Antianginal and Antiischemic Effects of Ivabradine, an I_f Inhibitor, in Stable Angina
A Randomized, Double-Blind, Multicentered, Placebo-Controlled Trial

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Background—Heart rate reduction should benefit patients with chronic stable angina by improving myocardial perfusion and reducing myocardial oxygen demand. This study evaluated the antianginal and antiischemic effects of ivabradine, a new heart rate–lowering agent that acts specifically on the sinoatrial node.

Methods and Results—In a double-blind, placebo-controlled trial, 360 patients with a ≥3-month history of chronic stable angina were randomly assigned to receive ivabradine (2.5, 5, or 10 mg BID) or placebo for 2 weeks, followed by an open-label 2- or 3-month extension on ivabradine (10 mg BID) and a 1-week randomized withdrawal to ivabradine (10 mg BID) or placebo. Primary efficacy criteria were changes in time to 1-mm ST-segment depression and time to limiting angina during bicycle exercise (exercise tolerance tests), performed at trough of drug activity. In the per-protocol population (n = 257), time to 1-mm ST-segment depression increased in the 5 and 10 mg BID groups (P < 0.005); time to limiting angina increased in the 10 mg BID group (P < 0.05). Deterioration in all exercise tolerance test parameters occurred in patients who received placebo during randomized withdrawal (all P < 0.02) but not in those still receiving ivabradine. No rebound phenomena were observed on treatment cessation.

Conclusions—Ivabradine produces dose-dependent improvements in exercise tolerance and time to development of ischemia during exercise. These results suggest that ivabradine, representing a novel class of antianginal drugs, is effective and safe during 3 months of use; longer-term safety requires additional assessment. (Circulation. 2003;107: 817-823.)

Key Words: angina • coronary disease • ischemia

Stable angina pectoris is common and disabling, affecting 30 000 to 40 000 per 1 million people in Europe and the United States.1 Angina often seriously limits everyday activities and frequently leads to premature retirement from work.1 Angina results from an imbalance between myocardial perfusion and myocardial metabolic demands. Heart rate reduction can alter both elements of this imbalance beneficially. The resulting increase in diastolic filling time should improve myocardial perfusion; myocardial oxygen demand varies directly with heart rate.

Ivabradine (Procoralan) is a member of a new class of selective heart rate–lowering agents that act specifically on the sinoatrial node (SAN). Ivabradine selectively and specifically inhibits I_f, a primary SAN pacemaker current,2–5 reducing heart rate at rest and during exercise in experimental animals6–8 and in healthy human volunteers.9 Therefore, the efficacy and safety of 3 doses of ivabradine for relieving angina and underlying ischemia and the relation between drug-induced heart rate slowing and ischemia relief were explored in patients with stable angina.

Methods
A randomized, double-blind, placebo-controlled, parallel-arm trial (Figure 1) was performed to investigate the effects of ivabradine (2.5, 5, or 10 mg BID) on time to 1-mm ST-segment depression and time to limiting angina during standardized bicycle exercise tolerance tests (ETT). Placebo washout of antianginal medications (including β-blockers, calcium channel blockers, and long-acting nitrates) and drugs that could interfere with ST-segment changes (including class I antiarrhythmic agents, digitalis, and monoamine oxidase inhibitors) lasted 2 to 7 days, depending on half-life; stability of ETT performance and protocol compliance then was assessed during a 1-week, single-blind, placebo run-in. Other drugs were unaffected by the protocol. Patients then were randomly assigned, in double-blind fashion, to receive ivabradine or placebo for 2 weeks. This was followed by a 2- or 3-month open-label extension phase (participation voluntary, depending on administrative constraints in participating countries), during which all patients received 10 mg
BID ivabradine and received no other antianginal drugs except short-acting nitrates. Patients then underwent double-blind random assignment to continue on 10 mg BID ivabradine or to withdraw to placebo for 1 week, followed by another ETT.

The ethical principles of the Declaration of Helsinki (1964, revised 1989) were observed, with written informed consent by each patient after protocol approval by independent ethics committees.

Inclusion criteria included age >18 years, 3-month history of chronic, stable, effort-induced angina (without prior mechanical therapy or >3 months after CABG or >6 months after PTCA) relieved by rest or nitroglycerin, plus catheterization-documented coronary artery disease or previous myocardial infarction >3 months before random assignment; all patients needed to manifest positive ETT (with both limiting angina and ST-segment depression ≥1 mm compared with rest) at selection (D-7) and at inclusion (D0). ETT performance between D-7 and D0 could not differ by >20% or >1 minute in time to 1-mm ST-segment depression. Female participants needed to be of nonchildbearing potential.

Exclusion criteria included unstable angina, Prinzmetal angina or “microvascular angina,” significant valvular disease, atrial fibrillation/flutter or indwelling pacemaker, 2° and 3° atrioventricular block, or inability to perform ETT.

Primary efficacy criteria were changes in time to 1-mm horizontal or downsloping ST-segment depression ≥0.08 seconds after the J point and time to limiting angina during ETT performed at the trough of drug activity (12 hours after last drug administration). Changes in ETT at peak drug activity (4 hours after drug administration) and angina attack frequency, from patients’ diaries, also were measured. ETT were performed on an ergometric bicycle; initial workload (30 W) was increased by 30 W every 2 minutes. For efficacy evaluation, ETT ECGs were reanalyzed centrally by a blinded physician independent of study recruitment (Prof. A. Cohen-Solal, Beaujon Hospital, Clichy, France).

Safety measures included adverse events, vital signs, blood pressure during ETT, ECG at rest, 24-hour Holter monitoring (in a subset of 75 patients equally distributed between treatment groups), and clinical chemistry/hematology analyses.

Groups comprising 63 patients are sufficient to detect a 1-minute increase in time to 1-mm ST-segment depression with 80% power at the 5% significance level when anticipated standard deviation is 120 seconds. To account for uninterpretable data, ≥70 per-protocol patients per group were planned.

Treatments were assigned by random permutation blocks (fixed block size=4, 1 to 3 complete blocks per center) according to chronological order of inclusion within each center. During double-blind phases, participants, investigators, and outcome assessors were blinded to the treatment assignments. Placebo and the 3 ivabradine doses were supplied in tablets of identical shape, appearance, and taste, in blister packs identified by the study phase number and patient random assignment number. At study onset, investigators received a set of randomization envelopes for secure storage enabling code-breaking in emergencies.

Comparisons between groups were performed with the use of a 1-way ANOVA and the Kruskal-Wallis test. The 3 active groups also
were compared with placebo by use of the 2-tailed Dunnett’s test and the equivalent nonparametric approach. Dose-effect relation was studied by means of linear regression.

Efficacy analyses were performed in the per-protocol and intention-to-treat populations; unless otherwise stated, results are presented for the per-protocol population (comprising study compliers without major protocol violations, with trough ETT results at end of study, and evaluable time to 1-mm ST-segment depression at baseline). The safety population included all randomly assigned patients who took at least one treatment dose (even if inclusion in per-protocol or intention-to-treat populations was precluded because ETT at 2 weeks on drug [D14] was not performed). Safety measures were analyzed with the use of descriptive statistics.

Results are expressed as mean±SD unless otherwise indicated; a value of \( P<0.05 \) was considered significant.

Results

Of 529 patients screened, 400 were selected for study (Figure 1). Forty selected patients were not randomly assigned at the end of the run-in phase, usually because ETT at D0 was negative.

During the double-blind, dose-ranging phase, 103 (28.6%) randomly assigned patients were excluded from the per-protocol population (reasons included baseline ETT negative on central reading \( n=51 \); timing of treatment administration incorrect in relation to ETT \( n=17 \); ETT on D0 not evaluable \( n=15 \); baseline ETT not stable between D-7 and D0 \( n=13 \); dropout before D14 with no end-of-trial ETT \( n=9 \)). No clinically relevant differences in baseline characteristics were observed between the randomly assigned and per-protocol populations (Table 1) or between the different treatment groups.

### Efficacy

**ETT at Trough of Drug Activity**

Between the start (D0) and end (D14) of the double-blind, dose-ranging phase, resting heart rate at trough of drug activity fell relative to placebo in all 3 active treatment groups \( (P<0.05, \text{Figure 2}) \). Maximal heart rate during exercise decreased in parallel (Figure 2). Heart rate varied inversely with dose at rest \( (r=−0.45) \) and during exercise \( (r=−0.46, \text{both} \ P<0.0001) \).

Time to 1-mm ST-segment depression during ETT increased with ivabradine treatment (Table 2). The change was significant relative to placebo in the 5 mg BID and 10 mg BID groups; a dose effect was seen across all doses \( (r=0.17, \text{Figure 2}) \).

**Table 1. Baseline Characteristics of Randomly Assigned and Per-Protocol Populations in the Double-Blind, Dose-Ranging Phase**

<table>
<thead>
<tr>
<th></th>
<th>Randomly Assigned Population ( n=360 )</th>
<th>Per-Protocol Population ( n=257 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.5±9.2 (35–86)</td>
<td>58.1±8.9 (37–86)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>89.7</td>
<td>90.7</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>79.0±11.2 (50–118)</td>
<td>79.6±11.1 (57–118)</td>
</tr>
<tr>
<td>Supine SBP, mm Hg</td>
<td>133.7±16.3 (95–197)</td>
<td>132.7±16.3 (95–197)</td>
</tr>
<tr>
<td>Supine DBP, mm Hg</td>
<td>81.3±8.2 (55–112)</td>
<td>81.2±7.9 (55–100)</td>
</tr>
<tr>
<td>Supine heart rate, bpm</td>
<td>69.7±10.3 (47–106)</td>
<td>69.1±9.7 (47–104)</td>
</tr>
<tr>
<td>Coronary artery disease duration, mo</td>
<td>68.1±63.9 (2–300)</td>
<td>67.9±61.2 (3–300)</td>
</tr>
<tr>
<td>Mean frequency of angina attacks per wk</td>
<td>5.3±7.9 (0–78)</td>
<td>5.4±8.2 (0–78)</td>
</tr>
<tr>
<td>Mean duration of drug, U/wk</td>
<td>3.4±7.6 (0–80)</td>
<td>3.4±7.9 (0–80)</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>218 (60.6)</td>
<td>152 (59.1)</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td>59 (16.4)</td>
<td>43 (16.7)</td>
</tr>
<tr>
<td>Previous PTCA, n (%)</td>
<td>66 (18.3)</td>
<td>39 (15.2)</td>
</tr>
</tbody>
</table>

Mean±SD (range), except where indicated. DBP indicates diastolic blood pressure; MI, myocardial infarction; and SBP, systolic blood pressure.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Changes in heart rate at rest (A) and at peak exercise (B) in the different treatment groups during double-blind dose-ranging. Error bars, Standard error of the mean. *\( P<0.05 \) vs placebo in pairwise comparison.
TABLE 2. ETT Parameters at Trough of Drug Activity During Double-Blind, Dose-Ranging Phase

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n=68)</th>
<th>Ivabradine 2.5 mg BID (n=64)</th>
<th>Ivabradine 5 mg BID (n=59)</th>
<th>Ivabradine 10 mg BID (n=66)</th>
<th>Between Group P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to 1-mm ST-depression, s</td>
<td>369.1±119.0</td>
<td>343.7±120.7</td>
<td>364.1±119.3</td>
<td>370.2±120.8</td>
<td></td>
</tr>
<tr>
<td>D0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D14</td>
<td>378.0±124.2</td>
<td>375.7±121.2</td>
<td>408.2±122.8</td>
<td>416.4±155.7</td>
<td></td>
</tr>
<tr>
<td>D14-D0</td>
<td>9.0±63.6</td>
<td>32.0±74.3</td>
<td>44.1±80.1*</td>
<td>46.2±78.2*</td>
<td>0.016</td>
</tr>
<tr>
<td>Time to limiting angina, s</td>
<td>417.8±115.6</td>
<td>402.5±121.0</td>
<td>432.8±124.0</td>
<td>430.5±125.4</td>
<td></td>
</tr>
<tr>
<td>D0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D14</td>
<td>430.5±119.0</td>
<td>425.0±116.4</td>
<td>460.0±115.1</td>
<td>471.3±148.4</td>
<td></td>
</tr>
<tr>
<td>D14-D0</td>
<td>12.7±51.3</td>
<td>22.5±55.4</td>
<td>27.2±56.8</td>
<td>40.8±69.3*</td>
<td>0.049</td>
</tr>
<tr>
<td>Time to angina onset, s</td>
<td>352.8±98.2</td>
<td>330.5±105.4</td>
<td>355.6±110.9</td>
<td>351.5±123.1</td>
<td></td>
</tr>
<tr>
<td>D0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D14</td>
<td>377.5±116.3</td>
<td>368.1±112.5</td>
<td>394.4±132.3</td>
<td>420.8±148.8</td>
<td></td>
</tr>
<tr>
<td>D14-D0</td>
<td>24.7±64.2</td>
<td>37.6±57.7</td>
<td>38.8±61.7</td>
<td>69.4±74.8*</td>
<td>0.003</td>
</tr>
<tr>
<td>RPP at peak of exercise, bpm/mm Hg</td>
<td>23057±5498</td>
<td>23924±4885</td>
<td>24772±5577</td>
<td>24183±4623</td>
<td>0.011</td>
</tr>
<tr>
<td>D0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D14</td>
<td>23323±5488</td>
<td>23187±5052</td>
<td>23630±5253</td>
<td>22640±4540</td>
<td></td>
</tr>
<tr>
<td>D14-D0</td>
<td>266±3074</td>
<td>−737±2950</td>
<td>−1142±3354*</td>
<td>−1543±3526*</td>
<td>0.011</td>
</tr>
<tr>
<td>Total work performed, W/min</td>
<td>501.7±246.2</td>
<td>473.9±240.6</td>
<td>538.0±269.6</td>
<td>534.0±278.8</td>
<td></td>
</tr>
<tr>
<td>D0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D14</td>
<td>529.1±256.8</td>
<td>515.6±241.8</td>
<td>588.3±260.2</td>
<td>633.1±373.5</td>
<td></td>
</tr>
<tr>
<td>D14-D0</td>
<td>27.4±104.7</td>
<td>41.7±112.7</td>
<td>50.3±122.4</td>
<td>99.1±192.0*</td>
<td>0.019</td>
</tr>
</tbody>
</table>

RPP indicates rate-pressure product.

*Significantly different from placebo in pairwise comparison.

$P=0.005$). Times to angina onset and to limiting angina nominally increased at all doses but reached significance only for 10 mg BID ivabradine (Table 2). Similar changes were found in the intention-to-treat population, except that reduction in time to limiting angina did not reach statistical significance ($P=0.058$; data not shown). Effects of drug were qualitatively similar between men and women.

Angina and ischemia reduction were associated with significant reductions in rate-pressure product (heart rate × systolic blood pressure) at peak exercise ($P=0.011$) and increases in total work performed at ETT ($P=0.019$) among ivabradine-treated patients (Table 2); both changes showed significant dose-dependence ($P=0.002$ for both). Individual dose comparisons revealed significant superiority of 10 mg BID ivabradine versus placebo for total work performed.

Ivabradine-mediated improvements in time to 1-mm ST-segment depression (Figure 3A) and time to limiting angina (Figure 3B) in the double-blind phase were maintained in the open-label phase; also, patients who had received placebo in the double-blind phase showed a reduction in ischemia and angina when ivabradine was given (Figure 3, A and B). For the entire population, time to 1-mm ST-segment depression improved by >1 minute from before therapy to the end of the open-label extension. This change and the change in time to limiting angina were significant in both the per-protocol and intention-to-treat populations ($P<0.001$ in all cases).

During double-blind randomized withdrawal, patients who continued treatment with 10 mg BID ivabradine maintained reductions in resting heart rate and increases in time to 1-mm ST-segment depression and to limiting angina; in patients withdrawn to placebo, ETT parameters deteriorated significantly (Table 3).

ETT at Peak of Drug Activity

During the double-blind dose-ranging phase, ETT results at peak of drug activity mirrored those at trough, but the effects were larger (Figure 2, Table 4) and were significant for time to 1-mm ST-segment depression and time to limiting angina at 5 mg and 10 mg BID doses and for heart rate and rate-pressure product at all doses. Hypotension was not observed at peak or at trough with any dose, and average blood pressure changed little relative to that on placebo.

Angina Attacks

Angina attacks and the consumption of short-acting nitrates nominally were reduced by ivabradine during double-blind dose ranging, although these changes did not reach statistical significance. However, for those patients who continued into open-label extension, angina attacks decreased from $4.14±5.59$ attacks per week at baseline to $0.95±2.24$ attacks per week at the end of the open-label extension ($P<0.001$). Consumption of short-acting nitrates decreased from $2.28±3.74$ U/wk to $0.50±1.14$ U/wk during the same interval ($P<0.001$). During the subsequent randomized withdrawal, angina attack frequency was unchanged in patients continuing with ivabradine but increased by $0.74±1.95$ attacks per week in patients withdrawn to placebo ($P=0.067$).
Safety
The incidence of adverse events during double-blind dose-ranging was low and generally similar to placebo in all treatment groups. The only exception was visual symptoms (photopsia [n=10], stroboscopic effect [n=4], nontypical blurred vision [n=1]), which were reported by no patients in the placebo group, by 1 patient in each of the ivabradine 2.5 and 5 mg BID groups, and by 13 patients (14.8%) in the 10 mg BID ivabradine group and were commonly associated with abrupt changes in light intensity. The pattern of adverse events was similar during the open-label extension phase, with 31 patients (17.9%) having visual symptoms (graded as mild for 29 patients). One patient had visual symptoms during randomized withdrawal. Three patients withdrew from the study because of visual symptoms; these withdrawals all were voluntary rather than at the investigators’ insistence because of safety concerns. All visual symptoms resolved spontaneously during or after drug discontinuation.

No serious cardiac events were reported after treatment withdrawal, suggesting absence of rebound phenomena.

Discussion
This study is the first large clinical trial of the novel selective I_{	ext{f}} inhibitor ivabradine in patients with chronic stable angina pectoris. Antianginal efficacy was documented by improved exercise tolerance, reduction in angina attack rate and short-acting nitrate use, and antiischemic efficacy by reduction in exercise-induced ECG ST-segment depression. These clinical benefits were associated with the observed drug-mediated, dose-dependent reductions in heart rate, at rest and peak exercise, when measured at either peak or trough of drug activity. All improvements in efficacy measures were maintained throughout the duration of the trial, as confirmed by worsening of all major ETT criteria in patients randomly assigned to placebo during the final withdrawal phase, compared with those continuing ivabradine treatment.

A range of medical treatments and invasive interventions (principally PTCA and CABG) are available for prevention of stable angina. Present guidelines and a recent review recommend treatment initiation with a medical rather than invasive strategy unless the patient is at substantial imminent risk of death. If symptoms are not controlled adequately after some weeks of optimal medical treatment, the use of PTCA and CABG can be considered. A recent meta-analysis of randomized trials comparing PTCA with
medical treatment also concluded that PTCA should be reserved for patients whose symptoms are not well controlled on medical treatment.13

Nitrates, β-blockers, and calcium channel blockers are the predominant classes of drugs prescribed to prevent angina by reducing myocardial ischemia. β-Blockers generally are recommended as initial therapy in the absence of contraindications, particularly after myocardial infarction.1,10 The antiischemic benefit of β-blockers is due, at least in part, to heart rate reduction.1,14,15 However, β-blockers also reduce myocardial contractility and can cause paradoxical vasoconstriction of large epicardial arteries, both at rest and during exercise.8,16,17 β-Blockers may be contraindicated in patients with peripheral vascular disease18 (which often coexists with coronary artery disease), hypotension, heart block >1°,19 or obstructive airway disease20 and may have adverse effects on lipid and carbohydrate metabolism.21–24 A study of patients in primary care with stable angina found that although 64% of patients were taking >1 cardiovascular drug, angina often was poorly controlled, with a median angina frequency of ~2 per week.25 Therefore, additional pharmacological antianginal therapy is likely to be useful; specific heart rate–lowering agents plausibly may be particularly helpful.

Ivabradine is a selective and specific inhibitor of the hyperpolarization-activated, mixed sodium/potassium inward If current, which contributes importantly to SAN pacemaker activity.3 In animal studies, at therapeutic concentrations, ivabradine has had little action on other cardiac ionic currents or cardiac action potential shape.5,6 This may account for the drug’s lack of significant effects on myocardial contractility.8,26

In the present study, undertaken only in patients with stable angina, heart rate reduction by 10 mg BID ivabradine was similar to that reported after repeated 10 mg BID doses in healthy volunteers.9 The only adverse effects linked to treatment were the visual symptoms observed primarily with 10 mg BID. These symptoms were expected, having been reported in an earlier study in healthy volunteers,9 and did not adversely affect the tolerability of the drug for most patients. Visual symptoms may be linked to the presence of retinal ion channels similar to those mediating If.27–29

In contrast with the known effects of short-acting β-blockers,30,31 there were no “rebound” phenomena on ivabradine withdrawal.

In summary, in patients with stable angina, ivabradine, a prototype of the novel class of selective If inhibitors, produced dose-dependent reductions in resting and exercise heart rates, improved exercise tolerance, increased time to exercise-induced ischemia, and reduced the frequency of ambient angina attacks, without pharmacological tolerance or rebound phenomena. Ivabradine may be useful in angina prevention; drug safety now must be evaluated during more prolonged exposure.

Appendix

Ivabradine Investigators Group


Acknowledgments

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References

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