

Intravenous Inotropic Support – an Overview

Shaul Atar, MD

Western Galilee Medical Center, Nahariya

Affiliated with the Faculty of Medicine of the Galilee,
Safed, Israel

INOTROPES in Acute HF (not vasopressors)

When?

Which patients?

Which inotrope?

Duration?

What Does the Literature Tell Us?

Very little

Very few randomized, placebo-controlled trials of inotropes for the management of ADHF

“Standard of care” is based almost entirely upon expert opinion and case studies

Acute Heart Failure syndromes: Clinical Classification

Group 1: Acute HF in cardiogenic shock, sudden increase in BP, MI, arrhythmias (5% of patients).

Group 2: End stage advanced HF with severe LV systolic dysfunction (Low CO - 5% of the patients, transplant candidates).

Group 3: Worsening chronic HF with either reduced or preserved LV systolic function (90% of the patients).

2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Table 26. Intravenous Inotropic Agents Used in Management of HF

Inotropic Agent	Dose (mcg/kg)		Drug Kinetics and Metabolism	Effects				Adverse Effects	Special Considerations
	Bolus	Infusion (/min)		CO	HR	SVR	PVR		
<i>Adrenergic agonists</i>									
Dopamine	N/A	5 to 10	t _{1/2} : 2 to 3 min	↑	↑	↔	↔	↑/↓BP, HA, T, N, F, hypersensitivity	Caution: MAO-I
	N/A	10 to 20		↑	↑	↔	↔		
Dobutamine	N/A	2.5 to 5.0	t _{1/2} : 2 to 3 min H	↑	↑	↓	↔	↑/↓BP, HA, T, N, F, hypersensitivity	Caution: MAO-I; CI: sulfite allergy
	N/A	5 to 20		↑	↑	↔	↔		
<i>PDE inhibitor</i>									
Milrinone	N/R	0.125 to 0.75	t _{1/2} : 2.5 h H	↑	↑	↓	↓	T, ↓BP	Renal dosing, monitor LFTs

t_{1/2} indicates elimination half-life; BP, blood pressure; CI, contraindication; CO, cardiac output; F, fever; H, hepatic; HA, headache; HF, heart failure; HR, heart rate; LFT, liver function test; MAO-I, monoamine oxidase inhibitor; N, nausea; N/A, not applicable; N/R, not recommended; P, plasma; PDE, phosphodiesterase; PVR, pulmonary vascular resistance; R, renal; SVR, systemic vascular resistance; and T, tachyarrhythmias.

Milrinone

Pharmacologic Category- Phosphodiesterase-3 Enzyme Inhibitor

Mechanism of Action- A selective phosphodiesterase inhibitor in cardiac and vascular tissue, resulting in vasodilation and inotropic effects with little chronotropic activity.

Dosing: Hepatic Impairment- No dose adjustment

Dosing: Renal Impairment- Dose adjustment

FDA

Indications and Usage for Milrinone

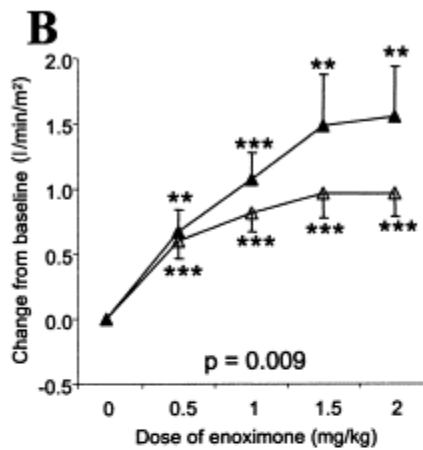
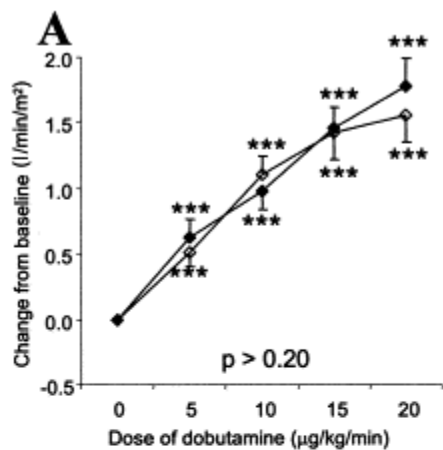
- Milrinone is indicated for the short-term intravenous treatment of patients with acute decompensated heart failure.
- The majority of experience with intravenous Milrinone has been in patients receiving digoxin and diuretics.
- There is no experience in controlled trials with infusions of Milrinone for periods exceeding 48 hours.

Advantage of Milrinone over dobutamine

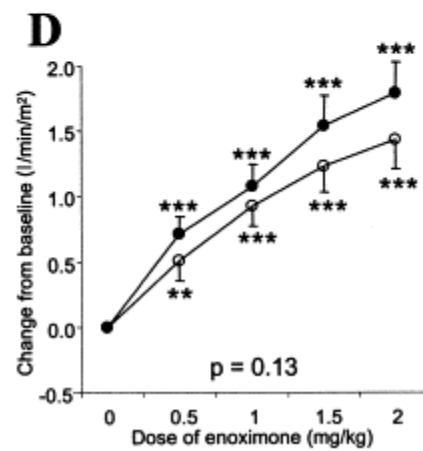
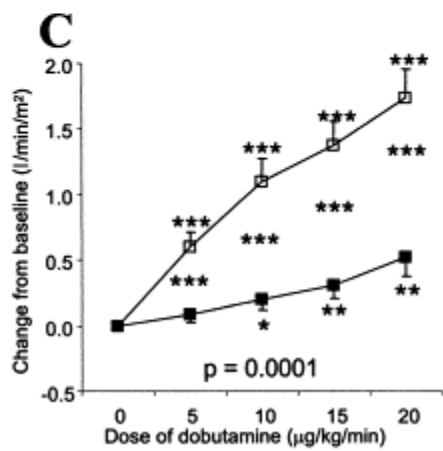
1. Concomitant β -blocker use: the risk of death is higher in patients who discontinue beta-blocker therapy or have their dose reduced. The increase in mortality is only partially explained by the worse prognostic profile of these patients.
2. Milrinone acts independently of adrenergic receptors, and is still effective despite the down-regulation of β -adrenergic receptors in patients with chronic heart failure.
3. PVR reduction – due to its PDE inhibiting effects.

Enoximone or Milrinone are preferable to Dobutamine in Patients on Beta-blockers

Cardiac Index



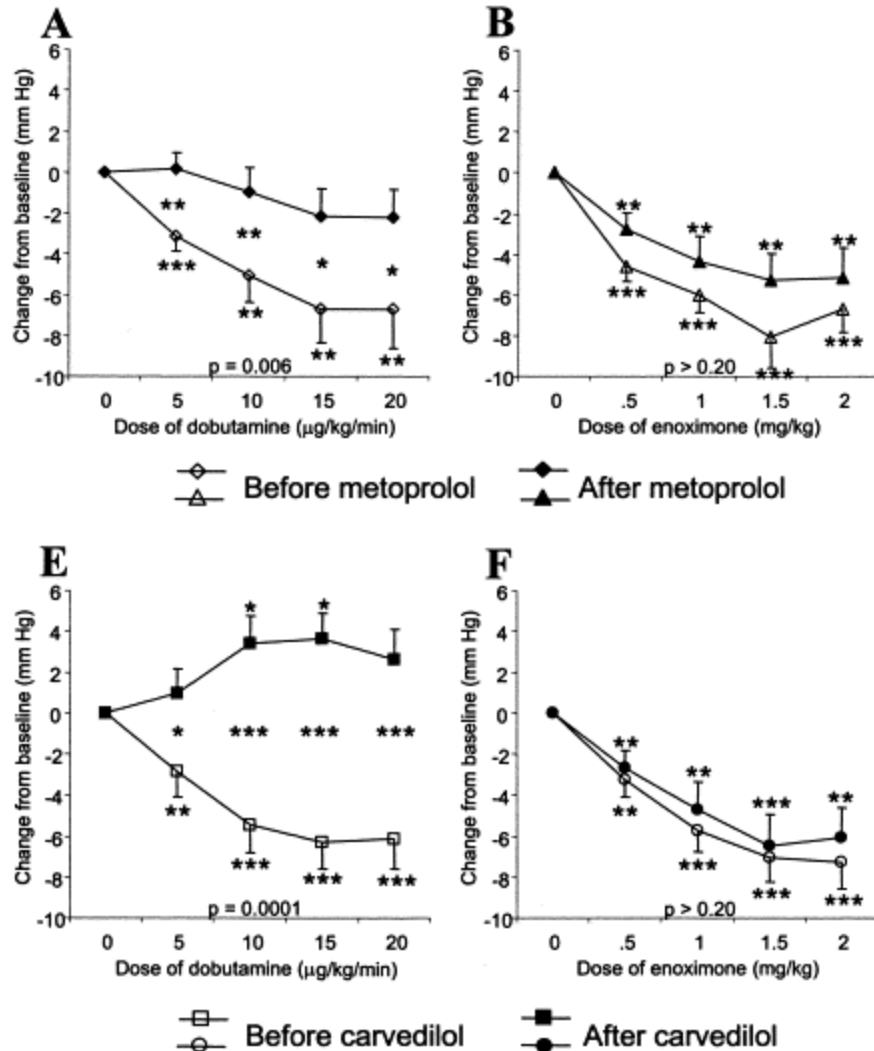
◇ Before metoprolol ● After metoprolol



□ Before carvedilol ● After carvedilol

Enoximone or Milrinone are preferable to Dobutamine in Patients on Beta-blockers

Pulmonary Wedge Pressure



Optimal Pharmacologic and Non-pharmacologic Management of Cardiac Transplant Candidates: Approaches to Be Considered Prior to Transplant Evaluation: **International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates—2006**

Phosphodiesterase inhibitors.

1. In patients with preserved systolic blood pressure, phosphodiesterase inhibitors are preferred over dobutamine, especially in patients with concomitant β -blocker use.
2. Because they act independent of adrenergic receptors, they are still effective despite the down-regulation of β -adrenergic receptors in patients with chronic heart failure. Short-term administration of phosphodiesterase inhibitors may improve myocardial performance and the clinical condition of patients with chronic heart failure.

Dobutamine advantages over Milrinone



Bad News for Inotropes

Cuffe MS, et al. JAMA 2002; 287:1541-47

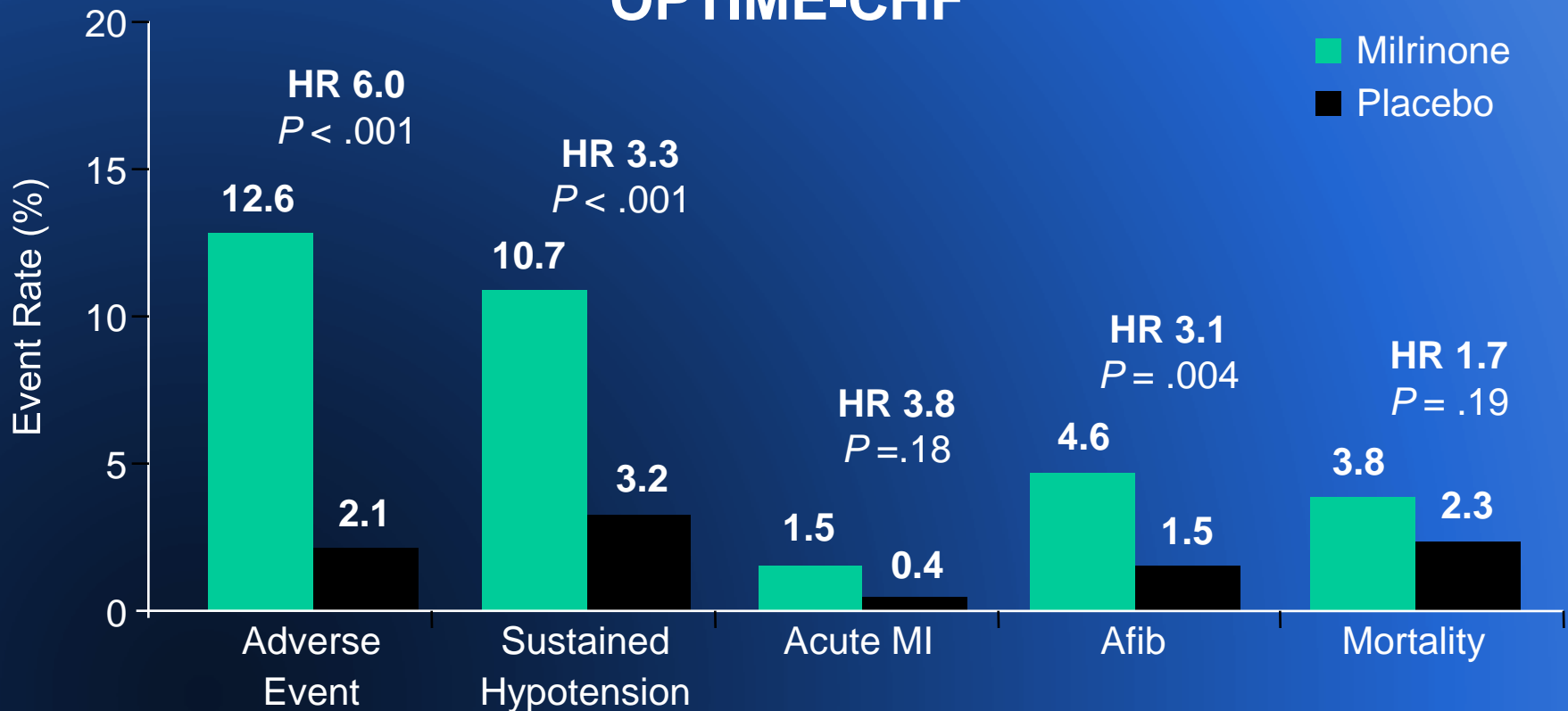
OPTIME-CHF Trial

Entry criteria: 951 patients with ADHF and systolic dysfunction who did not require inotropic support.

Intervention: Milrinone or placebo x 48 hours

Intravenous Milrinone for Decompensated Heart Failure

OPTIME-CHF



HR, hazard ratio; MI, myocardial infarction; Afib, atrial fibrillation.
Cuffe MS et al. *JAMA*. 2002;287:1541-1547.

HF Etiology and Response to Milrinone in Decompensated HF (OPTIME-CHF Study)

	Ischemic		Non-Ischemic		<i>P</i> value*
	Milrinone	Placebo	Milrinone	Placebo	
Days hospitalized at 60 days	13.6±15.5	12.4±12.7	10.9±12.4	12.6±15.3	.055
In-hospital mortality	5.0%	1.6%	2.6%	3.1%	.04
60-day mortality	13.3%	10.0%	7.3%	7.7%	.21
Death + rehospitalization	42%	36%	28%	35%	.02

**P* value for the etiology *treatment interaction term in the multivariable model.
Felker et al. *J Am Coll Cardiol.* 2003;41:997-1003.

Inotropes: A Sword with Two Edges

Pro-arrhythmic

Probably increase mortality in ischemic patients

Ischemic/injured myocardium may “hibernate” as a protective mechanism

Inotropes recruit hibernating myocytes and may hasten cell injury or apoptosis

Short-term gains appear to be offset by higher mid and long-term mortality

Levosimendan

First in a new class of calcium sensitizers

Enhances the Ca^{++} sensitivity of the myofilament by binding to troponin C

Opener of ATP -dependent K^+ channels in vascular smooth muscle

Pharmacokinetic Profile

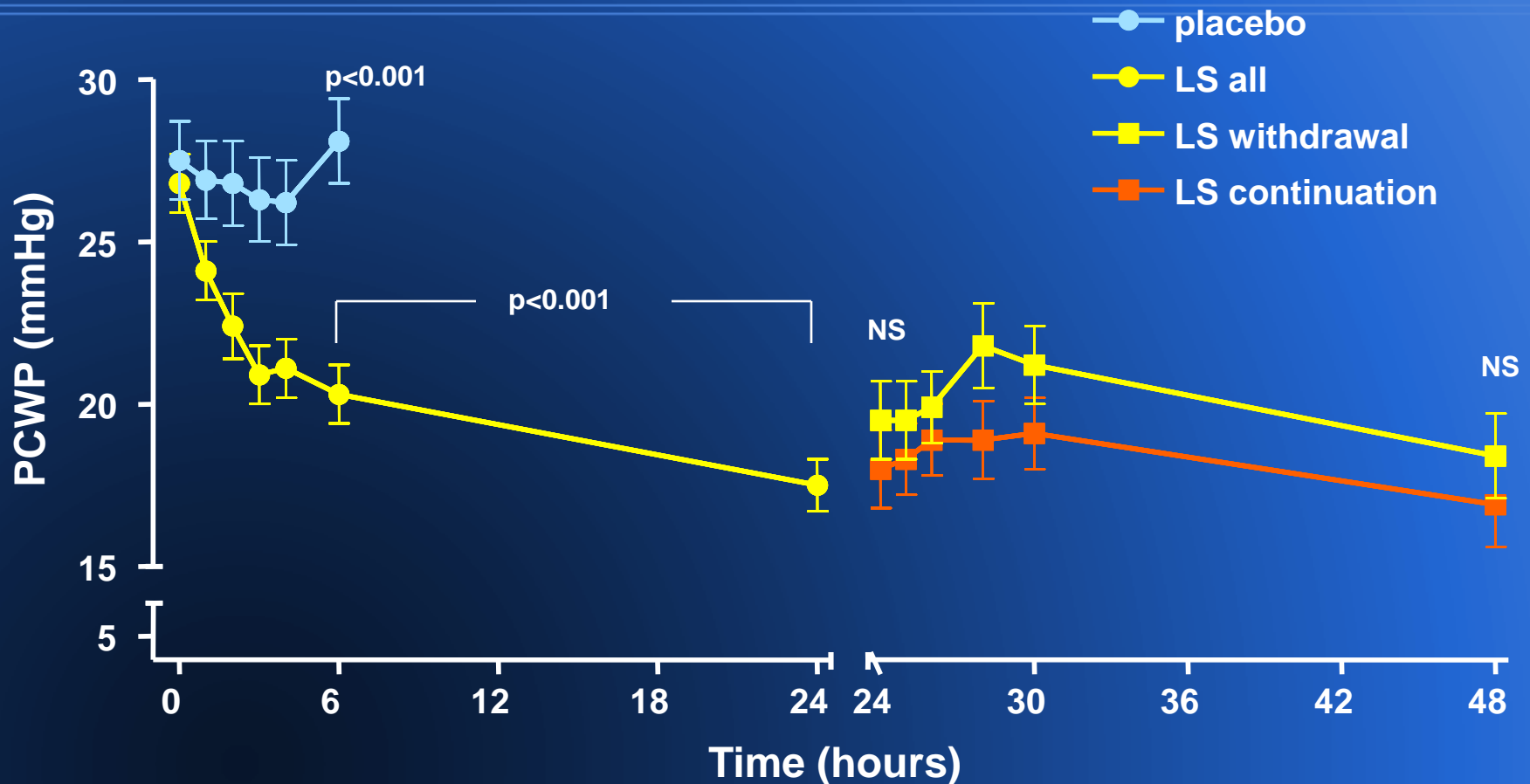
Active drug ($t_{1/2} = 1\text{h}$)

Rapid onset of action

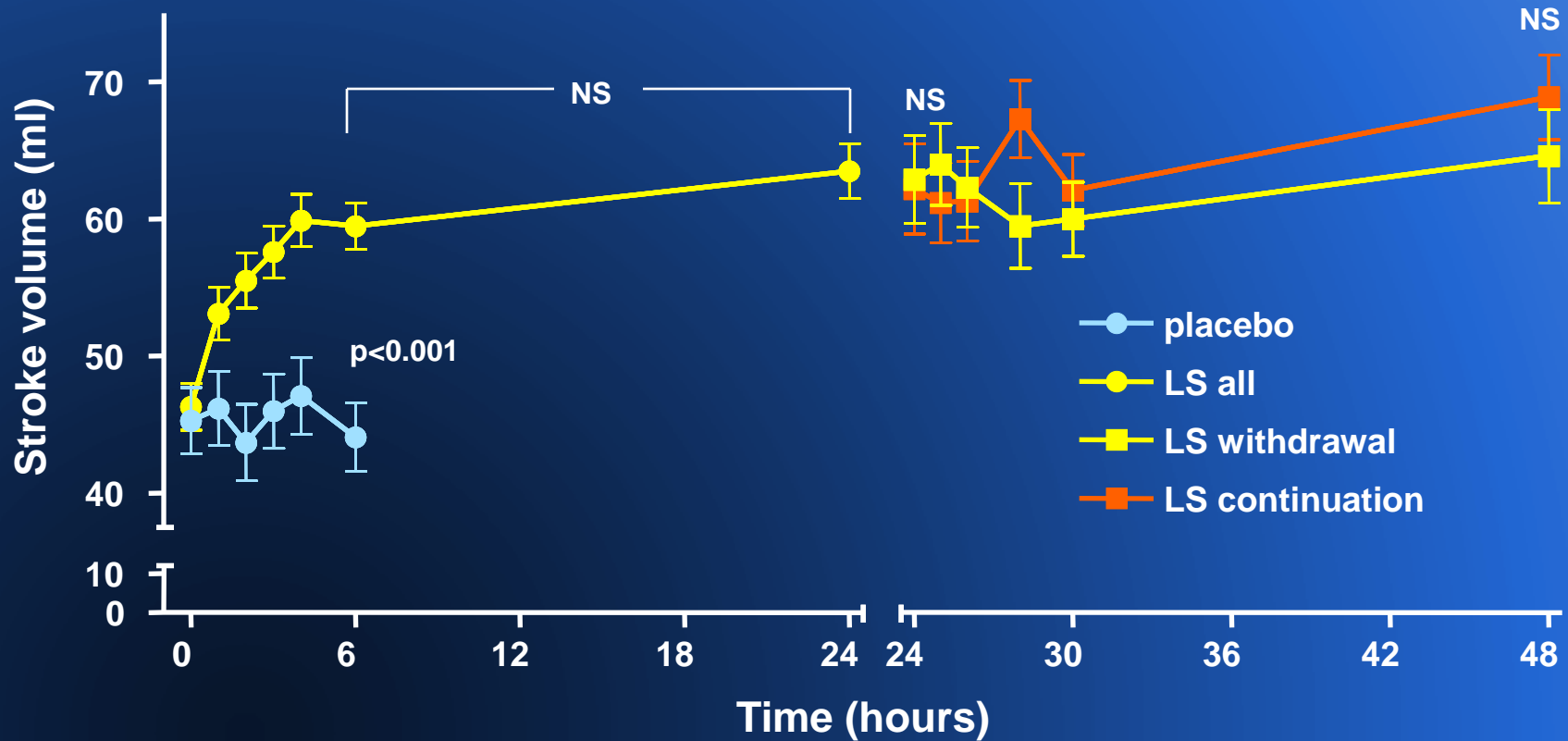
Active metabolite ($t_{1/2} = \sim 80\text{h}$)

Sustained hemodynamic response

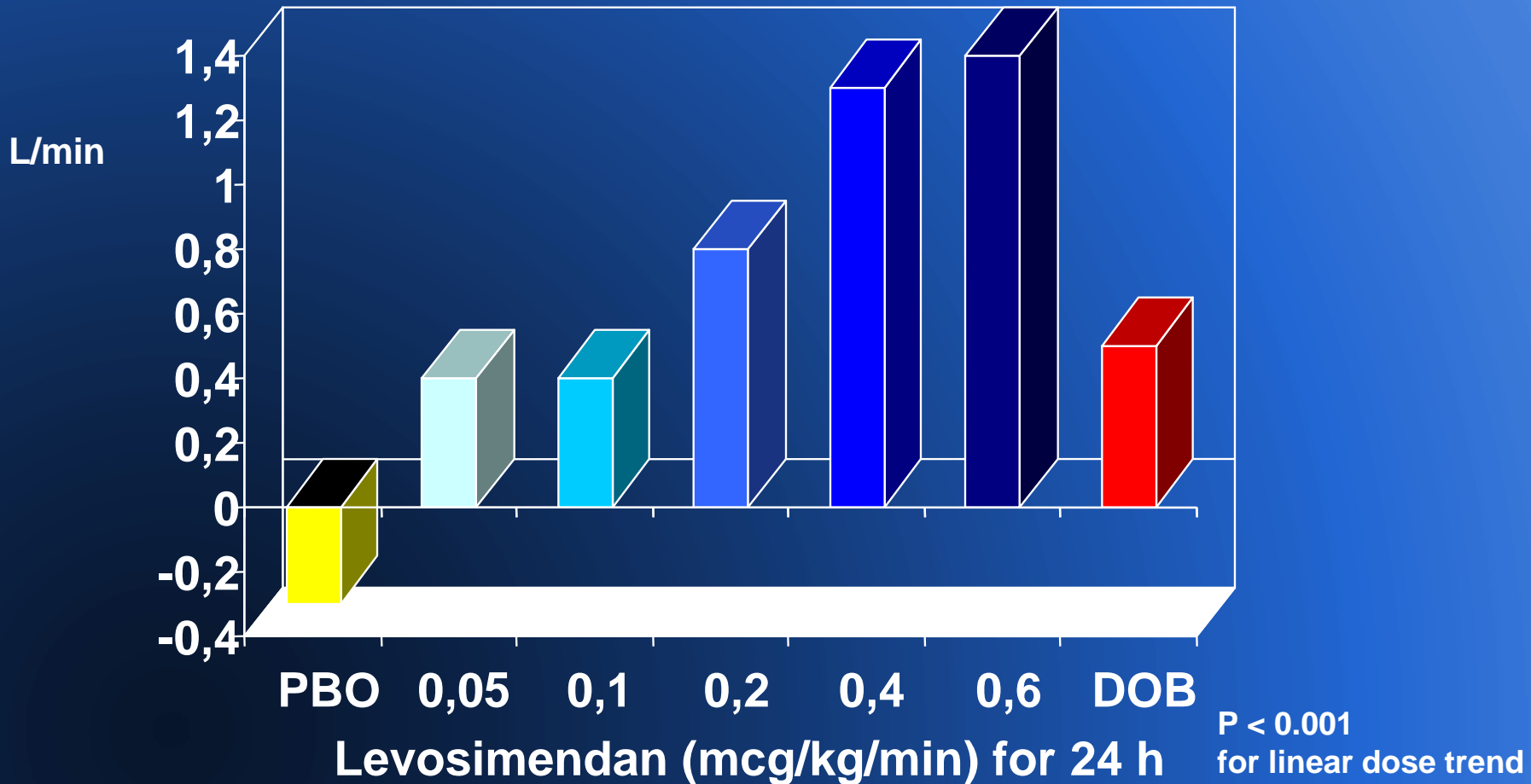
Levosimendan, 24 vs 48 hrs infusion: Change in PCWP



Levosimendan, 24 vs 48 hrs infusion: Change in stroke volume

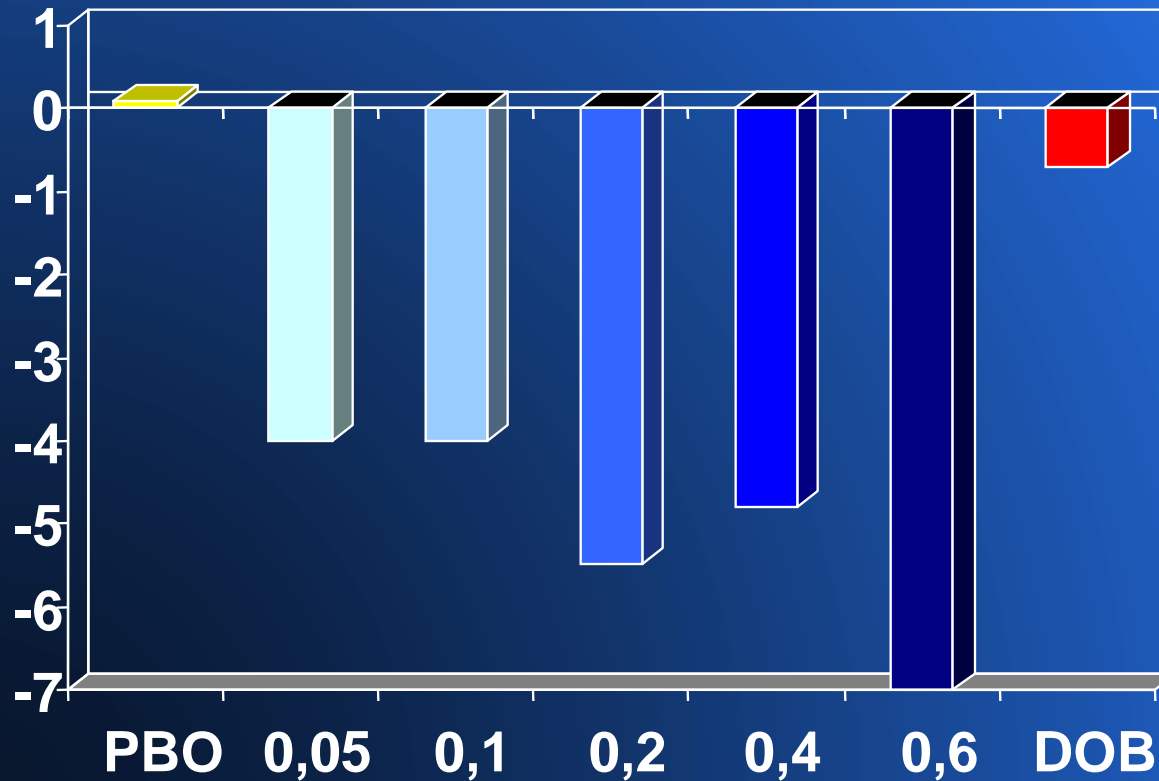


Change in cardiac output at 24 hours



Change in PCWP at 24 hours

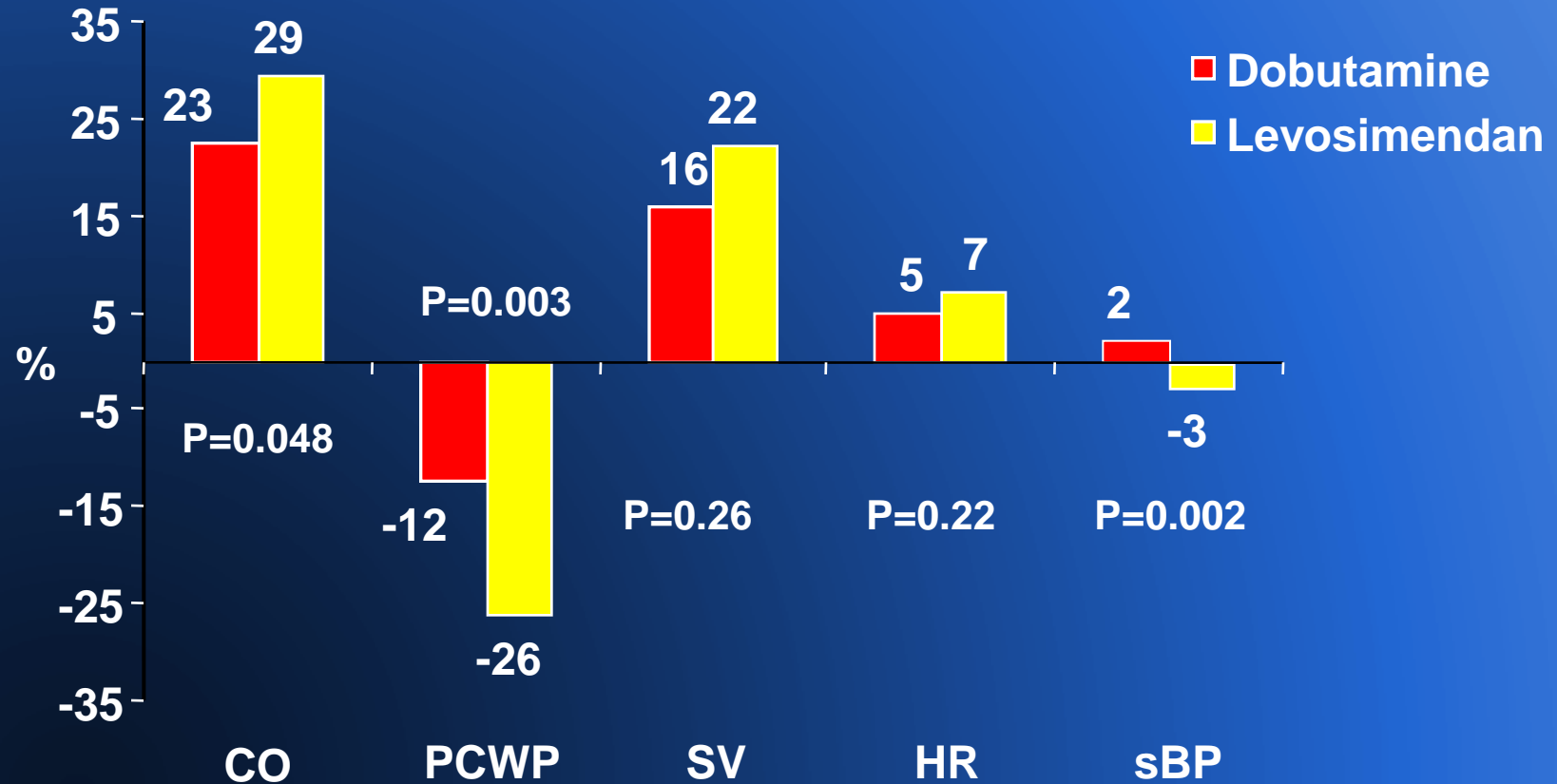
mmHg



Levosimendan (mcg/kg/min) for 24 h

$P < 0.001$
for linear dose trend

LIDO: change (%) in hemodynamic variables at 24 hours



SURVIVE: Overview

Mortality trial: levosimendan versus dobutamine

Double-blind, double-dummy, phase III study

**700 patients: 350 in levosimendan
350 in dobutamine**

Study duration: 180 days

**In 92 centers in Europe (France, UK, Germany, Israel,
Poland, Latvia, Finland, Russia)**

No requirement for invasive monitoring

SURVIVE

Demographics and Characteristics

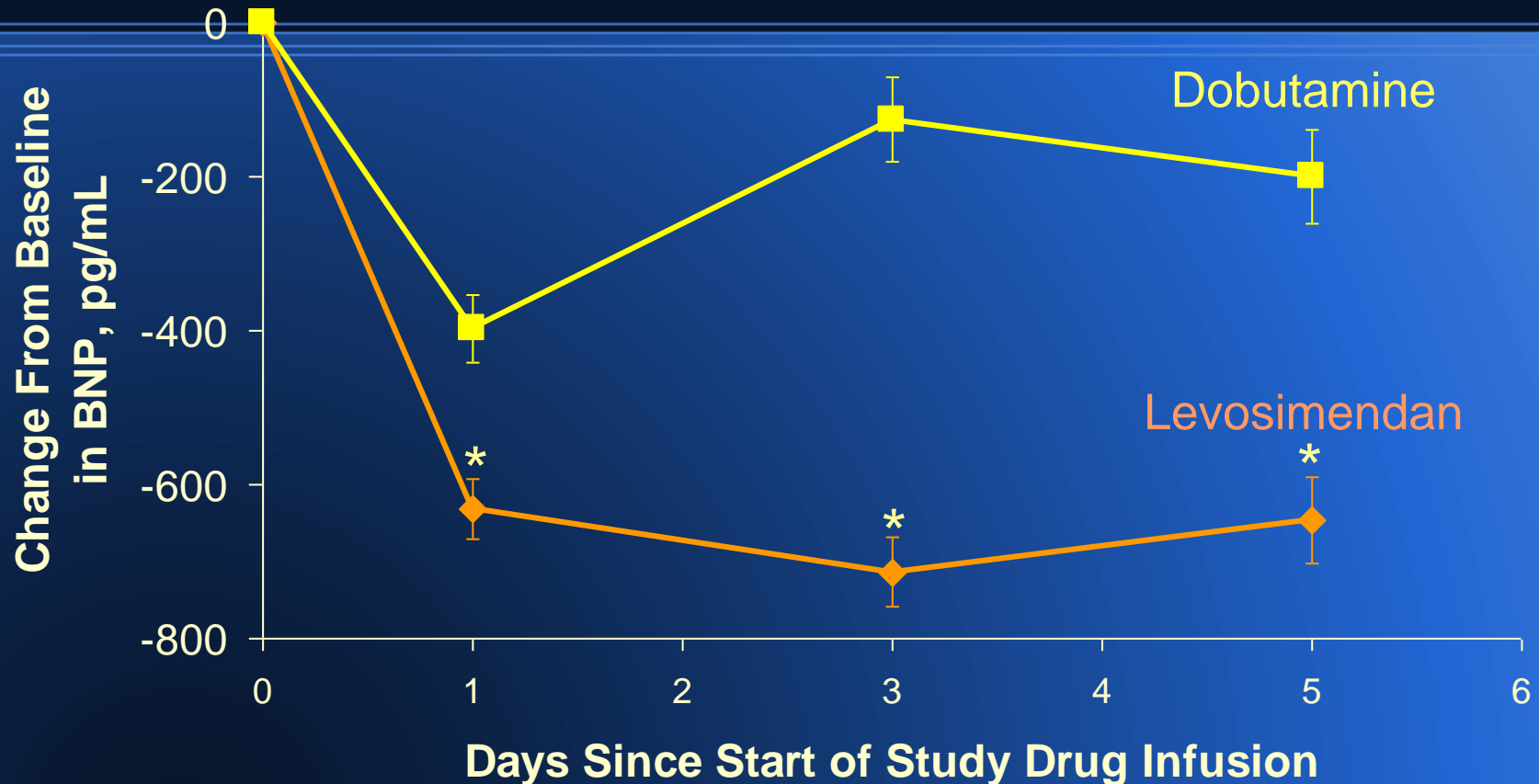
Variable	Levosimendan (n = 664)	Dobutamine (n = 663)
Male, %	74	70
Age, years, mean (SD)	67 (12)	66 (12)
Weight, kg	79 (18)	79 (16)
Previous history of HF, %	88	88
Ischemic etiology for acute HF, %	76	76
NYHA Class IV, %	86	85
LVEF, %	24 (5)	24 (5)
Median BNP*, pg/mL (Normal BNP in non-HF subjects < 135 pg/mL)	1178	1231
Heart rate, bpm	84 (17)	83 (17)
SBP, mm Hg	116 (18)	116 (19)

*AXSYM® BNP Assay

* Mebazaa et al , AHA , Dallas , November 2005

SURVIVE

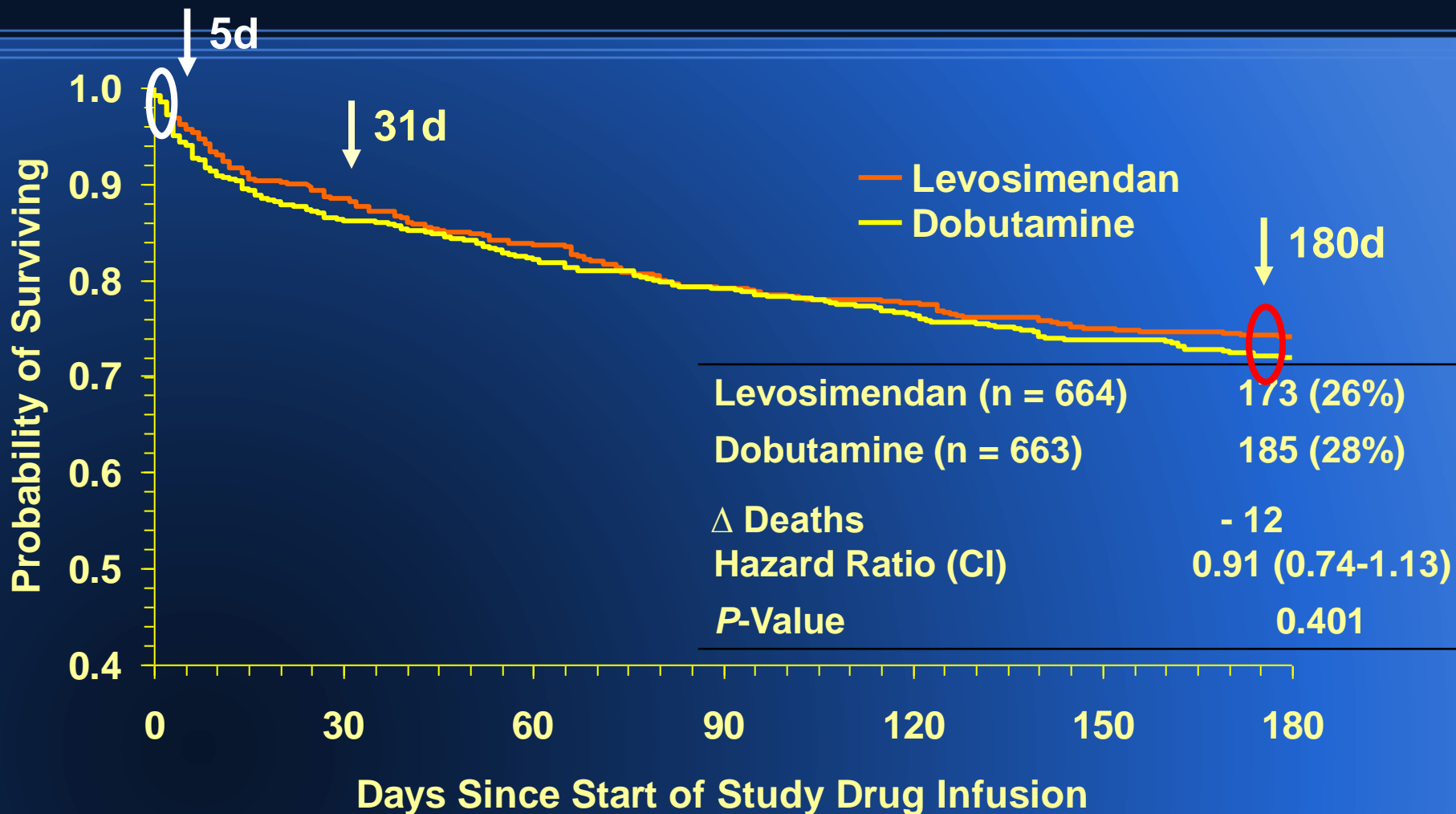
Mean Change From Baseline in BNP



* $P < 0.0001$ for the comparison between treatment groups at all time points
Values are mean (SE)

SURVIVE

180-Day All-Cause Mortality



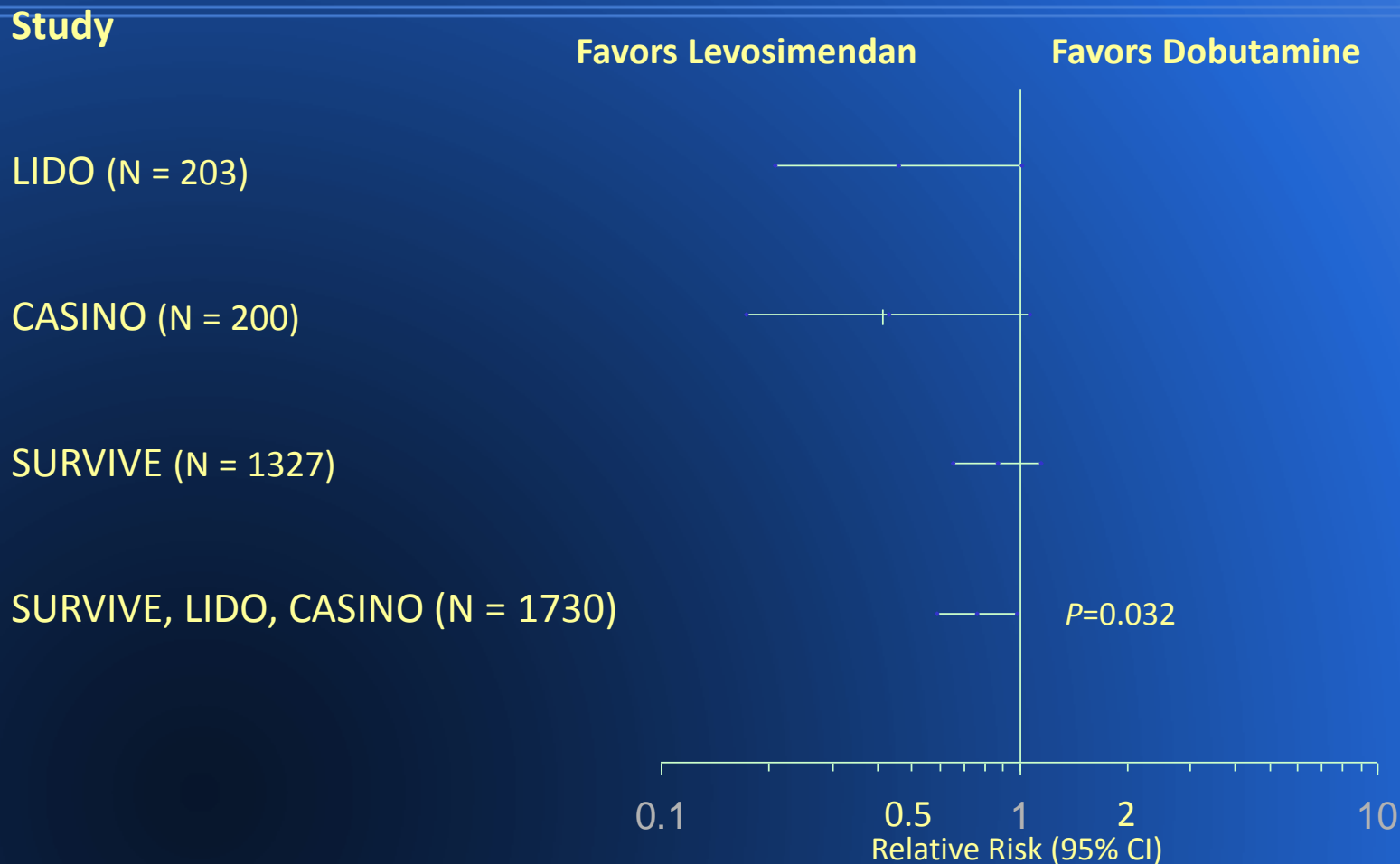
SURVIVE

All-Cause Mortality

	5 d	31 d	180 d
Levosimendan (n = 664)	29 (4.4%)	79 (11.9%)	173 (26.1%)
Dobutamine (n = 663)	40 (6.0%)	91 (13.7%)	185 (27.9%)
Δ Deaths	- 11	- 12	- 12
Hazard Ratio (CI)	0.72 (0.44-1.16)	0.85 (0.63-1.15)	0.91 (0.74-1.13)

SURVIVE

Mortality Comparison - 31 Days



* Mebazaa et al , AHA , Dallas , November 2005

Advantages of levosimendan

Dual action: contractility ↑ + vasodilation ↑

Relief of symptoms of HF

Effects maintained also with beta-blockers

Rapid onset of effects with a bolus

Long-lasting effects due to an active metabolite

Advantages of levosimendan

- **Not arrhythmogenic**
- **No increase in myocardial oxygen consumption**
- **Mortality benefit (?)**

DURATION?

Effects of serial levosimendan infusions on left ventricular performance and plasma biomarkers of myocardial injury and neurohormonal and immune activation in patients with advanced heart failure

John T Parissis, Stamatis Adamopoulos, Dimitrios Farmakis, Gerasimos Filippatos, Ioannis Paraskevaidis, Fotios Panou, Efstathios Iliodromitis and Dimitrios Th Kremastinos

Heart published online 18 Jul 2006;

Background: Levosimendan is a novel inodilator agent that improves central hemodynamics and symptoms of patients with decompensated chronic heart failure. The role, however, of repeated levosimendan infusions in the management of these patients has not been properly assessed.

Purpose: This randomized placebo-controlled trial investigated the effects of serial levosimendan administrations on cardiac geometry and function and on biomarkers of myocardial injury and neurohormonal and immune activation (Troponin-T, NT-proBNP, C-reactive protein, interleukin-6) in advanced heart failure.

Methods: Twenty five patients with decompensated chronic heart failure were randomized (2:1) to receive five serial 24-hour infusions (every 3 weeks) of either levosimendan (n=17) or placebo (n=8), and evaluated echocardiographically and biochemically before and after each drug administration and 30 days after the final administration.

Results: Post-treatment, cardiac end-systolic and end-diastolic dimension and volume indexes were significantly reduced only in the levosimendan-treated patients ($p < 0.01$). A significant decrease of NT-pro BNP ($p < 0.01$), high-sensitivity C-reactive protein ($p < 0.01$) and plasma interleukin-6 ($p = 0.05$) was also observed in the levosimendan group, while these markers remained unchanged in the placebo group; similar changes were observed after each single drug infusion. The number of patients with a positive troponin-T (≥ 0.01 ng/mL), although not different between the two groups at baseline, it was significantly higher in the placebo-treated group during the final evaluation.

Conclusion: Serial levosimendan administrations improved left ventricular performance and modulated beneficially neurohormonal and immune activation in advanced heart failure, without having increased myocardial injury.

ACC/AHA guidelines 2013

- Parenteral inotropes remain a therapeutic option for the subset of patients with HF who are refractory to other therapies and suffer from the consequences of end-organ hypoperfusion.
- Inotropes should be considered only in those patients with systolic dysfunction who have low cardiac output/index and evidence of systemic hypoperfusion and/or congestion.

Inotropic Support



Until definitive therapy (e.g., coronary revascularization, MCS, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance.



Continuous intravenous inotropic support is reasonable as “bridge therapy” in patients with stage D refractory to GDMT and device therapy who are eligible for and awaiting MCS or cardiac transplantation.

Bridge



*Helping Cardiovascular Professionals
Learn. Advance. Heal.*



Inotropic Support (cont.)



Short-term, continuous intravenous inotropic support may be reasonable in those hospitalized patients presenting with documented severe systolic dysfunction who present with low blood pressure and significantly depressed cardiac output to maintain systemic perfusion and preserve end-organ performance.



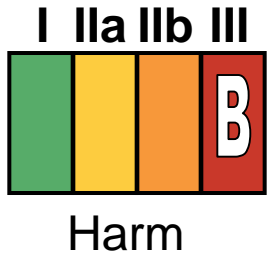
Long-term, continuous intravenous inotropic support may be considered as palliative therapy for symptom control in select patients with stage D despite optimal GDMT and device therapy who are not eligible for either MCS or cardiac transplantation.



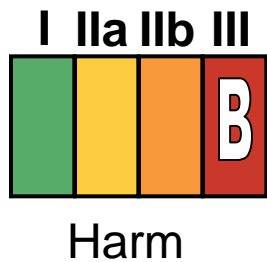
*Helping Cardiovascular Professionals
Learn. Advance. Heal.*



Inotropic Support (cont.)



Long-term use of either continuous or intermittent, intravenous parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, **is potentially harmful** in the patient with HF.



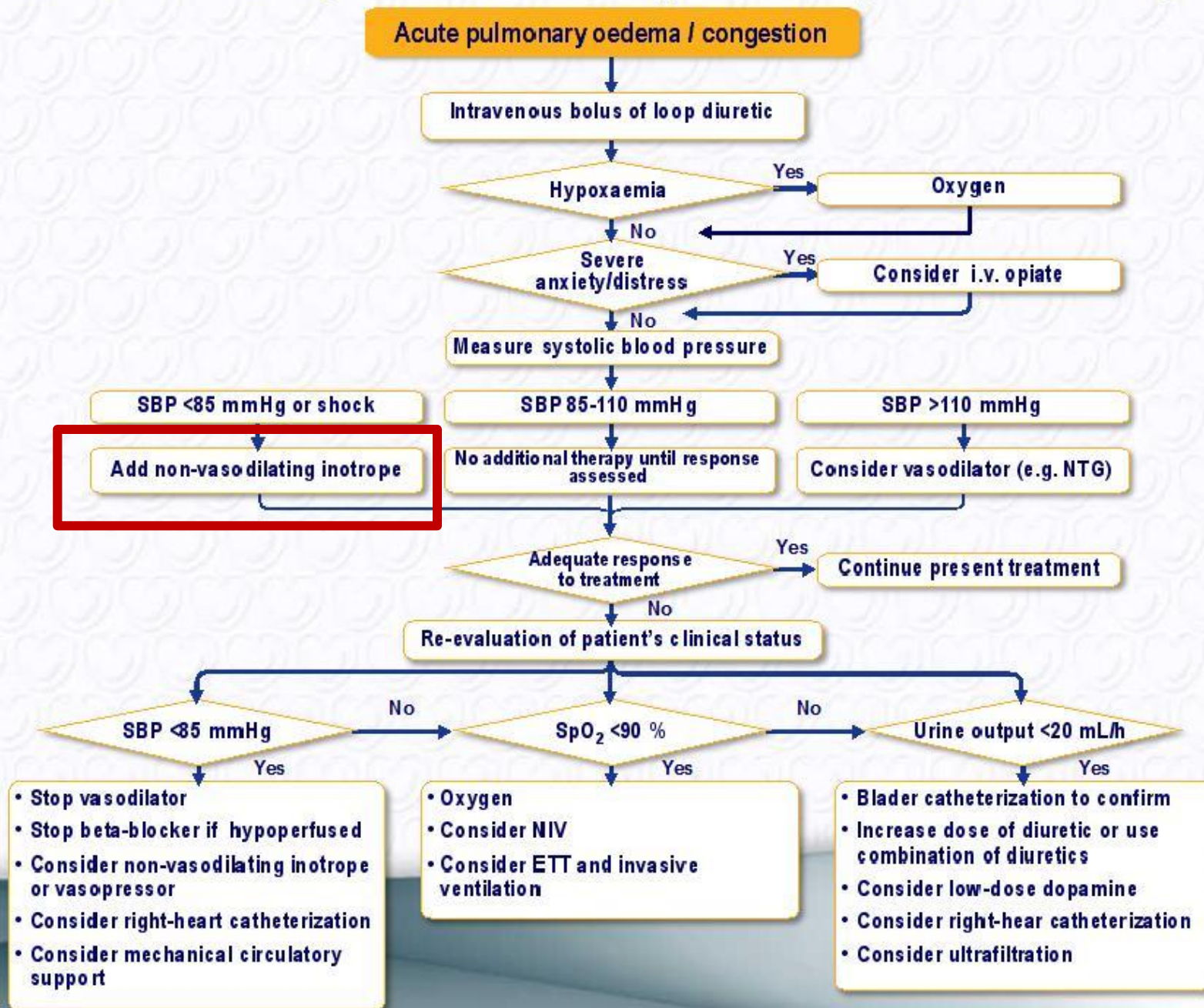
Use of parenteral inotropic agents in hospitalized patients without documented severe systolic dysfunction, low blood pressure, or impaired perfusion, and evidence of significantly depressed cardiac output, with or without congestion, **is potentially harmful**.



*Helping Cardiovascular Professionals
Learn. Advance. Heal.*



Algorithm for management of acute pulmonary oedema/congestion



ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

Inotropes

Use of an inotrope such as dobutamine should usually be reserved for patients with such severe reduction in cardiac output that vital organ perfusion is compromised. Such patients are almost always hypotensive ('shocked'). Inotropes cause sinus tachycardia and may induce myocardial ischemia and arrhythmias. There is long-standing concern that they may increase mortality. There is pharmacological rationale to use levosimendan (or a phosphodiesterase III inhibitor such as milrinone) if it is felt necessary to counteract the effect of a beta-blocker.

Executive Summary: HFSA 2010 Comprehensive Heart Failure Practice Guideline

HEART FAILURE SOCIETY OF AMERICA

Intravenous inotropes (milrinone or dobutamine) may be considered **(IIB)** to relieve symptoms and improve end-organ function in patients with advanced HF characterized by LV dilation, reduced LVEF, and diminished peripheral perfusion or end-organ dysfunction (low out-put syndrome), particularly if these patients have marginal systolic blood pressure (90 mm Hg), have symptomatic hypotension despite adequate filling pressure, or are unresponsive to, or intolerant to intravenous vasodilators. **(Strength of Evidence C)**.

These agents may be considered in similar patients with evidence of fluid overload if they respond poorly to intravenous diuretics or manifest diminished or worsening renal function. **(Strength of Evidence C)**.

Optimal Pharmacologic and Non-pharmacologic Management of Cardiac Transplant Candidates: Approaches to Be Considered Prior to Transplant Evaluation: **International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates—2006**

Long-term continuous inotropic treatment

For some patients on inotropic support, weaning of inotropic support is not possible, primarily because of the recurrence of symptomatic hypotension, congestive symptoms or the worsening renal function early after discontinuation of inotropic therapy.

In these acutely inotrope-dependent patients, institution of a continuous infusion of the inotropic agent may be considered. As most studies have consistently shown an increase in mortality using long-term inotropes, this treatment option is used as a pharmacologic bridge to heart transplantation or mechanical support. In patients with end-stage (Class D) heart failure, where no other therapeutic alternatives are feasible, long-term inotropic support may be considered for symptomatic relief at the end of life, taking into account the individual patient preferences while balancing the potential symptomatic benefit with the potential risks

OUR RECOMENDATIONS

Rapid Assessment of Hemodynamic Status

Congestion at Rest

		Congestion at Rest	
		NO	YES
Low Perfusion at Rest	NO	Warm & Dry CI: NI PCWP: NI	Warm & Wet CI: NI PCWP: High 67%
	YES	Cold & Dry CI: Low PCWP: NI 5%	Cold & Wet CI: Low PCWP: High 28% ← Inotropes

USE OF INOTROPES

Short term

1. Given the known concerns about increased mortality with short-term intravenous therapy with milrinone or dobutamine in patients with AHF, these drugs must **not** be used in the routine management of such patients. (**consider vasodilatation and diuretics first**)
2. However, administration of an inotrope (**preferably levosimendan**) should be considered in patients with hemodynamic compromise that is not adequately managed by diuretics and vasodilators.

Long-term

1. Long-term infusion of an inotropic agent may be useful as a “bridge” to definitive therapy (eg, coronary revascularization, mechanical circulatory support, or heart transplantation) or resolution of the acute precipitating factor.
2. **Long-term infusion of an inotropic agent may be considered as palliative therapy** for **symptom relief** in selected patients with stage D HF despite optimal medical and device therapy.

Thank You for Your Attention



©Edward Galagan