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Ivabradine in Inappropriate Sinus Tachycardia

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Clinical Efficacy of Ivabradine in Inappropriate Sinus Tachycardia

Introduction

- Inappropriate sinus tachycardia (IST) is characterized by nonparoxysmal palpitations at rest and/or early during exercise associated with a relative or absolute increase in sinus heart rate our of proportion to physiological need

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Introduction

- The clinical manifestions of IST are diverse and variable
- Affectd pts are mainly young women
- Symptoms range from intermittent palpitations to multisystem symptoms

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Multisystem symptoms

- Light-headedness
- Pre-syncope
- Syncope
- Orthostatic intolerance
- Chest pain or pressure
- Headache
- Myalgia
- Dyspnea
- Fatigue
- Abdominal discomfort
- Anxiety
- Depression

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Diagnosis

- On 12-lead 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 bpm or sinus rate increase from a supine/semiorthostatic to an orthostatic position > 25 to 30 bpm provides some quantifiable parameters for IST, the diagnosis may be elusive

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Diagnosis

- In IST, diagnosis may be elusive as 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 the single patient

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Pathophysiology

- Poorly understood, although following mechanisms proposed, alone or in combination
  - excessive sympathetic influences (impairment of efferent limb)
  - reduced parasympathetic influences (impairment of efferent limb)
  - excessive intrinsic HR
  - ectopic activity of the sinus node
  - β-receptor antibodies

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Study rationale

- Regardless of the primary mechanism, a common denominator potentially involved in an accelerated sinus rate is higher-than-normal activation during diastole of the "pace-maker" ***I***f current
- Ivabradine is a specific ***I***f blocker with no interaction with the cardiovascular system

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Study rationale

- Based on its unique mechanism, ivabradine offers a unique opportunity to test the impact of pure ***I****f* blockade on cardiac chronotropy and the variable symptoms assciated with IST
- Preliminary reports suggest that this drug can be effective at reducing HR in patients with this arrhythmia

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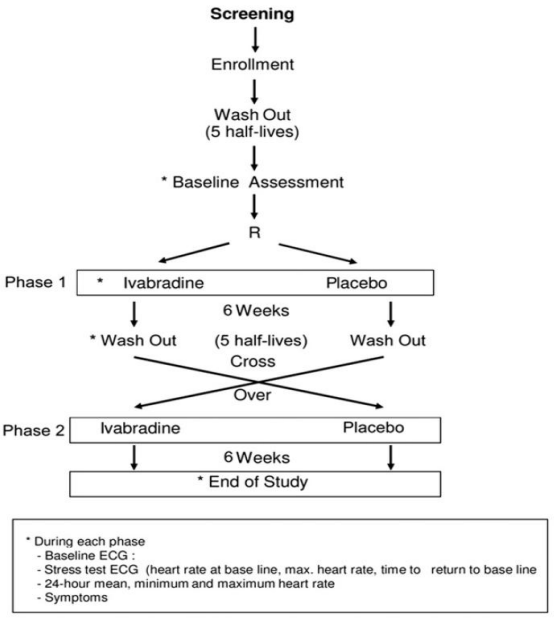
Aim of the study

- To investigate the role of oral ivabradine in the treatment of patients with IST
- Use of a prospective, randomized, double-blind, placebo-controlled, crossover design

Study Protocol



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Methods

- Randomization made based on computer-generated random numbering
- Placebo pills identical to ivabradine pills and taken according to the same schedule (twice daily)
- 3 doses of each drug were made available for both study arms: 2.5 mg, 5 mg and 7.5 mg
- Initial dose 5 mg twice daily and down- or up-graded in case of side effects or good tolerance at 3 weeks from onset of each crossover phase

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Methods

- **Group A**: patients first assigned to placebo and then to ivabradine
- **Group B**: patients first assigned to ivabradine and then to placebo

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Methods

- All patients informed about the investigational nature of the study and gave informed consent
- Study approved by local ethical committeee

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Inclusion criteria

- Symptomatic mean resting HR > 95 bpm during daytime hours of 24-hour Holter monitoring and/or
- Stable symptomatic increase in resting HR > 25 bpm when moving from a supine to a standing position or in response to physiological stress

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Exclusion criteria

- Underlying heart disease
- Hx of paroxysmal supraventricular tachycardia
- Hx of sick sinus syndrome
- Ortostatic hypotension
- Conditions causing commpensatory sinus tachycardia
- Renal or hepatic insufficiency
- Patients receiving potent inhibitors of P450 3A4
- Patients receiving antiarrhythmic therapy

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Primary efficacy outcome

- Resolution of symptoms associated with assignement to ivabradine

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Statistics

Sample size calculations

- Pre-specification of clinically relevant minimum detectable degree of ivabradine-related overall symptom elimination of 70% within a pool of symptom indicators (aasociated with HR beyond physiological levels) associated with IST
  - palpitations,
  - pre-syncope/syncope
  - orthostatic intolerane
  - chest pain
  - dyspnea
  - anxiety

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Statisitics

Sample size calculations

- Sample size of 8 patients in each treatment sequence for an overall sample size to have an 80% power to detect the pre-specified minimum difference at a 2-sided significance level of 0.05.

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

Demographic and Clinical Characteristics of the 19 Patients Completing Follow-Up

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

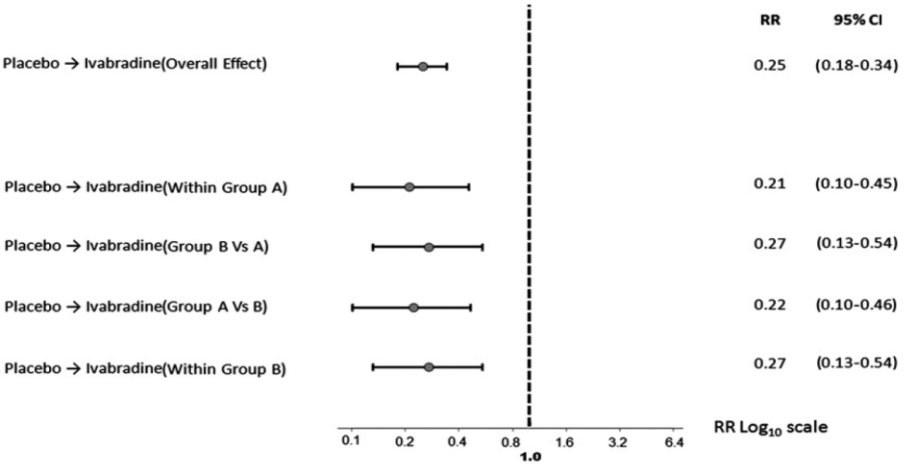
Values are mean ± SD or n.

Summary Statistics for HR Measurements, Speed During Exercise, Exercise Duration, and METs During Exercise at Different Treatment Phase

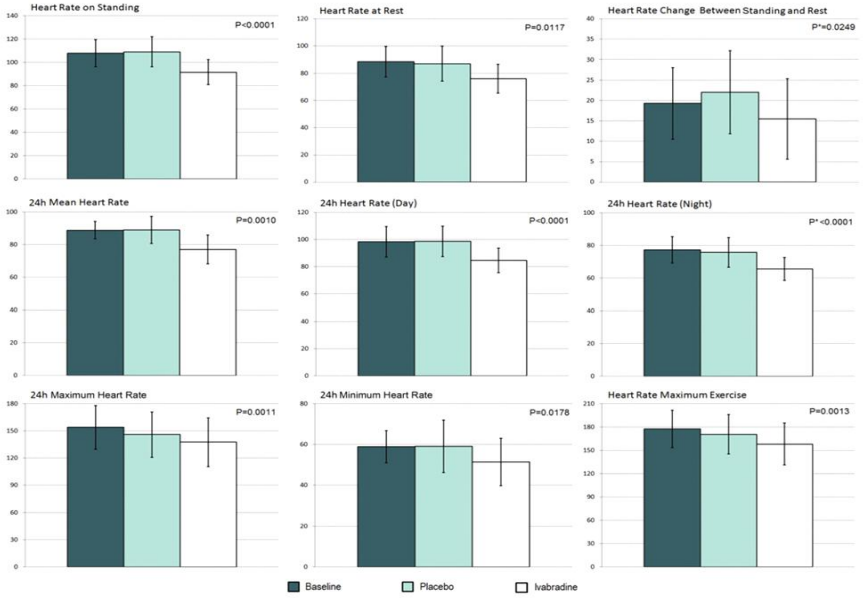
Variable	Baseline	Placebo	Ivabradine	p Value	R^2	p Value
HR on standing	107.7 ± 11.5	109.0 ± 12.9	91.6 ± 10.7	<0.0001	0.35	0.0004
HR at rest	88.5 ± 11.2	87.1 ± 13.0	76.1 ± 10.5	0.0117	0.28	0.004
HR change between rest and standing	19.3 ± 8.8	22.0 ± 10.2	15.5 ± 9.9	0.0249*	0.13	0.2029
24-h HM mean HR	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. *Use of *t* test for comparison.
HM = Holter monitoring; HR = heart rate.

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



Histograms of Heart Rates



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Results

- Doscontinuation of administared drug in 1 patient during ivabradine (phosphenes) and 1 patient during placebo administration (dizziness and nausea)

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Conclusions

- Early after onset of oral ivabradine administration, > 70% of the variable symptoms associated with IST are eliminated
- Complete elimination observed in about 50% of patients

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Conclusions

- The long-term efficacy and safety of ivabradine for the therapy of IST is worthy of further investigation