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Brief Report

Safety and Efficacy of Istaroxime 1.0 and 1.5 μg/kg/min for Patients With Pre-Cardiogenic Shock

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ABSTRACT

Introduction: Istaroxime was shown, in a small study, to increase systolic blood pressure (SBP) in patients with pre-cardiogenic shock (CS) due to acute heart failure (AHF).

Objectives: In the current analysis, we describe the effects of 2 doses of istaroxime 1.0 (Ista-1) and 1.5 μg/kg/min (Ista-1.5).

Methods: The target dose of istaroxime, administered in a double-blind, placebo-controlled fashion, was 1.5 μg/kg/min in the first cohort (n = 24), and it was reduced to 1.0 μg/kg/min in subsequent patients (n = 36).

Results: Ista-1 was associated with numerically larger effects on SBP area under the curve, with a 93.6% relative increase from baseline during the first 6 hours with Ista-1 vs 39.5% for Ista-1.5, and with a 49.4% and 24.3% relative increase, respectively, at 24 hours. Compared to placebo, Ista-1.5 had more worsening HF events until day 5 and fewer days alive out of hospital (DAOH) through day 30. Ista-1 had no worsening HF events, and DAOH to day 30 were significantly increased. Effects on echocardiographic measures were similar, although decreases in left ventricular end systolic and diastolic volumes were numerically larger in the Ista-1 group. Ista-1, but not Ista-1.5, showed numerically smaller creatinine increases and larger decreases in natriuretic peptides as compared to placebo. There were 5 serious adverse events in Ista-1.5 (4 of which were cardiac) but only 1 in Ista-1.

Conclusions: In patients with pre-CS due to AHF, istaroxime 1.0 μg/kg/min induced beneficial effects on SBP and DAOH. Clinical benefits appear to be reached at dosages less than 1.5 ug/kg/min. (*J Cardiac Fail 2023;00:1–7*)

Key Words: Acute heart failure, istaroxime, SERCA2a, cardiogenic shock, blood pressure, therapeutics.

Cardiogenic shock (CS) continues to be associated with high rates of morbidity and mortality, posing a therapeutic challenge for clinicians and requiring interventions to prevent deterioration to overt CS.[1–4] Namely, interventions able to increase blood pressure and be well tolerated seem particularly

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needed because hypotension is a major cause of end-organ injury and poor outcome. Current vasopressors are limited because they act through adrenergic-receptor stimulation, which is associated with tachycardia, malignant arrhythmias and, in many studies, poorer outcomes.[1,5] Istaroxime exerts its effects through dual mechanisms of action: (1) inhibition of the Na^+/K^+-ATP-ase activity, increasing intracellular calcium, and (2) activation of the sarcoplasmic reticulum calcium ATPase isoform 2a (SERCA2a).[6] This is a secondary analysis of the SEISMiC study (a multicenter, randomized, double-blind, placebo-controlled, parallel-group study on the Safety and Efficacy of Istaroxime for Pre-Cardiogenic Shock)[7]; we describe the results of the SEISMIC study in the patients who received the 2 different doses of istaroxime, 1.0 and 1.5 μg/kg/min, respectively.

Methods

Study Design

The design and primary results of the SEISMiC trial have been published.[7] Briefly, eligible patients were hospitalized with pre-CS with Society for Cardiovascular Angiography (SCAI) stage B related to AHF; they were 18−85 years of age, had left ventricular ejection fractions of 40% or less, persistent hypotension (systolic blood pressure [SBP] of 75−90 mmHg), were without signs of peripheral hypoperfusion, had venous lactate levels ≥ 2 mmol/L, and were not receiving mechanical support or treatment with intravenous vasodilators, inotropes or vasopressors.

Patients were randomized to receive istaroxime or placebo at a ratio of 1:1. The original protocol had a target and maximum dose of 1.5 μg/kg/min; however, after 26 of the 60 patients were recruited, the sponsor's medical monitor recommended reducing the dose of istaroxime, based on blinded review of serious adverse events, to 1.0 μg/kg/min, a recommendation that was accepted by the sponsor and the data and safety monitoring committee.

The primary efficacy endpoint was the area under the curve (AUC) representing the change in SBP from baseline, start of study drug infusion, through 6 hours (SBP AUC). Secondary endpoints included changes from baseline to 24 hours in echocardiography parameters and changes in estimated glomerular filtration rates, N-terminal pro-B-type natriuretic peptide (NT-proBNP), lactate and troponin levels through 96 hours; SBP AUC through 24 hours; in-hospital worsening heart failure through day 5; length of stay (LOS) in hospital; LOS in intensive care or coronary care units (ICUs/CCUs); and days alive and out of the hospital (DAOH), all-cause mortality, and all-cause mortality or HF readmission through 30 days.

Statistical Analysis

Unadjusted results for continuous variables are presented as the mean and standard deviation and as frequencies and percentages for categorical variables. Treatment groups were compared within cohorts where indicated (Ista-1 vs placebo-1 and Ista-1.5 vs placebo-1.5). The AUCs of the changes in SBP through hours 6 and 24 were computed by trapezoidal rule, and the treatment groups were compared using adjusted least square means and associated standard errors from an ANCOVA model that included baseline SBP, pooled site, treatment, cohort, and treatment by cohort interaction. Changes in estimated glomerular filtration rates and NT-proBNP, lactate and troponin levels were compared between treatment groups within cohorts by using mixed model repeated measures with baseline value, cohort, treatment, pooled study site, time, and the 3-way interaction cohort-by-treatment-by-time, along with all lower-order interactions. Contrasts were used for comparing treatments within each cohort. Whether treatment effects on changes in echocardiographic measures at 24 hours differed by cohort was examined using ANCOVA, with baseline value, treatment, dose, cohort, pooled study site, and the treatment-by-cohort interaction in the models. Results presented are the adjusted least squares means changes and associated standard errors and least squares means difference between active and placebo within each cohort. The van Elteren test, stratified by pooled study centers, was used to compare groups within each cohort separately regarding length of hospital stay, stay in ICU/CCU and DAOH through day 30; the cohort-by-treatment interaction was assessed by a test-statistic based on the difference between the Mann-Whitney estimates of each cohort and their associated standard errors. Treatment groups for binary clinical endpoints were compared using the Cochran-Mantel-Haenszel test within each cohort separately, controlling for pooled study sites with the cohort-by-treatment effect as assessed by a logistic regression model, with cohort, treatment and the cohort-by-treatment interaction. A 2-sided $P < 0.05$ was considered statistically significant. No adjustments for multiple testing were made. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for analyses.

Results

SEISMIC included 2 phases. The first phase occurred between September 28, 2020, and September 3, 2021, and included 26 patients who were randomized to a 24-hour infusion of istaroxime 1.5 μg/kg/min (Ista-1.5, n = 14) or placebo (placebo-1.5, n = 12). The second phase, occurring between

September 3, 2021, and March 9, 2022, included 34 patients who were randomized to a 24-hour infusion of istaroxime 1.0 μg/kg/min (Ista-1, n = 15) or placebo (placebo-1, n = 19). The mean duration of the study drug's infusion was 22.6 ± 5.2 hours for patients in the Ista-1 and 23.6 ± 1.4 hours for those in the Ista-1.5 ($P = 0.328$). Maximum dosage was 0.97 ± 0.06 μg/kg/min in the Ista-1, and maximum dosage was 1.40 ± 0.15 μg/kg/min in the Ista-1.5 ($P = 0.001$). Time at maximum dose was significantly shorter in the Ista-1.5 than in the Ista-1 by approximately 7 hours ($P = 0.001$). Total dosage was 1339 ± 325 μg/kg in the Ista-1 and 1760 ± 358 μg/kg in the Ista-1.5 ($P = 0.0530$). The study drug's dosage was decreased in 6 patients in the Ista-1.5 group but in none of the patients in the Ista-1 group ($P = 0.034$).

Both dosages of istaroxime increased SBP (Fig. 1). The adjusted mean difference in 6-hour SBP AUC in favor of Ista-1 over the placebo1 was 23.41 (95% CI 1.11−47.93; $P = 0.061$) mmHg·hour, representing a 93.6% relative increase, and the adjusted mean difference in 6-hour SBP AUC for the Ista-1.5 vs the placebo-1.5 was 17.10 (95% CI -10.27−44.48; $P = 0.215$) mmHg·hour, a 39.5% relative increase in SBP change. Regarding 24-hour SBP AUC, the adjusted mean difference comparing Ista-1 to the placebo and the Ista-1.5 to the placebo were 94.07 (95% CI -5.08−193.22; $P = 0.063$) and 59.19 (95% CI -51.50−169.88; $P = 0.288$) mmHg·hour, respectively, representing a 49.4% and 24.3% relative increase in SBP change.

Worsening heart failure through day 5 occurred in 5 patients in the Ista-1.5 group and in 1 patient in the placebo-1.5 group ($P = 0.043$). Worsening heart failure events did not occur in the istaroxime 1.0 cohort. There were no statistically significant differences in LOS in the hospital or in the ICU/CCU between the istaroxime and placebo groups in either cohort, although a trend to reduction in LOS was observed in the Ista-1.0 group (10.00 ± 6.31 vs 11.58 ± 6.43 days in the placebo group; $P = 0.1054$). At 30 days, the mean number of DAOH was approximately 2 days greater for the Ista-1 group than for the placebo-1 group (21.27 ± 5.97 vs 19.00 ± 5.93 days; $P = 0.0218$). A greater number of deaths

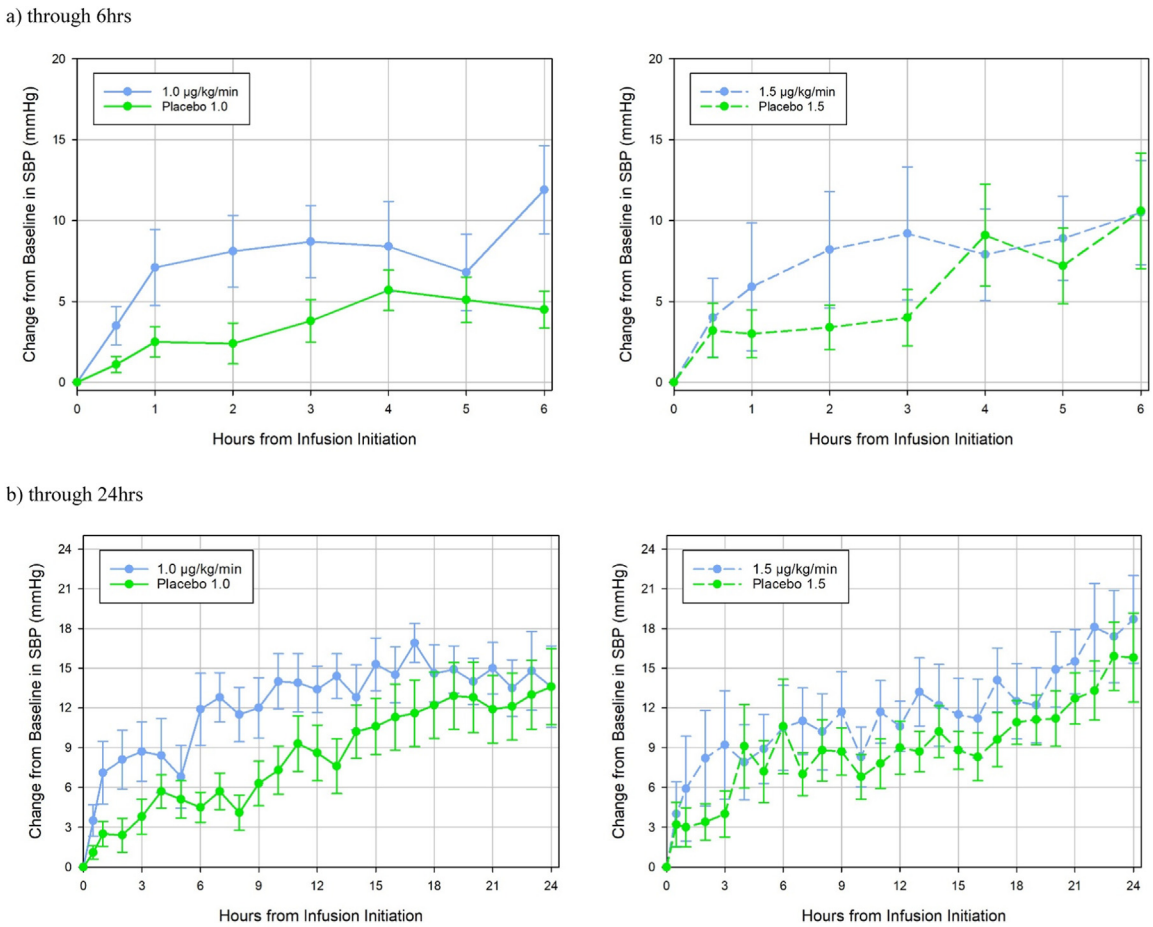

Fig. 1. Changes in systolic blood pressure by dose. a, through 6 hours; b, through 24 hours. Unadjusted mean changes from baseline and associated standard errors are shown.

Table 1. Changes in echocardiography 24-hours post treatment by dose

Parameter	Istaroxime 1.0 μg/kg/min (n = 15)	Placebo 1.0 μg/kg/min (n = 19)	*P* value Ista 1.0 vs. Placebo 1.0 [a]	Istaroxime 1.5 μg/kg/min (n = 14)	Placebo 1.5 μg/kg/min (n = 12)	*P* value Ista 1.5 vs. Placebo 1.5[1]	Cohort-by-Treatment Interaction *P* value
Cardiac index (L/min/m^2)	0.16 (0.08)	−0.03 (0.08)		0.14 (0.09)	−0.09 (0.11)		
Treatment effect (Ista vs placebo)	0.20 (−0.04, 0.44)		0.0967	0.24 (−0.03, 0.52)		0.0800	0.8187
Cardiac output (L/min)	0.22 (0.17)	−0.01 (0.15)		0.25 (0.19)	−0.02 (0.22)		
Treatment effect (Ista vs placebo)	0.24 (−0.23, 0.71)		0.3132	0.28 (−0.28, 0.83)		0.3217	0.9201
E/e' ratio	−0.88 (1.21)	−2.17 (1.12)		−0.28 (1.34)	−1.92 (1.57)		
Treatment effect (Ista vs placebo)	1.30 (−1.96, 4.56)		0.4274	1.64 (−2.15, 5.42)		0.3888	0.8929
Ejection time (msec)	−12.3 (8.27)	−2.43 (7.47)		9.57 (9.21)	14.39 (10.23)		
Treatment effect (Ista vs placebo)	−9.92 (−32.0, 12.12)		0.3696	−4.82 (−30.0, 20.40)		0.7022	0.7640
Inferior vena cava diameter (mm)	−2.71 (0.96)	−2.08 (0.84)		−2.24 (1.07)	−2.00 (1.20)		
Treatment effect (Ista vs placebo)	−0.63 (−3.17, 1.91)		0.6203	−0.24 (−3.21, 2.72)		0.8705	0.8440
Left atrium area (cm^2)	−1.67 (0.68)	−0.36 (0.62)		−1.95 (0.76)	0.59 (0.81)		
Treatment effect (Ista vs placebo)	−1.31 (−3.13, 0.51)		0.1535	−2.55 (−4.59, −0.51)		0.0155	0.3719
Left atrium volume (mL)	−9.59 (2.55)	−2.79 (2.33)		−4.84 (2.83)	−3.19 (3.17)		
Treatment effect (Ista vs placebo)	−6.80 (−13.6, 0.05)		0.0516	−1.66 (−9.48, 6.17)		0.6720	0.3275
Left ventricle end diastolic volume (mL)	−10.5 (6.55)	10.11 (5.74)		−2.03 (7.35)	−1.37 (7.79)		
Treatment effect (Ista vs placebo)	−20.6 (−37.9, -3.37)		0.0201	−0.66 (−20.2, 18.85)		0.9459	0.1001
Left ventricle end systolic volume (mL)	−13.6 (5.71)	5.03 (4.99)		−2.74 (6.41)	1.68 (7.20)		
Treatment effect (Ista vs placebo)	−18.6 (−33.7, −3.61)		0.0161	−4.42 (−21.9, 13.08)		0.6137	0.2251
Left ventricular ejection fraction (%)	2.99 (1.00)	1.90 (0.88)		2.22 (1.11)	0.28 (1.20)		
Treatment effect (Ista vs placebo)	1.09 (−1.55, 3.73)		0.4115	1.95 (−1.07, 4.96)		0.2003	0.6723
Pulmonary artery systolic pressure (mmHg)	−7.32 (2.51)	−3.67 (2.21)		−6.95 (2.91)	−6.85 (3.02)		
Treatment effect (Ista vs placebo)	−3.64 (−10.3, 3.00)		0.2753	−0.11 (−7.77, 7.55)		0.3883	0.4905
Stroke volume index (mL/m2)	4.29 (1.87)	1.04 (1.67)		3.62 (2.04)	0.62 (2.32)		
Treatment effect (Ista vs placebo)	3.25 (−1.68, 8.19)		0.1914	3.00 (−2.69, 8.69)		0.2947	0.9471

[1]LS means, LS mean difference, and *P* values from ANCOVA model adjusted for pooled site, treatment and baseline value.

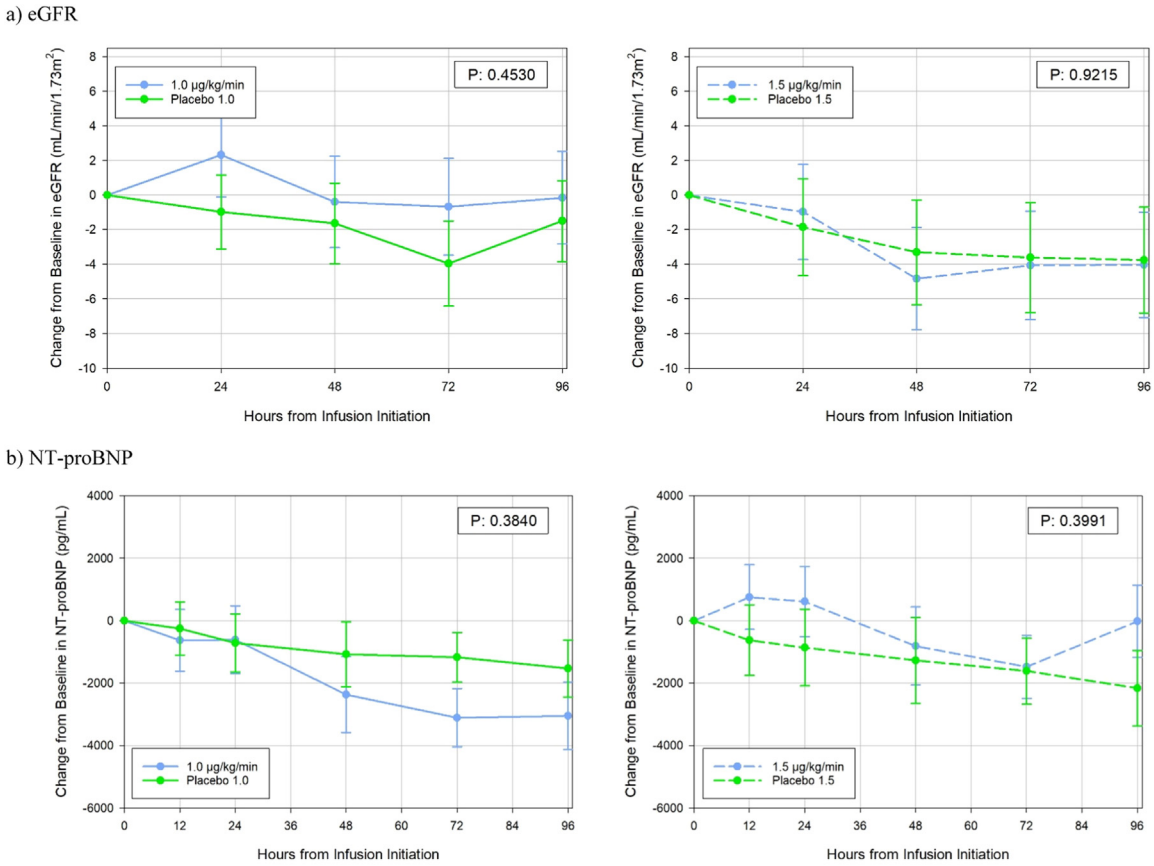

Fig. 2. Changes in biomarkers through 96 hours by dose. a, eGFR. b, NT-proBNP. c, Lactate. D, Troponin. Adjusted least square means with associated standard errors derived from a mixed model repeated measures with baseline value, cohort, treatment, pooled study site, time, and the 3-way interaction cohort-by-treatment-by-time along with all lower-order interactions are shown.

occurred in the Ista-1.5 (3) than in the Ista-1 (1) or the placebo group (placebo 1.0:1, placebo 1.5:0; *P* = nonsignificant). One patient in the Ista-1, 3 patients in the placebo-1, 3 patients in the Ista-1.5, and 1 patient in the placebo-1.5 group experienced the composite outcome of death or readmission due to heart failure through day 30 (all *P* = nonsignificant). Both istaroxime-treatment groups were associated with a trend toward increased cardiac index on 24-hour echocardiographic cardiac index, but only Ista-1 administration measures improved left ventricular end-diastolic volume and left atrial volume (Table 1). Changes in laboratory values between the istaroxime- and placebo-treated patients are presented in Fig. 2. Serious adverse events were observed in 1 patient (7%) in the Ista-1 group, in 4 patients (21%) in the placebo-1 group, in 5 patients (36%) in the Ista-1.5 group, and in 2 patients (17%) in the placebo-1.5 group. Arrhythmias through 72 hours after the study drug's administration, as determined by Holter monitoring, were not affected by treatment.

Discussion

The SEISMiC study assessed the effects of istaroxime on blood pressure, echocardiographic measures, safety, and outcomes in patients with AHF-related pre-CS SCAI stage B.[7] The increase in SBP in patients randomized to istaroxime 1.0 μg/kg/min was numerically and relatively higher than in those treated with 1.5 μg/kg/min. Similarly, echocardiographic changes, especially those pertaining to atrial and ventricular size, were more pronounced in patients treated with 1.0 μg/kg/min increase relative to those treated with 1.5 μg/kg/min. In addition, istaroxime 1.5 μg/kg/min administration was associated with some early serious adverse events that translated into lack of, or even negative, effects on worsening HF, LOS, DAOH, and even death or HF readmissions compared with the concurrent placebo. On the other hand, istaroxime 1.0 μg/kg/min was associated with less SAEs and was associated with numerically shorter LOS, significantly longer DAOH to day 30 and numerically fewer deaths or HF readmissions compared with its concurrent control group. Indeed,

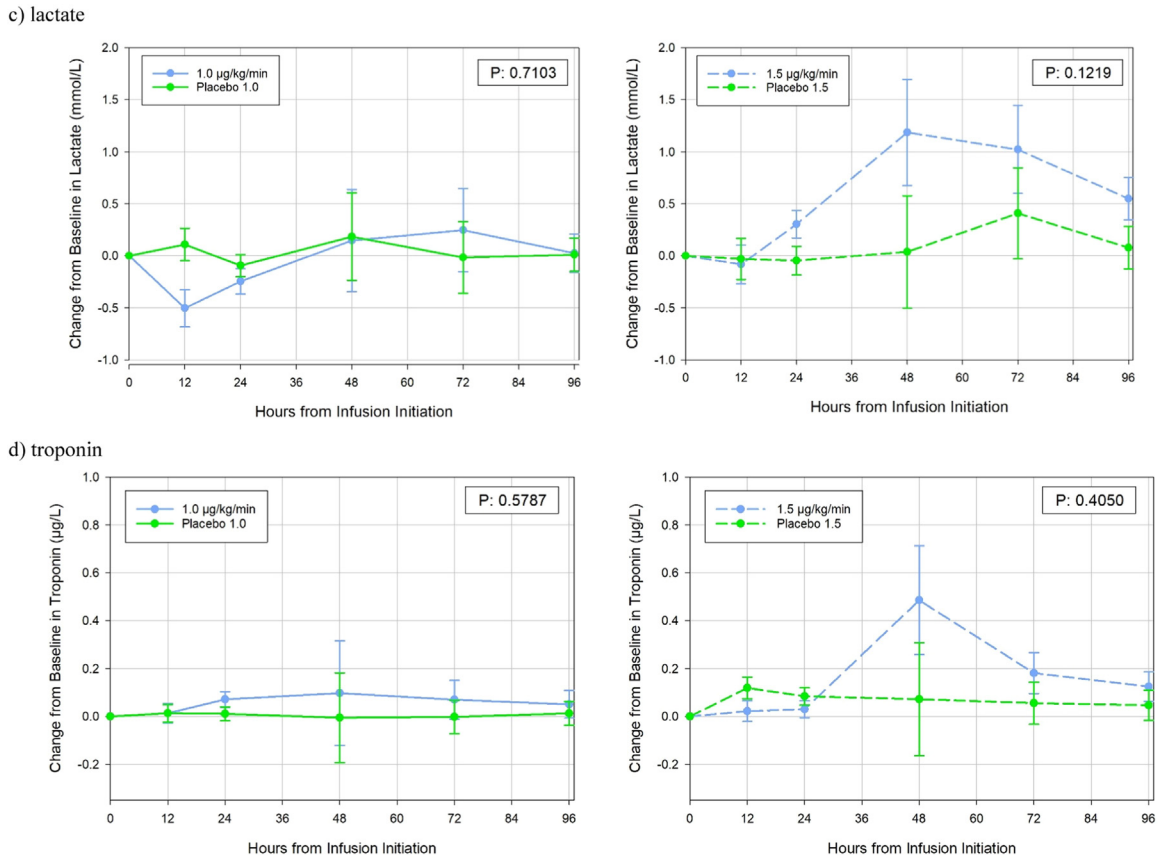

Fig. 2 Continued.

due to the increased serious adverse events, investigators tended more commonly to down-titrate and discontinue the study's drug during the first cohort when istaroxime 1.5 μg/kg/min was administered than during the second cohort (as evidenced by time in maximal dosage). Biomarker analysis based on site measurements of natriuretic peptides, creatinine, lactate, and troponin levels also show some interesting results; patients treated with istaroxime 1.0 μg/kg/min had numerically smaller increases in creatinine levels and improvement in NT-proBNP levels, whereas patients treated with istaroxime 1.5 μg/kg/min showed no improvement in creatinine or NT-proBNP levels and had numerical increases in troponin and lactate levels.

Limitations

This is a pilot study in which a small number of patients were enrolled. It focused on patients with stage B CS, and although pathophysiologically beneficial, to what extent the trial results could be extended to other CS stages is still unclear. This was a pilot study, and the comparisons of the 1.0 μg/kg/min and 1.5 μg/kg/min were done post hoc, based on a decision midstudy to reduce the dosage of istaroxime administered. Furthermore, the trial has not directly evaluated (head-to-head) Ista 1 vs Ista 1.5, only the individual effects of the 2 dosages compared to placebo. These results need to be further explored in larger studies.

Conclusions

In this pilot phase 2 study of patients with AHF-related SCAI stage B pre-CS, istaroxime 1.0 μg/kg/min seemed to improve simultaneously blood pressure and cardiac function, with trends to early improvement in some biomarkers and outcomes. Istaroxime 1.5 μg/kg/min had smaller effects on blood pressure and was associated with more severe adverse events, leading to fewer or negative effects on biomarkers and outcomes. Further studies may explore the response to istaroxime in patients with cardiogenic shock.

Disclosures

MM received personal fees of minimal amounts in the past 3 years from Amgen, Livanova, and Vifor pharma as a member of Executive or Data Monitoring Committees of sponsored clinical trials; from Astra-Zeneca, Abbott vascular, Bayer, Boheringer Ingelhelm, and Edwards Therapeutics for participation on advisory boards and/or speeches at

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