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Efficacy of ivabradine in heart failure patients with a high-risk profile (analysis from the SHIFT trial)

Amr Abdin^{1*}, Michel Komajda², Jeffrey S. Borer³, Ian Ford⁴, Luigi Tavazzi⁵, Cécile Batailler⁶, Karl Swedberg⁷, Giuseppe M.C. Rosano⁸, Felix Mahfoud¹, Michael Böhm¹ and on behalf of the SHIFT Investigators

¹Department of Internal Medicine III, Cardiology, Angiology, Intensive Care Medicine, Saarland University Medical Center, Kirrberger Strasse 100, Homburg/Saar, 66421, Germany; ²Department of Cardiology, Hospital Saint Joseph, Paris, France; ³The Howard Gilman Institute for Heart Valve Diseases and Schiavone Institute for Cardiovascular Translational Research, State University of New York Downstate Health Sciences University, Brooklyn and New York, NY, USA; ⁴Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK; ⁵Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy; ⁶Institut de Recherches Internationales Servier, Suresnes, France; ⁷Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden; and ⁸Centre for Clinical and Basic Research, IRCCS San Raffaele Roma, Rome, Italy

Abstract

Aims Early start and patient profile-oriented heart failure (HF) management has been recommended. In this post hoc analysis from the SHIFT trial, we analysed the treatment effects of ivabradine in HF patients with systolic blood pressure (SBP) < 110 mmHg, resting heart rate (RHR) ≥ 75 b.p.m., left ventricular ejection fraction (LVEF) ≤ 25%, New York Heart Association (NYHA) Class III/IV, and their combination.

Methods and results The SHIFT trial enrolled 6505 patients (LVEF ≤ 35% and RHR ≥ 70 b.p.m.), randomized to ivabradine or placebo on the background of guideline-defined standard care. Compared with placebo, ivabradine was associated with a similar relative risk reduction of the primary endpoint (cardiovascular death or HF hospitalization) in patients with SBP < 110 and ≥ 110 mmHg [hazard ratio (HR) 0.89, 95% confidence interval (CI) 0.74–1.08 vs. HR 0.80, 95% CI 0.72–0.89, *P* interaction = 0.34], LVEF ≤ 25% and > 25% (HR 0.85, 95% CI 0.72–1.01 vs. HR 0.80, 95% CI 0.71–0.90, *P* interaction = 0.53), and NYHA III–IV and II (HR 0.83, 95% CI 0.74–0.94 vs. HR 0.81, 95% CI 0.69–0.94, *P* interaction = 0.79). The effect was more pronounced in patients with RHR ≥ 75 compared with < 75 (HR 0.76, 95% CI 0.68–0.85 vs. HR 0.97, 95% CI 0.81–0.1.16, *P* interaction = 0.02). When combining these profiling parameters, treatment with ivabradine was also associated with risk reductions comparable with patients with low-risk profiles for the primary endpoint (relative risk reduction 29%), cardiovascular death (11%), HF death (49%), and HF hospitalization (38%; all *P* values for interaction: 0.40). No safety concerns were observed between study groups.

Conclusions Our analysis shows that RHR reduction with ivabradine is effective and improves clinical outcomes in HF patients across various risk indicators such as low SBP, high RHR, low LVEF, and high NYHA class to a similar extent and without safety concern.

Keywords Heart failure; Ivabradine; Risk indicators; High risk; Heart rate

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*Correspondence to: Amr Abdin, MD, FESC, FEHRA, FHFA, Department of Internal Medicine III, Cardiology, Angiology, Intensive Care Medicine, Saarland University Medical Center, Kirrberger Strasse 100, 66421 Homburg/Saar, Germany. Tel: +49 6841 161 5029; Fax: +49 6841 1615032. Email: amr.abdin@uks.eu

Introduction

The current guidelines of the European Society of Cardiology (ESC)¹ and the American Heart Association (AHA)² on heart failure (HF) strongly recommend the rapid establishment of outcome-modifying therapies in patients with HF with reduced ejection fraction (HFrEF). Many patients in the real world are treated with doses that are lower than those with

proven efficacy utilized in clinical trials,^{3,4} which might be due to inertia of physicians or fear of tolerability issues related to low blood pressure (BP) and heart rate, impaired renal function, severely impaired left ventricular ejection fraction (LVEF), disease severity, or hyperkalaemia.^{3,5–7} Furthermore, the clinical course of patients with chronic HF (CHF) is variable and the prognosis depends on comorbidities and the severity of CHF.⁷ Due to the individual var-

iability and patient phenotypes, selecting drugs with the highest likelihood of efficacy and with the lowest adverse event rates can be challenging.⁷ To attain this, individual patient profiling was recommended when selecting and initiating HFREF drugs.^{5,6}

HF patients with low BP and high resting heart rate (RHR) are at greater risk of in-hospital and post-discharge morbidity and mortality.^{8–12} Low BP often coexists with severely reduced LVEF (low cardiac output)¹³ or high New York Heart Association (NYHA) functional class.¹⁴ Those factors are also predictors of cardiovascular (CV) outcomes, including all-cause and CV mortality and HF hospitalizations.^{8,13} Subsequently, the treatment effect size is important to select treatments in patients with different profiles.

Ivabradine is recommended by guidelines in patients with symptomatic HF with reduced LVEF ($\leq 35\%$) in sinus rhythm with an RHR ≥ 70 b.p.m. despite maximally tolerated beta-blocker (BB) doses.^{1,2} Data exist additionally to support its use as an adjunct to facilitate up-titration of BB.^{15,16}

As it may be challenging to treat HF patients with low BP, high RHR, and severely reduced LVEF, ivabradine can play an important role in the management of these patients, as it does not reduce BP.¹⁰ The current analysis investigates whether ivabradine provides similar benefits across various patient profiles, which identify patients at different risk levels. We studied the impact of RHR reduction with ivabradine on outcomes in HF patients with high-risk profile including low systolic BP (SBP), high RHR, low LVEF, high NYHA class, and their combination from the Systolic Heart failure treatment with the IF inhibitor ivabradine Trial (SHIFT).

Methods

The SHIFT trial was a multicentre, randomized, double-blind, placebo-controlled, parallel-group trial performed in 677 centres in 37 countries. The design and results of the study have been published previously.^{17,18} Patients with moderate to severe HF and LVEF $\leq 35\%$ in sinus rhythm with RHR ≥ 70 b.p.m. were included in this study. All patients were receiving guideline-recommended background treatments. Patients were randomly assigned to treatment with ivabradine or placebo. The starting dose was 5 mg of ivabradine twice daily; doses were adjusted upward or downward (2.5, 5, or 7.5 mg twice daily) at every visit according to RHR and tolerability.

The primary outcome was the composite of CV death or hospitalization for worsening HF. All the study endpoints were adjudicated by an independent endpoint validation committee. Other endpoints included the individual components of the primary endpoint, all-cause death, HF death,

and hospitalization for any cause. Outcomes were analysed on a time-to-first event basis. NYHA class was recorded at baseline and at every four-monthly visit throughout the trial. The median follow-up was 22.9 months.

In this post hoc sub-analysis from the SHIFT trial, the effects of ivabradine on outcomes were analysed according to each of the following phenotypes: a high-risk patients' profile with SBP < 110 mmHg, RHR ≥ 75 b.p.m., LVEF $\leq 25\%$, NYHA III–IV, and their combination, as well as a low-risk patients' profile with SBP ≥ 110 mmHg, RHR < 75 b.p.m., LVEF $> 25\%$, NYHA II, and their combination. At baseline, patients had to be in sinus rhythm and the trial did not enrol patients with severe renal disease (serum creatinine > 220 $\mu\text{mol/L}$). Thus, these characteristics were not included in this analysis.

The study was conducted according to the Declaration of Helsinki and has been approved by the local ethics committee, and all patients or their legal representatives gave written informed consent.

Statistical analysis

All continuous variables are presented as medians with interquartile range (IQR) for reasons of uniformity. Categorical data are presented as counts or proportions with the corresponding percentages. For comparison of continuous variables, Student's *t*-test or Mann–Whitney's test was used; for comparison of categorical variables, Fisher's exact test or χ^2 test was used, as appropriate. To study the effect of the relationship between patients at higher risk and CV outcomes, treatment effects were estimated using a Cox proportional hazards model, adjusted for BB use, to produce hazard ratios (HRs) with 95% confidence intervals (CIs). Between-group differences (*P* values) in adverse events were calculated with a χ^2 or Fisher's exact test, as appropriate. SAS software (Version 9.2; SAS Institute Inc., Cary, North Carolina) was used.

Results

A total of 6505 patients were randomized (3241 to ivabradine vs. 3264 to placebo). The baseline characteristics of patients with high- and low-risk profiling are presented in the Supporting Information, *Table S1*.

Out of the 6505 randomized patients, 186 patients had the high-risk profiling parameters: SBP < 110 mmHg, RHR ≥ 75 b.p.m., LVEF $\leq 25\%$, and NYHA Class III/IV. Of these 186 patients, 92 (49%) received ivabradine. Compared with patients with low-risk profiling, the mean LVEF was 20.5% vs. 29.3%. Patients with high-risk profiling had more frequently non-ischaeamic cardiomyopathy (35.7% vs. 31.4%, $P \leq 0.0001$) and renal insufficiency (10.2% vs. 6.3%,

$P = 0.03$). The mean ivabradine dose prescribed according to treatment duration did not differ between the two groups (high- vs. low-risk profiling): 6.93 vs. 6.77 mg, $P = 0.81$. The proportion of patients achieving the BB target dose was 12.80% and 26.45% in the high- and low-risk profile groups, respectively ($P < 0.001$).

Compared with placebo, ivabradine was associated with a similar relative risk reduction of the primary endpoint (CV death or HF hospitalization) in patients with SBP < 110 and ≥ 110 mmHg (HR 0.89, 95% CI 0.74–1.08 vs. HR 0.80, 95% CI 0.72–0.89, P interaction = 0.34), LVEF $\leq 25\%$ and $> 25\%$ (HR 0.85, 95% CI 0.72–1.01 vs. HR 0.80, 95% CI 0.71–0.90, P interaction = 0.53), and NYHA II and III–IV (HR 0.81, 95% CI 0.69–0.94 vs. HR 0.83, 95% CI 0.74–0.94, P interaction = 0.79) (Table 1). The treatment effect was stronger in patients with RHR ≥ 75 b.p.m. compared with RHR < 75 b.p.m. (HR 0.76, 95% CI 0.68–0.85 vs. HR 0.97, 95% CI 0.82–1.16, $P = 0.02$) (Table 1).

The event rate of the primary endpoint in patients with high-risk profiling was numerically lower in the ivabradine compared with placebo groups (39.13% vs. 52.13%, $P = 0.12$) (Table 1 and Figures 1 and 2). In the low-risk profiling group, the rate of the primary endpoint was significantly lower in the ivabradine compared with placebo groups (24.05% vs. 28.02%, $P = 0.0001$) (Table 1 and Figures 1 and 2). Treatment with ivabradine was associated with substantial reductions in relative risk for the primary endpoint, and these reductions did not vary across groups (Table 1 and Figures 1 and 2). Similar differences were observed for all other outcomes: hospitalization for worsening HF (Figure 2), CV death, and HF death (Supporting Information, Figure S1).

There were substantial relative risk reductions for the primary composite endpoint (29% reduction), CV death (11%), HF death (49%), and HF hospitalization (38%) (all P values for interaction: 0.40).

Adverse events

As reported in the global population, the rate of serious adverse events was lower in the ivabradine group compared with placebo in both high- and low-risk profile patients. Focusing on all adverse events and as it was also reported in the global population, ivabradine-treated patients had higher rate of bradycardia, hypotension, and phosphenes with no difference in drug withdrawal rate (Table 2).

Discussion

Our study shows that HF patients included in the SHIFT trial with SBP < 110 mmHg, RHR ≥ 75 b.p.m., LVEF $\leq 25\%$, NYHA Class III/IV, and their combination were at greater risk for all

Table 1 Outcomes in patients with high-risk profiling [systolic blood pressure (SBP) < 110 mmHg, resting heart rate (RHR) ≥ 75 b.p.m., left ventricular ejection fraction (LVEF) $\leq 25\%$, and New York Heart Association (NYHA) Class III/IV] compared with patients with low-risk profiling (SBP ≥ 110 mmHg or RHR < 75 b.p.m. or LVEF $> 25\%$ or NYHA II)

	Number of patients		Event rate (%)		Primary endpoint			P for interaction
	Ivabradine	Placebo	Ivabradine	Placebo	HR (95% CI)	P value	NNT	
SBP ≥ 110 mmHg	2626	2637	594 (22.62)	715 (27.11)	0.80 (0.72–0.89)	0.0001	22.3	0.34
SBP < 110 mmHg	615	627	199 (32.36)	222 (35.41)	0.89 (0.74–1.08)	0.025	32.8	
LVEF $> 25\%$	2429	2466	522 (21.49)	641 (25.99)	0.80 (0.71–0.90)	0.0001	22.2	0.53
LVEF $\leq 25\%$	812	798	271 (33.37)	296 (37.09)	0.85 (0.72–1.01)	0.05	26.9	
NYHA Class II	1585	1584	300 (18.93)	356 (22.47)	0.81 (0.69–0.94)	0.006	28.2	0.79
NYHA Class III or IV	1655	1979	493 (29.79)	580 (34.54)	0.83 (0.74–0.94)	0.002	21.2	
RHR < 75 b.p.m.	1188	1163	248 (20.88)	249 (21.41)	0.97 (0.82–1.16)	0.77	188.7	0.02
RHR ≥ 75 b.p.m.	2052	2098	545 (26.56)	688 (32.79)	0.76 (0.68–0.85)	< 0.0001	16.1	
RHR < 75 , SBP ≥ 110 , LVEF > 25 , and NYHA II	3147	3166	757 (24.05)	887 (28.02)	0.83 (0.75–0.91)	0.0001	23.6	0.4
RHR ≥ 75 , SBP < 110 , LVEF ≤ 25 , and NYHA III–IV	92	94	36 (39.13)	49 (52.13)	0.71 (0.46–1.10)	0.12	15.2	

b.p.m., beats per minute; CI, confidence interval; HR, hazard ratio; NNT, number needed to treat.

Figure 1 Hazard ratios (HRs) and event rate for ivabradine compared with placebo according to patients with high- and low-risk profiling for the primary outcome. CI, confidence interval; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RHR, resting heart rate; SBP, systolic blood pressure.

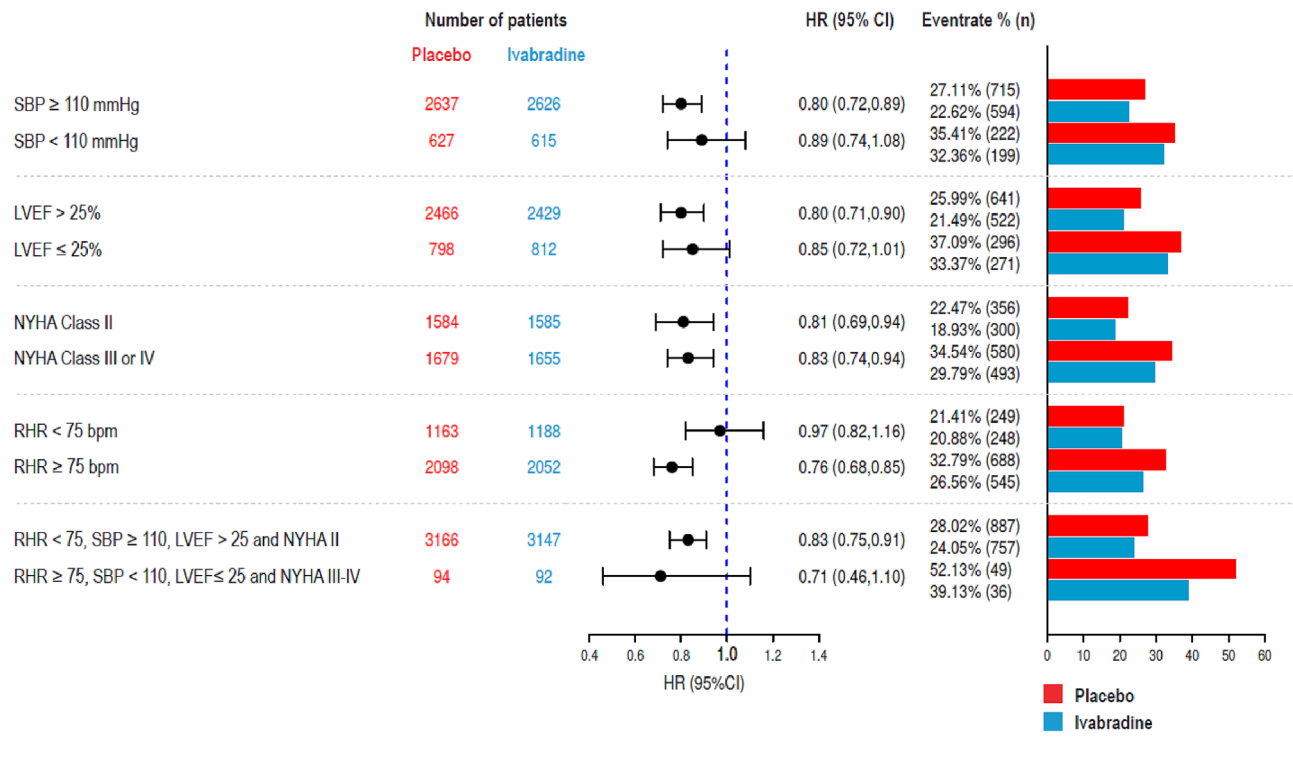
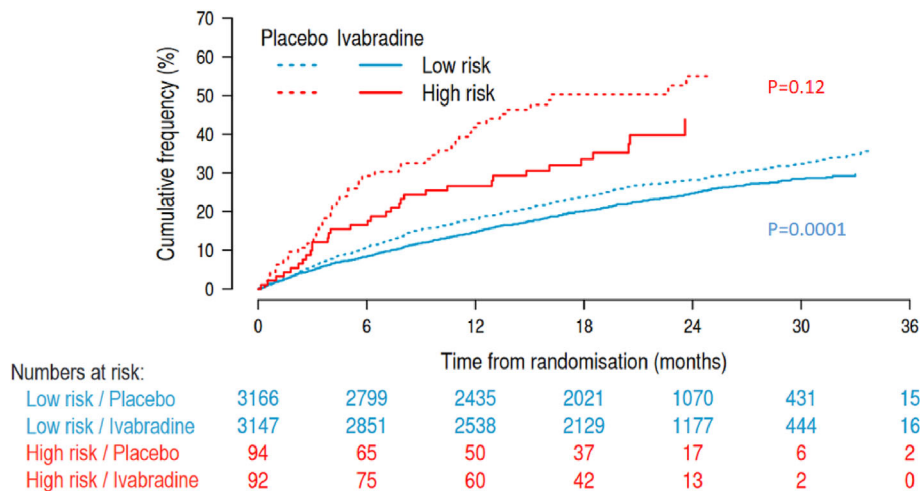


Figure 2 Incidence of the primary composite endpoint (cardiovascular death or hospitalization for worsening HF) in patients with high-risk profiling defined as systolic blood pressure < 110 mmHg, heart rate ≥ 75 b.p.m., left ventricular ejection fraction ≤ 25%, and New York Heart Association Class III/IV, compared with low-risk profiling defined as systolic blood pressure ≥ 110 mmHg, heart rate < 75 b.p.m., left ventricular ejection fraction > 25%, and New York Heart Association Class II, displayed as time-to-first event.



study outcomes. The effect of ivabradine on reducing the primary outcome, HF death, and hospitalization for worsening HF is consistent across patients with high-risk profiling parameters and was not associated with safety concerns.

Initiation of HF treatments can be challenging in high-risk patients, which frequently present with low SBP, high RHR, low ejection fraction (EF), and higher NYHA class.^{5,6} Renin-angiotensin-aldosterone system (RAAS) inhibitors and BBs

Table 2 Safety in the SHIFT population according to risk profiling

	High-risk profiling			Low-risk profiling		
	Ivabradine (N = 92)	Placebo (N = 93)	P value	Ivabradine (N = 3138)	Placebo (N = 3163)	P value
Any serious adverse event	53 (57.61%)	67 (72.04%)	0.046	1396 (44.49%)	1484 (46.92%)	0.055
Any adverse event	72 (78.26%)	83 (89.25%)	0.05	2366 (75.4%)	2337 (73.89%)	0.174
Cardiac failure	35 (38.04%)	46 (49.46%)	0.14	735 (23.42%)	854 (27%)	0.001
Bradycardia	2 (2.17%)	0 (0%)	0.25	148 (4.72%)	32 (1.01%)	<0.001
Atrial fibrillation	9 (9.78%)	8 (8.6%)	0.81	297 (9.46%)	242 (7.65%)	0.10
Phosphenes	1 (1.09%)	0 (0%)	0.49	6 (0.19%)	3 (0.09%)	0.34
Hypotension	5 (5.53%)	0 (0%)	0.03	84 (2.68%)	17 (0.54%)	<0.001

High risk: systolic blood pressure (SBP) < 110 mmHg, resting heart rate (RHR) ≥ 75 b.p.m., left ventricular ejection fraction (LVEF) ≤ 25%, and New York Heart Association (NYHA) Class III/IV, compared with patients with low risk: SBP ≥ 110 mmHg or RHR < 75 b.p.m. or LVEF > 25% or NYHA II.

have been shown to reduce outcomes in a broad population^{1,2} but are often limited in their applicability in the most critically ill patients because of hypotension and other tolerability barriers and particularly renal failure and hypokalaemia.^{7,19–21} According to the treatment profiling approach by the European Heart Failure Association,^{5,6} no such data exist for RHR reduction with ivabradine. Ivabradine can be safely used to lower RHR in HF with higher symptom burden and critically ill patients. The results presented herein with ivabradine have implications for the management of these patients as it has been suggested that patients with low BP could have differential treatment effects of recommended treatments.^{22,23} Furthermore, HF patients in particular often have a higher RHR as a result of compensatory neurohormonal activation that increases sympathetic activity. As a result, oxygen demand increases, and ventricular efficiency decreases, which leads to a worsening HF. Ivabradine works by specifically suppressing the pacing current (If) of the sinus node. As the cardiac effects of ivabradine are confined to the sinus node, ivabradine has no effect on BP, cardiac conduction, myocardial contractility, or ventricular repolarization, and the effects are well tolerated in HF patients.^{22,23}

High RHR²¹ and low BP^{22,23} independently indicate poor outcomes in HF. Herein, a combination of low SBP and high RHR placed HF patients at significantly higher risk for mortality and morbidity. This has implications for the management of HF patients with low BP and elevated RHR.

NYHA class and LVEF were also used as combined criteria indicative of HF severity.¹⁴ In the COPERNICUS trial, the addition of carvedilol in patients with severe HF (NYHA III/IV) improves HF severity and reduces the risk of clinical deterioration.²⁴ Next, we combined NYHA class, low LVEF, low BP, and high RHR to study treatment effects in patients at particularly high risk. Each single measure of the used criteria independently predicts mortality and morbidity.^{10,11,14,21} Across all these groups, ivabradine led to a similar risk reduction of outcomes. Notably, in the presence of similar relative risk reduction but higher absolute

risk, patients with adverse outcome predictors such as low BP, high RHR, low NYHA class, and low EF particularly benefit from treatments as absolute treatment effects are pronounced. Although often difficult to treat, they might benefit from high-risk absolute risk reduction and low number needed to treat to prevent events.

Among the different risk markers, low BP often represents a complex clinical situation. Interestingly, treatment with ivabradine rather increased than decreased SBP (+12.0 ± 14.9 mmHg vs. 11.1 ± 14.2 mmHg in the placebo group).¹⁰ Hence, treatment with ivabradine in these groups with high risk does not come at a cost of meaningfully increased adverse events or drug withdrawal rate.

Currently, ivabradine is recommended by guidelines in patients with symptomatic HF with reduced LVEF (HFrEF) in sinus rhythm with a heart rate ≥ 70 b.p.m. despite maximally tolerated BB and HF therapies.¹ According to recommended patient phenotyping algorithms,^{5,6} it could be helpful when BBs are started in vulnerable patients. Ivabradine has been shown to facilitate up-titration of BBs providing earlier reduction of NYHA classes and improvement of CV outcomes.^{15,16} The data herein support a role of ivabradine to improve outcomes in patients with high-risk profiling parameters and to support BB initiation in these patients.

Limitations

There are limitations of this study worth to be acknowledged. First, this is a post hoc analysis and studied groups were not subject of randomization. Another limitation is the relatively small number of patients with particular high-risk HF limiting statistical power. Nevertheless, it is worth investigating the treatment effect in such patients with high-risk profiling parameters, as they are often not specifically investigated in randomized HF clinical trials. No additional information was available on the lowest heart rate at which the benefit of ivabradine disappears.

Conclusions

Our analysis shows that heart rate reduction with ivabradine in HF patients with low BP, high RHR, low LVEF, and high NYHA class improves clinical outcomes across several risk conditions. With similar relative risk reductions, higher absolute risk reductions and lower number needed to treat have been observed in high-risk HF patients.

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Conflict of interest

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Supporting information

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

Table S1. Baseline characteristics of the patients with high-risk profiling (systolic blood pressure < 110 mmHg, heart rate \geq 75 bpm, left ventricular ejection fraction \leq 25% and New York Heart Association Class III/IV) compared to patients with low-risk profiling (systolic blood pressure \geq 110 mmHg, heart rate < 75 bpm, left ventricular ejection fraction > 25% and New York Heart Association Class II). ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, CHF: chronic heart failure, DBP: diastolic blood pressure, LVEF: left ventricular ejection fraction; NYHA: New York Heart Association, SBP: systolic blood pressure.

Table S2. Baseline characteristics of the patients with SBP < 110 and \geq 110 mmHg. ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, CHF: chronic heart failure, DBP: diastolic blood pressure, LVEF: left ventricular ejection fraction; NYHA: New York Heart Association, SBP: systolic blood pressure.

Table S3. Baseline characteristics of the patients with HRa < 75 and \geq 75 bpm. ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, CHF: chronic heart failure, DBP: diastolic blood pressure, HRa: heart rate, LVEF: left ventricular ejection fraction; NYHA: New York Heart Association, SBP: systolic blood pressure.

Table S4. Baseline characteristics of the patients with LVEF \leq 25 and $>$ 25%. ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, CHF: chronic heart failure, DBP: diastolic blood pressure, LVEF: left ventricular ejection fraction; NYHA: New York Heart Association, SBP: systolic blood pressure.

Table S5. Baseline characteristics of the patients with NYHA class II and III, IV. ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, CHF: chronic heart failure, DBP: diastolic blood pressure, LVEF: left ventricular ejection fraction; NYHA: New York Heart Association, SBP: systolic

Figure S1 A–C. Incidence of cardiovascular death, hospitalization for worsening HF, and hospitalization for worsening heart failure, in patients with high-risk profiling defined as: systolic blood pressure < 110 mmHg and heart rate \geq 75 bpm and left ventricular ejection fraction \leq 25% and New York Heart Association Class III/IV, compared to low-risk profiling defined as: systolic blood pressure \geq 110 mmHg or heart rate < 75 bpm or left ventricular ejection fraction > 25% or New York Heart Association Class II, displayed as time-to-first event.

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