S. received research support from Servier and honoraria from Amgen, AstraZeneca, and Novartis. M.B. received grants from Medtronic and personal fees from Servier and Bayer, outside the submitted work. J.B. received consultancy fees from Servier, Amgen, Novartis, Pfizer, Cardiorentis, Astrazeneca, Celladon, Takeda USA, ARMAGO (Stockholder Bio MARIN) and speakers Bureau Amgen. A.M. is an employee of Servier. I.F. reports grants and personal fees from Servier and Amgen while conducting the study.

References

1. Cowie MR, Anker SD, Cleland JGF, Felker GM, Filippatos G, Jaarsma T, Jourdain P, Knight E, Massie B, Ponikowski P, Lopez-Sendon J. Improving care for patients with acute heart failure - before, during and after hospitalization. *ESC Heart Failure* 2014;**1**:110-145.

2. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Crespo LM, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Fabbri G, Urso R, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors AA, Wendelboe NO, Zannad F, Tavazzi L. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail* 2013;**15**:808-817.

3. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, Pfeffer MA. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation* 2007;**116**:1482-1487.

4. O'Connor CM, Miller AB, Blair JE, Konstam MA, Wedge P, Bahit MC, Carson P, Haass M, Hauptman PJ, Metra M, Oren RM, Patten R, Pina I, Roth S, Sackner-Bernstein JD, Traver B, Cook T, Gheorghiade M. Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction: results from Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) program. *Am Heart J* 2010;**159**:841-849.

5. Abrahamsson P, Swedberg K, Borer JS, Böhm M, Kober L, Komajda M, Lloyd SM, Metra M, Tavazzi L, Ford I. Risk following hospitalization in stable chronic systolic heart failure. *Eur J Heart Fail* 2013;**15**:885-891.

6. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, Van Gilst WH, Widimsky J, Freemantle N, Eastaugh J, Mason J. The EuroHeart Failure survey programme-a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J* 2003;**24**:442-463.

7. Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M. The vulnerable phase after hospitalization for heart failure. *Nat Rev Cardiol* 2015;**12**:220-229.

8. Maggioni AP, Orso F, Calabria S, Rossi E, Cinconze E, Baldasseroni S, Martini N. The real-world evidence of heart failure: findings from 41 413 patients of the ARNO database. *Eur J Heart Fail* ;doi: 10.1002/ejhf.471. Published online ahead of print 11 Jan 2016.

9. Swedberg K, Komajda M, Böhm M, Borer J, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled trial. *Lancet* 2010;**376**:875-885.

10. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Tavazzi L. Rationale and design of a randomized, double-blind, placebo-controlled outcome trial of ivabradine in chronic heart failure : the Systolic Heart Failure Treatment with the I(f)Inhibitor Ivabradine Trial (SHIFT). *Eur J Heart Fail* 2010;**12**:75-81.

11. O'Meara E, Chong KS, Gardner RS, Jardine AG, Neilly JB, McDonagh TA. The Modification of Diet in Renal Disease (MDRD) equations provide valid estimations of glomerular filtration rates in patients with advanced heart failure. *European Journal of Heart Failure* 2006;**8**:63-67.

12. Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. *J Am Coll Cardiol* 2004;**43**:1534-1541.

13. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy C, Young JB. Carvedilol use at discharge in patients hospitalized for heart failure is associated with improved survival: an analysis from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J* 2007;**153**:82-11.

14. Ahmed A, Centor RM, Weaver MT, Perry GJ. A propensity score analysis of the impact of angiotensin-converting enzyme inhibitors on long-term survival of older adults with heart failure and perceived contraindications. *Am Heart J* 2005;**149**:737-743.

15. Girerd N, Collier T, Pocock S, Krum H, McMurray JJ, Swedberg K, Van Veldhuisen DJ, Vincent J, Pitt B, Zannad F. Clinical benefits of eplerenone in patients with systolic heart failure and mild symptoms when initiated shortly after hospital discharge: analysis from the EMPHASIS-HF trial. *Eur Heart J* 2015;**36**:2310-2317.

16. Gheorghiade M, Gattis WA, O'Connor CM, Adams KF, Jr., Elkayam U, Barbagelata A, Ghali JK, Benza RL, McGrew FA, Klapholz M, Ouyang J, Orlandi C. Effects of

tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA* 2004;**291**:1963-1971.

17. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Massie BM, McMurray JJ, Nieminen MS, Reist CJ, Rouleau JL, Swedberg K, Adams KF, Jr., Anker SD, Atar D, Battler A, Botero R, Bohidar NR, Butler J, Clausell N, Corbalan R, Costanzo MR, Dahlstrom U, Deckelbaum LI, Diaz R, Dunlap ME, Ezekowitz JA, Feldman D, Felker GM, Fonarow GC, Gennevois D, Gottlieb SS, Hill JA, Hollander JE, Howlett JG, Hudson MP, Kociol RD, Krum H, Laucevicius A, Levy WC, Mendez GF, Metra M, Mittal S, Oh BH, Pereira NL, Ponikowski P, Tang WH, Tanomsup S, Teerlink JR, Triposkiadis F, Troughton RW, Voors AA, Whellan DJ, Zannad F, Califf RM. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* 2011;**365**:32-43.

18. Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Weatherley BD, Cleland JG, Givertz MM, Voors A, DeLucca P, Mansoor GA, Salerno CM, Bloomfield DM, Dittrich HC. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. *N Engl J Med* 2010;**363**:1419-1428.

19. Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Ponikowski P, Unemori E, Voors AA, Adams KF, Jr., Dorobantu MI, Grinfeld LR, Jondeau G, Marmor A, Masip J, Pang PS, Werdan K, Teichman SL, Trapani A, Bush CA, Saini R, Schumacher C, Severin TM, Metra M. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. *Lancet* 2013;**381**:29-39.

20. Gheorghiade M, Bohm M, Greene SJ, Fonarow GC, Lewis EF, Zannad F, Solomon SD, Baschiera F, Botha J, Hua TA, Gimpelewicz CR, Jaumont X, Lesogor A, Maggioni AP. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial. *JAMA* 2013;**309**:1125-1135.

21. Borer JS, Böhm M, Ford I, Komajda M, Tavazzi L, Sendon JL, Alings M, Lopez-de-Sa E, Swedberg K. Effect of ivabradine on recurrent hospitalization for worsening heart failure in patients with chronic systolic heart failure: the SHIFT Study. *Eur Heart J* 2012;**33**:2813-2820.

22. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Pieper K, Sun JL, Yancy C, Young JB. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. *JAMA* 2007;**297**:61-70.

23. Bottle A, Goudie R, Cowie MR, Bell D, Aylin P. Relation between process measures and diagnosis-specific readmission rates in patients with heart failure. *Heart* 2015;**101**:1704-1710.

24. Bhatia V, Bajaj NS, Sanam K, Hashim T, Morgan CJ, Prabhu SD, Fonarow GC, Deedwania P, Butler J, Carson P, Love TE, Kheirbek R, Aronow WS, Anker SD, Waagstein F, Fletcher R, Allman RM, Ahmed A. Beta-blocker Use and 30-day All-cause Readmission in Medicare Beneficiaries with Systolic Heart Failure. *Am J Med* 2015;**128**:715-721.

25. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni

AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;**14**:803-869.

26. Lee DS, Tu JV, Juurlink DN, Alter DA, Ko DT, Austin PC, Chong A, Stukel TA, Levy D, Laupacis A. Risk-treatment mismatch in the pharmacotherapy of heart failure. *JAMA* 2005;**294**:1240-1247.

27. Sargento L, Satendra M, Longo S, Lousada N, dos Reis RP. Heart rate reduction with ivabradine in patients with acute decompensated systolic heart failure. *Am J Cardiovasc Drugs* 2014;**14**:229-235.

28. DeVore AD, Mi X, Mentz RJ, Fonarow GC, Van Dyke MK, Maya JF, Hardy NC, Hammill BG, Hernandez AF. Discharge Heart Rate and β-Blocker Dose in Patients Hospitalized With Heart Failure: Findings From the OPTIMIZE-HF Registry. *American Heart Journal* 2015;doi: 10.1016/j.ahj.2015.10.026. Published online ahead of print 21 December 2015.

29. Greene SJ, Vaduganathan M, Wilcox JE, Harinstein ME, Maggioni AP, Subacius H, Zannad F, Konstam MA, Chioncel O, Yancy CW, Swedberg K, Butler J, Bonow RO, Gheorghiade M. The prognostic significance of heart rate in patients hospitalized for heart failure with reduced ejection fraction in sinus rhythm: insights from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan) trial. *JACC Heart Fail* 2013;**1**:488-496.

30. Laskey WK, Alomari I, Cox M, Schulte PJ, Zhao X, Hernandez AF, Heidenreich PA, Eapen ZJ, Yancy C, Bhatt DL, Fonarow GC. Heart rate at hospital discharge in patients with heart failure is associated with mortality and rehospitalization. *J Am Heart Assoc* 2015;**4**:

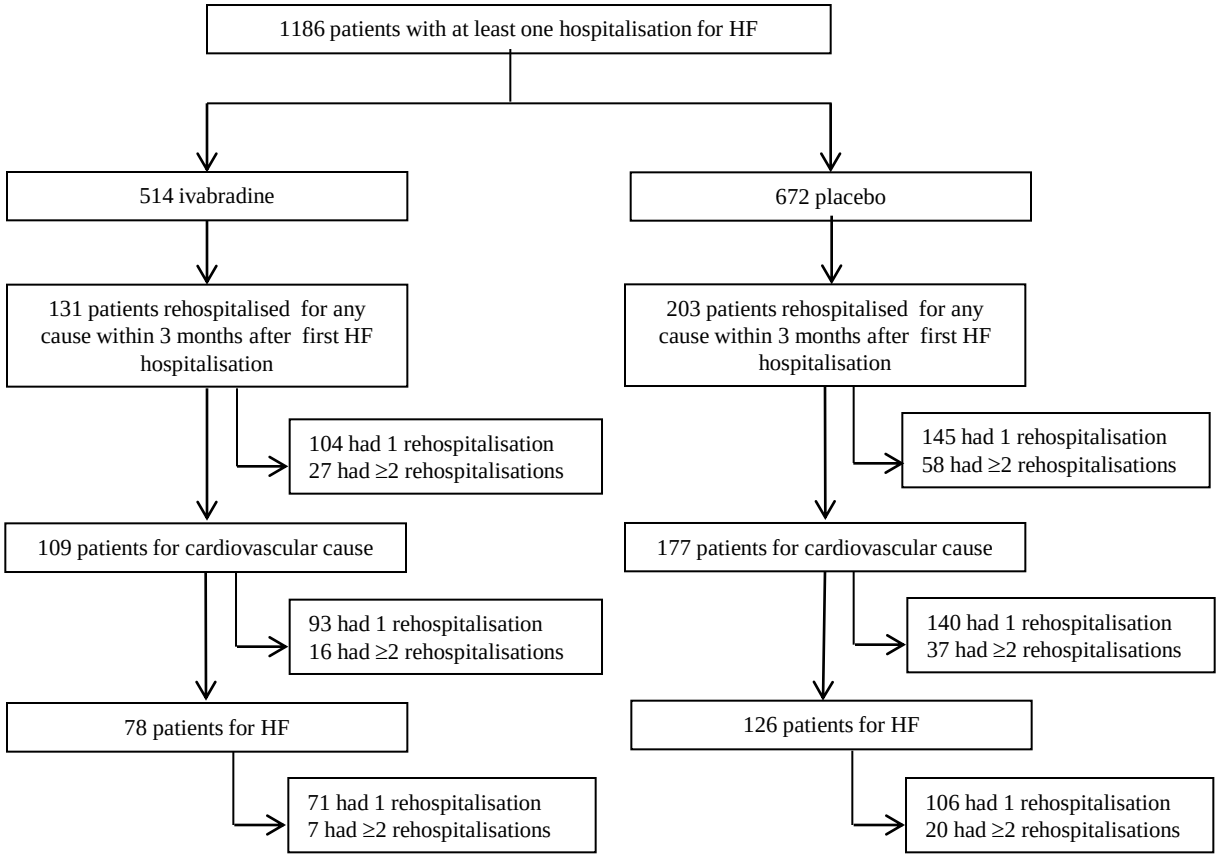
31. Habal MV, Liu PP, Austin PC, Ross HJ, Newton GE, Wang X, Tu JV, Lee DS. Association of heart rate at hospital discharge with mortality and hospitalizations in patients with heart failure. *Circ Heart Fail* 2014;**7**:12-20.

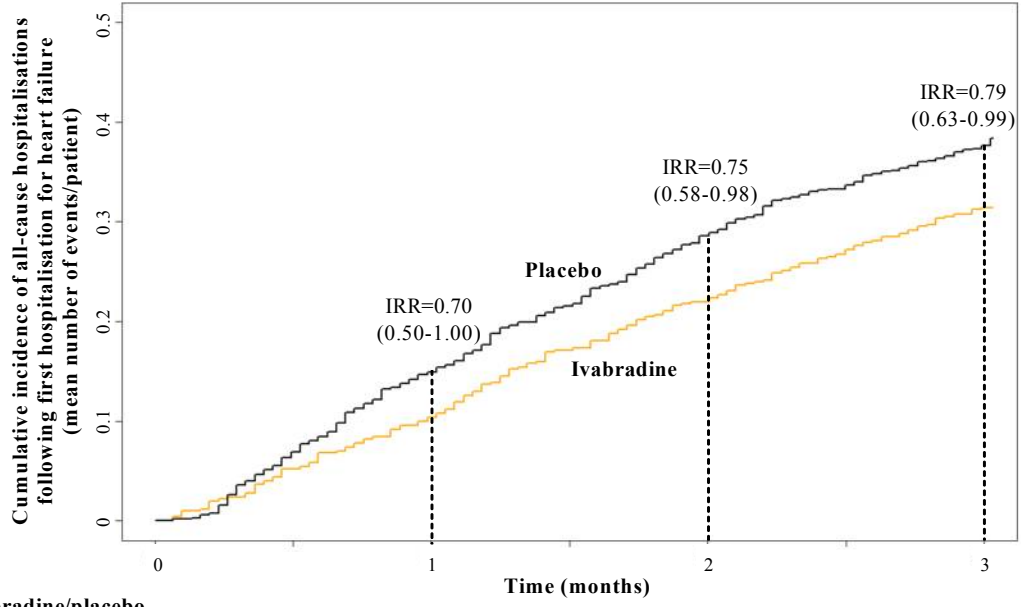
32. Reil JC, Tardif JC, Ford I, Lloyd SM, O'Meara E, Komajda M, Borer JS, Tavazzi L, Swedberg K, Böhm M. Selective heart rate reduction with ivabradine unloads the left ventricle in heart failure patients. *J Am Coll Cardiol* 2013;**62**:1977-1985.

33. De Ferrari GM, Mazzuero A, Agnesina L, Bertoletti A, Lettino M, Campana C, Schwartz PJ, Tavazzi L. Favourable effects of heart rate reduction with intravenous administration of ivabradine in patients with advanced heart failure. *Eur J Heart Fail* 2008;**10**:550-555.

34. Sargento L, Satendra M, Longo S, Lousada N, Palma dos RR. Early NT-proBNP decrease with ivabradine in ambulatory patients with systolic heart failure. *Clin Cardiol* 2013;**36**:677-682.

35. Zugck C, Martinka P, Stockl G. Ivabradine treatment in a chronic heart failure patient cohort: symptom reduction and improvement in quality of life in clinical practice. *Adv Ther* 2014;**31**:961-974.


1186 patients with at least one hospitalisation for HF
514 ivabradine
672 placebo
131 patients rehospitalised for any cause within 3 months after first HF hospitalisation
203 patients rehospitalised for any cause within 3 months after first HF hospitalisation
104 had 1 rehospitalisation
27 had ≥2 rehospitalisations
145 had 1 rehospitalisation
58 had ≥2 rehospitalisations
109 patients for cardiovascular cause
177 patients for cardiovascular cause
93 had 1 rehospitalisation
16 had ≥2 rehospitalisations
140 had 1 rehospitalisation
37 had ≥2 rehospitalisations
78 patients for HF
126 patients for HF
71 had 1 rehospitalisation
7 had ≥2 rehospitalisations
106 had 1 rehospitalisation
20 had ≥2 rehospitalisations



Ivabradine/placebo				
Patients at risk	514/672	454/590	424/551	398/524
Number of events	0/0	54/102	115/201	166/278

Table 1. Baseline characteristics of patients with a least one heart failure hospitalisation, patients rehospitalised for any cause within 3 months after the first heart failure hospitalisation, and patients with no heart failure hospitalisation during the SHIFT study.

	At least one heart failure hospitalisation (n=1186)		No hospitalisation for heart failure (n=5319)	p-value*
	All (n=1186)	Readmission for any cause within 3 months (n=334)		
Demographic characteristics				
Age (years)	62.2±11.5	62.1±12.0	60.0±11.3	<.0001
Male	901 (76%)	263 (79%)	4069 (76%)	0.70
Current smoker	191 (16%)	51 (15%)	927 (17%)	0.080
Body mass index (kg/m^2)	27.8±5.3	27.7±5.4	28.0±5.0	0.060
Cardiac parameters				
Heart rate (bpm)	82.5±11.2	83.0±11.7	79.3± 9.2	<.0001
Systolic blood pressure (mmHg)	119.0±16.7	118.5±17.9	122.3±15.7	<.0001
Diastolic blood pressure	74.3± 9.9	73.4±10.0	76.0±9.4	<.0001
Left ventricular ejection fraction	27.6±5.4	27.3±5.5	29.3± 5.0	<.0001
NYHA class				<.0001
Class II	445 (38%)	148 (44%)	2724 (51%)	
Class III	707 (60%)	178 (53%)	2516 (47%)	
Class IV	34 (3%)	8 (2%)	77 (1%)	
eGFR (mL/min/1.73m^2)	69.8±23.6	70.3±26.6	75.8±22.7	<.0001
Medical history				
Duration of heart failure (years)	4.3±4.6	4.7±5.1	3.3±4.1	<.0001
Ischemic cause of heart failure	813 (69%)	217 (65%)	3605 (68%)	0.61
Coronary artery disease	869 (73%)	236 (71%)	3863 (73%)	0.65
Myocardial infarction	680 (57%)	175 (52%)	2986 (56%)	0.45
Renal failure	129 (11%)	39 (12%)	291 (5%)	<.0001
Hypertension	769 (65%)	200 (60%)	3545 (67%)	0.23
Diabetes	427 (36%)	130 (39%)	1552 (29%)	<.0001
Stroke	125 (11%)	37 (11%)	398 (7%)	0.0005
History of atrial fibrillation	133 (11%)	36 (11%)	389 (7%)	<.0001
Treatment at randomisation				
Beta-blockers	1023 (86%)	279 (84%)	4797 (90%)	<.0001
≥50% target dose	473 (47%)	109 (39%)	2708 (58%)	<.0001
ACE inhibitors	900 (76%)	258 (77%)	4216 (79%)	0.0103
ARB	186 (16%)	53 (16%)	741 (14%)	0.12

Mineralocorticoid receptor	824 (69%)	215 (64%)	3098 (58%)	<.0001
Diuretics	1079 (91%)	303 (91%)	4335 (82%)	<.0001
Digitalis	377 (32%)	107 (32%)	1039 (20%)	<.0001

Values are means±SD or numbers (%) of patients. *p-values comparing patients with at least one heart failure hospitalisation versus patients with no heart failure hospitalisation (Kruskal-Wallis test for continuous variables, or χ^2 test for categorical variables). ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; eGFR=estimated glomerular filtration rate; NYHA=New York Heart Association.

Table 2. Incidence rate ratios for cardiovascular and heart failure hospitalisations up to 3 months after a first hospitalisation for worsening heart failure during the SHIFT study.

	Cumulative number of events		Incidence rate ratio (95% CI)
	Ivabradine (N=514)	**Placebo (N=672)**	**(adjusted for prognostic factors)**
Cardiovascular hospitalisations			
1 month	38	76	0.66 (0.44–1.01)
2 months	90	155	0.77 (0.57–1.02)
3 months	131	221	0.79 (0.62–1.01)
Heart failure hospitalisations			
1 month	21	42	0.67 (0.40–1.13)
2 months	56	97	0.77 (0.55–1.09)
3 months	86	148	0.78 (0.59–1.02)

Number of events corresponds to the total number of readmissions within the indicated timeframe after a first heart failure hospitalisation. CI=confidence interval.