ESC European Society of Cardiology

European Journal of Heart Failure (2022) **24**, 1967–1977
doi:10.1002/ejhf.2629

RESEARCH ARTICLE

Safety and efficacy of istaroxime in patients with acute heart failure-related pre-cardiogenic shock – a multicentre, randomized, double-blind, placebo-controlled, parallel group study (SEISMiC)

Marco Metra[1]*, Ovidiu Chioncel[2,3], Gad Cotter[4,5], Beth Davison[4,5], Gerasimos Filippatos[6], Alexandre Mebazaa[5,7], Maria Novosadova[4], Piotr Ponikowski[8], Phillip Simmons[9], Joseph Soffer[9], and Steven Simonson[9]

[1]Cardiology Unit, ASST Spedali Civili, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; [2]Emergency Institute for Cardiovascular Diseases 'Prof. C.C. Iliescu', Bucharest, Romania; [3]University of Medicine Carol Davila, Bucharest, Romania; [4]Momentum Research, Inc, Chapel Hill, NC, USA; [5]Cardiovascular Markers in Stress Conditions (MASCOT), Université Paris Cité; Inserm UMR-S 942, Paris, France; [6]Department of Cardiology, University of Cyprus, School of Medicine & National and Kapodistrian University of Athens, School of Medicine, Attikon University Hospital, Athens, Greece; [7]Department of Anesthesiology and Critical Care and Burn Unit, Hôpital Saint-Louis Lariboisière, FHU PROMICE, DMU Parabol, APHP.Nord, Paris, France; [8]Department of Heart Diseases, Wroclaw Medical University, Wrocław, Poland; and [9]Windtree Therapeutics, Inc., Warrington, PA, USA

Received 22 April 2022; revised 24 June 2022; accepted 15 July 2022; online publish-ahead-of-print 22 August 2022

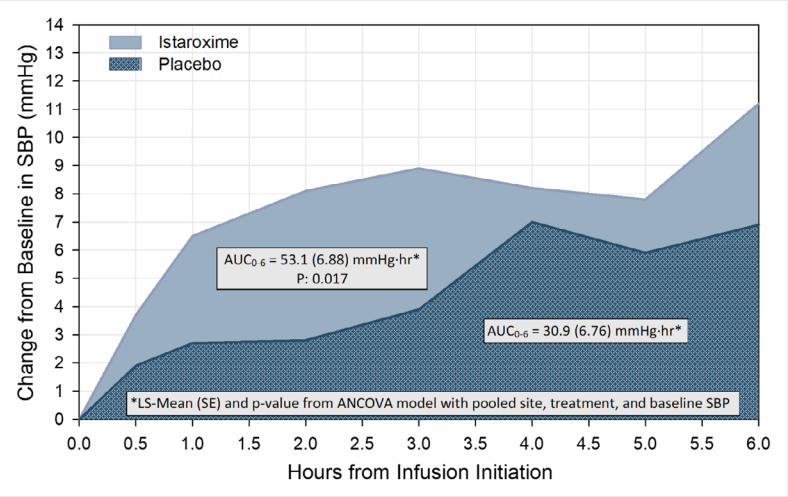
Aims We examined the effects of istaroxime in patients hospitalized for acute heart failure (AHF) related Society for Cardiovascular Angiography and Interventions (SCAI) stage B pre-cardiogenic shock (CS).

Methods and results Sixty patients with AHF without acute myocardial infarction with pre-CS, defined as systolic blood pressure (SBP) <90 mmHg without hypoperfusion, venous lactate ≥2 mmol/L and/or mechanical or inotropic support, were randomized to istaroxime 1.0–1.5 μg/kg/min or placebo for 24 h. The primary endpoint, the adjusted area under the curve (AUC) change in SBP from time of treatment to 6 h, was 53.1 (standard error [SE] 6.88) mmHg × hour versus 30.9 (SE 6.76) mmHg × hour with istaroxime versus placebo ($p = 0.017$). Adjusted SBP AUC at 24 h was 291.2 (SE 27.5) versus 208.7 (SE 27.0) mmHg × hour ($p = 0.025$). At 24 h, some echocardiographic measurements improved with istaroxime versus placebo including cardiac index (+0.21 L/min/m^2; $p = 0.016$), left atrial area (−1.8 cm^2; $p = 0.008$), and left ventricular end-systolic volume (−12.0 ml; $p = 0.034$). There were no significant differences in pulse pressure, laboratory measurements, serious adverse events or adverse events between the treatment groups except for more nausea, vomiting and infusion site pain in the istaroxime-treated patients. In a post-hoc analysis, patients receiving ≤1.0 μg/kg/min versus 1.5 μg/kg/min had similar increase in blood pressure, but a trend towards less adverse events.

Conclusion In a phase 2a study of patients with AHF related pre-CS, istaroxime improved blood pressure and some echocardiography measures related to heart failure and was well tolerated.

*Corresponding author. Cardiology Unit, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Piazzale Spedali Civili 1, 25123 Brescia, Italy. Email: metramarco@libero.it

Graphical Abstract



Sixty patients with acute heart failure-related cardiogenic shock with systolic blood pressure <90 mmHg but without hypoperfusion, without acute coronary event, and not on any intravenous or mechanical support were randomized to intravenous istaroxime or placebo for 24 h. Istaroxime-treated patients had greater increases in systolic blood pressure (SBP) and cardiac index during study drug administration as well as decreases in left ventricular end-systolic volume and left atrial area. AUC, area under the curve; LS, least square; SE, standard error.

Keywords Acute heart failure • Istaroxime • SERCA2a • Cardiogenic shock • Blood pressure • Therapeutics

Introduction

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] A classification of CS into five stages has recently been proposed by the Society for Cardiovascular Angiography and Interventions (SCAI) to better characterize the patients and possibly target treatment[5] and to enrich studied population in CS trials.[6] Pre-CS, stage B, defined by hypotension and/or tachycardia without evidence of peripheral hypoperfusion, is a condition of high-risk with frequent deterioration. Low blood pressure (BP) in patients with acute heart failure (AHF) is associated with significant morbidity and mortality. Hence, those patients are in need for therapies that improve their BP and therefore stabilize them enabling early initiation of lifesaving therapies.[7] To date, most pharmacological interventions including the traditional inotropic agents (e.g. dobutamine, milrinone, enoximone) and vasoactive agents (e.g. norepinephrine), and newer inotropes that do not increase intracellular calcium have not been shown to improve outcomes despite transient improvements in haemodynamic status.[8,9] Of note, all agents that lead to increasing cardiac contractility and may temporarily lead to elevated BP have sympathetic activation as their main mechanism of action and this is associated with tachycardia, increased risk of tachyarrhythmias, including malignant tachyarrhythmias, increased myocardial oxygen consumption and myocardial ischaemia.[8,10]

Istaroxime is a derivative of androstenedione, chemically unrelated to cardiac glycosides, that exerts its effects through dual mechanisms of action: (1) the inhibition of the Na^+/K^+-ATPase activity, thereby causing an increase in intracellular calcium, which increases cardiomyocyte contractility (inotropy); and (2) the activation of the sarcoplasmic reticulum calcium ATPase isoform 2a (SERCA2a) by modulating SERCA–phospholamban interaction, promoting sarcoplasmic reticulum calcium reuptake, thus improving both relaxation (lusitropy) and contractility,[11] as well as potentially reducing risk for arrhythmias. Istaroxime has been shown to improve pulmonary capillary wedge pressure and diastolic cardiac function and produces dose-related increases in systolic BP (SBP) without activating the adrenergic system.[12,13]

The SEISMiC study was designed to compare the safety and efficacy of istaroxime with placebo in patients hospitalized for AHF-related stage B SCAI pre-CS persistent hypotension but no clinical signs of hypoperfusion.

Methods

This study was a phase II, multicentre, randomized, double-blind, placebo-controlled, parallel group trial, conducted at nine sites in the US, Italy, Russia, Romania, and Poland. The study protocol was

developed by the steering committee together with the sponsor, was approved by independent ethics committees and was conducted in accordance with Good Clinical Practice guidelines, the guiding principles of the Declaration of Helsinki, and applicable local laws and regulations. All patients provided written informed consent. The study was approved by each respective country regulatory authority and by local institutional review boards. The trial is registered in the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT 2020−000885-40) and ClinicalTrials.gov (NCT04325035).

Study population

Inclusion criteria included AHF-related SCAI stage B pre-CS, 18−85 years of age, an ongoing hospitalization for AHF, left ventricular ejection fraction ≤40%, persistent hypotension (SBP between 75 and 90 mmHg), heart rate of 75−150 bpm and no need at time of screening or planned use for 6 h thereafter of mechanical support or intravenous therapy to increase BP.

According to the stage B SCAI classification, patients with clinical signs of peripheral hypoperfusion, venous lactate ≥2 mmol/L and/or on mechanical support or treatment with intravenous vasodilators, inotropes or vasopressors were excluded. Other exclusion criteria were concomitant or planned treatment with oral digoxin (could be randomized if the plasma concentration of digoxin at screening was <0.5 ng/ml); acute coronary syndrome or stroke within the past 3 months; coronary artery bypass graft or percutaneous coronary intervention within the past month or planned in the next month; life-threatening ventricular arrhythmia or implantable cardioverter defibrillator shock within the past month; sustained ventricular tachycardia in the last 3 months or uncontrolled arrhythmia; fever >38°C; estimated glomerular filtration rate (eGFR) <30 ml/min/m^2; serum potassium >5.3 or <3.5 mmol/L; stroke or transient ischaemic accident within the past 3 months; and acute respiratory distress syndrome. The full inclusion and exclusion criteria are presented in online supplementary *Table S1*.

Study drug administration

Patients were randomized centrally, using an interactive response technology, to receive istaroxime or placebo at a ratio of 1:1. Study medication was supplied in uniquely-numbered kits containing identical vials of lyophilized powder (istaroxime plus lactose), reconstituted by adding 5 ml saline to the vial. Istaroxime was administered as a continuous infusion 1.0 μg/kg/min for 24 h. The infusion rate could be decreased at the discretion of the investigator based on the development of tolerability issues (such as nausea), significant bradycardia, or greater than desired BP elevation. The original protocol had a target and maximum dose infusion of 1.5 μg/kg/min; however, after 26 of the 60 patients were recruited, the sponsor and executive steering committee amended the protocol to limit the dose of istaroxime to 1.0 μg/kg/min, after which all patients were to receive a target and maximum dose of 1.0 μg/kg/min of istaroxime. This change was not mandated by the Data Monitoring Committee (DMC), but they supported this action.

Clinical endpoints

The primary efficacy endpoint was the area under the curve representing the change in SBP from baseline, start of study drug infusion, through 6 h (SBP AUC). Secondary endpoints included SBP AUC through 24 h; changes from baseline in SBP (particularly at 6 and 24 h), diastolic blood pressure (DBP) and mean arterial pressure (MAP); changes from baseline in heart rate (HR); treatment failure score (based on death, circulatory, respiratory, or renal mechanical support or intravenous inotrope or vasopressor treatment, and changes in SBP); treatment failure defined as death or need for circulatory, respiratory, or renal mechanical support or intravenous inotrope or vasopressor treatment; increase from baseline in SBP ≥5% and/or ≥10 mmHg; changes in quality of life measured by the EuroQol 5 Dimension 5 Level (EQ-5D-5L); change from baseline to 24 h in echocardiography parameters; changes in troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP); hospital readmission for heart failure and for any cause by day 30; in-hospital worsening heart failure to day 5; and length of hospital stay. In-hospital worsening heart failure was defined as worsening signs and/or symptoms of heart failure since the previous assessment that required an intensification of intravenous therapy for heart failure or mechanical ventilatory, renal, or circulatory support.

Safety endpoints were assessed throughout the study and included the incidence of adverse events; changes in vital signs and in 12-lead electrocardiogram (ECG) parameters; incidence of clinically or haemodynamically significant episodes of supraventricular or ventricular arrhythmias detected by continuous ECG monitoring; standard laboratory parameters; renal function measures; cardiac troponin I or T; and mortality through day 30.

Statistical analysis

Based on the results from the previous study,[12] it was assumed that 30 subjects/group would be sufficient to show a qualitative improvement for the active group.

The primary efficacy analysis population was a modified intention-to-treat (mITT) population defined as subjects who received study treatment (any istaroxime or placebo infused to patient) and had at least one post-baseline BP assessment. Supportive efficacy analyses were conducted in an ITT population including all randomized patients, and a per-protocol population including subjects who received study drug infusion without an excluding protocol violation. Safety analyses included all patients who received any study medication. As all patients who were randomized received study treatment and had at least one post-baseline BP assessment, the mITT, ITT, and safety populations were the same. Because the dosing regimen was changed after the trial was underway, patients in the active group were classified by the maximum istaroxime dose received (all ≤1.0 vs. any >1.0 μg/kg/min), and additional pairwise comparisons were made.

Unadjusted results for continuous variables are presented as the mean and standard deviation while adjusted changes are presented as least square mean change and corresponding standard error (SE). Frequencies are presented for categorical variables. Sites that enrolled fewer than six patients were pooled and treated as one site for adjustment by pooled site. Frequencies are reported for categorical variables and binary clinical endpoints.

The primary endpoint, SBP AUC through hour 6, was computed by trapezoidal rule. Treatment groups were compared using ANCOVA with baseline value, pooled site, and treatment in the model. Changes in creatinine clearance, heart rate, MAP, natriuretic peptides, and troponin were compared between treatment groups using mixed model repeated measures with baseline value, treatment, pooled study site, time, and treatment by time interaction in the models. Changes in EuroQol visual analogue scale from baseline to 96 h and 30 days, and changes in echocardiographic measures at 24 and 30 h were compared between treatment groups at each time point using ANCOVA with baseline value, treatment, and pooled study site in the models. Van

Elteren test stratified by pooled study centre was used to compare groups regarding treatment failure score (through 24 h), length of hospital stay, stay in intensive care or coronary care units (ICU/CCU), days alive out of the hospital, and days alive out of acute care through day 30. The proportion of subjects who sustained treatment failure, with any hospital readmission through day 30, or with increases from baseline in SBP ≥5% and ≥10 mmHg at a timepoint between 4 and 6 h after dosing, were compared using the Cochran–Mantel–Haenszel (CMH) test controlling for pooled sites.

An independent DMC conducted a scheduled interim safety analysis of unblinded data after 20 patients had been enrolled.

Two-sided $p < 0.05$ was considered statistically significant. No adjustments for multiple testing were made. SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) was used for analyses.

Results

Between 28 September 2020 and 9 March 2022, 60 patients in Italy, Poland, Romania, Russia and the United States were randomized. Baseline characteristics are presented in *Table 1*. A CONSORT flow diagram for the study is presented in *Figure 1*. The infusion duration was a mean of 23.1 ± 3.85 h in the istaroxime group and 24.0 ± 0.029 h in the placebo group. The infusion was interrupted for one istaroxime-treated patient due to BP decrease.

Effects on blood pressure and vital signs

The primary endpoint was the AUC representing the change in SBP from time of infusion start to hour 6. The adjusted mean 6 h AUC was 53.1 (SE 6.88) mmHg × hour in the istaroxime-treated patients versus 30.9 (SE 6.76) mmHg × hour in the placebo group ($p = 0.017$), an increase of 72% (*Graphical Abstract*). The adjusted mean 24 h SBP AUC was 291.2 (SE 27.5) mmHg × hour in the istaroxime group versus 208.7 (SE 27.0) mmHg × hour in the placebo group ($p = 0.025$), an increase of 40%. The adjusted SBP increase at 6 h was 12.3 (SE 1.71) mmHg in the istaroxime-treated group versus 7.5 (SE 1.64) mmHg in the placebo group ($p = 0.045$). The corresponding adjusted changes in SBP at 24 h (*Figure 2*) were 17.1 (SE 2.36) mmHg and 15.1 (SE 2.25) mmHg in the istaroxime group versus placebo ($p = 0.543$). Additionally, increases were noted in DBP (*Figure 2*) and MAP, the latter two persisting beyond the 24 h of study drug administration. Unadjusted changes in SBP, DBP and MAP are presented in *Figure 2*. There were no significant differences in pulse and other vital signs changes between the istaroxime and placebo groups (online supplementary *Table S2*).

Clinical signs and symptoms of heart failure, and clinical events

Urine output was 2983 ± 1629 ml in the istaroxime-treated patients in the first 24 h of treatment versus 2740 ± 1238 ml ($p = 0.526$) in the placebo-treated patients. Weight decreased at 24 h −1.7 (SE 0.30) kg in the istaroxime-treated patients versus −1.5 (SE 0.28) kg in the placebo-treated patients ($p = 0.53$) after adjustment. Adjusted weight changes at 48 h were −2.7 (SE 0.35) kg versus −2.1 (SE 0.33) kg ($p = 0.21$) and at 72 h were −3.3 (SE 0.48) kg versus -2.8 (SE 0.42) kg ($p = 0.42$) in the istaroxime and placebo-treated patients, respectively. The total dose of loop diuretics administered through 96 h was 385 ± 412 mg of furosemide in the istaroxime-treated patients versus 431 ± 397 mg of furosemide in the placebo-treated patients ($p = 0.53$).

Treatment failure during the first 24 h of therapy, defined as death, need for intravenous vasopressors, inotropes, and/or mechanical cardiac or renal support through 24 h occurred in 2 (7%) patients in the istaroxime group versus 0 (0%) in the placebo group ($p = 0.19$). In the first 96 h of treatment, there were five in-hospital worsening heart failure events in the istaroxime group and one in the placebo group ($p = 0.031$). No effects were observed on EQ-5D quality of life measures at either 96 h or 30 days from infusion start (online supplementary *Table S3*).

There were no differences in length of stay in the hospital or in the ICU between the istaroxime and placebo groups, nor in days alive and out of hospital and days alive and out of acute care. Four istaroxime-treated and four placebo-treated patients experienced the composite outcome of death or heart failure readmission through day 30 ($p = 0.99$). Of those, there were four deaths in the istaroxime group versus one in the placebo group ($p = 0.17$) and no heart failure readmissions in the istaroxime group versus three in the placebo group ($p = 0.087$). Clinical endpoints are presented in online supplementary *Table S4*.

Laboratory assessments

Changes in laboratory values between the istaroxime and placebo-treated patients are presented in online supplementary *Table S5*. There were no differences in changes in laboratory values between the istaroxime and placebo-treated patients. Those include no significant differences in changes in troponin, lactate, or NT-proBNP.

Echocardiographic assessments

Echocardiographic changes during the first 24 h of the study are presented in *Table 2*. Among the echocardiographic measures assessed, there were significant improvements at 24 h in some measures after adjustment that included cardiac index (+0.16 ± 0.1 vs. −0.06 ± 0.1 L/min/m^2; $p = 0.016$), left atrial area (−1.8 ± 0.5 vs. 0.0 ± 0.5 cm^2; $p = 0.008$), left ventricular end-systolic volume (−8.7 ± 4.2 vs. 3.3 ± 4.2 ml; $p = 0.034$) and left ventricular end-diastolic volume (−6.5 ± 4.9 vs. 5.6 ± 4.8 ml; $p = 0.061$) in the istaroxime-treated patients as compared to the placebo-treated patients.

Safety

A total of 25 patients (86%) had a non-serious adverse event (SAEs) in the istaroxime group versus 23 (74%) in the placebo group. Treatment emergent adverse events (TEAEs) were observed in 27 patients (93%) in the istaroxime group versus 25 (81%) in the placebo group. There were more TEAEs of nausea (8 [28%] vs. 2 [6%]), vomiting (4 [14%] vs. 0 [0%]) and infusion site pain (4 [14%]

Table 1 Baseline characteristics

Variable	Placebo ($n = 31$)	Istaroxime ($n = 29$)
Age (years)	63.0 ± 12.6	65.2 ± 10.0
Male sex	27 (87)	22 (76)
Race		
Caucasian	30 (97)	29 (100)
Asian	1 (3)	0 (0)
BMI (kg/m^2)	27.3 ± 6.12	28.0 ± 6.35
Atrial fibrillation at screening	11 (35)	10 (34)
Systolic blood pressure (mmHg)	87.1 ± 2.82	87.5 ± 3.47
Heart rate (bpm)	83.5 ± 18.6	83.8 ± 15.9
QRS duration (ms)	120.0 ± 40.7	101.9 ± 25.6
Medical history		
Diabetes mellitus	14 (45)	9 (31)
Hyperlipidaemia	23 (74)	21 (72)
Hypertension	23 (74)	25 (86)
Renal failure	9 (29)	7 (24)
Ischaemic heart disease by imaging	5 (16)	4 (14)
Prior myocardial infarction	21 (68)	13 (45)
Prior percutaneous intervention	17 (55)	9 (31)
Prior coronary artery bypass graft	3 (10)	4 (14)
History of unstable angina	2 (6)	1 (3)
Stable angina pectoris	1 (3)	0 (0)
Cerebrovascular accident/stroke	1 (3)	1 (3)
Prior transient ischaemic attack	0 (0)	1 (3)
Aortic regurgitation	7 (23)	10 (34)
Aortic stenosis	0 (0)	2 (7)
Mitral regurgitation	24 (77)	23 (79)
Mitral stenosis	0 (0)	1 (3)
Tricuspid regurgitation	20 (65)	18 (62)
History of heart failure	31 (100)	29 (100)
Atrial fibrillation	18 (58)	16 (55)
Automatic defibrillator	7 (23)	5 (17)
Cardiac resynchronization therapy	2 (6)	4 (14)
Pulmonary hypertension	13 (42)	17 (59)
Cancer	2 (6)	2 (7)
Chronic obstructive pulmonary disease	2 (6)	2 (7)
Laboratory		
eGFR (ml/min/1.73 m^2)	53.0 [47–66]	41.8 [37–65]
NT-proBNP (pg/ml)	3907.5 [1864–6947]	6867.0 [4038–14 026]
Troponin (ng/ml)	0.02 [0.01–0.20]	0.03 [0.02–0.10]
Serum lactate (mmol/L)	1.44 ± 0.25	1.45 ± 0.40
Sodium (mmol/L)	138.4 ± 4.4	138.3 ± 4.1
Potassium (mmol/L)	4.1 ± 0.4	4.1 ± 0.4
Glucose (mmol/L)	6.9 ± 2.4	7.0 ± 1.6
Urea (mmol/L)	9.7 ± 4.5	10.2 ± 4.7
AST (U/L)	38.4 ± 41.3	27.0 ± 12.3
White blood cell count (×10^{13}/L)	7.8 ± 2.7	8.3 ± 2.3
Haematocrit (%)	37 ± 13.0	33 ± 14.5
Medications within 30 days prior to screening		
Angiotensin-converting enzyme inhibitors	11 (36)	14 (48)
Angiotensin II receptor blockers	14 (45)	13 (45)
Beta-blockers	23 (74)	21 (72)
Aldosterone antagonists	21 (68)	22 (76)
Digitalis glycoside	0 (0)	1 (3)
IV loop diuretic pre-dose	30 (97)	25 (86)

Table 1 (Continued)

Variable	Placebo (n = 31)	Istaroxime (n = 29)
Echocardiography		
LV end-diastolic volume (ml)	202.3 ± 60.5	202.0 ± 78.2
LV end-systolic volume (ml)	151.2 ± 55.0	146.6 ± 65.6
LV ejection fraction	25.7 ± 7.40	26.6 ± 7.03
TAPSE (mm)	13.7 ± 4.39	15.1 ± 5.34
Stroke volume index (ml/beat/m^2)	23.7 ± 6.54	24.4 ± 6.41
E/e′ ratio	13.1 ± 5.45	12.1 ± 5.44
E/A ratio	1.8 ± 0.84	1.9 ± 1.27
Left atrial area (cm^2)	29.0 ± 8.19	29.5 ± 6.62
Left atrial volume (ml)	118.0 ± 62.6	105.9 ± 46.6
Mitral regurgitation, moderate[a]	16 (52)	21 (72)
IVC diameter (mm)	22.3 ± 5.73	22.5 ± 4.56

Data are shown as mean ± standard deviation, n (%), or median [interquartile range].
AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; IV, intravenous; IVC, inferior vena cava; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TAPSE, tricuspid annular plane systolic excursion.
[a]No patient reported a history of severe mitral regurgitation.

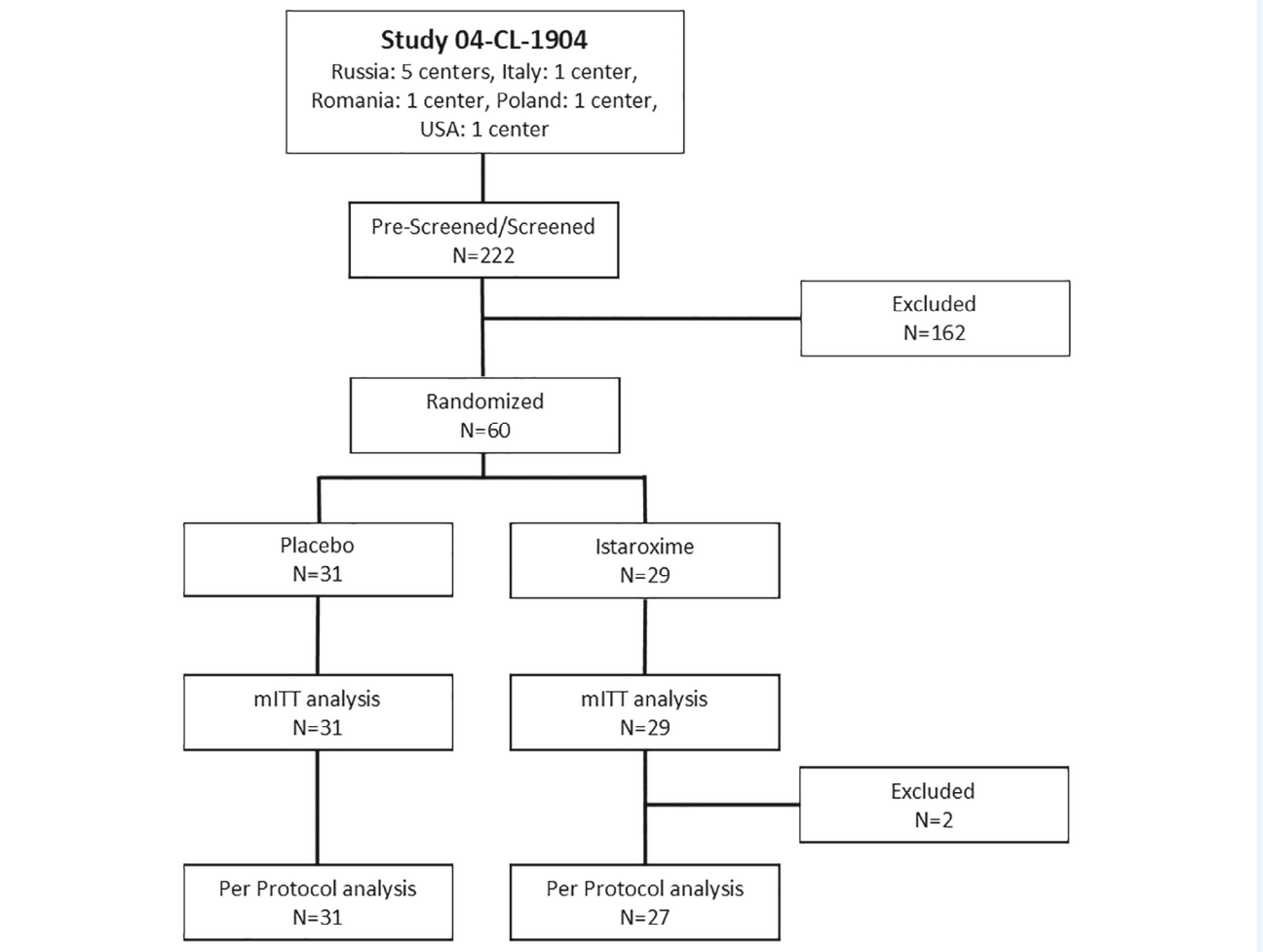


Figure 1 CONSORT diagram for the SEISMiC study.

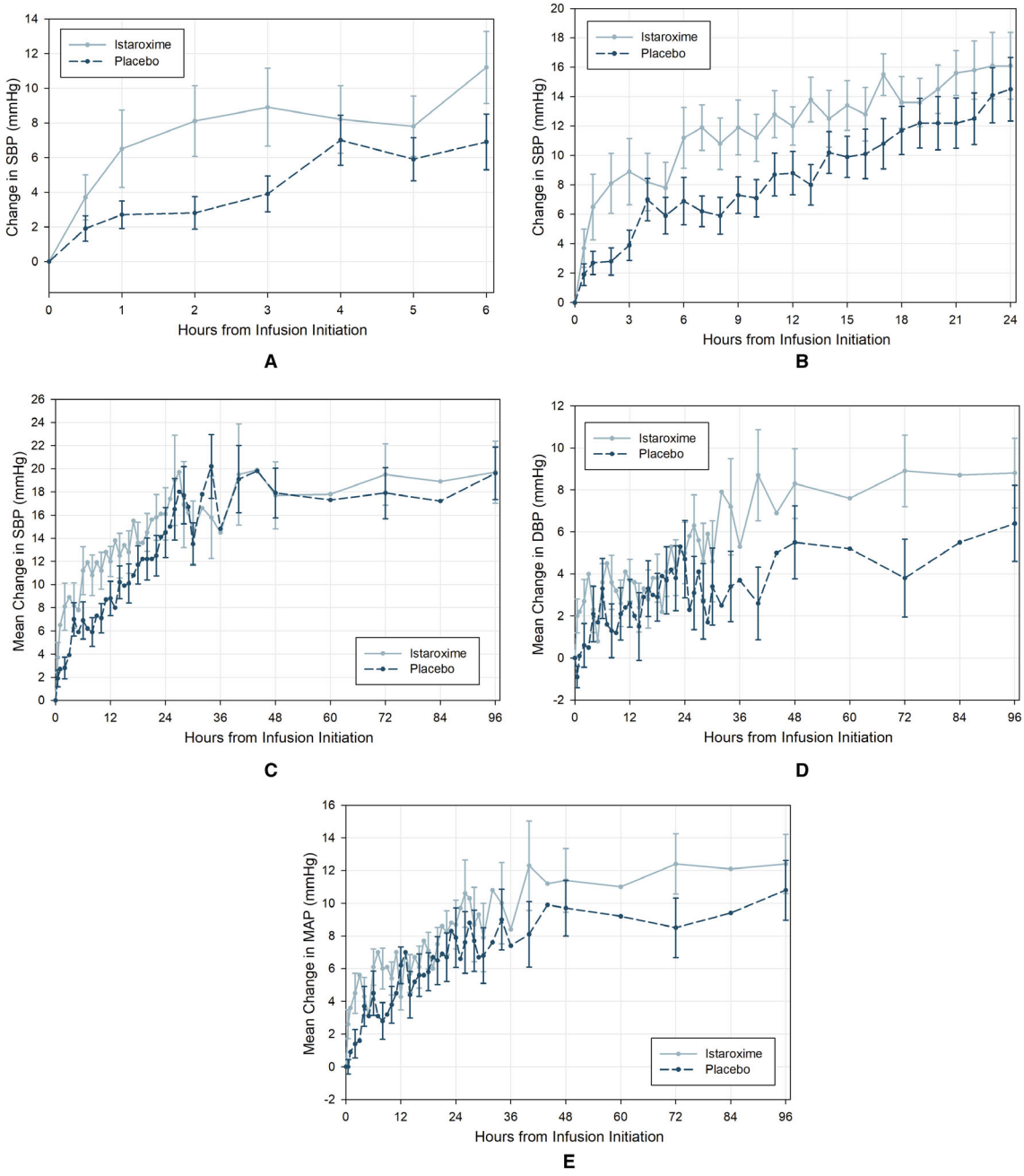


Figure 2 Blood pressure changes in the SEISMiC study. (*A*) Systolic blood pressure (SBP) through 6 h, (*B*) SBP through 24 h, (*C*) SBP through 96 h, (*D*) diastolic blood pressure (DBP) through 96 h, and (*E*) mean arterial pressure (MAP) through 96 h. Error bars shown are standard errors and are presented at every other timepoint for figures through 96 h.

vs. 0 [0%]) in the istaroxime patients compare to placebo. There were six SAEs each in the istaroxime and placebo-treated patients. All SAEs are detailed in *Table 3* and TEAEs are detailed in online supplementary *Table S6a*. There were no differences in arrhythmias through the 48 h after study drug administration as determined by Holter monitoring. Arrhythmias by Holter monitoring observed during the study are detailed in online supplementary *Table S6b*.

Post-hoc comparisons of 1.0 and 1.5 μg/kg/min dose

As described in the Methods section, after 26 patients were recruited to the study the maximum dose was limited to 1.0 μg/kg/min. In a post-hoc analysis, the above-mentioned measures of efficacy and safety were compared between patients enrolled in the placebo arm to those who received 1.0 and

Table 2 Changes in echocardiographic measurements

Parameter/time point	Istaroxime (n = 29)		Placebo (n = 31)		p-value
	Observed	Change from baseline	Observed	Change from baseline	
Cardiac index (L/min/m^2)					
Baseline (pre-dose)	1.9 (0.57)		2.0 (0.63)		
24 h post-treatment	2.1 (0.60)	0.156 (0.065)	1.9 (0.61)	−0.057 (0.067)	0.016
Cardiac output (L/min)					
Baseline (pre-dose)	3.63 (1.12)		3.87 (1.30)		
24 h post-treatment	3.93 (1.19)	0.23 (0.13)	3.93 (1.35)	−0.02 (0.13)	0.141
E/A ratio					
Baseline (pre-dose)	1.9 (1.27)		1.8 (0.84)		
24 h post-treatment	1.5 (1.06)	−0.380 (0.172)	1.8 (0.93)	0.049 (0.187)	0.090
E/Ea ratio					
Baseline (pre-dose)	12.1 (5.44)		13.1 (5.45)		
24 h post-treatment	12.2 (6.09)	−0.615 (0.893)	11.2 (5.42)	−2.139 (0.929)	0.195
Ejection time (ms)					
Baseline (pre-dose)	223.5 (62.12)		231.8 (51.66)		
24 h post-treatment	219.0 (55.80)	−2.807 (6.197)	230.6 (59.33)	2.201 (6.288)	0.545
Inferior vena cava diameter (mm)					
Baseline (pre-dose)	22.5 (4.56)		22.3 (5.73)		
24 h post-treatment	19.5 (5.49)	−2.503 (0.700)	20.0 (6.06)	−2.080 (0.695)	0.647
Left atrial area (cm^2)					
Baseline (pre-dose)	29.5 (6.62)		29.0 (8.19)		
24 h post-treatment	27.1 (6.27)	−1.817 (0.501)	29.0 (7.12)	0.004 (0.500)	0.008
Left atrial volume (ml)					
Baseline (pre-dose)	105.9 (46.63)		118.0 (62.57)		
24 h post-treatment	95.2 (39.70)	−7.440 (1.876)	112.5 (61.40)	−3.170 (1.906)	0.095
Left ventricular end-diastolic volume (ml)					
Baseline (pre-dose)	202.0 (78.19)		202.3 (60.45)		
24 h post-treatment	194.3 (79.36)	−6.501 (4.864)	206.3 (65.94)	5.641 (4.755)	0.061
Left ventricular end-systolic volume (ml)					
Baseline (pre-dose)	146.6 (65.59)		151.2 (54.98)		
24 h post-treatment	135.7 (70.57)	−8.692 (4.202)	151.2 (59.83)	3.312 (4.186)	0.034
Left ventricular ejection fraction (%)					
Baseline (pre-dose)	26.6 (7.03)		25.7 (7.40)		
24 h post-treatment	29.5 (7.64)	2.678 (0.739)	27.6 (8.61)	1.383 (0.723)	0.184
Left ventricular end-diastolic diameter (mm)					
Baseline (pre-dose)	62.5 (8.25)		65.7 (9.12)		
24 h post-treatment	61.3 (8.64)	−0.668 (0.438)	64.1 (9.30)	−0.807 (0.434)	0.811
Left ventricular end-systolic diameter (mm)					
Baseline (pre-dose)	54.4 (9.66)		54.9 (12.92)		
24 h post-treatment	52.8 (9.89)	−0.719 (1.457)	56.0 (9.68)	2.252 (1.464)	0.125
Mitral regurgitation					
Baseline (pre-dose)					
None	0 (0%)		0 (0%)		
Mild	8 (28%)		15 (48%)		
Moderate	21 (72%)		16 (52%)		
24 h post-treatment					
None	1 (4%)		0 (0%)		
Mild	11 (39%)		14 (47%)		
Moderate	16 (57%)		16 (53%)		
Pulmonary artery systolic pressure (mmHg)					
Baseline (pre-dose)	44.9 (14.97)		46.0 (18.38)		
24 h post-treatment	36.8 (14.58)	−7.084 (1.878)	39.4 (16.12)	−4.790 (1.798)	0.348

Table 2 (Continued)

Parameter/time point	Istaroxime ($n = 29$)		Placebo ($n = 31$)		p-value
	Observed	Change from baseline	Observed	Change from baseline	
Stroke volume index (ml/m^2)					
Baseline (pre-dose)	24.4 (6.41)		23.7 (6.54)		
24 h post-treatment	28.3 (9.19)	4.001 (1.346)	24.8 (6.96)	0.930 (1.355)	0.088
Tricuspid annular plane systolic excursion (mm)					
Baseline (pre-dose)	15.1 (5.34)		13.7 (4.39)		
24 h post-treatment	15.9 (5.02)	0.860 (0.493)	14.1 (3.83)	0.492 (0.484)	0.573

Observed results presented as mean (standard deviation). Change from baseline results are least square (adjusted) means with corresponding standard error. Change from baseline results and p-values are estimated from an ANCOVA model adjusted for treatment, pooled site, and baseline value.

Table 3 Serious adverse events

System Organ Class/ preferred term	Istaroxime ($n = 29$)	Placebo ($n = 31$)
Any serious adverse event	6 (21%)	6 (19%)
Cardiac disorders	4 (14%)	5 (16%)
Cardiac arrest	1 (3%)	0 (0%)
Heart failure	2 (7%)	2 (6%)
Heart failure, acute	0 (0%)	1 (3%)
Intraventricular thrombus	0 (0%)	1 (3%)
Newly diagnosed coronary artery disease	0 (0%)	1 (3%)
Ventricular fibrillation	1 (3%)	0 (0%)
Ventricular tachycardia	1 (3%)	0 (0%)
Infections and infestations	1 (3%)	1 (3%)
Coronavirus infection	0 (0%)	1 (3%)
Pneumonia	1 (3%)	0 (0%)
Renal and urinary disorders	1 (3%)	0 (0%)
Acute kidney injury	1 (3%)	0 (0%)

1.5 μg/kg/min dose. The results of these comparisons are presented in online supplementary *Table S7*. Of note, none of the differences are statistically significant, including changes in BP that were largely similar between the two active doses. Adjusted mean 6 h SBP change AUC was 51.4 (SE 8.98) mmHg × hour in the 16 patients receiving the 1.0 dose, 55.6 (SE 11.06) mmHg × hour in the 13 patients receiving the 1.5 dose, and 31.2 (SE 6.87) mmHg × hour in the 31 patients assigned to placebo. p-values comparing 1.0 versus placebo and 1.5 versus placebo were 0.049 and 0.051 respectively. As described in online supplementary *Table S7*, some safety variables seem to favour the 1.0 dose.

Discussion

The purpose of the SEISMiC study was to assess whether the findings from previous studies[12,13] of istaroxime that revealed beneficial effects on BP and echocardiographic measures of left ventricular function in patients with heart failure could be achieved in patients with AHF-related SCAI stage B pre-CS. Therefore, patients with SCAI stage B CS due to AHF having persistent SBP <90 mmHg at screening but without evidence of hypoperfusion both clinically and as evident by venous lactate levels <2.0 mmol/L were included in the study. Such patients are at increased risk for adverse outcomes and, hence, there is a need for newer therapies that can enable their rapid stabilization leading to initiation of lifesaving therapies, improving their outcomes. To enable objective assessments of BP and echocardiographic measures, patients were enrolled if not receiving any mechanical or inotrope support at inclusion with no anticipated need for such therapy in the hours after randomization. Hence, in these patients with relatively stable AHF-related SCAI stage B pre-CS, some improvement in BP in the placebo-treated patients was observed with supportive therapy only. Istaroxime treatment led to an increase in SBP from start of treatment to 24 h by both AUC at 6 and 24 h. The BP changes associated with istaroxime treatment observed in the current study are in line with those observed in the previous istaroxime studies enrolling more stable patients hospitalized with AHF.[12,13] Of note, this study is the first to show a beneficial effect on BP in CS patients with any non-adrenergic drug, and hence without effects on pulse.

Similarly, in line with previous studies,[12,13] some improvements in echocardiographic measures were observed including increases in cardiac index and reduction in left ventricular and atrial dimensions. These findings suggest that istaroxime improved cardiac function in this patient population, a finding which is in line with both previous clinical and experimental data. The concomitant increase in both cardiac index and BP is unique and has not been observed with any previous intravenous drugs administered to patients with CS. This improvement can potentially allow for faster stabilization of patients with CS and earlier initiation of other lifesaving therapies.

The morbidity and mortality observed in the study (8 out of 60 patients, 13.3% death or heart failure readmission in the first 30 days) suggests that the patients enrolled have had significant AHF-related pre-CS, a patient population that is in need for new supportive therapies. Of note, this pilot study was not powered for such endpoints which typically require many more patients to be enrolled.[14] Importantly, laboratory evaluation did not suggest in this study an effect of istaroxime on end-organ damage, commonly seen in AHF patients, although, again, this pilot study was not powered towards laboratory changes and biomarkers.

No significant difference was noted with regard to SAEs between treatment groups. As expected, based on the results of previous

studies, istaroxime treatment was associated with more adverse events of nausea, vomiting and pain at infusion site.

The target dose of istaroxime administered was 1.0–1.5 μg/kg/min in the first part of the study; however, after 26 of the 60 patients were recruited, the dose of istaroxime was limited to 1.0 μg/kg/min, after which all patients were to receive a target and maximum dose of 1.0 μg/kg/min. This change was not mandated by the DMC, but the DMC was supportive of this decision. Post-hoc comparisons of patients receiving 1.0 and 1.5 μg/kg/min suggest that most of the improvement in cardiovascular physiology occurs at doses of 1.0 μg/kg/min; however, there was a trend towards more adverse events in patients treated with 1.5 μg/kg/min that was not observed in those treated with 1.0 μg/kg/min. These findings suggest that the dose of 1.0 μg/kg/min should be further explored in this patient population.

The effects of istaroxime on BP and echocardiographic measures of heart failure may have implications in patients with AHF-related CS. Those patients with low BP at admission have high event rates, including morbidity and mortality,[7] as has been seen in the current study (13.3% died or had a heart failure readmission in the first 30 days). In those patients, BP increase enables early stabilization and earlier initiation of lifesaving therapies, potentially improving their outcomes. As previous drugs developed for this indication have not improved both BP and cardiac index at the same time and were associated with increases in pulse and substantial arrhythmic and non-arrhythmic adverse events, the findings of this study, if confirmed, can create a new treatment option for those patients in dire need for such therapies.

Limitations

This is a pilot study in patients with AHF-related SCAI class B pre-CS who did not require inotropic support and did not display signs of hypoperfusion. As such, these results are preliminary and need to be confirmed in larger studies. The comparisons of the 1.0 μg/kg/min and 1.5 μg/kg/min istaroxime doses were done post-hoc and were not randomized.

Conclusions

In this pilot phase 2 study of patients with AHF-related SCAI stage B pre-CS, istaroxime improved BP and some echocardiography measures of heart failure without adverse effects, including arrhythmias or renal function.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgement

Open Access Funding provided by Universita degli Studi di Brescia within the CRUI-CARE Agreement.

Funding

The SEISMiC study was funded by Windtree Therapeutics, Inc.

Conflict of interest: M.M. received personal fees of minimal amounts in the last 3 years from Actelion, Amgen, Livanova, Servier and Vifor pharma as member of Executive or Data Monitoring Committees of sponsored clinical trials; from AstraZeneca, Abbott Vascular, Bayer, Boehringer Ingelheim and Edwards Therapeutics for participation to advisory boards and/or speeches at sponsored meetings. O.C. is a member of Boehringer Ingelheim Advisory Board. G.C., B.D., and M.N. are employees of Momentum Research, Inc. which has received grants from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics Inc., Corteria Pharmaceuticals, Roche Diagnostics Inc., Sanofi, Windtree Therapeutics Inc. and XyloCor Therapeutics. G.F. is an executive committee member and consultant to Corthera (a Novartis company), Bayer, Amgen, Servier, Medtronic, Vifor, Boehringer Ingelheim and has received research grants from the European Union. A.M. reports personal fees from Orion, Roche, Adrenomed and Fire 1 and grants and personal fees from 4TEEN4, Abbott, Roche and Sphyngotec. P.P. reports other from Trevena, during the conduct of the study; reports grants and personal fees from Amgen, Inc., Servier, Boehringer Ingelheim, Vifor Pharma, Novartis, Bayer, Cibiem, AstraZeneca, BMS, Renal Guard Solutions, Impulse Dynamics, Abbott Vascular, personal fees from Berlin Chemie, outside the submitted work. P.S., J.S., and S.S. are employees of Windtree Therapeutics, Inc.

References

1. Chioncel O, Parissis J, Mebazaa A, Thiele H, Desch S, Bauersachs J, et al. Epidemiology, pathophysiology and contemporary management of cardiogenic shock – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2020;**22**:1315–41.
2. Van DS, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation*. 2017;**136**:e232–68.
3. Bers DM. Altered cardiac myocyte Ca regulation in heart failure. *Physiology (Bethesda)*. 2006;**21**:380–7.
4. Singh T, Samson R, Ayinapudi K, Motwani A, Le JTH. Precardiogenic shock: a new clinical entity. *Cardiol Rev*. 2019;**27**:198–201.
5. Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, Henry TD, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock: this document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. *Catheter Cardiovasc Interv*. 2019;**94**:29–37.
6. Arrigo M, Price S, Baran DA, Pöss J, Aissaoui N, Bayes-Genis A, et al. Optimising clinical trials in acute myocardial infarction complicated by cardiogenic shock: a statement from the 2020 Critical Care Clinical Trialists Workshop. *Lancet Respir Med*. 2021;**9**:1192–202.
7. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA*. 2006;**296**:2217–26.
8. Maack C, Eschenhagen T, Hamdani N, Heinze FR, Lyon AR, Manstein DJ, et al. Treatments targeting inotropy. *Eur Heart J*. 2019;**40**:3626–3640D.
9. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, et al.; SURVIVE Investigators. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE randomized trial. *JAMA*. 2007;**297**:1883–91.
10. Psotka MA, Gottlieb SS, Francis GS, Allen LA, Teerlink JR, Adams KF, et al. Cardiac calcitropes, myotropes, and mitotropes: JACC review topic of the week. *J Am Coll Cardiol*. 2019;**73**:2345–53.
11. Chioncel O, Collins SP, Butler J. Istaroxime in acute heart failure: the holy grail is at HORIZON? *Eur J Heart Fail*. 2020;**22**:1694–7.

12. Gheorghiade M, Blair JEA, Filippatos GS, Macarie C, Ruzyllo W, Korewicki J, et al.; HORIZON-HF Investigators. Hemodynamic, echocardiographic, and neurohormonal effects of istaroxime, a novel intravenous inotropic and lusitropic agent: a randomized controlled trial in patients hospitalized with heart failure. *J Am Coll Cardiol*. 2008;**51**:2276–85.
13. Carubelli V, Zhang Y, Metra M, Lombardi C, Felker GM, Filippatos G, et al.; Istaoxime ADHF Trial Group. Treatment with 24 hour istaroxime infusion in patients hospitalised for acute heart failure: a randomised, placebo-controlled trial. *Eur J Heart Fail*. 2020;**22**:1684–93.
14. Chioncel O, Mebazaa A, Harjola VP, Coats AJ, Piepoli MF, Crespo-Leiro MG, et al.; ESC Heart Failure Long-Term Registry Investigators. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2017;**19**:1242–54.