

# Istaroxime: A rising star in acute heart failure

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## ABSTRACT

Heart failure in India is a growing epidemic. Around 30 to 40% of patients die from heart failure within one year of receiving the diagnosis. Currently available inotropes have not only failed to show consistent results but are also associated with adverse outcomes. Istaroxime is a novel intravenous agent with luso-inotropic properties that acts by inhibition of Na<sup>+</sup>/K<sup>+</sup> adenosine triphosphatase and stimulation of sarco/endoplasmic reticulum calcium ATPase isoform 2. In clinical studies, it significantly decreased left ventricular end diastolic pressure, pulmonary capillary wedge pressure, heart rate and increased systolic blood pressure and cardiac index with no change in neurohormones, renal function or troponin I. Istaroxime is a promising alternative for patients presenting with acute heart failure syndrome for whom the therapeutic options are currently limited.

**Key words:** Acute heart failure syndromes, lusitropic, sarco/endoplasmic reticulum calcium

## INTRODUCTION

Congestive heart failure (CHF) describes a common final pathway for expression of myocardial dysfunction. In India, coronary artery disease, diabetes, hypertension, valvular heart diseases are the leading causes for heart failure. Though reliable estimates of heart failure are lacking in India, one study estimated the prevalence of heart failure from 1.3 to 4.6 million with an annual incidence of 491600-1.8 million.<sup>[1]</sup> There is enough evidence that it is a leading public health problem which is going to escalate in the future.

AHFS can be defined as a rapid or gradual change in signs and symptoms in patients with chronic heart failure or new

onset HF that necessitates urgent therapy. 80% of patients hospitalized with AHFS carry a previous diagnosis of HF. Regardless of the underlying etiology, the most common presentations include pulmonary congestion, defined by increase in left ventricular filling pressure (LVFP) or preload and reflected hemodynamically by increase in PCWP and systemic congestion resulting in jugular venous distension, peripheral edema and increase in body weight. While impaired cardiac output is less commonly seen in AHFS, it is characterized by tissue hypoperfusion with cool extremities and the potential for end organ damage.

Acute decompensated heart failure requires unscheduled hospitalization and use of parenteral inotropes (dopamine/dobutamine) and diuretics. Selection of parenteral agent is guided by data obtained from an indwelling pulmonary artery catheter. Despite availability of a number of pharmacological agents, prognosis remains poor for these patients. Use of inotropes is under scrutiny and data indicates that they should not be used routinely. Short term hemodynamic benefits afforded by them (dobutamine, milrinone, levosimendan) are important for alleviation of signs and symptoms of HF but they do not prevent myocardial or renal injuries and therefore

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|-------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Quick Response Code:                                                                | Website:<br><a href="http://www.jpharmacol.com">www.jpharmacol.com</a> |
|  | DOI:<br>10.4103/0976-500X.103705                                       |

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are not only ineffective in improving clinical outcomes but may even be deleterious. Indeed, trials like OPTIME-HF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure), SURVIVE (Survival of Patients with Acute Heart Failure In Need Of Intravenous Inotropic Support), ADHERE (Acute Decompensated Heart Failure National Registry) have demonstrated absence of benefit coupled with increased adverse effects. What is even more perplexing is that patients have shown low in-hospital but very high early after-discharge mortality and rehospitalization rates. Limitations of use of currently available inotropic agents include tachyarrhythmias and myocardial damage exacerbated by hypotension and coronary hypoperfusion, increased oxygen consumption and direct myocyte toxicity due to intracellular calcium overload.<sup>[2]</sup> Digoxin is seldom used in acute heart failure as it suffers from drawbacks including a narrow therapeutic-toxic window and hypotension as well as atrial and ventricular arrhythmias. Therefore, there is unmet need for acute heart failure therapies that reduce symptoms and improve both diastolic and systolic myocardial functions without worsening renal function, promoting arrhythmias, exacerbating ischemia or increasing mortality.

### Mechanism of action of istaroxime in AHFS

Istaroxime- (E, Z) - 3 - [(2-aminoethoxy) -imino] androstane-6,17-dione is a steroidal drug unrelated to cardiac glycosides that improves cellular calcium cycling by dual action—SERCA 2a stimulation causes rapid  $\text{Ca}^{2+}$  sequestration in sarcoplasmic reticulum (SR) during diastole (lusitropism); without enhancing spontaneous  $\text{Ca}^{2+}$  efflux from the SR. Secondly,  $\text{Na}^+$ - $\text{K}^+$  ATPase inhibition induces cytosolic calcium accumulation during systole (inotropism).<sup>[3]</sup>

During systole, the action potential induces the increase of intracellular  $\text{Ca}^{2+}$  through L-type  $\text{Ca}^{2+}$  channels (LTCC), which triggers further  $\text{Ca}^{2+}$  release from the SR through ryanodine receptor 2 (RyR2) opening (termed calcium induced calcium release). This increase in intracellular calcium from 0.1-0.2  $\mu\text{M}$  to 2-10  $\mu\text{M}$  facilitates sarcomere shortening and cardiac contraction.

Cardiac relaxation (diastole) is due to RyR closing,  $\text{Ca}^{2+}$  dissociation from the troponin myofilaments, and  $\text{Ca}^{2+}$  reuptake into SR via SERCA 2a. It removes almost 70% of cytosolic  $\text{Ca}^{2+}$  while  $\text{Na}^+$ - $\text{Ca}^{2+}$  exchanger (NCX) and plasma membrane  $\text{Ca}^{2+}$  ATPase remove 28% and 2% respectively.<sup>[3,4]</sup>

SERCA is the predominant mechanism responsible for lowering diastolic cytoplasmic  $\text{Ca}^{2+}$  by pumping it into SR. SERCA affects both relaxation and contraction as contraction is a function of amount of  $\text{Ca}^{2+}$  available which in turn is a balance between SERCA mediated  $\text{Ca}^{2+}$  uptake and RyR mediated  $\text{Ca}^{2+}$  efflux. Efficient SERCA2a improves SR  $\text{Ca}^{2+}$  reloading during diastole and rapidly decreases cytosolic  $\text{Ca}^{2+}$ , thus improving

cardiac relaxation and avoiding an increase in cytosolic  $\text{Ca}^{2+}$  to pro arrhythmogenic levels.

SERCA2a activity is inhibited by unphosphorylated phospholamban (PLB). Phosphorylation of PLB by protein kinase A (PKA) and  $\text{Ca}^{2+}$  calmodulin dependent kinase undoes SERCA2a inhibition, increasing its affinity for  $\text{Ca}^{2+}$  and accelerating its activity causing increased SR  $\text{Ca}^{2+}$  uptake.

In heart failure, excitation contraction coupling is significantly altered and frequency dependent increase of contractile force is significantly blunted largely due to abnormal  $\text{Ca}^{2+}$  accumulation of SR. The contractile dysfunction of failing cardiomyocytes occurs in conjunction with reduced SR  $\text{Ca}^{2+}$  release and elevated resting  $\text{Ca}^{2+}$  concentration. Molecular abnormalities in HF include reduced expression and/or activity of SERCA2a leading to decreased reuptake and increased  $\text{Ca}^{2+}$  elimination outside the cell. Secondly, increased inhibitory function of PLB decreases efficiency of SERCA. Thirdly, upregulation of RyR2 function (due to hyperphosphorylation) causes abnormal SR  $\text{Ca}^{2+}$  leak. Fourthly, the upregulation of NCX causes  $\text{Ca}^{2+}$  extrusion leading to further reduction in SR  $\text{Ca}^{2+}$  content-enhancing the slow decay of intracellular  $\text{Ca}^{2+}$  transient contributing to slower relaxation of muscles and diastolic dysfunction. These changes predispose to arrhythmias, cardiomyocyte apoptosis and increase in energy expenditure.<sup>[3-5]</sup>

Istaroxime improves the impaired  $\text{Ca}^{2+}$  cycling in HF. It augments myocardial contractility by stimulating  $\text{Ca}^{2+}$  entry via NCX and additionally increases diastolic free cytosolic  $\text{Ca}^{2+}$ . Increased  $\text{Ca}^{2+}$  uptake in SR allows release of greater amounts of  $\text{Ca}^{2+}$  at the subsequent systole leading to increased contractility.

### Differences between istaroxime and digoxin

Qualitative differences stand out between istaroxime and digoxin. Firstly, istaroxime increases contractility up to 60% without appearance of after contractions, while digoxin induces delayed after contractions when the increase in contractility is lower than 20%.

Secondly, the safety ratio [ratio between lethal and inotropic dose (LD/ED 80)] is 20 for istaroxime compared to 3 for digoxin reflecting its safety when compared to digoxin. This lower toxicity by istaroxime may reflect improved  $\text{Ca}^{2+}$  confinement within the SR, due to concomitant SERCA2a stimulation.

Thirdly, heart rate reduction induced by istaroxime seems to be secondary to baroreceptor response to blood pressure as transient increase in SBP occurs simultaneously. It differs from digoxin whose bradycardiac effect is due to vagal activation.

Fourthly, rate of onset and decay of inotropic effect is faster for istaroxime.

Comparative studies with digoxin in mouse cardiomyocytes at equi-inotropic concentration showed that istaroxime induces lower increases in resting and in diastolic  $\text{Ca}^{2+}$  during pacing than digoxin without affecting the relationship between  $\text{RyR2}$  mediated SR  $\text{Ca}^{2+}$  leak and  $\text{Ca}^{2+}$  content - enhancing SR  $\text{Ca}^{2+}$  reuptake rate differently from digoxin.<sup>[6]</sup>

Comparison of istaroxime on contractility and energetics with dobutamine in anesthetized pig demonstrated that myocardial oxygen consumption was more with dobutamine implying that istaroxime can increase total cardiac work per beat while maintaining stable oxygen consumption thus displaying a high efficiency.<sup>[7]</sup>

### Clinical studies done with istaroxime

A phase II randomised, double-blind, placebo-controlled dose-escalating trial to assess hemodynamic effects of istaroxime in patients with worsening HF and reduced LV systolic function (HORIZON-HF) was carried out in 120 patients.<sup>[8]</sup> 3 cohorts of 40 patients each, with a history of heart failure and a PCWP >20 mm Hg were administered 0.5  $\mu\text{g/kg/min}$ , 1  $\mu\text{g/kg/min}$  and 1.5  $\mu\text{g/kg/min}$  istaroxime intravenously over 6 hours to patients with a history of heart failure and a PCWP >20 mmHg.

The study included patients in range of 18-25 years with left ventricular ejection fraction (LVEF) <35%, hospitalized with HF with a SBP <150 and >90 mmHg, heart rate (HR) <110 and >60 beats/min, and on standard HF therapy.

The main exclusion criteria were use of intravenous inotropes, serum digoxin concentration >0.5 ng/ml, recent acute coronary syndromes or coronary revascularization, atrial fibrillation, left bundle branch block, implanted electrical devices, serum creatinine level >3 mg/dL and severe liver enzyme abnormalities.

All 3 dose groups showed reduction in PCWP ( $-3.2 \pm 6.8$  mmHg,  $-3.3 \pm 5.5$  mmHg and  $-4.7 \pm 5.9$  mmHg for 0.5, 1 and 1.5  $\mu\text{g/kg/min}$  infusion compared to  $0.0 \pm 3.6$  mmHg for placebo). There was an increase in SBP, no significant change in DBP and a transient increase in cardiac index with the highest dose and a decrease in heart rate and diastolic and systolic volumes without a change in ejection fraction.

There were no significant changes in neurohormones, blood urea nitrogen, creatinine or troponin I. There was significant shortening of the QTc interval with all doses of istaroxime.

Echocardiographic analysis showed its lusitropic effects with an increase in the lateral mitral annulus, early diastolic velocity ( $E'$ ), a prolongation of E-wave deceleration half time - a marker of LV stiffness, a decrease in the E/Ea ratio of transmitral flow velocity - indicating improved diastolic function.

However, limitation of this study was that patients included had milder forms of acute heart failure, not requiring inotropic interventions according to current guidelines.

### Adverse effects

The main side effects observed were gastrointestinal distress and infusion site reactions, namely vomiting and pain at infusion site. To minimize the side effect of pain, encapsulated formulations using liposomes have been designed.

## CONCLUSION

HF is characterized by progressive maladaptive remodeling wherein excitation contraction coupling is affected at several levels of intracellular  $\text{Ca}^{2+}$  signaling. Unique hemodynamic, electrophysiological and metabolic characteristics make istaroxime a novel and safe inotropic agent for short term treatment of acute decompensated heart failure. It improves both systolic and diastolic function and additionally, has beneficial effects on myocardial energetics. The road to approval is long and ongoing trials will clarify whether it will act as a bridge to heart transplantation or mechanical circulatory support. It may potentially fulfill an unmet critical need in AHFS with low cardiac output.

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**How to cite this article:** Aditya S, Rattan A. Istaroxime: A rising star in acute heart failure. *J Pharmacol Pharmacother* 2012;3:353-5.

**Source of Support:** Nil, **Conflict of Interest:** None declared.