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

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Aims During the post-discharge phase following a heart failure hospitalization (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 hospitalized for heart failure during the course of the SHIFT study (Systolic Heart Failure treatment with the I_f inhibitor ivabradine Trial).

Methods and results A total of 1186 of the 6505 randomized patients experienced at least one HFH during the study, and had a more severe profile than those without HFH. Of these 1186 patients, 334 patients (28%) were rehospitalized within 3 months for any reason, mostly for cardiovascular causes (86%), including HFH (61%). Ivabradine was associated with fewer all-cause hospitalizations at 1 month [incidence rate ratio (IRR) 0.70, 95% confidence interval (CI) 0.50–1.00, $P < 0.05$], 2 months (IRR 0.75, 95% CI 0.58–0.98, $P = 0.03$), and 3 months (IRR 0.79, 95% CI 0.63–0.99, $P = 0.04$). A trend for a reduction in cardiovascular and HF hospitalizations 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 hospitalizations 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 hospitalized for HF.

Keywords Ivabradine • Hospitalizations • Heart failure • Outcomes • Vulnerable phase

Introduction

The number of hospitalizations for heart failure remains high in many European countries, representing 1–2% of all hospital admissions.[1] In comparison with outpatients with chronic heart failure, patients hospitalized for heart failure have high rates of readmission. A recent European registry reports a rate of 1-year hospitalization as high as 44% after discharge, vs. 32% in outpatients.[2] These alarming figures have a considerable impact on both healthcare cost and prognosis. Patients hospitalized for heart failure are particularly at risk for death or rehospitalization in the first weeks following discharge, while risk decreases significantly

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after 3–6 months.[3–5] In Europe, 3 months after discharge, a quarter of patients had been rehospitalized, and 13.5% had died.[6] This immediate post-discharge period has been referred to as the 'vulnerable phase'.[7]

Patients with heart failure often present with multiple co-morbidities, which put them at a higher risk for recurrent hospitalizations, whatever the cause.[8] The need for an effective treatment reducing the global burden of rehospitalization—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 hospitalization, and an 11% risk reduction of first all-cause hospitalization.[9]

Since reducing the burden of rehospitalizations during the vulnerable phase is of critical clinical importance, we analyse here the effect of chronic exposure to ivabradine vs. placebo on all-cause recurrent hospitalizations occurring up to 3 months after a hospitalization 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 randomized, double-blind, placebo-controlled trial in outpatients with symptomatic and stable heart failure (≥4 weeks), systolic dysfunction (LVEF ≤35%), heart rate ≥70 b.p.m., and in sinus rhythm. All subjects had been hospitalized for worsening heart failure in the year before inclusion. In total, 6505 patients treated with guideline-recommended therapy were randomized to placebo or ivabradine (starting dose 5 mg b.i.d., titrated to 7.5 mg or 2.5 mg b.i.d., according to heart rate and tolerability). The primary study endpoint was a composite of cardiovascular mortality or hospitalization for worsening heart failure. Secondary endpoints included both individual components of the composite endpoint, all-cause mortality, heart failure mortality, and all-cause hospitalization, among others. All hospitalizations were adjudicated by an endpoint validation committee. Diagnosis of heart failure as a main reason for hospitalization had to be confirmed.

In the present study, we identified SHIFT patients who had had at least one heart failure hospitalization during the trial, and analysed events subsequent to that hospitalization during the vulnerable phase. This vulnerable phase was defined as the 3 months after the date of admission for a first hospitalization due to worsening heart failure, and, thus, includes the period of hospitalization. In this population, the median duration of hospitalization was 8 days. We considered the total number of events that occurred during a selected time frame (1, 2, and 3 months) after the first admission for worsening heart failure. Readmissions after a heart failure hospitalization are known to be driven by both cardiac and non-cardiac causes.[4] Thus our analysis focuses on all-cause rehospitalizations. Hospitalizations 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 the analysed population were selected *a posteriori*. The 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 deviation (SD) for continuous variables, and numbers and percentages for categorical variables. Baseline characteristics of patients with at least one heart failure hospitalization during the study were compared with those of patients who had no heart failure hospitalization. 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 rehospitalized for any cause within 3 months after the first heart failure hospitalization. Treatment effect between ivabradine and placebo groups was measured as the incidence rate ratio (IRR) for recurrent hospitalizations 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 randomization); NYHA class; ischaemic cause of heart failure; age; systolic blood pressure; heart rate; LVEF; and glomerular filtration rate, estimated using the Modification in Diet in Renal Disease equation.[11] Associated 95% confidence intervals (CIs) and *P*-values (two-sided test) are presented, with a *P*-value <0.05 considered as significant. The cumulative incidence rate of all-cause rehospitalizations 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 the ivabradine and placebo group. SAS (statistical analysis system) version 9.1 and R version 2.14.0 were used for analyses.

Results

In total, 1186 of the 6505 randomized patients experienced at least one hospitalization 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 rehospitalized within 3 months for any reason [131 (25%) in the ivabradine group, and 203 (30%) in the placebo group). The reasons for rehospitalizations 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 hospitalizations for any cause after the first heart failure hospitalization during the study (27 ivabradine, 58 placebo). Of these, 53 had at least two recurrent hospitalizations 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 hospitalization for heart failure during the study were compared with those who had no heart failure hospitalization (*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 hospitalization were more likely to be older, to have a higher heart rate, a lower blood pressure, LVEF, and glomerular filtration rate, and were more likely to be in NYHA class III or IV. As regards their medical history, hospitalized 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 hospitalized 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

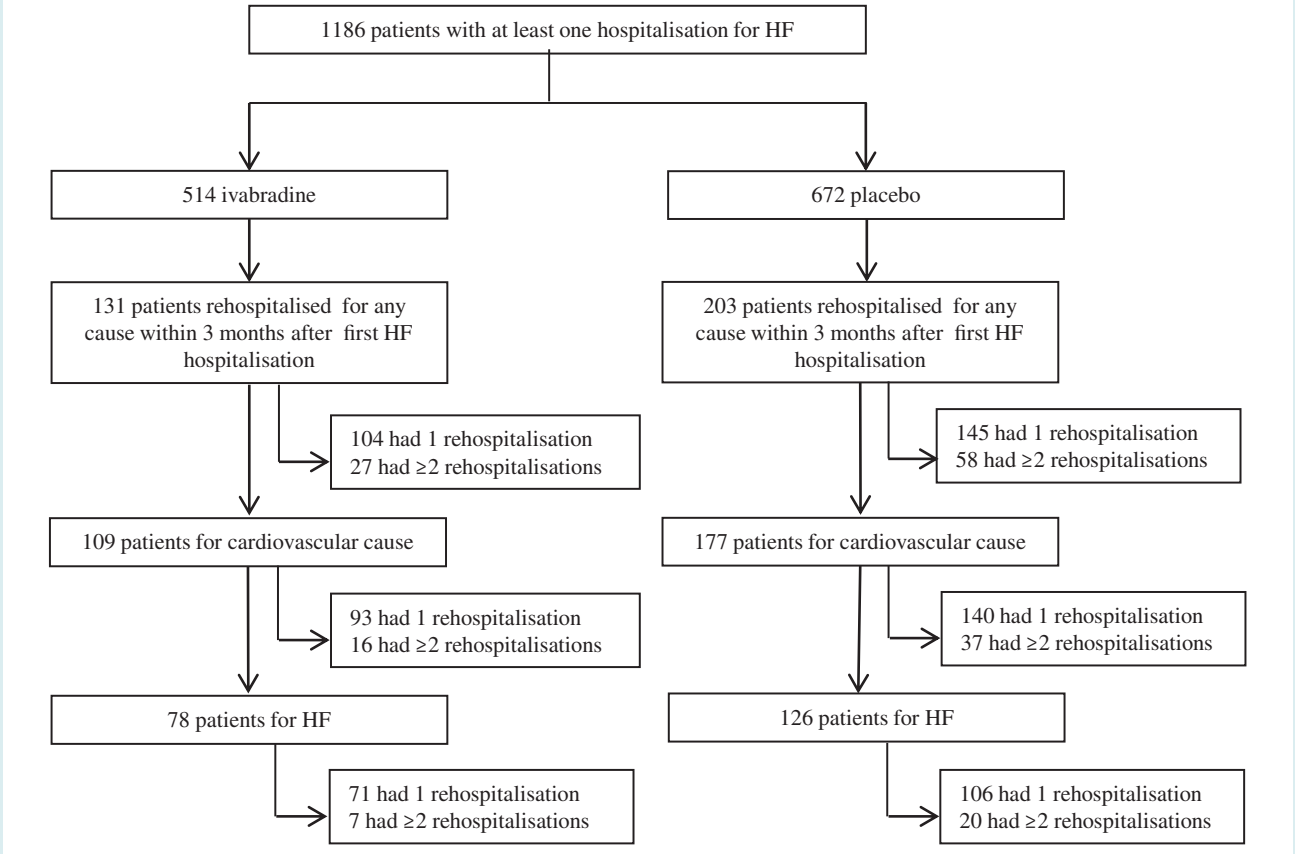

Figure 1 Patient disposition. HF, heart failure.

heart failure rehospitalization. On the other hand, patients hospitalized for heart failure during the study were less likely to be prescribed beta-blockers or 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 rehospitalized for any cause within 3 months after the first heart failure hospitalization had similar baseline characteristics as compared with all patients who had an hospitalization for heart failure during the study, with the exception of the dose of beta-blockers at randomization: fewer (39%) patients rehospitalized within 3 months were receiving ≥50% of target dose, vs. 47% of all patients hospitalized for heart failure (*Table 1*).

The cumulative incidence of all-cause hospitalizations 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 hospitalizations as compared with placebo at 1 month (54 events with ivabradine vs. 102 events with placebo, IRR 0.70, 95% CI 0.50–1.00, $P < 0.05$), 2 months (115 vs. 201 events, IRR 0.75, 95% CI 0.58–0.98, $P = 0.03$), and 3 months (166 vs. 278 events, IRR 0.79, 95% CI 0.63–0.99, $P = 0.04$) after the first heart failure hospitalization.

As regards the other endpoints, there was a trend towards reduction in the recurrence of hospitalizations due to cardiovascular causes in the ivabradine group as compared with placebo at 1 month (38 vs. 76 events, IRR 0.66, 95% CI 0.44–1.01, $P = 0.05$), 2 months (90 vs. 155 events, IRR 0.77, 95% CI 0.57–1.02, $P = 0.07$), and 3 months (131 vs. 221 events, IRR 0.79, 95% CI 0.62–1.01, $P = 0.06$) after the first heart failure hospital admission event (*Table 2*). A similar pattern of effect was identified for rehospitalizations due to heart failure at 1 month (21 vs. 42 events, IRR 0.67, 95% CI 0.40–1.13, $P = 0.13$), 2 months (56 vs. 97 events, IRR 0.77, 95% CI 0.55–1.09, $P = 0.14$), and 3 months (86 vs. 148 events, IRR 0.78, 95% CI 0.59–1.02, $P = 0.07$). Death rates were similar in both treatment groups at 1 month (8% with ivabradine vs. 9% with placebo), 2 months (11% vs.12%), and 3 months (13% vs. 14%) after the first heart failure hospitalization.

Discussion

Our analysis showed that patients hospitalized for heart failure during the study had a more severe profile as compared with their counterparts who had no heart failure hospitalization with respect to clinical status, cardiac function, and co-morbidities. In line with the more severe heart failure profile, these patients had more concomitant treatment with diuretics, digitalis, and mineralocorticoid receptor antagonists. Moreover, patients hospitalized for heart failure who had been randomized to ivabradine had a lower incidence

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

	At least one heart failure hospitalization ($n = 1186$)		No hospitalization for heart failure ($n = 5319$)	*P*-value[a]
	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	<0.0001
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 (b.p.m.)	82.5 ± 11.2	83.0 ± 11.7	79.3 ± 9.2	<0.0001
Systolic blood pressure (mmHg)	119.0 ± 16.7	118.5 ± 17.9	122.3 ± 15.7	<0.0001
Diastolic blood pressure (mmHg)	74.3 ± 9.9	73.4 ± 10.0	76.0 ± 9.4	<0.0001
Left ventricular ejection fraction (%)	27.6 ± 5.4	27.3 ± 5.5	29.3 ± 5.0	<0.0001
NYHA class				<0.0001
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/1.73 m^2)	69.8 ± 23.6	70.3 ± 26.6	75.8 ± 22.7	<0.0001
Medical history				
Duration of heart failure (years)	4.3 ± 4.6	4.7 ± 5.1	3.3 ± 4.1	<0.0001
Ischaemic 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%)	<0.0001
Hypertension	769 (65%)	200 (60%)	3545 (67%)	0.23
Diabetes	427 (36%)	130 (39%)	1552 (29%)	<0.0001
Stroke	125 (11%)	37 (11%)	398 (7%)	0.0005
History of atrial fibrillation and/or flutter	133 (11%)	36 (11%)	389 (7%)	<0.0001
Treatment at randomization				
Beta-blockers	1023 (86%)	279 (84%)	4797 (90%)	<0.0001
≥50% target dose	473 (47%)	109 (39%)	2708 (58%)	<0.0001
ACE inhibitors	900 (76%)	258 (77%)	4216 (79%)	0.0103
ARBs	186 (16%)	53 (16%)	741 (14%)	0.12
Mineralocorticoid receptor antagonists	824 (69%)	215 (64%)	3098 (58%)	<0.0001
Diuretics	1079 (91%)	303 (91%)	4335 (82%)	<0.0001
Digitalis	377 (32%)	107 (32%)	1039 (20%)	<0.0001

Values are means ± SD or numbers (%) of patients.
eGFR, estimated glomerular filtration rate.
[a]*P*-values comparing patients with at least one heart failure hospitalization vs. patients with no heart failure hospitalization (Kruskal–Wallis test for continuous variables, or χ^2 test for categorical variables).

of early recurrent hospitalizations following a first heart failure hospitalization during the trial than those on placebo. This reduction of risk was significant when considering all-cause rehospitalizations, and ranged from 21% to 30% within the first 3 months after a first event of heart failure hospitalization. A consistent trend for reduction in the same range of magnitude (from 21% to 34%) was observed for both cardiovascular and heart failure rehospitalizations. 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 initiation of beta-blockers on outcome. However, it demonstrated that in-hospital initiation of carvedilol was associated with its higher use 90 days after discharge, supporting the 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

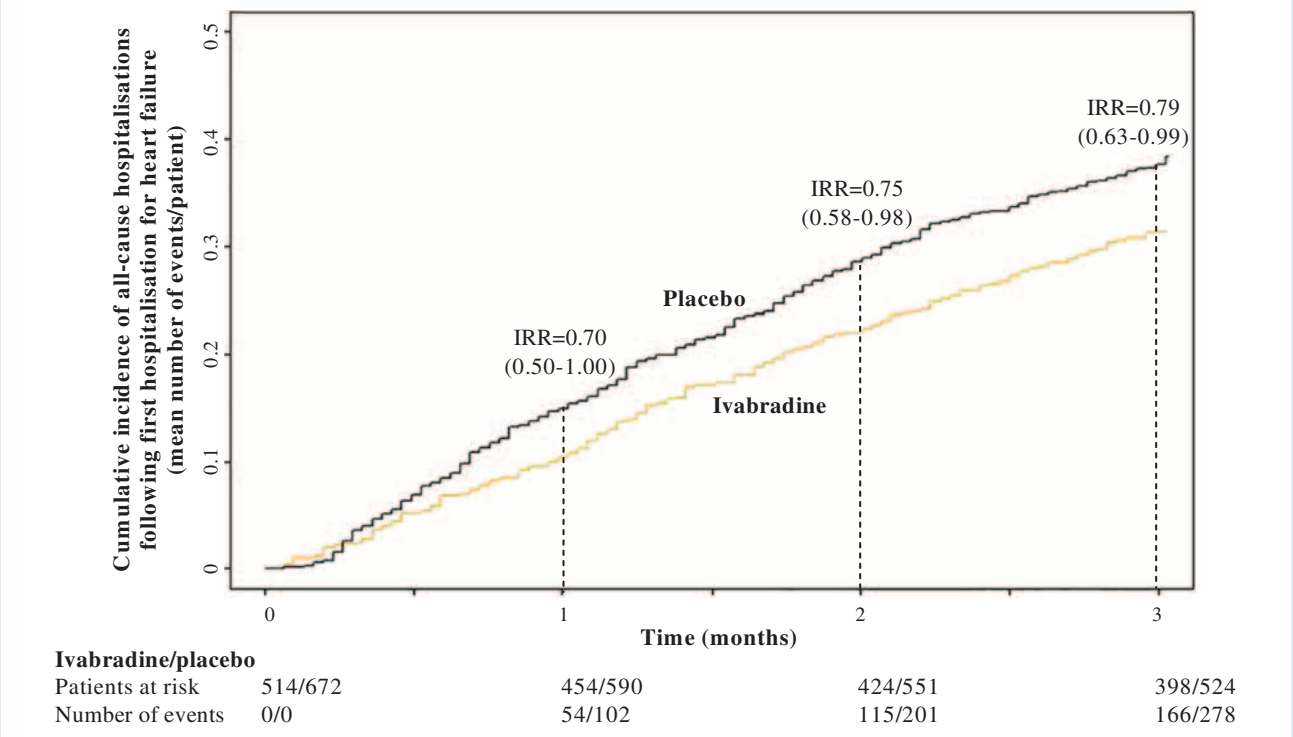

Figure 2 Cumulative rate of all-cause hospitalization. IRR, incidence rate ratio adjusted for prognostic factors at 1, 2, and 3 months (95% confidence interval).

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

	Cumulative number of events		IRR (95% CI) (adjusted for prognostic factors)
	Ivabradine ($n = 514$)	Placebo ($n = 672$)	
Cardiovascular hospitalizations			
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 hospitalizations			
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 time frame after a first heart failure hospitalization.
CI, confidence interval; IRR, incidence rate ratio.

(EMPHASIS-HF) trial demonstrated that eplerenone prevents readmission when initiated soon after a cardiovascular hospitalization in patients with systolic heart failure and mild symptoms.[15] Only a few randomized clinical trials have explored the effect of treatment during the vulnerable phase after hospitalized heart failure, by analysing outcomes early post-discharge.[16–20] In a randomized phase II 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 rehospitalization 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 hospitalization 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 randomization and who experienced a first heart failure admission. In a previous analysis, we demonstrated that ivabradine reduced the total burden of heart failure hospitalizations 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 hospitalizations.

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 ARBs was associated with a lower rate of readmission and/or mortality up to 90 days after discharge.[22−24] Accordingly, European Society of Cardiology (ESC) guidelines recommend the initiation of evidence-based therapy as soon as patients are stabilized after a hospitalization 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 those with a less severe profile. One of the obstacles limiting the early prescription or up-titration of standard care therapy after a heart failure hospitalization 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 hospitalization. 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 rehospitalization in the early post-discharge period.[29−31] In a cohort study of heart failure patients with heart rate ≥75 b.p.m. at discharge, each 10 b.p.m. increment was associated with an increase of 30% in risk of all-cause death, and 13% in risk of rehospitalizations 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 b.p.m. increment; and no increase in risk for all-cause rehospitalizations). 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 b.p.m. at hospital discharge, despite being treated with beta-blockers. Overall, the authors estimated that ∼40% of patients hospitalized for heart failure could qualify for initiation of ivabradine at the time of discharge.[28]

The reduction in readmissions in the ivabradine group was observed as early as 1 month after first hospitalization. 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 LV function.[33] This rapid stabilizing effect is further supported by the short-term reduction in NT-proBNP 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 chronic treatment with ivabradine could rapidly stabilize patients after a hospitalization for heart failure, by preventing degradation of LV 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 time of randomization.

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 hospitalized for heart failure. Therefore, we cannot assess the respective role of exposure to ivabradine before vs. after hospitalization in the observed effects on early readmissions. The IRRs 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 heart failure hospitalization during the study. On the other hand, this is the first analysis that describes the effect of a treatment on repeated hospitalization during the critical 3-month period after a hospitalization for heart failure. Our analysis is based on the date of hospitalization 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 hospitalization, 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 randomization planned in the original design. Although a beneficial trend in favour of ivabradine was observed on heart failure and on cardiovascular rehospitalizations, 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 noted that the vast majority

(86%) of all-cause rehospitalizations during the vulnerable phase were due to a cardiovascular cause, and 61% were due to heart failure.

Conclusion

Development of new therapeutic strategies to prevent early recurrent hospitalizations is a major goal for heart failure management. Here, we demonstrated that chronic exposure to ivabradine is associated with a decrease in all-cause hospitalization during the critical 3 months after a hospitalization 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 hospitalized heart failure patients.

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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, and Servier. 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, and ARMAGO (Stockholder Bio MARIN), and speakers bureau forAmgen. A.M. is an employee of Servier. I.F. reports grants and personal fees from Servier and Amgen while conducting the study.

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