European Heart Journal (2005) **26**, 2529–2536
doi:10.1093/eurheartj/ehi586

Efficacy of ivabradine, a new selective I_f inhibitor, compared with atenolol in patients with chronic stable angina

Jean-Claude Tardif[1]*, Ian Ford[2], Michal Tendera[3], Martial G. Bourassa[1], and Kim Fox[4] for the INITIATIVE Investigators

[1] *Montreal Heart Institute, 5000 Belanger Street, Montreal, Quebec H1T 1C8, Canada;* [2] *University of Glasgow, Scotland, UK;* [3] *Slaska Akademia Medyczna, Katowice, Poland; and* [4] *Royal Brompton Hospital, London, UK*

Received 13 June 2005; revised 16 September 2005; accepted 22 September 2005; online publish-ahead-of-print 7 October 2005

See page 2482 for the editorial comment on this article (doi:10.1093/eurheartj/ehi575)

KEYWORDS
Angina;
Heart rate;
Pharmacology

Aims Ivabradine, a new I_f inhibitor which acts specifically on the pacemaker activity of the sinoatrial node, is a pure heart rate lowering agent. Ivabradine has shown anti-ischaemic and anti-anginal activity in a placebo-controlled trial. The objective of this study was to compare the anti-anginal and anti-ischaemic effects of ivabradine and the beta-blocker atenolol.
Methods and results In a double-blinded trial, 939 patients with stable angina were randomized to receive ivabradine 5 mg bid for 4 weeks and then either 7.5 or 10 mg bid for 12 weeks or atenolol 50 mg od for 4 weeks and then 100 mg od for 12 weeks. Patients underwent treadmill exercise tests at randomization (M_0) and after 4 (M_1) and 16 (M_4) weeks of therapy. Increases in total exercise duration (TED) at trough at M_4 were 86.8 $\pm$ 129.0 and 91.7 $\pm$ 118.8 s with ivabradine 7.5 and 10 mg, respectively and 78.8 $\pm$ 133.4 s with atenolol 100 mg. Mean differences (SE) when compared with atenolol 100 mg were 10.3 (9.4) and 15.7 (9.5) s in favour of ivabradine 7.5 and 10 mg ($P < 0.001$ for non-inferiority). TED at M_1 improved by 64.2 $\pm$ 104.0 s with ivabradine 5 mg and by 60.0 $\pm$ 114.4 s with atenolol 50 mg ($P < 0.001$ for non-inferiority). Non-inferiority of ivabradine was shown at all doses and for all criteria. The number of angina attacks was decreased by two-thirds with both ivabradine and atenolol.
Conclusion Ivabradine is as effective as atenolol in patients with stable angina.

Introduction

Angina results when myocardial perfusion is insufficient to meet myocardial metabolic demand. A high heart rate (HR) induces myocardial ischaemia and subsequent angina as it both increases myocardial oxygen demand and decreases myocardial perfusion, the latter by shortening the duration of diastole. Beta-blockers are effective at reducing angina largely by decreasing HR[1] and are usually preferred as initial therapy in the absence of contraindications.[2] Despite the demonstrated safety and effectiveness of beta-blockers, physician use and patient compliance may be somewhat limited by the side effects of these agents, including fatigue, sexual dysfunction, depression, cold extremities, light-headedness, gastrointestinal disturbances, bronchospasm, and atrioventricular (AV) block.[3–6]

I_f, a mixed Na^+–K^+ inward current activated by hyperpolarization and modulated by the autonomic nervous system, is one of the most important ionic currents for regulating pacemaker activity in the sinoatrial (SA) node. Ivabradine (Procoralan®) is a novel specific HR lowering agent that acts in SA-node cells by selectively inhibiting the pacemaker I_f current in a dose-dependent manner.[7,8] It slows the diastolic depolarization slope of SA-node cells[9] and reduces HR at rest and during exercise in animals[9–12] and human volunteers.[13] Ivabradine has demonstrated anti-ischaemic and anti-anginal activity at doses of 5 and 10 mg bid in a placebo-controlled study involving 360 patients with stable angina.[14] The primary objective of this trial was to compare the effects of ivabradine and the beta-blocker atenolol on exercise capacity in patients with stable angina.

Methods

Study population

A randomized double-blinded, parallel-group, trial involving 144 centres in 21 countries was performed to compare the effects of (1) 4 weeks of 5 mg ivabradine bid vs. 50 mg atenolol od and (2) 12 additional weeks of 7.5 or 10 mg ivabradine bid vs. 100 mg atenolol od (*Figure 1*). Eligible patients were aged $\geq$18 years with (1) a history of stable effort angina for $\geq$3 months prior to study entry; (2) evidence of CAD manifested by $\geq$1 of five criteria (myocardial infarction $\geq$3 months before study entry, coronary angioplasty $\geq$6 months or bypass surgery $\geq$3 months before entry, coronary angiogram showing $\geq$1 diameter stenosis $\geq$50%, or

* Corresponding author. Tel: +514 376 3330 ext. 3564; fax: +514 376 1355.
E-mail address: jean-claude.tardif@icm-mhi.org

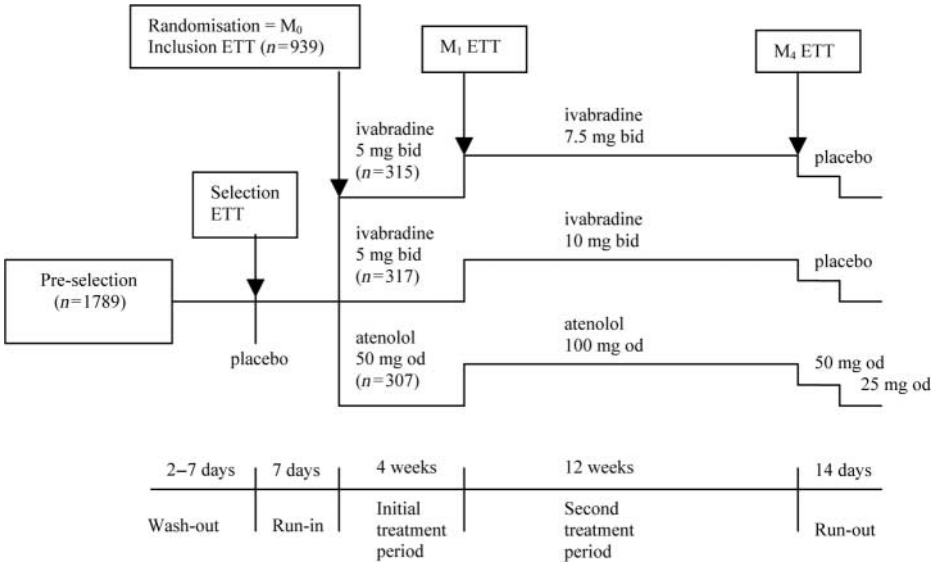

Figure 1 Study design summary.

scintigraphic/echocardiographic evidence of exercise-induced reversible myocardial ischaemia); (3) two positive exercise tolerance tests (ETT) prior to randomization defined as occurrence of limiting angina (moderate/severe pain ordinarily causing the patient to stop exercise during normal daytime activity) and 1 mm horizontal or downsloping ST-segment depression (measured 0.08 s after the J-point on $\geq$3 consecutive complexes) between 3 and 12 min of initiation; and (4) time to 1 mm ST-segment depression (TST) of the two ETTs within $\pm$20% or $\pm$1 min of each other.

Exclusion criteria included significant heart disease other than CAD; known high-grade left main CAD; congestive heart failure stage III/IV NYHA; symptomatic hypotension or uncontrolled hypertension [resting systolic blood pressure (SBP) $>$180 mmHg or diastolic blood pressure (DBP) $>$100 mmHg]; atrial fibrillation/flutter, pacemaker, or implanted defibrillator; second/third degree AV block, resting HR $<$50 bpm or sick sinus syndrome; any condition that interferes with ability to perform or interpret exercise tests (e.g. Wolff–Parkinson–White, left bundle branch block, left ventricular hypertrophy); contraindications to atenolol; recent treatment with amiodarone ($<$3 months) or bepridil ($<$7 days); ALT $>$3 times normal value; serum creatinine $>$180 μmol/L; electrolyte disorders; thyroid disorders unless controlled by thyroxine for $\geq$3 months; haemoglobin $<$100 g/L; or history of severe psychiatric disorders. Written informed consent was obtained from all patients. The study was approved by the institutional review board of each participating hospital.

Study protocol

The study design is shown in *Figure 1*. Placebo washout of anti-anginal medications first lasted 2–7 days depending on the previously administered treatment ($\geq$5 half-lives). At the end of this period, a first ETT was performed (selection visit). A 7-day single-blind placebo run-in period followed during which the patient underwent a second ETT to meet qualifying and stability criteria. Patients were then randomized using permutation blocks into one of the three treatment groups: ivabradine 5 mg bid for 4 weeks increasing to 7.5 mg bid for 12 weeks, ivabradine 5 mg bid for 4 weeks increasing to 10 mg bid for 12 weeks, or atenolol 50 mg od for 4 weeks increasing to 100 mg for 12 weeks. Capsules of ivabradine (taken twice daily), atenolol (taken in the morning), and placebo (for evening administration in the atenolol group) were identical in appearance and taste. Patients, investigators, central readers of ETT data, and the sponsor were blinded to the treatment received by the patients. After 4 weeks (M_1) and 16 weeks (M_4) of therapy, treadmill ETTs were performed at trough (12 ± 1 h after previous evening administration) and at peak of drug activity (4 ± 1 h after morning administration). At each visit, tolerability and symptoms were evaluated through questioning and diary records (for frequency of angina attacks and short-acting nitrate consumption), and patients also underwent a physical examination and resting 12-lead electrocardiogram (ECG). Samples for blood biochemistry and haematology were taken prior to randomization, at M_1 and M_4, and analysed by a central laboratory. The M_4 visit was followed by a 2-week double blind run-out period during which atenolol was progressively decreased, whereas patients in the ivabradine groups received placebo during that period.

Concomitant treatment with drugs that could interfere with the natural course of angina (long-acting nitrates, calcium antagonists, other beta-blockers, potassium-channel openers, molsidomine, or trimetazidine) or interpretation of the ST-segment changes (anti-arrhythmic agents, digitalis, MAO inhibitors) was not allowed during the trial.

Exercise testing

Symptom-limited ETTs (modified Bruce protocol[15]) included a minimum of three continuously monitored ECG leads and a 12-lead ECG recorded every 30 s, with smoking and nitroglycerin prohibited for $\geq$2 h prior to the test. The ST segment was measured at 0.08 s after the J-point in three consecutive QRS complexes with a flat baseline. If ST-segment depression was present at rest (maximum allowed $\leq$0.5 mm at rest), the change was calculated from the value at rest to the value during exercise. If ST-segment elevation was present at rest, ST depression during exercise was calculated from the ECG-isoelectric line. TST was calculated as the duration to 1 mm ST depression in the case of an isoelectric or elevated ST segment at rest or the duration to a further 1 mm depression compared with the negative basal value for those patients with ST depression at rest. When 1 mm ST depression did not occur during the randomized treatment phase, TED was used as the measure of TST. Reasons for terminating exercise were limiting angina, dyspnea, or extreme fatigue. For efficacy analyses, the original ECG printouts from the ETTs were re-analysed centrally by an independent physician blinded to treatment allocation.

Endpoints

The primary efficacy criterion was the change in TED during ETT from inclusion (M_0) to end of treatment (M_4) performed at trough of drug activity. Secondary efficacy criteria included changes in time to limiting angina (TLA), time to angina onset (TAO), TST, HR, and rate pressure product (RPP), and TED and other ETT criteria at peak of drug activity; TED, TLA, TAO, and TST from M_0 to M_1 and angina attack frequency and short-acting nitrate consumption as recorded in patients' diaries.

Statistical analysis

Sample size was estimated to demonstrate the non-inferiority of ivabradine (for the 7.5 and 10 mg bid groups) in comparison to atenolol (100 mg od) on the changes in TED from M_0 to M_4 at trough of drug activity. Because no established equivalence limit existed in stable angina, it was agreed with the European Medicines Agency that the equivalence limit for TED should be set between 30 and 40 s. Committee for Proprietary Medicinal Products (CPMP)-approved independent expert committee subsequently recommended a clinically plausible equivalence standard of 35 s (i.e. change in TED with atenolol could exceed that with ivabradine by no more than 35 s), on the basis of the mean change from baseline in TED and its standard deviation (SD), calculated by independent statisticians in a blinded review of the first 203 patients. This equivalence limit represented less than one-third of the SD of the TED changes. With a one-sided test, a Type 1 error rate of 2.5% and a power of 95%, the analysis of non-inferiority was estimated to require 285 patients per group. The main analysis of outcomes was performed on the full analysis set (all randomized patients with documentation of coronary artery disease, having taken at least one dose of study medication and who had an evaluation of the primary efficacy criterion during the randomized therapy period).

To ensure the robustness of the main analysis conclusion, an additional analysis was performed using the per-protocol population, defined as randomized patients with documentation of the studied disease, with an evaluation of the main study criterion (TED) at baseline and 4 months, without deviation interfering with these evaluations and with sufficient exposure to study drug. Additional analyses were carried out on the randomized set. For patients without ETT post-baseline, a 'maximal bias method', designed to emphasize any difference between the two treatments, was used. This assumed no change in TED at M_4 in the ivabradine groups (worst case imputation) and a clear increase in TED in the atenolol group (the third quartile of TED observed in this group at M_4, a best case imputation).

The non-inferiority of ivabradine was tested on the primary efficacy criterion using a covariance analysis with adjustment for country factor and baseline as a covariate, taking into account the equivalence limit and according to a stepwise procedure (first comparing ivabradine 7.5 mg to atenolol 100 mg and then ivabradine 10 mg to atenolol 100 mg). The comparison of ivabradine 5 mg to atenolol 50 mg at M_1 was performed independently of this stepwise procedure. The same analyses were performed on secondary efficacy criteria to which the equivalence limit applied. For other ETT criteria, number of angina attacks and short-acting nitrate consumption, the 95% confidence intervals (CI) of treatment differences were calculated. Safety analyses were performed on all patients having received $\geq$1 dose of study drug.

Results

Patient characteristics

Patients ($n = 939$) were randomized to treatment with either ivabradine 5/7.5 mg bid (315 patients) or ivabradine 5/10 mg bid (317 patients) or atenolol 50/100 mg od (307 patients), and 884 (94%) were included in the full analysis set (300, 298, and 286 patients, respectively). Baseline clinical and ETT characteristics for all randomized patients were similar in the three study groups (*Table 1*). A total of 121 patients withdrew early from study medications: 43 (13.7%) in the ivabradine 5/7.5 mg group, 43 (13.5%) in the ivabradine 5/10 mg group, and 35 patients (11.4%) in the atenolol group (*Figure 2*).

Efficacy

In the full analysis set, TED at trough increased from M_0 to M_4 by 86.8 $\pm$ 129.0 s with ivabradine 7.5 mg bid, 91.7 $\pm$ 118.8 s with ivabradine 10 mg bid, and 78.8 $\pm$ 133.4 s with atenolol 100 mg od (*Table 2*). The estimated differences (SE) when compared with atenolol 100 mg and adjusted for baseline value and country were 10.3 (9.4) s and 15.7 (9.5) s in favour of ivabradine 7.5 and 10 mg, respectively ($P < 0.001$ for non-inferiority, *Figure 3*). The adjusted estimated difference (SE) in TED (*Table 3*) between the treatment groups at M_1 was 6.7 (7.2) s in favour of ivabradine 5 mg bid ($P < 0.001$ for non-inferiority, *Figure 3*). The analyses in the per-protocol population yielded similar results. When all randomized patients were analyzed and a maximal bias hypothesis was used, the non-inferiority of ivabradine nevertheless persisted. Non-inferiority of both ivabradine groups compared with atenolol was also demonstrated for TST, TLA, and TAO (*Tables 2* and *3*, *Figure 4*). HR was consistently reduced in all treatment groups at rest and peak exercise (*Table 4*).

At peak of drug activity at M_4, the non-inferiority of both ivabradine groups vs. atenolol was shown for TED and all secondary criteria except TST. TED increased by 93.8 $\pm$ 150.9 s with ivabradine 7.5 mg bid, 99.8 $\pm$ 132.5 s with ivabradine 10 mg bid, and 108.9 $\pm$ 33.0 s with atenolol 100 mg od ($P \leq 0.01$ for non-inferiority). TST increased by 108.4 $\pm$ 165.8 s with ivabradine 7.5 mg bid, 95.4 $\pm$ 133.6 s with ivabradine 10 mg bid, and 140.5 $\pm$ 141.9 s with atenolol 100 mg od. At peak of drug activity at M_1, the non-inferiority of ivabradine 5 mg compared with atenolol 50 mg was demonstrated for all ETT criteria.

The number of angina attacks per week and consumption of short-acting nitrates were reduced in all treatment groups (*Table 5*). There were small changes in supine blood pressure from baseline to last value on treatment ($+2.3 \pm 16.5$ [95% CI: 0.41; 4.12] and $+0.9 \pm 17.3$ [-1.00; 2.73] mmHg in SBP and -1.6 ± 9.2 [-2.65; -0.57] and -1.8 ± 9.5 [-2.89; -0.80] mmHg in DBP with ivabradine 7.5 and 10 mg bid, respectively, and -4.9 ± 15.9 [-6.81; -3.02] mmHg in SBP and -3.5 ± 9.1 [-4.54; -2.42] mmHg in DPB with atenolol 100 mg od).

Safety

Ivabradine was well-tolerated, with the most frequent adverse drug reaction being visual symptoms. Most of these were mainly phosphenes (luminous phenomena) described as increases in brightness in limited areas of the visual field. These symptoms were transient, rated as non-serious, appeared on average after 40 days of treatment, occurred under well-defined conditions, such as light variation, and did not disturb patients' activities. Only five patients withdrew because of visual symptoms (two and three in the ivabradine 7.5 and 10 mg bid groups,

Table 1 Baseline characteristics of randomized population

	Ivabradine 5/7.5 mg ($n = 315$)	Ivabradine 5/10 mg ($n = 317$)	Atenolol 50/100 mg ($n = 307$)
Age, year	60.8 ± 8.5	61.1 ± 8.4	61.6 ± 6.6
Male, *n* (%)	266 (84.4)	275 (86.8)	257 (83.7)
Angina class			
I	64 (20.3)	68 (21.5)	62 (20.2)
II	225 (71.4)	222 (70.0)	215 (70.0)
III	26 (8.3)	27 (8.5)	30 (9.8)
Previous MI, *n* (%)	168 (53.3)	171 (53.9)	167 (54.4)
Previous PCI, *n* (%)	65 (20.6)	73 (23.0)	48 (15.6)
Previous CABG, *n* (%)	60 (19.0)	63 (19.9)	52 (16.9)
Supine BP (mmHg) systolic	135.6 ± 16.5	136.5 ± 16.9	136.3 ± 17.3
Supine BP (mmHg) diastolic	80.8 ± 8.9	81.5 ± 9.4	81.0 ± 8.8
Total exercise duration (s)			
Mean ± SD	592.1 ± 145.4	590.7 ± 144.9	575.7 ± 148.4
Min–max	232–1025	86–1054	163–929
Time to limiting angina (s)			
Mean ± SD	584.0 ± 141.2	583.5 ± 140.7	565.0 ± 144.6
Min–max	232–980	86–1069	163–929
Time to angina onset (s)			
Mean ± SD	466.0 ± 149.4	476.6 ± 147.3	455.1 ± 147.3
Min–max	122–780	75–920	120–780
Time to 1 mm ST depression (s)			
Mean ± SD	504.4 ± 163.9	505.3 ± 157.0	494.2 ± 156.8
Min–max	120–840	60–840	120–900
Heart rate at rest (bpm)			
Mean ± SD	80.2 ± 13.4	78.3 ± 13.7	79.1 ± 13.6
Min–max	53–140	53–137	46–120
Heart rate at peak exercise (bpm)			
Mean ± SD	125.1 ± 17.0	124.3 ± 17.3	124.7 ± 17.8
Min–max	78–175	58–170	80–194
RPP at rest (bpm × mmHg)			
Mean ± SD	10 943 ± 2482	10 683 ± 2522	10 801 ± 2418
Min–max	6440–19 992	5850–22 040	6270–17 646
RPP at peak exercise (bpm × mmHg)			
Mean ± SD	21419 ± 4621	21 127 ± 4629	21 643 ± 5195
Min–max	10 032–35 190	11 900–39 500	11 440–43 680

BP, blood pressure; CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention.

respectively). Sinus bradycardia was reported as an adverse event in 2.2 and 5.4% in the ivabradine 7.5 and 10 mg groups and in 4.3% with atenolol. Headache was reported in 2.6, 4.8, and 1.6% in the three groups, respectively.

The corrected QT interval (QTc) decreased by 10 ± 40 and 9 ± 35 ms in the ivabradine 7.5 and 10 mg groups, respectively, and by 12 ± 38 ms with atenolol from baseline to end of treatment. QTc increased by >60 ms in one, two, and two patients in the ivabradine 7.5 and 10 mg bid and in the atenolol groups, respectively. A total of six deaths (all cardiac) occurred during the treatment or run-out periods: two in the ivabradine 7.5 mg bid group, three in the ivabradine 10 mg bid group, and one in the atenolol 100 mg od group. No rebound phenomenon was observed after ivabradine discontinuation.

Discussion

In this 4 month randomized, double-blind, multicenter study, the non-inferiority of ivabradine 7.5 and 10 mg bid compared with atenolol 100 mg od was demonstrated for all exercise parameters in both the full analysis set and per-protocol population. The increase in TST by ~1.5 min indicates that the improvement in total exercise capacity is associated with a relevant anti-ischaemic effect. When compared with baseline, HR and RPP were reduced at end of treatment, at rest, and peak of exercise in all study groups. The decrease in HR at peak exercise was greater with atenolol (14.0 bpm) than with ivabradine (8.6–10.3 bpm with 7.5–10 mg), showing that ivabradine induced a similar or greater improvement in exercise capacity than atenolol for a comparatively smaller reduction in RPP and HR. The improvement in exercise test parameters was associated with marked decreases in the number of angina attacks and short-acting nitrate consumption. At M_1, the non-inferiority of ivabradine 5 mg bid vs. atenolol 50 mg od was also demonstrated. At peak of drug activity at M_4, the non-inferiority of ivabradine was shown for all criteria except TST.

The doses of ivabradine 5 and 10 mg bid were known to be active in the treatment of angina in a placebo-controlled dose-ranging study.[14] In the current study, the dose of 7.5 mg bid was studied because it was expected to retain

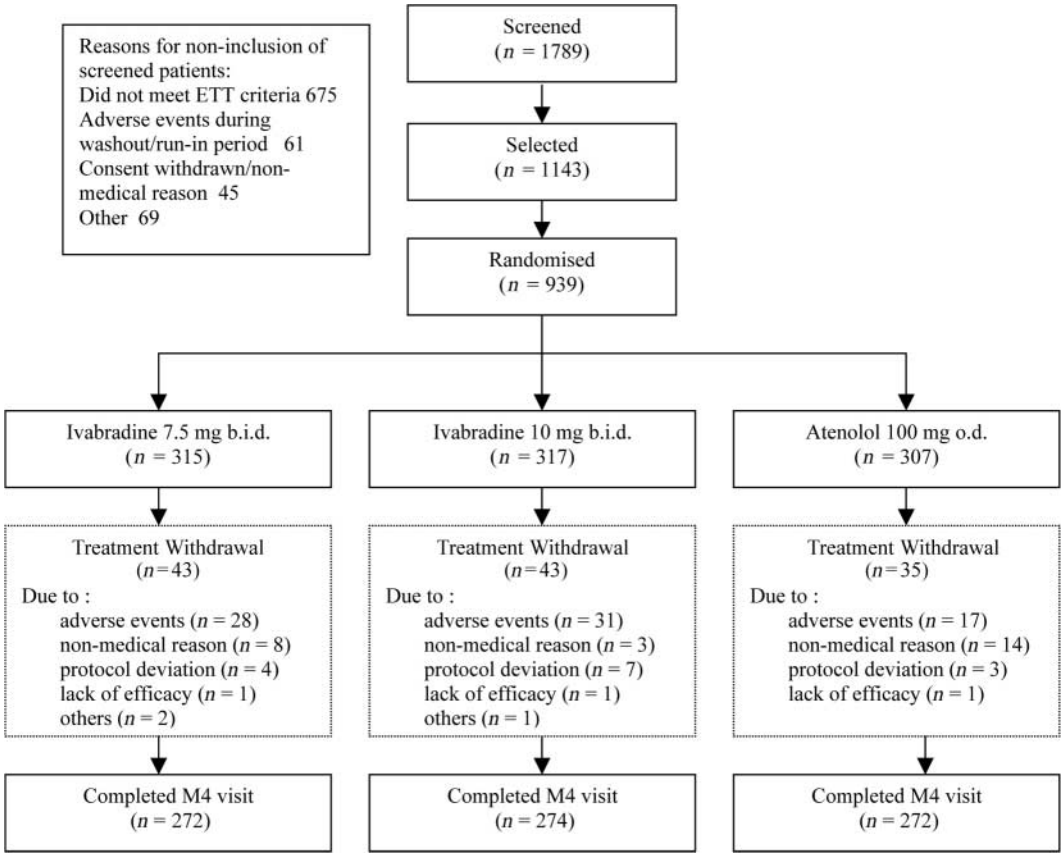

Figure 2 Patient disposition in study. The difference in number of withdrawals due to adverse events was not statistically significant.

Table 2 Changes in exercise tests from M_0 to M_4 at trough of drug activity in the full analysis set

	Ivabradine 7.5 mg bid ($n = 300$)	Ivabradine 10 mg bid ($n = 298$)	Atenolol 100 mg od ($n = 286$)
Total exercise duration (s)			
Baseline	594.9 ± 141.6	590.8 ± 142.9	578.2 ± 144.2
Change	86.8 ± 129.0	91.7 ± 118.8	78.8 ± 133.4
Difference[a] (SE)	10.3 (9.4)	15.7 (9.5)	
95% CIs	[−8.3; 28.8]	[−2.9; 34.3]	
P-value, non-inferiority	$P < 0.001$	$P < 0.001$	
Time to limiting angina (s)			
Baseline	587.0 ± 138.0	583.5 ± 139.6	568.1 ± 139.8
Change	91.8 ± 131.1	96.9 ± 121.2	85.4 ± 133.7
Difference[a] (SE)	9.3 (9.7)	15.1 (9.7)	
95% CIs	[−9.6; 28.3]	[−3.9; 34.0]	
P-value, non-inferiority	$P < 0.001$	$P < 0.001$	
Time to angina onset (s)			
Baseline	468.0 ± 147.1	477.0 ± 147.8	457.4 ± 145.0
Change	145.2 ± 153.4	139.6 ± 140.6	135.2 ± 154.7
Difference[a] (SE)	12.1 (11.5)	10.1 (11.6)	
95% CIs	[−10.5; 34.7]	[−12.5; 32.8]	
P-value, non-inferiority	$P < 0.001$	$P < 0.001$	
Time to 1 mm ST depression (s)			
Baseline	521.7 ± 164.3	528.6 ± 161.8	510.7 ± 156.0
Change	98.0 ± 153.7	86.9 ± 128.2	95.6 ± 147.5
Difference[a] (SE)	4.3 (10.7)	−3.3 (10.8)	
95% CIs	[−16.8; 25.3]	[−24.4; 17.8]	
P-value, non-inferiority	$P < 0.001$	$P = 0.002$	

SE, standard error.
[a]Ivabradine–atenolol, estimate adjusted for baseline and country factors.

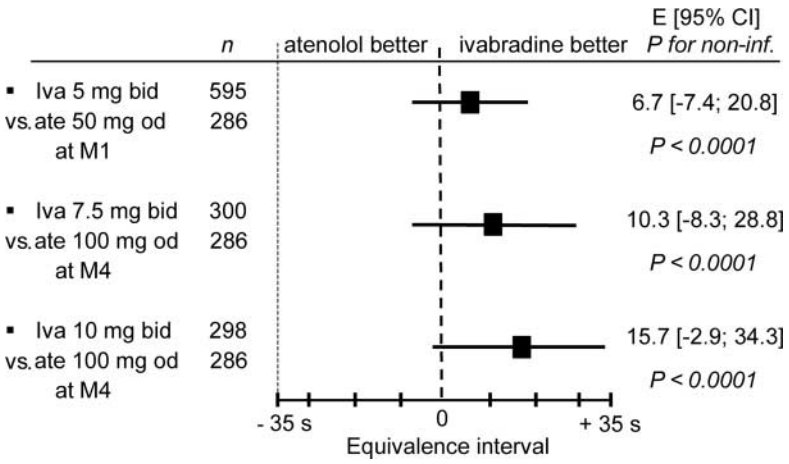

Figure 3 Effects on total exercise duration at trough of drug activity.

Table 3 Changes in exercise tests from M_0 to M_1 at trough of drug activity in the full analysis set

	Ivabradine 5 mg bid ($n = 595$)	Atenolol 50 mg od ($n = 286$)
Total exercise duration (s)		
Baseline	593.6 ± 141.8	578.2 ± 144.2
Change	64.2 ± 104.0	60.0 ± 114.4
Difference (SE)	6.7 (7.2)	
95% CIs	[−7.4; 20.8]	
P-value, non-inferiority	$P < 0.001$	
Time to limiting angina (s)		
Baseline	586.0 ± 138.4	568.1 ± 139.8
Change	68.5 ± 104.7	66.3 ± 114.1
Difference (SE)	5.0 (7.3)	
95% CIs	[−9.3; 19.3]	
P-value, non-inferiority	$P < 0.001$	
Time to angina onset (s)		
Baseline	473.5 ± 146.9	457.6 ± 145.3
Change	100.2 ± 134.9	102.8 ± 138.3
Difference (SE)	0.7 (9.4)	
95% CIs	[−17.7; 19.2]	
P-value, non-inferiority	$P < 0.001$	
Time to 1 mm ST depression (s)		
Baseline	523.9 ± 162.8	509.8 ± 156.7
Change	68.8 ± 122.5	67.2 ± 132.3
Difference (SE)	4.9 (8.5)	
95% CIs	[−11.9; 21.7]	
P-value, non-inferiority	$P < 0.001$	

most of the efficacy of the 10 mg bid dose while minimizing side effects. The efficacy of ivabradine was assessed against a positive control in agreement with CPMP guidelines, which recognize that it would be unethical to conduct a 4 months study using only placebo in some patients. The reference medication selected was atenolol, a selective beta-blocker well-established in the treatment of stable angina with a long duration of action which allows a once-daily regimen.[16–20] Maximal efficacy of atenolol is reached after 4–6 weeks and preserved over 1 year.[21]

Regulatory guidelines specify that total exercise capacity measured as TED at trough of drug activity, should be the primary efficacy criterion in anti-anginal trials such as this one (CPMP, 1996). The guidelines also specify how studies assessing the non-inferiority of a new drug against an active comparator should be conducted, and these recommendations were followed in the INITIATIVE trial. The anti-anginal and anti-ischaemic effects of ivabradine were initially established in a placebo-controlled trial involving 360 patients.[14] The 5 and 10 mg bid dosages of ivabradine demonstrated superiority to placebo in the prevention of angina and ischaemia and showed the absence of rebound phenomena or tolerance. In contrast to ivabradine, the other HR reducing agent zatebradine did not provide anti-ischaemic benefit.[22] One important reason for this difference is likely that ivabradine is a better I_f channel inhibitor,[23] and its half-block concentration being 1.5 μmol/L whereas that of zatebradine is 80 μmol/L.[24]

The design of this study does not allow to strictly compare the safety of ivabradine and atenolol, because about two-thirds of the patients had previously received beta-blockers and were known to tolerate these drugs; patients with known intolerance or contraindications to atenolol were specifically excluded. Ivabradine was well tolerated, with transient visual symptoms being the main drug-related adverse event. These symptoms may be linked to the presence in the retina of ion channels similar to cardiac I_f channels and did not adversely affect the tolerability of the drug for most patients. The incidence of sinus bradycardia with ivabradine was similar to or lower than that usually reported with beta-blockers. There was a slightly higher number of deaths in the ivabradine groups (2 [0.6%] and 3 [1.0%], respectively) than in the atenolol group (1 [0.3%]) that was not statistically significant and falls within the expected mortality range for patients with chronic stable angina. Although this is likely a chance finding, a larger study in CAD patients will assess the effect of ivabradine on cardiovascular mortality.

Study limitations

One study limitation was the lack of an established placebo-controlled equivalence limit for the effect of atenolol. A clinically plausible equivalence standard of 35 s during ETT was estimated by an independent expert committee following a rule approved by the regulatory agency. At the doses employed, ivabradine tended to provide a nominally greater improvement in exercise tolerance than atenolol,

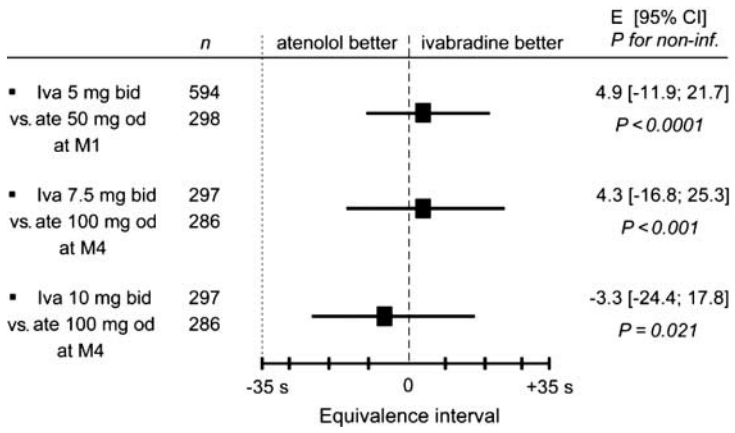

Figure 4 Effects on time to 1 mm ST segment depression (TST) at trough of drug activity.

Table 4 Changes in heart rate and rate pressure product (RPP) at trough of drug activity

	Ivabradine 5 mg bid[a] ($n = 594$)	Atenolol 50 mg od[a] ($n = 286$)	Ivabradine 7.5 mg bid[b] ($n = 299$)	Ivabradine 10 mg bid[b] ($n = 298$)	Atenolol 100 mg od[b] ($n = 286$)
Heart rate at rest (bpm)					
Baseline	79.2 ± 13.5	78.9 ± 13.6	80.1 ± 13.4	78.4 ± 13.6	78.9 ± 13.6
Change	−10.3 ± 11.1	−12.8 ± 11.4	−14.3 ± 11.9	−14.3 ± 13.3	−15.6 ± 12.0
Difference (SE)	2.7 (0.6)		2.1 (0.8)	1.1 (0.8)	
95% CIs	[1.4; 4.0]		[0.6; 3.7]	[−0.4; 2.7]	
Heart rate at peak exercise (bpm)					
Baseline	124.7 ± 17.1	124.4 ± 17.2	125.2 ± 17.1	124.3 ± 17.1	124.4 ± 17.2
Change	−7.5 ± 12.7	−11.1 ± 12.8	−8.6 ± 13.7	−10.3 ± 14.1	−14.0 ± 14.4
Difference (SE)	3.6 (0.8)		5.6 (1.0)	3.6 (1.0)	
95% CIs	[2.0; 5.3]		[3.5; 7.6]	[1.6; 5.6]	
RPP at rest (bpm × mmHg)					
Baseline	10 809 ± 2499	10 758 ± 2407	10 919 ± 2494	10 721 ± 2499	10 759 ± 2400
Change	−1357 ± 1966	−1967 ± 1949	−1845 ± 2145	−1852 ± 2400	−2417 ± 1969
Difference (SE)	643 (115)		682 (135)	555 (136)	
95% CIs	[417; 869]		[417; 948]	[288; 821]	
RPP at peak exercise (bpm × mmHg)					
Baseline	21 338 ± 4629	21 587 ± 5254	21 435 ± 4658	21 063 ± 4653	21 599 ± 5214
Change	−957 ± 3533	−2571 ± 3573	−1068 ± 4085	−1449 ± 3595	−3152 ± 3924
Difference (SE)	1534 (255)		1980 (302)	1466 (300)	
95% CIs	[1035; 2037]		[1387; 2573]	[878; 2054]	

[a] $M_1 - M_0$.
[b] $M_4 - M_0$.

Table 5 Treatment effects on angina attacks and nitrate consumption

	Ivabradine 5[a] ($n = 606$)	Atenolol 50[a] ($n = 293$)	Ivabradine 7.5[b] ($n = 307$)	Ivabradine 10[b] ($n = 303$)	Atenolol 100[b] ($n = 294$)
Weekly number of angina attacks (mean ± SD)					
Baseline	3.2 ± 5.4	3.7 ± 4.5	3.1 ± 5.3	3.3 ± 5.4	3.7 ± 14.5
Last post M_0	1.6 ± 3.4	1.5 ± 5.9	1.0 ± 2.3	1.0 ± 2.5	1.0 ± 3.3
Change	−1.6 ± 3.6	−2.2 ± 9.4	−2.2 ± 4.3	−2.3 ± 4.2	−2.7 ± 12.3
Short-acting nitrate consumption (units/week) (mean ± SD)					
Baseline	2.2 ± 5.0	1.7 ± 4.5	2.2 ± 4.9	2.1 ± 5.1	1.8 ± 4.5
Last post M_0	1.1 ± 3.3	0.7 ± 2.1	0.6 ± 2.1	0.8 ± 2.6	0.6 ± 2.2
Change	−1.1 ± 3.7	−1.0 ± 3.4	−1.6 ± 4.1	−1.4 ± 4.7	−1.2 ± 3.4

[a] $M_1 - M_0$.
[b] $M_4 - M_0$.

and the equivalence limits were therefore not approached. No effort was made to titrate either drug to maximally tolerable doses; therefore, no inferences can be made about relative superiority of one to the other. Rather, these data indicate that, at clinically plausible doses, ivabradine is not inferior to atenolol. Although no important safety concerns were raised by this trial and, specifically, no severe or irreversible ophthalmologic problems were observed, the limited duration of observation suggests the need for longer follow-up before firm conclusions about safety in chronic use can be drawn.

In conclusion, the I_f inhibitor ivabradine is as effective as atenolol, a well-established reference drug for the treatment of stable angina.

Acknowledgement

This study was supported by Servier, France.

Conflict of interest: none declared.

References

1. Guth BD, Heusch G, Seitelberger R, Ross J Jr. Mechanisms of beneficial effect of beta-adrenergic blockade on exercise-induced myocardial ischemia in conscious dogs. *Circ Res* 1987;**60**:738–746.
2. North of England Stable Angina Guideline Development Group. Summary version of evidence based guideline for the primary care management of angina. *Br Med J* 1996;**312**:827–832.
3. Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA* 2002;**288**:351–357.
4. Fogari R, Zoppi A, Corradi L, Mugellini A, Poletti L, Lusardi P. Sexual function in hypertensive males treated with lisinopril or atenolol: a cross-over study. *Am J Hypertens* 1998;**11**:1244–1247.
5. Tafreshi MJ, Weinacher AB. Beta-adrenergic-blocking agents in bronchospastic diseases: a therapeutic dilemma. *Pharmacotherapy* 1999;**19**:974–978.
6. Freytag F, Schelling A, Meinicke T, Deichsel G. Telmisartan comparison of 26-week efficacy and tolerability of telmisartan and atenolol, in combination with hydrochlorothiazide as required, in the treatment of mild to moderate hypertension: a randomised, multicenter study. *Clin Ther* 2001;**23**:108–123.
7. DiFrancesco D. Characterization of single pacemaker channels in cardiac sino-atrial node cells. *Nature* 1986;**324**:470–473.
8. DiFrancesco D. The contribution of the "pacemaker" current (I_f) to generation of spontaneous activity in rabbit sino-atrial node myocytes. *J Physiol* 1991;**34**:23–40.
9. Thollon C, Cambarrat C, Vian J, Prost JF, Peglion JL, Vilaine JP. Electrophysiological effects of S 16257, a novel sino-atrial node *Pharmacol* modulator, on rabbit and guinea-pig cardiac preparations: comparison with UL-FS 49. *Br J Pharmacol* 1994;**112**:37–42.
10. Bois P, Bescond J, Renaudon B, Lenfant J. Mode of action of bradycardic agent, S16257, on ionic currents of rabbit sinoatrial node cells. *Br J Pharmacol* 1996;**118**:1051–1057.
11. Gardiner SM, Kemp PA, March JE, Bennett T. Acute and chronic cardiac and regional haemodynamic effects of the novel bradycardic agent, S16257, in conscious rats. *Br J Pharmacol* 1995;**115**:579–586.
12. Simon L, Ghaleb B, Puybasset L, Giudicelli JF, Berdeaux A. Coronary and hemodynamic effects of S16257, a new bradycardic agent, in resting and exercising conscious dogs. *J Pharmacol Exp Ther* 1995;**275**:659–666.
13. Ragueneau I, Laveille C, Jochemsen R, Resplandy G, Funck-Brentano C, Jaillon P. Pharmacokinetic–pharmacodynamic modeling of the effects of ivabradine, a direct sinus node inhibitor, on heart rate in healthy volunteers. *Clin Pharmacol Ther* 1998;**64**:192–203.
14. Borer JS, Fox K, Jaillon P, Lerebours G; Ivabradine Investigators Group. Anti-anginal and anti-ischemic effects of ivabradine, an I_f inhibitor, in stable angina: a randomized, double-blinded, multicentered, placebo-controlled trial. *Circulation* 2003;**107**:817–823.
15. McInnis KJ, Balady GJ, Weiner DA, Ryan TJ. Comparison of ischaemic and physiologic responses during exercise tests in men using the standard and modified Bruce protocols. *Am J Cardiol* 1992;**69**:84–89.
16. Wadworth A, Murdveh D, Brogders R. Atenolol a reappraisal of its pharmacological properties and therapeutic use in cardiovascular disorders. *Drugs* 1991;**42**:468–510.
17. de Muinck ED, Buchner-Moell D, van de Ven LL, Lie KI. Comparison of the safety and efficacy of bisoprolol versus atenolol in stable exercise-induced angina pectoris. *J Cardiovasc Pharmacol* 1992;**19**:870–875.
18. Rodrigues EA, Lawrence JD, Dasgupta P, Hains AD, Lahiri A, Wilkinson PR, Raftery EB. Comparison of bevantolol and atenolol in chronic stable angina. *Am J Cardiol* 1988;**61**:1204–1209.
19. Shapiro W. Comparison of once-daily atenolol and placebo in the treatment of stable angina. *Cardiovasc Rev Reports* 1985;**6**:1292–1304.
20. Shapiro W, Narahara KA, Kostis JB, Thandroyen F, Zohman LR. Comparison of atenolol and nifedipine in chronic stable angina pectoris. *Am J Cardiol* 1989;**64**:186–190.
21. Schwartz JB, Jackson G, Kates RE, Harrison DC. Long-term benefit of cardioselective beta blockade with one-daily atenolol therapy in angina pectoris. *Am Heart J* 1981;**101**:380–385.
22. Frishman WH, Pepine CJ, Weiss RJ, Baiker WM. Addition of zatebradine provides no greater exercise tolerance benefit in patients with angina taking extended-release nifedipine. *J Am Coll Cardiol* 1995;**26**:305–312.
23. Di Francesco D. I_f inhibition: a novel mechanism of action. *Eur Heart J* 2003;**5**(Suppl. G):G19–G25.
24. Van Bogaert PP, Goethals M, Simoens C. Use- and frequency-dependent blockade by UL-FS 49 of the I_f pacemaker current in sheep cardiac Purkinje fibres. *Eur J Pharmacol* 1990;**187**:241–256