ORIGINAL ARTICLE

Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure

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ABSTRACT

BACKGROUND

An elevated heart rate is an established marker of cardiovascular risk. Previous analyses have suggested that ivabradine, a heart-rate–reducing agent, may improve outcomes in patients with stable coronary artery disease, left ventricular dysfunction, and a heart rate of 70 beats per minute or more.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial of ivabradine, added to standard background therapy, in 19,102 patients who had both stable coronary artery disease without clinical heart failure and a heart rate of 70 beats per minute or more (including 12,049 patients with activity-limiting angina [class ≥II on the Canadian Cardiovascular Society scale, which ranges from I to IV, with higher classes indicating greater limitations on physical activity owing to angina]). We randomly assigned patients to placebo or ivabradine, at a dose of up to 10 mg twice daily, with the dose adjusted to achieve a target heart rate of 55 to 60 beats per minute. The primary end point was a composite of death from cardiovascular causes or nonfatal myocardial infarction.

RESULTS

At 3 months, the mean (±SD) heart rate of the patients was 60.7±9.0 beats per minute in the ivabradine group versus 70.6±10.1 beats per minute in the placebo group. After a median follow-up of 27.8 months, there was no significant difference between the ivabradine group and the placebo group in the incidence of the primary end point (6.8% and 6.4%, respectively; hazard ratio, 1.08; 95% confidence interval, 0.96 to 1.20; P=0.20), nor were there significant differences in the incidences of death from cardiovascular causes and nonfatal myocardial infarction. Ivabradine was associated with an increase in the incidence of the primary end point among patients with activity-limiting angina but not among those without activity-limiting angina (P=0.02 for interaction). The incidence of bradycardia was higher with ivabradine than with placebo (18.0% vs. 2.3%, P<0.001).

CONCLUSIONS

Among patients who had stable coronary artery disease without clinical heart failure, the addition of ivabradine to standard background therapy to reduce the heart rate did not improve outcomes. (Funded by Servier; SIGNIFY Current Controlled Trials number, ISRCTN61576291.)

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An elevated heart rate is established as a marker of cardiovascular risk in the general population and among patients with cardiovascular disease.[1-5] Ivabradine inhibits the I_f (pacemaker) current in the sinoatrial node[6] and reduces the heart rate without affecting blood pressure or left ventricular systolic function. It has been shown to lessen symptoms and reduce ischemia in patients with stable angina pectoris.[7,8] Ivabradine is known to improve outcomes in patients with systolic heart failure.[9] A trial of ivabradine involving patients with coronary artery disease and left ventricular systolic dysfunction did not show clinical benefit,[10] but post hoc analyses suggested that ivabradine improved outcomes in patients who had a heart rate of 70 beats per minute or more, particularly in those with angina.[11] To confirm these findings, we conducted the Study Assessing the Morbidity–Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY), a large, randomized, controlled trial of ivabradine involving patients who had stable coronary artery disease without clinical heart failure.

Methods

Trial Design and Oversight

We conducted this randomized, double-blind, parallel-group, placebo-controlled, event-driven study at 1139 centers in 51 countries. The study was designed to determine the effect of the addition of ivabradine to standard therapy in patients with stable coronary artery disease.[12] The study protocol, available with the full text of this article at NEJM.org, was approved by the ethics committee at each participating institution.

The trial was sponsored by Servier. The executive committee, which included nonvoting representatives of the sponsor, was responsible for the study design, the interpretation of the results, the writing of the manuscript, and the decision to submit the manuscript for publication. The sponsor was responsible for data management. All the statistical analyses were performed by the Robertson Centre for Biostatistics at the University of Glasgow. The trial was overseen by an independent data monitoring committee. The executive committee had full access to the data and takes full responsibility for the accuracy and completeness of the data and analyses reported, as well as for the fidelity of this report to the trial protocol.

Participants

Eligible patients were at least 55 years of age and had documented and treated stable coronary artery disease but no evidence of clinical heart failure.[12] Participants had to be in sinus rhythm, have a resting heart rate of 70 beats per minute or more on two consecutive electrocardiographic readings, and have at least one major adverse prognostic factor (angina pectoris of class ≥II on the Canadian Cardiovascular Society [CCS] scale, which ranges from I to IV, with higher classes indicating greater limitations on physical activity owing to angina; evidence of myocardial ischemia within the previous year; or hospital discharge after a major coronary event within the previous year) or two minor adverse prognostic factors (a high-density lipoprotein cholesterol level <40 mg per deciliter [1 mmol per liter, according to the study protocol] or a low-density lipoprotein cholesterol level >160 mg per deciliter [4 mmol per liter, according to the study protocol], despite lipid-lowering treatment; type 1 or 2 diabetes mellitus; peripheral artery disease; current smoking; or an age of ≥70 years). Patients with left ventricular dysfunction (left ventricular ejection fraction ≤40%) or an unstable cardiovascular condition were excluded. Additional details of the selection, inclusion, and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org.

Interventions and Assessments

After providing written informed consent, all the participants entered a 2-to-4-week placebo run-in phase to confirm eligibility and clinical stability. All the patients whose eligibility and clinical stability were confirmed and who had complied with taking the study drug during the run-in phase were randomly assigned by means of an interactive voice-response or Web-response system to receive ivabradine at a dose of 7.5 mg twice daily or matching placebo (except for patients ≥75 years of age, who received 5.0 mg twice daily). Randomization was stratified according to study center and baseline status with respect to angina (no symptoms or CCS class I vs. CCS class ≥II). Patients and investigators were unaware of the treatment assignments.

In addition to the study drug, participants were

to receive stable background therapy according to contemporary guidelines (notably aspirin, statins, angiotensin-converting–enzyme [ACE] inhibitors [class I, level of evidence A in all guidelines], and beta-blockers [class I, level of evidence B in all guidelines]).[13,14] The treating clinicians were given recommendations for adjusting the beta-blocker dose to achieve the greatest efficacy prior to the run-in phase and for keeping the dose constant thereafter.

Follow-up visits occurred at 1, 2, 3, and 6 months and every 6 months thereafter. The study-drug dose could be adjusted to 5.0, 7.5, or 10.0 mg twice daily, according to the heart rate as measured by electrocardiography at every visit (target heart rate, 55 to 60 beats per minute) and symptoms of bradycardia. If a patient was receiving the lowest dose, treatment was stopped if the heart rate was less than 45 beats per minute, if there was symptomatic bradycardia, or if they had a heart rate of less than 50 beats per minute that persisted at a newly scheduled control visit 1 week later.

END POINTS

The primary end point was a composite of death from cardiovascular causes or nonfatal myocardial infarction. The secondary end points included the components of the primary end point — death from cardiovascular causes and nonfatal myocardial infarction — as well as death from any cause. A description of all the secondary end points is provided in Table S2 in the Supplementary Appendix. Other variables assessed during the trial included heart rate (in all the patients) and change in angina symptoms (in patients with angina at baseline). All outcomes were adjudicated by an independent end-point validation committee.

STATISTICAL ANALYSIS

We estimated that we would need to enroll 16,850 patients for the study to have 90% power to detect an 18% reduction in the relative risk of the primary composite end point with ivabradine, assuming a 2.7% annual incidence with placebo and a mean follow-up period of 2.75 years, at a significance level of 5%. Additional details of the sample-size calculations are provided in the Supplementary Appendix. During the trial, the data monitoring committee performed two planned interim analyses — after 35% and 60% of the anticipated number of primary end points had occurred. A P value of less than 0.001 was required for early termination due to benefit.

The baseline characteristics are shown according to study group as means and standard deviations for continuous variables and as numbers and percentages for categorical variables. The efficacy analysis was based on the intention-to-treat principle. A Cox proportional-hazards model was used to estimate the effect of study treatment on the primary end point and other time-to-event end points, with adjustment for the presence or absence of activity-limiting angina pectoris (CCS class ≥II) at baseline. Results are presented as hazard ratios and 95% confidence intervals with corresponding P values. Prespecified subgroup analyses were performed according to the presence or absence of activity-limiting angina (CCS class ≥II) at baseline (the main subgroup analysis), as well as according to seven other prespecified subgroup variables. Time-to-event curves were prepared with the use of the Kaplan–Meier method. Adverse events were tabulated according to study group with appropriate P values (calculated with the use of the chi-square test or Fisher's exact test). The type I error was set at 5% (two-sided) for all statistical tests. SAS software, version 9.2 (SAS Institute), was used for statistical analyses.

RESULTS

RANDOMIZATION AND FOLLOW-UP

Between October 12, 2009, and April 30, 2012, a total of 19,102 patients underwent randomization; 9550 were assigned to ivabradine and 9552 to placebo (Fig. S1 in the Supplementary Appendix). The last patient visit occurred on January 24, 2014. The median duration of follow-up was 27.8 months (interquartile range, 21.0 to 35.2).

CHARACTERISTICS OF THE PARTICIPANTS

The two groups were well balanced with respect to baseline characteristics (Table 1). The mean age of the study population was 65 years, 72.4% of the patients were men, and the mean resting heart rate was 77.2 beats per minute. A total of 73.3% of the study population had had a previous myocardial infarction, 67.8% had had previous coronary revascularization, and 63.1% had activity-limiting angina (CCS class ≥II). There was no evidence of left ventricular systolic dysfunction in the overall study population (mean ejection fraction, 56.4%).

Table 1. Characteristics of the Study Population at Baseline.*

Characteristic	Ivabradine (N=9550)	Placebo (N=9552)
Age — yr	65.0±7.2	65.0±7.3
Body-mass index†	28.8±4.6	28.7±4.6
Heart rate — beats/min	77.1±6.9	77.2±7.1
Male sex — no. (%)	6949 (72.8)	6890 (72.1)
Race — no. (%)‡		
White	7788 (81.5)	7745 (81.1)
Asian	1262 (13.2)	1285 (13.5)
Other	500 (5.2)	522 (5.5)
Blood pressure — mm Hg		
Systolic	131±13	130±14
Diastolic	78±8	78±8
Cardiovascular risk factors and medical history		
Duration of coronary artery disease — yr	6.2±6.3	6.1±6.2
Previous myocardial infarction — no. (%)	7009 (73.4)	6993 (73.2)
Previous coronary revascularization — no. (%)	6453 (67.6)	6496 (68.0)
Angina status — no. (%)		
No symptoms	2400 (25.1)	2416 (25.3)
CCS class§		
I	1113 (11.7)	1124 (11.8)
≥II	6037 (63.2)	6012 (62.9)
Dyslipidemia — no. (%)	6844 (71.7)	6853 (71.7)
Diabetes mellitus — no. (%)	4103 (43.0)	4127 (43.2)
Peripheral artery disease — no. (%)	1974 (20.7)	2042 (21.4)
Current smoker — no. (%)	2285 (23.9)	2320 (24.3)
Hypertension — no. (%)	8275 (86.6)	8191 (85.8)
Left ventricular ejection fraction — %	56.4±8.5	56.5±8.6
Previous stroke — no. (%)	634 (6.6)	631 (6.6)
Concomitant treatment — no. (%)		
Antiplatelet agent or anticoagulant	9329 (97.7)	9343 (97.8)
Aspirin	8756 (91.7)	8736 (91.5)
Statin	8819 (92.3)	8791 (92.0)
Beta-blocker	7934 (83.1)	7944 (83.2)
ACE inhibitor	5719 (59.9)	5617 (58.8)
Angiotensin II–receptor blocker	2218 (23.2)	2255 (23.6)
Dihydropyridine calcium-channel blocker	2574 (27.0)	2544 (26.6)
Nitrate	3871 (40.5)	3770 (39.5)
Diltiazem or verapamil	438 (4.6)	403 (4.2)
Antidiabetic agent	3787 (39.7)	3799 (39.8)

* Plus–minus values are means ±SD. There were no significant differences (at $P<0.05$) between the study groups in any of the baseline characteristics. ACE denotes angiotensin-converting enzyme.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race was determined by the investigator during the patient's interview.
§ Classes on the Canadian Cardiovascular Society (CCS) scale range from I to IV, with higher classes indicating greater limitations on physical activity owing to angina.

Most patients were receiving appropriate therapy for cardiovascular disease (antiplatelet therapy or anticoagulants in 97.7% of the patients, statins in 92.2%, beta-blockers in 83.1%, and ACE inhibitors in 59.3%). Details of beta-blocker use at baseline are shown in Table S3 in the Supplementary Appendix. Patients with angina of CCS class II or higher were more likely than patients without angina or with CCS class I angina to have a history of myocardial infarction (75.3% vs. 69.8%) and to be receiving beta-blockers (86.9% vs. 76.7%) and nitrates (49.5% vs. 23.8%) and were less likely to have undergone coronary revascularization (61.1% vs. 79.3%) (Table S4 in the Supplementary Appendix).

STUDY-DRUG USE AND HEART RATE

The mean study-drug dose throughout the trial was 8.2±1.7 mg twice daily in the ivabradine group and 9.5±0.9 mg twice daily in the placebo group. At 3 months, the mean heart rate was reduced to 60.7±9.0 beats per minute with ivabradine and to 70.6±10.1 beats per minute with placebo (Fig. S2 in the Supplementary Appendix). The difference in the mean heart rate between the ivabradine group and the placebo group was maintained for the duration of the study in the total population and in the subgroups of patients with activity-limiting angina at baseline and those without angina at baseline (Fig. S2 in the Supplementary Appendix). The mean proportion of patients who complied with taking the study drug (as assessed by means of pill counts) was 96.2±9.2% in the ivabradine group and 96.6±8.3% in the placebo group.

The rates of permanent discontinuation of the study drug were 20.6% in the ivabradine group (1972 patients) and 14.5% in the placebo group (1384 patients). The main reason for study-drug withdrawal in the ivabradine group was asymptomatic bradycardia (leading to withdrawal in 272 patients, vs. 17 in the placebo group) and, to a lesser extent, symptomatic bradycardia (194 vs. 33). Few patients changed the beta-blocker dose during the study, with 3.2% of the patients in the ivabradine group increasing the dose, 6.1% decreasing, and 3.5% stopping, as compared with 5.8%, 3.7%, and 2.3%, respectively, in the placebo group (Table S3 in the Supplementary Appendix).

STUDY END POINTS

Results with respect to study end points are presented in Table 2 and Figure 1. There was no sig-

Table 2. Primary and Secondary End Points.*

End Point	Ivabradine (N=9550)	Placebo (N=9552)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Primary composite end point: death from cardiovascular causes or nonfatal myocardial infarction	654 (6.8)	611 (6.4)	1.08 (0.96–1.20)	0.20
Secondary end point				
Death				
Any cause	485 (5.1)	458 (4.8)	1.06 (0.94–1.21)	0.35
Cardiovascular causes	329 (3.4)	301 (3.2)	1.10 (0.94–1.28)	0.25
Coronary causes	263 (2.8)	249 (2.6)	1.06 (0.89–1.26)	0.52
Coronary revascularization				
Any	562 (5.9)	564 (5.9)	1.00 (0.89–1.12)	0.98
Elective	270 (2.8)	305 (3.2)	0.89 (0.75–1.04)	0.15
Admission to hospital for heart failure	216 (2.3)	181 (1.9)	1.20 (0.99–1.46)	0.07
Myocardial infarction				
Fatal or nonfatal	392 (4.1)	372 (3.9)	1.06 (0.92–1.22)	0.43
Nonfatal	351 (3.7)	339 (3.5)	1.04 (0.90–1.21)	0.60
Fatal or nonfatal myocardial infarction or coronary revascularization	718 (7.5)	739 (7.7)	0.97 (0.88–1.08)	0.59
Fatal or nonfatal myocardial infarction, coronary revascularization, or unstable angina	766 (8.0)	782 (8.2)	0.98 (0.89–1.08)	0.70
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	774 (8.1)	731 (7.7)	1.06 (0.96–1.18)	0.22
Death from coronary causes or nonfatal myocardial infarction	590 (6.2)	562 (5.9)	1.05 (0.94–1.18)	0.37
Nonfatal myocardial infarction, coronary revascularization, or unstable angina	734 (7.7)	759 (7.9)	0.97 (0.87–1.07)	0.53

* Estimates were based on a Cox proportional-hazards model, with adjustment for the presence or absence of angina pectoris (CCS class ≥II) at baseline. Death from coronary causes included death due to heart failure, death due to myocardial infarction, death related to a coronary-artery procedure, death from presumed arrhythmia, and sudden death of unknown cause. Death from cardiovascular causes included all deaths from coronary causes, death related to cardiovascular procedures other than coronary-artery procedures, fatal stroke, other deaths from cardiovascular causes, nonsudden death of unknown cause, and unclassifiable deaths. CI denotes confidence interval.

nificant difference in the incidence of the primary end point between the ivabradine group and the placebo group (6.8% and 6.4%, respectively; hazard ratio, 1.08; 95% confidence interval [CI], 0.96 to 1.20; P=0.20). There were also no significant differences between the two groups in the incidences of the components of the primary end point, death from cardiovascular causes (hazard ratio, 1.10; 95% CI, 0.94 to 1.28; P=0.25) and nonfatal myocardial infarction (hazard ratio, 1.04; 95% CI, 0.90 to 1.21; P=0.60). The rate of death from any cause also did not differ significantly between the two groups (hazard ratio, 1.06; 95% CI, 0.94 to 1.21; P=0.35). There was virtually no between-group difference in the incidence of sudden death (201 cases with ivabradine and 202 with placebo). Finally, there were no significant between-group differences in any other secondary end points.

SUBGROUP ANALYSES

There was a significant interaction between the study treatment and the presence of angina at baseline in the prespecified subgroup defined according to CCS class (P=0.02) (Fig. 2, and Table S5 in the Supplementary Appendix), but there was no significant interaction in the seven other prespecified subgroups (Fig. 2) or in an analysis per-

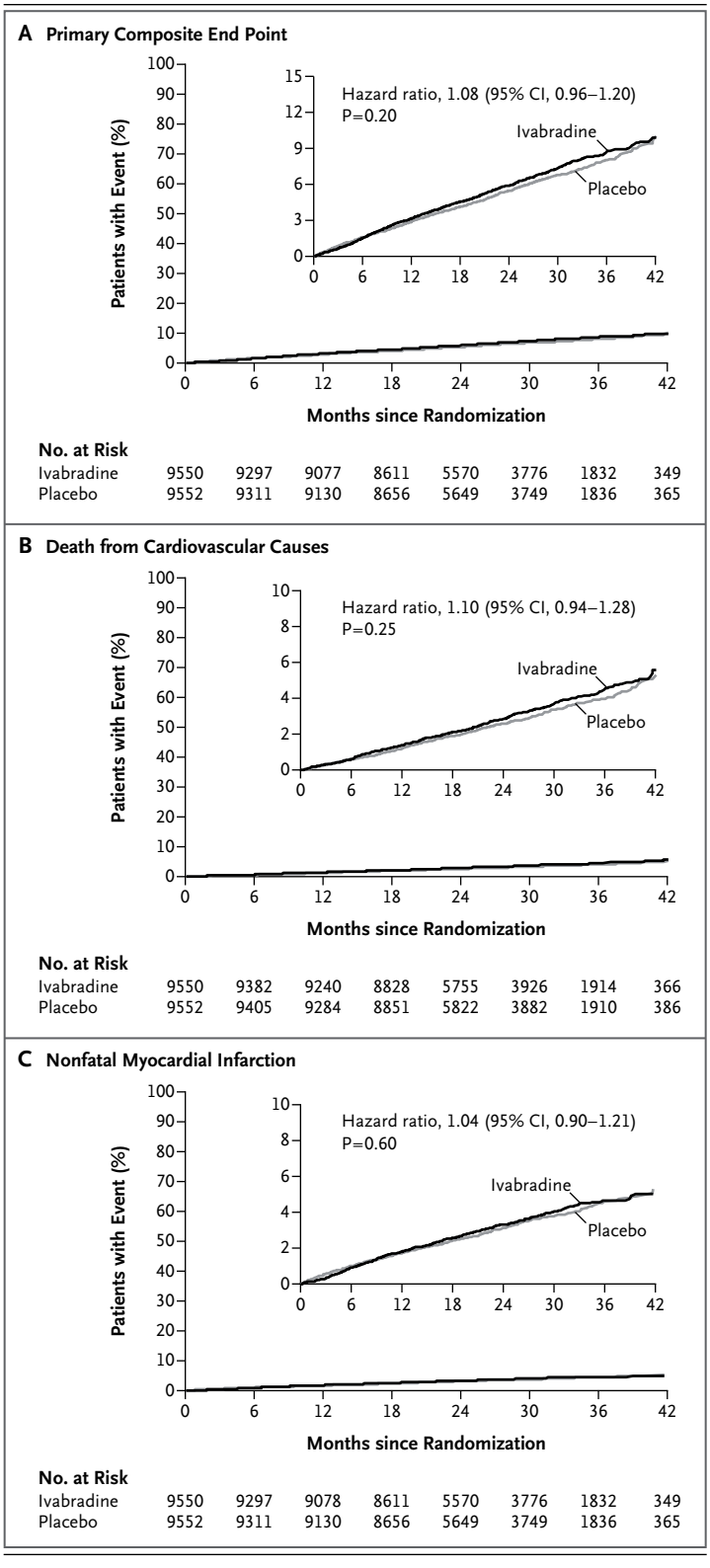

Figure 1. Kaplan–Meier Plots of the Primary Composite End Point and Its Components.

The primary end point was a composite of death from cardiovascular causes or nonfatal myocardial infarction The insets show the same data on an enlarged y axis. CI denotes confidence interval.

formed according to country of origin (data not shown). Ivabradine was associated with an increase in the incidence of the primary end point among patients who had angina of CCS class II or higher (7.6%, vs. 6.5% with placebo; hazard ratio, 1.18; 95% CI, 1.03 to 1.35; P=0.02) but not among patients without angina or those who had angina of class I (hazard ratio, 0.89; 95% CI, 0.74 to 1.08; P=0.25) (Table S5 and Fig. S3 in the Supplementary Appendix). The effect of ivabradine among patients with angina of CCS class II or higher appeared to be consistent between the two components of the primary end point (hazard ratio for death from cardiovascular causes, 1.16; 95% CI, 0.97 to 1.40; P=0.11; and hazard ratio for nonfatal myocardial infarction, 1.18; 95% CI, 0.97 to 1.42; P=0.09). In the subgroup of patients with angina of CCS class II or higher, 1446 patients in the ivabradine group (24.0%) had an improvement in the CCS angina class at 3 months, as compared with 1131 in the placebo group (18.8%) (P=0.01).

ADVERSE EVENTS

Adverse events during the study occurred in 73.3% of the patients in the ivabradine group and in 66.9% of those in the placebo group (P<0.001) (Table 3). Ivabradine increased the frequency of symptomatic bradycardia (7.9%, vs. 1.2% with placebo), asymptomatic bradycardia (11.0% vs. 1.3%), atrial fibrillation (5.3% vs. 3.8%), and phosphenes (5.4% vs. 0.5%) (P<0.001 for all comparisons). A serious adverse event occurred during the study in 3588 patients in the ivabradine group (37.6%) and in 3375 in the placebo group (35.4%) (P=0.001) (Table S6 in the Supplementary Appendix). These events were classified as cardiac disorders in 19.0% and 16.7% of the patients, respectively. Adverse events led to study-drug withdrawal in 13.2% of the patients in the ivabradine group and in 7.4% of those in the placebo group (P<0.001) (Table S7 in the Supplementary Appen-

Subgroup	No. of Patients	Ivabradine	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events/total no. (%)			
Angina class at baseline					0.02
Class I or no symptoms	7,053	195/3513 (5.6)	221/3540 (6.2)	0.89 (0.74–1.08)	
Class ≥II	12,049	459/6037 (7.6)	390/6012 (6.5)	1.18 (1.03–1.35)	
Beta-blocker use at randomization					0.98
Yes	15,878	543/7934 (6.8)	506/7944 (6.4)	1.08 (0.95–1.21)	
No	3,224	111/1616 (6.9)	105/1608 (6.5)	1.07 (0.82–1.40)	
Heart rate					0.69
<75 beats/min	9,170	289/4589 (6.3)	263/4581 (5.7)	1.10 (0.93–1.30)	
≥75 beats/min	9,931	365/4960 (7.4)	348/4971 (7.0)	1.05 (0.91–1.22)	
Age					0.35
<65 yr	10,205	309/5109 (6.1)	272/5096 (5.3)	1.14 (0.97–1.34)	
≥65 yr	8,897	345/4441 (7.8)	339/4456 (7.6)	1.02 (0.88–1.19)	
Sex					0.46
Male	13,839	485/6949 (7.0)	460/6890 (6.7)	1.05 (0.92–1.19)	
Female	5,263	169/2601 (6.5)	151/2662 (5.7)	1.16 (0.93–1.44)	
History of diabetes					0.83
Yes	8,230	324/4103 (7.9)	301/4127 (7.3)	1.09 (0.93–1.27)	
No	10,872	330/5447 (6.1)	310/5425 (5.7)	1.06 (0.91–1.24)	
Previous myocardial infarction					0.84
Yes	14,002	519/7009 (7.4)	487/6993 (7.0)	1.07 (0.94–1.21)	
No	5,100	135/2541 (5.3)	124/2559 (4.9)	1.10 (0.86–1.41)	
Previous coronary revascularization					0.66
Yes	12,949	397/6453 (6.2)	380/6496 (5.8)	1.05 (0.92–1.21)	
No	6,153	257/3097 (8.3)	231/3056 (7.6)	1.11 (0.93–1.32)	

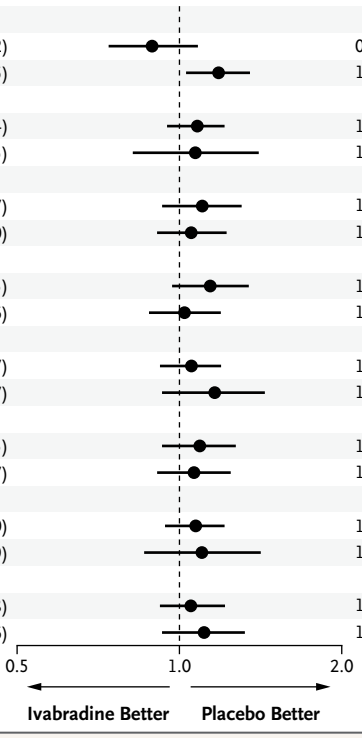

Figure 2. Forest Plot of the Primary Composite End Point in Prespecified Subgroups.

The data are the numbers and proportions of patients with a first event. Estimates are based on a Cox proportional-hazards model, with adjustment for the presence or absence of angina at baseline (class ≥II on the Canadian Cardiovascular Society scale, which ranges from I to IV, with higher classes indicating greater limitations on physical activity owing to angina).

dix). Safety data for the angina subgroups are presented in Tables S6, S7, and S8 in the Supplementary Appendix.

DISCUSSION

Our study evaluated the use of ivabradine, added to background guideline-based medical treatment, in patients who had stable coronary artery disease without clinical heart failure. We found no benefit of ivabradine in reducing the risk of cardiovascular events.

Previous observational studies have shown that an elevated heart rate is associated with an increased risk of cardiovascular events in populations with stable coronary artery disease.[2-4,15,16] The lack of benefit of ivabradine in SIGNIFY contrasts with results from previous post hoc analyses with this agent suggesting that it would improve outcomes in patients with stable coronary artery disease.[10,11] In addition, in patients with heart failure, the reduction in heart rate with ivabradine has been shown to improve clinical outcomes, beyond the improvements observed with beta-blockers.[9,17]

Although the study population in SIGNIFY had a high prevalence of risk factors owing to the inclusion criteria, the annual incidence of the primary end point was relatively low (approximately 2.8%), probably owing to the background therapy the patients were receiving, which was administered according to current guidelines. Treatment with ivabradine had the intended effect on heart rate, with a between-group difference of approximately 10 beats per minute. The incidences of bradycardia and atrial fibrillation

Table 3. Adverse Events during the Study.*

Event	Ivabradine (N=9539)	Placebo (N=9544)	P Value
	no. of patients with event (%)		
Any adverse event	6990 (73.3)	6382 (66.9)	<0.001
Selected adverse events†			
Bradycardia	1718 (18.0)	223 (2.3)	<0.001
Symptomatic	757 (7.9)	110 (1.2)	<0.001
Asymptomatic	1047 (11.0)	126 (1.3)	<0.001
Phosphenes	512 (5.4)	52 (0.5)	<0.001
Blurred vision	117 (1.2)	37 (0.4)	<0.001
Atrioventricular block			
Second degree	44 (0.5)	31 (0.3)	0.13
Third degree	20 (0.2)	19 (0.2)	0.87
Atrial fibrillation	508 (5.3)	362 (3.8)	<0.001
QT-interval prolongation‡	171 (1.8)	65 (0.7)	<0.001
Supraventricular tachyarrhythmia	137 (1.4)	113 (1.2)	0.13
Immune disorder	22 (0.2)	28 (0.3)	0.40
Severe ventricular arrhythmia	79 (0.8)	66 (0.7)	0.28

* The incidence of adverse events is provided for all the patients who had at least one dose of study drug. Patients may have had more than one type of adverse event (including symptomatic and asymptomatic bradycardia).
† Selected adverse events were those listed in the risk-management plan for ivabradine.
‡ Data include prolongation of the corrected QT interval and uncorrected QT interval as assessed by means of electrocardiography.

were higher with ivabradine than with placebo. Bradycardia occurred more often in SIGNIFY than in previous ivabradine trials, most likely owing to the dose regimen in SIGNIFY, which included higher initiation and maintenance doses than those that are currently recommended.

There are a number of hypotheses to explain the lack of a benefit in SIGNIFY. It is possible that ivabradine decreased the heart rate too much or that there may be a J-shaped curve for the relationship between heart rate and outcome. Ivabradine may have unintended effects (e.g., adjustment of the doses of other heart-rate–lowering agents) that may have affected the potential benefits of the lowering of heart rate with ivabradine. However, the use and dosing of beta-blockers after randomization differed only slightly between patients who received ivabradine and those who received placebo.

It is also possible that heart-rate–reducing antianginal agents have no effect on outcomes in patients with stable coronary artery disease. Although there is historical evidence of a benefit of beta-blockers after myocardial infarction, there is little current evidence of their benefit with respect to hard clinical outcomes in patients who have stable coronary artery disease without left ventricular dysfunction. In fact, a recent observational analysis has suggested the opposite.[18] This contrasts with the results of trials testing the effects of beta-blockers or ivabradine in patients with systolic heart failure, including those with heart failure of ischemic origin.[9,19]

The benefit observed with lowering the heart rate in patients with heart failure but not in those with stable coronary artery disease may reflect the fact that an elevated heart rate is due to different pathophysiological mechanisms in these two conditions.[1] In patients with heart failure, there is neurohormonal activation, which in itself leads to ventricular remodeling, further left ventricular dysfunction, and a vicious cycle of decline. In contrast, there is no neurohormonal activation in stable coronary artery disease without left ventricular dysfunction.

There was a significant interaction between

the effect of ivabradine and the presence of angina (CCS class ≥II) at baseline. In that subgroup, ivabradine increased the absolute risk of the primary composite end point of death from cardiovascular causes or nonfatal myocardial infarction by 1.1 percentage points. The explanation for this surprising finding is uncertain, although it should be treated with caution since the results of the primary efficacy analysis were not significant.

In conclusion, the results of SIGNIFY show that ivabradine, added to guideline-recommended medical therapy, did not improve the outcome in patients who had stable coronary artery disease without clinical heart failure. There is a signal for an increase in the risk of cardiovascular events among patients with angina of CCS class II or higher. Given that the primary cardiovascular effect of ivabradine is to reduce heart rate, these results suggest that an elevated heart rate is only a marker of risk — but not a modifiable determinant of outcomes — in patients who have stable coronary artery disease without clinical heart failure.

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