

BRIEF REPORT

Istaroxime's Effect on Hemodynamics and Arrhythmias in Cardiogenic Shock

A Pooled Analysis of SEISMic Trials

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Acute heart failure (HF) and cardiogenic shock (CS) represent 2 clinical manifestations of decompensated HF that often overlap and may evolve into one another. One of the key pathophysiological features of both acute HF and CS is impaired central hemodynamics and reduced tissue perfusion, which contribute to multiorgan dysfunction and are associated with prognosis. To date, no inotropic agent has demonstrated both an acceptable safety margin and a prognostic benefit in this population. In most cases, the use of available inotropes has been associated with an increased risk of life-threatening arrhythmias, which limits their clinical utility.

Istaroxime, an investigational inotropic agent with a unique dual mechanism of action— Na^+/K^+ -ATPase inhibition and SERCA2a (sarcoplasmic reticulum calcium ATPase isoform 2a) stimulation, was evaluated in the SEISMic prospective, randomized, placebo-controlled trials in patients with CS due to decompensated HF—in SCAI (Society for Cardiovascular Angiography and Interventions) stage B CS in SEISMic parts A and B, and in SCAI stage C CS in SEISMic-C.¹⁻⁵ This analysis assesses the totality of data on istaroxime's hemodynamic effect, arrhythmic burden, and clinical outcomes in a pooled population of critically ill patients.

METHODS

Data from SEISMic part B (n = 30) and SEISMic-C (n = 20) were combined for analyzing hemodynamic, cardiac, and arrhythmogenic effects of istaroxime, and part A data were also pooled to analyze clinical events (n = 84). The SEISMic trials recruited patients at different stages of CS and randomized them to receive a continuous intravenous infusion of 0.5-1.5 $\mu\text{g}/\text{kg}/\text{min}$ istaroxime or placebo. The detailed differences between the protocols for each SEISMic part are presented in the design and main results papers.^{1,3,4}

What is the clinical question being addressed?

What is the clinical impact (on central hemodynamics, on arrhythmia burden, and clinical outcomes) of Istaroxime in patients with cardiogenic shock?

What is the main finding?

Compared with placebo, Istaroxime significantly improved systolic blood pressure and central hemodynamics, including cardiac output and pulmonary artery wedge pressure, and was associated with a lower incidence of ventricular arrhythmias.

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**ABBREVIATIONS
AND ACRONYMS****CS** = cardiogenic shock**HF** = heart failure**IRR** = incidence rate ratio**PCWP** = pulmonary capillary
wedge pressure**SBP** = systolic blood pressure**Svo₂** = mixed venous oxygen
saturation**WHF** = worsening heart failure

The primary endpoint of the SEISMic trials was the area under the curve (AUC) of change from baseline in systolic blood pressure (SBP) over the first 6 hours after infusion initiation. SBP AUC through 48 hours was a key secondary or exploratory endpoint.

INVASIVE HEMODYNAMIC MEASUREMENTS, HOLTER MONITORING. In patients with a pulmonary artery catheter, invasive hemodynamic measurements were collected, including cardiac output, pulmonary capillary

wedge pressure (PCWP), and mixed venous oxygen saturation (Svo₂). Holter electrocardiogram monitoring was implemented from ≤24 hours before study drug initiation through 72 hours after infusion. Holter data were processed at a central laboratory.

CLINICAL EVENTS. Investigator-reported worsening heart failure (WHF) adverse events and mortality through 30 days are summarized. Patients in part A treated with a maximum of 1.0 µg/kg/min istaroxime or concurrent control were included in this analysis.

STATISTICAL CONSIDERATIONS. For the primary and secondary endpoints, the AUC of change from baseline in SBP (imputed after intercurrent events such as death or rescue therapy) was used, following prespecified algorithms. The between-treatment comparisons used analysis of covariance, considering study part, treatment, and baseline SBP. Post-infusion Holter monitoring count outcomes were modeled using negative binomial regression, accounting for Holter monitoring time, treatment, study part, and their interactions, and the reporting incidence rates, incidence rate ratios (IRRs), and *P* values. An offset of the log (monitoring duration in hours) through 72 hours after infusion was included in the model to account for variability in Holter monitoring duration across patients. A forest plot shows IRRs for counts (Figure 1B).

RESULTS

BASELINE CHARACTERISTICS. In the pooled cohort (*n* = 50), the mean age was 65.6 ± 11.8 years, the mean ejection fraction was 23.2 ± 8.2%, and the mean systolic blood pressure was 94.4 ± 7.4 mm Hg. Several characteristics of the part C cohort indicated that they are at a more advanced stage of the CS, including higher levels of serum creatinine, N-terminal pro-B-type natriuretic peptide, and serum lactates (all *P* < 0.05).

IMPACT ON THE PRIMARY OUTCOME. Similar and larger-than-placebo increases in SBP through

6 hours, as denoted by the primary endpoint, the AUC of the change from baseline, were seen in both parts B and C. Pooled data showed a significant difference between the groups with an adjusted mean difference of 38.0 (95% CI: 12.6-63.3 mm Hg·hour; *P* = 0.0042) (Figure 1A), without treatment-by-study-part interaction (*P* = 0.7610).

EFFECT ON HEMODYNAMIC MEASURES. The baseline cardiac output was the same in both study groups: 3.65 ± 1.1 vs 3.76 ± 0.99 L/min. At 6 hours, there was already a trend toward improvement in cardiac output in the istaroxime group: the mean difference compared with placebo was 0.71 L/min (95% CI: -0.01 to 1.44; *P* = 0.0539). Up to 48 hours, the difference was not significant; at 48 hours, there was a significant difference favoring the istaroxime arm, with a mean difference of 0.84 (95% CI: 0.31-1.37; L/min; *P* = 0.0028).

PCWP decreased significantly in the istaroxime group at 6 hours, a mean intergroup difference of -3.18 mm Hg (95% CI: -5.83 to -0.53 mm Hg; *P* = 0.0200). At 48 hours, the mean difference was significantly lower in the active arm: -3.18 (95% CI: -5.83 to -0.53; *P* = 0.0457). Compared with placebo, Svo₂ improved significantly at 12 hours and 48 hours with istaroxime (*P* < 0.05).

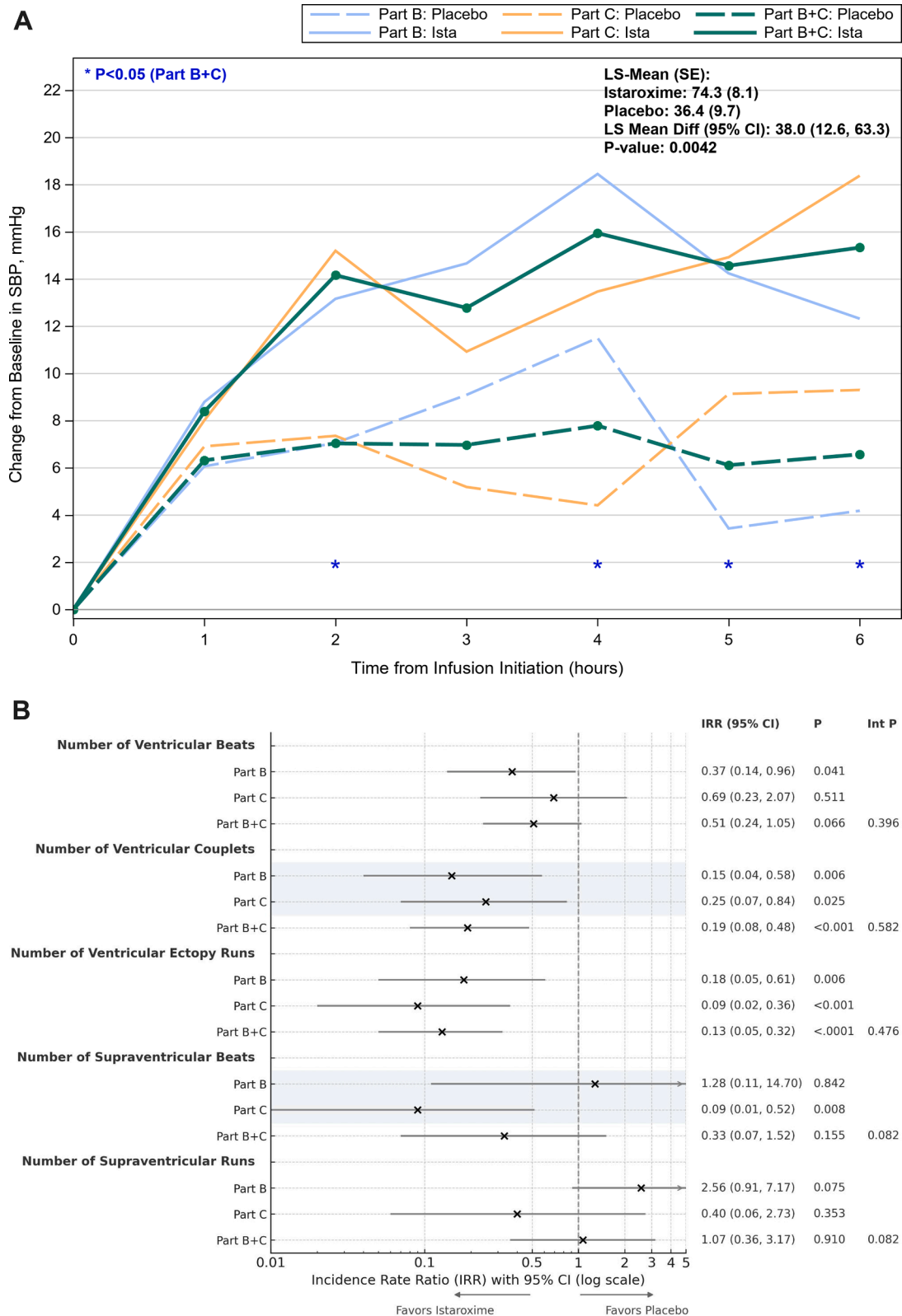
EFFECT ON ARRHYTHMIA. There was no significant difference in the incidence of ventricular beats per hour in the istaroxime vs the placebo arm, with an IRR of 0.51 (95% CI: 0.24-1.05; *P* = 0.0659).

The incidence rate of ventricular couplets per hour in the istaroxime arm was significantly lower than in the placebo: 4.8 (95% CI: 3.1-7.4) vs 25.3 (95% CI: 11.2-57.2), with an IRR of 0.19 (95% CI: 0.08-0.48; *P* = 0.0004, respectively). There was also a significantly lower incidence rate of ventricular ectopic runs per hour: 0.58 (95% CI: 0.37-0.92) vs 4.61 (95% CI: 2.05-10.38), with an IRR of 0.13 (95% CI: 0.05-0.32; *P* < 0.001) (Figure 1B).

EFFECT ON WORSENING HF AND ALL-CAUSE MORTALITY. In the pooled cohort, the incidence of worsening HF (13.3% vs 17.9%) or combined worsening HF adverse events or death events (17.8% vs 23.1%) was numerically lower with istaroxime than with placebo (all *P* > 0.05).

DISCUSSION

In the pooled cohort analysis of the SEISMic trials, istaroxime demonstrated consistent multidimensional hemodynamic benefits across CS stages. Per protocol, part C patients had a more advanced clinical state. Istaroxime led to early and sustained

FIGURE 1 Clinical Impact of Istaroxime

(A) The impact of istaroxime on systolic blood pressure. (B) The associations of istaroxime with arrhythmias. Ista = istaroxime; LS-mean diff = least squares mean difference; SBP = systolic blood pressure.

improvements in SBP and central hemodynamics, with a significant increase in cardiac output (~ 0.7 L/min) and a reduction in intracardiac pressures, including PCWP (~ 3 mm Hg), suggesting enhanced left ventricular unloading and improved flow.

Importantly, the risk of developing any arrhythmia (especially ventricular arrhythmia) during the study tended to be lower in the istaroxime group. Interaction analyses, however, showed that istaroxime's treatment effect was consistent across both study parts, indicating comparable effects across varied clinical severity and hemodynamic states. This suggests that istaroxime may improve hemodynamics and reduce HR without the proarrhythmic activity classically seen with catecholamine-dependent inotropes. In conclusion, these findings collectively point to a coherent physiological mechanism that appears independent of acute HF stage or severity and does not trigger arrhythmogenicity.

STUDY LIMITATIONS. This analysis has several limitations, including a small sample size, short 30-day follow-up, and trials powered for hemodynamic rather than clinical endpoints. Variability in Holter monitoring duration required statistical adjustment.

CONCLUSIONS

In a pooled population of patients with SCAI stage B and C cardiogenic shock, istaroxime consistently improved systolic blood pressure and central

hemodynamics, including cardiac output and intra-cardiac filling pressures, without increasing arrhythmic burden.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Pagnesi has received personal fees from Abbott Vascular, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Novartis, Novo Nordisk, Roche Diagnostics, Viatris, and Vifor Pharma. Dr Chioncel is a member of the Boehringer Ingelheim Advisory Board. Drs Davison and Cotter are employees of Momentum Research, which has received grants for research from the Heart Initiative, Corteria, Windtree, Echosens, and 4teen4; and have ownership interest in istaroxime. Mr Edwards is an employee of Momentum Research, which has received grants for research from the Heart Initiative, Corteria, Windtree, Echosens, and 4teen4. Dr Ponikowski has received support from Trevena during the conduct of the study; has received grants and personal fees from Amgen Inc, Servier, Boehringer Ingelheim, Vifor Pharma, Novartis, Bayer, Cibiem, AstraZeneca, BMS, Renal Guard Solutions, Impulse Dynamics, and Abbott Vascular; and has received personal fees from Berlin Chemie, outside the submitted work. Dr Metra has received personal fees of minimal amounts in the last 3 years from Amgen, Livanova, and Vifor Pharma as a member of the executive or data monitoring committees of sponsored clinical trials; and has received honoraria from AstraZeneca, Abbott Vascular, Bayer, Boehringer Ingelheim, and Edwards Therapeutics for participation in advisory boards and/or speeches at sponsored meetings. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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