CLINICAL RESEARCH   **Clinical Trials**

Clinical Efficacy of Ivabradine in Patients With Inappropriate Sinus Tachycardia

A Prospective, Randomized, Placebo-Controlled, Double-Blind, Crossover Evaluation

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Objectives   The purpose of this study was to investigate the role of ivabradine in the treatment of symptomatic inappropriate sinus tachycardia using a double-blind, placebo-controlled, crossover design.

Background   Due to its I_f blocking properties, ivabradine can selectively attenuate the high discharge rate from sinus node cells, causing inappropriate sinus tachycardia.

Methods   Twenty-one patients were randomized to receive placebo (n = 10) or ivabradine 5 mg twice daily (n = 11) for 6 weeks. After a washout period, patients crossed over for an additional 6 weeks. Each patient underwent symptom evaluation and heart rate assessment at the start and finish of each phase.

Results   After taking ivabradine, patients reported elimination of >70% of symptoms (relative risk: 0.25; 95% CI: 0.18 to 0.34; p < 0.001), with 47% of them experiencing complete elimination. These effects were associated with a significant reduction of heart rate at rest (from 88 ± 11 beats/min to 76 ± 11 beats/min, p = 0.011), on standing (from 108 ± 12 beats/min to 92 ± 11 beats/min, p < 0.0001), during 24 h (from 88 ± 5 beats/min to 77 ± 9 beats/min, p = 0.001), and during effort (from 176 ± 17 beats/min to 158 ± 16 beats/min, p = 0.001). Ivabradine administration was also associated with a significant increase in exercise performance. No cardiovascular side effects were observed in any patients while taking ivabradine.

Conclusions   In this cohort, ivabradine significantly improved symptoms associated with inappropriate sinus tachycardia and completely eliminated them in approximately half of the patients. These findings suggest that ivabradine may be an important agent for improving symptoms in patients with inappropriate sinus tachycardia.   (J Am Coll Cardiol 2012;60:1323–9) © 2012 by the American College of Cardiology Foundation

Inappropriate sinus tachycardia (IST) is a clinical syndrome characterized by nonparoxysmal palpitations at rest and/or early during exercise associated with a relative or absolute increase in sinus rate out of proportion to physiological need (1–4). The clinical manifestations of this syndrome are diverse and variable. Patients are mainly young women, and

clinical symptoms range from intermittent palpitations to multisystem symptoms including light-headedness, presyncope, syncope, orthostatic intolerance, chest pain or pressure, headache, myalgia, dyspnea, fatigue, abdominal discomfort, anxiety, and depression (5). On 12-lead electrocardiography (ECG), the P-wave morphology during tachycardia is nearly identical to that in sinus rhythm. Although the mean 24-h or daytime heart rate (HR) exceeding 95 beats/min or sinus rate increase from a supine/semiorthostatic to a

standing position >25 to 30 beats/min provides some quantifiable parameters for IST, the diagnosis may be elusive. In fact, symptoms can be different from palpitations and may reproducibly occur with HRs lower than those conventionally

accepted. In addition, reproducibility and correlation of symptoms, activity, and HR can be elusive in a single patient (6).

The pathophysiology of IST is poorly understood, although mechanisms such as excessive sympathetic influences, reduced parasympathetic influences, excessive intrinsic HR, ectopic activity of the sinus node, and β-receptor antibodies have been proposed as substrates for this arrhythmia (1,4,7). In patients in whom neural imbalance is suspected, the integrity of the baroreceptor reflex response appears to focus on impairment of efferent stimulation rather than on alterations of the neural reflex mechanisms as a possible cause of IST (4). The extent to which each of these and other possible mechanisms contribute to tachycardia and associated symptoms is unknown.

Regardless of the primary mechanism, a common denominator potentially involved in an accelerated sinus rate is higher-than-normal activation during diastole of the "pacemaker" I_f current, the ionic current known to generate the spontaneous diastolic depolarization of the sinoatrial node (8). A class of drugs investigated in patients with IST is represented by β-adrenergic antagonists. Although effective, their main limitation is the wide range of actions on the cardiovascular and other systems, which both complicate interpretation of the effects of HR lowering and often cause intolerable side effects (9).

The recent introduction of ivabradine (10,11), a specific I_f blocker with no interactions with the cardiovascular system, has provided investigators with the unique opportunity to test the impact of pure I_f blockade on cardiac chronotropy and the variable symptoms associated with this syndrome. Preliminary reports suggest that ivabradine may be effective in patients with this arrhythmia (12–15). Using a prospective, randomized, placebo-controlled, crossover design, we investigated the role of ivabradine in the treatment of patients with IST.

Methods

Study design. This study is a randomized, double-blind, placebo-controlled, crossover trial of oral ivabradine conducted in patients with IST. After a baseline screening assessment, patients were randomized to start with a 6-week course of either placebo or ivabradine according to a double-blind model (phase 1, Fig. 1). Randomization was performed on the basis of computer-generated random numbering. Next, after a washout period of 7 days at the end of which HRs and exercise performance were reassessed, patients switched treatment for an additional 6 weeks (phase 2), with each patient acting as his or her own control. All enrolled patients underwent 12-lead ECG in the supine and standing positions, 24-h Holter monitoring, and exercise 12-lead ECG at baseline and at the end of each phase for a

total of 3 assessments. Placebo pills were identical in appearance to ivabradine pills and were taken according to the same schedule (2 times per day). Three doses of delivered drug were available for both arms of this study: a low dose, a high dose, and an intermediate dose. Such doses corresponded to ivabradine 2.5 mg, 7.5 mg, and 5 mg, respectively. Group A comprised patients first assigned to placebo and then switched to ivabradine, whereas group B comprised patients first assigned to ivabradine and then switched to placebo. Regardless of randomization, the assigned drugs were taken twice daily at the initial intermediate dose and downgraded to the low dose in case of intolerable side effects or upgraded to the high dose if well tolerated at 3 weeks from onset of each crossover phase. All patients were informed about the investigational nature of the study and gave their written informed consent. The study protocol was approved by the ethics committee and the institutional committee on human research of our hospital.

Inclusion/exclusion criteria. Entry criteria included a symptomatic mean resting HR >95 beats/min during the daytime hours of 24-h Holter monitoring and/or a rapid stable symptomatic increase in resting HR >25 beats/min when moving from a supine to a standing position or in
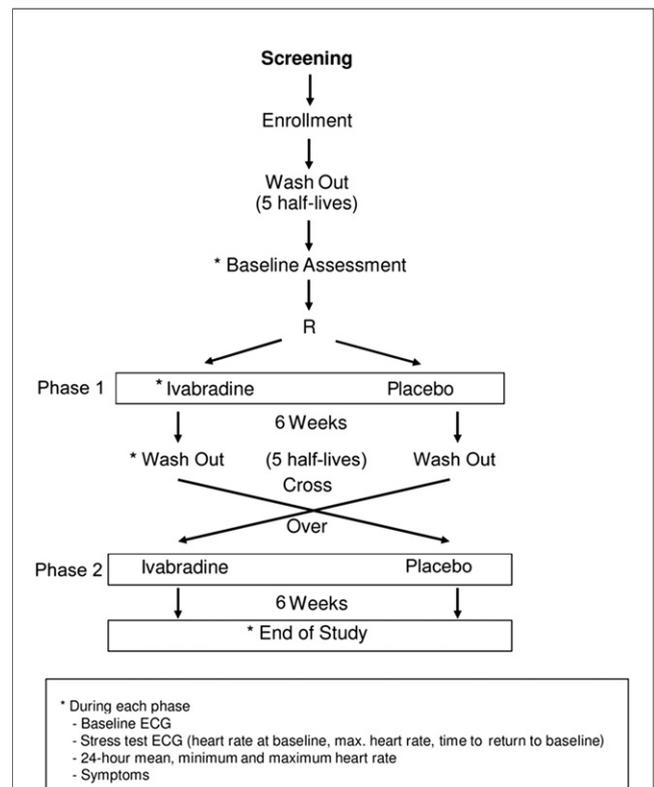
Figure 1 **Flowchart of Study Protocol**

After enrollment, washout and baseline assessments were performed before randomization. Patients were kept in the assigned treatment arm for 6 weeks and subsequently crossedover to the alternate treatment arm after a washout period. ECG = electrocardiography.

response to physiological stress. Exclusion criteria included the presence of underlying heart disease, a history of paroxysmal supraventricular tachycardia, history of sick sinus syndrome, diagnosis of orthostatic hypotension, conditions causing compensatory sinus tachycardia (anemia, hyperthyroidism, infections, hypovolemia, pheochromocytoma, diabetes mellitus, or drug abuse), receiving antiarrhythmic therapy, renal or hepatic insufficiency, and receiving potent inhibitors of P450 3A4. Structural heart disease was excluded in all patients by means of transthoracic echocardiography (Vivid 7 Dimension, GE Healthcare, Inc., London, United Kingdom).

Adverse effects and compliance. Adverse effects were collected by patient report and periodic interviews with dedicated research personnel. To ensure medication compliance, a pill count was performed at the end of each study period. The minimum compliance rate for inclusion in the study period of the analysis was 80%. No patients were excluded from the analysis because of noncompliance.

Sample size calculation. The primary efficacy outcome was resolution of symptoms associated with assignment to ivabradine. We pre-specified a clinically relevant minimum detectable degree of ivabradine-related overall symptom elimination of 70% within a pool of 7 symptom indicators (palpitations, pre-syncope/syncope, orthostatic intolerance, chest pain, dyspnea, and anxiety) associated with IST. To this aim, investigators were required to complete a patient symptom form at baseline, after phase 1, and after phase 2 during a scheduled patient interview. Each of the 7 symptom indicators was scrutinized and filed according to a yes or no dichotomy criterion. Therefore, we identified a sample size in each treatment sequence (placebo → ivabradine and ivabradine → placebo) of 8 for an overall sample size to have 80% power to detect the pre-specified minimum difference at a 2-sided significance level of 0.05. Sample size calculation was performed by Proc Power of the SAS statistical software package version 9.2 (SAS Institute, Cary, North Carolina).

Statistical analysis. Baseline and demographic characteristics were summarized by the use of mean ± SD for continuous variables and percentage for categorical variables. The influence of tested therapies on symptoms associated with IST was evaluated using a conditional mixed-effects logistic interpolation model. Relative risk reduction and 95% confidence intervals were reported across treatment phases, and the overall mixed-effects interpolation was performed.

The power analysis of HR was performed by simulation considering an HR reduction (effect size) of ~10 to 15 beats/min, group variability (SD) of ~10 to 15 beats/min, and a correlation coefficient between post- and pre-treatment values ranging from 0.3 to 0.5 to detect the pre-specified minimum difference at a 2-sided significance level of 0.05.

Continuous variables were investigated by means of a mixed-effects generalized linear model having secondary continuous outcomes as response to variable and treatment-phase interaction as covariate. Paired differences between post-placebo and post-ivabradine status were investigated by Wilcoxon signed rank test or *t* test according to variable skewness. Analysis results are reported in Table 1.

All statistical evaluations were performed using SAS statistical software package version 9.2 (SAS Institute), the alpha value of 0.05 was considered statistically significant, and all tests were 2-tailed.

Results

Demographics and baseline data. Of 29 eligible patients identified by the study team, 21 met the entry criteria and were enrolled in the study after providing written informed consent. Of them, 2 could not complete the follow-up due to side effects experienced during treatment with ivabradine in 1 patient (phosphenes) and placebo in the other patient (dizziness and nausea). Overall, 19 patients completed the follow-up. Of them, 10 were first assigned to ivabradine and

Table 1	Summary Statistics for HR Measurements, Speed During Exercise, Exercise Duration, and METs During Exercise at Different Treatment Phase					
Variable	**Baseline**	**Placebo**	**Ivabradine**	**p Value***	**R^2**	**p Value†**
HR on standing	107.7 ± 11.5	109.0 ± 12.9	91.6 ± 10.7	<0.0001	0.35	0.0004
HR at rest	88.5 ± 11.2	87.1 ± 13.0	76.1 ± 10.5	0.0117	0.28	0.004
HR change between rest and standing	19.3 ± 8.8	22.0 ± 10.2	15.5 ± 9.9	0.0249*	0.13	0.2029
24-h HM mean HR	88.8 ± 5.3	88.9 ± 8.3	77.0 ± 8.8	0.0010	0.37	0.0002
24-h HM rather during the daytime	98.4 ± 11.2	98.6 ± 11.1	84.7 ± 9.0	<0.0001	0.39	<0.0001
24-h HM HR during the nighttime	77.3 ± 8.0	75.6 ± 9.1	65.6 ± 7.1	<0.0001*	0.35	0.0004
24-h HM maximum HR	153.8 ± 23.9	145.9 ± 25.1	137.5 ± 26.8	0.0011	0.09	0.4200
24-h HM minimum HR	58.9 ± 7.8	59.1 ± 12.8	51.4 ± 11.6	0.0178*	0.24	0.0132
HR during maximum exercise	177.5 ± 16.6	170.7 ± 15.7	158.1 ± 16.3	0.0013	0.24	0.0128
Speed during exercise, km/h	5.9 ± 1.1	6.1 ± 1.3	6.6 ± 1.7	0.0006*	0.03	0.8855
Exercise duration, min	7.2 ± 2.5	7.6 ± 2.8	8.9 ± 2.8	0.0156	0.05	0.7093
METs during exercise	10.1 ± 2.6	10.2 ± 3.0	11.1 ± 3.0	0.0005	0.03	0.9173

Values are mean ± SD. Placebo and ivabradine p values calculated with the Wilcoxon test. *Paired comparison results; †mixed-effect generalized linear model analysis results.

HM = Holter monitoring; HR = heart rate.

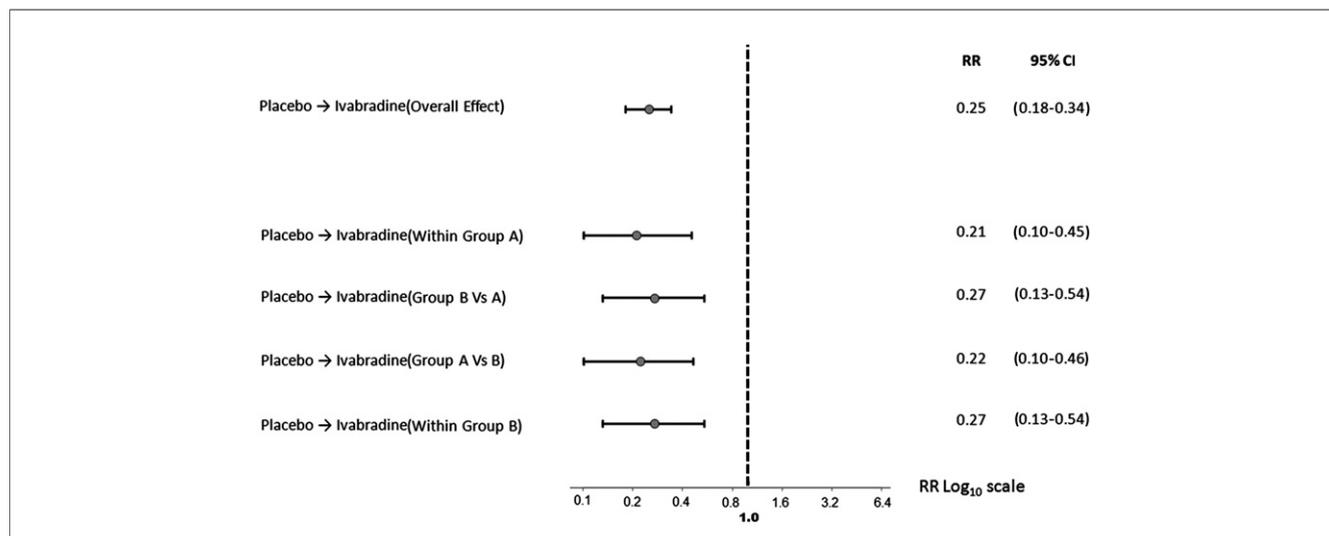| Table 2	Demographic and Clinical Characteristics of the 19 Patients Completing Follow-Up	
Age, yrs		37.1 ± 12.7
Female		17
Symptoms		
Palpitations		
At rest		3
During exercise		2
At rest and during exercise		14
Pre-syncope/syncope		1
Intolerance on standing		6
Chest pain		4
Dyspnea		
At rest		1
During exercise		7
At rest and during exercise		1
Fatigue		
At rest		3
During exercise		9
At rest and during exercise		1
Anxiety		2
Risk factors for cardiomyopathy		
Smoking		4
Hypertension		0
Hypercholesterolemia		2
Diabetes		0
Previous therapy		
No. of patients with previously taking beta-blockers		14
No. of patients with previous nondihydropyridine calcium antagonists		4
Echocardiographic data		
Left ventricular end-diastolic diameter, mm		43.6 ± 3.6
Left ventricular ejection fraction		0.64 ± 7.7
Septal wall thickness, mm		8.6 ± 1.2
Posterior wall thickness, mm		9.0 ± 1.1
Left atrium maximum anteroposterior diameter, mm		32.8 ± 3.3

Values are mean ± SD or n.

9 to placebo. Table 2 summarizes the demographic and clinical characteristics of the study population. Seventeen patients were female with a mean age of 37.1 ± 12.7 years. Three patients presented with 1 or more symptoms at rest, 2 had symptoms only during effort, and 14 had symptoms during both conditions. Symptoms were predominantly characterized by palpitations, but other symptoms were reported either alone or in association with palpitations.

The mean HR at enrollment was 88.5 ± 11.2 beats/min in the supine position and 107.7 ± 11.5 beats/min in the orthostatic position, with a mean change of 19.3 ± 8.8 beats/min. During 24-h Holter monitoring, the mean, minimum, and maximum HR were 88.8 ± 5.3 beats/min, 58.9 ± 7.8 beats/min, and 153.8 ± 23.9 beats/min, respectively. During the daytime, the mean HR was 98.4 ± 11.2 beats/min, whereas during the nighttime, it was 77.3 ± 8.0 beats/min. The maximal HRs assessed during stress ECG were 177.5 ± 16.6 beats/min with a mean change of 69.5 ± 12.3 beats/min relative to baseline standing HR. During a

7.2 ± 2.5-min exercise duration, patients expended 10.1 ± 2.6 METs at a speed of 5.9 ± 1.1 km/h.

Effects of ivabradine on symptoms and HR. After the initial dose of 5.0 mg twice daily, ivabradine was increased to 7.5 mg twice daily in 11 patients according to the protocol and was decreased to 2.5 mg twice daily in 2 patients because of weakness or dizziness. Similarly, in the placebo arm, an increase to the maximum dose was possible in 10 patients, whereas a decrease to the minimal dose was required in 2 patients because of patient discomfort such as nausea and weakness. Elimination of ≥70% of symptoms at baseline was observed in 14 patients (67%) in response to ivabradine, with 9 patients experiencing complete elimination. Another 5 patients (24%) reported elimination of 50% of symptoms at baseline in response to ivabradine. The remaining 2 patients reported elimination of 33% of symptoms at baseline in response to ivabradine. Figure 2 shows the fiducial point and the 95% confidence interval of the relative risk (RR) estimate of symptom evaluation when comparing placebo and ivabradine in the overall population (overall effect). Also shown are the fiducial points and the RR estimate of subgroup comparisons obtained within group A patients, within group B patients, between patients assigned to groups A and B during study phase 1 (group A vs. B), and between patients assigned to groups A and B during study phase 2 (group B vs. A). Overall, >70% of baseline symptoms were abolished after ivabradine administration compared with placebo (RR: 0.25; 95% confidence interval, 0.18 to 0.34; p < 0.001). This difference was confirmed when comparing ivabradine and placebo within each combination of subgroup RR estimate analysis (p < 0.001 for all comparisons). Nine patients (4 in group A and 5 in group B) reported elimination of all symptoms within few days after starting on ivabradine. Table 3 is a summary of a symptom evaluation report as collected at baseline and after completion of the 6-week periods of placebo and ivabradine. Complete elimination of symptoms in 9 patients during ivabradine therapy was not associated with significantly greater degrees of HR reduction compared with patients with incomplete elimination of symptoms. Among the 10 patients first randomized to ivabradine, 9 (90%) experienced recurrence or an increase in symptoms when crossed over to placebo. Among the 11 patients first randomized to placebo, all (100%) experienced improvement or elimination of symptoms when crossed over to ivabradine.

Summary statistics of HR measurement and exercise capacity are reported in Table 1 and Figure 3. Compared with placebo, ivabradine significantly decreased baseline supine (76.1 ± 10.5 beats/min; p vs. baseline = 0.0117) and orthostatic HR (91.6 ± 10.7 beats/min; p < 0.0001) as well as HR change (15.5 ± 9.9 beats/min; p = 0.0249). Similarly, the mean (77.0 ± 8.8 beats/min; p = 0.001), minimum (51.4 ± 11.6 beats/min; p = 0.0178), and maximum (137.5 ± 26.8 beats/min; p = 0.0011) HRs were also significantly reduced. HR also decreased during the

	RR	95% CI
Placebo → Ivabradine(Overall Effect)	0.25	(0.18-0.34)
Placebo → Ivabradine(Within Group A)	0.21	(0.10-0.45)
Placebo → Ivabradine(Group B Vs A)	0.27	(0.13-0.54)
Placebo → Ivabradine(Group A Vs B)	0.22	(0.10-0.46)
Placebo → Ivabradine(Within Group B)	0.27	(0.13-0.54)

Figure 2 **Comparative Assessment of Symptoms in Patients With Inappropriate Sinus Tachycardia Receiving Placebo Versus Patients Receiving Ivabradine**

Comparisons include overall effect, effects within group A (receiving placebo first), effects within group B (receiving ivabradine first), effects when comparing group B and group A and effects when comparing group A and group B. CI = confidence interval; RR = relative risk.

daytime (84.7 ± 9.0 beats/min; $p < 0.0001$) as well as during the nighttime (65.6 ± 7.1 beats/min; $p < 0.0001$). Finally, ivabradine reduced maximum HR during stress ECG (158.1 ± 16.3 beats/min; $p = 0.0013$). Changes in maximum HR were associated with longer exercise duration (8.9 ± 2.8 min; $p = 0.0156$), larger expenditure capabilities (11.1 ± 3.0 METs; $p = 0.0005$) at higher speed (6.6 ± 1.7 km/h). All possible combinations but 1 of data comparison between placebo and ivabradine groups had a power calculation >0.8.

Discussion

This study is the first randomized, double-blind, placebo-controlled, crossover trial to evaluate the impact of ivabradine on symptoms and HR at various conditions in patients with IST. The crossover design allowed each subject to serve as his or her own internal control, thereby reducing the possibility of confounding, given the variable symptoms and their uncertain association with HR changes induced by ivabradine. We found that ivabradine eliminated >70% of symptoms reported at baseline with ~50% of patients reporting elimination of all symptoms. These effects were associated with a significant reduction of HR at baseline, after standing, during 24 h, during the daytime, during the nighttime, and at maximum stress test.
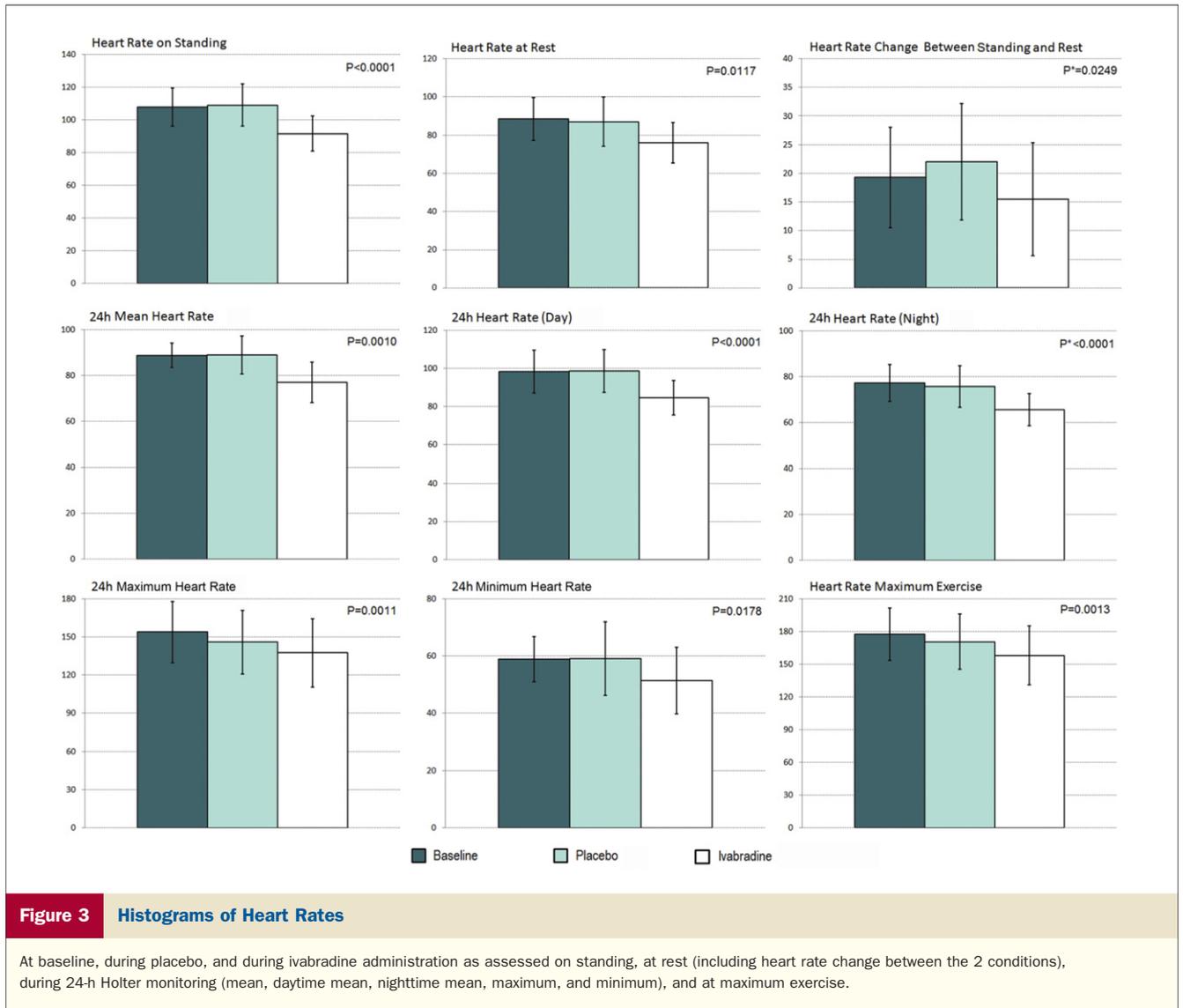
The benefit of ivabradine to reduce HR is well documented. In patients with chronic heart failure, treatment with ivabradine has been associated with reduced adverse clinical outcomes directly correlated with the drug-dependent degree of HR reduction (15,16). In patients with stable coronary artery disease, ivabradine-dependent HR reduction may result in a reduction of adverse clinical outcomes in subgroups with a baseline HR of ≥ 70 beats/min (17). Recent data suggest that ivabradine may also be effective in patients with IST. The specific mechanism of action is likely to be related to the ivabradine-mediated I_f attenuation, ultimately resulting in HR reduction. However, most such studies are case reports or uncontrolled studies. In one study, Schulze et al. (12) reported the case of a young female patient affected by IST in whom sustained success was achieved by administering 10 mg/day of oral ivabradine. In another study, Calò et al. (18) reported the efficacy of ivabradine administration in 16 consecutive patients. Data from this study suggest that ivabradine significantly reduces the mean and maximum 24-h HR and that the impact of ivabradine on HR reduction tends to improve over time, as suggested by the greater degree of change observed at 6 months compared with that observed at 3 months. Unfortunately, no data on the impact of HR reduction on symptoms were available in this cohort.

Significance. In this study, ivabradine-mediated effects on patient symptoms were a significant reduction of HR in

Table 3	Symptom Evaluation as Reported During Patient Interview at Baseline and 6 Weeks After Placebo and Ivabradine Administration		
Symptom	**Baseline**	**Placebo**	**Ivabradine**
Overall	65	60	19
Palpitations	17	15	7
Pre-syncope/syncope	1	0	0
Orthostatic intolerance	6	6	1
Chest pain	4	1	1
Dyspnea	9	8	2
Fatigue	13	12	3
Anxiety	2	4	2

Values are n.

Figure 3   Histograms of Heart Rates

At baseline, during placebo, and during ivabradine administration as assessed on standing, at rest (including heart rate change between the 2 conditions), during 24-h Holter monitoring (mean, daytime mean, nighttime mean, maximum, and minimum), and at maximum exercise.

various conditions, thus suggesting that increased HR is a determinant of symptom manifestation in these patients. Notably, in some patients, symptoms were not reduced or eliminated despite similar degrees of ivabradine-mediated HR reduction. This latter observation suggests that increased HR may not be the only determinant of symptoms or that patients with similar HRs may experience different degrees of symptoms or present with variable symptom threshold. Based on previous data (18), it is possible that ivabradine administration for >6 weeks considered in our study would be associated with a further reduction of HR and a possible additional beneficial effect on symptoms, although this observation is only speculative and will require further assessment.

The uniform ability of ivabradine to reduce HR in patients with IST is a result of its specific mechanism of action. In fact, the ivabradine-dependent reduction in the slope of slow diastolic depolarization (19) produces a reduced rate of firing regardless of the mechanisms, whether intrinsic or autonomi-

cally mediated, ultimately causing IST. This may justify the potential efficacy of ivabradine in a significant proportion of patients with this arrhythmia regardless of the underlying mechanism in each single case. Drug-related reduced HR and increased cardiac output may result in a reduction of symptoms and better exercise tolerance in these patients.

The incidence of ivabradine-related side effects does not appear to be as relevant as in trials of patients with congestive heart failure or coronary artery disease, thus making administration of this drug rather comfortable. It is possible that this finding is associated with the younger age and lower incidence of comorbidities in patients with IST compared with patients with heart failure or coronary artery disease. The lack of general cardiovascular effects makes administration of ivabradine the preferred choice compared with beta-blocking agents for the treatment of IST. Ivabradine appears to be the preferred choice also compared with catheter modulation of the sinus node because this technique has not proved to be very effective and may be

associated with long-term chronotopic incompetence (20). It is possible that mechanisms other than increased expression of the I_f current are responsible for IST in the group of nonresponders to ivabradine in our study. Among such mechanisms, aberrations in the calcium clock may also be considered (21).

Study limitations. Although we had sufficient power to detect significant differences in symptom reduction, the sample size did not allow us to differentiate between drug responders and nonresponders and identify possible predictors of response. Given the relatively short follow-up, efficacy and safety of oral ivabradine could not be tested according to a long-term treatment schedule. Based on previous studies, ivabradine efficacy tends to increase further from 3 to 6 months follow-up in patients with IST (18). However, there are no data on the long-term safety of the drug, and further studies with longer follow-up are required to address this issue. Based on these observations, larger randomized trials designed to evaluate long-term safety and efficacy and to detect responders versus nonresponders should be performed before routine adoption of ivabradine for the treatment of IST.

Conclusions

The present study shows that after 4 weeks of oral administration, ivabradine eliminates >70% of the variable symptoms associated with IST and that complete elimination of symptoms can be expected in ~50% of cases. The long-term efficacy and safety profile of ivabradine for the therapy of this arrhythmia is worthy of further investigation.

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