Bradycardia and atrial fibrillation in patients with stable CAD treated with ivabradine: The SIGNIFY Study

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Abstract (249 words)

Aim To determine the impact of emergent bradycardia and atrial fibrillation (AF) on cardiovascular outcomes in 19 083 patients with stable coronary artery disease (CAD) receiving ivabradine or placebo (SIGNIFY).

Methods and Results Emergent bradycardia (resting heart rate <50 bpm on 12-lead electrocardiogram) with ivabradine was reported in 3572 patients (37.4%) overall, and in 2242 (37.2%) of patients with Canadian Cardiovascular Society (CCS) class ≥2 angina. There was no difference in outcomes over the course of the study in ivabradine-treated patients with and without emergent bradycardia in the whole population (2.5% versus 2.9% per year, respectively, for primary composite endpoint of cardiovascular death or nonfatal myocardial infarction) or in the angina subgroup (2.5% versus 3.2% per year). Neither was there an increase in the rate of primary endpoint after emergent bradycardia was recorded compared with those without emergent bradycardia. There were 754 cases of emergent AF on treatment (2.2% per year ivabradine versus 1.5% per year placebo) and 469 in the patients with angina (2.2% versus 1.5% per year). While outcomes occurred more frequently in patients in whom emergent AF had been recorded, there was no treatment-placebo difference in outcomes, including stroke, and no difference in treatment effect in patients with limiting angina.

Conclusion Both in the overall population as well as in the angina subset, bradycardia was common in ivabradine-treated patients, but did not appear to impact outcomes. Emergent AF was relatively rare and did not appear to have an impact on outcomes relative to placebo.

Keywords: ivabradine; CAD; angina; atrial fibrillation; bradycardia; adverse event

Introduction

SIGNIFY (Study assessInG the morbidity–mortality beNefits of the I_f inhibitor ivabradine in patients with coronarY artery disease) analysed the effect of heart rate lowering with the I_f inhibitor ivabradine in patients with coronary artery disease (CAD) without clinical heart failure and with preserved left ventricular function.[1] It was found that heart rate lowering with ivabradine did not improve outcomes, in particular the primary composite endpoint of cardiovascular death or nonfatal myocardial infarction, with an aggressive dosage regimen for ivabradine, starting at 7.5 mg twice daily and uptitrating to 10 mg twice daily to achieve a heart rate of 55 to 60 bpm. This regimen involved particularly high dosages of ivabradine, and neither the initiation nor the maintenance dosage employed in SIGNIFY is approved for ivabradine in clinical practice. Moreover, it was found that patients with limiting angina (Canadian Cardiovascular Society [CCS] class ≥2) appeared to fair less well in terms of outcomes with ivabradine compared with placebo. There was, however, evidence demonstrating symptomatic improvement with ivabradine in patients with angina.

An explanation for these results has not been forthcoming. Indeed, the a priori hypothesis was that bradycardia would be associated with a lower risk of myocardial infarction. Among the most frequent cardiovascular adverse events in SIGNIFY were symptomatic and asymptomatic bradycardia, as well as atrial fibrillation, both of which were more frequent in the ivabradine-treated patients who were otherwise well balanced versus placebo for prognostic risk factors. The purpose of the analysis described herein is to determine the role of bradycardia and atrial fibrillation in the SIGNIFY trial, and to explore whether they could account for the adverse finding in these patients.

Methods

Study design and patients

The results and design of the SIGNIFY trial have been published in detail elsewhere.[1,2] Briefly, this was a randomized, double-blind, event-driven, international

trial. Ethical approval was obtained in all centres in the 51 participating countries and the trial was registered (ISRCTN61576291). To be eligible for inclusion, patients had to be aged 55 years or older with stable CAD, without clinical heart failure (left ventricular ejection fraction >40%). They also had to be in sinus rhythm with a resting heart rate of 70 bpm or higher on two consecutive electrocardiography (ECG) readings. They had to have at least one major or two minor cardiovascular risk factors and be receiving appropriate standard background therapy. Patients with permanent atrial fibrillation or flutter were excluded from the trial. All patients provided written informed consent.

After a 2- to 4-week placebo run-in, patients were randomly allocated to receive 7.5 mg bid ivabradine or matched placebo (except for patients aged ≥75 years, who were initiated on 5 mg bid). Randomization was stratified according to centre and the presence of CCS class ≥2 angina at baseline. Dosages could be adjusted to 5.0, 7.5, or 10 mg bid at every visit to achieve a resting heart rate between 55 and 60 bpm. The decision to modify the dosage of study treatment was made on the basis of ECG resting heart rate measurements at every visit, and symptoms of bradycardia.[1,2] Study visits were scheduled at 1, 2, 3, and 6 months, and then every 6 months thereafter. All analyses described here are presented in the safety set, i.e. all patients who received at least one dose of study drug; this constituted 19 083 patients in the whole population and 12 039 patients with CCS class ≥2 angina at baseline.

Analysis of emergent bradycardia

We divided the SIGNIFY population according to the emergence of bradycardia, defined as resting heart rate <50 bpm on treatment, according to 12-lead ECG evaluation performed at every visit. In these routine evaluations, it was not formally recorded whether bradycardia was symptomatic or asymptomatic. The rates of bradycardia reported here differ from those reported in the main study,[1] since they come from routine ECG evaluations and not from formal reports of adverse events by the investigator. Data relative to emergent bradycardia are presented as descriptive statistics only, since it was reported for too few patients in the placebo group for the purposes of comparison. Therefore, we report the rate of primary composite endpoint (cardiovascular death or non-fatal myocardial infarction) events with ivabradine and

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placebo over the course of the study, as well as after the occurrence of bradycardia in the whole population and in the prespecified subgroup of patients with CCS class ≥2 angina at baseline.

Analysis of emergent atrial fibrillation

We also divided the SIGNIFY population according to the occurrence of emergent atrial fibrillation on treatment. Diagnosis, signs, and symptoms of all adverse events related to rhythm and conduction disorders were reported by the investigator on the case report form, and this information was used to identify emergent atrial fibrillation.

We analysed outcomes in patients with and without emergent atrial fibrillation for ivabradine versus placebo in the whole population and in the prespecified subgroup of patients with CCS class ≥2 angina at baseline. The outcomes analysed were the primary composite endpoint, and fatal or nonfatal stroke. For the outcomes analyses described here, only events that occurred after emergent atrial fibrillation were taken into account. If the outcome in question (notably myocardial infarction or stroke) occurred before the presentation of atrial fibrillation, then the patient was excluded from the outcomes analysis.

Statistical methods

Baseline characteristics are presented as descriptive statistics and compared using a Chi^2 test for categorical variables and a Kruskall-Wallis test for continuous variables. A Cox proportional hazards model was used to estimate the effect of treatment on outcomes in patients with and without emergent atrial fibrillation or bradycardia, and was adjusted for prognostic factors (peripheral artery disease, previous myocardial infarction, hypertension, hypercholesterolemia, diabetes, sedentary lifestyle, obesity, smoking, heart rate, age, gender, and CCS class <2/≥2) at baseline. The Cox models were evaluated for fit and the proportional hazards assumption appears to be acceptable in the subgroups of patients concerned. Results are expressed in terms of hazard ratios and 95% confidence intervals (CIs). The ivabradine-placebo difference between the rate of emergent atrial fibrillation was evaluated with the Wilson test and

the corresponding p value is presented. SAS software, version 9.2, was used for all statistical analyses.

Results

Our analyses covered 19 083 patients (9539 ivabradine, 9544 placebo) with a median follow-up of 27.8 months. There were 12 039 patients (6030 ivabradine, 6009 placebo) in the subgroup with CCS class ≥2 angina.

Bradycardia

Emergent bradycardia (resting heart rate <50 bpm on 12-lead ECG) with ivabradine was reported in 3572 patients in the whole population (37.4%) and 2242 patients in the subgroup with CCS class ≥2 angina (37.2%). The rates of emergent bradycardia in the placebo groups were 367 patients (3.8%) for the whole population and 261 patients (4.3%) for the angina subgroup, respectively.

The baseline characteristics of the ivabradine patients with CCS class ≥2 angina who went on to have emergent bradycardia during the study are presented in **Table 1**. Patients who had emergent bradycardia had lower resting heart rate at baseline (75.5±5.4 versus 78.1±7.4 bpm). They were less likely to have a history of diabetes (29% versus 39%) or myocardial infarction (73% versus 77%), but more likely to have been revascularized (64% versus 59%).

In the whole population in whom emergent bradycardia was recorded on treatment with ivabradine, there were 211 patients (5.9%, 2.5% per year) who had a primary composite endpoint; this should be compared with 338 patients (5.8%, 2.9% per year) without emergent bradycardia. There were 132 (3.7%, 2.5% per year) who went on to have a primary composite endpoint after presenting with emergent bradycardia (**Table 2**), of whom 12 patients (9%) had a primary composite endpoint within the month. In the group of patients with CCS class ≥2 angina with emergent bradycardia on treatment with ivabradine, there were 149 patients (6.7%, 2.8% per year) with a primary composite endpoint; this compares with 243 (6.6%, 3.2% per year) with a primary composite endpoint on treatment with ivabradine, but without emergent

bradycardia. There were 86 patients (3.9%, 2.5% per year) who went on to have a primary composite endpoint after presenting with emergent bradycardia (**Table 2**), of whom 10 patients (12%) had the event within 1 month. Similar results were observed when bradycardia reported as an adverse event was taken into account. In the group of 1063 patients with CCS class ≥2 angina for whom bradycardia was reported as an adverse event on treatment with ivabradine, there were 43 patients (4.1%, 2.9% per year) with a primary composite endpoint; this compares with 302 patients (6.1%, 3.0% per year) with a primary composite endpoint on treatment with ivabradine, but without emergent bradycardia reported as an adverse event (N=4948).

Atrial fibrillation

There were 754 cases of emergent atrial fibrillation on treatment (438 in the ivabradine group, 4.6% [2.2% per year], and 316 in the placebo group, 3.3% [1.5% per year], p<0.001). In the patients with CCS class ≥2 angina, there were 469 cases of emergent atrial fibrillation: 277 in the ivabradine patients (4.6% [2.2% per year]) and 192 in the placebo patients (3.2% [1.5% per year]).

Table 3 shows the baseline characteristics of ivabradine patients with CCS class ≥2 angina with and without emergent atrial fibrillation and placebo patients with CCS class ≥2 angina with emergent atrial fibrillation. Patients with emergent atrial fibrillation were older (67.8±7.1 years in ivabradine patients with emergent atrial fibrillation versus 64.3±6.9 years in ivabradine patients without) and had a higher body mass index. They were more likely to have a history of hypertension (95% versus 88%) or peripheral artery disease (23% versus 16%). There was no relevant difference in baseline characteristics between ivabradine and placebo. Even though patients with emergent atrial fibrillation were more likely to have a history of atrial fibrillation prior to study entry (22% versus 4%), the majority of patients in whom emergent atrial fibrillation was recorded did not have a previous history of atrial fibrillation (74%), and again there was no relevant difference between ivabradine and placebo.

Of the whole population in whom emergent atrial fibrillation was recorded on treatment with ivabradine, 14% (n=58, 10.9% per year) had a primary composite

endpoint; this compares with 13.9% (n=42, 11.2% per year) in whom emergent atrial fibrillation was recorded on placebo. **Table 4** shows events for the primary composite endpoint, and fatal or nonfatal stroke in patients after emergent atrial fibrillation compared with patients without emergent atrial fibrillation in the whole population. Fatal and nonfatal stroke occurred at rates of 4.6% and 4.2% in the ivabradine and placebo groups after emergent AF was recorded, respectively.

In the patients with CCS class ≥2 angina in whom emergent AF was recorded on treatment with ivabradine, there were 15.2% (n=40, 11.5% per year) who had a primary composite endpoint; this compares with 13.5% (n=25, 10.8% per year) in whom emergent AF was recorded on placebo. The results on outcomes in angina patients after emergent atrial fibrillation was recorded and those without emergent AF are presented in **Table 4**. The frequency of the primary composite endpoint and fatal and nonfatal stroke in this angina subgroup was greater following a recording of emergent atrial fibrillation in both treatment groups than in those who did not have emergent atrial fibrillation. However, there was no difference in the frequency of the primary composite endpoint in these patients with limiting angina according to the treatment they received and whether or not emergent atrial fibrillation occurred.

There was no relevant ivabradine–placebo difference in the proportion of the patients with a cardiovascular event prior to the occurrence of emergent atrial fibrillation. In the subgroup with CCS class≥2 angina, there were 13 patients (4.7%) with a nonfatal myocardial infarction before the occurrence of atrial fibrillation in the ivabradine group versus 7 patients (3.6%) in the placebo group, and 4 patients (1.4%) with a nonfatal stroke before the occurrence of atrial fibrillation on ivabradine versus 4 patients (2.1%) on placebo.

Discussion

A prespecified analysis of the BEAUTIFUL (morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left-ventricULar dysfunction) study indicated that heart rate lowering with ivabradine in patients whose resting heart rate was ≥70 bpm was likely to be associated with a reduction in fatal and non-fatal myocardial infarction.[3] The SIGNIFY study has demonstrated that

this is not the case in patients without left ventricular dysfunction in whom heart rate lowering with ivabradine had no effect on the frequency of myocardial infarction.[1] On the other hand, the SIGNIFY study did suggest that heart rate lowering with ivabradine was associated with an increase in the primary composite endpoint of cardiovascular death and non-fatal myocardial infarction in a prespecified subgroup of patients with CCS class ≥2 angina.[1]

Whereas this conclusion appeared to be counterintuitive, we have explored the SIGNIFY database to try and obtain a better understanding of potential mechanisms that might explain these findings. Ivabradine has only a single known cardiovascular mechanism of action, namely I_f current inhibition, which reduces heart rate, possibly leading to bradycardia and the development of atrial fibrillation. It has no direct effects on blood pressure, coronary vascular resistance, or the myocardium.[4]

In the SIGNIFY study, the frequency with which emergent bradycardia was recorded was much greater than previously described in patients treated with ivabradine,[3] in spite of the higher heart rate at which treatment was initiated. This was to be expected because of the aggressive treatment regimen employed in SIGNIFY with titration of ivabradine to a heart rate of 55 to 60 bpm. Moreover, the risk profile of patients presenting with emergent bradycardia was no worse than those without. Our results on emergent bradycardia do not suggest that heart rate <50 bpm on resting ECG is associated with an adverse outcome in terms of the primary composite endpoint.

Our results in the placebo group indicate that 1.5% of patients with stable CAD and without clinical heart failure may expect to have an onset of atrial fibrillation within 1 year. This is in line with epidemiological observations, which report an incidence of between 3 and 9 cases per 1000 person-years in the general population aged 65 years old.[5] Registry data in patients with stable CAD suggest that between 2% and 19% have atrial fibrillation or flutter.[6-10] The ivabradine and placebo groups were balanced in terms of demographic characteristics and cardiovascular risk factors, and the majority of patients with emergent atrial fibrillation did not have a previous history of atrial fibrillation. The patients presenting with emergent atrial fibrillation were generally at higher risk, being older and more obese, having a longer history of CAD, and having more peripheral vascular disease and hypertension. Treatment with

ivabradine appears to increase the absolute incidence of atrial fibrillation by 0.7% per year in stable CAD patients, including those with angina (p<0.001). The majority of cases of emergent atrial fibrillation with ivabradine in SIGNIFY were paroxysmal in nature and were managed according to current European guidelines.[11,12] As would be expected,[13] the outcome of SIGNIFY patients who developed atrial fibrillation was worse than in those without, independently of whether they were on ivabradine or placebo. On the other hand, the presence of atrial fibrillation did not affect the impact of treatment on incidence of primary composite endpoint or fatal or nonfatal stroke versus placebo. Indeed, our results do not suggest that atrial fibrillation was a relevant component of the apparent increase in the primary composite endpoint found in stable CAD patients with limiting angina.[1]

The main limitation of our analysis is that we have created subgroups using post-randomisation variables (emergent bradycardia or emergent atrial fibrillation). This means that, because the rate of occurrence of these events was different in the two treatment groups, then the usual subgroup interaction test cannot be interpreted in the usual manner. Moreover, adjustment on post-randomisation variables could hide or exaggerate a treatment effect if the covariate is affected by the treatment either through direct causation or through association with another factor. This limits the conclusions that can be drawn from such comparisons.

In summary, neither the development of bradycardia nor the small increase in emergent atrial fibrillation appear to explain the increase in outcomes observed in the patients with CCS class ≥2 angina.

Acknowledgement:

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Table 1. Baseline characteristics in ivabradine patients with and without emergent bradycardia (<50 bpm) in the SIGNIFY participants with Canadian Cardiovascular Society (CCS) class angina ≥2 at baseline.

Values are n (%) or means±SD.

***p<0.0001 versus patients without emergent bradycardia (chi^2 test for continuous variables and a Kruskall-Wallis test for categorical variables).

Characteristic	Ivabradine patients with emergent bradycardia (n=2242)	Ivabradine patients without emergent bradycardia (n=3678)
Demographic characteristics		
Age (years)	64.3±6.8	64.4±7.1
Male	1562 (69.7%)	2649 (72.0%)
Body mass index, kg/m^2	28.6±4.2	29.3±4.7
Cardiovascular risk factors and medical history		
Duration CAD (years)	6.5±6.2	6.6±6.4
Heart rate (bpm)	75.5±5.4***	78.1±7.4
Left ventricular ejection fraction (%)	56.7±8.5***	55.5±8.2
Diabetes mellitus	638 (28.5%)***	1444 (39.3%)
Hypertension	1960 (87.4%)	3260 (88.6%)
Peripheral artery disease	372 (16.6%)	608 (16.5%)
Previous stroke	126 (5.6%)	259 (7.0%)
Previous myocardial infarction	1636 (73.0%)***	2830 (76.9%)
Previous coronary revascularization	1430 (63.8%)***	2170 (59.0%)
Previous atrial fibrillation	108 (4.8%)	166 (4.5%)

Table 2. Outcomes in patients with and without emergent bradycardia (resting heart rate <50 bpm on treatment, according to 12-lead ECG evaluation performed at every visit) in the whole population and in the population with Canadian Cardiovascular Society (CCS) class angina ≥2 at baseline.

Patients with primary composite endpoint (cardiovascular death or non-fatal myocardial infarction) events occurring before the emergence of bradycardia were excluded from the analysis.

	Ivabradine			Placebo			Hazard ratio (95% confidence interval)
	n	Events, n (%)	Events, % per year	n	Events, n (%)	Events, % per year	
Whole population (N=19 083)							
Primary composite endpoint							
• No emergent bradycardia	5797	338 (5.8%)	2.9%	9032	487 (5.4%)	2.5%	1.09 (0.95–1.26)
• Emergent bradycardia	3538	132 (3.7%)	2.5%	358	14 (3.9%)	3.1%	0.78 (0.45–1.36)
Patients with CCS class ≥2 angina (N=12 039)							
Primary composite endpoint							
• No emergent bradycardia	3678	243 (6.6%)	3.2%	5651	314 (5.6%)	2.6%	1.20 (1.01–1.42)
• Emergent bradycardia	2215	86 (3.9%)	2.5%	255	10 (3.9%)	3.1%	0.86 (0.45–1.67)

Table 3. Baseline characteristics in patients with and without emergent atrial fibrillation (AF) in the SIGNIFY participants with Canadian Cardiovascular Society (CCS) class angina ≥2 at baseline.

Values are n (%) or means±SD.

*p<0.05, **p<0.001, ***p<0.0001 versus patients without emergent atrial fibrillation (chi^2 test for continuous variables and a Kruskall-Wallis test for categorical variables).

Characteristic	Ivabradine patients with emergent AF (n=277)	Ivabradine patients without emergent AF (n=5753)	Placebo patients with emergent AF (n=192)	Placebo patients without emergent AF (n=5817)
Demographic characteristics				
Age (years)	67.8±7.1***	64.3±6.9	66.4±7.7**	64.3±7.0
Male	190 (68.6%)	4089 (71.1%)	144 (75.0%)	4088 (70.3%)
Body mass index, kg/m^2	30.4±4.8	28.9±4.6	30.0±4.7	28.8±4.6
Cardiovascular risk factors and medical history				
Duration CAD (years)	8.4±6.7***	6.5±6.3	8.6±7.2***	6.3±6.1
Heart rate (bpm)	77.8±6.8*	77.1±6.8	77.2±8.0	77.1±7.0
Left ventricular ejection fraction (%)	55.8±7.9	56.0±8.4	54.3±7.6	56.0±8.6
Diabetes mellitus	109 (39.4%)	2004 (34.8%)	81 (42.2%)	2076 (35.7%)
Hypertension	262 (94.6%)**	5050 (87.8%)	180 (93.8%)**	5074 (87.2%)
Peripheral artery disease	64 (23.1%)*	930 (16.2%)	50 (26.0%)*	993 (17.1%)
Previous stroke	23 (8.3%)	369 (6.4%)	20 (10.4%)	362 (6.2%)
Previous myocardial infarction	208 (75.1%)	4333 (75.3%)	142 (74.0%)	4390 (75.5%)
Previous coronary revascularization	178 (64.3%)	3494 (60.7%)	115 (59.9%)	3564 (61.3%)
Previous atrial fibrillation	62 (22.4%)	223 (3.9%)	61 (31.8%)	229 (3.9%)

Table 4. Outcomes in patients with and without emergent atrial fibrillation (AF) in the whole population and in the population with Canadian Cardiovascular Society (CCS) class angina ≥2 at baseline.

Patients with primary composite endpoint (cardiovascular death or non-fatal myocardial infarction) and stroke events occurring before the emergence of atrial fibrillation were excluded from the analysis.

	Ivabradine			Placebo			Hazard ratio (95% confidence interval)
	n	Events, n (%)	Events, % per year	n	Events, n (%)	Events, % per year	
Whole population (N=19 083)							
Primary composite endpoint							
• No emergent AF	9101	572 (6.3%)	2.8%	9228	556 (6.0%)	2.7%	1.05 (0.94–1.18)
• Emergent AF	414	58 (14.0%)	10.9%	303	42 (13.9%)	11.2%	1.02 (0.68–1.52)
Fatal or nonfatal stroke							
• No emergent AF	9101	142 (1.6%)	0.7%	9228	138 (1.5%)	0.7%	1.06 (0.84–1.34)
• Emergent AF	434	20 (4.6%)	3.5%	309	13 (4.2%)	3.2%	1.13 (0.55–2.30)
Patients with CCS class ≥2 angina (N=12 039)							
Primary composite endpoint							
• No emergent AF	5753	406 (7.1%)	3.1%	5817	358 (6.2%)	2.7%	1.16 (1.01–1.34)
• Emergent AF	264	40 (15.2%)	11.5%	185	25 (13.5%)	10.8%	1.14 (0.69–1.90)
Fatal or nonfatal stroke							
• No emergent AF	5753	95 (1.7%)	0.7%	5817	89 (1.5%)	0.7%	1.10 (0.82–1.46)
• Emergent AF	273	10 (3.7%)	2.7%	188	8 (4.3%)	3.2%	0.91 (0.35–2.37)