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Antianginal Efficacy and Safety of Ivabradine Compared with Amlodipine in Patients with Stable Effort Angina Pectoris

A 3-Month Randomised, Double-Blind, Multicentre, Noninferiority Trial

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Abstract

Background and objective: Current medical therapies for the symptoms of angina pectoris aim to improve oxygen supply and reduce oxygen demand in the myocardium. Not all patients respond to current antianginal monotherapy, or even combination therapy, and a new class of antianginal drug that complements existing therapies would be useful. This study was undertaken to compare the antianginal and anti-ischaemic effects of the novel heart-rate-lowering agent ivabradine and of the calcium channel antagonist amlodipine.

Patients and methods: Patients with a ≥3-month history of chronic, stable effort-induced angina were randomised to receive ivabradine 7.5mg (n = 400) or 10mg (n = 391) twice daily or amlodipine 10mg once daily (n = 404) for a 3-month, double-blind period. Bicycle exercise tolerance tests were performed at baseline and monthly intervals. The primary efficacy criterion was the change from baseline in total exercise duration after 3 months of treatment. Secondary efficacy criteria included changes in time to angina onset and time to 1mm ST-segment depression, rate-pressure product at trough drug activity, as well as short-acting nitrate use and anginal attack frequency (as recorded in patient diaries).

Results: At 3 months, total exercise duration was improved by 27.6 ± 91.7, 21.7 ± 94.5 and 31.2 ± 92.0 seconds with ivabradine 7.5 and 10mg and amlodipine, respectively, both ivabradine groups were comparable to amlodipine (p-value for noninferiority < 0.001). Similar results were observed for time to angina onset and time to 1mm ST-segment depression. Heart rate decreased significantly by 11–13 beats/min at rest and by 12–15 beats/min at peak of exercise with ivabradine but not amlodipine, and rate-pressure product decreased more with ivabradine than amlodipine (p-value vs amlodipine <0.001, at rest and at peak of exercise). Anginal attack frequency and short-acting nitrate use decreased substantially in all

treatment groups with no significant difference between treatment groups. The most frequent adverse events were visual symptoms and sinus bradycardia with ivabradine (0.8% and 0.4% withdrawals, respectively) and peripheral oedema with amlodipine (1.5% withdrawals).

Conclusions: In patients with stable angina, ivabradine has comparable efficacy to amlodipine in improving exercise tolerance, a superior effect on the reduction of rate-pressure product (a surrogate marker of myocardial oxygen consumption) and similar safety.

Angina pectoris occurs when the oxygen demand of the myocardium exceeds oxygen supply, usually as a consequence of atheromatous narrowing of the coronary arteries. Current medical therapies for the symptoms of angina (principally β-adrenoceptor antagonists [β-blockers], long-acting calcium channel antagonists and nitrates) aim to improve this balance by improving the oxygen supply and reducing the oxygen demand in various ways. However, all of the current antianginal therapies are associated with adverse effects, and not all patients respond to monotherapy or even combination therapy. A new class of antianginal drug that complements existing therapies, while avoiding some of their drawbacks, would therefore be useful. Ivabradine is the first approved agent in a new class of pure heart-rate-lowering drugs that act selectively to inhibit the I_f pacemaker current in the sinoatrial node.[1] Ivabradine induces a significant and dose-dependent reduction in heart rate, both at rest and during exercise in experimental animals and in healthy volunteers, preserves myocardial contractility, atrio-ventricular conduction and ventricular repolarisation.[2,3] By reducing the heart rate, ivabradine prevents exercise-induced myocardial ischaemia as effectively as a β-blocker, while offering better protection of regional myocardial contractility.[4] Ivabradine has been shown to produce dose-dependent improvements, relative to placebo, in exercise tolerance and time to development of ischaemia at the dosages of 5 and 10mg twice daily in patients with stable angina.[5] The anti-ischaemic and antianginal efficacy of ivabradine was comparable to that of a β-blocker (atenolol) in a study in 939 patients with stable angina.[6]

This study compared the antianginal efficacy of ivabradine with that of amlodipine, a long-acting dihydropyridine-type calcium channel antagonist that is recommended as second-line therapy in angina.[7] The aim was to demonstrate noninferiority in efficacy of ivabradine, relative to amlodipine, at the trough of drug activity.

Patients and Methods

Patients

A randomised, double-blind, three-arm parallel-group, international trial involving 133 centres was performed to compare the effects of 3 months of ivabradine 7.5 and 10mg twice daily with amlodipine 10mg once daily. Eligible patients were men or women aged ≥18 years and ≤90 years, with (i) a ≥3-month history of chronic stable effort-induced angina, relieved by rest or short-acting nitrates; (ii) coronary artery disease (CAD) documented by occurrence of a myocardial infarction (MI) ≥3 months previously, or coronary artery bypass graft surgery (CABG) ≥3 months previously, or percutaneous coronary angioplasty (PTCA) ≥6 months previously, or by coronary angiography, stress echocardiography or scintigraphy; and (iii) a positive bicycle exercise tolerance test (ETT) [with both limiting angina and ST-segment depression ≥1mm compared with rest] at selection (D–7) and at inclusion (M0). On days D–7 and M0, the time to 1mm ST-segment depression could not differ by >20% or >1 minute. Female participants needed to be of non-child-bearing potential.

Exclusion criteria included inability to perform ETT, ECG abnormalities that would confound ETT

interpretation, unstable angina, Prinzmetal angina or 'microvascular angina', New York Heart Association class III or IV heart failure, atrial fibrillation/flutter or indwelling pacemaker, clinically significant heart disease other than CAD, symptomatic hypotension, uncontrolled hypertension, treatment with defined unauthorised concomitant medications that could interact with ivabradine or amlodipine and that could not be interrupted for the duration of the study, treatment with bepridil <7 days prior to selection, treatment with amiodarone <3 months prior to selection, resting bradycardia ([heart rate <50 beats/min] or sick sinus syndrome), and any contraindication to amlodipine.

Study Design

The study was performed in accordance with the ethical principles of the Declaration of Helsinki. The protocol was approved by independent ethics committees at participating institutions, and all patients provided written informed consent.

A single-blind, placebo wash-out of antianginal medications (except short-acting nitrates), if applicable, was performed for 2–7 days (at least 5 half-lives of the previous therapy), followed by a first ETT (D–7). This was followed by a 1-week, single-blind, placebo run-in and a second ETT (M0). Patients were then randomised to receive ivabradine 7.5mg or 10mg twice daily or amlodipine 10mg once daily for a 3-month double-blind period.

The randomisation list was designed by the Biometry Department of Servier. Treatments were randomly assigned using permutation blocks without stratification, according to the chronological order of inclusions within each centre. Participants, investigators and outcome assessors were blinded to the treatment assignments. At study onset, investigators received a set of sealed envelopes containing the assigned treatment for secure storage, so that the code could be broken for individual patients in emergencies. Patients in the amlodipine group received amlodipine in the morning and placebo in the evening. The two ivabradine doses, amlodipine and placebo were supplied as capsules of identical appearance packed in blister packs and marked to be used 'am' or 'pm'.

Trial Outcomes

ETTs were performed on an ergometric bicycle at the trough of drug activity (in the morning, 12 ± 1 hour after the preceding evening's drug intake), in line with current regulatory requirements.[8] The initial workload (50W) was increased by 10W every minute. The primary efficacy criterion was change from baseline in total exercise duration (TED) after 3 months of treatment. Secondary efficacy criteria included changes in time to angina onset and time to 1mm ST-segment depression, as well as the rate-pressure product, all at the trough of drug activity. Short-acting nitrate use and anginal attack frequency (as recorded in patient diaries) were also assessed. ETTs were performed at 1 and 2 months, in addition to the ETT at end of treatment, in order to examine the time-course of efficacy.

All ECG print-outs were read centrally by physicians independent of the study recruitment and blind to the treatment allocation. The values of TED, time to angina onset and time to 1mm ST-segment depression from this centralised reading were used for the statistical analysis of the data.

Safety

A clinical examination was carried out at each visit. Adverse events were derived from diaries kept by patients, spontaneous complaints and investigators' observations. Other safety measures included vital signs, blood pressure during ETT, ECG at rest, 24-hour Holter monitoring (in a subset of 370 patients equally distributed between treatment groups) and clinical chemistry/haematology analyses.

Statistical Analysis

As there was no consensus *a priori* regarding the noninferiority margin to be defined for ETT criteria in noninferiority trials, a tentative margin of between −30 and −40 seconds was set in the study protocol. It was planned that this would be reassessed during the trial by an independent Expert

Committee blinded to treatment groups. This procedure was followed and, after a blind review of the first 521 patients included (all three treatment groups pooled together), the independent Expert Committee recommended a noninferiority limit for TED of −30 seconds.

The sample size was estimated on the change from baseline of TED over a 3-month treatment period at trough of drug activity in order to demonstrate the noninferiority of ivabradine compared with amlodipine using a one-sided Student's t-test at a 2.5% type I error. For a 90-second standard deviation and a 30-second clinical equivalence limit, 235 patients per treatment group were necessary to show the noninferiority of ivabradine versus amlodipine with 95% power.

Efficacy was analysed on an intention-to-treat (ITT) basis (all randomised patients who had an evaluation of the primary efficacy criterion). An additional analysis was performed using the per-protocol population. For analyses of angina attacks and short-acting nitrate use, the ITT population consisted of all randomised patients with at least one evaluation of the appropriate endpoint. Safety analyses were performed on all patients having received at least one dose of study drug. Statistical analyses were performed using SAS software. The noninferiority of ivabradine was tested on the primary efficacy criterion, TED, using an analysis of covariance model with treatment, baseline and country factors, taking into account the noninferiority limit and according to a stepwise procedure (first comparing ivabradine 10mg twice daily with amlodipine 10mg once daily, then ivabradine 7.5mg twice daily with amlodipine 10mg once daily). The same analyses were performed on time to angina onset and time to 1mm ST-segment depression. Each comparison was performed using a parametric approach based on a general linear model (least-squares norm) estimating treatment effect after adjustment on baseline and country factor. This analysis of covariance model was a mixed model with treatment and country (random effect) factors, baseline as covariate and without interaction.

A common statistical model (including the three treatment groups) was used in order to take into account all design information for each pairwise comparison.

For the rate-pressure product, number of angina attacks and short-acting nitrate consumption, the 95% confidence intervals of treatment differences were calculated. The number and percentage of patients having experienced at least one emergent adverse event were provided for each group. Unless otherwise stated, all results of the form $x \pm y$ relate to mean ± standard deviation.

Results

Patient Population

The study was carried out in ten countries (Czech Republic, Denmark, Finland, Hungary, Norway, Poland, Russia, Slovak Republic, Sweden, The Netherlands) between December 1999 and February 2002. During the study, new countries were invited to participate in order to recruit the required number of patients, once these new centres were added, recruitment increased rapidly, resulting in treatment groups that were larger than the number required. Of 1693 patients screened, 1195 were randomised to treatment with ivabradine 7.5mg twice daily (400 patients), ivabradine 10mg twice daily (391 patients) or amlodipine (404 patients) [figure 1]. The ITT population consisted of 1155 patients (96.7%) and was defined as all randomised patients having stable effort angina with documented coronary artery disease, having taken at least one dose of the study treatment, having at least one post-M0 value of total exercise test duration (central reading value) measured during an ETT planned at the trough of drug activity. The per-protocol population included 975 patients (81.6%) compliant with the protocol in terms of disease, exposure to treatment, allocation of treatment, and with clinically relevant TED assessment at M0 and M3.

Baseline characteristics of the patients are shown in table I. There were no clinically significant differences between the treatment groups. No patients were lost to follow-up.

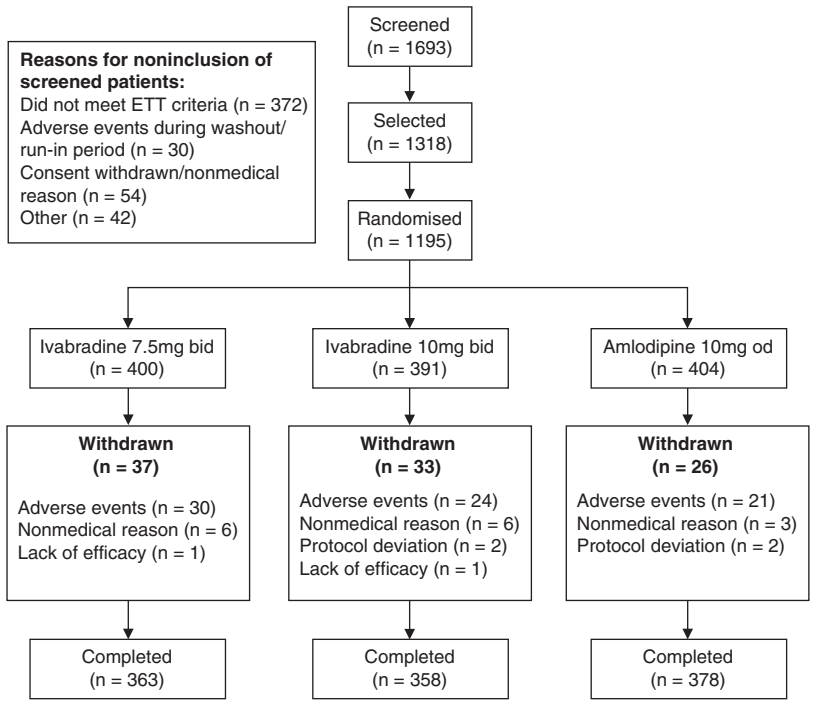

Fig. 1. Disposition of patients. **bid** = twice daily; **ETT** = exercise tolerance test; **od** = once daily.

Efficacy

Exercise Tolerance Test at the Trough of Drug Activity

In the ITT population over 3 months, at the trough of drug activity, ivabradine 7.5 and 10mg twice daily produced improvements in TED of 27.6 ± 91.7 and 21.7 ± 94.5 seconds, respectively, compared with 31.2 ± 92.0 seconds for amlodipine 10mg once daily, and noninferiority ($p < 0.001$) was established (table II). Noninferiority was also confirmed in the per-protocol population (data not shown).

Similar results were obtained in the ITT population for the secondary efficacy criteria time to angina onset and time to 1mm ST-segment depression, at the trough of drug activity (table II). Both doses of ivabradine were shown to be non-inferior to amlodipine 10mg once daily and these results were confirmed in the per-protocol population (data not shown).

For all three treatments, maximum improvement in TED, time to angina onset and time to 1mm ST-segment depression was reached by the end of the first month. TED, as well as time to 1mm ST-segment depression and time to angina onset, remained essentially constant at months 2 and 3 (data not shown).

Other Efficacy Parameters

At the trough of drug activity, heart rate was significantly decreased at rest and peak of exercise in the ivabradine groups, whereas it was unchanged with amlodipine (table III). The maximal decrease in heart rate was reached within the first month of treatment, with a similar profile at rest and at peak of exercise, and values remained stable subsequently.

The decrease in the rate-pressure product (heart rate × blood pressure) was markedly and significantly greater in the two ivabradine groups than in the amlodipine group (table III), particularly at peak of exercise. In both ivabradine groups, the maximal decrease in the rate-pressure product was reached within the first month of treatment and was sustained thereafter.

Table I. Baseline characteristics of randomised population (n = 1195)

Characteristic	Ivabradine		Amlodipine
	7.5mg bid (n = 400)	10mg bid (n = 391)	10mg od (n = 404)
Age (y)	59.7 ± 9.0	59.6 ± 8.9	60.0 ± 8.9
Male (%)	341 (85.3)	346 (88.5)	347 (85.9)
Caucasian (%)	99.8	100	100
Angina grade[a]			
I (%)	14.3	17.1	11.4
II (%)	66.0	63.4	72.5
III (%)	19.8	19.4	16.1
Disease duration (mo)	72.5 ± 71	67.6 ± 64	73.6 ± 71
Previous MI (%)	43.8	42.7	45.5
Previous CABG (%)	13.3	15.1	13.9
Previous PTCA (%)	10.8	12.0	11.6
Heart rate at rest (beats/min)[b]	79 ± 13	78 ± 14	79 ± 13
Heart rate at peak of ETT (beats/min)[b]	132 ± 19	132 ± 19	131 ± 18

a Canadian Cardiovascular Society Functional Classification.

b Data obtained in the intention-to-treat population.

bid = twice daily; **CABG** = coronary artery bypass graft surgery; **ETT** exercise tolerance test; **MI** = myocardial infarction; **od** = once daily; **PTCA** = percutaneous transluminal coronary angioplasty.

After 3 months, all the treatment groups showed a marked reduction of about 60% in the frequency of angina attacks, with mean decreases in the ITT population of 3.0 ± 5.0, 3.2 ± 6.3 and 3.0 ± 6.0 attacks/week for ivabradine 7.5 and 10mg twice daily and amlodipine 10mg once daily, respectively (table IV). The results for short-acting nitrate use were broadly similar to those for anginal attack frequency, with significant reductions in use of about 50–60% in the three treatment groups (table IV).

Safety

Overall, 557 patients (46.6%) reported at least one emergent adverse event, with a higher frequency in the ivabradine 7.5 and 10mg twice daily groups (47.8% and 54.7%, respectively) than with amlodipine (37.6%). There were clinically relevant differences between the groups in the incidence of visual symptoms and sinus bradycardia (more in the ivabradine groups) and peripheral oedema (more in the amlodipine group) [table V].

A majority of the reported visual symptoms were luminous phenomena (mainly phosphenes) especially in the ivabradine groups: 96.2% of the patients in the ivabradine 7.5mg twice daily group, 95.0% in the ivabradine 10mg twice daily group, and 77.8% in the amlodipine 10mg once daily group. These symptoms were transient, generally mild and well tolerated, and did not disturb patients' daily activity. None were classified as a serious adverse event. Among the patients overall, visual symptoms resolved spontaneously during treatment (86.5% in the ivabradine 7.5mg twice daily group, 78.0% in the ivabradine 10mg twice daily group and 83.3% in the amlodipine group) or after the last intake of drug. Six patients withdrew as a result of visual symptoms (four and two in the ivabradine 7.5 and 10mg twice daily groups, respectively), in all six patients, the symptoms resolved after the last intake of study drug.

Most cases of sinus bradycardia were mild, and none were severe or serious. Two patients in the ivabradine 7.5mg group and one in the 10mg group withdrew as a result of sinus bradycardia (0.4%). Six patients (1.5%) withdrew from amlodipine treatment as a result of peripheral oedema.

The frequency of ventricular extrasystoles (from spontaneous complaints or brief ECG recordings) was slightly higher in the ivabradine groups than with amlodipine. However, analysis of 24-hour Holter recordings in the subset of 370 patients, using

Table II. Exercise tolerance test parameters at baseline and 3 months in the intention-to-treat population, measured at trough of drug activity

Variable	Amlodipine 10mg od (n = 398)	Ivabradine 7.5mg bid (n = 381)	Difference vs amlodipine, E (SE)[a] [95% CI]	p-Value for noninferiority[b]	Ivabradine 10mg bid (n = 376)	Difference vs amlodipine, E (SE)[a] [95% CI]	p-Value for noninferiority[b]
Total exercise duration (sec)							
Baseline	400.1 ± 131.9	414.4 ± 133.0			423.6 ± 142.6		
3 months	431.2 ± 140.9	442.0 ± 154.4			445.3 ± 155.5		
Change at 3 months	31.2 ± 92.0	27.6 ± 91.7	−1.8 (6.6) [−14.6, 11.1]	<0.001	21.7 ± 94.5	−6.6 (6.6) [−19.5, 6.3]	<0.001
Time to angina onset (sec)							
Baseline	313.0 ± 121.8	325.2 ± 119.9			331.4 ± 125.7		
3 months	379.5 ± 143.2	389.9 ± 156.4			391.1 ± 157.2		
Change at 3 months	66.6 ± 99.1	64.7 ± 104.9	−0.6 (7.4) [−15.2, 14.0]	<0.001	59.7 ± 110.8	−4.6 (7.5) [−19.3, 10.1]	<0.001
Time to 1mm ST-segment depression (sec)							
Baseline	347.4 ± 123.9	355.0 ± 122.4			366.9 ± 130.9		
3 months	387.1 ± 138.4	400.0 ± 152.2			401.5 ± 149.6		
Change at 3 months	39.7 ± 103.2	44.9 ± 98.6	6.5 (7.2) [−7.6, 20.6]	<0.001	34.7 ± 104.5	−1.8 (7.2) [−16.0, 12.3]	<0.001

a E (SE) and CI of the difference between ivabradine effect and amlodipine effect, based on a covariance analysis adjusted on baseline and country factors. Other values are mean ± standard deviation.

b For a noninferiority margin of −30 seconds.

bid = twice daily; **CI** = confidence interval; **E (SE)** = estimate (standard error); **od** = once daily.

Table III. Changes in heart rate and rate-pressure product (mean ± standard deviation) at 3 months in the intention-to-treat population, measured at trough of drug activity

Variable	Amlodipine 10mg od (n = 398)	Ivabradine 7.5mg bid (n = 381)	Difference vs amlodipine E (SE)[a] [95% CI]	Ivabradine 10mg bid (n = 376)	Difference vs amlodipine E (SE)[a] [95% CI]
Heart rate at rest					
Baseline	78.8 ± 13.4	78.6 ± 13.0		78.1 ± 14.1	
3 months	78.6 ± 13.2	67.4 ± 11.8		65.1 ± 12.8	
Change at 3 months	−0.2 ± 12.2	−11.2 ± 12.5	−11.1 (0.8)	−13.1 ± 13.5	−13.1 (0.8)
[95% CI][b]	[−1.5, 1.0]	[−12.5, −10.0]	[−12.6, −9.6]	[−14.4, −11.8]	[−14.7, −11.6]
p-Value[c] vs baseline	p = 0.720	p < 0.001		p < 0.001	
p-Value[d] vs amlodipine		p < 0.001		p < 0.001	
Heart rate at peak of exercise					
Baseline	131.0 ± 18.4	132.1 ± 18.9		132.1 ± 18.8	
3 months	130.8 ± 17.5	119.7 ± 7.1		117.0 ± 17.6	
Change at 3 months	−0.2 ± 12.8	−12.4 ± 15.3	−11.8 (0.9)	−15.1 ± 14.4	−14.5 (0.9)
[95% CI][b]	[−1.6, 1.3]	[−13.9, −11.0]	[−13.6, −10.1]	[−16.5, −13.4]	[−16.3, −12.7]
p-Value[c] vs baseline	p = 0.829	p < 0.001		p < 0.001	
p-Value[d] vs amlodipine		p < 0.001		p < 0.001	
Rate-pressure product at rest					
Baseline	10 377 ± 2 284	10 437 ± 2 282		10 428 ± 2 418	
3 months	9 827 ± 2 112	8 990 ± 2 019		8 764 ± 2 064	
Change at 3 months	−550 ± 1 978	−1 447 ± 2 071	−865 (122)	−1 664 ± 2 238	−1 078 (123)
[95% CI][b]	[−756, −344]	[−1 658, −1 236]	[−1 105, −625]	[−1 876, −1 452]	[−1 319, −838]
p-Value[c] vs baseline	p < 0.001	p < 0.001		p < 0.001	
p-Value[d] vs amlodipine		p < 0.001		p < 0.001	
Rate-pressure product at peak of exercise					
Baseline	23 483 ± 5 084	23 850 ± 5 203		24 158 ± 5 240	
3 months	23 012 ± 4 955	21 925 ± 5 002		21 854 ± 5 012	
Change at 3 months	−471 ± 4 042	−1 926 ± 3 848	−1 325 (258)	−2 304 ± 4077	−1 588 (259)
[95% CI][b]	[−865, −77]	[−2 328, −1 526]	[−1 831, −819]	[−2 709, −1 900]	[−2 095, −1 080]
p-Value[c] vs baseline	p = 0.019	p < 0.001		p < 0.001	
p-Value[d] vs amlodipine		p < 0.001		p < 0.001	

a E (SE) and CI of the difference between ivabradine effect and amlodipine effect, based on a covariance analysis adjusted on baseline and country factors. Other values are mean ± standard deviation.

b CI of the change within treatment group based on an analysis of variance without adjustment.

c Student's t-test based on the overall general linear model (least-squares norm).

d Student's t-test based on the overall general linear model (least-squares norm) with baseline as a covariate and country as a random factor.

bid = twice daily; **CI** = confidence interval; **E (SE)** = estimate (standard error); **od** = once daily.

Table IV. Changes in anginal attack frequency and short-acting nitrate use in the intention-to-treat population

Variable	Amlodipine 10mg od (n = 398)	Ivabradine 7.5mg bid (n = 389)	Difference E (SE)[a] [95% CI]	Ivabradine 10mg bid (n = 381)	Difference E (SE)[a] [95% CI]
Anginal attack frequency (attacks/week)					
Run-in period	5.1 ± 7.8	5.1 ± 7.7		5.1 ± 7.6	
3 months	2.0 ± 5.7	2.1 ± 5.0		1.9 ± 3.6	
Change at 3 months	−3.0 ± 6.0	−3.0 ± 5.0	0.1 (0.4) [−0.7, 0.9]	−3.2 ± 6.3	−0.2 (0.4) [−1.0, 0.6]
p-Value[b] vs baseline	p < 0.001	p < 0.001		p < 0.001	
p-Value[b] vs amlodipine		p = 0.564		p = 0.318	
Short-acting nitrate use (units/week)					
Run-in period	4.3 ± 8.2	3.7 ± 7.1		4.5 ± 8.3	
3 months	1.6 ± 3.8	1.7 ± 4.5		1.9 ± 4.5	
Change at 3 months	−2.7 ± 6.3	−1.9 ± 4.5	0.8 (0.4) [−0.0, 1.6]	−2.7 ± 6.3	0.0 (0.4) [−0.8, 0.9]
p-Value[b] vs baseline	p < 0.001	p < 0.001		p < 0.001	
p-Value[b] vs amlodipine		p = 0.972		p = 0.541	

a E (SE) and CI of the difference between ivabradine effect and amlodipine effect, based on an analysis of variance without adjustment. Other values are mean ± standard deviation.

b Student's t-test based on the overall general linear model (least-squares norm).

bid = twice daily; **CI** = confidence interval; **E (SE)** = estimate (standard error); **od** = once daily.

published criteria for proarrhythmia[9] showed that the new onset or aggravation of ventricular extrasystoles with ivabradine is not greater than with amlodipine. A total of nine cardiovascular deaths occurred during the treatment period: four (1%) in the ivabradine 7.5mg twice daily group, three (0.7%) in the ivabradine 10mg twice daily group and two (0.5%) in the amlodipine group. None of the deaths were judged as being related to treatment.

At the trough of drug activity, mean QTcB values (QTc corrected for heart rate according to the Bazett formula) decreased by 7.8 ± 24.1ms and 7.9 ± 25.0ms in the ivabradine 7.5 and 10mg groups, respectively, and by 1.6 ± 21.9ms with amlodipine, between baseline and end of treatment. At peak of drug activity (3–5 hours after drug administration, after 2 months of treatment), the decreases were greater; however, none of these mean differences in QTcB were clinically relevant. QTcB increases of ≥60ms were observed in two patients receiving ivabradine 10mg twice daily and one patient receiving amlodipine, but final values were <450ms (male) and 470ms (female) [the generally accepted thresholds for concern].

Over the treatment period no clinically relevant changes were detected in weight or in any biochemical or haematological parameters, except for a decrease in uric acid (–24.6 ± 51.8 μmol/L) in the amlodipine group. Supine systolic and diastolic blood pressures decreased by 5.7 ± 15.8 and 3.4 ± 8.4mm Hg, respectively, in the amlodipine group and remained stable in the ivabradine groups.

Table V. Emergent adverse events that occurred in >3% of patients during the 3-month treatment period

Adverse event (%)[a]	Ivabradine 7.5mg bid (n = 400)	Ivabradine 10mg bid (n = 391)	Amlodipine 10mg od (n = 404)
Visual symptoms	13.0	25.1	4.5
Peripheral oedema	0.8	1.3	7.9
Sinus bradycardia	6.5	10.5	1.7
Ventricular extrasystoles	4.5	4.1	2.7

a Percent patients reporting emergent adverse event.

bid = twice daily; **od** = once daily.

Discussion

Despite the availability of three classes of antianginal drugs (β-blockers, calcium channel antagonists and long-acting nitrates), symptom control remains poor in many patients with stable angina taking monotherapy or even combination therapy.[10] Ivabradine is a pure heart-rate-lowering agent that reduces heart rate without affecting myocardial contractility. It does this by selectively inhibiting the I_f current, a hyperpolarisation-activated Na^+/K^+ current, which is an important determinant of pacemaker activity in the sinoatrial node.[11] A reduction in heart rate reduces myocardial oxygen demand and increases diastolic filling time, which improves myocardial oxygen supply; heart-rate reduction thus acts beneficially on both sides of the oxygen 'imbalance' that gives rise to anginal symptoms. In addition, there is considerable evidence that, in terms of cardiovascular disease outcomes, a low resting heart rate in the general population or a reduction in heart rate in patients with cardiac disease are associated with a favourable prognosis.[12-14]

As a class, β-blockers are established for first-line therapy in stable angina in the absence of contraindications.[7,15] Their benefits are based mainly on heart-rate reduction.[16,17] However, the use of β-blockers is limited because of their negative inotropic effect and is restricted in patients with obstructive airway disease or peripheral artery disease. An agent such as ivabradine that reduces heart rate without any of the aforementioned limitations of β-blockers may be advantageous.[2]

The first large-scale clinical trial of ivabradine demonstrated its antianginal efficacy relative to placebo during 2 weeks of use, and continued efficacy of ivabradine was demonstrated during an open-label 2- or 3-month extension of the study.[5] The doses of 7.5 and 10mg twice daily were selected on the basis of this placebo-controlled study, which showed ivabradine 10mg twice daily to have greater efficacy than 5mg twice daily, albeit accompanied by a higher rate of adverse events.

Ivabradine has been shown to have anti-ischaemic and antianginal efficacy comparable with that of a representative β-blocker (atenolol) in 939 patients with stable angina.[6] In the current trial, ivabradine was compared with a representative calcium channel antagonist. Calcium channel antagonists are recommended as second-line therapy for stable angina[7,15] and are also frequently used as first-line therapy.[18] They have been reported to be preferred for first-line use ahead of β-blockers by 62% of a sample of European cardiologists.[19] Amlodipine is the most widely used long-acting dihydropyridine calcium channel antagonist in stable angina, with fairly homogeneous administration recommendations across countries. The 10mg once daily dose of amlodipine was selected because it has been clearly demonstrated to be efficacious in stable angina[20,21] and is the maximum dose for this indication.

In this study, ivabradine was shown to be noninferior to amlodipine in improving exercise capacity in patients with stable angina. The improvement in ETT parameters was paralleled by an improvement in symptom control, as shown by a reduction in anginal attacks and the use of short-acting nitrates. Maximal or near-maximal efficacy was attained by 1 month and was maintained for months 2 and 3. Pharmacological tolerance did not develop.

The 7.5 and 10mg twice daily doses of ivabradine were both noninferior to amlodipine in improving the primary efficacy criterion, TED, and the secondary criteria, time to angina onset and time to 1mm ST-segment depression. There was good consistency between the results in the ITT and per-protocol populations, and between the different ETT parameters. As can be seen in table II, even if the noninferiority limit had been set at −20 seconds, noninferiority of the 7.5 and 10mg doses of ivabradine would still have been established.

In all three treatment groups, the frequency of angina attacks and short-acting nitrate use were significantly decreased from baseline, with no difference between groups.

As expected on the basis of earlier reports,[3,5] the improvement in ETT parameters seen with ivabradine was accompanied by significant decreases in heart rate both at rest and at peak of

exercise (table III), whereas heart rate did not change in the amlodipine group. As a result, the decrease in the rate-pressure product (a marker of the oxygen requirement of the heart), was significantly greater in both ivabradine groups than in the amlodipine group, particularly at peak of exercise. Therefore, we may speculate that, although ivabradine and amlodipine improved ETT parameters to a similar extent, the long-term myocardial protection offered by ivabradine may be superior to that of amlodipine. In addition to relief from anginal symptoms, long-term protection of the myocardium is an important goal in antianginal therapy. A reduction in heart rate predicts an improved outcome in terms of cardiovascular mortality and morbidity,[14,22,23] and it has been suggested that much of the benefit of β-blockers in stable angina is a result of their heart-rate-lowering action.[14,24]

The higher incidence of peripheral oedema in the amlodipine group, and of sinus bradycardia in the ivabradine groups, could be expected on the basis of the two drugs' respective mechanisms of action. The higher rate of visual symptoms observed in the ivabradine groups was also expected, being related to a pharmacological mechanism of action: although the channels that conduct the I_f current are located almost exclusively in the sinoatrial node, similar ion channels are found in the retina.[25] Experimental studies demonstrated that ivabradine induces reversible inhibition of I_h current,[26] without any alterations of retinal morphology, channel distribution and pigment content.[27] In clinical studies the most reported visual symptoms were luminous phenomena (mainly phosphenes), which were transient, generally mild and well tolerated. Only 1% and 0.5% of patients in the 7.5 and 10mg groups, respectively, withdrew from treatment because of visual symptoms, while six patients (1.5%) withdrew from amlodipine treatment because of peripheral oedema.

The number of deaths observed in the three treatment groups, all resulted from a cardiovascular cause (except for one due to violent injury), are consistent with the annual mortality rate of 2–3% expected in patients with chronic stable angina.[18]

Conclusion

In summary, in patients with stable angina, ivabradine 7.5mg or 10mg twice daily was shown to have similar efficacy to amlodipine 10mg once daily in reducing anginal symptoms. Ivabradine was superior to amlodipine in reducing myocardial oxygen consumption as demonstrated by the significantly greater effect on the rate-pressure product. This study adds to the existing evidence[5,6] that pure heart-rate reduction with the specific and selective I_f inhibitor ivabradine represents a novel and attractive alternative for the treatment of patients with CAD and stable angina. Trials are ongoing to further assess the therapeutic potential of I_f inhibition. The efficacy of ivabradine in reducing major cardiovascular events in patients with coronary artery disease is currently being tested in the large-scale BEAUTIFUL trial (the morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction), which is a randomised, controlled study in patients with coronary artery disease and moderate-to-severe left ventricular dysfunction.[28]

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