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RESEARCH ARTICLE

Time to benefit of heart rate reduction with ivabradine in patients with heart failure and reduced ejection fraction

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Aims In the SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial, ISRCTN70429960) study, ivabradine reduced cardiovascular death or heart failure (HF) hospitalizations in patients with HF and reduced ejection fraction (HFrEF) in sinus rhythm and with a heart rate (HR) ≥70 bpm. In this study, we sought to determine the clinical significance of the time durations of HR reduction and the significant treatment effect on outcomes among patients with HFrEF.

Methods and results The time to statistically significant reduction of the primary outcome (HF hospitalization and cardiovascular death) and its components, all-cause death, and HF death, were assessed in a post-hoc analysis of the SHIFT trial in the overall population (HR ≥70 bpm) and at HR ≥75 bpm, representing the approved label in many countries. Compared to placebo, the primary outcome and HF hospitalizations were significantly reduced at 102 days, while there was no effect on cardiovascular death, all-cause death, and HF death at HR ≥70 bpm. In the population with a baseline HR ≥75 bpm, a reduction of the primary outcome occurred after 67 days, HF hospitalization after 78 days, cardiovascular death after 169 days, death from HF after 157 days and all-cause death after 169 days.

Conclusion Treatment with ivabradine should not be deferred in patients in sinus rhythm with a HR of ≥70 bpm to reduce the primary outcome and HF hospitalizations, in particular in patients with HR ≥75 bpm. At HR ≥75 bpm, the time to risk reduction was shorter for reduction of hospitalization and mortality outcomes in patients with HFrEF after initiation of guideline-directed medication, including beta-blockers at maximally tolerated doses.

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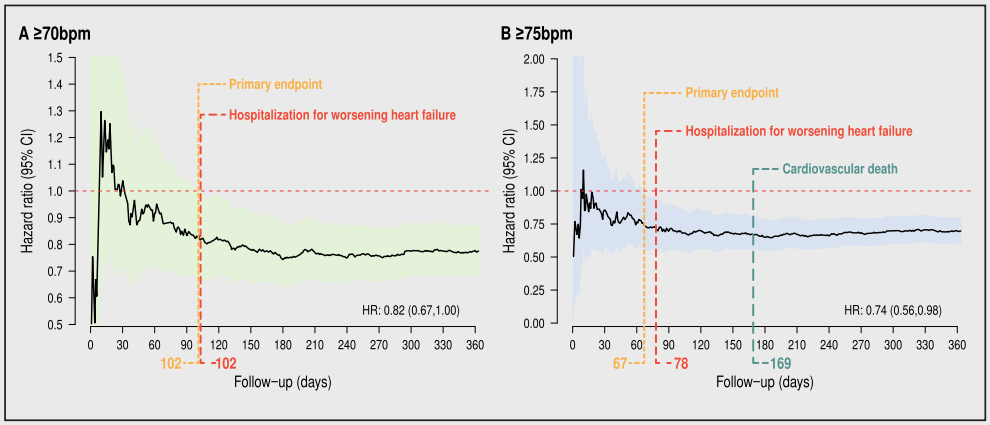
Graphical Abstract

Key question(s)	Key finding(s)	Take-home message
When does the benefit of heart rate (HR) reduction with ivabradine translate into a beneficial effect depending on baseline HR?	The primary outcome (hospitalization for heart failure and cardiovascular (CV) death) was significant at 102 days for HR ≥ 70bpm. It was significant at 67 days for HR ≥ 75bpm, 78 days for heart failure hospitalization and 169 days for CV death at ≥ 75bpm.	Time to risk reduction for the primary endpoint was shorter at ≥ 75bpm than at ≥ 70bpm and extends to CV death reduction at ≥ 75bpm. HR reduction in heart failure should not be deferred in particular in patients at ≥ 75bpm.



Time to benefit of heart rate reduction with ivabradine in patients with HFrEF: summary of the key findings.

Keywords Heart rate • Ivabradine • Heart failure • Cardiovascular outcomes

Introduction

Patients with chronic heart failure (HF) and reduced ejection fraction (HFrEF) have a high risk for cardiovascular death and HF hospitalization.[1] Shortly after recompensation from an acute event of worsening HF, rehospitalization and death rates are particularly high[2] leading to the concept that time is important in treatment initiation.[3] Accordingly, contemporary guidelines recommend an early start followed by up-titration of guideline-recommended HF drugs.[4,5] Heart rate (HR) is a modifiable risk factor in HFrEF,[6,7] and HR reduction with ivabradine has been shown to reduce cardiovascular death and HF hospitalizations.[8] It is recommended by guidelines, if HR in sinus rhythm remains high (≥70 bpm).[4,5] Among patients at a higher baseline HR ≥75 bpm, HR reduction has been reported to more convincingly reduce cardiovascular death, all-cause death, HF hospitalization, HF death, and all-cause cardiovascular hospitalizations.[9] In SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial), patients treated with beta-blockers at a maximally tolerated dose were randomized,[8] providing evidence that additional HR reduction can be beneficial.[9] While current guideline-directed medical therapy, such as sodium–glucose cotransporter 2 (SGLT2) inhibitors,[10,11] angiotensin receptor–neprilysin inhibitors[12] but also angiotensin-converting enzyme inhibitors and mineralocorticoid receptor antagonists[13,14] have an early onset of significant therapeutic effects, they lack HR reducing effects.[10–14] An analysis of early onset effects is not available for HR reduction with ivabradine. We investigated the treatment effect of ivabradine over time by conducting a post-hoc analysis of SHIFT and explored time to treatment effect in patients with a HR ≥70 bpm and ≥75 bpm on the primary composite of cardiovascular death and HF hospitalization, components of the composite, HF death (for the HR ≥75 bpm group) and all-cause death (for the HR ≥75 bpm group).

Methods

Study design

The complete design and results of the SHIFT trial have been previously reported.[7,8] Briefly, SHIFT was a randomized, double-blind,

placebo-controlled trial in outpatients with symptomatic and stable HF, left ventricular ejection fraction ≤35% and HR in sinus rhythm ≥70 bpm. All subjects have been hospitalized for worsening of HF the year before inclusion. A total of 6505 patients with guideline-directed medications were either assigned to placebo or ivabradine (starting dose 5 mg bid, titrated to 7.5 mg and 2.5 mg bid according to HR and tolerability). The primary endpoint was a composite of cardiovascular death or hospitalization for worsening of HF. Secondary endpoints included the components of the composite, all-cause mortality, and all-cause hospitalization among others. All hospitalization and death cases were adjudicated. The ethical committees of each of the participating institutions approved the protocol and all patients gave written informed consent. The trial is registered under ISRCTN70429960.

In the present post-hoc analysis from SHIFT, we explored the composite of cardiovascular death and HF hospitalization and the components of the composite continuously according to treatment time. In SHIFT, ivabradine reduced the composite of cardiovascular death or hospital admission for worsening HF, HF hospitalization and HF death in patients with HR ≥70 bpm. We explored the time to a significant treatment effect in the overall population (HR ≥70 bpm) as well as patients at a HR ≥75 bpm.

Statistical analysis

The statistical methods and analysed population were selected *a posteriori*. Baseline characteristics are shown as means ± standard deviation for continuous variables and numbers with percentages for categorical variables. Comparisons were done with a Kruskal–Wallis test for continuous variables and a Chi-square test for categorical variables. The estimate of the hazard ratio (HR) and its 95% confidential interval (CI) using an adjusted Cox proportional hazards model was based on the adjudication criteria and the trial was conducted as time to event under the intention-to-treat principle. All analyses were performed by the sponsor after agreeing on a statistical analysis plan using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). *P*-values reported are two-sided and $p < 0.05$ was considered as statistically significant in all cases. Adjustments for multiple testing were not made due to the exploratory nature of the study.

Results

A total of 6505 patients were randomly assigned to receive either ivabradine ($n = 3241$) or matched placebo ($n = 3264$). From

Table 1 Baseline characteristics according to baseline heart rate

	≥70 bpm ($n = 6505$)		≥75 bpm ($n = 4150$)	
	Ivabradine ($n = 3241$)	**Placebo ($n = 3264$)**	**Ivabradine ($n = 2052$)**	**Placebo ($n = 2098$)**
Age (years)	60.7 ± 11.2	60.1 ± 11.5	59.7 ± 11.2	59.5 ± 11.7
Male sex	2462 (76)	2508 (77)	1570 (77)	1617 (77)
Current smoker	541 (17)	577 (18)	381 (19)	402 (19)
Body mass index (kg/m^2)	28.0 ± 5.1	28.0 ± 5.0	28.1 ± 5.3	27.9 ± 5.1
Cardiac parameters				
Heart rate (bpm)	79.7 ± 9.5	80.1 ± 9.8	84.3 ± 9.1	84.6 ± 9.4
SBP (mmHg)	122.0 ± 16.1	121.4 ± 15.9	121.6 ± 16.7	121.2 ± 16.1
DBP (mmHg)	75.7 ± 9.6	75.6 ± 9.4	75.8 ± 9.9	75.7 ± 9.5
LVEF (%)	29.0 ± 5.1	29.0 ± 5.2	28.7 ± 5.2	28.5 ± 5.3
Creatinine clearance (ml/min/1.73 m^2)	74.6 ± 22.9	74.8 ± 23.1	75.7 ± 23.5	75.5 ± 23.1
NYHA class				
II	1585 (49)	1584 (49)	977 (48)	975 (46)
III	1605 (50)	1618 (50)	1035 (50)	1076 (51)
IV	50 (2)	61 (2)	40 (2)	47 (2)
Medical history				
Duration of heart failure (years)	3.5 ± 4.2	3.5 ± 4.2	3.46 ± 4.13	3.38 ± 4.00
Ischaemic cause of heart failure	2215 (68)	2203 (67)	1359 (66)	1363 (65)
Myocardial infarction	1829 (56)	1837 (56)	1124 (55)	1138 (54)
Hypertension	2162 (67)	2152 (66)	1333 (65)	1349 (64)
Diabetes	973 (30)	1006 (31)	638 (31)	665 (32)
Previous stroke	228 (7)	295 (9)	141 (7)	189 (9)
Atrial fibrillation and/or flutter	263 (8)	259 (8)	154 (8)	162 (8)
Treatment at randomization				
Beta-blockers	2897 (89)	2923 (90)	1794 (87)	1845 (88)
ACE inhibitor and/or ARB	3020 (93)	3023 (93)	1852 (90)	1896 (90)
Diuretics	2719 (84)	2695 (83)	1743 (85)	1741 (83)
Aldosterone antagonists	1981 (61)	1941 (59)	1286 (63)	1271 (61)
At least one device	110 (3)	134 (4)	66 (3)	94 (4)

Data are given as *n* (%) or mean ± standard deviation.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DBP. diastolic blood pressure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

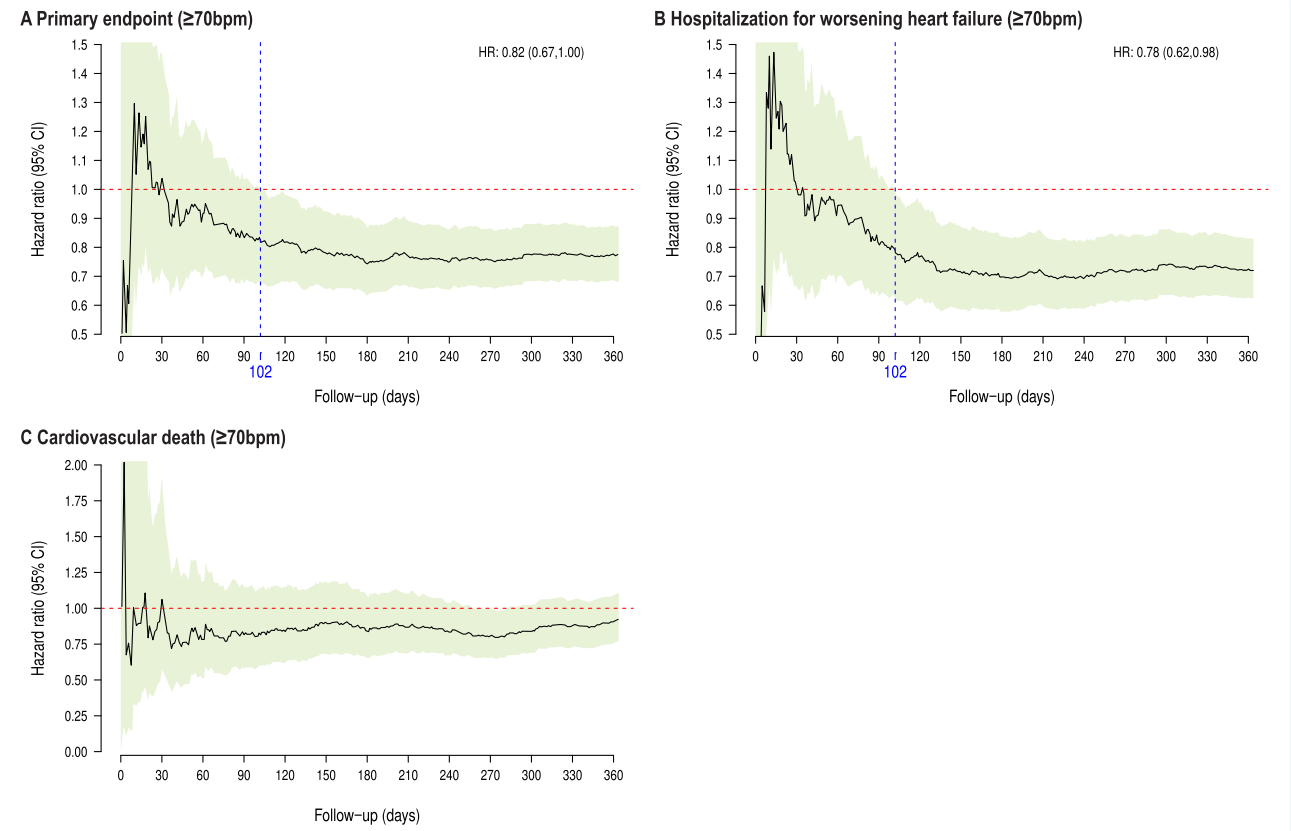


Figure 1 Timing of statistical demonstration of benefit of heart rate reduction with ivabradine versus placebo on the primary outcome (cardiovascular death or heart failure hospitalization (*A*), hospitalization for worsening of heart failure (*B*) and cardiovascular death (*C*) in patients with a baseline heart rate ≥ 70 bpm. Follow-up was truncated at 360 days for all analyses. CI, confidence interval; HR, hazard ratio.

the total population, we separated patients with a HR ≥75 bpm ($n = 4150$). Baseline characteristics are summarized in *Table 1*. There were no meaningful clinical differences compared to the overall population. In the group with a HR ≥75 bpm, there were also no significant differences in clinical characteristics between those randomized to ivabradine ($n = 2052$) or placebo ($n = 2098$).

For the overall population in SHIFT (HR ≥70 bpm), a significant statistical reduction of the primary endpoint was observed at 102 days of treatment with ivabradine compared to placebo (HR 0.82 [95% CI 0.67–1.00]; *Figure 1A*). The effects were driven mainly by hospitalization for worsening HF at 102 days (HR 0.78 [0.62–0.98]; *Figure 1B*). Cardiovascular death was not significantly reduced (*Figure 1C*). Similar results were observed for all-cause death, which was not significantly reduced in the overall population as was HF death (not shown). In the population with a HR ≥75 bpm, time for significant reduction of primary outcome occurred at 67 days (HR 0.74 [0.56–0.98]; *Figure 2A*), while hospitalization for worsening of HF became significant at 78 days (HR 0.72 [0.53–0.99]; *Figure 2B*) and cardiovascular death at 169 days (HR 0.72 [0.52–1.00]; *Figure 2C*). After 157 days, there was a significant reduction of death from HF (HR 0.49 [0.24–0.97]; *Figure 3A*) and also of all-cause death after 169 days (HR 0.73 [0.53–0.99]; *Figure 3B*) and. The numbers of all outcomes with different HR ≥75 bpm, <75 bpm and for all patients are separated in online supplementary *Table S1*. The relevant adverse outcomes are listed in online supplementary *Table S2*. No meaningful differences were observed between the groups.

Discussion

High HR represents an important indicator of mortality in patients with HFrEF,[6–9] HF with preserved ejection fraction,[15,16] post-discharge HF[17] and critical disease states.[16] In HFrEF, HR represents a modifiable risk factor associated with hospitalization and death being sensitive to HR reduction with beta-blockers[18] and ivabradine.[7,8] Different societal guidelines recommend initializing the guideline-directed medical treatment soon following diagnosis and subsequently up-titration of disease-modifying agents based on patients' clinical tolerance,[4,5] taking into account the patient profiling.[19,20] Ivabradine is recommended by guidelines in patients with a remaining HR ≥70 bpm in the presence of maximally tolerated beta-blocker doses.[4,5] However, it is approved by the European Medicines Agency (EMA) for use in Europe at a HR ≥75 bpm, because in this group ivabradine confirmed its survival benefits.[9] This study is the first to determine the timing of significant reduction of HF hospitalizations and mortality after

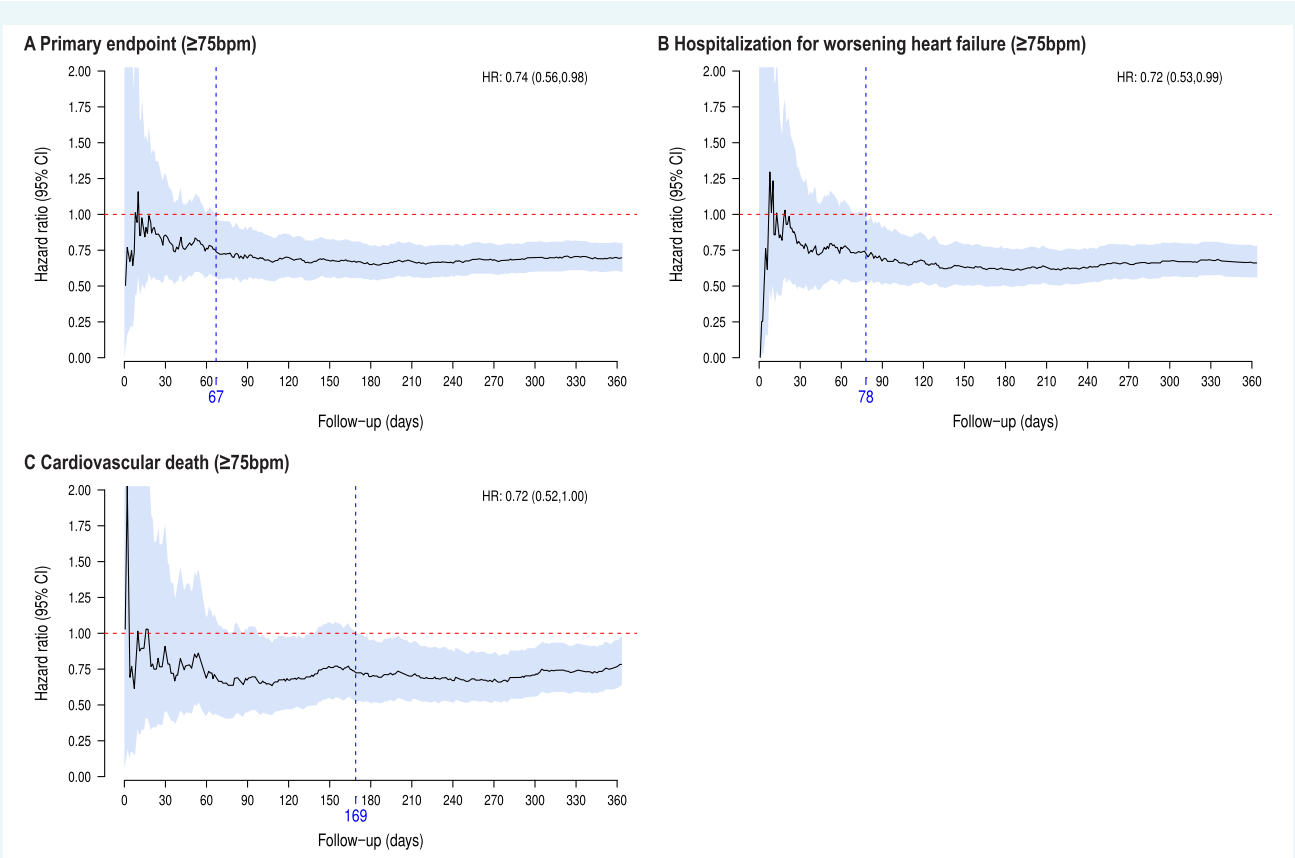


Figure 2 Timing of statistical demonstration of benefit of heart rate reduction with ivabradine versus placebo on the primary outcome (cardiovascular death and heart failure hospitalization (*A*), hospitalization for worsening of heart failure (*B*) and cardiovascular death (*C*) in patients with a baseline heart rate ≥75 bpm. Follow-up was truncated at 360 days for all analyses. CI, confidence interval; HR, hazard ratio.

ivabradine initiation in patients with HFrEF and a HR of ≥70 bpm or ≥75 bpm. In patients after HF hospitalization during the study, 28% were rehospitalized within 3 months[21] for any reason mostly for cardiovascular causes (86%), including HF hospitalization (61%). In these patients, there was an early effect of ivabradine at 1 month and a risk reduction for all-cause hospitalization by 30%, 25% at 2 months and 21% at 3 months. Herein, we extend those findings by exploring the time to a statistically significant treatment effect in all patients and in a high-risk population at an elevated HR (i.e. ≥75 bpm), which is not only associated with hospitalization for HF but also with cardiovascular death. These findings show that within approximately 3 months (102 days), the primary endpoint was significantly reduced, which was primarily driven by a reduction of hospitalization for HF. In the population with a HR ≥75 bpm, the time to significant reduction for the primary outcome occurred 35 days earlier at day 67 compared to HR >70 bpm (102 days). This was again associated with a significant risk reduction at 78 days for HF hospitalization. In the group of ≥75 bpm, there was a significant reduction of HF death at 157 days, cardiovascular and all-cause death at 169 days. This finding is in concordance with reports on other drugs[13,14] demonstrating that HR reduction with ivabradine should not be deferred when HR remains above 70 bpm and particularly above 75 bpm despite beta-blocker treatment.

Despite an intensive beta-blocker treatment, the median HR in recent trials providing benefit with sacubitril/valsartan[22,23] and SGLT2 inhibitors[24,25] was high. The mean HR in PARADIGM-HF[22] was 72–73 ± 12 bpm.[24] In patients shortly after recompensation from an acute worsening of HF, HR was even higher (median 80–81, in the quartile range 72–91 bpm).[23] In DAPA-HF, mean HR was 71.5 ± 11.6–11.8 bpm[24] and in EMPEROR-Reduced 71–71.5 ± 11.7–11.8 bpm.[25] These findings demonstrate high HR above 70 bpm is potentially associated with outcomes in up to 50% of HF patients.[22–25] These recent studies, proving benefits of contemporary guideline-recommended treatments,[4,5] suggest that even now, there is still a need to consider and further control HR to provide even better benefit in patients treated with these guideline-directed medications.

A HR of ≥75 bpm was associated with significantly elevated incidence of cardiovascular death, and ivabradine versus placebo reduced cardiovascular death at this higher HR.[9] Therefore, the EMA approved ivabradine for the treatment of patients with HFrEF receiving guideline-recommended background therapy including beta-blockers provided a resting HR ≥75 bpm. Consistently, there was a significant reduction of all-cause mortality, cardiovascular

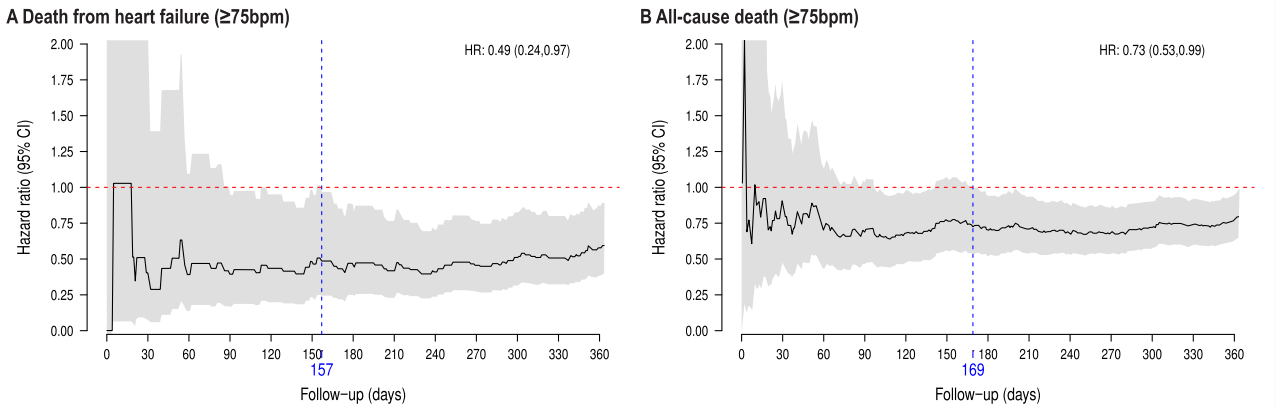


Figure 3 Timing of statistical demonstration of benefit of heart rate reduction with ivabradine versus placebo for death from heart failure (*A*) and all-cause death (*B*) in patients with a baseline heart rate ≥75 bpm. Follow-up was truncated at 360 days for all analyses. CI, confidence interval; HR, hazard ratio.

mortality, and death from HF in this group with higher HR at baseline (i.e. ≥75 bpm).[9] This study extends those findings by exploring that at higher baseline HR values and showing the significant effect is also occurring earlier. For the reduction of HF hospitalization, the treatment should be started early to achieve significant treatment effects at <3 months for HR ≥75 bpm and approximately 5 months for HR ≥70 bpm. By doing so, a reduction of mortality can be also expected before 6 months when HR is ≥75 bpm (*Graphical Abstract*).

Limitations

This analysis has few limitations inherent to its nature as a post-hoc analysis. Separating the overall population to subgroups, which were not subject to randomization, may cause invisible confounding. However, the large number of patients in each subgroup provides adequate statistical power to detect reliably meaningful differences.

Conclusion

In this post-hoc analysis, time to treatment effect for the primary endpoint was short, in particular at HR ≥75 bpm. As treatment of patients with beta-blockers and ivabradine in HFrEF and HR ≥70 bpm, and particularly at ≥75 bpm in sinus rhythm, reduces events relatively timely after treatment initiation, HR reducing treatment should not be deferred because treatment delay leaves patients at high risk of events, including death.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: none declared.

Acknowledgement

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