

# Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study



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## Summary

**Background** Chronic heart failure is associated with high mortality and morbidity. Raised resting heart rate is a risk factor for adverse outcomes. We aimed to assess the effect of heart-rate reduction by the selective sinus-node inhibitor ivabradine on outcomes in heart failure.

**Methods** Patients were eligible for participation in this randomised, double-blind, placebo-controlled, parallel-group study if they had symptomatic heart failure and a left-ventricular ejection fraction of 35% or lower, were in sinus rhythm with heart rate 70 beats per min or higher, had been admitted to hospital for heart failure within the previous year, and were on stable background treatment including a  $\beta$  blocker if tolerated. Patients were randomly assigned by computer-generated allocation schedule to ivabradine titrated to a maximum of 7.5 mg twice daily or matching placebo. Patients and investigators were masked to treatment allocation. The primary endpoint was the composite of cardiovascular death or hospital admission for worsening heart failure. Analysis was by intention to treat. This trial is registered, number ISRCTN70429960.

**Findings** 6558 patients were randomly assigned to treatment groups (3268 ivabradine, 3290 placebo). Data were available for analysis for 3241 patients in the ivabradine group and 3264 patients allocated placebo. Median follow-up was 22.9 (IQR 18–28) months. 793 (24%) patients in the ivabradine group and 937 (29%) of those taking placebo had a primary endpoint event (HR 0.82, 95% CI 0.75–0.90,  $p < 0.0001$ ). The effects were driven mainly by hospital admissions for worsening heart failure (672 [21%] placebo vs 514 [16%] ivabradine; HR 0.74, 0.66–0.83;  $p < 0.0001$ ) and deaths due to heart failure (151 [5%] vs 113 [3%]; HR 0.74, 0.58–0.94,  $p = 0.014$ ). Fewer serious adverse events occurred in the ivabradine group (3388 events) than in the placebo group (3847;  $p = 0.025$ ). 150 (5%) of ivabradine patients had symptomatic bradycardia compared with 32 (1%) of the placebo group ( $p < 0.0001$ ). Visual side-effects (phosphenes) were reported by 89 (3%) of patients on ivabradine and 17 (1%) on placebo ( $p < 0.0001$ ).

**Interpretation** Our results support the importance of heart-rate reduction with ivabradine for improvement of clinical outcomes in heart failure and confirm the important role of heart rate in the pathophysiology of this disorder.

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## Introduction

Chronic heart failure is common, disabling, and serious. It affects roughly 2–3% of the population in many industrialised countries.<sup>1</sup> Even with existing treatment, which has substantially improved outcomes in the past two decades,<sup>2,3</sup> prognosis is fairly poor. Development of novel therapeutic approaches for the treatment of this disorder is crucial. Standard pharmacological treatment includes  $\beta$  blockers and renin-angiotensin-aldosterone system (RAAS) antagonists.<sup>1</sup>  $\beta$  blockers have reduced morbidity and mortality beyond what is achieved with RAAS antagonists alone.<sup>4</sup> Additional benefits of these drugs in the management of chronic heart failure include improved left-ventricular remodelling<sup>5</sup> and reduction in sudden deaths.<sup>6</sup> These benefits seem to be linked, at least in part, to their heart-rate-lowering properties.<sup>7,8</sup> Heart-rate reduction could be particularly important in chronic heart failure—eg, by attenuating the effect of energy starvation of the myocardium.<sup>9</sup> However, in addition to their attenuating effect on heart rate,  $\beta$  blockers have other undesired

actions on the heart, including an effect on myocardial contractility.

Raised resting heart rate is a risk factor for mortality and cardiovascular outcomes in epidemiological and observational studies.<sup>10,11</sup> In patients with coronary artery disease and left-ventricular dysfunction, a heart rate of 70 beats per minute (bpm) or higher was associated with a 34% increased risk of cardiovascular death and a 53% increase in admission to hospital for heart failure compared with heart rate lower than 70 bpm.<sup>12</sup> Heart rate is also directly related to risk of death, cardiovascular death, or admission to hospital in patients with heart failure,<sup>13</sup> and heart-rate reduction is associated with improved outcomes.<sup>14</sup> However, heart rate remains increased in most patients treated with  $\beta$  blockers,<sup>15</sup> which constitutes a further reason to seek new therapeutic strategies.

Ivabradine is a specific inhibitor of the  $I_f$  current in the sinoatrial node.<sup>16</sup> Results of studies in healthy hearts suggest that, at concentrations achieved during therapeutic use, ivabradine has no action on other

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channels in the heart or vascular system. Unlike  $\beta$  blockers, ivabradine does not modify myocardial contractility and intracardiac conduction, even in patients with impaired systolic function.<sup>17</sup> We designed the Systolic Heart failure treatment with the  $I_f$  inhibitor ivabradine Trial (SHIFT) with the aim of evaluating the effect of ivabradine in addition to guidelines-based treatment on cardiovascular outcomes, symptoms, and quality of life in patients with chronic heart failure and systolic dysfunction.

## Methods

### Study design and patients

SHIFT was an event-driven, multinational, randomised, double-blind, placebo-controlled, parallel-group clinical trial in patients with moderate-to-severe heart failure and left-ventricular systolic dysfunction. The study was undertaken in 677 centres in 37 countries. Eligible patients were men or women aged 18 years and older who were in sinus rhythm and had a resting heart rate of 70 bpm or higher, as measured on 12-lead electrocardiography (ECG) after at least 5-min rest on two consecutive visits before randomisation, with stable symptomatic chronic heart failure of 4 or more weeks' duration, a previous admission to hospital for worsening heart failure within the previous 12 months, and a left-ventricular ejection fraction of 35% or lower. Any cause of heart failure was allowed apart from congenital heart disease or primary severe valvular disease.

Main exclusion criteria were recent (<2 months) myocardial infarction, ventricular or atrioventricular pacing operative for 40% or more of the day, atrial fibrillation or flutter, and symptomatic hypotension. Other inclusion and exclusion criteria together with design details have been described previously.<sup>18</sup> Patients needed to be on optimum and stable background treatment for at least 4 weeks. Treatments not allowed at inclusion and during the study included non-dihydropyridine calcium-channel blockers, class I anti-arrhythmics, and strong inhibitors of cytochrome P450 3A4.

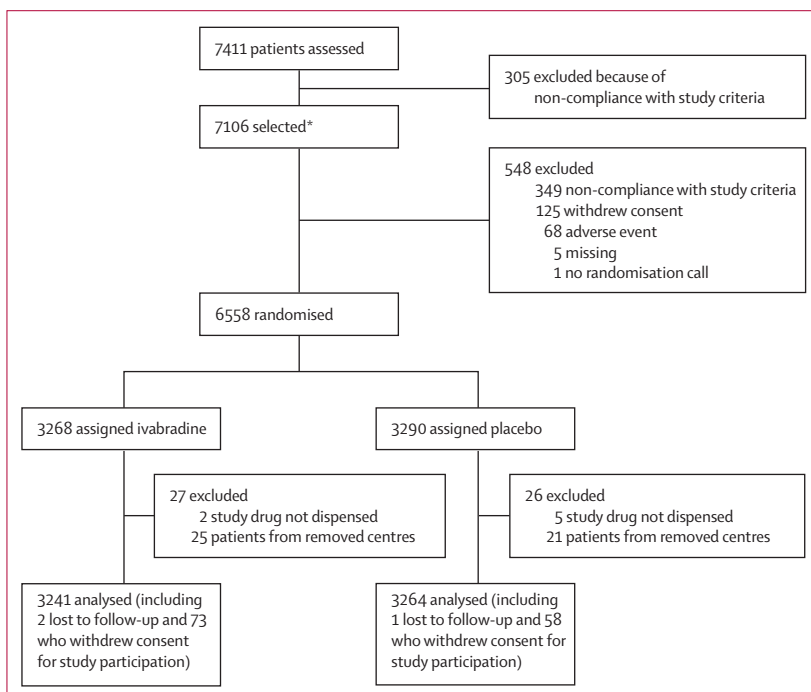
The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the ethics committee or institutional review board of every site. All patients provided written informed consent before randomisation.

### Randomisation and masking

After a run-in of 14 days without study treatment to enable confirmation of inclusion and exclusion criteria, patients were randomly allocated to treatment groups by computer-generated assignment through a telephone interactive voice response system. The allocation sequence was generated at the sponsor level through validated in-house application software; access was restricted to people responsible for study therapeutic units production until database lock. These people had no involvement in the rest of the trial. Eligible patients were allocated to receive ivabradine or placebo in addition to treatments appropriate to their heart failure, with particular emphasis on background treatment with a  $\beta$  blocker. Patients and investigators were masked to treatment allocation. The study drugs (ivabradine or placebo) were identical in appearance. Stratification was done by centre and treatment with or without a  $\beta$  blocker at inclusion. The first patient was randomly assigned on Oct 3, 2006, and the last patient on June 1, 2009. Study closure occurred between Feb 1, and March 31, 2010. The final visit was regarded as the end of the study for every patient.

### Procedures

The starting dose of study drug on day 0 was 5 mg twice daily of ivabradine or matching placebo. After a 14-day titration period, the ivabradine dose was increased to 7.5 mg twice daily (or corresponding placebo), unless the resting heart rate was 60 bpm or lower. If heart rate was between 50 bpm and 60 bpm, the dose was maintained at 5 mg twice daily. If the resting heart rate was lower than 50 bpm or the patient had signs or symptoms related to bradycardia, the dose was reduced to 2.5 mg twice daily. Starting at day 28, visits took place every 4 months until study closure. At each follow-up visit, investigators could maintain the study drug dose, or adjust the dose to the next highest dose, if the resting heart rate was higher than 60 bpm (up to 7.5 mg twice daily). If resting heart rate was lower than 50 bpm or if the patient had signs or



**Figure 1: Trial profile**

\*Selected patients entered the 7–30-day run-in period without study treatment for confirmation of inclusion or exclusion criteria.

symptoms related to bradycardia, investigators could adjust the study drug dose to the next lowest dose, unless patients were on 2.5 mg twice daily, in which case study treatment was stopped.

The primary endpoint was the composite of cardiovascular death or hospital admission for worsening heart failure. The first secondary endpoint was the composite of cardiovascular death or hospital admission for worsening heart failure in patients receiving at least 50% of the target daily dose of a  $\beta$  blocker (as defined by the European Society of Cardiology guidelines) at randomisation.<sup>19</sup> For metoprolol tartrate, for which a dose is not identified in the guidelines, we defined the target dose as 150 mg daily.<sup>20</sup> Other secondary endpoints were all-cause death, any cardiovascular death, hospital admission for worsening heart failure, all-cause admission to hospital, any cardiovascular admission, and death from heart failure, and the composite of cardiovascular death, hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction. All of these outcomes were analysed on a time-to-first-event basis. Changes in functional capacity were assessed by the New York Heart Association (NYHA) classification as well as by patient-reported and physician-reported global assessment.

We classified all deaths as cardiovascular unless an unequivocal non-cardiovascular cause was established. A hospital admission for worsening heart failure was defined as admission with new or increasing symptoms and new or increasing signs of the disorder, including signs of fluid retention or objective evidence of heart failure and a significant change in the treatment to improve heart failure, defined by initiation of intravenous diuretic agents or other intravenous drugs (excluding cardiac glycosides) or mechanical ventilation or mechanical support. A diagnosis of myocardial infarction was based on typical increase of biochemical markers of myocardial necrosis and at least one of ischaemic symptoms, ECG changes, or coronary artery intervention.

An executive committee was responsible for the design and the clinical and scientific conduct of the study. The steering committee was the representative body for the study investigators and consisted of the national study coordinators. An endpoint validation committee, masked to study treatment, reviewed and adjudicated all prespecified events according to definitions included in a charter. An independent data monitoring committee monitored the study safety and had access to unmasked data through an independent statistical centre.

### Statistical analysis

SAS (version 9.1) was used for all analyses. Baseline characteristics are summarised as number of patients (%) for categorical variables and as mean (SD) for continuous variables. All survival analyses were done on a time-to-first-event basis with an intention-to-treat principle. Cox's proportional hazards model including a factor for

	Ivabradine group (n=3241)	Placebo group (n=3264)
<b>Demographic characteristics</b>		
Age (years)	60.7 (11.2)	60.1 (11.5)
Sex (male)	2462 (76%)	2508 (77%)
Ethnic origin		
White	2879 (89%)	2892 (89%)
Asian	268 (8%)	264 (8%)
Other	94 (3%)	108 (3%)
Current smoking	541 (17%)	577 (18%)
BMI (kg/m <sup>2</sup> )	28.0 (5.1)	28.0 (5.0)
<b>Cardiac parameters</b>		
Heart rate (bpm)	79.7 (9.5)	80.1 (9.8)
SBP (mm Hg)	122.0 (16.1)	121.4 (15.9)
DBP (mm Hg)	75.7 (9.6)	75.6 (9.4)
LVEF (%)	29.0% (5.1)	29.0% (5.2)
eGFR (mL/min per 1.73 m <sup>2</sup> )	74.6 (22.9)	74.8 (23.1)
<b>NYHA class</b>		
Class II	1585 (49%)	1584 (49%)
Class III	1605 (50%)	1618 (50%)
Class IV	50 (2%)	61 (2%)
<b>Medical history</b>		
Duration of heart failure (years)	3.5 (4.2)	3.5 (4.2)
Primary cause of heart failure		
Ischaemic	2215 (68%)	2203 (67%)
Non-ischaemic	1026 (32%)	1061 (33%)
Myocardial infarction	1829 (56%)	1837 (56%)
Hypertension	2162 (67%)	2152 (66%)
Diabetes	973 (30%)	1006 (31%)
Previous stroke	228 (7%)	295 (9%)
History of atrial fibrillation or flutter	263 (8%)	259 (8%)
<b>Treatment at randomisation</b>		
$\beta$ blocker	2897 (89%)	2923 (90%)
ACE inhibitor	2565 (79%)	2551 (78%)
ARB	455 (14%)	472 (14%)
Diuretic drugs (excluding antialdosterone)	2719 (84%)	2695 (83%)
Antialdosterone agents	1981 (61%)	1941 (59%)
Cardiac glycosides	706 (22%)	710 (22%)
Devices	110 (3%)	134 (4%)
CRT	28 (1%)	44 (1%)
ICD	92 (3%)	115 (4%)
Data are number of patients (%) or mean (SD). BMI=body mass index. bpm=beats per min. SBP=systolic blood pressure. DBP=diastolic blood pressure. LVEF=left-ventricular ejection fraction. eGFR=estimated glomerular filtration rate (Modification in Diet in Renal Disease Formula). NYHA=New York Heart Association. ACE=angiotensin-converting enzyme. ARB=angiotensin II receptor blocker. CRT=cardiac resynchronisation therapy. ICD=implantable cardioverter defibrillator.		

**Table 1: Baseline characteristics**

randomised treatment group and adjusted for baseline  $\beta$ -blocker intake (yes or no) was used to estimate the treatment effect, 95% CI, and associated p value. The proportionality of hazard was checked by addition of an interaction between log(time) and randomised treatment to the Cox model.

Time-to-event curves were estimated with the Kaplan-Meier method. All survival analyses were done on adjudicated endpoints for the entire population and for the subgroup with at least 50% of the target daily dose of a  $\beta$  blocker. The number of patients who would need to be treated for 1 year to prevent one primary endpoint event was calculated as the inverse of the difference between treatment groups of the estimated probability of having an event at 1 year in the Kaplan-Meier curves. Treatment effects and 95% CIs were calculated in prespecified subgroups from Cox models containing treatment effect, baseline  $\beta$ -blocker status, and subgroup status. *p* values for interaction between randomised treatment and subgroup status were also provided by addition of treatment by subgroup interaction to the model.

See Online for webappendix

	Ivabradine group (n=3241)	Placebo group (n=3264)
Patients receiving $\beta$ blocker	2897 (89%)	2923 (90%)
Carvedilol	1323 (46%)	1281 (44%)
Bisoprolol	721 (25%)	765 (26%)
Metoprolol succinate	399 (14%)	416 (14%)
Metoprolol tartrate	303 (10%)	315 (11%)
Nebivolol	100 (3%)	98 (3%)
Other	55 (2%)	52 (2%)
Mean daily dosage of $\beta$ blocker (mg)		
Carvedilol	25.0 (17.8)	25.0 (17.7)
Bisoprolol	6.2 (3.3)	6.2 (3.4)
Metoprolol succinate	90.2 (59.9)	89.5 (60.0)
Metoprolol tartrate	66.8 (47.4)	71.2 (47.4)
Nebivolol	5.9 (2.8)	5.9 (3.0)
Patients at target dose of $\beta$ blocker*	743 (26%)	745 (26%)
Patients at $\geq 50\%$ target dose of $\beta$ blocker*	1581 (56%)	1600 (56%)
Reasons for failure to reach target dose**†		
Hypotension	933 (44%)	952 (45%)
Fatigue	676 (32%)	670 (32%)
Dyspnoea	284 (14%)	302 (14%)
Dizziness	267 (13%)	245 (12%)
Bradycardia	134 (6%)	125 (6%)
Other	199 (9%)	219 (10%)
Patients not receiving $\beta$ blocker	344 (11%)	341 (10%)
Reasons for non-prescription of $\beta$ blocker		
Chronic obstructive pulmonary disease	126 (37%)	109 (32%)
Hypotension	59 (17%)	68 (20%)
Asthma	35 (10%)	39 (11%)
Cardiac decompensation	23 (7%)	31 (9%)
Dizziness or bradycardia	24 (7%)	17 (5%)
Fatigue	17 (5%)	20 (6%)
Raynaud or peripheral arterial disease	16 (5%)	20 (6%)
Other	44 (13%)	37 (11%)

Data are number of patients (%) or mean (SD). Percentages of patients receiving or not receiving  $\beta$  blockers are proportions of overall treatment groups; all other percentages are proportions of patients receiving or not receiving  $\beta$  blockers, unless otherwise specified. \*For patients receiving carvedilol, bisoprolol, metoprolol succinate, metoprolol tartrate, or nebivolol. †More than one reason could be reported.

Table 2: Distribution of  $\beta$ -blocker use at baseline

Mean heart rates were summarised over time split by treatment group. The percentages of patients improving their NYHA class and patient-reported and physician-reported global assessment were compared with a  $\chi^2$  test. Serious adverse events, selected adverse events, and adverse events leading to definitive study-drug withdrawal were tabulated by randomised treatment group. *p* values were calculated with a Fisher's exact test. The independent data monitoring committee did two interim efficacy analyses. On the basis of the Peto procedure the nominal significance level for overwhelming evidence of benefit of ivabradine treatment was set at 0.001 at each interim analysis. This approach does not significantly affect the overall type I error rate used for the final analysis.

On the assumption of an average yearly incidence of the primary composite endpoint of 14% in the placebo group, a treatment effect for ivabradine of 15% relative risk reduction and a significance level of 0.05, 1600 first events were needed to provide 90% power. With an expected mean follow-up of 2.25 years, this assumption required randomisation of 6500 patients. Further details of the sample-size calculation are shown in the webappendix. We estimated that the patients receiving  $\beta$ -blocker treatment with at least 50% of the target daily dose at baseline would represent roughly 47% of the overall population. With the same risk assumptions as for the overall population, this proportion would result in about 633 events, allowing detection of a relative risk reduction of 20% in favour of ivabradine with 80% power in this subpopulation.

The study is registered, number ISRCTN70429960.

### Role of the funding source

The sponsor was responsible for data management and final data analyses. All analyses were verified by the independent statistical centre at Robertson Centre for Biostatistics, University of Glasgow, UK. The executive committee was responsible for the design of the study, the interpretation of the results, the development and writing of the report, and the decision to submit for publication and, after study conclusion and unmasking, 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

Figure 1 shows the trial profile. 6558 patients were randomly assigned to treatment groups (3268 ivabradine, 3290 placebo). Of these, no data were available for seven patients who were assigned to treatment, but not dispensed study drug. During follow-up, two centres (including their 46 patients) were removed from the trial before unmasking because of invalid data caused by misconduct as detected during study audit. Therefore, the results are based on 6505 patients (3241 ivabradine,

3264 placebo). The programme was completed as planned, with follow-up concluding on March 31, 2010. The median duration of follow-up was 22.9 (IQR 18–28) months. The vital status of all patients was ascertained at study closure, apart from three patients lost to follow-up and 131 (2%) patients who had withdrawn consent for study participation. These patients were censored at their last contact time.

Table 1 shows the baseline characteristics of the placebo and ivabradine groups. The allocation groups were well balanced. The average age was 60.4 (SD 11.4) years (722 [11%] patients aged  $\geq 75$  years), 4970 (76%) participants were men, and most were white (5771, 89%). Mean heart rate was 79.9 (SD 9.6) bpm and mean left-ventricular ejection fraction was 29.0% (SD 5.1). Heart failure was of ischaemic cause in 4418 (68%) patients. Patients were equally distributed between NYHA classes II and III or IV. A RAAS antagonist was used by 5923 (91%) patients and background treatment included a  $\beta$  blocker in 5820 (89%). Table 2 shows the distribution of  $\beta$ -blocker use. 3181 (56%) patients on  $\beta$  blockers were treated with at least 50% of the target doses as defined by European Society of Cardiology guidelines,<sup>19</sup> and 1488 (26%) were at target doses. Predominant reasons for patients not receiving target doses were hypotension and fatigue. 685 (11%) participants did not receive a  $\beta$  blocker at all because of chronic obstructive pulmonary disease or asthma, hypotension, or other reasons.

In patients treated with ivabradine, the mean dosage was 6.4 (SD 1.6) mg twice daily at 28 days (end of titration) and 6.5 (SD 1.6) mg twice daily at 1 year. Figure 2 shows changes in heart rate. At 28 days, heart rate in patients on ivabradine fell by a mean 15.4 (SD 10.7) bpm compared with pretreatment; when corrected for change in the placebo group, the net reduction with ivabradine was 10.9 (95% CI 10.4–11.4) bpm. At 1 year, the reduction in heart rate was 9.1 (95% CI 8.5–9.7) bpm corrected for placebo, and at study end the difference was 8.1 (95% CI 7.5–8.7) bpm.

Effects on the primary composite endpoint are shown in table 3 and figure 3. Cardiovascular deaths or hospital admissions for worsening heart failure occurred in 937 (29%) of the placebo group versus 793 (24%) of patients receiving ivabradine (hazard ratio [HR] 0.82, 95% CI 0.75–0.90,  $p < 0.0001$ ). There was no evidence of non-proportionality of hazards ( $p = 0.83$ ). On the basis of this absolute risk reduction, 26 patients would need treatment for 1 year to prevent one cardiovascular death or one hospital admission for heart failure. The effect was driven mainly by hospital admissions for worsening heart failure, which occurred in 672 (21%) of patients on placebo and 514 (16%) of those taking ivabradine (HR 0.74, 95% CI 0.66–0.83,  $p < 0.0001$ ; figure 3). Cardiovascular deaths were not significantly reduced in the ivabradine group ( $p = 0.128$ ; figure 3), but deaths due to heart failure did fall significantly (HR 0.74, 95% CI 0.58–0.94,  $p = 0.014$ ; figure 4). All-cause deaths did not

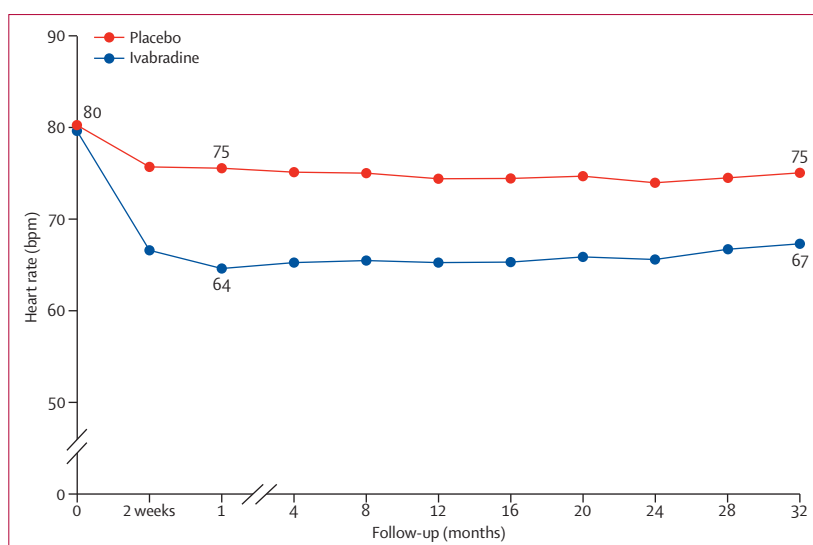


Figure 2: Mean heart rate during the study in the total study population, by allocation groups

differ between groups ( $p = 0.092$ ; figure 4), but all-cause hospital admissions were significantly reduced (HR 0.89, 95% CI 0.82–0.96,  $p = 0.003$ ). There was no difference in other cause-specific deaths, including sudden cardiac deaths (48% of cardiovascular deaths).

The reduction of the primary endpoint associated with ivabradine was consistent in the prespecified subgroups (figure 5), with the exception of the analysis by baseline heart rate ( $p$  value for interaction = 0.029). We noted evidence of a significant treatment effect only in the subgroup with baseline heart rate higher than the median 77 bpm. There was a small but significant improvement in NYHA class—at last recorded value, 887 (28%) of patients on ivabradine improved versus 776 (24%) of patients on placebo ( $p = 0.001$ ). Patient-reported global assessment improved in 2118 (72%) patients and physician-reported assessment in 1888 (61%) patients in the ivabradine group, versus 2017 (68%) and 1772 (57%) in the placebo group (test for difference in patient-reported assessment,  $p = 0.0005$ , and for physician-reported,  $p = 0.0011$ ).

In the subgroup of patients receiving at least 50% of the evidence-based target daily dose of a  $\beta$  blocker, heart rate fell by a mean of 15.5 (SD 10.7) bpm by day 28. In this subgroup, the effects of ivabradine were consistent with the overall findings, though less marked. The primary composite endpoint (HR 0.90, 95% CI 0.77–1.04,  $p = 0.155$ ) and the mortality components were not significantly reduced, whereas ivabradine reduced hospital admissions for worsening heart failure by 19% (HR 0.81, 95% CI 0.67–0.97,  $p = 0.021$ ).

There were 682 (21%) withdrawals in patients assigned to ivabradine and 605 (19%) in those given placebo (HR 1.14, 95% CI 1.02–1.27,  $p = 0.017$ ). However, serious adverse events occurred at a lower rate in the ivabradine group than in the placebo group ( $p = 0.025$ ; table 4). Table 5 shows selected adverse events and the corresponding

	Ivabradine group (n=3241)	Placebo group (n=3264)	HR (95% CI)	p value
<b>Primary endpoint</b>				
Cardiovascular death or hospital admission for worsening heart failure	793 (24%)	937 (29%)	0.82 (0.75–0.90)	<0.0001
<b>Mortality endpoints</b>				
All-cause mortality	503 (16%)	552 (17%)	0.90 (0.80–1.02)	0.092
Cardiovascular mortality	449 (14%)	491 (15%)	0.91 (0.80–1.03)	0.128
Death from heart failure	113 (3%)	151 (5%)	0.74 (0.58–0.94)	0.014
<b>Other endpoints</b>				
All-cause hospital admission	1231 (38%)	1356 (42%)	0.89 (0.82–0.96)	0.003
Hospital admission for worsening heart failure	514 (16%)	672 (21%)	0.74 (0.66–0.83)	<0.0001
Any cardiovascular hospital admission	977 (30%)	1122 (34%)	0.85 (0.78–0.92)	0.0002
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction	825 (25%)	979 (30%)	0.82 (0.74–0.89)	<0.0001

Data are number of first events (%), hazard ratio (HR; 95% CI), and p values.

**Table 3: Effects on primary and major secondary endpoints**

withdrawals. Symptomatic and asymptomatic bradycardia was more frequent in the ivabradine group than in patients taking placebo (both  $p < 0.0001$ ; table 5). Bradycardia led to permanent withdrawal from the study in 48 (1%) of patients on ivabradine and ten (<1%) of those in the placebo group. In the subgroup of 1577 patients on ivabradine receiving at least half the target dose of  $\beta$  blocker, 21 (1%) withdrew for this reason. Known visual symptoms of ivabradine (phosphenes) occurred in 89 (3%) of patients taking the drug, whereas the corresponding finding was reported in seven (<1%) placebo-treated patients ( $p < 0.0001$ ). There were no relevant between-group differences in laboratory parameters (data not shown).

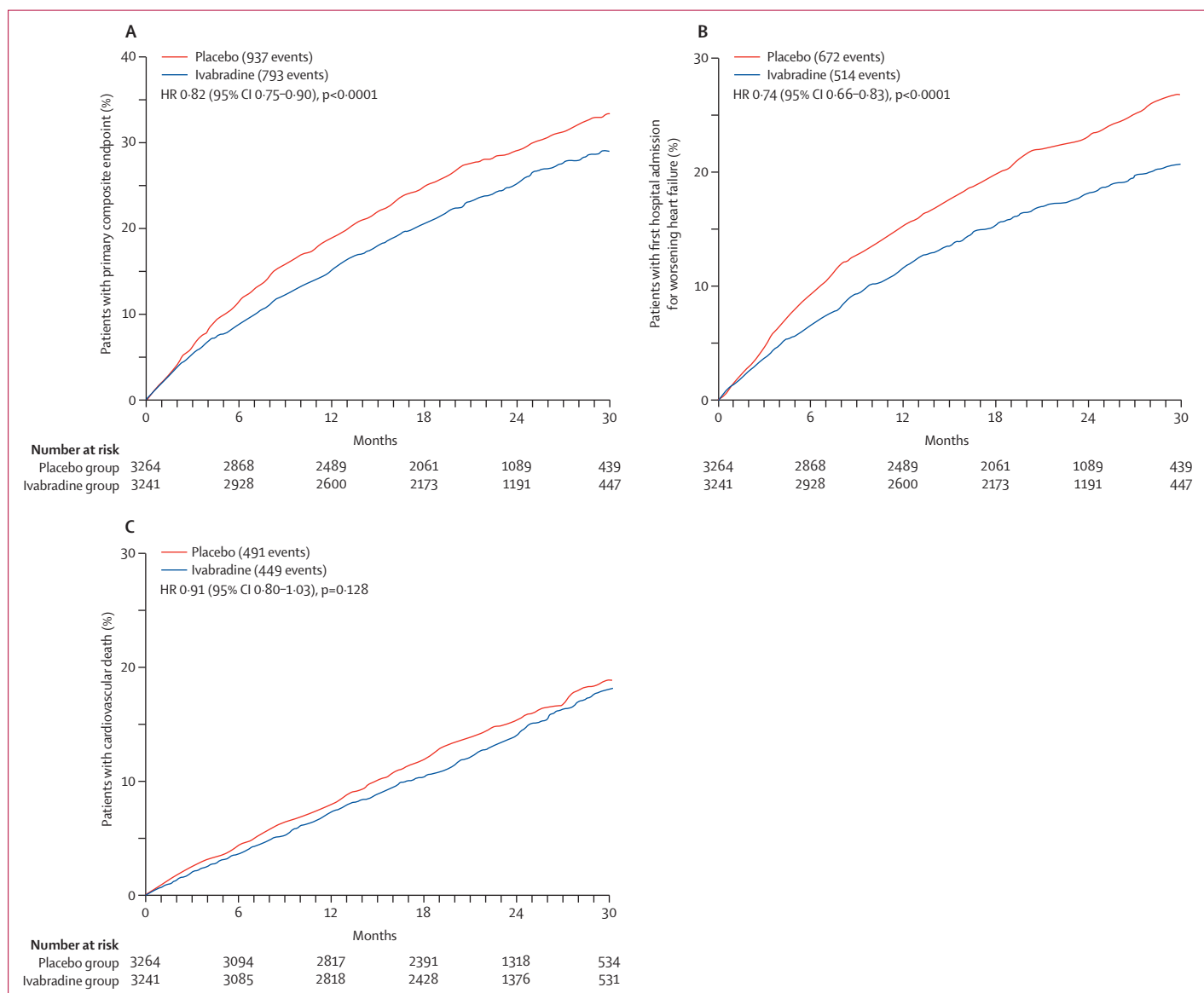
## Discussion

Our results show that ivabradine substantially and significantly reduced major risks associated with heart failure when added to guideline-based and evidence-based treatment. Thus, in patients treated with ivabradine, relative risk of the primary endpoint (cardiovascular death or hospital admission for worsening heart failure) fell by 18% compared with placebo treatment. This finding was mainly the result of a favourable effect on heart failure events (death or hospital admission due to heart failure), which became apparent within 3 months of initiation of treatment, and benefits were maintained through the course of the trial. The effect was consistent across all prespecified subgroups, although less striking in the subgroup with baseline heart rate lower than the median. SHIFT was undertaken in a population with heart failure and systolic dysfunction, selected on the basis of a heart rate of 70 bpm or higher at baseline. The population was treated according to international guidelines—most patients received  $\beta$  blockers and RAAS antagonists. The average doses of the  $\beta$  blockers were lower than doses used in clinical trials of  $\beta$  blockers, but are actually

higher than doses reported in surveys and more closely mirror clinical practice than do doses used in trials testing these drugs.<sup>15,21,22</sup>

Despite such background treatment, event risk in these patients was fairly high—the primary outcome occurred at a rate of 18% per year in the placebo group. The use of devices was low (cardiac resynchronisation therapy [CRT] 1% and implantable cardioverter defibrillator [ICD] 4%), but was attributable to study design (sinus rhythm had to be present  $\geq 40\%$  of the time and the pacing threshold had to be <60 bpm), which led to the exclusion of some patients with pacemakers, and also reflects the frequency of use in countries outside North America and some western European countries.<sup>23</sup>

SHIFT is the first trial to specifically test the effect of isolated heart-rate reduction on outcomes in a population with heart failure. Treatment with ivabradine was associated with an average reduction in heart rate of 15 bpm from a baseline value of 80 bpm, which was largely maintained throughout the course of the study. In the SHIFT population, patients with heart rates higher than the median were at increased risk of an event and received greater event-reducing benefit from ivabradine than did those with heart rates lower than the median. This finding suggests that the magnitude of benefit associated with ivabradine varies directly with pretreatment heart rate. This conclusion is in line with a meta-analysis of  $\beta$ -blocker trials in chronic heart failure suggesting that there is an association between the magnitude of heart-rate reduction and outcome.<sup>8</sup> Thus, our findings support the idea that heart rate plays an important part in the pathophysiology of heart failure and that heart-rate modulation can interfere with the progression of the disease. In a previous study with ivabradine, in patients with coronary artery disease and left-ventricular ejection fraction lower than 40% and heart rate of 60 bpm or more, there were no significant effects on outcomes apart from in patients with a resting



**Figure 3:** Kaplan-Meier cumulative event curves for (A) the primary composite endpoint of cardiovascular death or hospital admission for worsening heart failure, (B) hospital admission for worsening heart failure, and (C) cardiovascular death

heart rate of 70 bpm or higher, in whom ivabradine reduced both myocardial infarctions and coronary revascularisations.<sup>24</sup> Important differences between the populations included in these two trials were resting heart rate and background cardiac condition, as well as studied endpoints that could account for the recorded differences in outcomes.

Most cardiovascular endpoints (death from heart failure, hospital admission for heart failure, any cardiovascular admission, and the secondary composite of cardiovascular death, hospital admission for heart failure, or non-fatal myocardial infarction) were significantly reduced by ivabradine. Cardiovascular and all-cause deaths were not significantly reduced by ivabradine. Sudden cardiac death

did not seem to be affected by ivabradine. This finding could be attributable to the effect of the background  $\beta$ -blocker treatment (used in 89% of patients), which, unlike ivabradine, has intrinsic electrophysiological effects and is known to affect sudden cardiac death.<sup>6,25,26</sup>

In the subgroup of patients receiving at least 50% of the target dose of  $\beta$  blocker, the reduction in heart rate was similar to that in the overall population. Effects on cardiovascular outcomes were not significant apart from hospital admission for heart failure, which was significantly reduced by 19%. This finding might have been related to the lower event rate in this subgroup (13% per year for primary endpoint) than in the overall population, reducing the power of this secondary analysis.

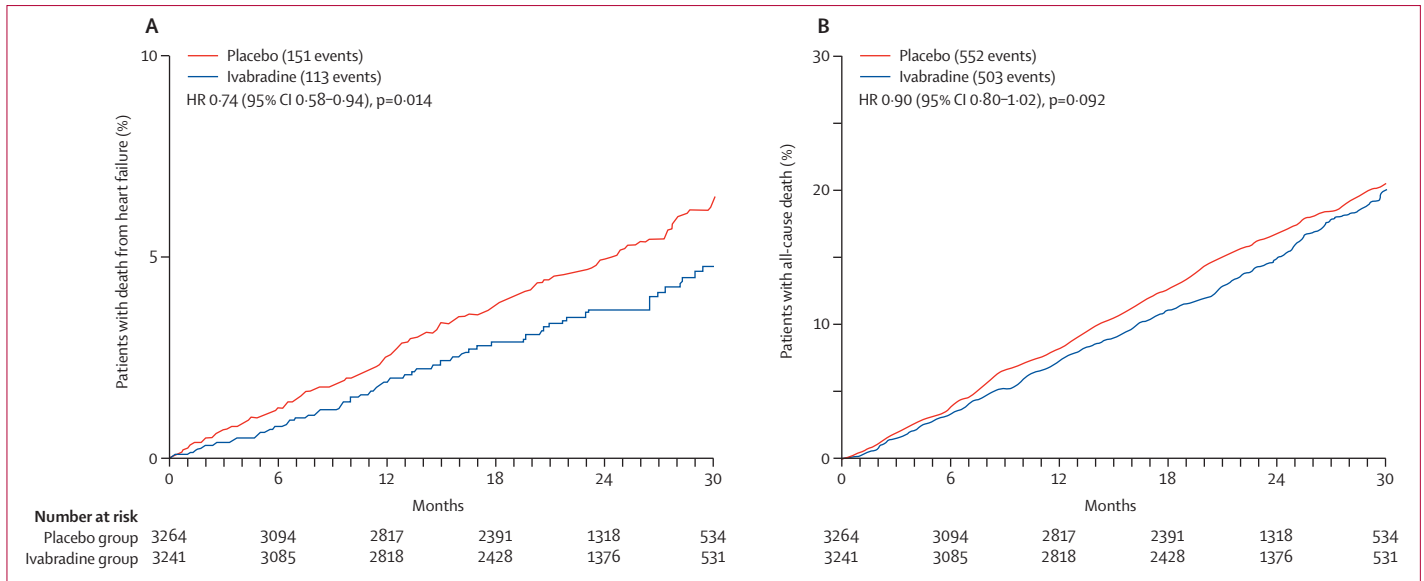


Figure 4: Kaplan-Meier cumulative event curves for (A) death from heart failure and (B) all-cause death

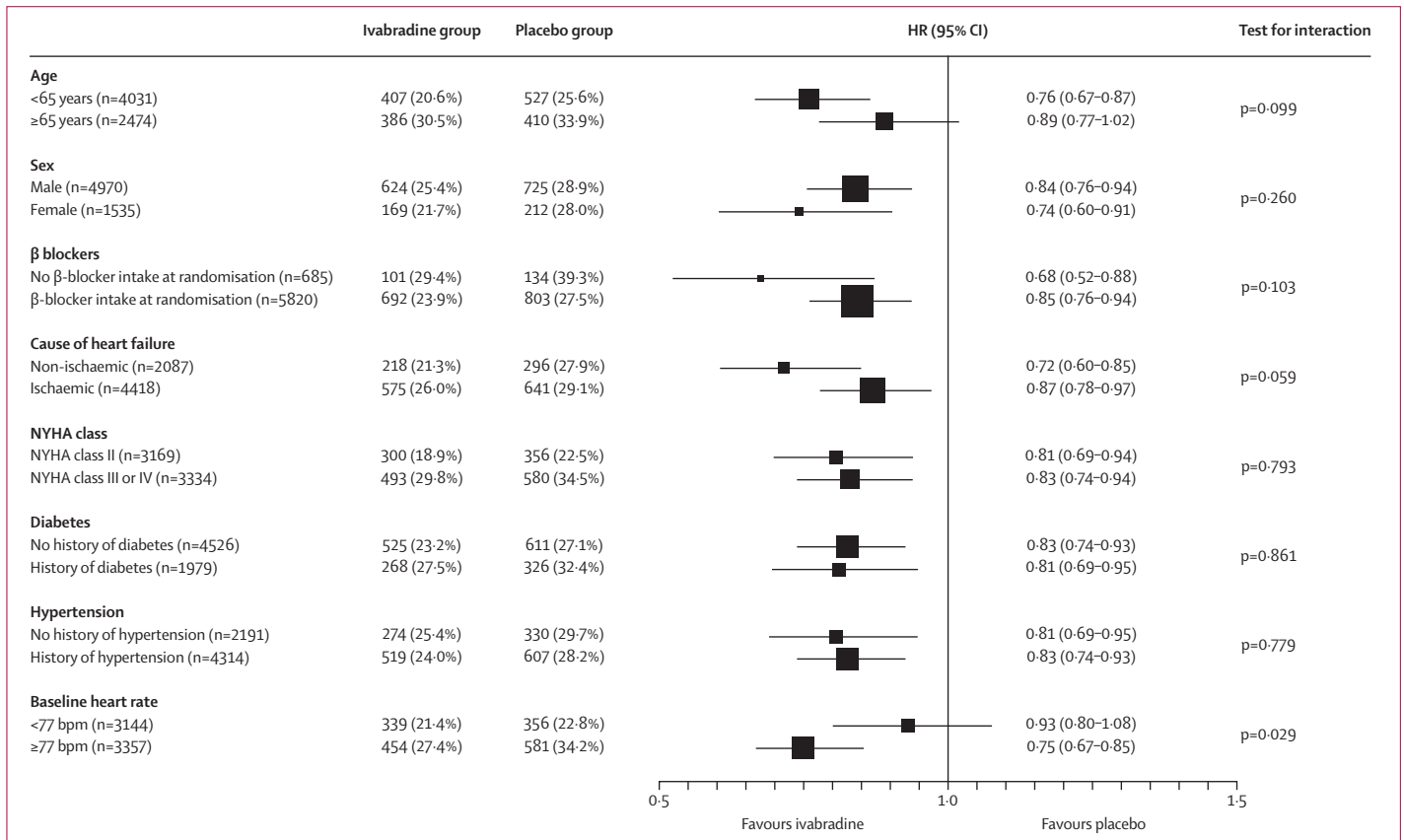


Figure 5: Effect of treatment on primary composite endpoint in prespecified subgroups

Data are number (%) of patients with first events. HR=hazard ratio. NYHA=New York Heart Association. bpm=beats per min.

Overall, ivabradine was well tolerated. Notably, although bradycardia was recorded in 10% of patients, the condition led to study withdrawal in only 1% of the overall population, which is remarkable considering that 89% were receiving β blockers. In patients receiving at least half the target dose of β blocker, only 21 (1%) withdrew for this reason.



	Ivabradine group (n=3232)		Placebo group (n=3260)		p value
	Events	Patients with an event	Events	Patients with an event	
All serious adverse events	3388	1450 (45%)	3847	1553 (48%)	0.025
Cardiac disorders	1804	920 (28%)	2051	991 (30%)	0.091
General disorders and administration site conditions	242	240 (7%)	262	254 (8%)	0.607
Infection and infestations	268	216 (7%)	294	236 (7%)	0.381
Nervous system disorders	144	130 (4%)	202	178 (5%)	0.007
Respiratory, thoracic, and mediastinal disorders	153	107 (3%)	174	122 (4%)	0.347
Surgical and medical procedures	117	102 (3%)	130	122 (4%)	0.197
Gastrointestinal disorders	101	89 (3%)	116	103 (3%)	0.342
Neoplasm (benign, malignant, and unspecified)	70	68 (2%)	66	61 (2%)	0.534
Renal and urinary disorders	59	51 (2%)	51	47 (1%)	0.685
Hepatobiliary disorders	30	29 (1%)	44	39 (1%)	0.273
Eye disorders	24	18 (1%)	15	13 (<1%)	0.374

Data are number of events or number of patients (%). Patients included in this safety analysis are those who had taken at least one dose of study drug. p values are calculated on the basis of number of patients.

**Table 4: Incidence of relevant serious adverse events during the study by system organ class**

	Patients with an adverse event			Patients with an adverse event leading to drug withdrawal		
	Ivabradine group (n=3232)	Placebo group (n=3260)	p value	Ivabradine group (n=3232)	Placebo group (n=3260)	p value
All	2439 (75%)	2423 (74%)	0.303	467 (14%)	416 (13%)	0.051
Heart failure	804 (25%)	937 (29%)	0.0005	70 (2%)	82 (3%)	0.367
Symptomatic bradycardia	150 (5%)	32 (1%)	<0.0001	20 (1%)	5 (<1%)	0.002
Asymptomatic bradycardia	184 (6%)	48 (1%)	<0.0001	28 (1%)	5 (<1%)	<0.0001
Atrial fibrillation	306 (9%)	251 (8%)	0.012	135 (4%)	113 (3%)	0.137
Phosphenes*	89 (3%)	17 (1%)	<0.0001	7 (<1%)	3 (<1%)	0.224
Blurred vision	17 (1%)	7 (<1%)	0.042	1 (<1%)	1 (<1%)	1.000

Data are number of patients (%). Patients included in this safety analysis are those who had taken at least one dose of study drug. p values are calculated on the basis of number of patients. \*Transient enhanced brightness in a restricted area of the visual field.

**Table 5: Selected adverse events and those leading to definitive withdrawal of study drug**

Visual symptoms were rare. No effect on laboratory values was recorded during the course of the study. From 1 year onward, at least 70% of patients were at the target dose of ivabradine 7.5 mg twice a day. By contrast, only 49% of the 6505 patients enrolled in the trial were able to reach at least 50% of target  $\beta$ -blocker dose at baseline because of contraindications or poor tolerability, and despite repeated recommendations from the SHIFT steering committee. Importantly, however, achieved  $\beta$ -blocker doses were generally maintained throughout the trial; there was no tendency to reduce  $\beta$  blockers to enable increasing doses of study drug. This finding reflects the good tolerability of ivabradine in patients with chronic heart failure and, conversely, the difficulties in initiation or uptitration of  $\beta$ -blocker treatment.

There are some limitations to our study. Our results apply to patients in sinus rhythm who were selected on the basis of a high baseline heart rate ( $\geq 70$  bpm). We also excluded patients with sustained atrial fibrillation or flutter who could not be affected by the drug, which solely affects the sinoatrial node, and a few patients with ICD or

CRT. Moreover, the proportion of elderly patients was low. We cannot therefore generalise the effect of ivabradine to the overall population with chronic heart failure. Additionally, our results were achieved alongside background treatment including a  $\beta$  blocker; thus, we can draw no inferences about the relative effects of ivabradine in absence of these background agents, including  $\beta$  blockers or by replacing them by ivabradine. Furthermore, despite repeated encouragement to the investigators to comply with conventional guidelines regarding treatment of heart failure, recommended target doses of background treatments were often not reached. Consequently, our findings should be interpreted as the effects of ivabradine in addition to normal clinical practice in the specific population of patients with heart failure and heart rates of 70 bpm or higher, who are unlikely to tolerate the highest dose of  $\beta$  blocker. Our results support the importance of heart-rate reduction with ivabradine for improvement of clinical outcomes in heart failure and confirm the important role of heart rate in the pathophysiology of heart failure.

**Contributors**

All authors participated in the design of the study, the interpretation of the data, and the writing of the Article. The statistical analysis was done by the sponsor, and was verified by the independent trial statistical centre in the Robertson Centre for Biostatistics, University of Glasgow, UK. All authors have read and approved the final version.

**Conflicts of interest**

KS, MK, MB, JSB, IF, and LT have received fees, research grants, or both from Servier. ADB and GL are employees of Servier. KS has received also research grants from Amgen and AstraZeneca, and honoraria from Amgen, Novartis, and AstraZeneca. MK has received consultancy fees from Nile Therapeutics and Bristol-Myers Squibb, and payment for service on speakers' bureau from Sanofi-Aventis, Menarini, Bristol-Myers Squibb, Merck, and AstraZeneca. IF has received fees from Medtronic, Biotronik, Solvay, Vifor Pharma, IKKF, and GlaxoSmithKline. MB has received fees AstraZeneca, Boehringer Ingelheim, Sanofi-Aventis, and Pfizer. JSB has received consulting fees from Celladon, Gilead, Sanofi-Aventis, ARMGO, Novartis, Novacardia (Merck), BioMarin, Roche, Pfizer, Rigel, BioTronik, Salix, XOMA, Lux, Cardiopep, Bristol-Myers Squibb, and Cardioxyl. LT has received consultancy fees from Medtronic and Menarini, and payment service for speakers' bureau from Abbot, AstraZeneca, and Pfizer.

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