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ORIGINAL PAPER

# Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study

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**Abstract**
*Background* We analysed the effect of ivabradine on outcomes in heart failure (HF) patients on recommended background therapies with heart rates ≥75 bpm and <75 bpm in the SHIFT trial. A cut-off value of ≥75 bpm was chosen by the EMEA for approval for the use of ivabradine in chronic heart failure.
*Methods* The SHIFT population was divided by baseline heart rate ≥75 or <75 bpm. The effect of ivabradine was analysed for primary composite endpoint (cardiovascular death or HF hospitalization) and other endpoints.
*Results* In the ≥75 bpm group, ivabradine reduced primary endpoint (HR 0.76, 95 % CI 0.68–0.85, $P < 0.0001$), all-cause mortality (HR 0.83, 95 % CI, 0.72–0.96, $P = 0.0109$), cardiovascular mortality (HR 0.83, 95 % CI, (0.71–0.97, $P = 0.0166$), HF death (HR 0.61, 95 % CI, 0.46–0.81, $P < 0.0006$), and HF hospitalization (HR 0.70, 95 % CI, 0.61–0.80, $P < 0.0001$). Risk reduction depended on heart rate after 28 days, with the best protection for heart rates <60 bpm or reductions >10 bpm. None of the endpoints was significantly reduced in the <75 bpm group, though there were trends for risk reductions in HF death and hospitalization for heart rate <60 bpm and reductions >10 bpm. Ivabradine was tolerated similarly in both groups.
*Conclusion* The effect of ivabradine on outcomes is greater in patients with heart rate ≥75 bpm with heart rates achieved <60 bpm or heart rate reductions >10 bpm predicting best risk reduction. Our findings emphasize the importance of identification of high-risk HF patients by high heart rates and their treatment with heart rate-lowering drugs such as ivabradine.

**Keywords** Heart failure · Heart rate · Cardiovascular outcomes · Systolic dysfunction · Ivabradine

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## Introduction

High resting heart rate is a well-validated risk marker in cardiovascular diseases [1] including hypertension [2], arteriosclerosis [3], myocardial infarction [4] and heart failure (HF) [5, 6]. In SHIFT (Systolic heart failure treatment with the $I_f$ inhibitor ivabradine trial) [5, 6], heart rate reduction with the $I_f$ inhibitor ivabradine significantly reduced major cardiovascular outcomes in HF patients in sinus rhythm with heart rate ≥70 bpm [6]. Thus, heart rate is not only a risk marker but also a modifiable risk factor in HF. A detailed analysis of heart rate in SHIFT showed that, beginning from a resting heart rate of 70 bpm, rising 5-bpm heart rate increments progressively increased risk for cardiovascular death or HF hospital admissions by 16 % [5]. However, while risk for HF hospital admissions (one component of the primary composite endpoint) clearly increased from 70 bpm upward, the threshold for a progressive increase in cardiovascular death was approximately 75 bpm. Accordingly, analyses of prespecified subgroups of SHIFT showed greater treatment effects in patients with heart rate above the median compared with those with lower heart rates [5]. Based in part on this observation, the European Medicines Agency recently approved ivabradine for treatment of patients with HF and systolic dysfunction receiving guidelines-based recommended background therapy, including beta-blockers or when beta-blockers are contraindicated or poorly tolerated, provided resting heart rate ≥75 bpm. Because no data are available in this group of heart failure patients in whom the drug is labelled now, we decided to perform an in-depth analysis on outcomes in patients at heart rates ≥75 bpm.

In the whole SHIFT population, patients who achieved heart rates <60 bpm with ivabradine had the lowest risk [5]. These findings suggest that, in addition to baseline heart rate, the impact of which is different for individual outcomes, the heart rate achieved after uptitration of ivabradine also determines outcomes. As the treatment effects were greater in patients with higher baseline heart rates [5, 6], we performed a detailed secondary analysis of the SHIFT study to determine the benefits in the patients with baseline heart rates ≥75 bpm compared to those <75 bpm. We also analysed the effect of heart rate achieved and heart rate reduction in these patient groups. Data from the Euro Heart Survey indicate that a substantial proportion of patients with systolic HF have a heart rate close to this value [7].

## Methods

### Study design and patients

The design [8] and the primary results [5, 6] of the SHIFT study were described previously. SHIFT was a randomised double-blind, placebo-controlled, parallel-group clinical trial in patients with moderate to severe HF and systolic dysfunction with left ventricular ejection fraction (LVEF) ≤35 % in sinus rhythm with heart rates ≥70 bpm measured by 12-lead electrocardiograms at two consecutive visits before randomisation. All patients were receiving guideline-recommended background treatments. Patients were randomly assigned to treatment with ivabradine or placebo. The starting dose was 5 mg ivabradine twice daily. Study drug was uptitrated over 28 days to a target dose of 7.5 mg twice daily (or matching placebo) unless the resting heart rate was ≤60 bpm or there were signs and symptoms of bradycardia. The investigators were encouraged to maintain patients as close as possible to guidelines-based target doses of beta-blockers.

We explored outcomes in patients with heart rates ≥75 and <75 bpm. The median follow-up was 22.5 months in the population ≥75 bpm and 23.4 months in the subgroup <75 bpm. We also assessed the effects of heart rate achieved and the effect of the reduction of heart rate. The outcomes analysed were the primary endpoint (the composite of cardiovascular death or hospital admission for worsening HF), as well as other secondary endpoints (all-cause mortality, cardiovascular mortality, death from HF, all-cause hospital admission, HF hospital admission, and cardiovascular hospital admission).

### Statistical analysis

Patients were categorised into two groups according to baseline resting heart rate ≥75 and <75 bpm. Baseline characteristics were compared between ivabradine and placebo in these two groups using mean ± SD for continuous variables and numbers (percentages) for categorical variables. The effects of ivabradine versus placebo on outcomes were provided in the ≥75 and <75 bpm groups using a Cox's proportional hazards model including treatment as a factor and adjusted for baseline beta-blocker intake. Hazard ratios (HR) and 95 % confidence intervals (CI) were estimated, and *P* values calculated from the Wald statistic. A Cox's proportional hazards model adjusted for prognostic factors at baseline (beta-blocker intake, heart rate, New York Heart Association [NYHA] class, LVEF, ischaemic cause of HF, age, systolic blood pressure, and creatinine clearance) was also performed and confirmed the trends observed with the other model. Time-to-event curves by treatment group were estimated using the Kaplan–Meier method. The number of patients needed to be treated (NNT) for 1 year in order to prevent one event was calculated as the inverse of the between-treatment group difference of the estimated probability of having an event at 1 year in the Kaplan–Meier curves.

Outcomes after day 28 were analysed separately in the ≥75 and <75 bpm groups in relation to heart rate achieved

and magnitude of heart rate reduction at 28 days, excluding patients with an event prior to that time. Heart rate achieved after day 28 was evaluated in ranges of 5 bpm (five classes from ≥75 to <60 bpm) and magnitude of heart rate reduction at 28 days in ranges of 10 bpm decrements (three classes, no change or increase, reduction less than 10 bpm and reduction above 10 bpm). The percentages of patients were calculated for ivabradine and placebo according to the two ranges defined previously. For the ivabradine group, time-to-event curves are presented on the primary composite endpoint for each range. For heart rate achieved, the HR with the associated 95 % CI and *P* values were calculated versus patients with heart rate ≥75 bpm at 28 days using the previous Cox model; for magnitude of reduction in heart rate, the same analysis was done versus patients with no change or an increase in heart rate at 28 days (≥0 bpm). Finally, annual incidence rates of the primary composite endpoint were determined in the ivabradine group according to both heart rate achieved at day 28 (three classes, <60 bpm, 60 to <70 bpm, and ≥70 bpm) and magnitude of heart rate reduction (three classes: ≤5 bpm; >5 and <15 bpm; ≥15 bpm).

**Table 1** Baseline characteristics according to baseline heart rate (<75 and ≥75 bpm)

| | Heart rate ≥75 bpm ($n$ = 4,150) | | Heart rate <75 bpm($n$ = 2,351) | |
|---|---|---|---|---|
| | Ivabradine ($n$ = 2,052) | Placebo ($n$ = 2,098) | Ivabradine ($n$ = 1,188) | Placebo ($n$ = 1,163) |
| *Demographic characteristics* | | | | |
| Age (years) | 59.7 ± 11.2 | 59.5 ± 11.7 | 62.5 ± 11.0 | 61.1 ± 11.1 |
| Sex (male) | 1,570 (77 %) | 1,617 (77 %) | 891 (75 %) | 889 (76 %) |
| Current smoker | 381 (19 %) | 402 (19 %) | 160 (13 %) | 175 (15 %) |
| Body mass index (kg/m$^2$) | 28.1 ± 5.3 | 27.9 ± 5.1 | 27.9 ± 4.7 | 28.1 ± 4.8 |
| *Cardiac parameters* | | | | |
| Heart rate (bpm) | 84.3 ± 9.1 | 84.6 ± 9.4 | 71.8 ± 1.6 | 71.9 ± 1.4 |
| SBP (mm Hg) | 121.6 ± 16.7 | 121.2 ± 16.1 | 122.6 ± 14.9 | 121.8 ± 15.4 |
| DBP (mm Hg) | 75.8 ± 9.9 | 75.7 ± 9.5 | 75.6 ± 9.1 | 75.4 ± 9.2 |
| LVEF ( %) | 28.7 ± 5.2 | 28.5 ± 5.3 | 29.7 ± 5.0 | 29.7 ± 4.9 |
| Creatinine clearance (mL/min/1.73 m$^2$) | 75.7 ± 23.5 | 75.5 ± 23.1 | 72.6 ± 21.7 | 73.8 ± 23.0 |
| *NYHA class* | | | | |
| Class II | 977 (48 %) | 975 (46 %) | 608 (51 %) | 609 (52 %) |
| Class III | 1,035 (50 %) | 1,076 (51 %) | 569 (48 %) | 539 (46 %) |
| Class IV | 40 (2 %) | 47(2 %) | 10(1 %) | 14(1 %) |
| *Medical history* | | | | |
| Duration of heart failure (years) | 3.46 ± 4.13 | 3.38 ± 4.00 | 3.61 ± 4.42 | 3.63 ± 4.41 |
| Ischaemic cause of heart failure | 1,359 (66 %) | 1,363 (65 %) | 856 (72 %) | 838 (72 %) |
| Myocardial infarction | 1,124 (55 %) | 1,138 (54 %) | 705 (59 %) | 698 (60 %) |
| Hypertension | 1,333 (65 %) | 1,349 (64 %) | 828 (70 %) | 800 (69 %) |
| Diabetes | 638 (31 %) | 665 (32 %) | 335 (28 %) | 339 (29 %) |
| Previous stroke | 141 (7 %) | 189 (9 %) | 87 (7 %) | 104 (9 %) |
| Atrial fibrillation and/or flutter | 154 (8 %) | 162 (8 %) | 108 (9 %) | 94 (8 %) |
| Renal failure | 122 (6 %) | 121 (6 %) | 96 (8 %) | 79 (7 %) |
| *Treatment at randomisation* | | | | |
| Beta-blockers | 1,794 (87 %) | 1,845 (88 %) | 1,102 (93 %) | 1,075 (92 %) |
| At least half target dose | 974 (55 %) | 1,012 (56 %) | 607 (57 %) | 585 (56 %) |
| At target dose | 467 (26 %) | 471 (26 %) | 276 (26 %) | 274 (26 %) |
| ACE inhibitor and/or ARB | 1,852 (90 %) | 1,896 (90 %) | 1,110 (93 %) | 1,061 (91 %) |
| Diuretics | 1,743 (85 %) | 1,741 (83 %) | 975 (82 %) | 951 (82 %) |
| Aldosterone antagonists | 1,286 (63 %) | 1,271 (61 %) | 694 (58 %) | 667 (57 %) |
| Digitalis | 478 (23 %) | 512 (24 %) | 227 (19 %) | 197 (17 %) |
| At least one device | 66 (3 %) | 94 (4 %) | 44 (4 %) | 39 (3 %) |

Data are numbers of patients (%) or mean ± SD

*bpm* Beats per minute, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *ACE* angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker

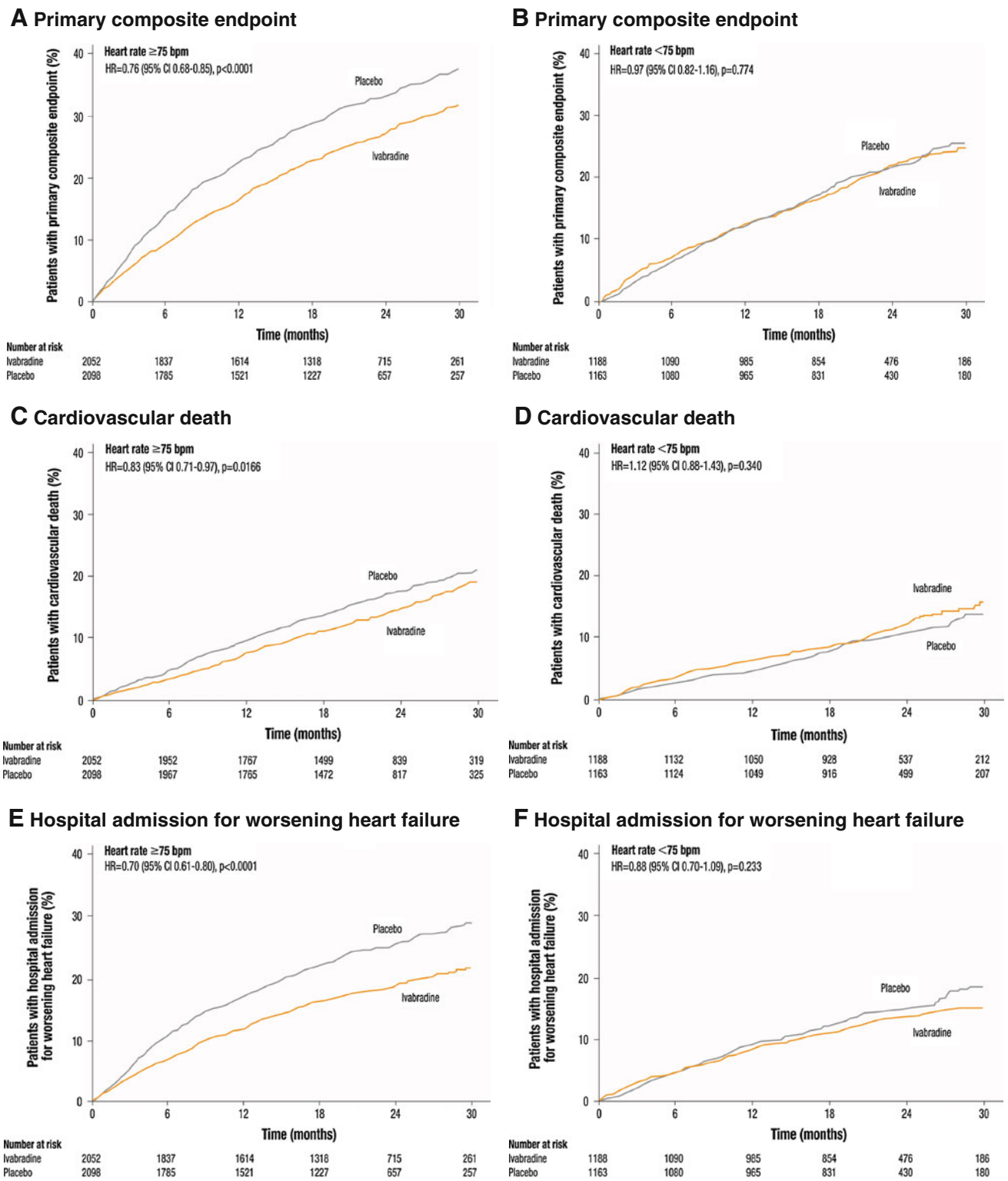


**Fig. 1** Kaplan–Meier cumulative event curves on ivabradine or placebo for the primary composite endpoint (**a**, **b**), cardiovascular death (**c**, **d**) and hospital admission for worsening of heart failure (**e**, **f**) in the ≥75 bpm (*left*) or <75 bpm (*right*) groups. HRs 95 % CIs and *p* values from the Cox's proportional hazards model adjusted for baseline beta-blocker intake are associated with the difference between the Kaplan Meier curves

**Table 2** Effect of ivabradine on outcomes in patients with heart rate ≥75 bpm ($n = 4,150$) and <75 bpm ($n = 2,351$)

| | Heart rate at baseline ≥75 bpm | | | | Heart rate at baseline <75 bpm | | | |
|---|---|---|---|---|---|---|---|---|
| | Ivabradine ($N = 2,052$) | Placebo ($N = 2,098$) | Hazard ratio (95 % CI) | *P* value | Ivabradine ($N = 1,188$) | Placebo ($N = 1,163$) | Hazard ratio (95 % CI) | *P* value |
| *Primary composite endpoint* | | | | | | | | |
| Cardiovascular death or hospital *admission for worsening heart failure* | 545 (27 %) | 688 (33 %) | 0.76 (0.68–0.85) | <0.0001 | 248 (21 %) | 249 (21 %) | 0.97 (0. 82–1.16) | 0.774 |
| *Mortality endpoints* | | | | | | | | |
| All-cause mortality | 340 (17 %) | 407 (19 %) | 0.83 (0.72–0.96) | 0.0109 | 163 (14 %) | 145 (13 %) | 1.11 (0.88–1.38) | 0.382 |
| Cardiovascular mortality | 304 (15 %) | 364 (17 %) | 0.83 (0.71–0.97) | 0.0166 | 145 (12 %) | 127 (11 %) | 1.12 (0.88–1.43) | 0.340 |
| Death from heart failure | 78 (4 %) | 126 (6 %) | 0.61 (0.46–0.81) | 0.0006 | 35 (3 %) | 25 (2 %) | 1.39 (0.83–2.32) | 0.211 |
| *Other endpoints* | | | | | | | | |
| Hospital admission for worsening heart | 363 (18 %) | 503 (24 %) | 0.70 (0.61–0.80) | <0.0001 | 151 (13 %) | 169 (15 %) | 0.88 (0.70–1.09) | 0.233 |
| *Failure* | | | | | | | | |
| All-cause hospital admission | 796 (39 %) | 932 (44 %) | 0.82 (0.75–0.90) | <0.0001 | 435 (37 %) | 423 (36 %) | 1.04 (0.91–1.19) | 0.560 |
| Any cardiovascular hospital admission | 640 (31 %) | 779 (37 %) | 0.79 (0.71–0.88) | <0.0001 | 337 (28 %) | 342 (29 %) | 0.98 (0.84–1.14) | 0.764 |

Hazard ratios between-treatment groups (ivabradine/placebo) based on an adjusted Cox's proportional hazards model with baseline beta-blocker intake as covariate. *P* value from the same model (Wald test). Data are number of first events (%), hazard ratio (HR 95 % CI), and *p* values

All survival analyses were based on endpoints adjudicated by an independent committee blinded to treatment allocation, and were conducted as time-to-first event using the intention-to-treat principle. Crude incidence rates of serious emergent adverse events, emergent adverse events leading to study drug withdrawal, and selected emergent adverse events on treatment were tabulated for ivabradine and placebo in the ≥75 and <75 bpm groups. SAS version 9.1 was used for all analyses.

Role of the funding source

The sponsor was responsible for data management and final data analyses. The SHIFT executive committee was responsible for the study design, the interpretation of the results, the development and writing of the report, and the decision to submit for publication and had full access to all data. Members of the medical and scientific departments of the sponsor supported the work of the executive committee, but did not make any scientific or research decisions independent of this committee.

## Results

Table 1 shows the baseline demographic and clinical characteristics of patients treated with ivabradine or placebo in the <75 bpm ($n = 2,351$) and ≥75 bpm ($n = 4,150$) groups. Patients in the ≥75 bpm group were younger and were more likely to be current smokers with lower LVEF and higher NYHA class; they were also more likely to have non-ischaemic cause of HF. Although fewer patients in the ≥75 bpm group were receiving beta-blockers, a similar proportion in both groups received the target beta-blocker dose or at least half the target dose. The rate of use of digitalis treatment was significantly higher in patients with HR ≥75 bpm than in patients with HR <75 bpm (23.9 vs. 18.0 %; $p < 0.0001$). Beyond that there was no difference between ivabradine- and placebo-treated patients in the two heart rate groups. At 28 days, heart rate in patients receiving ivabradine had fallen by 17.5 ± 11.5 bpm in the ≥75 bpm group (vs. 5.7 ± 11.3 bpm with placebo), and by 12.0 ± 8.1 bpm in the <75 bpm group (vs. 2.7 ± 9.0 bpm with placebo).

The effects of ivabradine on primary composite outcome and its components in the ≥75 and <75 bpm groups are shown in Fig. 1 and Table 2. In the ≥75 bpm group, ivabradine induced a 24 % reduction in primary outcome versus placebo (HR 0.76, 95 % CI, 0.68–0.85, $P < 0.0001$) versus no apparent difference in the <75 bpm group (HR 0.97, 95 % CI, 0.82–1.16, $P = 0.774$). There was also a significant reduction in cardiovascular death when patients in the ≥75 bpm group were treated with ivabradine (HR, 0.83, 95 % CI, 0.71–0.97, $P = 0.0166$); the effect in the

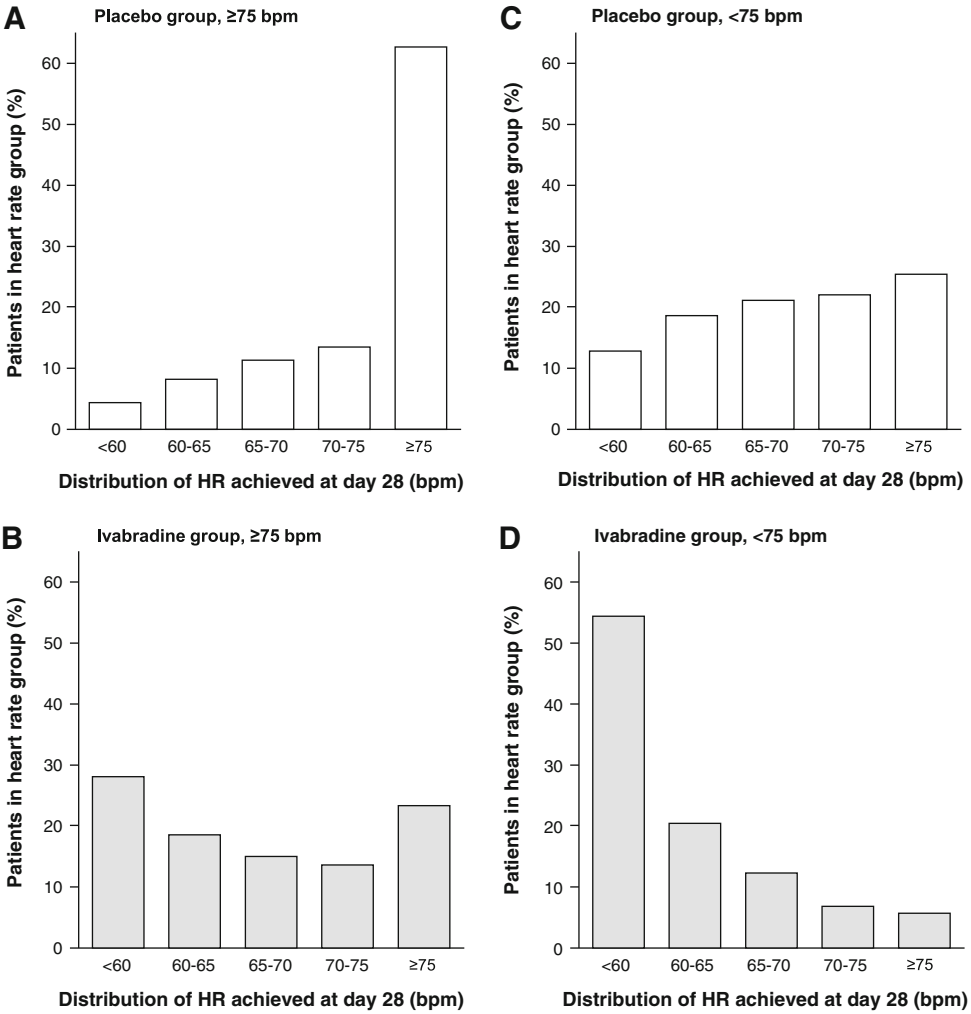


**Fig. 2** Distribution of patients in the ≥75 bpm (*left*) or <75 bpm (*right*) groups on placebo (**a, c**) or ivabradine (**b, d**) by heart rate achieved at 28 days after uptitration

<75 bpm group was not statistically significant ($P = 0.340$). Hospital admissions for HF were decreased by 30 % in ivabradine-treated patients in the ≥75 bpm group (HR, 0.70, 95 % CI, 0.61–0.80), $P<0.0001$); a similar tendency in the <75 bpm group did not reach statistical significance ($P = 0.233$).

As regards the other outcomes (Table 2), treatment with ivabradine in the ≥75 bpm group was associated with 17 % reductions in cardiovascular and all-cause mortality ($P = 0.0166$ and $P = 0.0109$, respectively) and a 39 % reduction in death from HF ($P = 0.0006$). All-cause hospital admissions were reduced by 18 % ($P < 0.0001$) and any cardiovascular hospital admissions by 21 % ($P < 0.0001$). The effects of ivabradine on these outcomes in the <75 bpm group did not reach statistical significance. These results imply that 17 patients with resting heart rate ≥75 bpm would have to be treated with ivabradine for 1 year to prevent 1 primary outcome, 19 for hospital admission for worsening HF, 52 for cardiovascular mortality, and 51 for all-cause mortality.

Figure 2 presents the distribution of patients according to the five classes of heart rate achieved after 28 days of ivabradine or placebo. In the ≥75 bpm group, the majority of patients on placebo remained at higher heart rates at 28 days, while there was a significant shift towards lower heart rate classes with ivabradine with more patients achieving heart rates <60 bpm. Although there was a similar trend in the <75 bpm group, it is noteworthy that about 25 % of the patients in that placebo group had a heart rate increase to values ≥75 bpm by 28 days. After treatment with ivabradine, 55 % had achieved heart rates <60 bpm.

Kaplan–Meier analyses of the primary outcome according to heart rate achieved at 28 days in ivabradine-treated patients in the ≥75 and <75 bpm groups are presented in Fig. 3. Incidence of outcomes progressively decreased as heart rate at 28 days fell among patients in the ≥75 bpm group. The relationship was less clear for those in the <75 bpm group due to the generally lower incidence of outcomes than in the ≥75 bpm group.

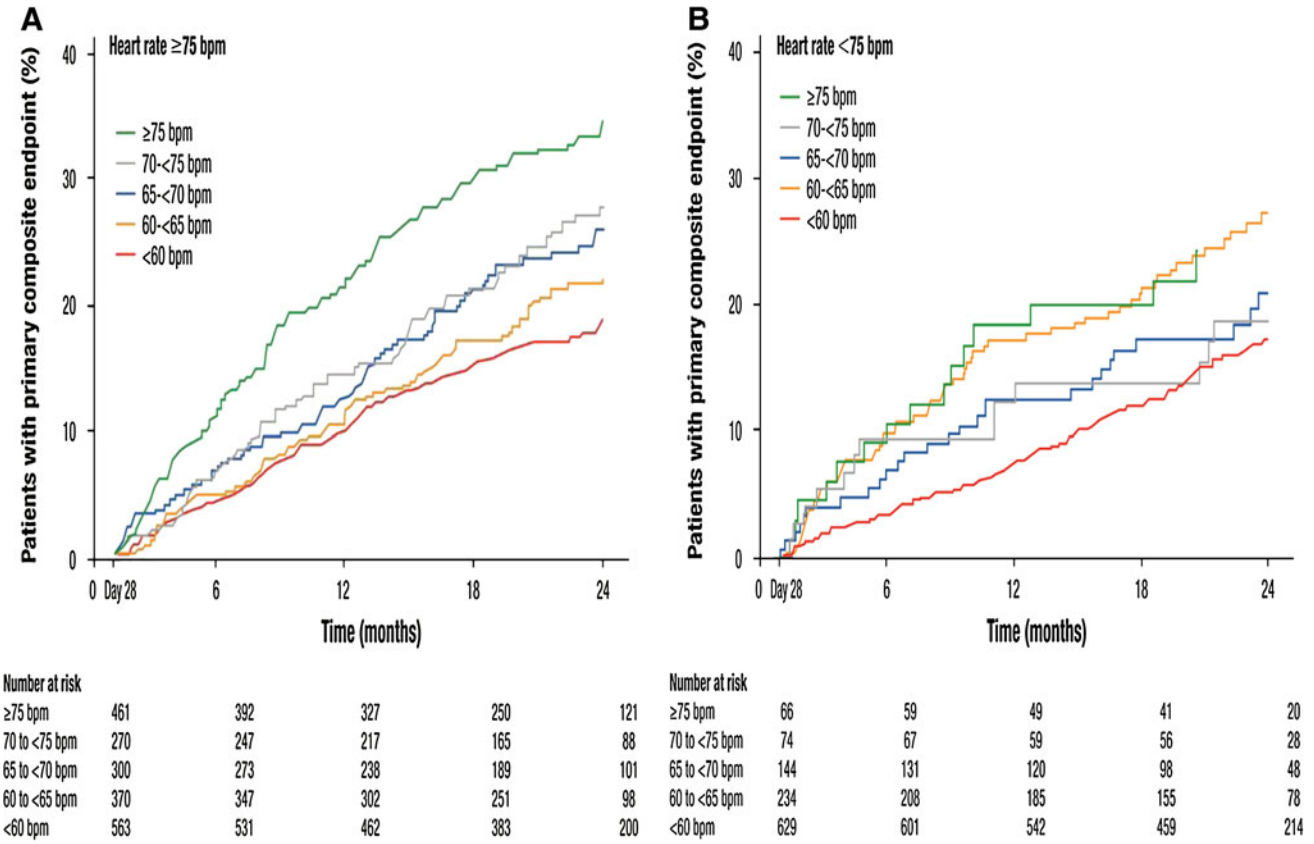


**Fig. 3** Kaplan Meier cumulative event curves for patients on ivabradine in the ≥75 bpm (**a**) or <75 bpm (**b**) groups for the primary composite endpoint events occurring after 28 days arranged according to heart rate achieved at 28 days after uptitration. Patients reaching primary composite endpoint during the first 28 days of follow-up were excluded

The magnitude of the ivabradine-associated reduction in primary outcome, cardiovascular mortality, hospital admission for HF, and death from HF in the ≥75 bpm group was directly related to heart rate achieved (Table 3). Thus, for example, patients who had achieved a heart rate of <60 bpm at 28 days had a 52 % reduction in risk for primary endpoint compared with those who remained at ≥75 bpm at 28 days ($P < 0.0001$). On the other hand, in the <75 bpm group, the trend was less clear and there were non-significant risk reductions for most endpoints for lower heart rates achieved. However, there was a significant reduction in risk for hospital admission for worsening HF and death from HF in patients who achieved heart rates <60 bpm at 28 days compared with those at ≥75 bpm at 28 days, despite a relatively low heart rate at baseline (<75 bpm).

Figure 4 presents the distribution of patients according to change in heart rate at 28 days. While the placebo group remained evenly distributed between the three classes (no change or increase, reduction <10 bpm, or reduction ≥10 bpm), 76 and 63 % of patients on ivabradine in the ≥75 and <75 bpm groups had reductions of more than 10 bpm.

The magnitude of risk reduction was directly related to the magnitude of heart rate reduction whatever the baseline heart rate group was. The reduction in the risk for primary outcome was related to the magnitude of heart rate reduction at day 28 in the ≥75 bpm group (Fig. 5a; Table 4). A less marked but non-significant trend was seen in the <75 bpm group (Fig. 5b; Table 4). In the ≥75 bpm group, there were 37 % risk reductions for the primary endpoint (HR 0.63, 95 % CI, 0.46–0.85, $P = 0.0026$) and cardiovascular mortality (HR 0.63, 95 % CI, 0.42–0.92, $P = 0.0018$) in patients with heart rate reduction greater than 10 bpm compared with patients with no change or increase in heart rate at day 28; there was also a 44 % reduction in risk for hospital admission for HF ($P = 0.0016$) and a 53 % reduction in risk for death from HF ($P = 0.0285$). In the <75 bpm group, no significant changes were observed for the primary endpoint and cardiovascular death, while hospital admissions for worsening HF were reduced by 56 % ($P = 0.0011$) and death from HF by 61 % ($P = 0.0516$).

Figure 6 summarizes the relationship between incidence of primary outcome and both heart rate achieved and reduction in heart rate with ivabradine at day 28 in the ≥75 bpm group. The greatest benefit was observed in patients with a reduction in heart rate greater than 15 bpm and who

**Table 3** Primary and major secondary endpoints in the ivabradine group according to heart rate achieved at 28 days (≥75 bpm, 70 to <75 bpm, 65 to <70 bpm, 60 to <65 bpm, or <60 bpm)

| | Heart rate at baseline ≥75 bpm | | | Heart rate at baseline <75 bpm | | |
|---|---|---|---|---|---|---|
| | Event rate, *n* (%) | Hazard ratio (95 % CI) | *P* value | Event rate, *n* (%) | Hazard ratio (95 % CI) | *P* value |
| *Primary composite endpoint* | | | | | | |
| ≥75 bpm | 156 (34 %) | 1.00 | | 15 (23 %) | 1.00 | |
| 70 to <75 bpm | 73 (27 %) | 0.73 (0.55–0.96) | 0.0241 | 18 (24 %) | 1.05 (0.53–2.09) | 0.883 |
| 65 to <70 bpm | 74 (25 %) | 0.66 (0.50–0.87) | 0.0028 | 28 (19 %) | 0.87 (0.46–1.63) | 0.655 |
| 60 to <65 bpm | 82 (22 %) | 0.59 (0.45–0.77) | 0.0001 | 62 (27 %) | 1.18 (0.67–2.07) | 0.572 |
| <60 bpm | 106 (19 %) | 0.48 (0.38–0.62) | <0.0001 | 101 (16 %) | 0.69 (0.40–1.18) | 0.173 |
| *Cardiovascular mortality* | | | | | | |
| ≥75 bpm | 90 (19 %) | 1.00 | | 7 (10 %) | 1.00 | |
| 70 to <75 bpm | 37 (14 %) | 0.65 (0.45–0.96) | 0.0302 | 9 (12 %) | 1.11 (0.41–2.98) | 0.843 |
| 65 to <70 bpm | 42 (14 %) | 0.67 (0.47–0.97) | 0.0345 | 16 (11 %) | 1.13 (0.46–2.75) | 0.791 |
| 60 to <65 bpm | 42 (11 %) | 0.56 (0.39–0.81) | 0.0022 | 34 (14 %) | 1.43 (0.63–3.23) | 0.390 |
| <60 bpm | 72 (13 %) | 0.61 (0.45–0.84) | 0.0020 | 71 (11 %) | 1.14 (0.52–2.49) | 0.740 |
| *Hospital admission for heart failure* | | | | | | |
| ≥75 bpm | 109 (24 %) | 1.00 | | 13 (20 %) | 1.00 | |
| 70 to <75 bpm | 53 (20 %) | 0.76 (0.55–1.05) | 0.0976 | 13 (18 %) | 0.86 (0.40–1.86) | 0.698 |
| 65 to <70 bpm | 45 (15 %) | 0.57 (0.41–0.81) | 0.0018 | 19 (13 %) | 0.66 (0.32–1.33) | 0.242 |
| 60 to <65 bpm | 57 (15 %) | 0.59 (0.43–0.81) | 0.0012 | 41 (18 %) | 0.88 (0.47–1.65) | 0.690 |
| <60 bpm | 61 (11 %) | 0.40 (0.29–0.55) | <0.0001 | 46 (7 %) | 0.35 (0.19–0.65) | 0.0009 |
| *Death from heart failure* | | | | | | |
| ≥75 bpm | 27 (6 %) | 1.00 | | 4 (6 %) | 1.00 | |
| 70 to <75 bpm | 13 (5 %) | 0.79 (0.41–1.54) | 0.495 | 3 (4 %) | 0.65 (0.15–2.94) | 0.578 |
| 65 to <70 bpm | 9 (3 %) | 0.50 (0.23–1.05) | 0.0679 | 6 (4 %) | 0.73 (0.21–2.61) | 0.630 |
| 60 to <65 bpm | 12 (3 %) | 0.57 (0.29–1.12) | 0.102 | 8 (3 %) | 0.59 (0.18–1.98) | 0.395 |
| <60 bpm | 13 (2 %) | 0.39 (0.20–0.76) | 0.0056 | 11 (2 %) | 0.31 (0.10–0.99) | 0.0474 |

Hazard ratios comparing classes of heart rate achieved versus heart rate achieved ≥75 bpm, based on an adjusted Cox's proportional hazards model with baseline beta-blocker intake as covariate. *P* value from the same model (Wald test). Data are number of first events (%), hazard ratio (HR, 95 % CI), with the HR for heart rate achieved ≥75 bpm fixed at unity, and *P* values versus heart rate achieved ≥75 bpm

achieved heart rates below 60 bpm. Patients whose heart rate remained at 70 bpm or higher with a small decrease (or an increase) in heart rate on ivabradine after uptitration had the higher incidence of outcomes.

There was no difference in the rate of adverse effects of ivabradine in the ≥75 and <75 bpm groups (Table 5). There was a higher prevalence of symptomatic bradycardia on ivabradine versus placebo, but there was no difference between the ≥75 and <75 bpm groups.

## Discussion

The results of this secondary analysis of the SHIFT database show that, in patients with HF in sinus rhythm with baseline heart rates ≥75 bpm in whom the drug was recently approved by the EMEA, ivabradine significantly reduces all prespecified clinical outcomes of SHIFT, including the primary composite of cardiovascular death or hospital admission for HF, and the secondary endpoints of all-cause death, cardiovascular death, and death from HF. In the ≥75 bpm group, the reduction in risk depended on both the heart rate achieved and the magnitude of heart rate reduction at 28 days after uptitration of ivabradine. In the <75 bpm group, the improvement in the SHIFT endpoints was generally not statistically significant. This might be explained by the lower risk for all endpoints in the <75 bpm group (e.g., the annual incidence for the primary endpoint with placebo was 12 vs. 21 % in the ≥75 bpm group) providing less power to demonstrate modification of risk if it occurs. Another likely basis for this observation is the pharmacology of ivabradine (i.e. its use dependence) [9] limiting the potential for heart rate reduction in the group with lower heart rates at baseline. Ivabradine was

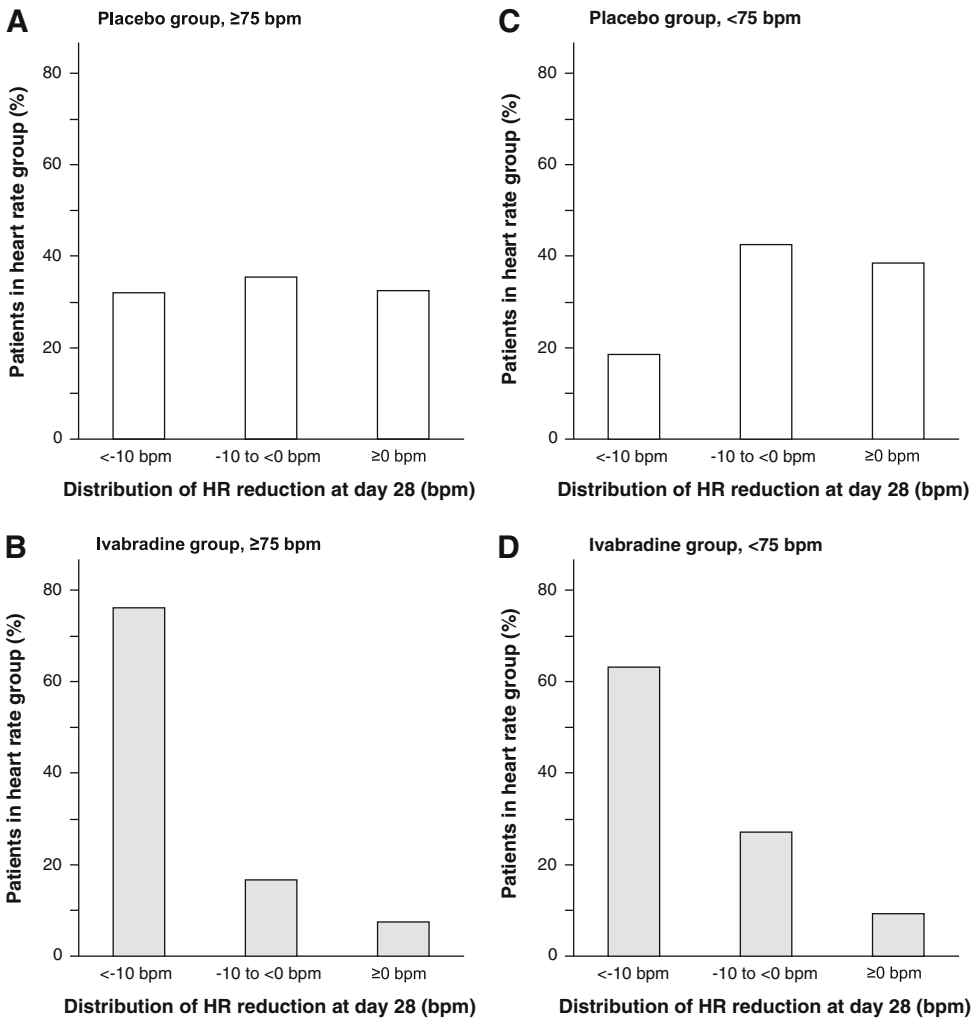


**Fig. 4** Distribution of patients in the ≥75 bpm (*left*) or <75 bpm (*right*) groups on placebo (**a, c**) or ivabradine (**b, d**) by magnitude of heart rate reduction at day 28 after uptitration

well tolerated, regardless of whether the heart rate was ≥75 or <75 bpm at baseline, with similar rates of symptomatic bradycardia and drug withdrawal on ivabradine and placebo.

The results of this analysis are consistent with the primary results of the SHIFT trial [5, 6], which showed a reduction of major cardiovascular events versus placebo when patients in sinus rhythm with heart rate ≥70 bpm received ivabradine in addition to guideline-based background therapy [6]. In the primary analyses of SHIFT, baseline heart rate had a significant impact on the size of the treatment effect of ivabradine [5, 6]. The most likely explanation, supported by the current analysis, is that modifiable risk is enhanced by baseline heart rates with a progressive increase in the primary composite endpoint by 16 % for every 5-bpm increase in baseline heart rate [5]. For the individual components of the cardiovascular endpoint, the risk increase was not linear. Risk increased for cardiovascular death at heart rates >75 bpm, while there was a progressive increase in risk from 70 to ≥87 bpm for hospital admission due to worsening of HF [5]. Ivabradine consistently reduced risk over the whole spectrum of heart rates for HF hospital admission, but only at baseline heart rates >80 bpm for cardiovascular death [5]. These findings indicate that the relationship between risk and baseline heart rate varies among the different endpoints. In the current analysis, we have verified that treatment with ivabradine modifies the risk for HF-related outcomes, cardiovascular death, and all-cause death in patients with heart rates ≥75 bpm. The benefits are primarily observed in this population, while the reduction of endpoints in patients with heart rate <75 bpm at baseline were either generally not apparent or not statistically significant.

In the present analysis, we have extended previous findings by investigating the magnitude of heart rate reduction after uptitration of ivabradine, in addition to the heart rates achieved, in patients with now EMEA approved indication of ivabradine at baseline heart rate ≥75 bpm and, separately, in those with baseline heart rate <75 bpm, and have related these changes to variation in cardiovascular outcomes. Our results indicate that risk reduction in the HF population of SHIFT results primarily from the

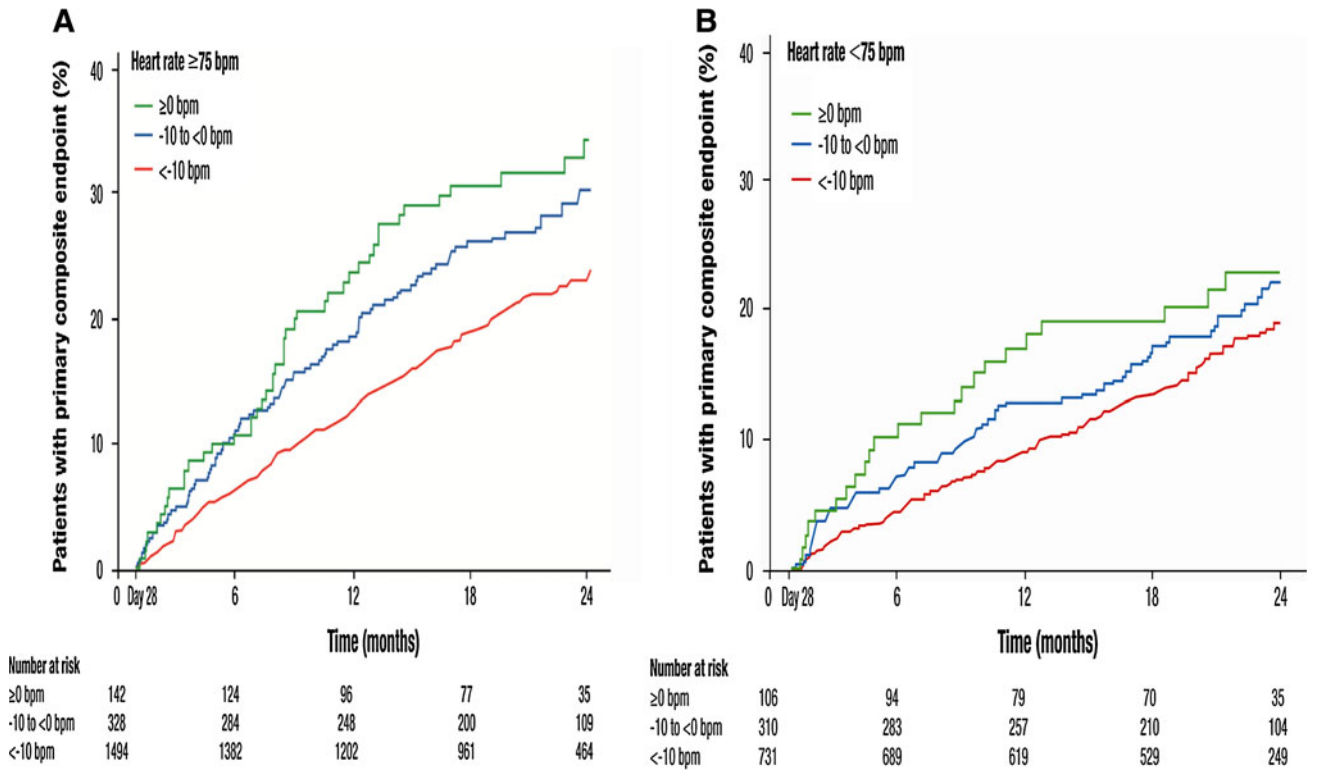


**Fig. 5** Kaplan Meier cumulative event curves for patients on ivabradine in the ≥75 bpm (*left*) or <75 bpm (*right*) groups for the primary composite endpoint occurring after 28 days arranged by magnitude of heart rate reduction at day 28 after uptitration. Patients reaching primary composite endpoint during the first 28 days of follow-up were excluded

effects of the drug in high-risk patients with baseline heart rate ≥75 bpm.

Resting heart rate is a strong predictor of cardiovascular mortality and morbidity in patients with cardiovascular disease [1] and, in particular, chronic HF [5]. The absolute risk is dependent on heart rate [1–5] The progressive risk of increasing heart rate is probably attributable to impaired contractility in the presence of a negative force–frequency relationship [10, 11], energy depletion [12], endothelial dysfunction [13], and impaired energy supply to the heart [14]. The magnitude of these detrimental mechanisms is greater at higher heart rates, which may explain the increase in the effectiveness of heart rate reduction with ivabradine at higher heart rates. In turn, ivabradine has progressively greater heart rate-reducing effect as baseline heart rate rises, due to its use dependency [9]. Consistent with these conclusions, heart rate reduction with ivabradine has been shown to reduce remodelling of the failing heart [15], associated with a reversal of the HF-associated phenotype of the failing myocyte [16, 17].

Importantly, our results indicate that the tolerability of ivabradine is not different between low and high baseline heart rates. Adverse events leading to drug withdrawals on ivabradine were 14 % at baseline heart rates <75 bpm and 15 % at heart rates ≥75 bpm, indicating that, even at lower heart rates, adverse events leading to withdrawals are not significantly enhanced. As in the main analysis, withdrawal rates for symptomatic adverse events were low and not related to baseline heart rates with 2.7 and 3 % at heart rates <75 and ≥75 bpm, respectively.

Our data have limitations and strengths. This post hoc analysis defines subpopulations not considered in the original protocol and so the conclusions must be approached with some caution. Baseline heart rate might be affected by underlying pathophysiology not considered in our categorizing patients, as well as by concomitant treatments, which, in our defined subpopulations, was not based on randomised allocation of the patients. However, the demographic and other baseline differences between the treatment groups were small and analyses adjusted for prognostic factors were performed. A large proportion of patients with systolic HF are considered to have a heart rate close to 75 bpm [7], and so the subpopulation on which our analysis is focused represents a sizable portion of the HF population, and includes patients at particularly high risk for major cardiovascular events. Therefore, our analysis

**Table 4** Primary and major secondary endpoints in the ivabradine group according to heart rate reduction at day 28 (≥0 bpm, –10 to <0 bpm, or <−10 bpm)

| | Heart rate at baseline ≥75 bpm | | | Heart rate at baseline <75 bpm | | |
|---|---|---|---|---|---|---|
| | Event rate, *n* ( %) | Hazard ratio (95 % CI) | *P* value | Event rate, *n* ( %) | Hazard ratio (95 % CI) | *P* value |
| *Primary composite endpoint* | | | | | | |
| >0 bpm | 47 (33 %) | 1.00 | | 25 (24 %) | 1.00 | |
| −10 to <0 bpm | 98 (30 %) | 0.84 (0.59–1.19) | 0.331 | 66 (21 %) | 0.90 (0.57–1.43) | 0.654 |
| <−10 bpm | 346 (23 %) | 0.63 (0.46–0.85) | 0.0026 | 133 (18 %) | 0.75 (0.49–1.15) | 0.180 |
| *Cardiovascular mortality* | | | | | | |
| >0 bpm | 29 (20 %) | 1.00 | | 11 (10 %) | 1.00 | |
| −10 to <0 bpm | 50 (15 %) | 0.69 (0.44–1.10) | 0.118 | 38 (12 %) | 1.24 (0.63–2.42) | 0.535 |
| <−10 bpm | 204 (14 %) | 0.63 (0.42–0.92) | 0.0180 | 88 (12 %) | 1.25 (0.67–2.34) | 0.493 |
| *Hospital admission for heart failure* | | | | | | |
| >0 bpm | 34 (24 %) | 1.00 | | 21 (20 %) | 1.00 | |
| −10 to <0 bpm | 68 (21 %) | 0.81 (0.54–1.22) | 0.319 | 44 (14 %) | 0.70 (0.42–1.18) | 0.180 |
| <−10 bpm | 223 (15 %) | 0.56 (0.39–0.80) | 0.0016 | 67 (9 %) | 0.44 (0.27–0.72) | 0.0011 |
| *Death from heart failure* | | | | | | |
| >0 bpm | 10 (7 %) | 1.00 | | 6 (6 %) | 1.00 | |
| −10 to <0 bpm | 11 (3 %) | 0.45 (0.19–1.06) | 0.0673 | 11 (4 %) | 0.65 (0.24–1.76) | 0.395 |
| <−10 bpm | 53 (4 %) | 0.47 (0.24–0.92) | 0.0285 | 15 (2 %) | 0.39 (0.15–1.01) | 0.0516 |

Hazard ratios comparing classes of heart rate reduction versus no change or increase in heart rate, based on an adjusted Cox's proportional hazards model with baseline beta-blocker intake as covariate. *P* value from the same model (Wald test). Data are number of first events (%), hazard ratio (HR, 95 % CI), with the HR for no change or increase in heart rate fixed at unity, and *P* values versus no change or increase in heart rate

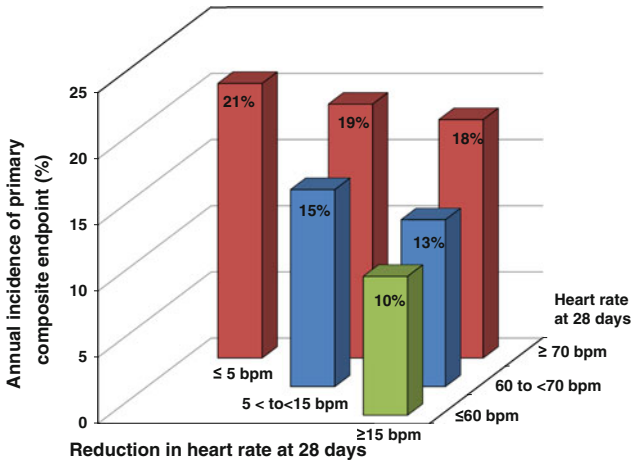


**Fig. 6** Annual incidence rates of the primary composite endpoint for ivabradine in relation to magnitude of heart rate reduction and by heart rate achieved at day 28 after uptitration. Patients reaching primary composite endpoint during the first 28 days of follow-up were excluded

provides potentially useful information for clinicians determining how to manage HF patients, because ivabradine was labelled by the EMEA specifically in this group of patients.

## Conclusion

Heart rate reduction with ivabradine prevents adverse cardiovascular outcomes in patients with HF and high heart rate when administered in addition to guideline-based therapies. This effect is particularly pronounced in patients with sinus rhythm ≥75 bpm. Ivabradine-associated risk reductions are related to both heart rates achieved and magnitude of heart rate reduction; patients achieving <60 bpm or displaying a >10 bpm reduction have the best prognosis. Our findings emphasize the importance of identifying HF patients with high heart rate and adding ivabradine to guidelines-based therapy in these patients to improve outcome.

**Table 5** Safety of ivabradine in patients with resting heart rate ≥75 bpm and <75 bpm

| | Heart rate at baseline ≥75 bpm | | Heart rate at baseline <75 bpm | |
|---|---|---|---|---|
| | Ivabradine ($N = 2,046$) | Placebo ($N = 2,095$) | Ivabradine ($N = 1,185$) | Placebo ($N = 1,162$) |
| All emergent adverse events | 1,554 (76 %) | 1,607 (77 %) | 860 (73 %) | 783 (67 %) |
| All serious emergent adverse events | 892 (44 %) | 1,020 (49 %) | 477 (40 %) | 361 (40 %) |
| All emergent adverse events leading to drug withdrawal | 300 (15 %) | 295 (14 %) | 167 (14 %) | 120 (10 %) |
| *Selected emergent adverse events* | | | | |
| Cardiac failure | 487 (24 %) | 609 (29 %) | 214 (18 %) | 236 (20 %) |
| Symptomatic bradycardia | 84 (4 %) | 14 (1 %) | 64 (5 %) | 14 (1 %) |
| Asymptomatic bradycardia | 98 (5 %) | 25 (1 %) | 83 (7 %) | 20 (2 %) |
| Atrial fibrillation | 161 (8 %) | 143 (7 %) | 106 (9 %) | 73 (6 %) |
| Phosphenes | 57 (3 %) | 11 (<1 %) | 32 (3 %) | 5 (<1 %) |
| Blurred vision | 11 (<1 %) | 7 (<1 %) | 6 (<1 %) | 0 (0 %) |

Patients in the safety analysis had been included and had taken at least one intake of study drug

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