Effects of istaroxime on diastolic stiffness in acute heart failure syndromes: Results from the *H*emodynamic, Ech*o*cardiographic, and Neu*r*ohormonal Effects of *I*staroxime, a Novel Intravenous Inotropic and Lusitropic Agent: a Randomized C*on*trolled Trial in Patients Hospitalized with *H*eart *F*ailure (HORIZON-HF) trial

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Background Istaroxime is a novel intravenous agent with inotropic and lusitropic properties related to inhibition of the Na^+/K^+ adenosine triphosphatase and stimulation of sarcoplasmic reticulum calcium adenosine triphosphatase activity. We analyzed data from HORIZON-HF, a randomized, controlled trial evaluating the short-term effects of istaroxime in patients hospitalized with heart failure and left ventricular ejection fraction ≤35% to test the hypothesis that istaroxime improves diastolic stiffness in acute heart failure syndrome.

Methods One hundred twenty patients were randomized 3:1 (istaroxime/placebo) to a continuous 6-hour infusion of 1 of 3 doses of istaroxime or placebo. All patients underwent pulmonary artery catheterization and comprehensive 2-dimensional/Doppler and tissue Doppler echocardiography at baseline and at the end of the 6-hour infusion. We quantified diastolic stiffness using pressure-volume analysis and tissue Doppler imaging of the lateral mitral annulus (E′).

Results Baseline characteristics were similar among all groups, with mean age 55 ± 11 years, 88% men, left ventricular ejection fraction 27% ± 7%, systolic blood pressure (SBP) 116 ± 13 mm Hg, and pulmonary capillary wedge pressure (PCWP) 25 ± 5 mm Hg. Istaroxime administration resulted in an increase in E′ velocities, whereas there was a decrease in E′ in the placebo group (P = .048 between groups). On pressure-volume analysis, istaroxime decreased end-diastolic elastance (P = .0001). On multivariate analysis, increasing doses of istaroxime increased E′ velocity (P = .043) and E-wave deceleration time (P = .001), and decreased E/E′ ratio (P = .047), after controlling for age, sex, baseline ejection fraction, change in PCWP, and change in SBP.

Conclusions Istaroxime decreases PCWP, increases SBP, and decreases diastolic stiffness in patients with acute heart failure syndrome. (Am Heart J 2009;157:1035-41.)

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Therapies for acute heart failure syndrome (AHFS) in patients with reduced ejection fraction (EF) have focused on alleviating congestion[1-3] with vasodilators,[4,5] diuretics,[6] or ultrafiltration[7] or increasing cardiac output with positive inotropes.[8] However, there has been little focus on examining or treating intrinsic left ventricular (LV) diastolic stiffness in patients with AHFS who have reduced EF. In patients with chronic heart failure (HF) who have reduced EF, echocardiographic parameters of increased intrinsic LV diastolic stiffness (eg, decreased early mitral annular tissue velocity [E′] and decreased early mitral

Table I. Baseline demographic and clinical characteristics

	Istaroxime (n = 89)	Placebo (n = 31)
Demographics		
Age (y)	55 ± 11	57 ± 10
Male (n [%])	80 (90)	25 (81)
Etiology of HF		
Coronary artery disease (n [%])	56 (63)	21 (68)
Idiopathic (n [%])	31 (35)	9 (29)
Other (n [%])	2 (2)	1 (3)
Medical history		
Myocardial infarction (n [%])	38 (43)	13 (42)
Coronary artery bypass grafting (n [%])	4 (4)	4 (13)
Percutaneous coronary intervention (n [%])	20 (22)	10 (32)
Diabetes mellitus (n [%])	16 (18)	5 (16)
Physical findings and symptoms		
Systolic blood pressure (mm Hg)	117 ± 12	114 ± 15
Diastolic blood pressure (mm Hg)	70 ± 7	70 ± 8
Heart rate (beats/min)	74 ± 9	72 ± 11
Elevated jugular venous pressure (n [%])	72 (81)	26 (84)
Rales (n [%])	58 (65)	14 (45)
Edema (n [%])	32 (36)	12 (39)
NYHA class II-III (n [%])	84 (94)	30 (97)
Medications		
Diuretic (n [%])	78 (88)	30 (97)
Angiotensin-converting enzyme inhibitor (n [%])	82 (92)	26 (84)
Angiotensin receptor blocker (n [%])	9 (10)	1 (3)
β-Blocker (n [%])	87 (98)	31 (100)
Spironolactone (n [%])	55 (62)	25 (81)
Digoxin (n [%])	5 (6)	4 (13)

*$P > .05$ for all comparisons.

inflow [*E*] deceleration time), along with echocardiographic parameters of increased LV filling pressure (eg, E/E′ ratio), have all been associated with increased mortality.[9,10] In patients with AHFS who have reduced EF, increased LV diastolic stiffness may impair LV filling in an already poorly contracting ventricle that cannot empty effectively, thereby worsening the HF syndrome. Therefore, given the aforementioned association between increased LV diastolic stiffness and poor outcomes, a pharmacologic agent that could improve LV diastolic compliance may be beneficial clinically in AHFS.

Istaroxime is a novel intravenous inotropic agent that inhibits Na^+/K^+ adenosine triphosphatase activity while stimulating sarcoplasmic reticulum Ca^{2+}adenosine triphosphatase isoform 2a.[11-13] The combined mechanism of istaroxime allows for cytosolic calcium accumulation during systole creating an inotropic response, as well as rapid sequestration of calcium during diastole creating a lusitropic response.[14,15] In animals with HF, intravenous istaroxime improved diastolic function without increasing myocardial oxygen consumption.[16,17] Taken together, these findings suggest a possible role of istaroxime in reducing LV diastolic stiffness in humans.

We hypothesized that istaroxime would improve LV diastolic stiffness (defined by both tissue Doppler imaging and pressure-volume analysis) in patients with AHFS and reduced EF. Therefore, we evaluated the effects of istaroxime on diastolic function in the HORIZON-HF study.

Table II. Baseline hemodynamic, echocardiographic, tissue Doppler, and pressure-volume analysis parameters

	Istaroxime (n = 89)	Placebo (n = 31)
Hemodynamics		
Right atrial pressure (mm Hg)	12.9 ± 3.8	14.3 ± 3.5
PCWP (mm Hg)	26.0 ± 6.0	25.0 ± 4.6
Cardiac index (L min^{-1} m^{-2})	2.8 ± 0.9	2.6 ± 0.6
Stroke volume index (mL/m^2)	39 ± 13	38 ± 12
Systemic vascular resistance index (dynes s^{-1} cm^{-5})	2308 ± 849	2354 ± 787
Stroke work index (g · m/m^2 per beat)	32 ± 13	32 ± 11
Echocardiography		
LV end-diastolic volume (mL)	207 ± 64	191 ± 52
LV end-systolic volume (mL)	157 ± 57	142 ± 38
LVEF (%)	27 ± 7	27 ± 7
E velocity (cm/s)	77 ± 25	74 ± 25
A velocity (cm/s)	56 ± 26	53 ± 26
E/A ratio	1.9 ± 1.3	1.9 ± 1.3
E-wave deceleration time (ms)	155 ± 57	165 ± 67
Tissue Doppler imaging		
S′ velocity (cm/s)	6.3 ± 3.3	6.7 ± 3.3
E′ velocity (cm/s)	7.8 ± 3.4	8.5 ± 4.4
E/E′ ratio	12.5 ± 10.2	11.2 ± 6.1
Pressure-volume analysis parameters		
End-systolic elastance (mm Hg/mL)	0.79 ± 0.27	0.84 ± 0.31
End-diastolic elastance (mm Hg/mL)	0.13 ± 0.04	0.14 ± 0.06

*$P > .05$ for all comparisons.
E, Early mitral inflow; *A*, late (atrial) mitral inflow; *S′*, systolic mitral annular tissue Doppler; *E′*, early diastolic mitral annular tissue Doppler.

Methods

Study patients and trial protocol

The design of the HORIZON-HF trial (www.clinicaltrials.gov identifier, NCT00616161) has been reported previously.[18] Briefly, HORIZON-HF was a randomized, double-blind, placebo-controlled study designed to test the effects of short-term infusion of istaroxime on hemodynamics, echocardiography, neurohormones, renal function, and troponin release in patients hospitalized with AHFS and EF ≤35%. 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.

The study included patients aged 18 to 85 years, systolic blood pressure (SBP) 90 to 150 mm Hg, and heart rate 60 to 110 beat/min, on standard HF therapy. The primary exclusion criteria included the 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 >3.0 mg/dL, and severe liver enzyme abnormalities.

Patients underwent pulmonary artery catheterization (PAC) within 48 hours of admission and were randomized to a 6-hour infusion of istaroxime or placebo at a ratio of 3:1 within 3 sequential cohorts of 40 patients each; the first to 0.5 μg/kg per minute, the second to 1.0 μg/kg per minute, and the third to

Table III. Changes in hemodynamic and echocardiographic parameters with drug infusion

	Istaroxime (n = 89)		Placebo (n = 31)		
	Change from baseline	*P* (within group)	Change from baseline	*P* (within group)	*P* (between groups)
Hemodynamic parameters					
Heart rate (beat/min)	−2.1 ± 10.3	.06	0.3 ± 6.0	.78	.24
Systolic blood pressure (mm Hg)	9.2 ± 12.9	<.0001	2.1 ± 11.0	.31	.008
Diastolic blood pressure (mm Hg)	1.4 ± 9.4	.17	0.4 ± 6.4	.71	.61
Mean arterial pressure (mm Hg)	4.0 ± 8.9	.0001	1.0 ± 6.9	.44	.10
Right atrial pressure (mm Hg)	−1.3 ± 3.2	.0006	−0.3 ± 2.2	.53	.13
PCWP (mm Hg)	−3.7 ± 6.0	<.0001	−0.2 ± 3.1	.97	.001
Cardiac index (L min^{-1} m^{-2})	0.12 ± 0.76	.16	0.03 ± 0.65	.83	.57
Stroke volume index (mL/m^2)	2.7 ± 12.7	.051	0.5 ± 10.2	.80	.39
Systemic vascular resistance index (dynes s^{-1} cm^{-5} m^{-2})	30 ± 799	.73	−47 ± 583	.67	.64
Stroke work index (g · m/m^2 per beat)	6.4 ± 13.3	<.0001	1.8 ± 9.9	.35	.09
Echocardiographic parameters					
LV end-diastolic volume (mL)	−4.6 ± 18.1	.02	4.4 ± 33.0	.49	.07
LV end-systolic volume (mL)	−8.8 ± 13.7	<.0001	−2.2 ± 25.9	.66	.08
LVEF (%)	3.0 ± 3.9	<.0001	3.4 ± 4.0	.0001	.65
E velocity (cm/s)	−3.2 ± 16.0	.07	−3.1 ± 11.2	.15	.99
A velocity (cm/s)	6.3 ± 16.1	.0005	2.6 ± 16.6	.41	.30
E/A ratio	−0.43 ± 0.83	<.0001	−0.28 ± 0.87	.10	.42
E-wave deceleration time (ms)	22.1 ± 49.6	.0001	3.9 ± 51.2	.69	.10

Table IV. Changes in tissue Doppler imaging and pressure-volume analysis parameters with drug infusion

	Istaroxime (n = 89)		Placebo (n = 31)		
	Change from baseline	*P* (within group)	Change from baseline	*P* (within group)	*P* (between groups)
Tissue Doppler imaging					
S′ velocity (cm/s)	1.0 ± 2.3	.0002	−0.3 ± 1.1	.21	.007
E′ velocity (cm/s)	0.5 ± 2.5	.10	−0.7 ± 2.5	.19	.048
E/E′ ratio	−1.3 ± 7.9	.045	3.4 ± 11.1	.22	.04
Pressure-volume analysis					
End-systolic elastance (mm Hg/mL)	0.13 ± 0.16	<.0001	0.00 ± 0.29	.99	.004
End-diastolic elastance (mm Hg/mL)	−0.014 ± 0.033	.0001	−0.010 ± 0.046	.56	.052

1.5 μg/kg per minute of istaroxime or placebo. No vasoactive medications were allowed after insertion of the PAC until 2 hours postinfusion of the study drug.

The primary end point of HORIZON-HF was change in pulmonary capillary wedge pressure (PCWP) compared to placebo after a 6-hour continuous infusion. Secondary end points included changes in hemodynamic parameters, EF, LV end-diastolic and end-systolic volumes, Doppler and tissue Doppler parameters, neurohormones, renal function, troponin, pharmacokinetics, and safety.

Hemodynamic, echocardiographic, and pressure-volume measurements

Hemodynamic variables were measured by PAC 6 hours before, during, and 2 hours after infusion. Cardiac index was measured continuously with a Vigilance II monitor (Edwards Lifesciences, LLC, Irvine, CA). All invasive hemodynamic tracings were centrally reviewed by a core laboratory. Stroke work and systemic vascular resistance were calculated using standard formulas and indexed to body surface area.

Comprehensive 2-dimensional, Doppler, and tissue Doppler echocardiography were performed immediately before and within the last 30 minutes of infusion. Left ventricular volumes were measured using the biplane method of discs.[19] Mitral inflow velocities were measured by pulsed-wave Doppler in the apical 4-chamber view as described previously.[20] Peak velocity of the early (E) and late (A) diastolic mitral inflow, and the E-wave deceleration time were recorded. Tissue Doppler measurements were obtained using real-time pulsed-wave Doppler of the lateral mitral annulus in the apical 4-chamber view. Peak systolic (S′) and early diastolic (E′) velocities were measured.[21]

Pressure-volume analysis was performed on all patients using pressures obtained by PAC and blood pressure cuff, and LV volumes obtained by echocardiography immediately before infusion and at the end of infusion. End-systolic elastance (the slope of the end-systolic pressure–volume relationship [ESPVR]) was calculated as the ratio of end-systolic pressure to LV end-

systolic volume[22] (end-systolic pressure was estimated using the equation $P_{es} = 0.9 \times SBP$, which has been previously validated[23]). End-diastolic elastance (the slope of the end-diastolic pressure–volume relationship [EDPVR]) was calculated as the ratio of the LV end-diastolic pressure (approximated by the PCWP) to LV end-diastolic volume: PCWP/LV end-diastolic volume.

Statistical analysis

Sample size estimate was based on change in tissue Doppler E′. Assuming $\alpha = .05$ and $\beta = .20$ (corresponding to a statistical power of 80%), and conducting a 2-tailed t test, using a common SD of 1.6 cm/s observed in a prior study of tissue Doppler imaging in HF and reduced EF, a total of 28 patients per group were required to detect a ≥30% treatment difference in E′.

All randomized patients were included in the statistical analysis, according to the intention-to-treat principle. Hemodynamic and echocardiographic parameters were compared at baseline and at the end of infusion because echocardiographic parameters were only obtained at these time points. The effects of istaroxime on hemodynamic parameters (recorded throughout the 6-hour infusion) have been published previously.[24] Data are summarized as mean ± SD unless otherwise noted.

To increase statistical power, all patients randomized to istaroxime were grouped together and compared to the placebo group. All variables were tested for normality of distribution using the Kolmogorov-Smirnov test and by examining skewness and kurtosis. Of the variables examined, PCWP, E/E′ ratio, and LV end-diastolic elastance were nonnormally distributed (all were right-skewed). Nonparametric statistical tests were used for analysis of these variables.

Pre- and postinfusion values of hemodynamic, echocardiographic, Doppler, tissue Doppler, and pressure-volume analysis variables were compared within groups using paired t tests (or nonparametric equivalent, where appropriate). The difference in each parameter (postinfusion minus preinfusion) was compared between groups (istaroxime vs placebo) using unpaired t tests (or nonparametric equivalent, where appropriate). Because istaroxime increased SBP and decreased PCWP significantly, we designed our statistical analyses to ensure that our findings were not simply due to these hemodynamic changes. Therefore, we created separate multivariate linear regression models for each diastolic function parameter. In these models, we controlled for age, sex, baseline EF, change in SBP, and change in PCWP. We ensured that none of these covariates were collinear. In these multivariate linear regression models, we examined the effect of increasing istaroxime dose on each diastolic function parameter. All statistical analyses were performed using Stata v.9 statistical software (StataCorp LP, College Station, TX).

The HORIZON-HF study was funded by Sigma-Tau i.f.r., SpA (Rome, Italy). The authors are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the paper and its final contents.

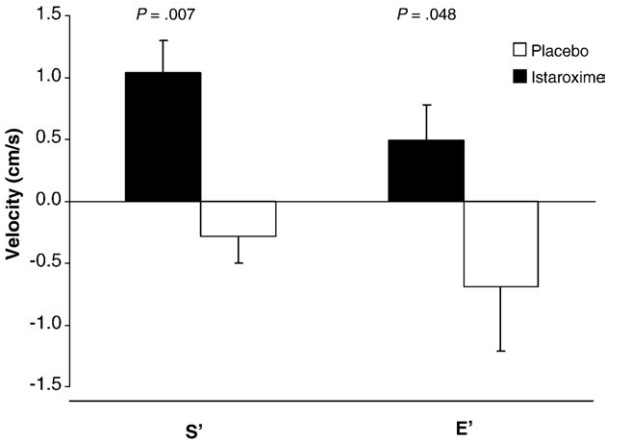
Results

The baseline characteristics of the study patients (Table I) have previously been reported in detail.[24] At baseline, the study patients had hemodynamic evidence of AHFS, with elevated right atrial pressure, elevated PCWP, and decreased cardiac index (Table II). Echocardiography confirmed that the study cohort was made up of patients with LV enlargement and severe LV systolic dysfunction (mean EF 27% ± 7%). Most of the study patients also had concomitant LV diastolic dysfunction evidenced by increased E/A ratio, decreased E-wave deceleration time, and decreased E′ velocity (Table II). Fifty percent of the study patients had ≥1 of the following echocardiographic parameters of severe LV diastolic dysfunction, each of which has been independently associated with death in patients with HF and reduced EF[10]: E/E′ >15, E′ velocity <3 cm/s, and/or E-wave deceleration time <140 milliseconds.

Compared to placebo, istaroxime improved almost every hemodynamic parameter measured (Table III). However, the most important, statistically significant, and unique effect of istaroxime (compared to placebo) was to decrease PCWP while increasing SBP. Istaroxime also decreased heart rate and increased stroke volume, although these findings were of borderline significance. Overall, cardiac index did not increase significantly in the istaroxime group, which is most likely because of its dual effects of increasing stroke volume and decreasing heart rate. Istaroxime did increase stroke work index, which was primarily due to an increase in SBP and decrease in PCWP. On echocardiography, istaroxime decreased LV end-systolic and end-diastolic volumes, and improved traditional diastolic function parameters by reducing E-wave velocity, increasing A-wave velocity, decreasing the E/A ratio, and prolonging the E-wave deceleration time.

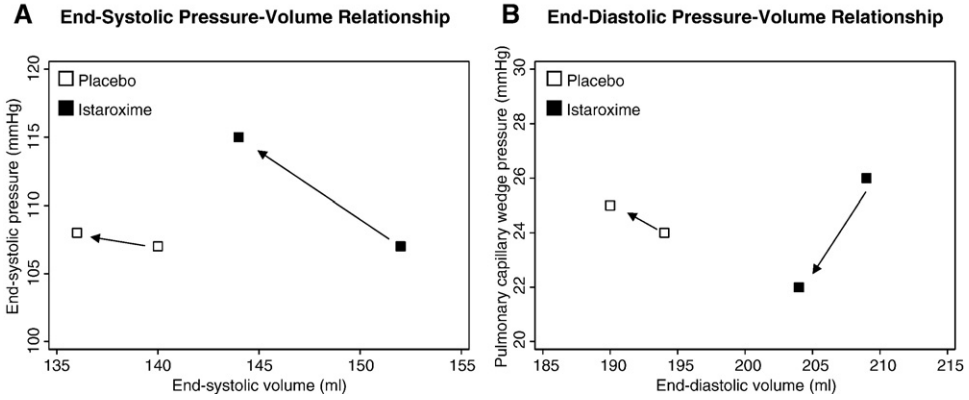
When examined by tissue Doppler imaging, istaroxime had beneficial effects on systolic and diastolic function (Table IV and Figure 1). Istaroxime administration resulted

Figure 1



Changes in systolic and diastolic tissue Doppler velocities: istaroxime versus placebo. S′ indicates peak systolic tissue Doppler velocity of the lateral mitral annulus; E′, peak diastolic tissue Doppler velocity of the lateral mitral annulus.

Figure 2



Changes in pressure-volume parameters: istaroxime versus placebo. The arrows represent direction of change from baseline to end of infusion.

Table V. Association of istaroxime and improvement in LV diastolic stiffness parameters

LV diastolic stiffness parameter	Multivariate analysis* β coefficient† (95% CI)	P
Change in E′ velocity	0.10 (0.003 to 0.20)	.043
Change in E/E′ ratio	–0.34 (–0.67 to –0.004)	.047
Change in E-wave deceleration time	3.2 (1.3 to 5.1)	.001
Change in LV end-diastolic elastance	0.001 (0.00 to 0.002)	.057

* Adjusted for age, sex, baseline EF, change in systolic blood pressure, and change in PCWP.
† Per 0.5 μg/kg per minute increase in istaroxime dose.

in an increase in S′ and E′ velocities compared to placebo ($P = .007$ and $P = .048$, respectively). In the placebo groups, there was a decrease in S′ and E′ velocities, although this change did not reach statistical significance. The E/E′ ratio decreased in the istaroxime group and increased in the placebo group. We also found that baseline S′ and E′ tissue Doppler velocities correlated at rest ($r = 0.61$, $P < .0001$), and changes in S′ and E′ velocities were also significantly correlated with each other ($r = 0.39$, $P = .001$). On pressure-volume analysis, istaroxime increased ESPVR (increased contractility), and decreased EDPVR (decreased diastolic stiffness), as shown in Table IV and Figure 2.

On multivariate analysis, after controlling for age, sex, baseline EF, change in SBP with istaroxime, and change in PCWP with istaroxime, increasing doses of istaroxime increased E′ velocity and E-wave deceleration time, and decreased E/E′ ratio and end-diastolic elastance, although the latter did not meet statistical significance (Table V).

There were no dose-dependent differences in diastolic stiffness in the istaroxime group. For every diastolic stiffness variable (E′, E/E′ ratio, and EDPVR), there were no differences in baseline value, postinfusion value, or change in value among the 3 istaroxime dose groups (P = not significant for all comparisons).

Discussion

Using tissue Doppler imaging and pressure-volume analysis, we have shown that istaroxime has a wide variety of beneficial effects on cardiac systolic and diastolic performance and appears to decreases LV diastolic stiffness compared to placebo. To our knowledge, this is the first randomized controlled trial in AHFS to use tissue Doppler imaging and pressure-volume parameters as outcomes.

Istaroxime, which allows for cytosolic calcium accumulation during systole (creating a positive inotropic response) and rapid sequestration of calcium during diastole (creating a positive lusitropic response), improved both systolic and diastolic functions in our study using multiple different quantitative methods of cardiac performance. Importantly, traditional parameters of LV systolic performance, such as cardiac index and EF, did not change dramatically with istaroxime compared to placebo. On the other hand, regional myocardial tissue velocity (S′) improved significantly, and the slope of the ESPVR (end-systolic elastance) also improved significantly, showing that istaroxime increases regional and global cardiac contractility. Diastolic stiffness decreased with istaroxime, based on increased E′ velocities and decreased slope of the EDPVR (decreased end-diastolic elastance). The fact that istaroxime caused an increase in E′ while simultaneously increasing SBP is remarkable given that increased afterload has previously been associated with decreased E′.[25] Our findings demonstrate that a more comprehensive evaluation of cardiovascular function that takes into account changes in preload and afterload is

important for the adequate evaluation of novel therapeutics in AHFS.

The increases in S′and E′ velocities, and the decrease in E/E′ ratio, induced by istaroxime infusion show that tissue Doppler imaging is a sensitive detector of improved myocardial function in patients with AHFS. Our finding that S′ and E′ velocities are significantly correlated suggests that in AHFS, regional myocardial systolic and diastolic functions are linked and both are improved with istaroxime.

The effects of other inotropes on diastolic function parameters have been previously studied.[26-30] However, many of these studies did not have the advantage of tissue Doppler imaging or pressure-volume analysis. The ones that have used these technologies have suffered from the use of nonhuman subjects, the use of healthy human subjects who do not have AHFS, and/or small sample sizes. Besides showing that istaroxime has promise as a novel therapy in AHFS, our use of tissue Doppler and pressure-volume parameters as end points in a relatively large phase II trial of patients with AHFS is novel and augers in favor of the use of these measures in the design and conduct of future similar trials of new therapies for AHFS.

As reported previously, in the HORIZON-HF trial,[24] there were no significant differences in major adverse events in the istaroxime group compared to placebo. The main side effects were vomiting and pain at the infusion site. In our study, 5 (6%) of 89 of patients in the istaroxime group and 4 (13%) of 31 in the placebo group were taking digoxin upon enrollment into the study. However, all of these patients had a digoxin level <0.5 ng/mL. Therefore, it is unlikely that digoxin had a significant effect on LV systolic or diastolic function in any of these patients. We could find no adverse interaction with digoxin in the istaroxime group (ie, within the istaroxime group, patients on digoxin did not have a higher number of adverse reactions compared to those who were not taking digoxin). Our study was not designed to analyze myocardial oxygen demand, although canine studies have shown that istaroxime does not increase myocardial oxygen demand.[16,17] As previously reported,[24] there were no differences in troponin release after study drug infusion in either the istaroxime or placebo group. These findings suggest that istaroxime-induced improvements in diastolic function do not increase myocardial oxygen demand or increase myocardial damage.

There are several limitations to our study, including the lack of a core laboratory for the review and quantification of echocardiographic images. However, increased variability in measurement techniques would have most likely biased the results toward the null, making it more difficult to detect differences in LV diastolic stiffness between active treatment groups and placebo. Pressure-volume analysis in our study was done using single beats, and we did not perform maneuvers such as preload reduction. Therefore, our pressure-volume analyses are quite crude. However, invasive pressure-volume analysis using conductance catheters and preload reduction is time-consuming and may not be feasible in larger randomized controlled trials of novel therapies for AHFS. Nevertheless, with our analysis, we cannot prove whether end-diastolic elastance improved immediately (ie, the EDPVR curve itself shifts downward and leftward) or whether istaroxime simply causes the individual patient to move downward and leftward on their intrinsic, unchanged EDPVR curve.

Pulse-wave tissue Doppler imaging has its limitations, including angle dependence of the Doppler beam that may be especially important in patients with large dilated hearts. However, any difficulties with tissue Doppler would have made it more difficult to detect differences between treatment groups. Future studies could benefit from the use color tissue Doppler or newer modalities such as 2- and 3-dimensional speckle tracking[31,32] to measure regional strain and strain rates as novel quantitative measurements of LV diastolic function in randomized controlled trials in patients with AHFS.

In summary, we have shown that tissue Doppler imaging and pressure-volume analysis give new insights into the effects of istaroxime, a novel inotropic and lusitropic agent, in patients with AHFS and reduced EF. Given the importance of diastolic function parameters in patients with AHFS with reduced EF, future clinical trials may benefit from the systematic and comprehensive evaluation of LV diastolic function as a novel end point.

Disclosures

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Drs. Ceracchi, Valentini, and Bianchetti are employees of Sigma-Tau.

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