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EXPEDITED PUBLICATIONS

Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent

A Randomized Controlled Trial in Patients Hospitalized With Heart Failure

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Objectives We examined the hemodynamic, echocardiographic, and neurohormonal effects of intravenous istaroxime in patients hospitalized with heart failure (HF).

Background Istaroxime is a novel intravenous agent with inotropic and lusitropic properties related to inhibition of Na/K adenosine triphosphatase (ATPase) and stimulation of sarcoplasmic reticulum calcium ATPase.

Methods One hundred twenty patients admitted with HF and reduced systolic function were instrumented with a pulmonary artery catheter within 48 h of admission. Three sequential cohorts of 40 patients each were randomized 3:1 istaroxime:placebo to a continuous 6-h infusion. The first cohort received 0.5 μg/kg/min, the second 1.0 μg/kg/min, and the third 1.5 μg/kg/min istaroxime or placebo.

Results All doses of istaroxime lowered pulmonary capillary wedge pressure (PCWP), the primary end point (mean $\pm$ SD: -3.2 ± 6.8 mm Hg, -3.3 ± 5.5 mm Hg, and -4.7 ± 5.9 mm Hg compared with 0.0 ± 3.6 mm Hg with placebo; $p < 0.05$ for all doses). Istaroxime significantly decreased heart rate (HR) and increased systolic blood pressure (SBP). Cardiac index increased and left ventricular end-diastolic volume decreased significantly only with 1.5 μg/kg/min. On echocardiography, left ventricular end diastolic volume and deceleration time improved with 1.5 μg/kg/min. There were no changes in neurohormones, renal function, or troponin I. Adverse events were not life threatening and were dose related.

Conclusions In patients hospitalized with HF, istaroxime improved PCWP and possibly diastolic function. In contrast to available inotropes, istaroxime increased SBP and decreased HR. (A Phase II Trial to Assess Hemodynamic Effects of Istaroxime in Pts With Worsening HF and Reduced LV Systolic Function [HORIZON-HF]; NCT00616161) (J Am Coll Cardiol 2008;51:2276–85) © 2008 by the American College of Cardiology Foundation

Hospitalizations for acute heart failure syndromes (AHFS) continue to increase, and are associated with high post-discharge mortality and hospitalizations (1). The main reason for admissions is related to congestion (2). Although most patients are normotensive or hypertensive on admission, approximately 10% present with a low cardiac output (3). For this group, existing guidelines recommend intravenous inotropes (4,5). Although available inotropes improve hemodynamics, their use has been associated with hypotension arrhythmias and possibly increased mortality (6–8).

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Istaroxime is a novel intravenous agent that inhibits sodium-potassium adenosine triphosphatase (ATPase) activity while stimulating sarcoplasmic reticulum calcium ATPase isoform 2. The combined mechanism of istaroxime allows for cytosolic calcium accumulation during systole (inotropic response), as well as rapid sequestration of calcium during diastole and myocardial relaxation (lusitropic response) (9,10). In the animal model, istaroxime improves systolic and diastolic function without increasing myocardial oxygen consumption (11,12). In chronic heart failure (HF), istaroxime is relatively safe in doses up to 5 μg/kg/min (13).

The objective of the present study was to determine the short-term effects of 3 different doses of istaroxime in patients with AHFS.

Methods

The HORIZON-HF (Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent: a Randomized Controlled Trial in Patients Hospitalized with Heart Failure) study was conducted in Poland, Romania, and Greece. The study protocol was approved by site-specific independent institutional ethics committees and conducted according to the amended Declaration of Helsinki. All patients provided informed written consent. An independent data and safety monitoring board had access to unblinded data for evaluation of safety results.

Patients. The study included patients age 18 to 85 years with a left ventricular ejection fraction (LVEF) ≤35%, hospitalized with HF with a systolic blood pressure (SBP) <150 and >90 mm Hg, heart rate (HR) <110 and >60 beats/min, and on standard HF therapy. The main exclusion criteria were use of intravenous inotropes, serum digoxin concentration >0.5 ng/ml, recent acute coronary syndromes or coronary revascularization, atrial fibrillation, left bundle branch block, implanted electrical devices, serum creatinine levels above 3.0 mg/dl, and severe liver enzyme abnormalities.

Study plan. This was a randomized, double-blind, placebo-controlled, dose-escalation study. After informed consent, patients were instrumented with a continuous cardiac output pulmonary artery catheter (PAC) within 48 h of admission and observed for 6 h, after which time a pulmonary capillary wedge pressure (PCWP) ≥20 mm Hg was required. This was followed by 2 h during which time PCWP variability was <10% on 3 consecutive determinations.

Patients were centrally randomized to istaroxime or placebo at a ratio of 3:1 within 3 sequential cohorts of 40 patients each. The first cohort was randomized to 0.5 μg/kg/min, the second cohort to 1.0 μg/kg/min, and the third to 1.5 μg/kg/min of istaroxime or placebo. Study medication was administered intravenously at a rate of

Abbreviations and Acronyms

AHFS = acute heart failure syndromes
CAD = coronary artery disease
CI = cardiac index
DBP = diastolic blood pressure
HF = heart failure
HR = heart rate
LV = left ventricular
LVEF = left ventricular ejection fraction
PAC = pulmonary artery catheter
PCWP = pulmonary capillary wedge pressure
SBP = systolic blood pressure

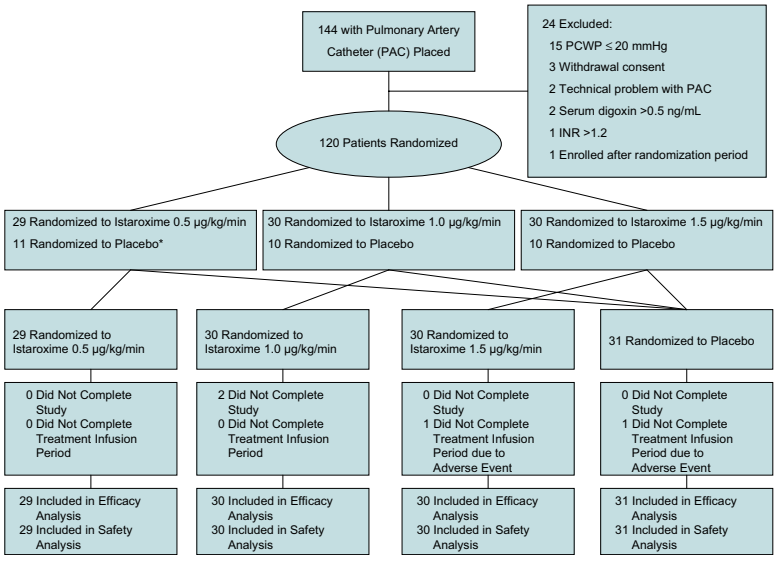

Figure 1 Enrollment

*The imbalance in number of patients (29 instead of 30 in the 0.5 μg/kg/min group) is due to an assignment error. INR = International Normalized Ratio for Prothrombin Time; PCWP = pulmonary capillary wedge pressure.

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100 ml/h for 6 h. Escalation to the next dose occurred after completion of the previous cohort as determined by the data and safety monitoring board. After insertion of the PAC until 2 h after infusion, no patients received new HF medications or intravenous inotropes or vasodilators.

Study end points. The primary end point was change in PCWP compared with placebo after a 6-h continuous infusion. Secondary end points included changes in cardiac index (CI), right atrial pressure, SBP, diastolic blood pressure (DBP), HR, and stroke work index. In addition, changes in LVEF, left ventricular (LV) end-diastolic and -systolic volumes, diastolic function indexes, neurohormones, renal function, troponin, pharmacokinetics, and safety were evaluated.

Hemodynamics. Hemodynamic variables were measured by PAC 8 h before, during, and 2 h after infusion. The CI was continuously measured with a Vigilance II monitor (Edwards Lifesciences, Irvine, California). The PCWP was obtained at end-expiration. The SBP, DBP, and HR were measured noninvasively. The pulmonary vascular resistance, systemic vascular resistance, and stroke work index were calculated using standard formulas. Study personnel had to pass all tests in the learning module of the Pulmonary Artery Catheter Education Project. All tracings were centrally reviewed.

Echocardiography. Echocardiography was performed before and within the last 30 min of infusion. Ventricular volumes were measured using the biplane method of discs, with LVEF calculated using the standard formula. Mitral regurgitation was observer graded on a scale of 0 to 3 (none, mild, moderate, and severe). Mitral inflow velocities were measured by pulsed-wave Doppler in the apical 4-chamber view. Peak velocity of the early and late diastolic mitral inflow (E and A waves), and the E-wave deceleration time were recorded. Tissue Doppler measurements were obtained using real-time pulsed-wave

Table 1 Baseline Clinical Features

	Istaroxime (μg/kg/min)			
	0.5 (n = 29)	1.0 (n = 30)	1.5 (n = 30)	Placebo (n = 31)
Demographics				
Age, mean (SD), yrs	54 (11)	56 (11)	54 (11)	57 (10)
Male, n (%)	26 (90)	26 (87)	28 (93)	25 (81)
Caucasian, %	100	100	100	100
Weight, mean (SD), kg	81 (13)	83 (14)	79 (14)	81 (13)
Height, mean (SD), cm	172 (9)	171 (8)	171 (8)	172 (8)
Physical findings and symptoms				
SBP, mean (SD), mm Hg	115 (10)	118 (9)	117 (15)	113 (15)
DBP, mean (SD), mm Hg	69 (8)	71 (6)	70 (8)	70 (8)
HR, mean (SD), beats/min	75 (10)	73 (8)	73 (9)	72 (11)
Jugular venous distension, n (%)	24 (83)	24 (80)	24 (80)	26 (84)
Rales, n (%)	18 (62)	22 (73)	18 (60)	14 (45)
Edema, n (%)	14 (48)	10 (33)	8 (27)	12 (39)
NYHA functional class, n (%)				
II	9 (31)	13 (43)	10 (33)	12 (39)
III	18 (62)	15 (50)	19 (63)	18 (58)
IV	2 (7)	2 (7)	1 (3)	1 (3)
Etiology of HF				
CAD, n (%)	17 (59)	18 (60)	21 (70)	21 (68)
Idiopathic, n (%)	10 (34)	12 (40)	9 (30)	9 (29)
Other, n (%)	2 (7)	0 (0)	0 (0)	1 (3)
Medical history				
Myocardial infarction, n (%)	14 (48)	12 (40)	12 (40)	13 (42)
CABG, n (%)	1 (3)	1 (3)	2 (7)	4 (13)
PCI, n (%)	8 (28)	6 (20)	6 (20)	10 (32)
Diabetes mellitus, n (%)	9 (31)	3 (10)	4 (13)	5 (16)
Medications before infusion				
Diuretic, n (%)	28 (96)	28 (93)	22 (73)	30 (97)
ACE, n (%)	29 (100)	26 (87)	27 (97)	26 (84)
ARB, n (%)	2 (7)	3 (7)	4 (13)	3 (10)
Beta-blocker, n (%)	29 (100)	28 (93)	30 (100)	31 (100)
Spironolactone, n (%)	20 (69)	18 (60)	17 (57)	25 (81)
Digoxin, n (%)	3 (10)	0 (0)	2 (7)	4 (13)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DBP = diastolic blood pressure; HR = heart rate; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

Doppler. Peak systolic and early diastolic velocities (Ea and Sa) were measured.

Neurohormones, renal function, and cardiac troponin. B-type natriuretic peptide, plasma renin activity, aldosterone, blood urea nitrogen, creatinine, serum sodium, and troponin I were measured before and after the infusion. All blood samples were analyzed by a core laboratory.

Pharmacokinetics. Blood samples were withdrawn before, during, and up to 18 h after starting infusion for pharmacokinetics. Analyses were calculated using the validated software Kinetica version 4.4 (Thermo Electron Corp., Waltham, Massachusetts).

Safety. Urinalysis, hematology, serum chemistry, and continuous 12-lead Holter monitoring were performed. Adverse events were monitored in the hospital during and 24 h after the beginning of infusion and telephonically at 7 and 30 days.

Statistical analysis. All randomized patients were included in the statistical analysis, according to the intention-to-treat principle. Patients included in the efficacy analysis underwent at least baseline and 1 post-baseline assessment in accordance with the last observation carried forward method. Safety analyses were carried out on all patients who started study treatment infusion. Data are summarized as mean ± SD.

Sample size estimate was based on the primary end point, PCWP. Assuming $\alpha = 0.05$ and $\beta = 0.20$ (corresponding to a power of 80%) and conducting a 2-tailed t test, using a common SD observed from previous studies of 6 mm Hg, a total of 24 patients per group was required to detect a treatment difference in PCWP of 5 mm Hg. Taking into account a higher variability of PCWP, an additional 20% of patients was added.

Two separate analyses were performed on all hemodynamic parameters. The analysis of variance model, with a single effect for treatment, was used for analyzing the changes from baseline to 6 h of infusion. An analysis of variance model for repeated measurements, including terms for treatment, time, and treatment–time interaction, was used to analyze trends during the 6 h of infusion. A step-down testing procedure to account for the multiple comparisons between the 3 doses of istaroxime versus placebo was used to interpret the results of all statistical tests. Therefore, the comparisons were considered in a predefined order, beginning with com-

Table 2 Baseline Hemodynamic, Echocardiographic, and Laboratory Variables

	Istaroxime (μg/kg/min)			
	0.5 (n = 29)	1.0 (n = 30)	1.5 (n = 30)	Placebo (n = 31)
Baseline hemodynamics				
PCWP, mm Hg	26.2 (6.2)	25.1 (5.7)	26.7 (6.2)	25.0 (4.6)
CI, l/min/m^2	2.7 (0.9)	2.90 (0.8)	2.7 (0.9)	2.6 (0.6)
RAP, mm Hg	12.9 (4.1)	12.5 (3.7)	13.4 (3.6)	14.3 (3.5)
Baseline echocardiography				
LVEF, %	26.8 (7.3)	27.5 (6.1)	28.6 (6.4)	26.1 (6.5)
LVESV, ml	161.3 (62.9)	167.7 (59.6)	140.7 (45.7)	142.0 (38.2)
LVEDV, ml	213.7 (65.6)	209.8 (71.8)	196.7 (53.9)	190.8 (51.1)
MR, grade	1.7 (0.8)	1.5 (0.8)	1.1 (0.8)	1.4 (0.8)
Sa, cm/s	5.4 (2.1)	7.1 (4.1)	6.4 (2.9)	6.8 (3.3)
E peak, cm/s	79 (27)	74 (18)	79 (29)	74 (25)
A peak, m/s	50 (22)	58 (21)	58 (32)	53 (26)
E/A ratio	2.0 (1.3)	1.5 (1.0)	2.1 (1.6)	1.9 (1.3)
Deceleration time, ms	146 (60)	162 (47)	155 (64)	165 (67)
Ea, cm/s	6.9 (2.9)	9.6 (3.8)	7.5 (2.8)	8.5 (4.4)
E/Ea ratio	16 (13)	10 (6)	13 (9)	11 (6)
Neurohormones, renal function, cardiac troponin and electrophysiology				
BNP, pg/ml*	328 (875.0)	171 (404.5)	201 (529.0)	207 (586.0)
PRA, ng/ml/h*	3.7 (6.9)	2.0 (4.7)	2.7 (6.4)	0.8 (5.9)
Aldosterone, pg/ml*	94.0 (257.0)	92.5 (154.5)	84.0 (159.0)	54.0 (51.0)
Na, mmol/l	136.9 (15.7)	127.2 (24.0)	129.7 (17.6)	124.4 (22.8)
BUN, mg/dl	25.7 (36.5)	20.3 (14.1)	18.6 (6.3)	23.5 (26.8)
Cr, mg/dl	1.07 (0.44)	1.05 (0.24)	1.02 (0.18)	1.00 (0.19)
TnI, ng/ml	0.24 (0.14)	0.23 (0.12)	0.22 (0.09)	0.19 (0.04)
QTc, ms	445.9 (27.5)	445.3 (25.6)	448.6 (30.1)	447.1 (34.3)

Data reported as mean (SD) or *median (interquartile range).

A peak = peak A-wave velocity; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CI = cardiac index; Cr = creatinine; Ea = early mitral annular velocity; E peak = peak E-wave velocity; LVEDV = LV end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = LV end-systolic volume; MR = mitral regurgitation; PCWP = pulmonary capillary wedge pressure; PRA = plasma renin activity; RAP = mean right atrial pressure; Sa = systolic mitral annular velocity; TnI = troponin I.

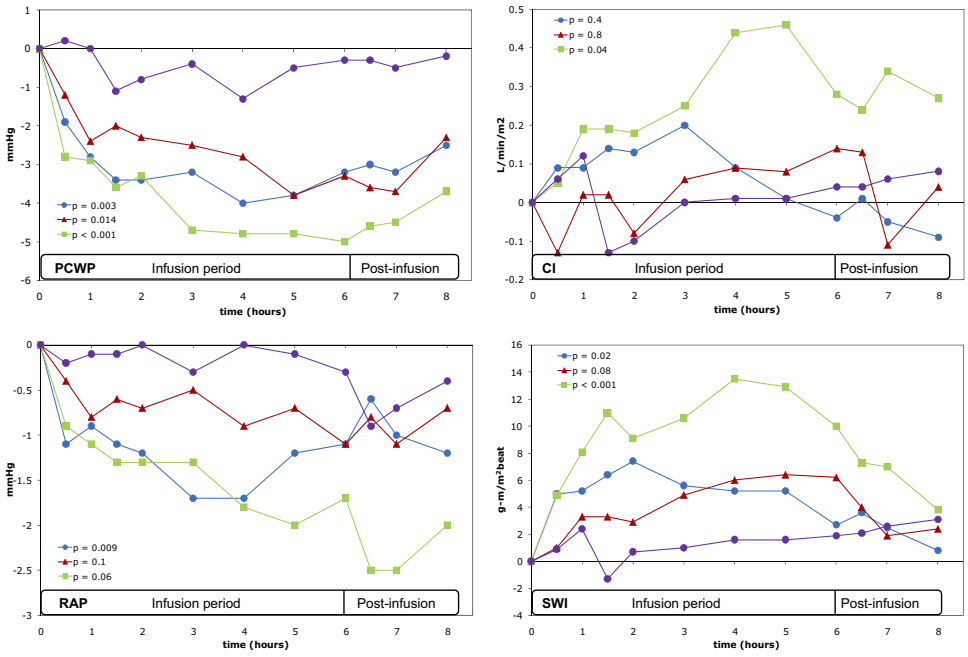

Figure 2 **Invasive Hemodynamics Over the Course of Infusion**

Pulmonary capillary wedge pressure (PCWP), cardiac index (CI), mean right atrial pressure (RAP), and stroke work index (SWI), plotted over the time course of treatment with placebo **(purple)** or istaroxime 0.5 μg/kg/min **(blue)**, 1.0 μg/kg/min **(red)**, and 1.5 μg/kg/min **(green)**. The p values refer to the main effect, by repeated-measures analysis.

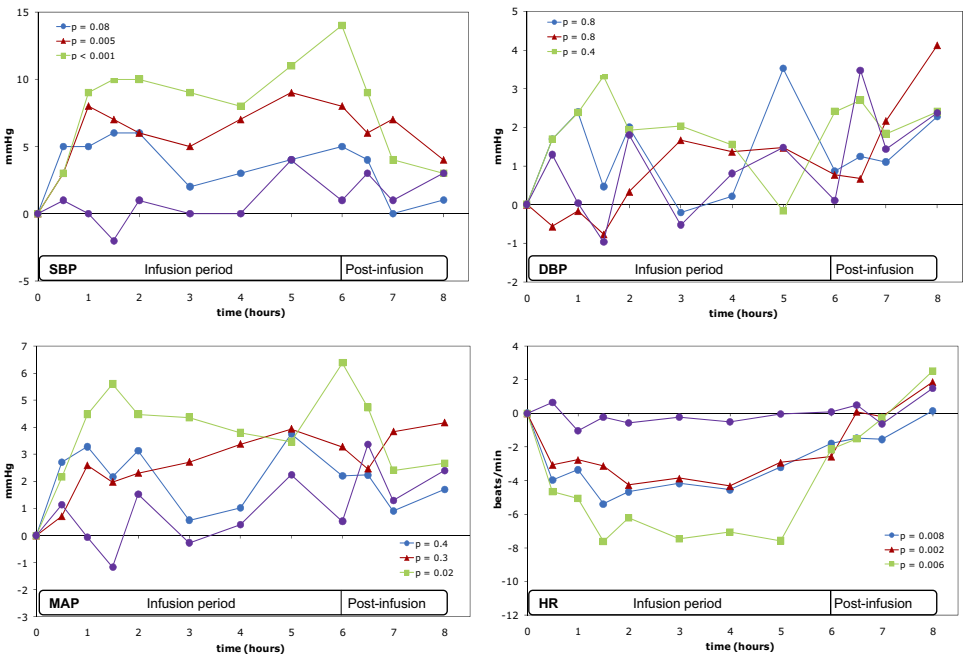

Figure 3 **Noninvasive Hemodynamic Parameters Over the Course of Infusion**

Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR), plotted over the time course of treatment with placebo **(purple)** or istaroxime 0.5 μg/kg/min **(blue)**, 1.0 μg/kg/min **(red)**, and 1.5 μg/kg/min **(green)**. The p values refer to the main effect, by repeated-measures analysis.

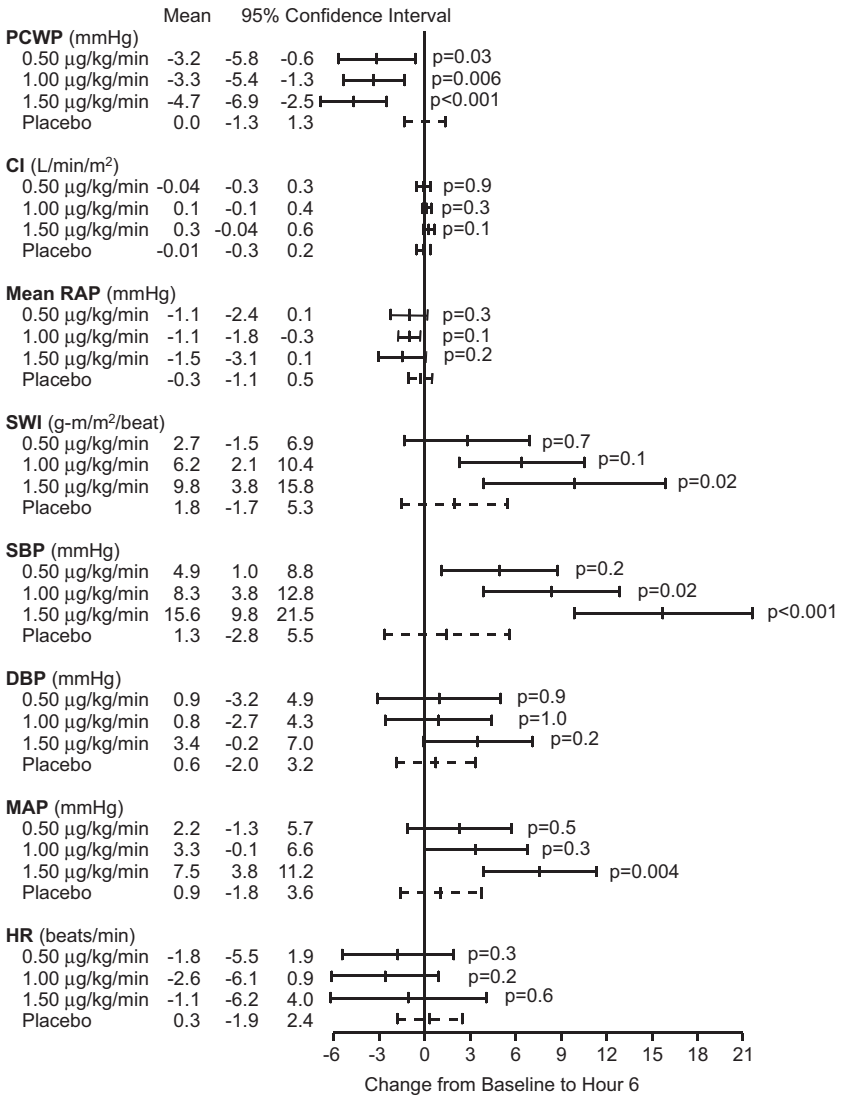

Figure 4 **Hemodynamics After Infusion**

The p values refer to the comparison of each dose versus placebo. Abbreviations as in Figures 1 to 3.

parison of the highest dose of istaroxime versus placebo and taking into account the next dose only if the previous comparison was statistically significant at the 0.05 level. All statistical analyses were performed using SAS software, version 8.2 (SAS Institute, Cary, North Carolina).

Results

Between August 7, 2006, and July 5, 2007, 120 patients were randomized to receive placebo or istaroxime over 6 h, out of a total of 144 patients who consented to treatment and were instrumented with a PAC (Fig. 1).

Baseline characteristics. Of the 120 randomized patients, 105 were men and 15 were women, with a mean age of 55 ± 11 years (Table 1). Before infusion, patients were receiving standard HF therapy (Table 1). The mean SBP was 116 ± 13 mm Hg, DBP 70 ± 8 mm Hg, HR 73 ± 10 beats/min, PCWP 25 ± 5 mm Hg, CI 2.7 ± 0.8 l/min/m^2, LVEF 27 ± 7%, and B-type natriuretic peptide 433 ± 524 pg/ml (Table 2).

Primary end point. A reduction in PCWP was observed with all 3 doses of istaroxime at the first measured time point (0.5 h) as well as at 6 h compared with placebo (Fig. 2). The mean change in PCWP at 6 h was −3.2 ± 6.8 mm Hg, −3.3 ± 5.5 mm Hg, and −4.7 ± 5.9 mm Hg, for the 0.5, 1.0, and 1.5 µg/kg/min istaroxime infusions, respectively, compared with 0.0 ± 3.6 mm Hg for placebo ($p < 0.05$ for all doses of istaroxime vs. placebo).

Secondary end points. HEMODYNAMICS. Changes in hemodynamics are shown in Figures 2 and 3, and changes

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after 6-h infusion are shown in Figure 4. During infusion, an increase was seen in SBP in the 1.0 and 1.5 μg/kg/min groups ($p = 0.005$ and < 0.001, respectively) compared with placebo; this pattern was consistent with the one observed at the end of the 6-h infusion (+8.3 ± 12.1 mm Hg and +15.6 ± 15.3 mm Hg [$p = 0.02$ and < 0.001, respectively] vs. +1.3 ± 11.3 mm Hg for the placebo group). No significant changes were noted in DBP. The HR decreased in a dose-dependent manner during istaroxime infusion ($p = 0.008$, 0.02, and 0.006, with 0.5, 1.0 and 1.5 μg/kg/min, respectively) compared with placebo, but did not achieve statistical significance at the 6-h time point. The CI increased during the 1.5 μg/kg/min infusion versus placebo in repeated-measures analysis ($p = 0.04$ vs. placebo), but not at the end of the 6-h infusion. There were no significant changes in systemic or pulmonary vascular resistance

ECHOCARDIOGRAPHY. The LV end-systolic volume was reduced in the 1.0 μg/kg/min istaroxime group compared with placebo (−15.8 ± 22.7 ml vs. −2.1 ± 25.5 ml; $p = 0.03$), and LV end-diastolic volume was reduced in the 1.5 μg/kg/min group compared with placebo (−14.1 ± 26.3 ml vs. +3.9 ± 32.4 ml; $p = 0.02$). There were no significant increases in LVEF in the istaroxime groups (Fig. 5). The Sa velocity increased in the 0.5 and 1.5 μg/kg/min groups (+1.0 ± 1.3 cm/s and 1.4 ± 1.6 cm/s; $p = 0.001$ for both doses) compared with −0.3 ± 1.1 cm/s with placebo (Table 3). E-wave deceleration time increased in the 1.5 μg/kg/min group (+30 ± 51 ms vs. +3 ± 51 ms; $p = 0.04$), and Ea velocity increased in the 0.5 and 1.5 μg/kg/min groups (+0.9 ± 2.9 cm/s and +0.6 ± 2.4 cm/s, respectively) compared with placebo (−0.7 ± 2.5 cm/s; $p = 0.06$ for both comparisons). There was a small decrease in the E/Ea ratio in the 0.5 μg/kg/min group compared with placebo (−3.8 ± 9.6 vs. +1.2 ± 4.2, $p = 0.03$). There was no significant change in E- or A-wave velocities or their ratio in any of the istaroxime groups compared with placebo.

NEUROHORMONES, RENAL FUNCTION, CARDIAC TROPONIN, AND ELECTROCARDIOGRAPHY. There were no significant changes in neurohormones, blood urea nitrogen, creatinine, or troponin I (Table 4). Serum sodium decreased in all groups and attained statistical significance in the 0.5 μg/kg/min group. There was significant shortening of the QTc interval with all doses of istaroxime compared with placebo.

PHARMACOKINETICS. Istaroxime has a half-life of less than 1 h. During the infusion, plasma istaroxime increased rapidly at first, and then gradually, reaching a steady state at 4 to 5 h. The short half-life may be due to the high systemic clearance (3.5 to 3.9 l/kg) despite a large volume of distribution (2 l/kg). Istaroxime does not appear to be excreted by the kidney and is converted into 3 metabolites that are less active than istaroxime.

ADVERSE EVENTS. No deaths occurred during the treatment period. Two patients died within 30 days of randomization: one due to worsened HF and the other due to sudden cardiac death (Table 5). Premature discontinuation of the infusion occurred in 1 patient in the 1.5 μg/kg/min group owing to treatment with a medication not allowed, and in 1 patient in the placebo group owing to clinical worsening. The main side effects were vomiting and pain at the infusion site.

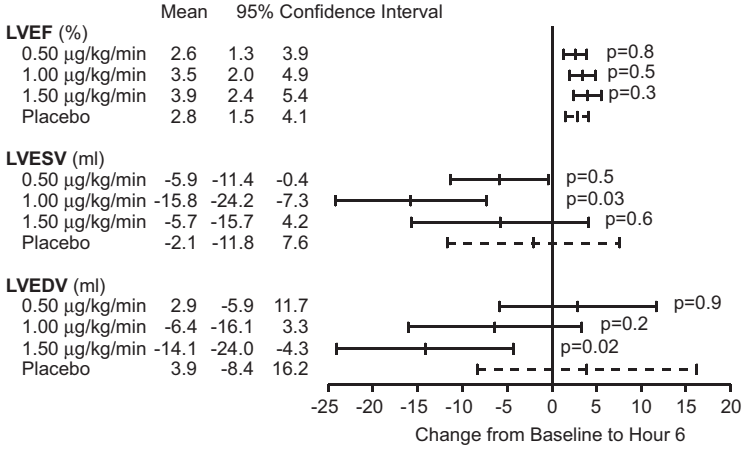

Figure 5 Left Ventricular Volumes After Infusion

The p values refer to the comparison of each dose versus placebo. LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume.

Table 3 Doppler and Tissue Doppler Echocardiography After Infusion

	Istaroxime (μg/kg/min)						
	0.5 (n = 29)		1.0 (n = 30)		1.5 (n = 30)		Placebo (n = 29)
	Mean Change (SD)	p Value	Mean Change (SD)	p Value	Mean Change (SD)	p Value	Mean Change (SD)
MR, grade	0 (0.3)	0.6	−0.1 (0.3)	0.6	−0.3 (0.4)	0.3	−0.05 (0.4)
Sa, cm/s*	1.0 (1.3)	0.001	0.6 (3.3)	0.2	1.4 (1.6)	0.001	−0.3 (1.1)
E peak, cm/s	−3 (13)	0.9	−8 (15)	0.1	1 (18)	0.3	−3 (11)
A peak, cm/s	3 (16)	0.9	7 (16)	0.3	10 (16)	0.1	3 (16)
E/A ratio	−0.3 (0.7)	1	−0.4 (0.7)	0.5	−0.6 (1.1)	0.2	−0.3 (0.9)
Deceleration time, ms	5 (32)	0.8	24 (63)	0.2	30 (51)	0.04	3 (51)
Ea, cm/s*	0.9 (2.9)	0.06	0.1 (2.3)	0.3	0.6 (2.4)	0.06	−0.7 (2.5)
E/Ea ratio†	−3.8 (9.6)	0.03	−1.1 (4.7)	0.06	−0.4 (9.2)	0.4	1.2 (4.2)

*n = 20, 27, 30, and 26 for 0.5, 1.0, and 1.5 μg/kg/min istaroxime and placebo, respectively. †n = 20, 27, 30, and 16 for 0.5, 1.0, and 1.5 μg/kg/min istaroxime and placebo, respectively. Abbreviations as in Table 2.

Discussion

The administration of intravenous istaroxime, a novel inotropic agent with lusitropic properties, when added to standard therapy, resulted in a rapid improvement in PCWP in patients hospitalized with HF and reduced LVEF. This was associated with an increase in SBP and decrease in HR and LV end-diastolic volume. The CI and stroke work index were improved only with the highest dose tested.

Doppler and tissue Doppler measurements demonstrated improvement in E-wave deceleration time, a marker of LV stiffness, as well as Ea and Sa velocities. Istaroxime was associated with reductions in QTc interval, independent of dose.

The majority of patients admitted with AHFS have pulmonary and systemic congestion related to high LV filling pressures rather than low cardiac output as the main cause for hospitalization (2). Although most are normotensive or hypertensive on admission, approximately 10% present with low blood pressure as a result of low cardiac output (3,6,7). Existing guidelines recommend inotropic agents for the management of such patients (4,5). These agents are known to improve hemodynamics, but their use is often associated with hypotension and arrhythmias (6–8).

In the REVIVE (Randomized Evaluation of Intravenous Levosimendan Efficacy) I and II trials, the short-term infusion of levosimendan resulted in a modest clinical improvement, but was associated with hypotension, atrial and ventricular arrhythmias, and a trend toward an increase in early mortality (14).

The SURVIVE (Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support) trial compared the effects of short-term infusion of levosimendan with dobutamine in patients admitted with severe HF (15). Both drugs led to severe hypotension in approximately 15% of patients.

The short-term use of intravenous inotropes with vasodilatory properties has been have been associated with an increase in post-discharge mortality (6,7). It is possible that this post-infusion effect is related to myocardial injury occurring during the short-term infusion (16). In the ischemic swine model, dobutamine given for a short period of time results in necrosis of hibernating myocardium (17). Available data suggest that troponin release is relatively common in patients admitted with AHFS who have CAD (18). In a retrospective analysis of the OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic

Table 4 Neurohormones, Renal Function, Cardiac Troponin, and Electrophysiology With Istaroxime at 6 h

	Istaroxime (μg/kg/min)						
	0.5 (n = 29)		1.0 (n = 30)		1.5 (n = 30)		Placebo (n = 31)
	Mean Change (SD)	p Value	Mean Change (SD)	p Value	Mean Change (SD)	p Value	Mean Change (SD)
BNP, pg/ml*	0 (189.0)	0.8	−16.0 (73.0)	0.3	14.5 (165.0)	0.3	−1.0 (77.0)
PRA, ng/ml/h*	−0.93 (3.13)	0.3	−0.725 (2.38)	0.2	−0.61 (3.45)	0.4	−0.47 (2.1)
Aldosterone, pg/ml*	−42.0 (234.5)	0.2	−30.5 (96.5)	0.7	−9.0 (139)	0.5	−18.0 (54.0)
Na, mmol/l	−3.7 (10.0)	0.006	-4.1 (21.5)	0.08	2.2 (7.5)	0.5	3.7 (10.4)
BUN, mg/dl	−0.4 (1.9)	0.5	−0.9 (3.0)	0.9	−0.7 (2.4)	0.9	−0.8 (2.8)
Cr, mg/dl	−0.07 (0.40)	0.3	0.002 (0.044)	0.5	0.091 (0.354)	0.2	0.011 (0.051)
TnI, ng/ml	−0.02 (0.17)	0.3	0.00 (0.11)	0.5	0.21 (1.17)	0.4	0.02 (0.08)
QTc, ms	−25.7 (22.2)	0.0001	−38.0 (17.7)	0.0001	−49.2 (30.3)	0.0001	−2.4 (17.0)

*Data reported as median (interquartile range). Abbreviations as in Table 2.

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Table 5 Adverse Events

	Istaroxime (μg/kg/min)			
	0.5 (n = 29)	1.0 (n = 30)	1.5 (n = 30)	Placebo (n = 31)
Events during infusion				
Bradycardia	0	0	2 (2)	0
Tachycardia	0	0	1 (1)*	1 (1)
Ventricular extrasystoles	0	1 (1)	0	0
Ventricular tachycardia	0	2 (3)	0	0
QT prolonged	0	2 (2)	0	0
Left bundle branch block	0	1 (1)	0	0
Electrocardiogram ST-T change	0	0	1 (1)*	0
Angina	0	0	1 (2)*	0
Chest pain	0	0	1 (1)	1 (1)
Dyspnea	0	0	1 (1)	0
Acute pulmonary edema	0	0	0	1 (1)
Nausea	1 (1)	1 (1)	3 (5)	0
Vomiting	1 (1)	1 (1)	5 (12)	0
Abdominal pain	0	1 (1)	0	1 (1)
Malaise	0	0	1 (1)	0
Injection site pain, irritation, inflammation, or pruritis	1 (1)	1 (1)	9 (9)	0
Catheter site pain	0	0	1 (1)	1 (1)
Extremity pain	1 (1)	1 (1)	3 (3)	0
Events within 30 days after infusion				
Sudden cardiac death	0	1 (1)†	0	0
Heart failure	0	1 (1)†	2 (2)	0
Angina pectoris	1 (1)	0	0	0
Atrial fibrillation	0	0	1 (1)	0
Conduction disorders	0	1 (1)	0	0
Ventricular extrasystoles	1 (1)	0	0	0
Ventricular fibrillation	1 (1)	0	0	0
Ischemic stroke	1 (1)	0	0	0
Transient ischemic attack	0	1 (1)	0	0
Left bundle branch block	0	0	0	1 (1)
Back pain	0	1 (1)	0	0
Arthralgia	0	0	0	1 (1)
Extremity pain	0	0	0	1 (1)
Leg ischemia	1 (1)	0	0	0

Values are no. of patients (no. of events). *Occurred in the same patient. †Death.

Heart Failure) study, the addition of short-term infusion of milrinone to standard therapy in patients with AHFS and CAD was associated with a 30% increase in post-discharge mortality (19). It is hypothesized that further decreases in blood pressure in patients with AHFS, as is seen with the available inotropic agents, may reduce coronary perfusion and thus result in injury, particularly in patients with CAD and ischemic or hibernating myocardium (16).

Although other inotropes improve cardiac performance to a similar or greater extent than istaroxime, the main difference with this agent is the effect of blood pressure and possibly HR and diastolic function.

Study limitations. We did not study the effects of istaroxime on symptoms. Patients who required inotropic support were excluded. However, it is not feasible to randomize patients with AHFS who require inotropes to placebo. Cardiac output was higher than that of other studies in AHFS. There was no core lab analysis of echocardiography, and therefore the results should be interpreted with caution. Patient enrollment occurred in 3 sequential blocks. In such a design the dose effect could be confounded with the period effect generated by changes in experimental conditions over time.

Conclusions

Istaroxime, with its dual inotropic and lusitropic properties, shows promise in the management of AHFS, given its effects on PCWP, HR, SBP and possibly diastolic function. However, the fate of istaroxime will depend on its effects on in-hospital and post-discharge clinical outcomes, especially in patients presenting with low cardiac output.

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APPENDIX

The HORIZON-HF Investigators

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