OSPEDALE NIGUARDA CA' GRANDA
"DE GASPERIS" CARDIO CENTER

Sistema Socio Sanitario
Regione Lombardia

UCIC-Unità di Cure Intensive Cardiologiche
Cardiologia 1-Emodinamica

LEVOSIMENDAN nell'Insufficienza Cardiaca. Dagli Studi Clinici alla Cardiologia di tutti i giorni: a che punto siamo in Italia e nel mondo

Fabrizio Oliva

X Congresso Nazionale
ECOCARDIOCHIRURGIA 2018
Milano, 9-11 Aprile 2018, Palazzo delle Stelline

Presenter Disclosure Information:

- ***Grant/Research support***: Orion Pharma
- ***Speaker's bureau:*** Orion Pharma

Sistema Socio Sanitario
Ospedale Niguarda
Regione Lombardia

AGENDA

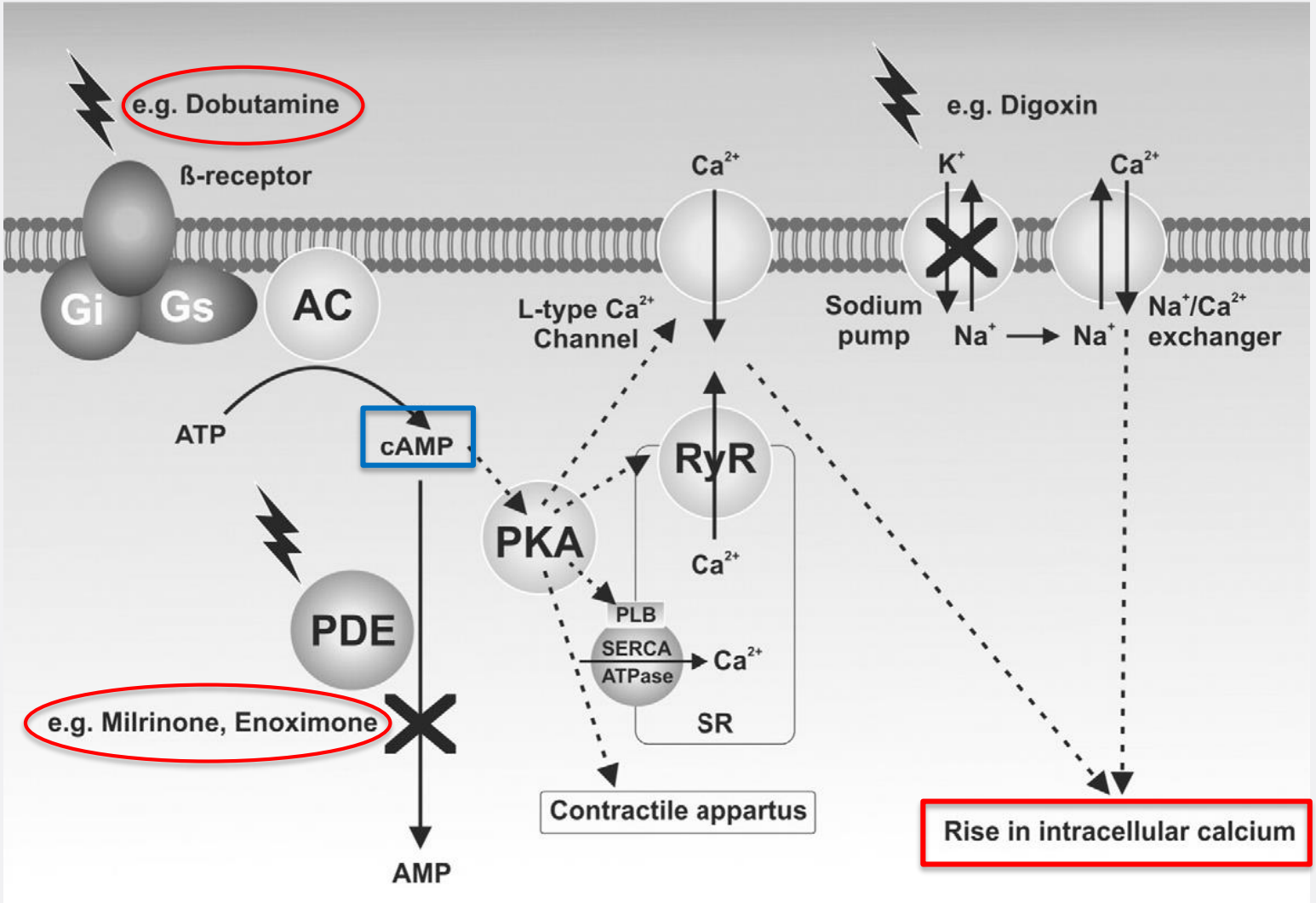
- **Di quale farmaco stiamo parlando** (caratteristiche, meccanismo d'azione, farmacocinetica)

- **Insufficienza Cardiaca ACUTA**
  - SC congestizio/bassa portata
  - Shock Cardiogeno
  - Sindromi coronariche acute

- **Insufficienza Cardiaca CRONICA**
  - SC avanzato/refrattario
  - SC cronico con Ipertensione Polmonare secondaria

Role of intravenous inotrope therapy in AHF

- A subject of controversy
- Lack of prospective, randomised, controlled trials
- Lack of clear recommendations from guidelines



Pollesello P et al. Int J Cardiol 2016

LEVOSIMENDAN

- Peculiarità rispetto ad altri inotropi -

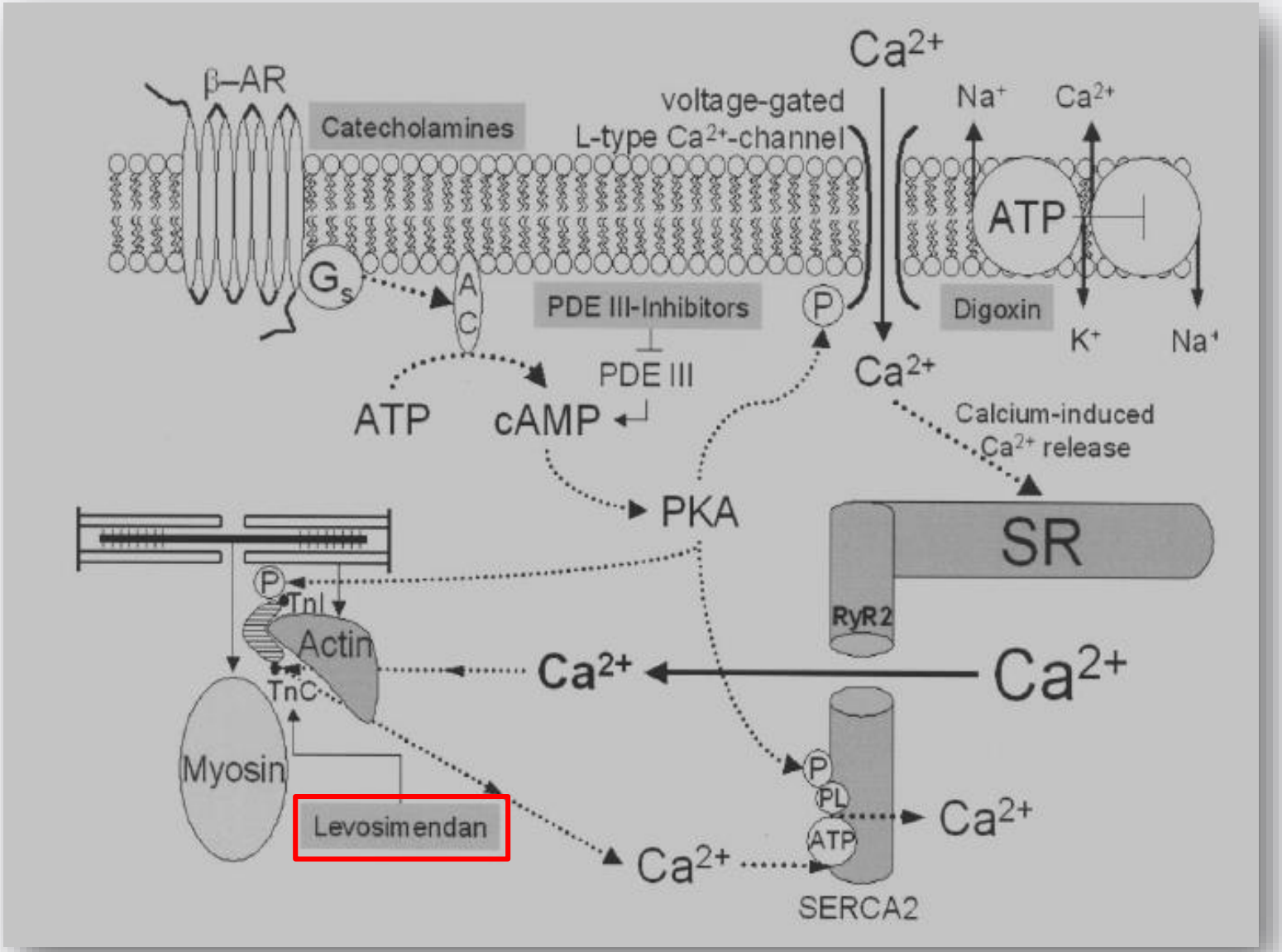
- Meccanismo d'azione
- Farmacocinetica

LEVOSIMENDAN

- Peculiarità rispetto ad altri inotropi -

- Meccanismo d'azione

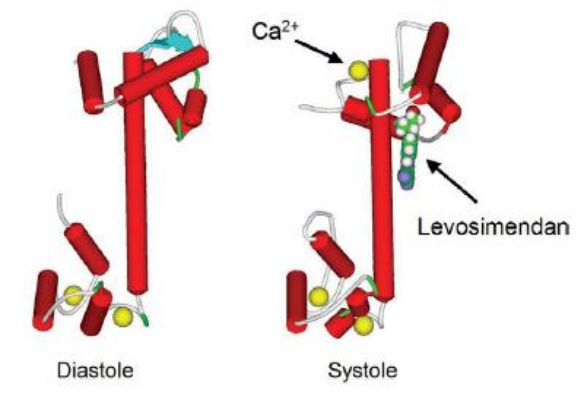
Levosimendan



Levosimendan

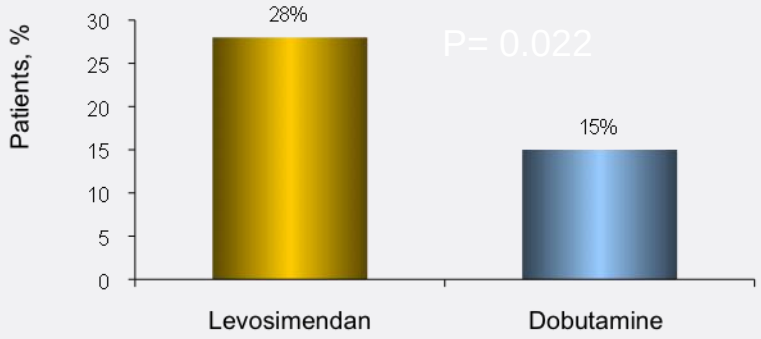
Utilizes a dual mechanism of action

- Ca^{++} sensitization of the contractile proteins
  - Inotropic effect
- Smooth muscle K^{+} channel opening
  - Peripheral vasodilation
- Potent acetylated metabolite
  - Ca^{++} sensitizer, 80 hs half-life



Lido Trial

Increase in Cardiac Output ≥30% and a Decrease in PCWP ≥25%

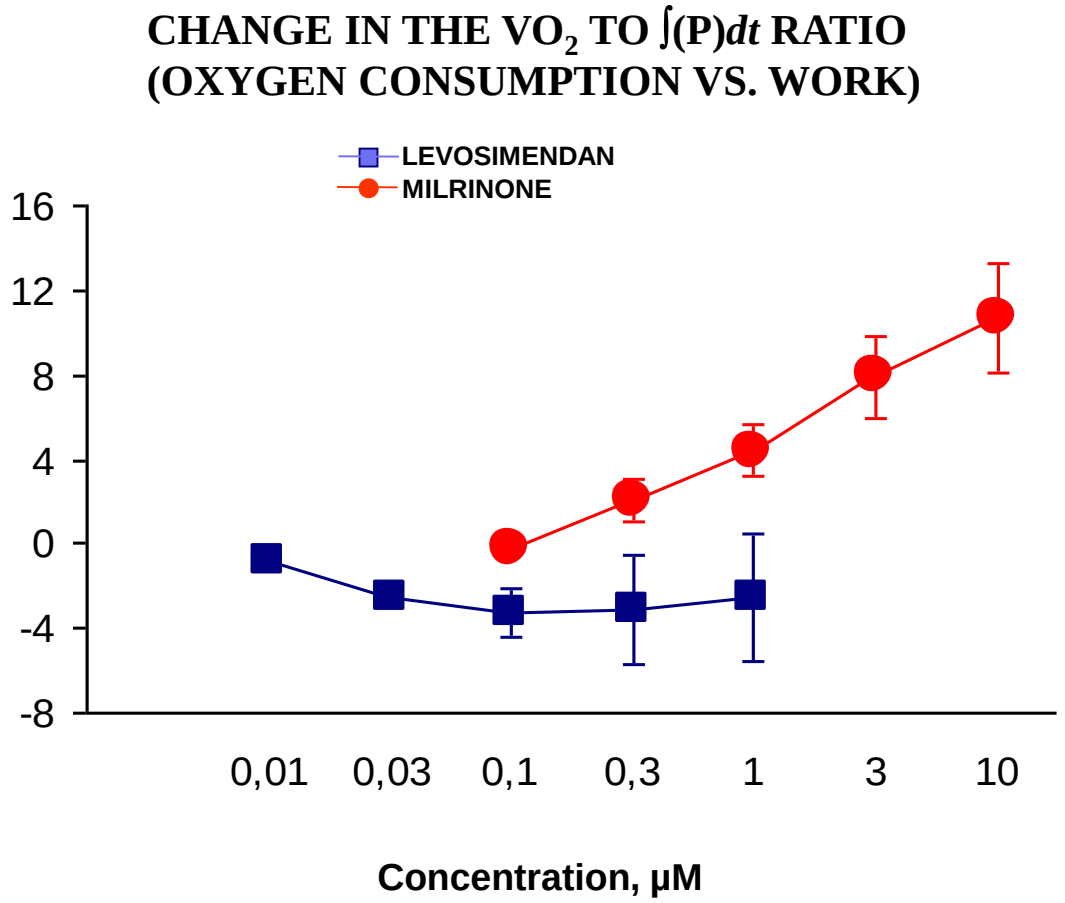


Follath et al. Lancet 2002

Levosimendan: a triple mechanism of action

- calcium dependent binding to cTnC
- opening of K_{ATP} channels on smooth muscle cells in vasculature
- opening of K_{ATP} channels in cardiac mitochondria

Levosimendan: no increase of oxygen consumption



Ex vivo guinea pig model

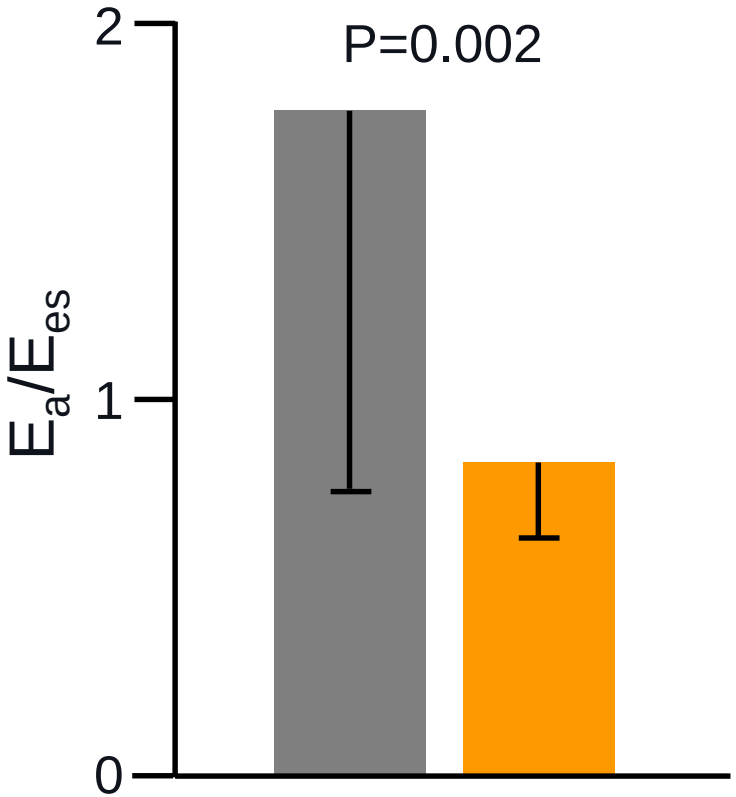
Kaheinen P et al. *J Cardiovasc Pharmacol* 2004;**43**:555-561

Levosimendan: a triple mechanism of action

- calcium dependent binding to cTnC
- opening of K_{ATP} channels on smooth muscle cells in vasculature
- opening of K_{ATP} channels in cardiac mitochondria

Levosimendan increases the efficiency

Ventriculo-arterial coupling: dynamic ratio between arterial elastance (E_a), an index of vascular systemic resistances, and ventricular elastance (E_{es}), an index of cardiac contractility

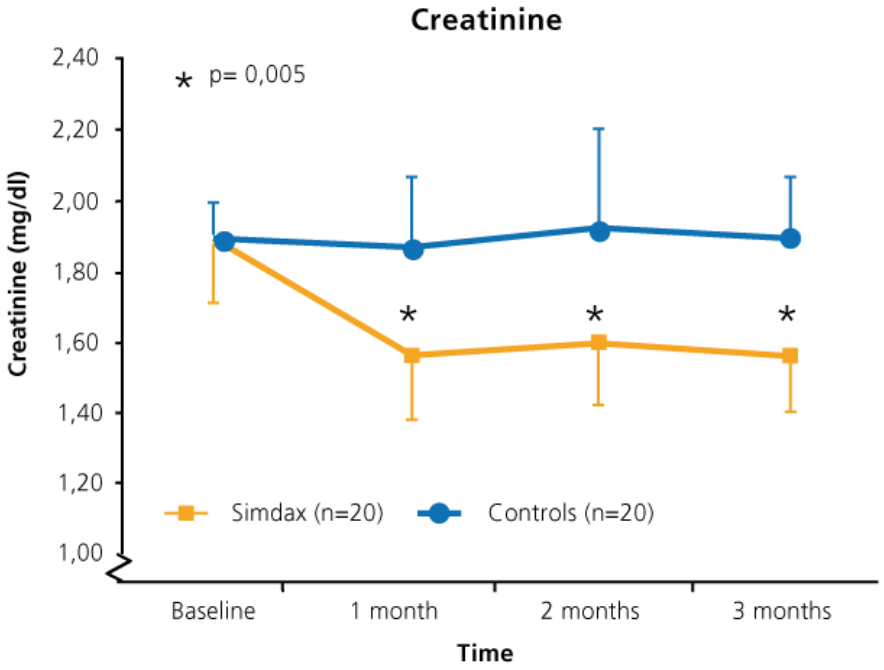


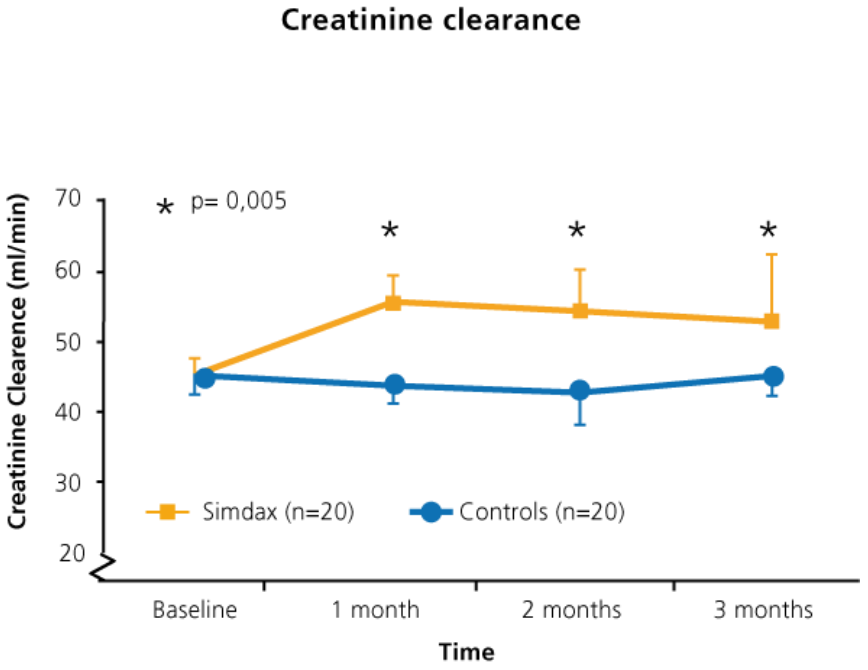
in patients with ischemic cardiomyopathy

human/clinical

Levosimendan increases kidney function

Levosimendan improves long-term renal function
in advanced chronic heart failure patients awaiting cardiac transplantation.





human/clinical

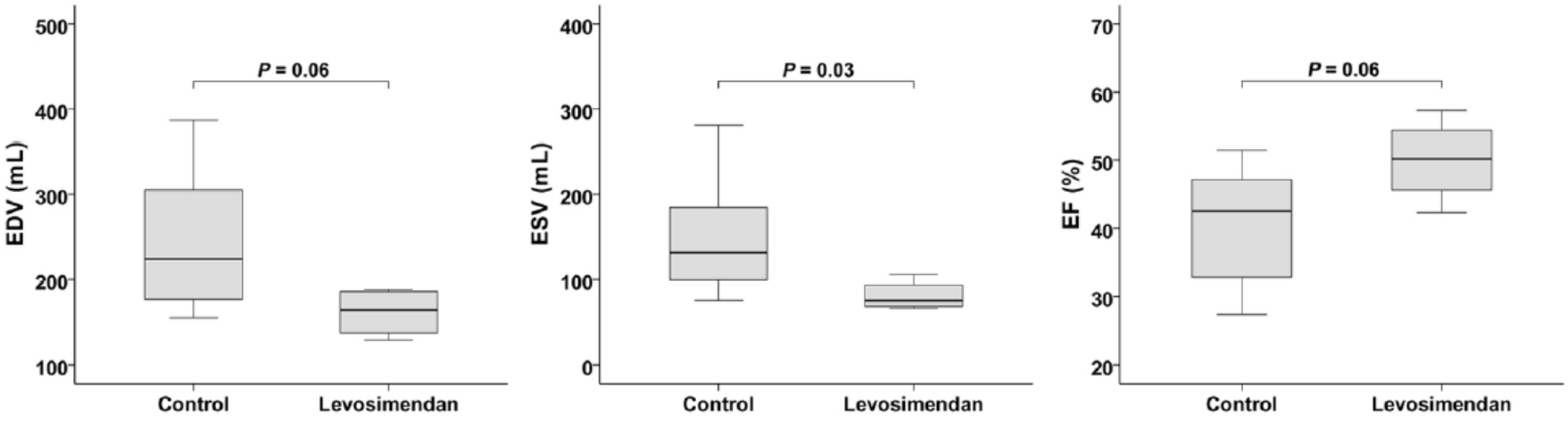
Zemljic G, et al. J Cardiac Fail 2007;13:417-21

Levosimendan: a triple mechanism of action

- calcium dependent binding to cTnC
- opening of K_{ATP} channels on smooth muscle cells in vasculature
- opening of K_{ATP} channels in cardiac mitochondria

Levosimendan has an anti-ischemic effect

levosimendan reduces myocardial infarct size and increase left ventricular function after acute coronary occlusion



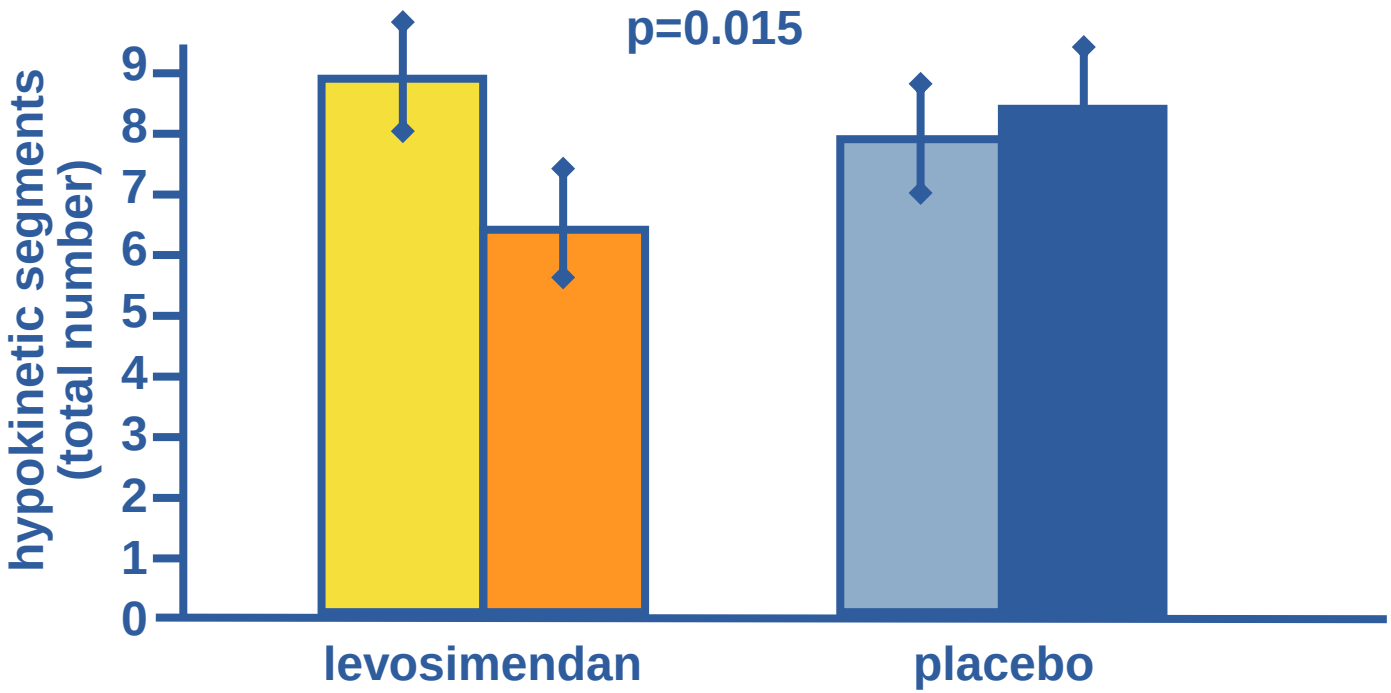
Levosimendan vs placebo after occlusion of the left anterior descending coronary artery. Left ventricle end-diastolic volume (EDV), end-systolic volume (ESV) and ejection fraction (EF) measured by CT after 8 weeks of levosimendan treatment (5 mg/kg/day) vs no therapy

In vivo pig model

Tarkia M et al. *Heart* 2016 [ePub Jan 13]

Levosimendan has an anti-stunning effect

In a 24 patient group with ACS the total number of hypokinetic segments decreased in the levosimendan group vs placebo



Human/clinical

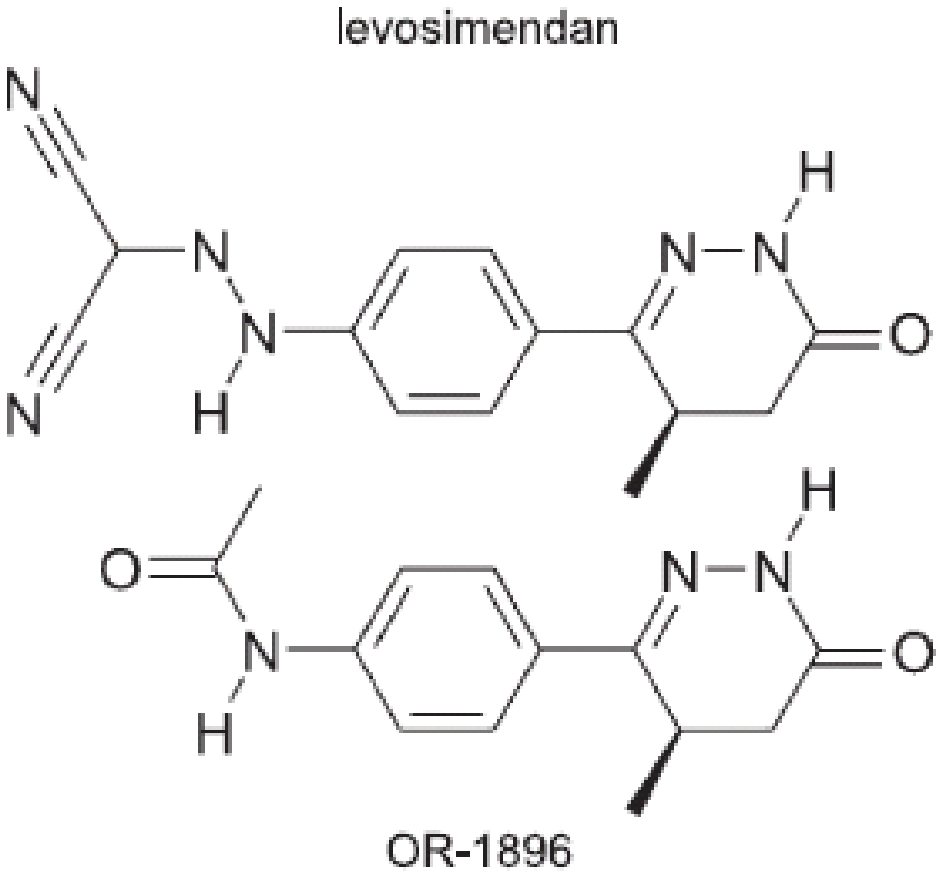
Sonntag S et al. *JACC* 2004;**43**:2177

LEVOSIMENDAN

- Peculiarità rispetto ad altri inotropi -

- Farmacocinetica

Levosimendan and its active metabolite



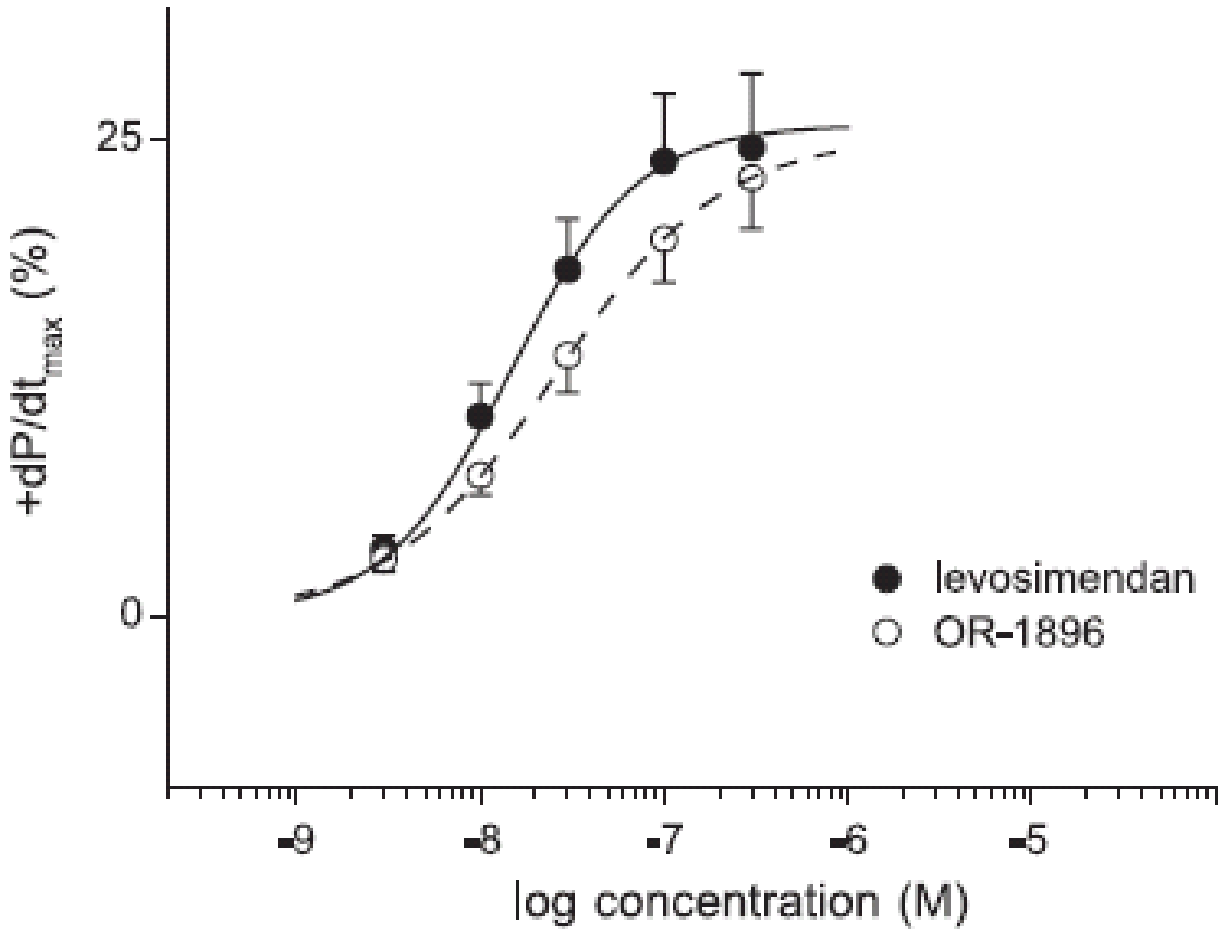
Szilagyi S et al. *Eur J Pharmacol* 2004;**486**:67-74

Farmacocinetica e metabolismo del levosimendan

- **Molecola madre (Levosimendan)**
  - Rapida insorgenza d'azione (circa 20 minuti dopo il bolo e 4 ore durante infusione continua).
  - Rapida eliminazione (t1/2 = 1 ora). E' completamente metabolizzato ed eliminato per via urinaria (55%) e attraverso le feci (45%).

- **Metabolita attivo (OR-1896)** (5%)
  - Lenta insorgenza d'azione (raggiunge il picco di concentrazione in 48 ore)
  - Lenta eliminazione (t1/2= ~80 ore)
  - OR-1896 è un "calcium sensitizer" potente come levosimendan
  - Il profilo emodinamico è simile a quello del levosimendan
  - Risposta emodinamica protratta

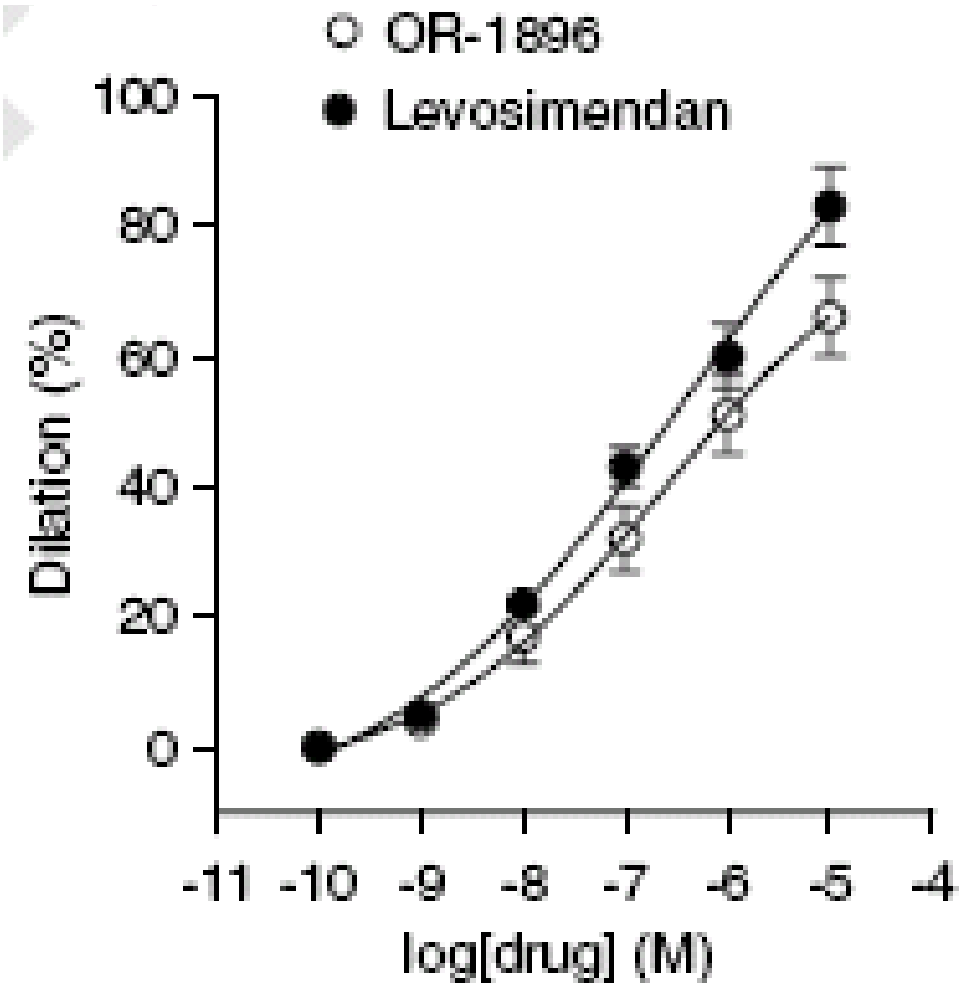
Levosimendan and its active metabolite have similar inotropic effects



In vitro cell model

Szilagyi S et al. *Eur J Pharmacol* 2004;**486**:67-74

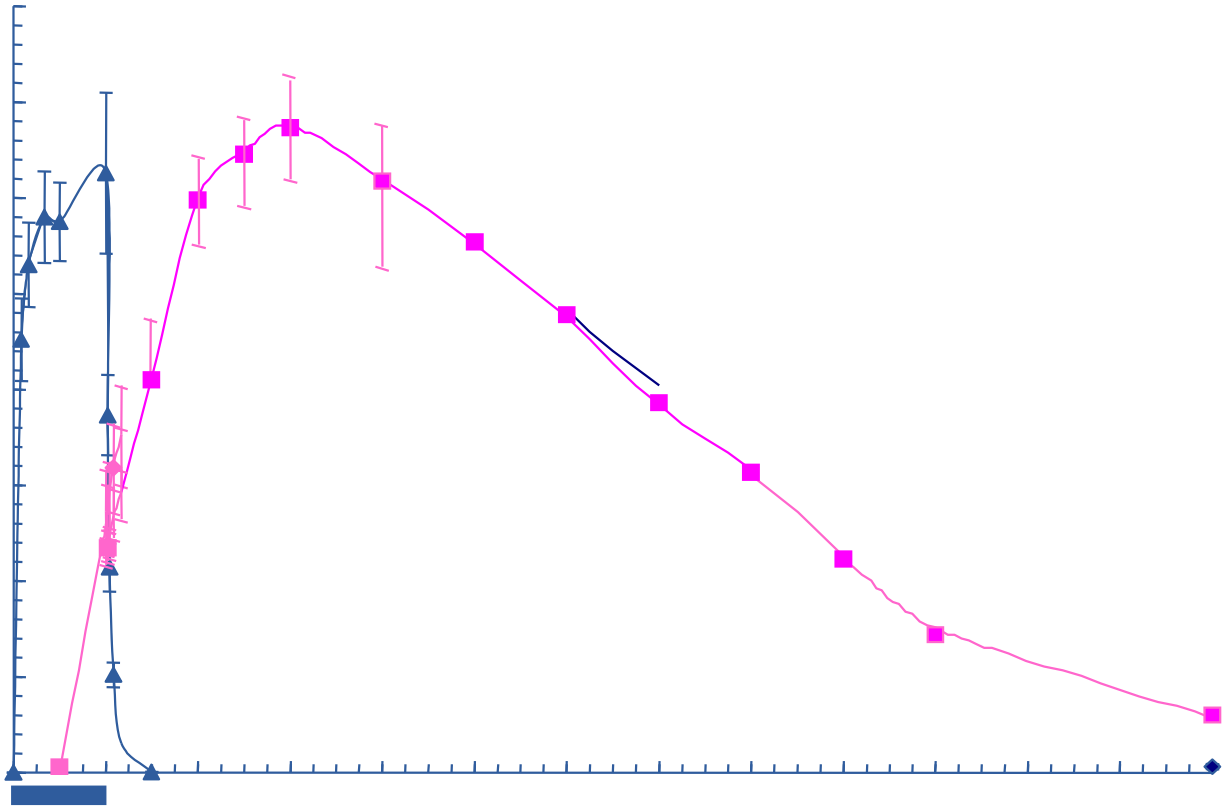
Levosimendan and its active metabolite have similar vasodilatory effects



Ex vivo rat model

Erdei N et al. *Br J Pharmacol* 2006;**148**:696-702

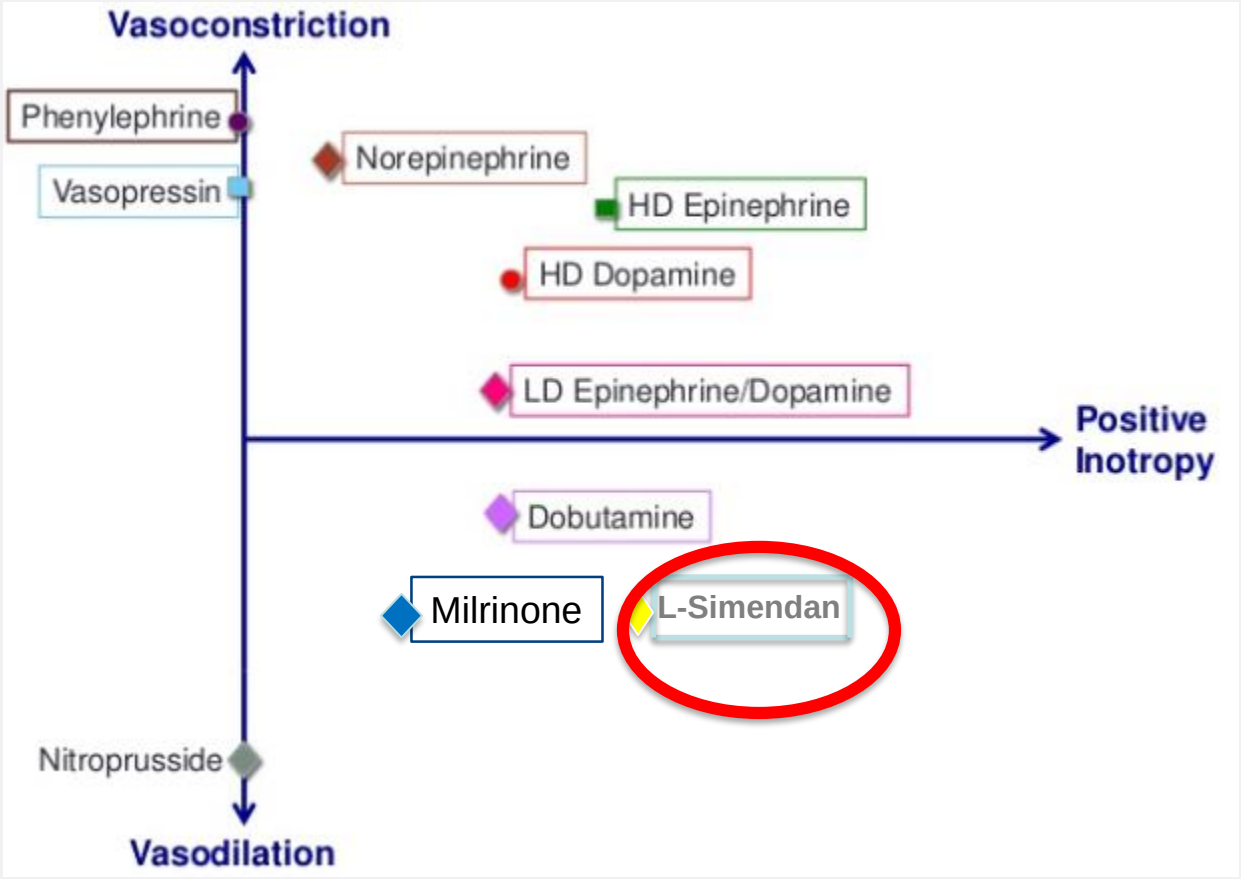
Levosimendan and its active metabolite non-protein boun plasma concentrations



Human/clinical

from Kivikko M et al. *Int J Clin Pharm & Ther* 2002;**40**:465

Different Haemodynamic effects of inotropic drugs



LEVOSIMENDAN

- INSUFFICIENZA CARDIACA ACUTA -

Clinical Presentation, Targets and Therapies

Clinical Presentation	Characteristics	Targets and Therapies
AHFS with hypertension	Often develops suddenly (hours). Predominantly pulmonary (radiographic/clinical) with or without systemic congestion. Preserved EF common. Acute pulmonary edema is an extreme form of this phenotype	Target: blood pressure and volume management, oxygenation in acute pulmonary edema Therapy: vasodilators ± loop diuretics, noninvasive mechanical ventilation for acute pulmonary edema
AHFS with hypotension	Symptoms related to low cardiac output, typically with decreased renal function; may have atypical symptoms (confusion, lethargy, abdominal pain). Typically accompanied by congestion as well, although may be subtle. Cardiogenic shock represents an extreme form of this phenotype	Target: cardiac performance, end-organ preservation Therapy: Inotropic drugs ± volume removal strategies listed above. Consider mechanical support such as intra-aortic balloon pump
AHFS due to other condi Atrial fibrillation Acute coronary syndro Acute valvular heart d (mitral regurgitation, a insufficiency) Myocarditis Pulmonary emboli Infections		e and target nderlying cause

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Circ Heart Fail 2010;3;314-325

When?

Guidelines?

Which inotrope?

Randomized trials?

How long?

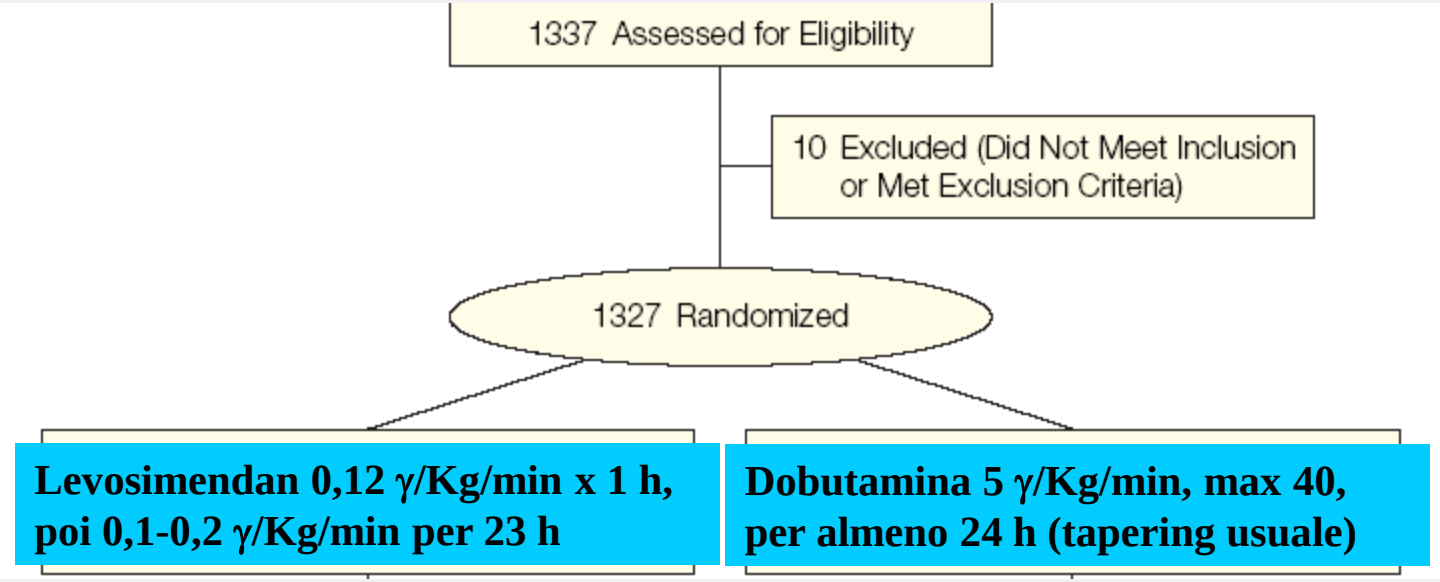
Clinical protocol?

Inotropes alone or with vasodilators?

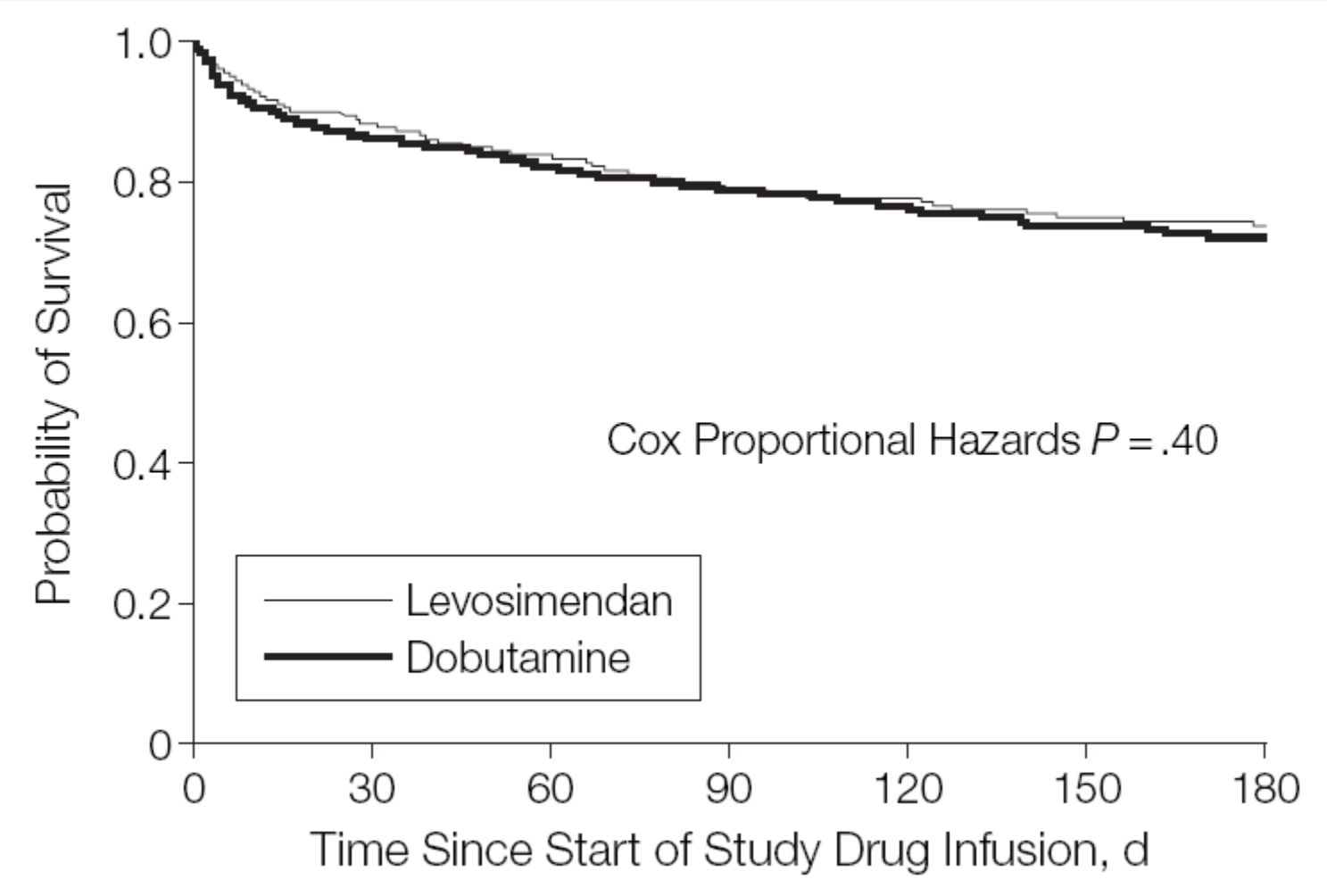
Inotropes alone or with vasoconstrictors?

LEVOSIMENDAN: Studio SURVIVE

- Età ≥18 a., FE ≤.30.
- Scompenso non responsivo a diuretici e vasodilatatori
- Uno o più dei seguenti sintomi/segni:
  - Dispnea o necessità di ventilazione
  - Oliguria non secondaria a ipovolemia
  - WP ≥18 mmHg e/o CI ≤2.2 l/min/m^2.
- End-point: mortalità a 6 mesi



LEVOSIMENDAN: SURVIVE Study



Mebazaa et al. JAMA 2007;297,1883-1891

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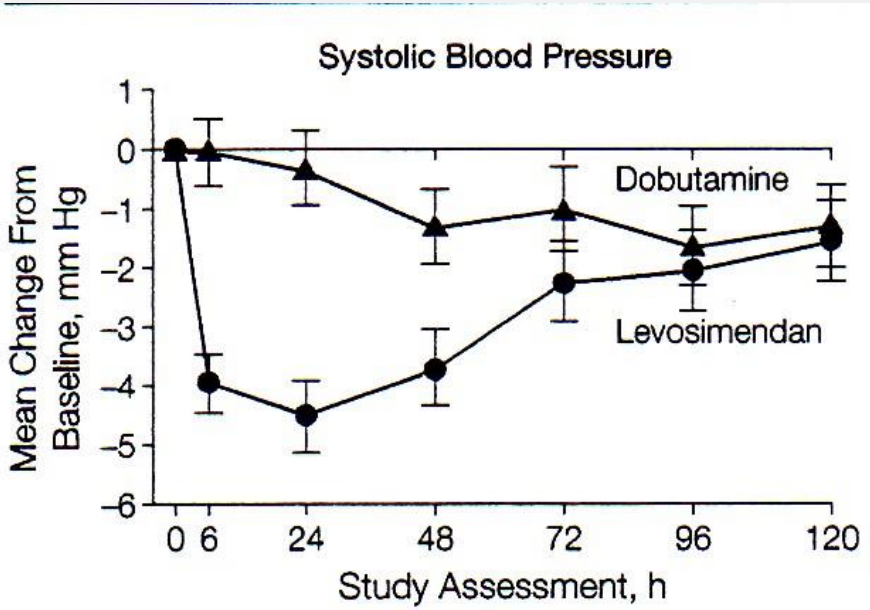
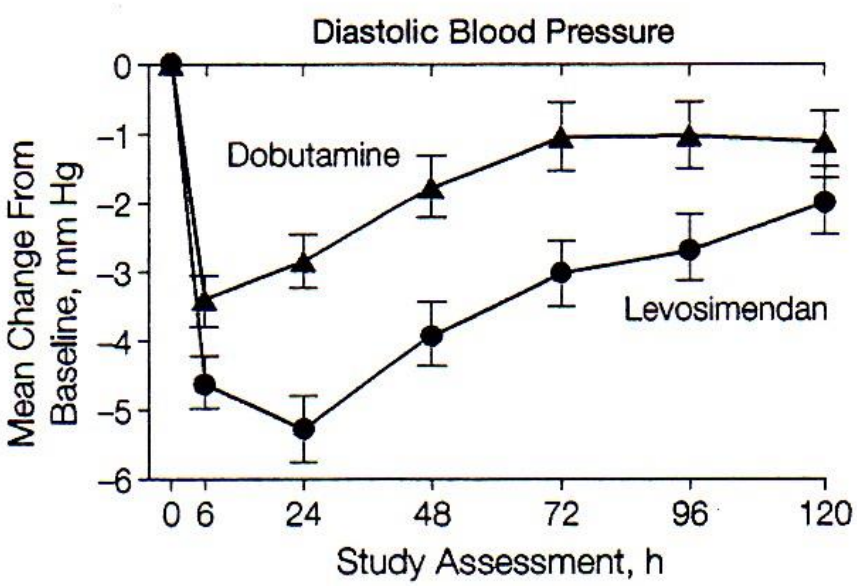
SURVIVE Study

Mean Change From Baseline in Systolic and Diastolic Blood Pressure Through 5 Days by Treatment Group

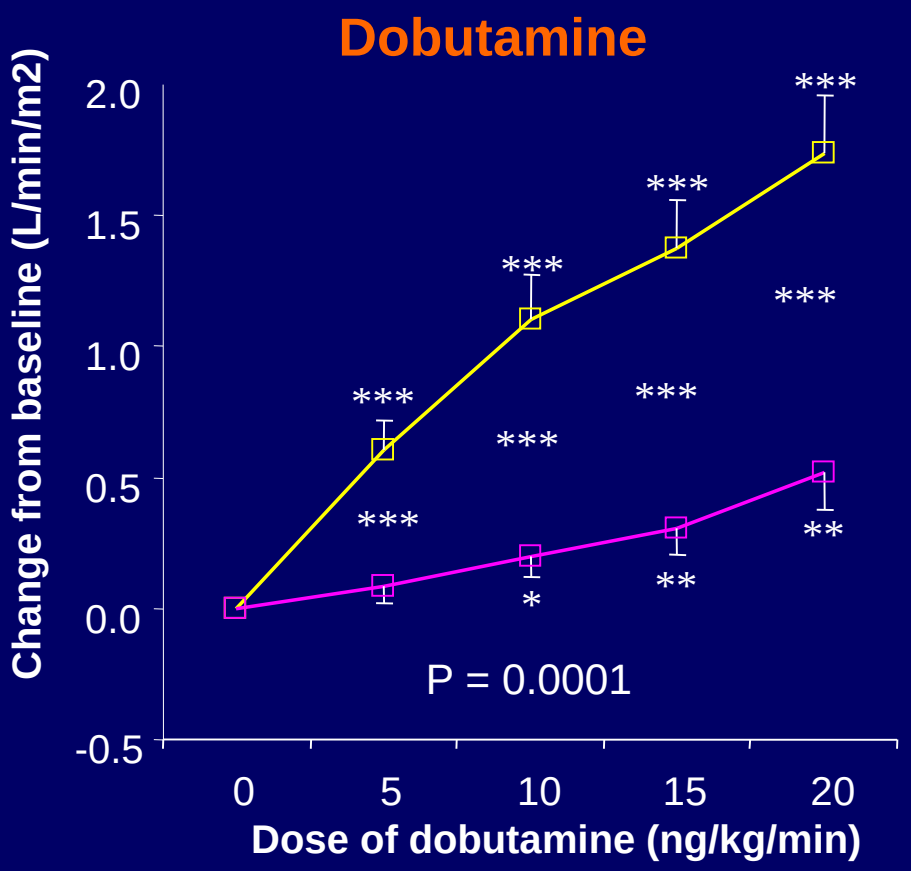


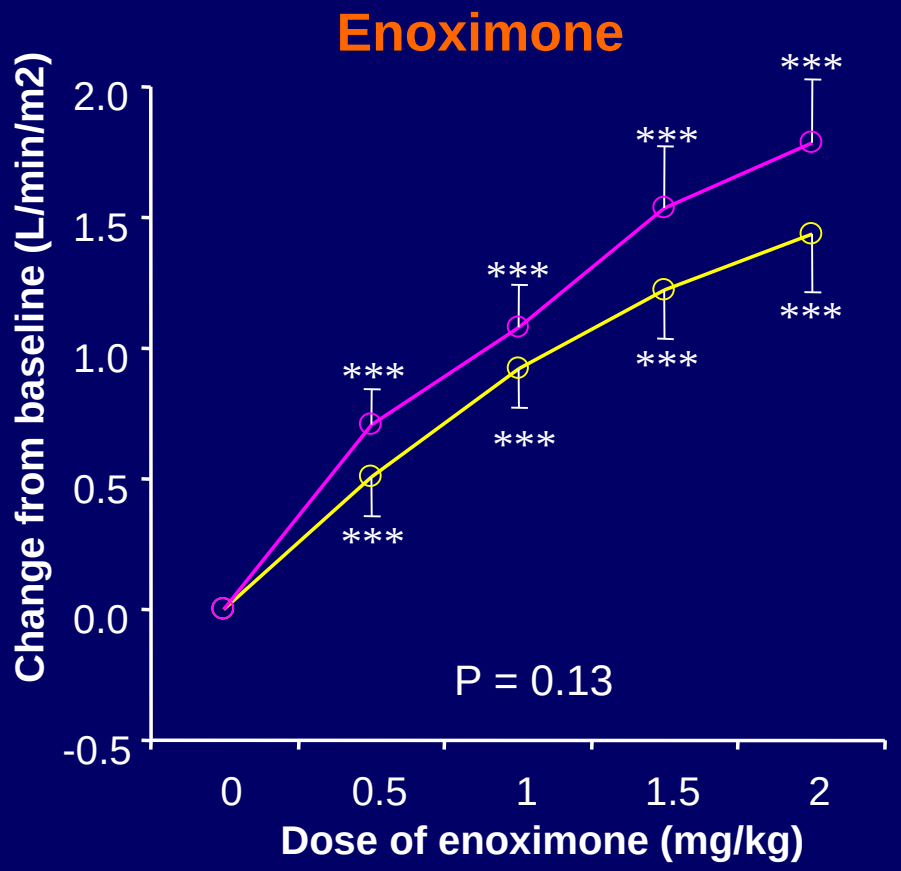


Mebazaa, A. et al. JAMA 2007;297:1883-1891

Inotropes and Beta-Blocker Therapy

Effects of Long-term Carvedilol on the Cardiac Index Response to Inotropic Agents





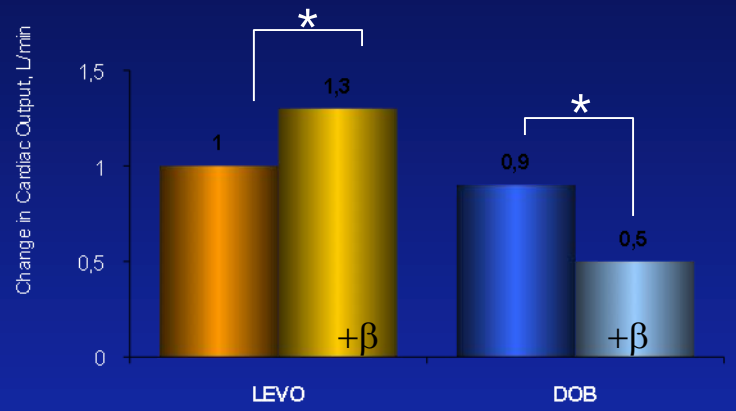
Control

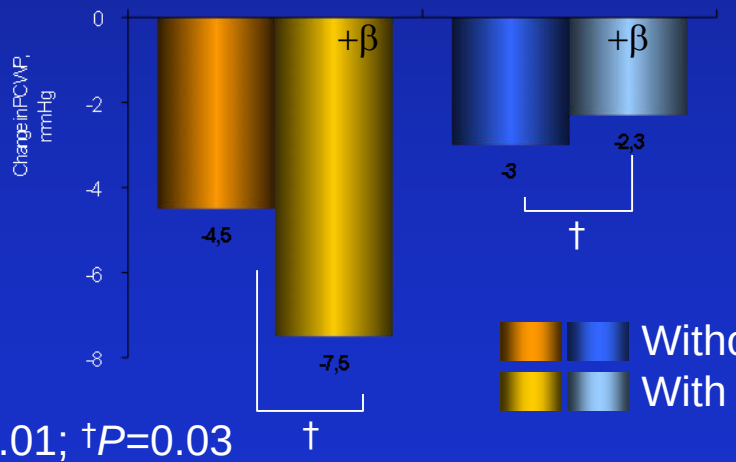
During long-term carvedilol

Metra, Dei Cas et al. J Am Coll Cardiol 2002; 40:1248

LIDO Effect of β-Blockers

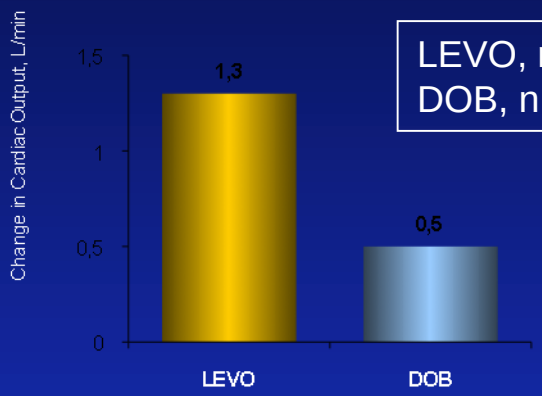
Subset Analysis of Patients Enrolled in the LIDO Study



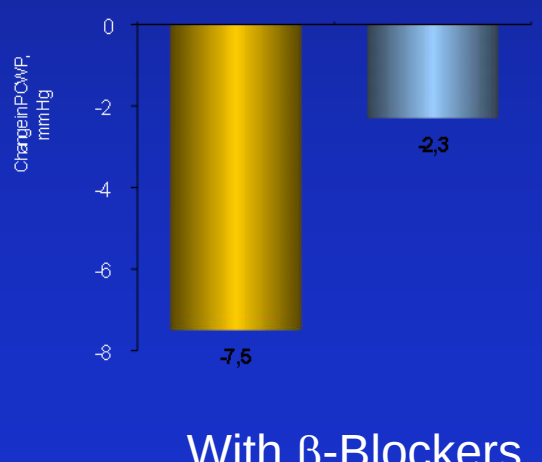


Without β-Blockers
With β-Blockers

*P=0.01; †P=0.03



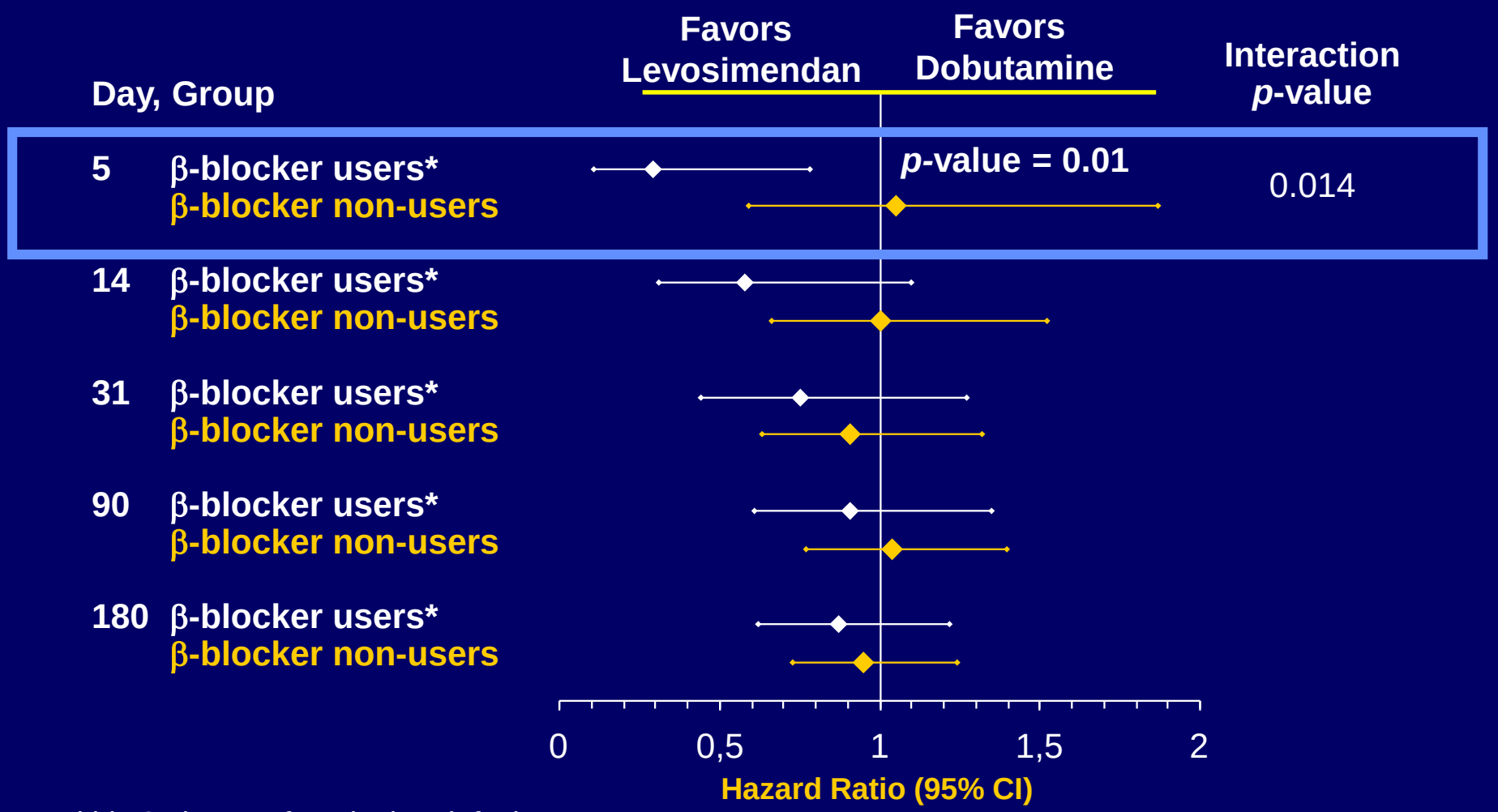
LEVO, n = 103
DOB, n = 100



With β-Blockers

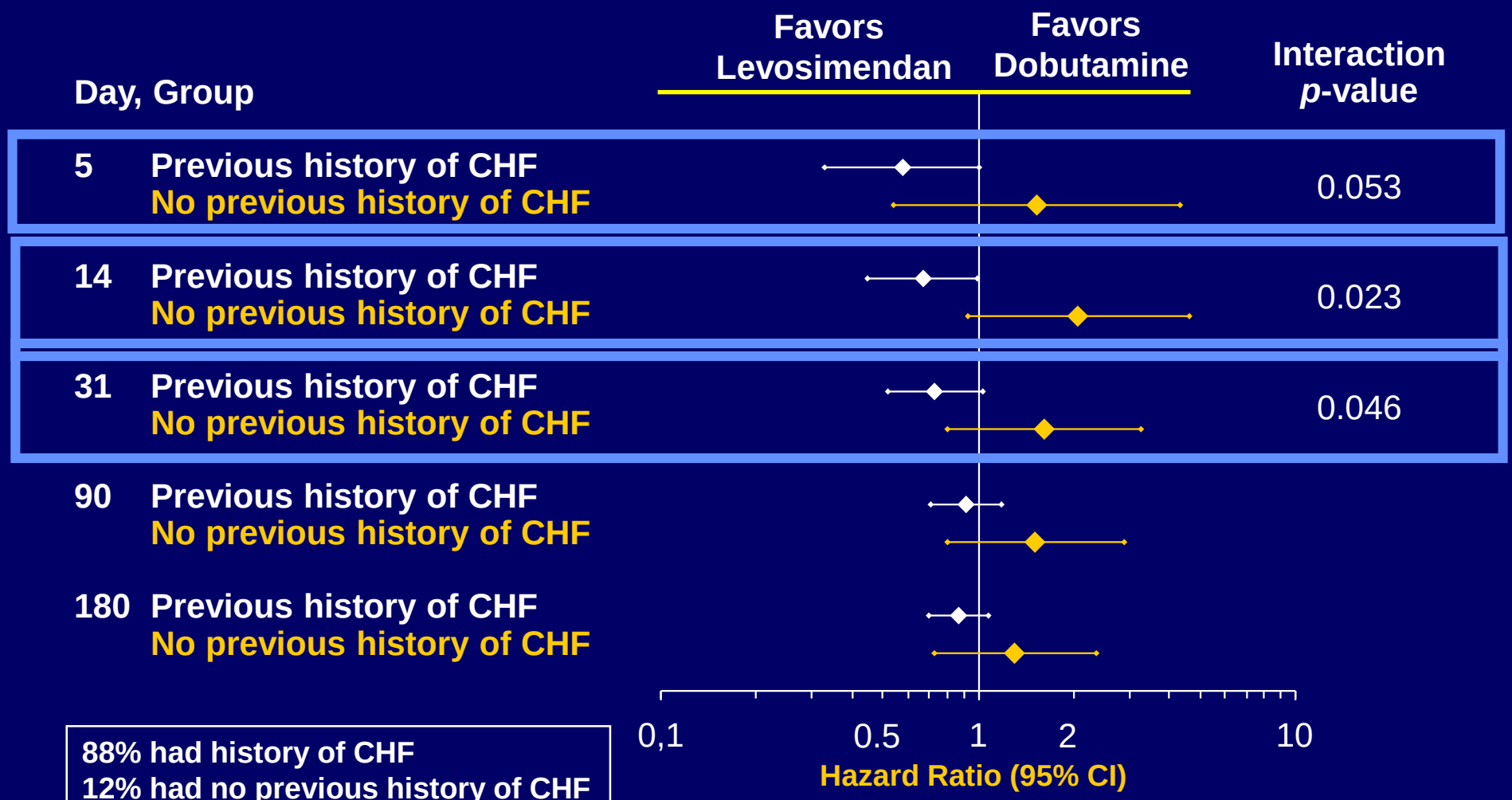
Follath F, et al. *Lancet*. 2002;360:196-202.

Hazard Ratios for Patients on Blockers at Baseline Appeared to Favor Levosimendan



* Within 24 hours of study drug infusion

SURVIVE

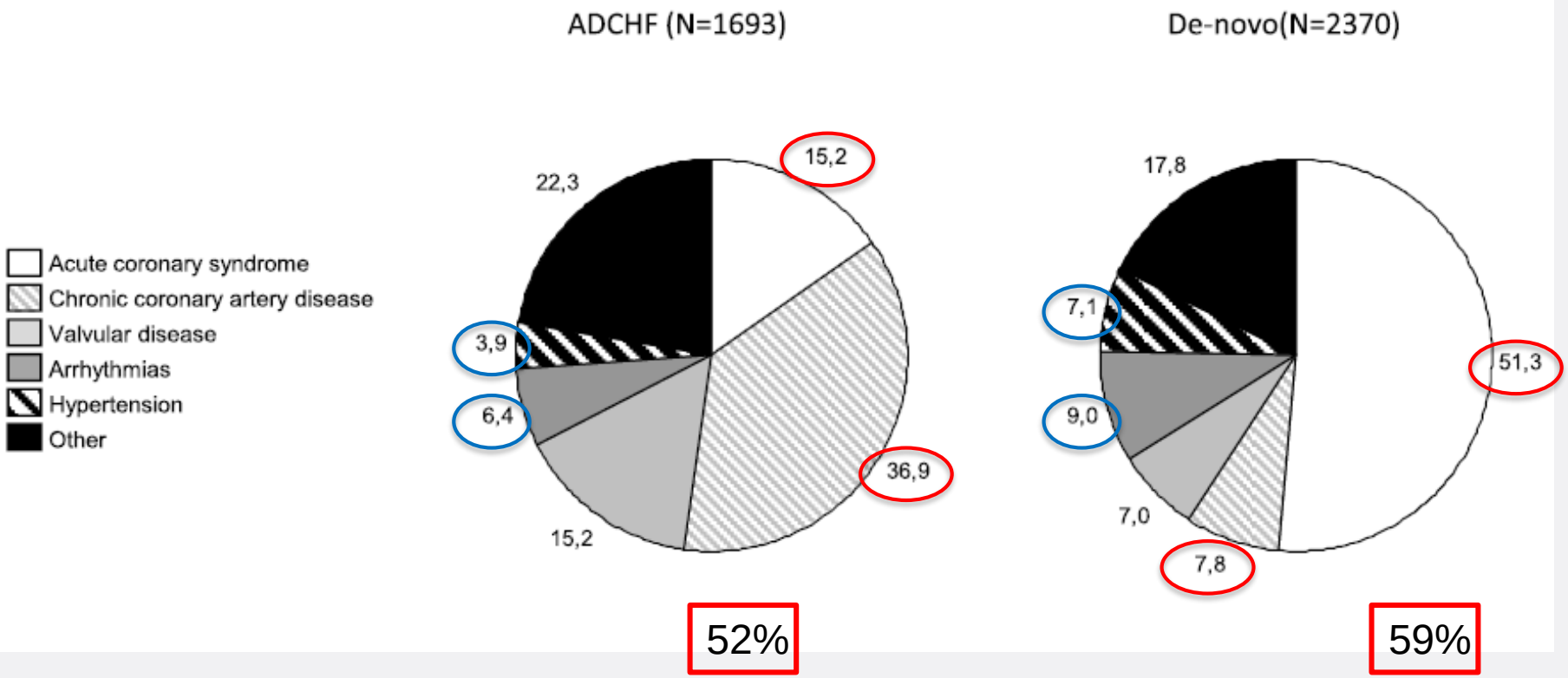


88% had history of CHF
12% had no previous history of CHF

Mebazaa et al. JAMA 2007;297,1883-1891

Inotropes and Ischemic Aetiology

Baseline characteristics and hospital mortality in the Acute Heart Failure Database (AHEAD) Main registry



Spinar J et al. Critical Care 2011

Inotropic agents and vasodilator strategies for acute myocardial infarction complicated by cardiogenic shock or low cardiac output syndrome (Review)

Main results

Four eligible, very small studies were identified from a total of 4065 references. Three trials with high overall risk of bias compared levosimendan to standard treatment (enoximone or dobutamine) or placebo. Data from a total of 63 participants were included in our comparisons, 31 were treated with levosimendan and 32 served as controls. Levosimendan showed an imprecise survival benefit in comparison with enoximone based on a very small trial with 32 participants (HR 0.33; 95% CI 0.11 to 0.97). Results from the other similarly small trials were too imprecise to provide any meaningful information about the effect of levosimendan in comparison with dobutamine or placebo. Only small differences in haemodynamics, length of hospital stay and the frequency of major adverse cardiac events or adverse events overall were found between study groups.

Only one small randomised controlled trial with three participants was found for vasodilator strategies (nitric oxide gas versus placebo) in AMI complicated by CS or LCOS. This study was too small to draw any conclusions on the effects on our key outcomes.

Authors' conclusions

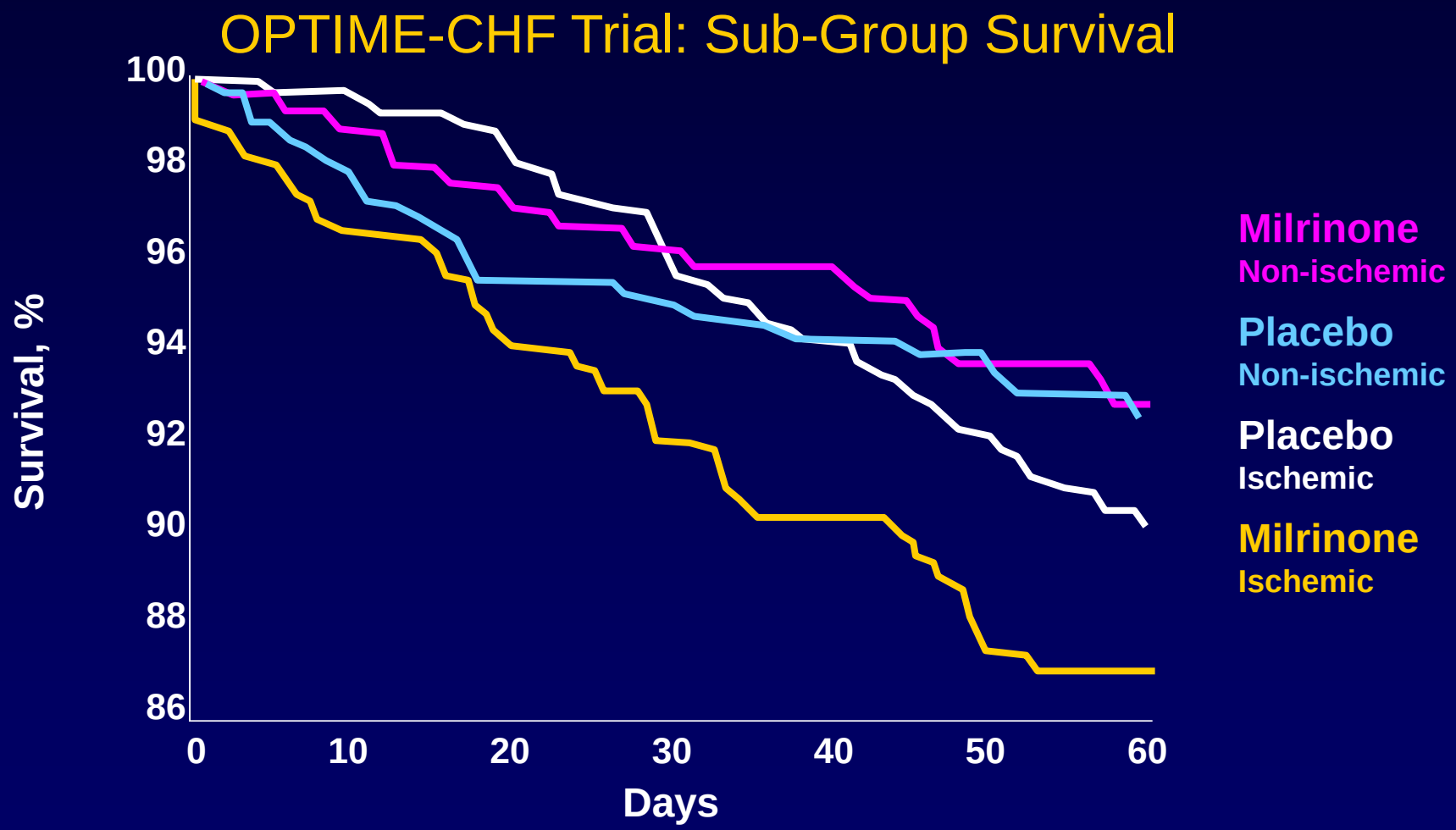
At present there are no robust and convincing data to support a distinct inotropic or vasodilator drug based therapy as a superior solution to reduce mortality in haemodynamically unstable patients with CS or low cardiac output complicating AMI.

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2014, Issue 1

http://www.thecochranelibrary.com

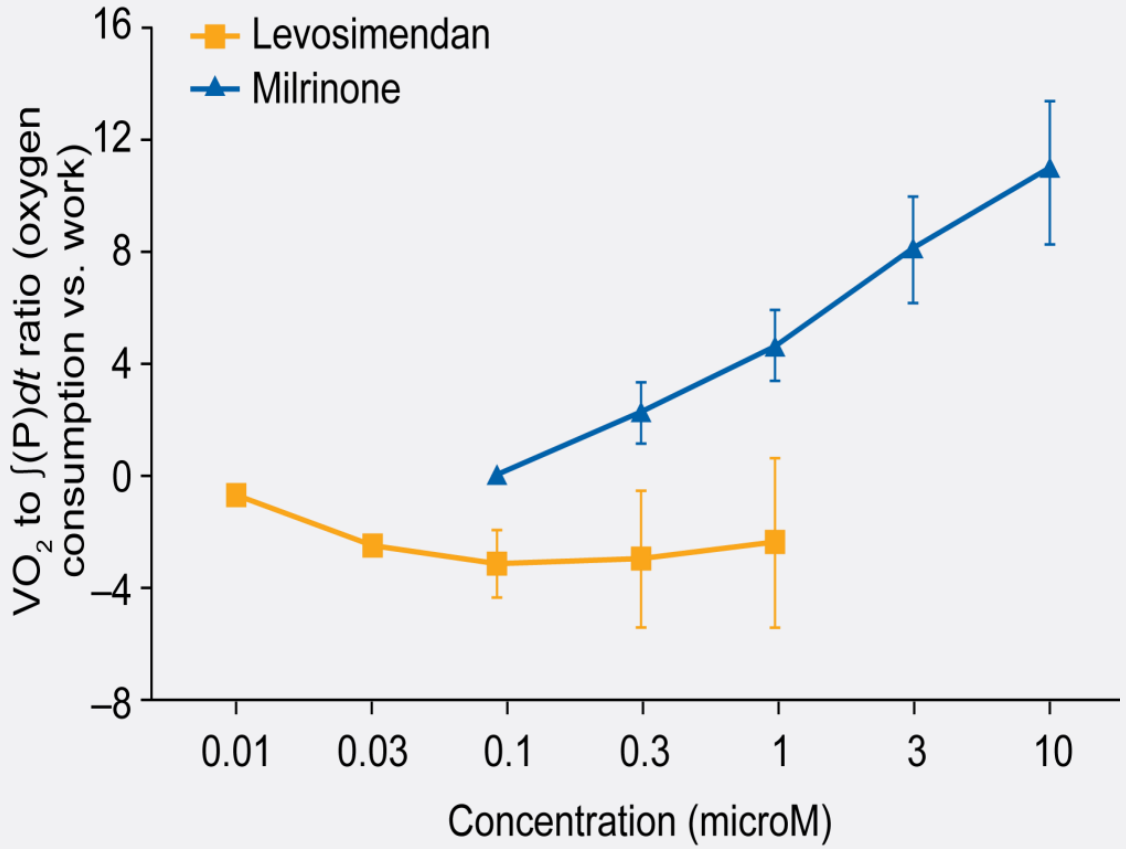
Effect of Milrinone on Survival

Kaplan-Meier Survival Curves to 60 Days by Heart Failure Etiology and Treatment Assignment



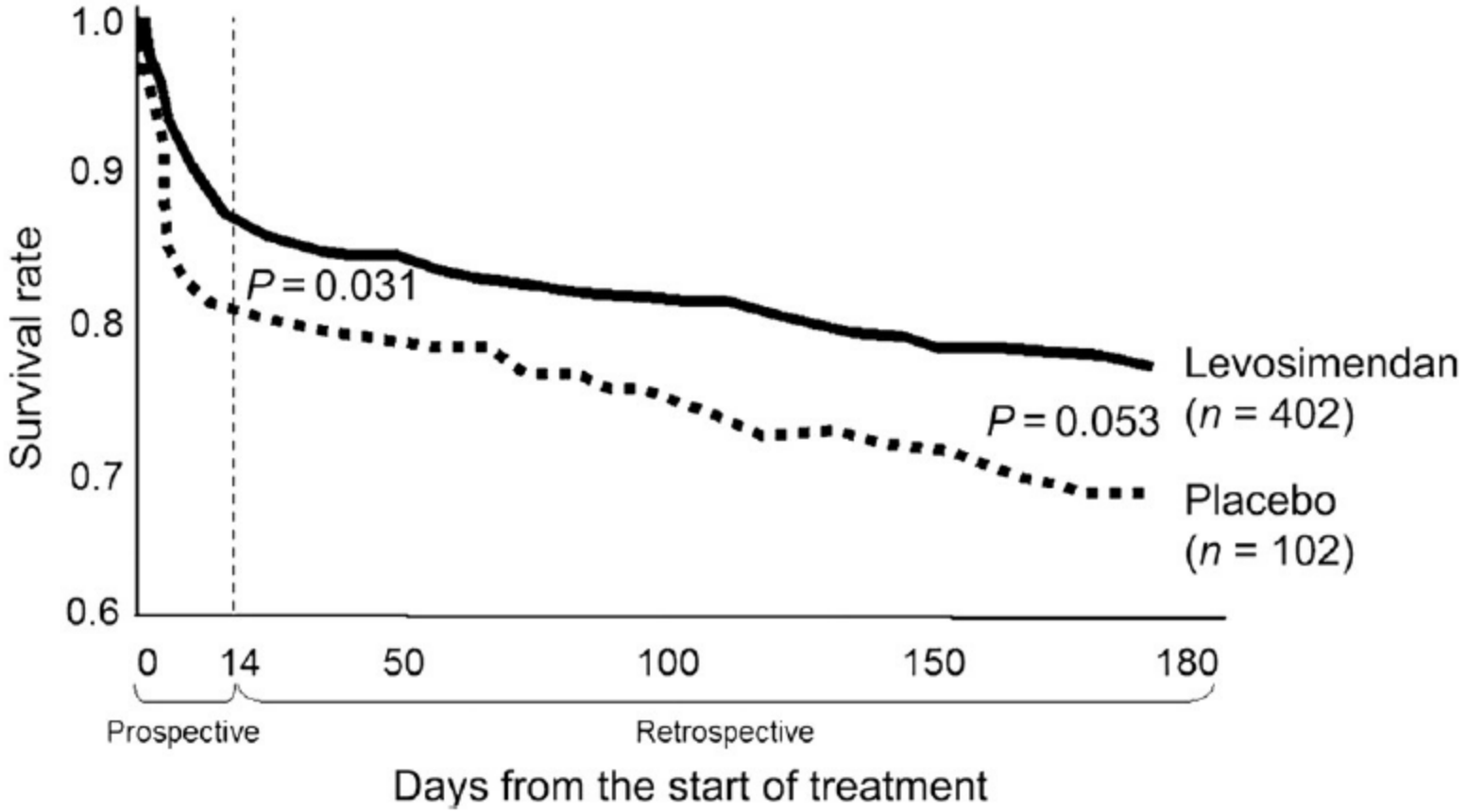
Felker GM, et al. *J Am Coll Cardiol*. 2003;41:997-1003.
Cuffe MS, et al. *JAMA*. 2002;287:1541-1547.

Effects of levosimendan and milrinone on oxygen consumption in isolated guinea-pig heart.



Kaheinen P et al. J Cardiovasc Pharmacol 2004

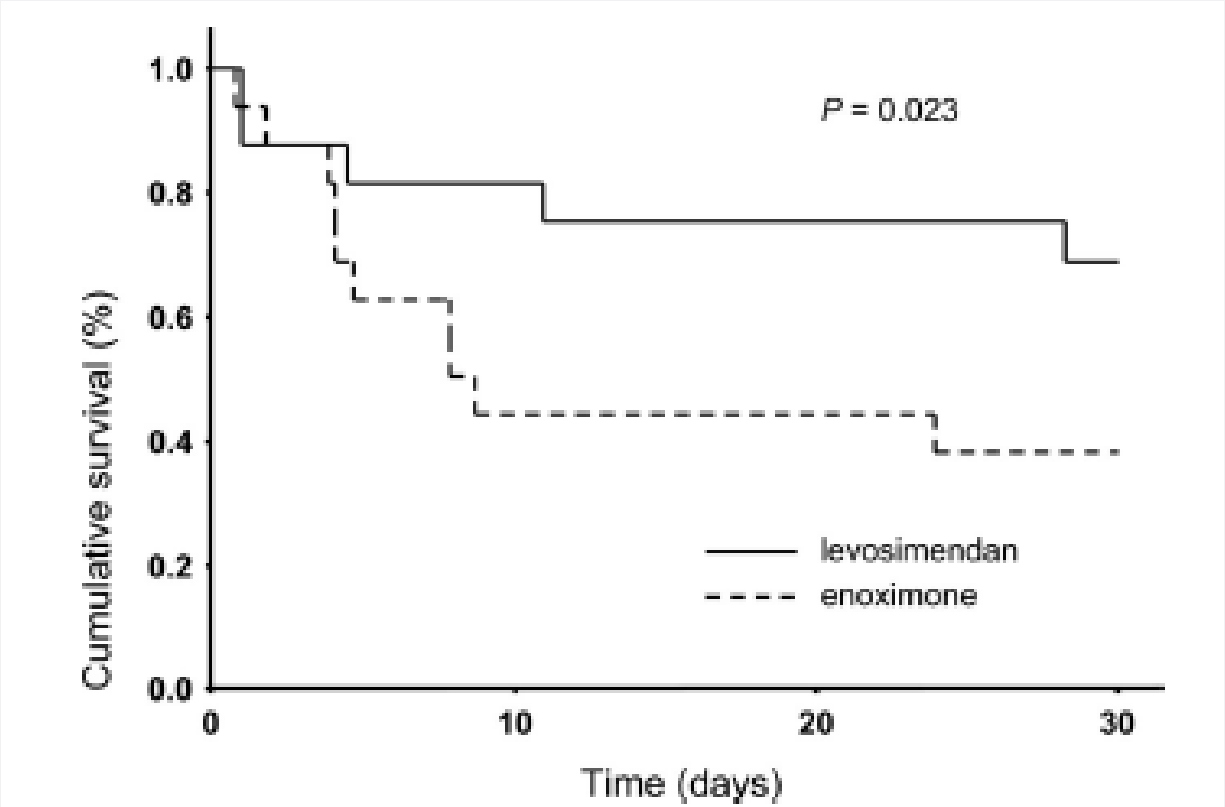
Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN).



Moiseyev VS et al. Eur Heart J 2002

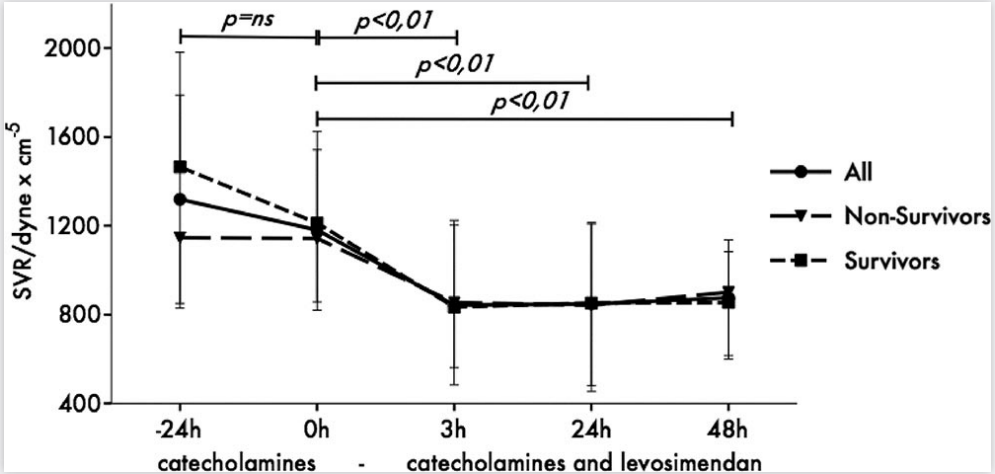
Levosimendan is superior to enoximone in refractory cardiogenic shock complicating acute myocardial infarction

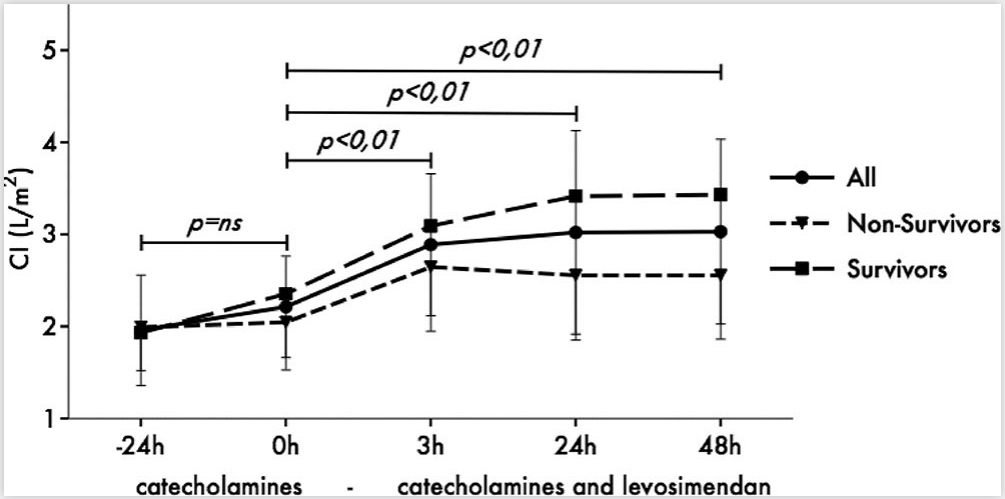
32 pts with refractory cardiogenic shock for >2 hrs requiring additional therapy.



Fuhrmann JT, et al. Crit Care Med 2008

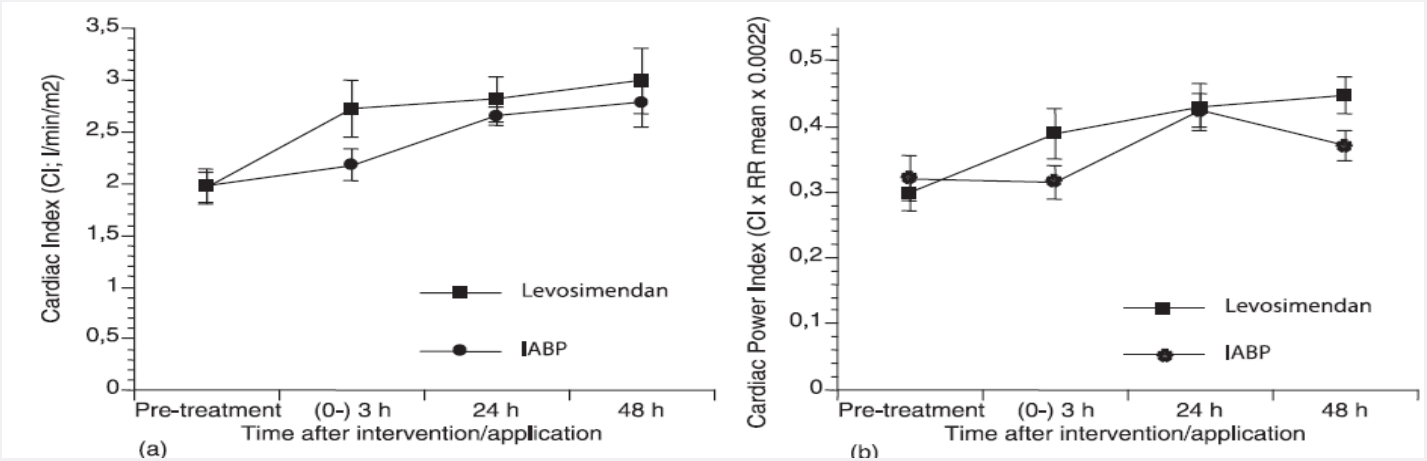
Hemodynamic improvement following levosimendan treatment in patients with acute myocardial infarction and cardiogenic shock*

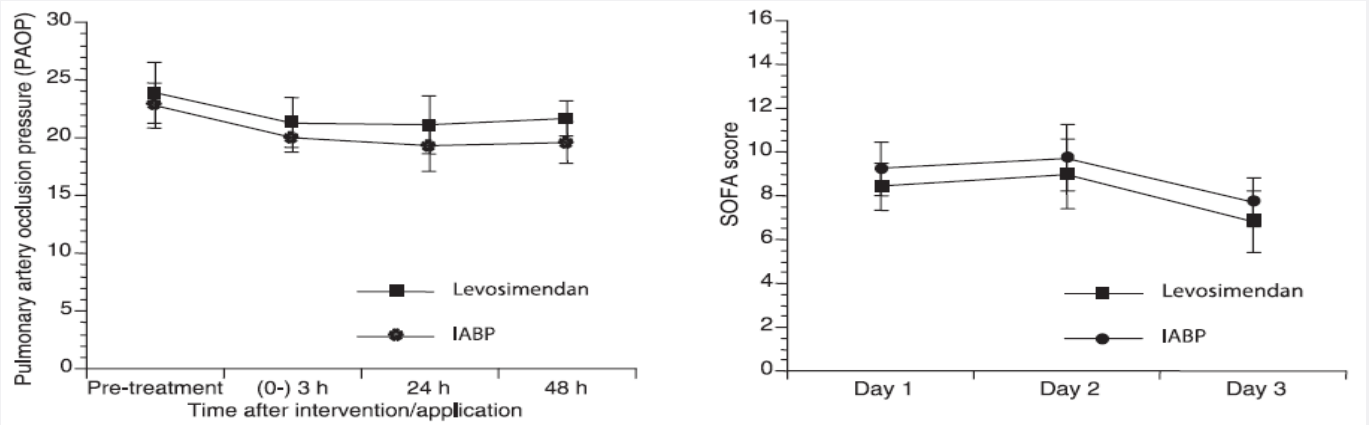




Russ MA et al. Crit Care Med 2007

Early and sustained haemodynamic improvement with levosimendan compared to intraaortic balloon counterpulsation (IABP) in cardiogenic shock complicating acute myocardial infarction.





Christoph A et al. Acute Card Care 2008

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Review

The role of levosimendan in acute heart failure complicating acute coronary syndrome: A review and expert consensus opinion

Markku S. Nieminen [a,*], Michael Buerke [b], Alain Cohen-Solál [c], Susana Costa [d], István Édes [e], Alexey Erlikh [f], Fatima Franco [d], Charles Gibson [g], Vojka Gorjup [h], Fabio Guarracino [i], Finn Gustafsson [j], Veli-Pekka Harjola [k], Trygve Husebye [l], Kristjan Karason [m], Igor Katsytadze [n], Sundeep Kaul [o], Matti Kivikko [p], Giancarlo Marenzi [q], Josep Masip [r], Simon Matskeplishvili [s], Alexandre Mebazaa [t], Jacob E. Møller [u], Jadwiga Nessler [v], Bohdan Nessler [w], Argyrios Ntalianis [x], Fabrizio Oliva [y], Emel Pichler-Cetin [z], Pentti Põder [aa], Alejandro Recio-Mayoral [ab], Steffen Rex [ac], Richard Rokyta [ad], Ruth H. Strasser [ae], Endre Zima [af], Piero Pollesello [p]

Medical treatment options in patients with AHF/CS and ACS after initial therapies[a].

Killip class	II, rales, pulmonary congestion		III, acute pulmonary oedema	IV, hypotension or CS
AHF/CS, segmentation by SBP	SBP > 110 mm Hg	85 < SBP < 110 mm Hg, worsening of HF	85 < SBP < 110 mm Hg, decreasing	SBP <; 85 mm Hg, evidence of peripheral vasoconstriction
Loop diuretic (e.g. furosemide i.v.)	+	+	+	+
β-blocker	maintain	reduce or withdraw according to patient status[b]	withdraw[b]	withdraw
Vasodilator (e.g. nitrate)	+	+ initially	+ initially	−
Inotrope i.v. (e.g. dobutamine)	−	+ initially	+ in case of poor response to standard therapy	+ initially
Vasopressor i.v. (e.g. norepinephrine)	−	− not initially	− not initially	+ (aiming for SBP > 90 mm Hg, with inotrope or inodilator)
Inodilator i.v. levosimendan	−/+ (when β-blocker is used and urinary output is insufficient after diuretics)	−/+ (when β-blocker is used and urinary output is insufficient after diuretics)	+ (when SBP > 90 mm Hg, if hypotensive response, consider filling or combining vasopressor)	+ (with vasopressor)
ECMO, LVAD, (IABP[c])	−	−	−	+ (with CI < 1.8 L/min and not responding to medical treatment)

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International Journal of Cardiology

www.elsevier.com/locate/ijcard

Levosimendan for the treatment of acute severe heart failure: A meta-analysis of randomised controlled trials

Anthony Delaney [a,b,*], Celia Bradford [a,b], John McCaffrey [a], Sean M. Bagshaw [c,d], Richard Lee [a,b]

Results: We identified 19 RCTs enrolling 3650 patients, only two studies fulfilled all of the validity criteria. There was a non-significant reduction in mortality with levosimendan compared with placebo (OR 0.83, 95%CI, 0.62–1.10, $p=0.20$). Levosimendan was associated with reduced mortality compared to dobutamine (OR 0.75, 95%CI, 0.61–0.92, $p=0.005$). Levosimendan was associated with improvements in haemodynamic parameters when compared to either placebo or dobutamine.

Conclusions: Levosimendan improved haemodynamic parameters when compared with placebo, without showing evidence of survival benefit. Levosimendan improved both haemodynamics and survival when compared with dobutamine.

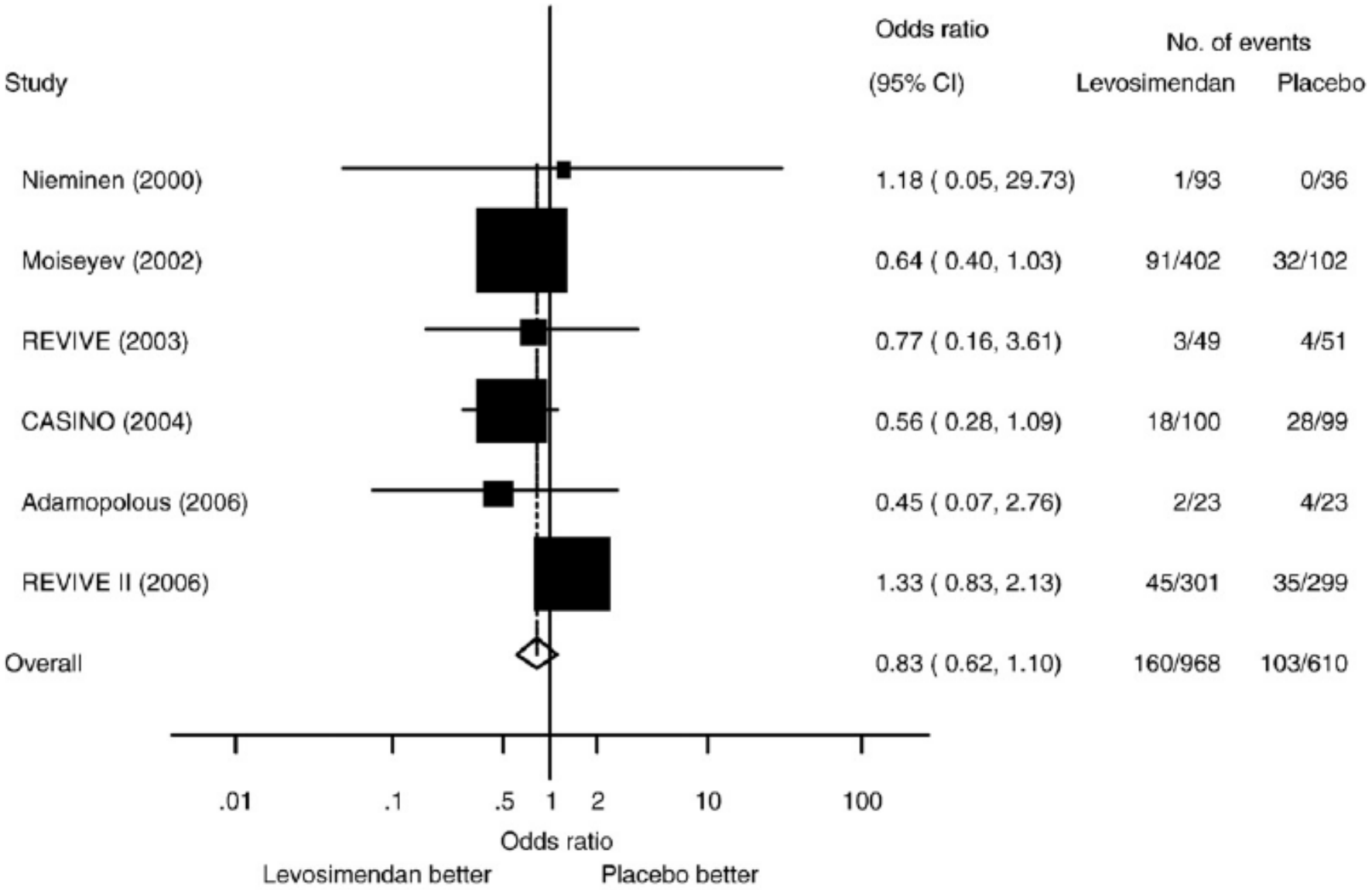


Fig. 2. The effect of levosimendan compared to placebo on mortality.

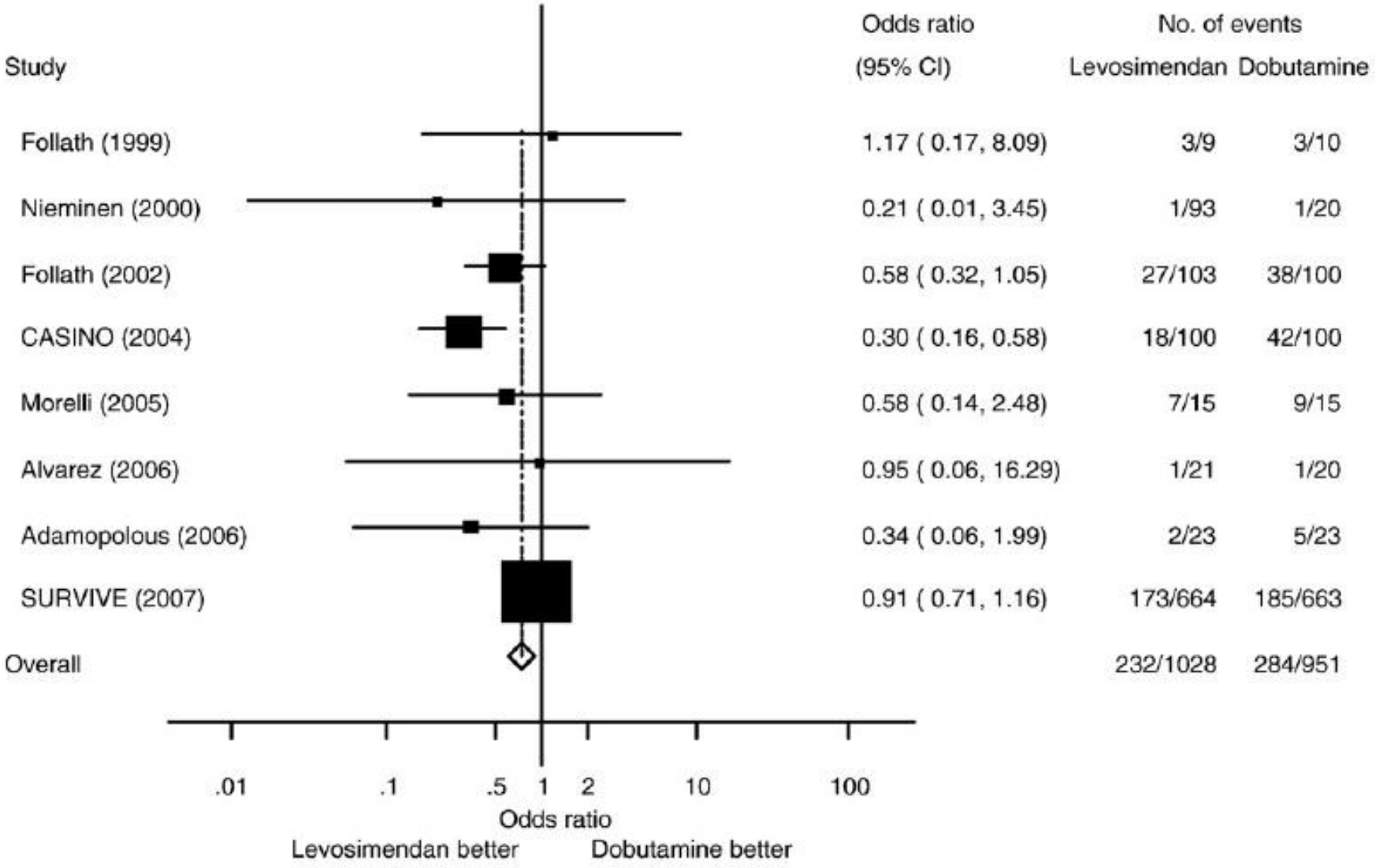


Fig. 3. The effect of levosimendan compared to dobutamine on mortality.

Levosimendan Treatment for Heart Failure: A Systematic Review and Meta-Analysis

Bojun Gong, MD, Zicheng Li, PhD, and Philip Ching Yat Wong, PhD

Study or Subgroup	Levosimendan Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Adamopoulos,2006	2	23	5	23	1.0%	0.40 [0.09, 1.86]
Bergh,2010	1	29	1	31	0.2%	1.07 [0.07, 16.31]
Bonios,2012	4	21	8	21	1.6%	0.50 [0.18, 1.41]
Dominguez-Rodriguez,2008	3	11	1	11	0.2%	3.00 [0.37, 24.58]
Farmakis,2010	5	69	3	29	0.9%	0.70 [0.18, 2.74]
Flevari,2006	3	30	1	15	0.3%	1.50 [0.17, 13.23]
Follath,2002	27	103	38	100	7.9%	0.69 [0.46, 1.04]
Levin,2008	6	69	19	68	3.9%	0.31 [0.13, 0.73]
Mavrogeni,2007	2	25	8	25	1.6%	0.25 [0.06, 1.06]
Mebazaa,2007	173	660	185	660	37.7%	0.94 [0.78, 1.12]
Mebazaa,2009	79	660	91	660	18.6%	0.87 [0.66, 1.15]
Nieminen,2000	1	23	1	20	0.2%	0.87 [0.06, 13.02]
Packer,2013	54	344	61	342	12.5%	0.88 [0.63, 1.23]
Qarawani,2013	2	42	5	22	1.3%	0.21 [0.04, 0.99]
Tosal,2013	45	219	75	334	12.1%	0.92 [0.66, 1.27]
Tritapepe,2009	0	52	0	50		Not estimable
Total (95% CI)		**2380**		**2411**	**100.0%**	**0.84 [0.75, 0.94]**
Total events	407		502			

Heterogeneity: Chi² = 17.26, df = 14 (P = 0.24); I² = 19%

Test for overall effect: Z = 2.94 (P = 0.003)

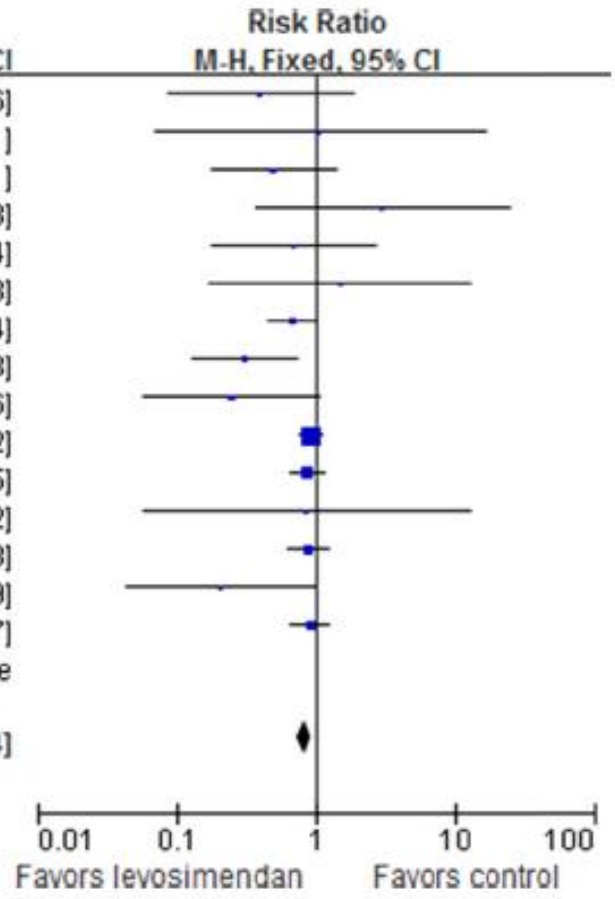
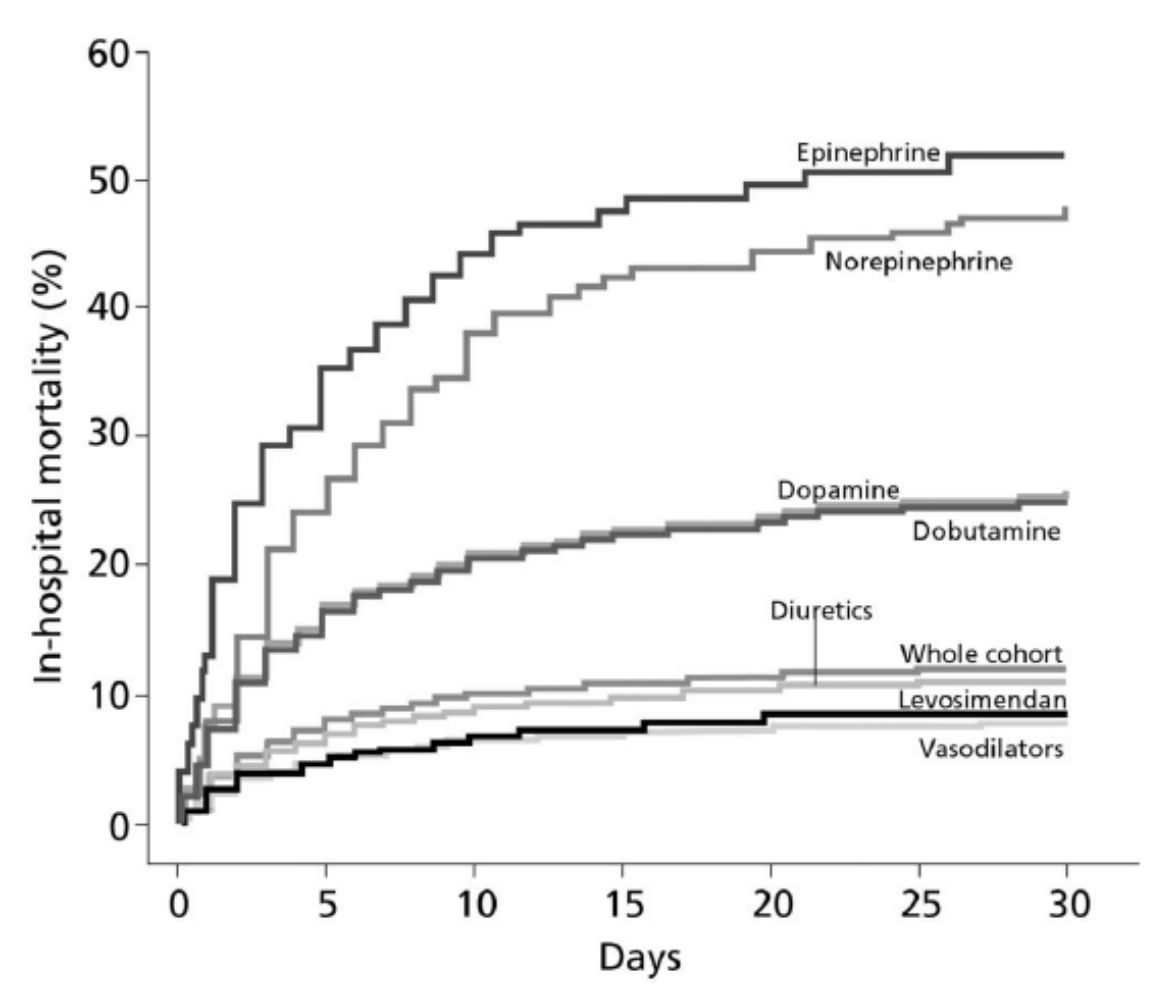


Fig 2. Total mortality during levosimendan treatment.

ALARM-HF Registry



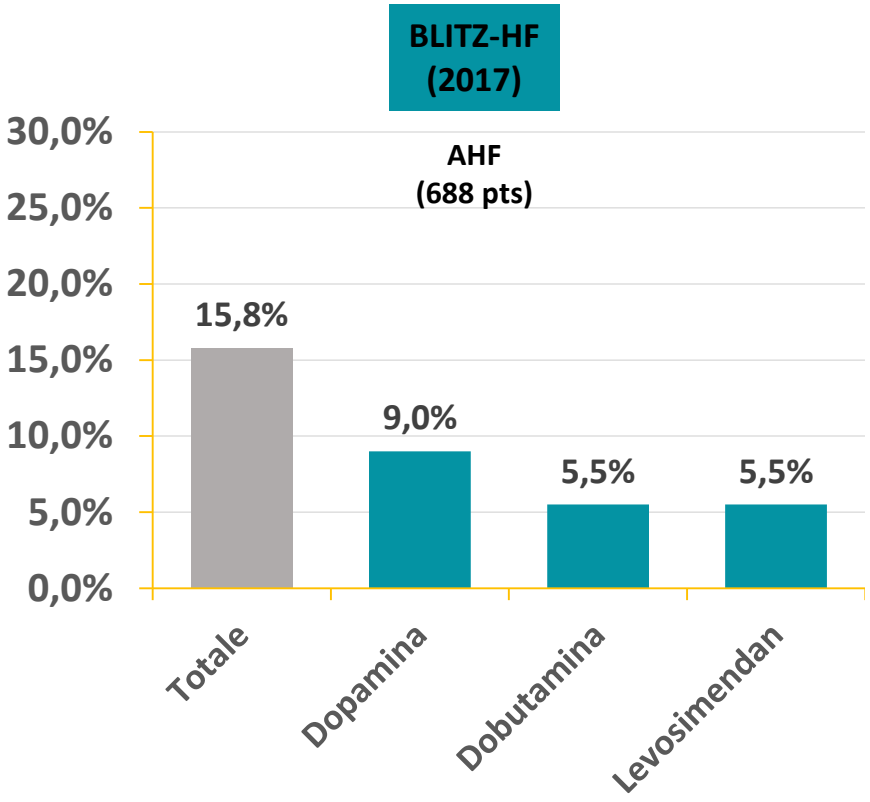
Mebazaa A ***Intensive Care Med 2011***

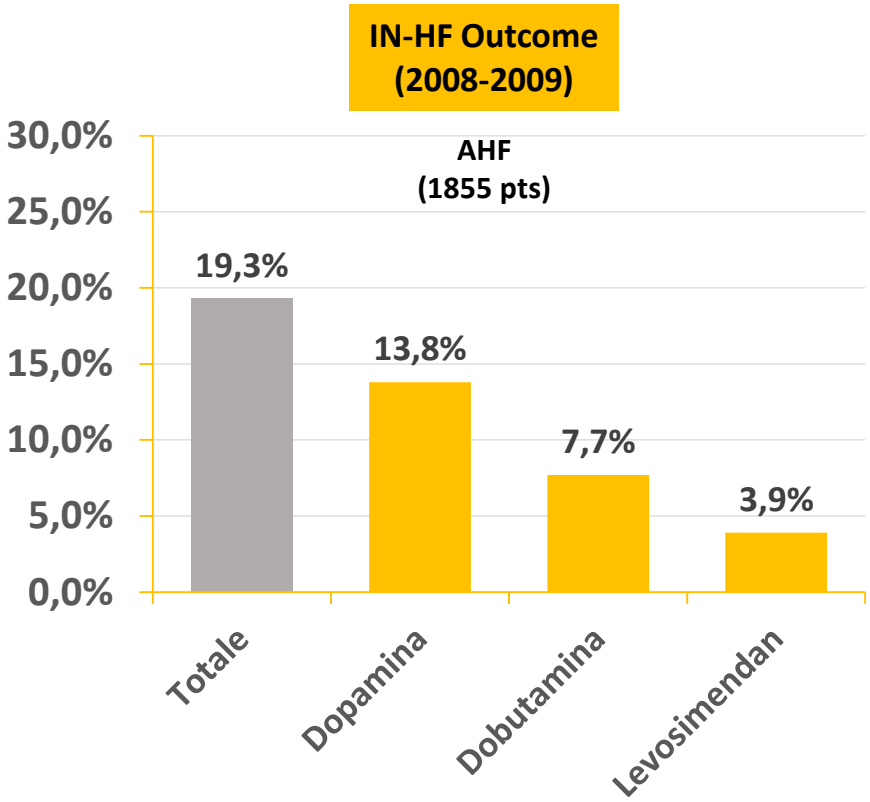
2016 ESC Guidelines

EUROPEAN SOCIETY OF CARDIOLOGY

Inotropic agents – dobutamine, dopamine, levosimendan, phosphodiesterase III (PDE III) inhibitors			
Short-term, i.v. infusion of inotropic agents may be considered in patients with hypotension (SBP <90 mmHg) and/or signs/symptoms of hypoperfusion despite adequate filling status, to increase cardiac output, increase blood pressure, improve peripheral perfusion and maintain end-organ function.	IIb	C	
An intravenous infusion of levosimendan or a PDE III inhibitor may be considered to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypotension with subsequent hypoperfusion.	IIb	C	
Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.	III	A	556, 557
Vasopressors			
A vasopressor (norepinephrine preferably) may be considered in patients who have cardiogenic shock, despite treatment with another inotrope, to increase blood pressure and vital organ perfusion.	IIb	B	558
It is recommended to monitor ECG and blood pressure when using inotropic agents and vasopressors, as they can cause arrhythmia, myocardial ischaemia, and in the case of levosimendan and PDE III inhibitors also hypotension.	I	C	540, 559–563
In such cases intra-arterial blood pressure measurement may be considered.	IIb	C	

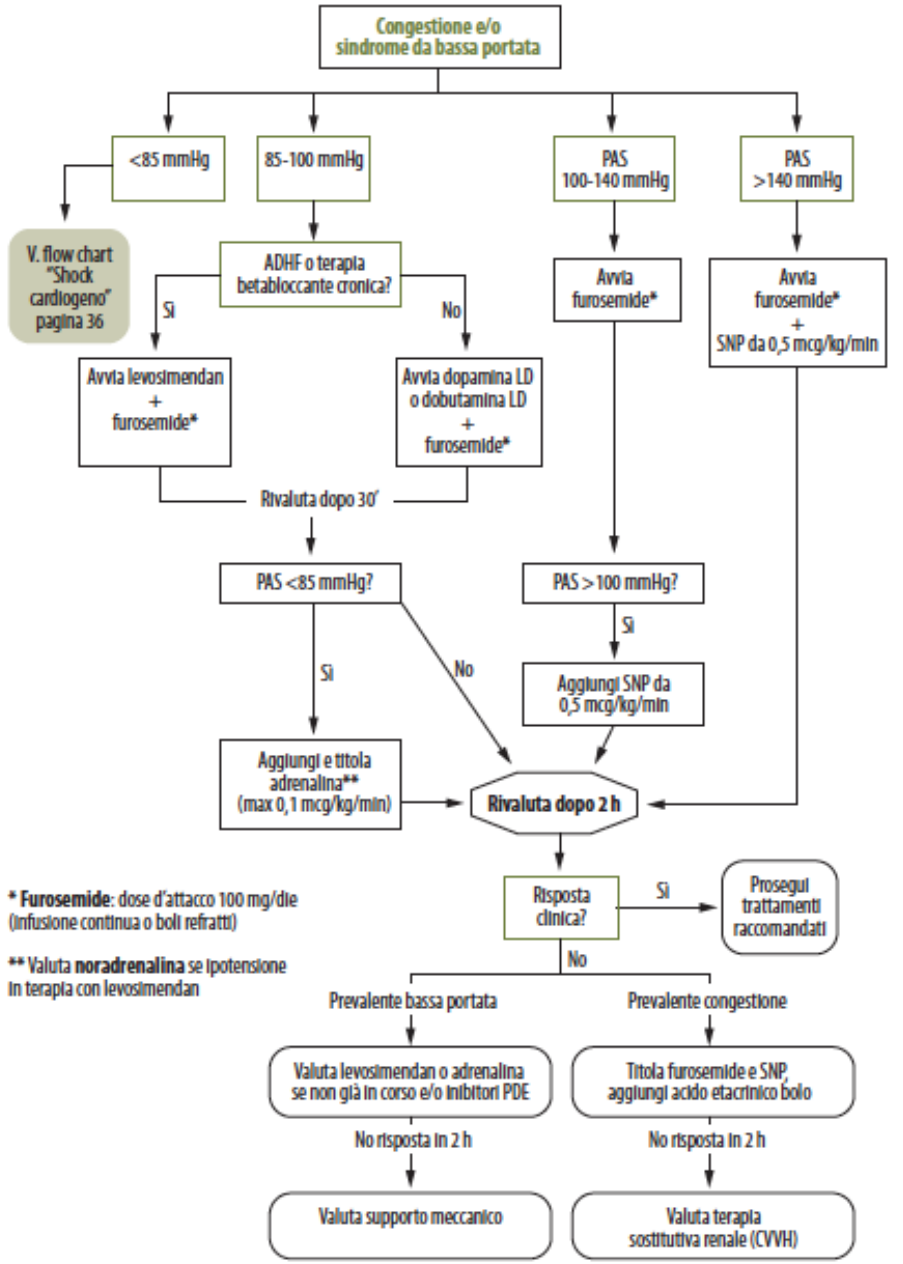
INOTROPI



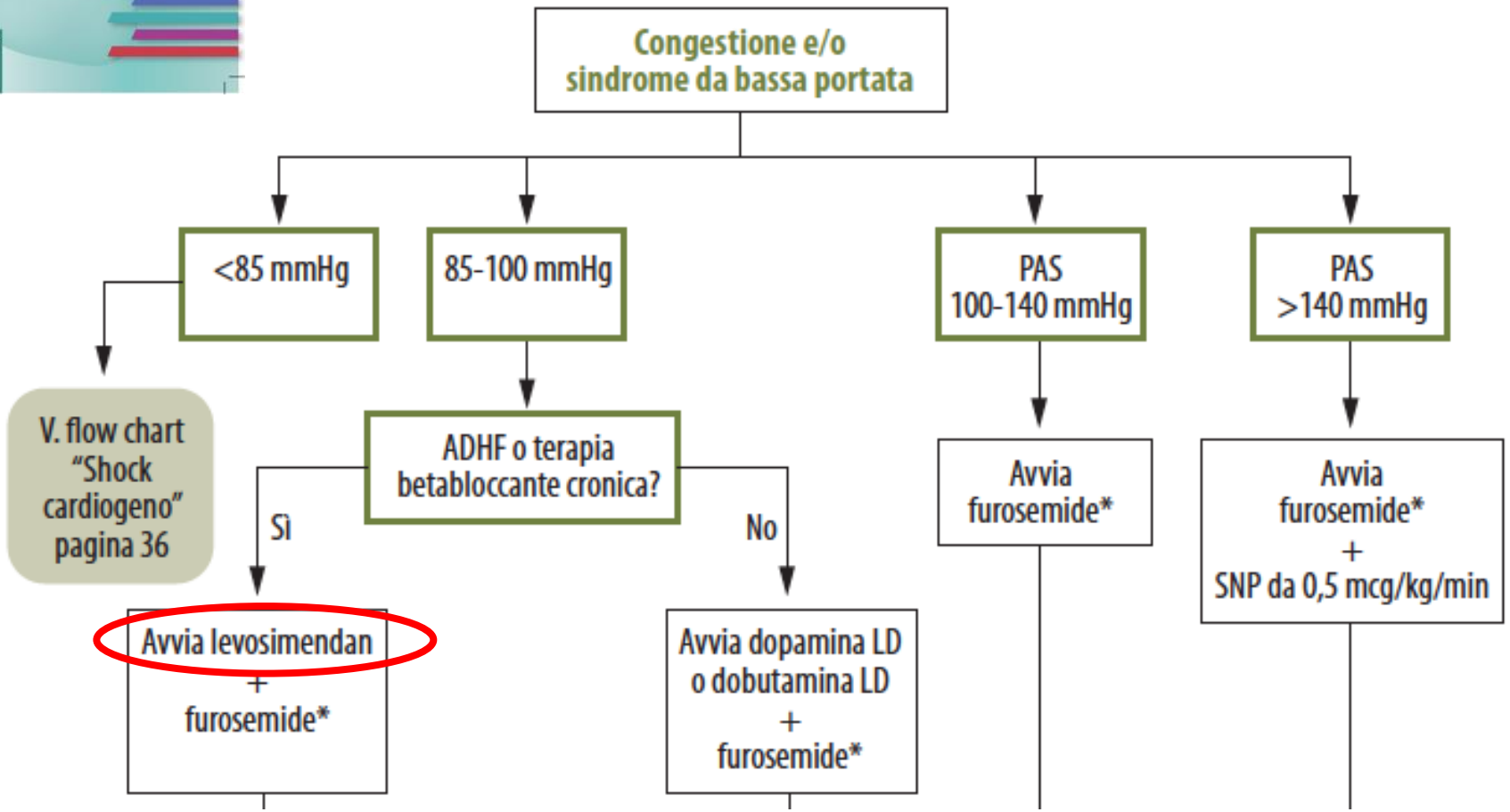


Mortara A, Oliva F et al. J Heart Lung Transplant 2014; 33: 1056-65.

INSUFFICIENZA CARDIACA ACUTA



INSUFFICIENZA CARDIACA ACUTA



Rivaluta dopo 30'

PAS <85 mmHg?

Sì

No

Aggiungi e titola adrenalina** (max 0,1 mcg/kg/min)

PAS >100 mmHg?

Sì

Aggiungi SNP da 0,5 mcg/kg/min

Rivaluta dopo 2 h

Risposta clinica?

Sì

Prosegui trattamenti raccomandati

No

Prevalente bassa portata

Valuta levosimendan o adrenalina se non già in corso e/o inibitori PDE

No risposta in 2 h

Valuta supporto meccanico

Prevalente congestione

Titola furosemide e SNP, aggiungi acido etacrinico bolo

No risposta in 2 h

Valuta terapia sostitutiva renale (CVVH)

* **Furosemide**: dose d'attacco 100 mg/die (infusione continua o boli refratti)

** Valuta **noradrenalina** se ipotensione in terapia con levosimendan

Sistema Socio Sanitario
Ospedale Niguarda
Regione Lombardia

Levosimendan in Acute and Advanced Heart Failure: An Appraisal of the Clinical Database and Evaluation of Its Therapeutic Applications

Expected effects of the use of levosimendan in AHF

1. Improvement of hemodynamics and tissue perfusion;
2. Relief of symptoms of congestion and fatigue.

Experience from recent large randomized trials indicates that levosimendan can be considered safe in high-risk patients who have been exposed to extensive previous polypharmacy, including beta-blockers.

Altenberger J ***J Cardiovasc Pharmacol 2018***

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LEVOSIMENDAN

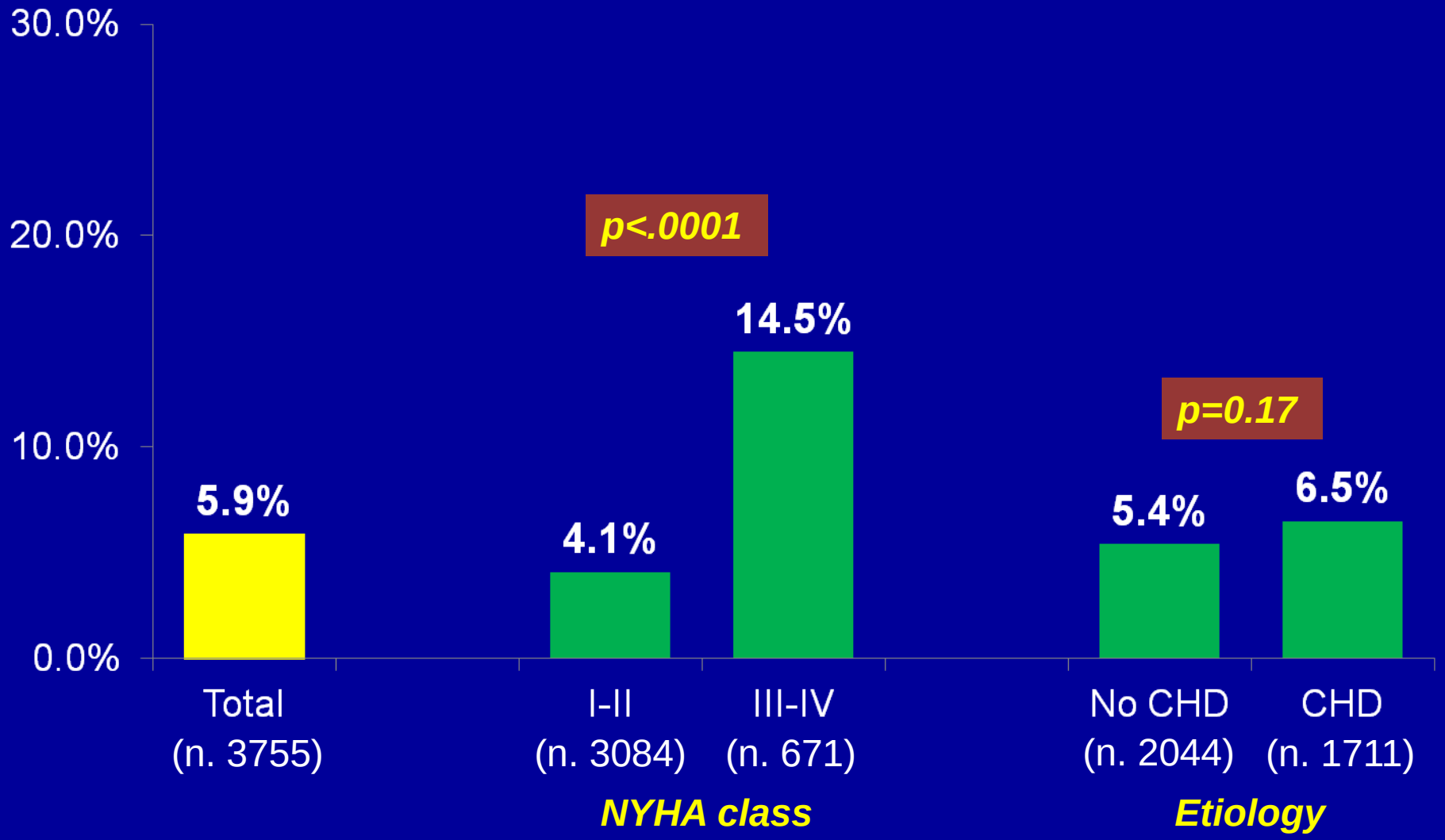
- INSUFFICIENZA CARDIACA Cronica Avanzata -

Advanced HF
Red Flags

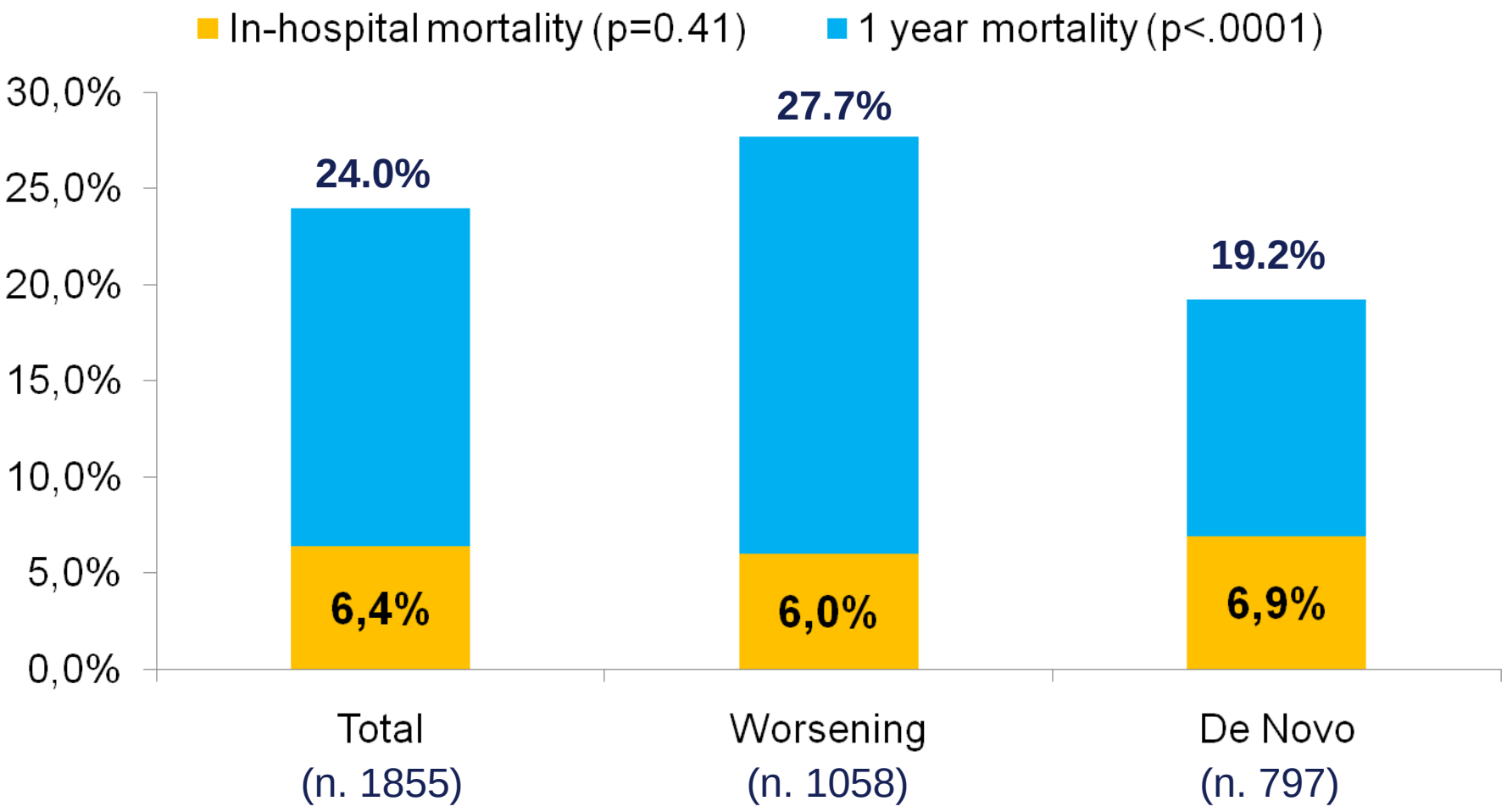
- Intolerance of beta-blockers and/or ACE I/ARB
- High diuretic requirement
- Persistence of elevated BNP/NT proBNP
- Recurrent hospitalizations
- Need for inotropes
- Hyponatremia
- Progressive renal insufficiency

F.Oliva

Chronic HF: All-cause mortality *by NYHA and etiology*

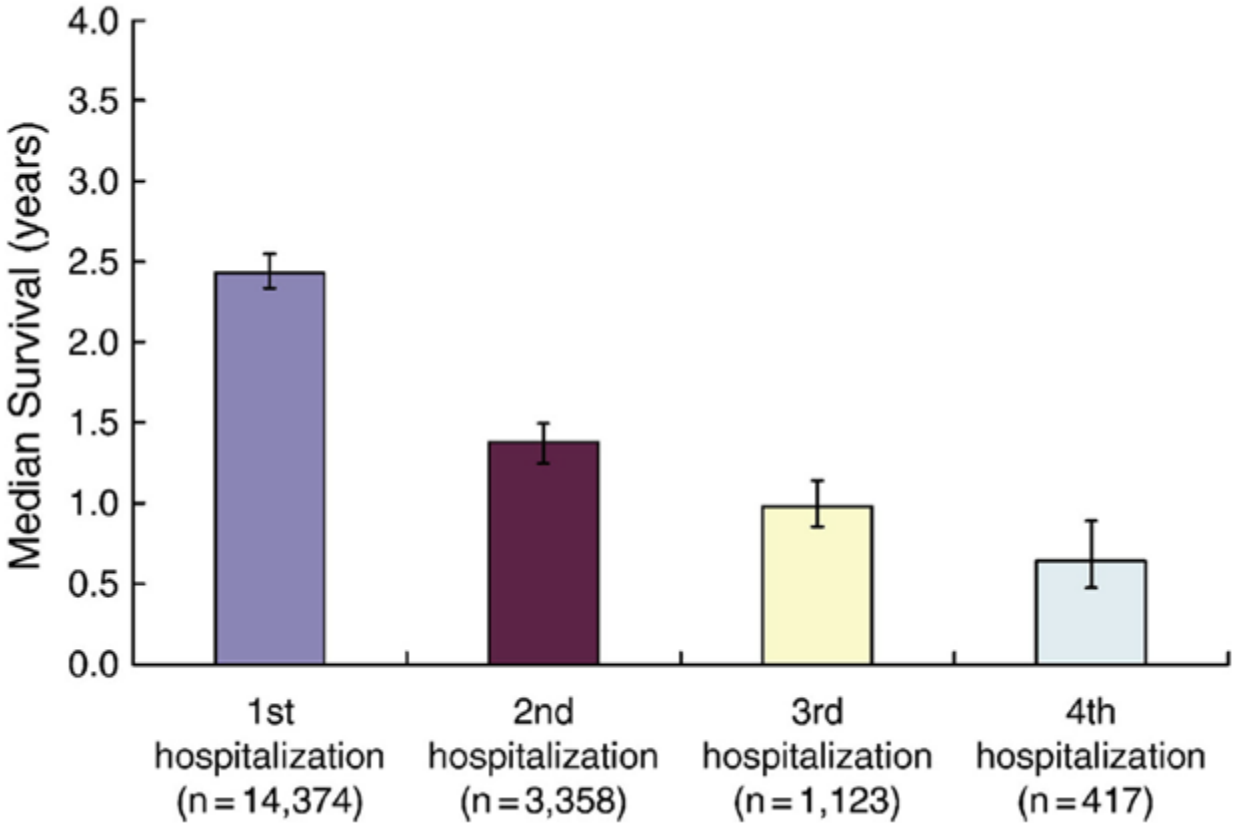


Acute HF: all-cause mortality



Oliva F, Mortara A, Cacciatore G et al EJHF 2012

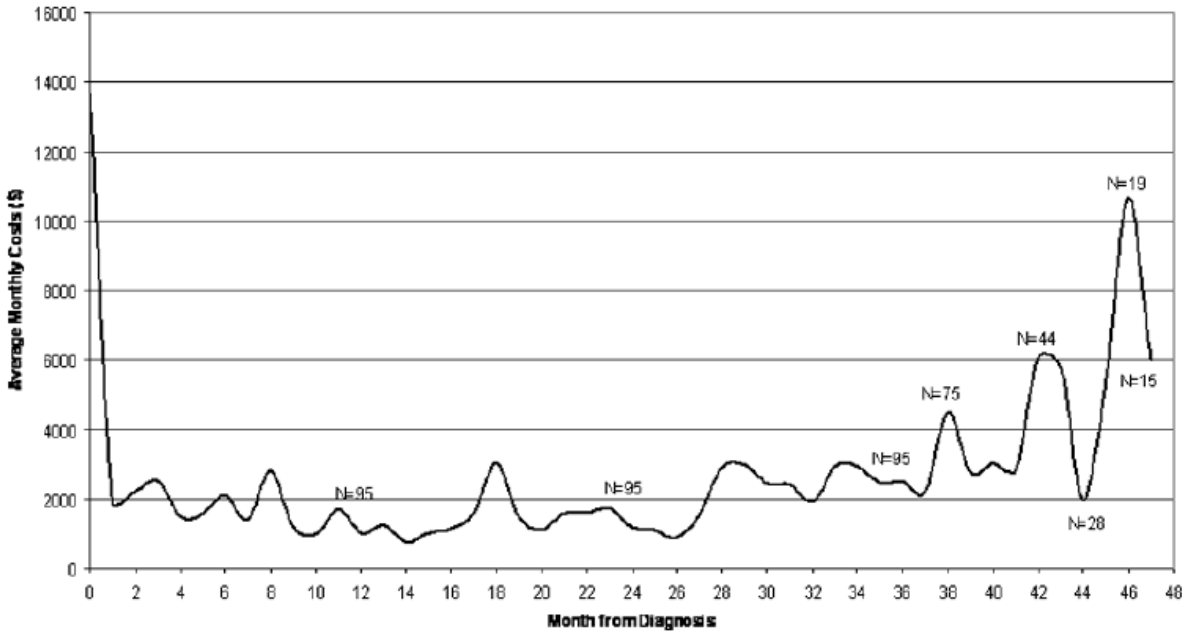
Recurrent hospitalisations – impact on outcome



Setoguchi S, et al. 2007;154(2):260-6

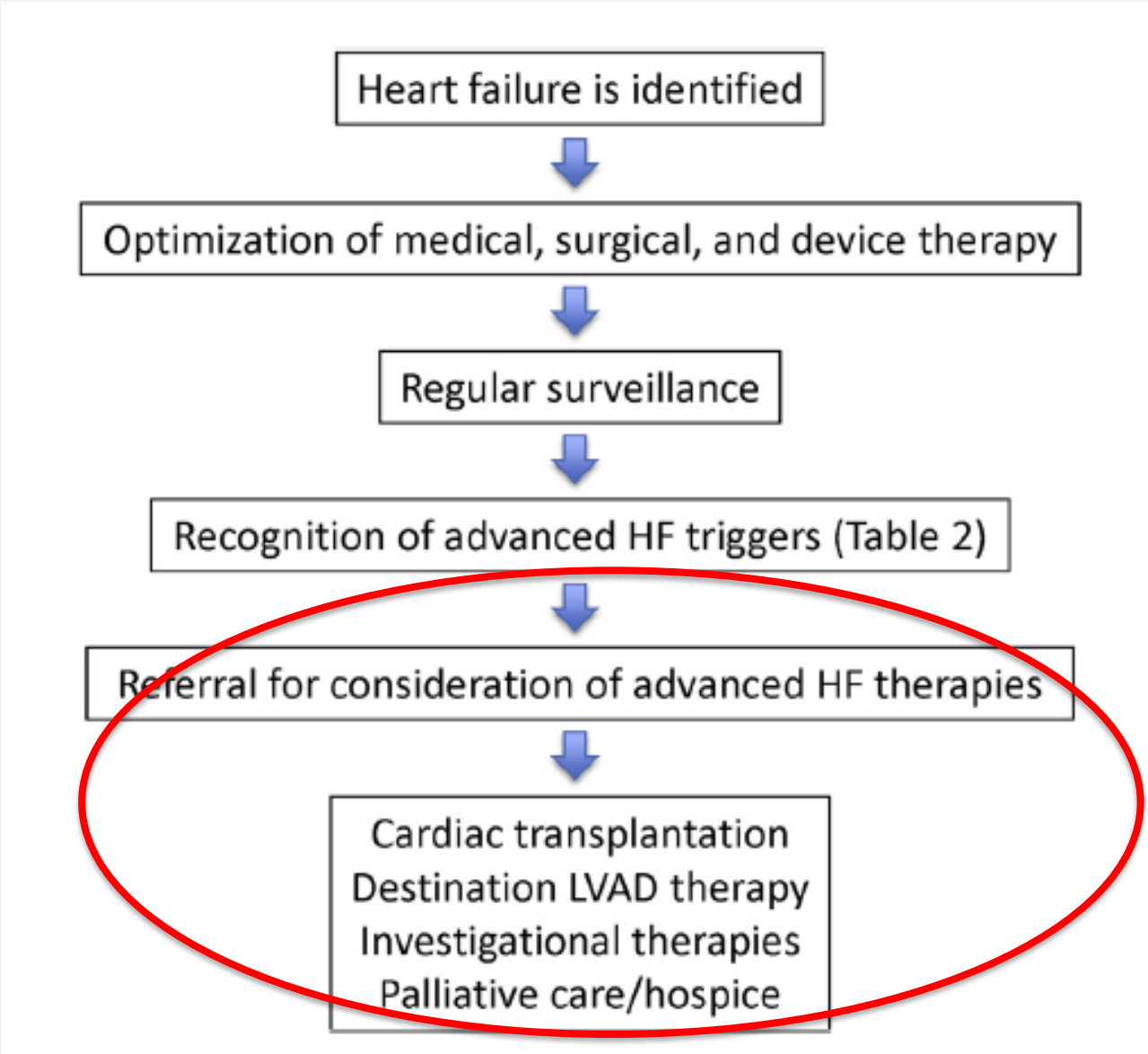
Economic burden

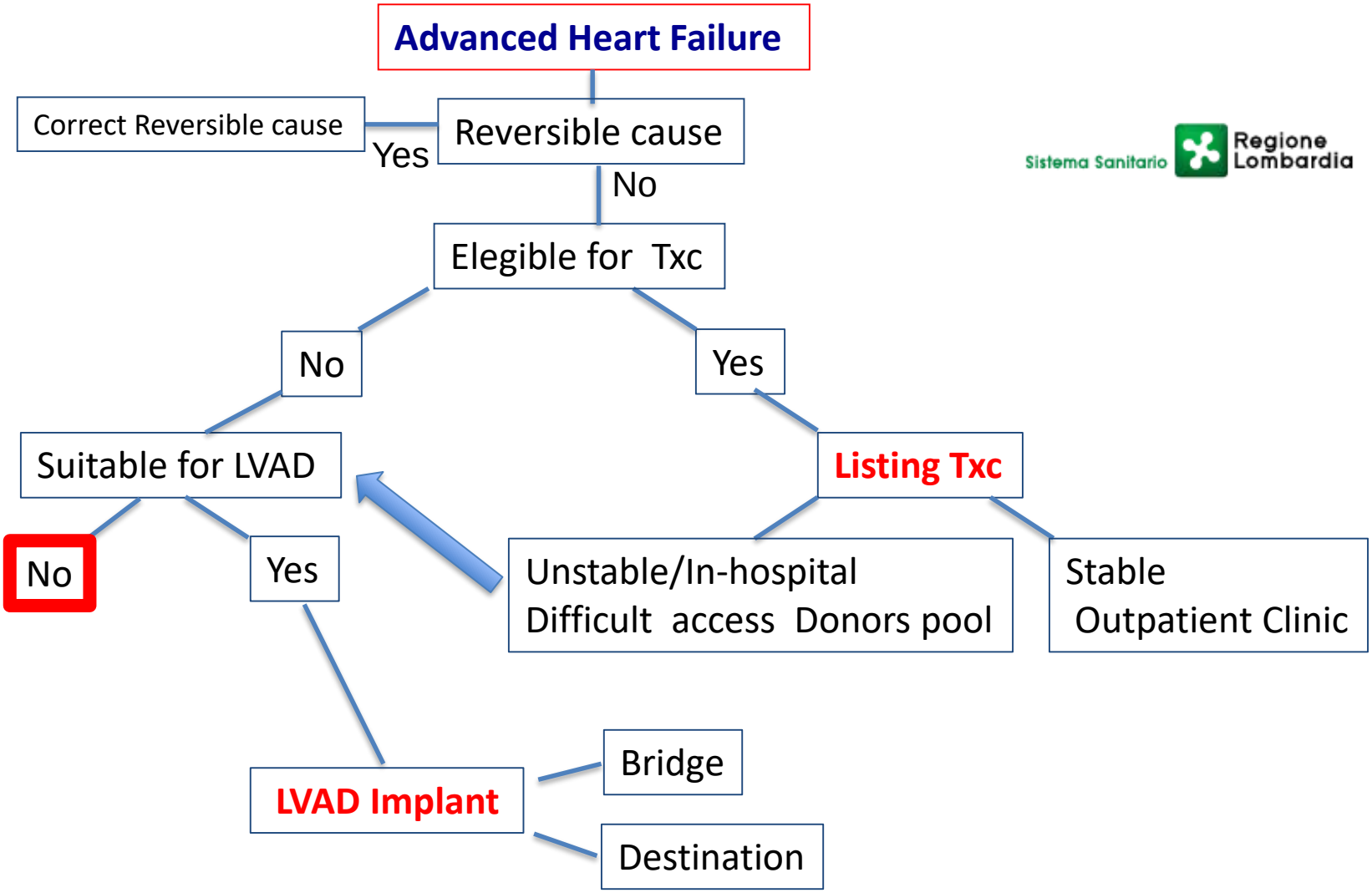
- Distribution of monthly medical costs from the time of HF diagnosis until death for those surviving 36–48 months after diagnosis



High costs at diagnosing phase and near end of life

Dunlay MS et al, Circ Cardiovasc Qual Outcomes. 2011;4(1):68–75

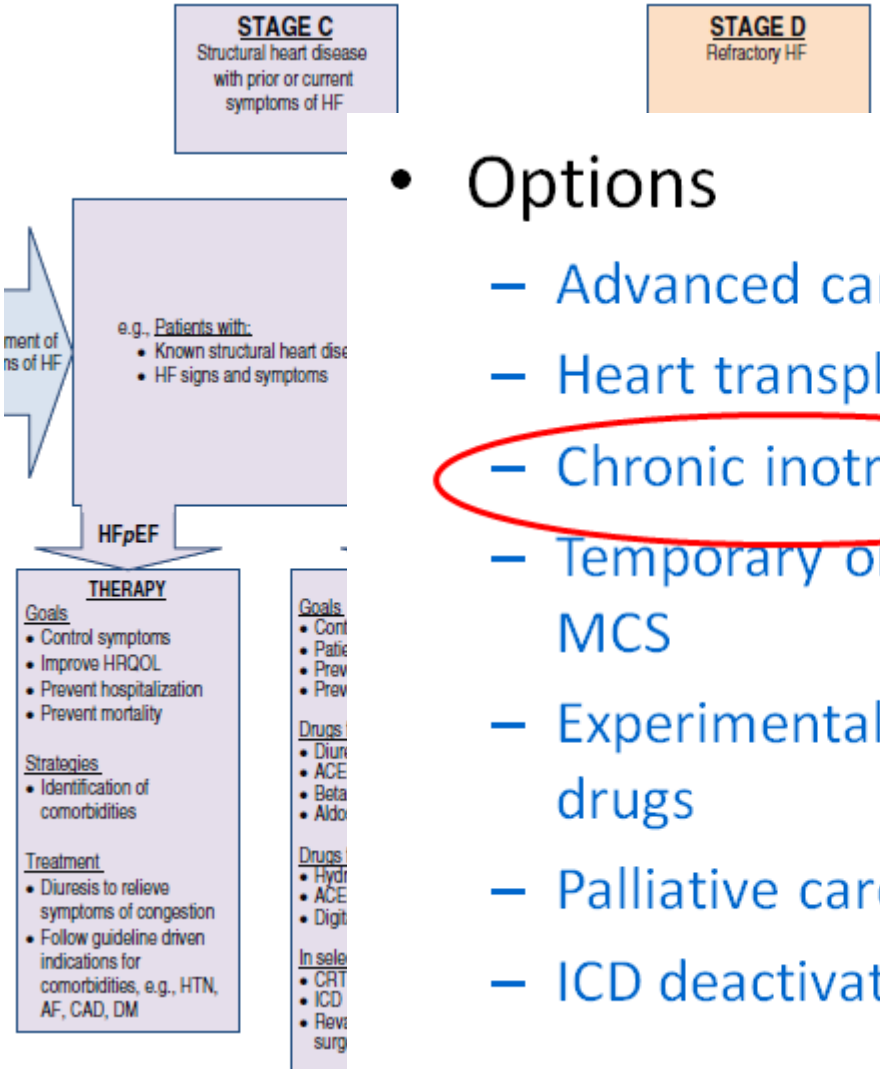

Heart failure is identified
Optimization of medical, surgical, and device therapy
Regular surveillance
Recognition of advanced HF triggers (Table 2)
Referral for consideration of advanced HF therapies
Cardiac transplantation
Destination LVAD therapy
Investigational therapies
Palliative care/hospice



Sistema Sanitario Regione Lombardia

Treatment of heart failure

- adapted from ACCF/AHA guideline



- Options
  - Advanced care measures
  - Heart transplant
  - Chronic inotropes
  - Temporary or permanent MCS
  - Experimental surgery or drugs
  - Palliative care or hospice
  - ICD deactivation

HRQOL = health-related quality of life
ICD = implantable cardioverter-defibrillator
MCS = mechanical circulatory support

Yancy CW. *Circulation*. 2013;128:e240-e327

2013 ACCF/AHA Guideline for the Management of Heart Failure

Inotropic Support: Recommendations

CLASS IIa

Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with stage D HF refractory to GDMT and device therapy who are eligible for and awaiting MCS or cardiac transplantation (647,648). *(Level of Evidence: B)*

CLASS IIb

Long-term, continuous intravenous inotropic support may be considered as palliative therapy for symptom control in select patients with stage D HF despite optimal GDMT and device therapy who are not eligible for either MCS or cardiac transplantation (651–653). *(Level of Evidence: B)*

CLASS III: Harm

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 (416,654–659). *(Level of Evidence: B)*

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DICE multicenter trial

Intermittent 6-month low-dose dobutamine infusion in severe HF:

	Control (19 patients)	Dobutamine (19 patients)
Total hospitalizations	17	11
Worsening HF hospitalizazion	11	7
≥ 2 hospitalizations	4	0
Death	3	5
Time to death, days	114	93
Withdrawals	4	

Oliva et al., Am Heart J 1999; 138:247

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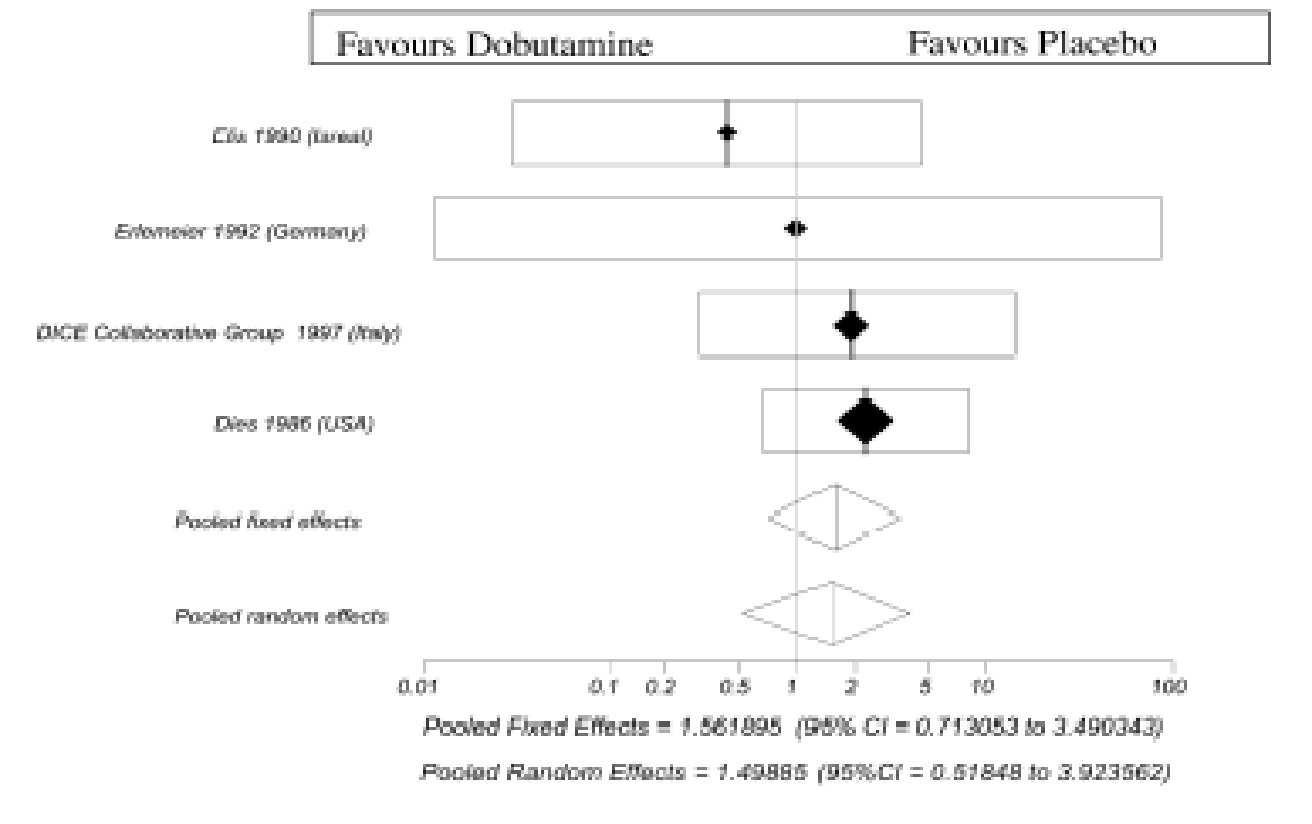
Meta-analysis 2002

(Thackray et al, Int J Cardiol)



4 randomized studies, intermittent dobutamine infusion

Doubt effect on mortality

Less use of ßB, amiodarone and ICD

Theoretical advantages of levosimendan (1)

- No increase in intracellular calcium concentration or myocardial oxygen demand (unlike dobutamine and milrinone)
- Beneficial haemodynamic effects (PCWP, CO)
- Beneficial symptomatic effects
- Beneficial effects on neurohormones (natriuretic peptides)
- Prolonged effects via formation of active metabolite(s)
- No attenuation of effects in beta-blocked patients (unlike in case of dobutamine)

Altenberger J et al. *Eur J Heart Fail* 2010;12:186–92

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Levosimendan REP

Authors	NANAS 2005	PARISSIS 2006	MAVROGENI 2007	PARLE 2008	PAPADOPOLOU 2009	BONIOS 2011
N patie						+ 21
Study design						dom s L vs L+D
Protoc						0,3 g/min 6 h ery week
Fw up (months)	3	6	6	6	6	6
Results	Survival improvement with L at 45 days	Improvement in NYHA class,Echo parameters and lab	Improvement in NYHA class,Echo parameters and lab, 6 month survival, safety	Improvement in NYHA class,Echo parameters and lab,	QoL and echo parameters	Survival Improvement with L at 6 month, NYHA, CI e PCP a 3 m

Singol-center study, low number of patient.

All patients with refractory HF with severe LV dysfunction (FEVS<30%).

In all the protocols repetitive planned treatment, mostly inpatient

→Significant improvement in QoL, NYHA class, echo parameters, BNP/NT-proBNP decrease

Repetitive Use of Levosimendan in AdvHF

Observations in the Levo-Rep, LION-Heart, and LAICA randomized clinical trials are indicative of clinical benefits from repetitive-use levosimendan in AdvHF including reduction in NT-pro-BNP levels and trends toward reductions in heart failure readmissions and heart failure–related mortality. Registry data also indicate a reduction in heart failure–related hospitalizations.

Use of levosimendan in repeated or intermittent cycles seems not to be associated with the increase in mortality associated with the use of conventional inotropes.

TABLE 2. Comparison of Patient Populations in the LEVO-Rep, LION-Heart, and LAICA Trials

Levo-Rep (n = 120)	LION-Heart (n = 69)	LAICA (n = 97)
NYHA class III or IV for >3 mo	NYHA class III/IV for >4 wk	NYHA class III/IV
LVEF <35%	LVEF <35%	One of the following:
Six-minute walk distance <350 m	Episode of pulmonary or systemic congestion requiring i.v. vasoactives within 12 mo	LVEF <30%
		Diastolic dysfunction ≥ grade III
		PCWP ≥16 mm Hg and/or CVP ≥12 mm Hg
		NT-pro-BNP >3000 ng/mL
		More than 1 hospitalization for HF within 6 mo

See text for further discussion.

Derived from www.ClinicalTrials.gov: NCT01065194 (Levo-Rep),[6] NCT01536132 (LION-Heart),[27] and NCT00988806 (LAICA).[28]

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

Altenberger J *J Cardiovasc Pharmacol 2018*

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NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

New insights into the effects of intermittent levosimendan in AdvHF are provided by the RELEVANT-HF registry,[37] which has compiled data from 185 patients treated at 6 centers in Lombardy, Italy.

Altenberger J *J Cardiovasc Pharmacol 2018*

RELEVANT-HF

REpetitive LEVosimendan in AdvaNced refracTory Heart Failure

- Registro multicentrico retrospettivo sull'effetto di Levosimendan periodico in pazienti con scompenso cardiaco avanzato refrattario (ARHF) per valutare efficacia e sicurezza di infusioni ripetute programmate.

- Obiettivi:
  - Giorni trascorsi in ospedale per scompenso cardiaco (DIH) nei 6 mesi dall'inizio del trattamento rispetto ai 6 mesi precedenti
  - Numero e durata dei ricoveri nei 6 mesi di trattamento rispetto ai 6 mesi precedenti
  - Variazioni rispetto al basale di classe NYHA, GFR, livelli di peptidi natriuretici
  - Combinazione di decesso/trapianto urgente/impianto di LVADnei 12 mesi dall'inizio del trattamento

F.Oliva

RELEVANT-HF
Criteri Inclusione

- Scompenso cardiaco avanzato refrattario (ARHF) avviati a LEVO-REP come palliazione o ponte a terapie di sostituzione cardiaca
- Storia di $\geq$ 2 ospedalizzazioni o accessi in DEA per scompenso cardiaco nei 6 mesi precedenti
- Classe NYHA III-IV INTERMACS 4-7
- HFrEF
- Terapia farmacologica ottimizzata da almeno 4 settimane
- GFR > 30 ml/min
- Infusioni periodiche , senza bolo, dose 0.05-0.2 mcg/kg/min, intervallo 2-8 settimane

F.Oliva

RELEVANT-HF

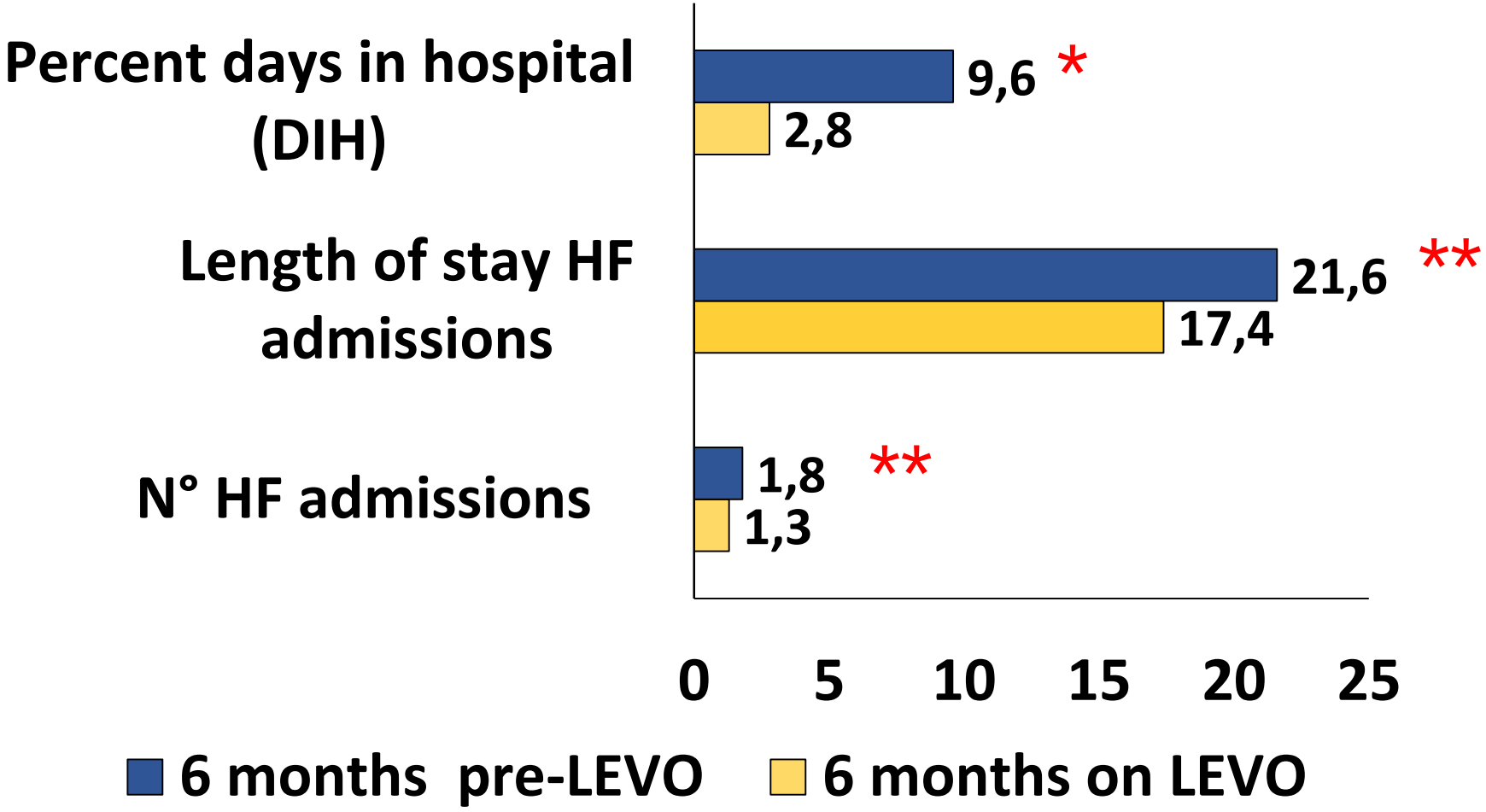
- 185 pazienti dal Maggio 2005 all'Ottobre 2016
- 7 centri cardiologici (range di arruolamento 8-50 pz)
- Età 66±13 anni 80% maschi

- Indicazione al trattamento:
  - Bridge to Txc/candidacy/decision 69 pz (37%)
  - Palliation 116 pz (63%)

- Modalità di trattamento:
  - 33% domicilio
  - 11% Day hospital
  - 56% ricovero breve

F.Oliva

RELEVANT-HF

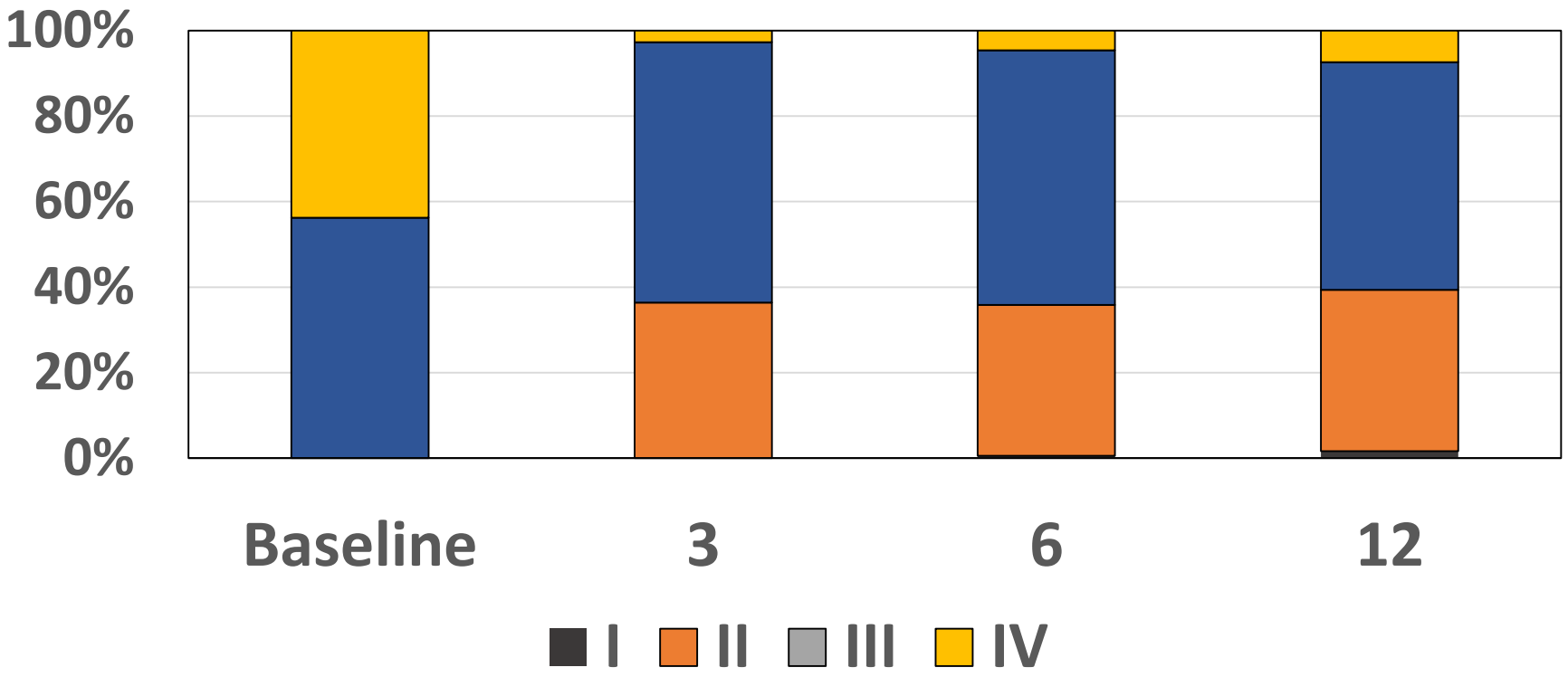


* p<0.0001 ** p=0.001

Oliva F. et al *ESC 2017*

RELEVANT-HF

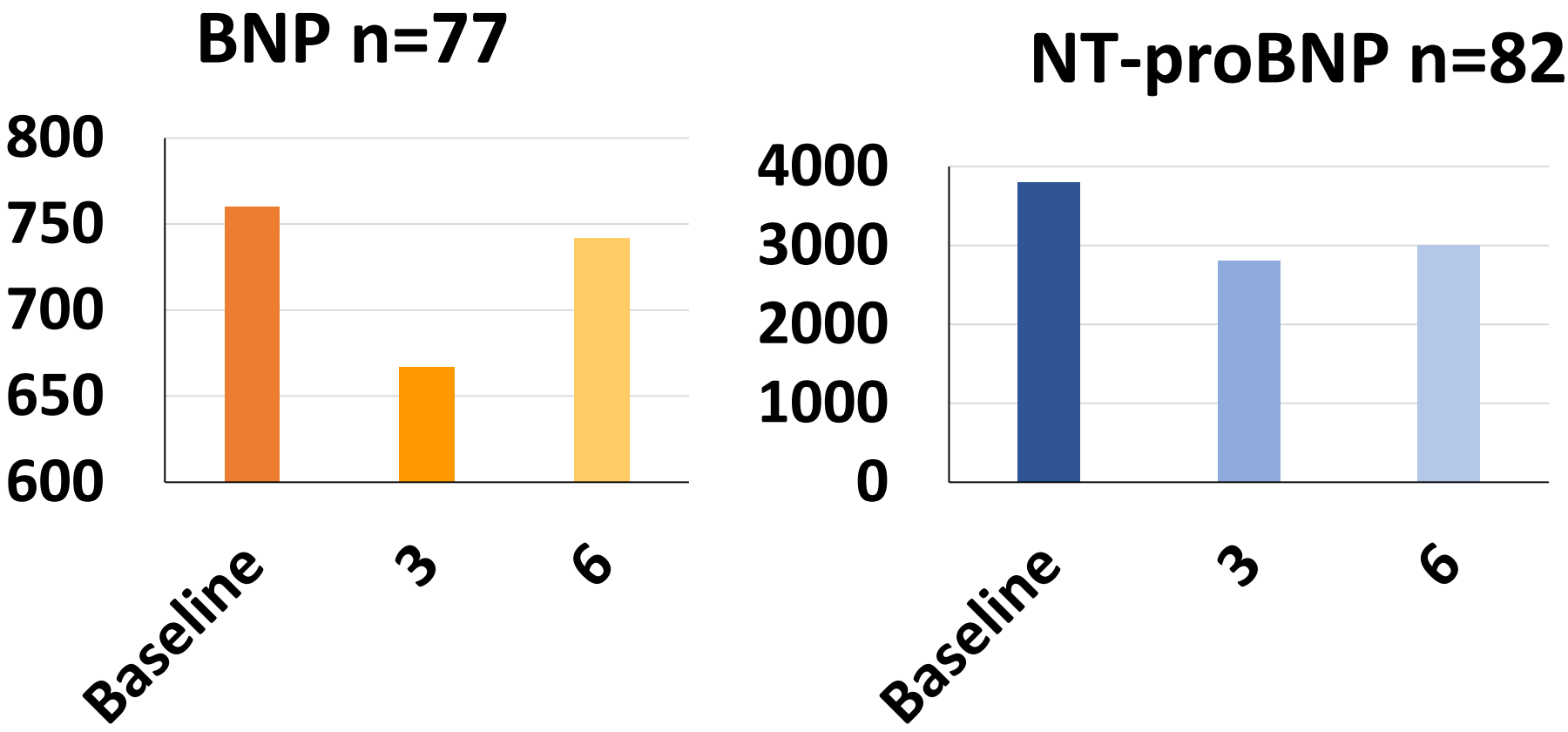
NYHA class changes over time



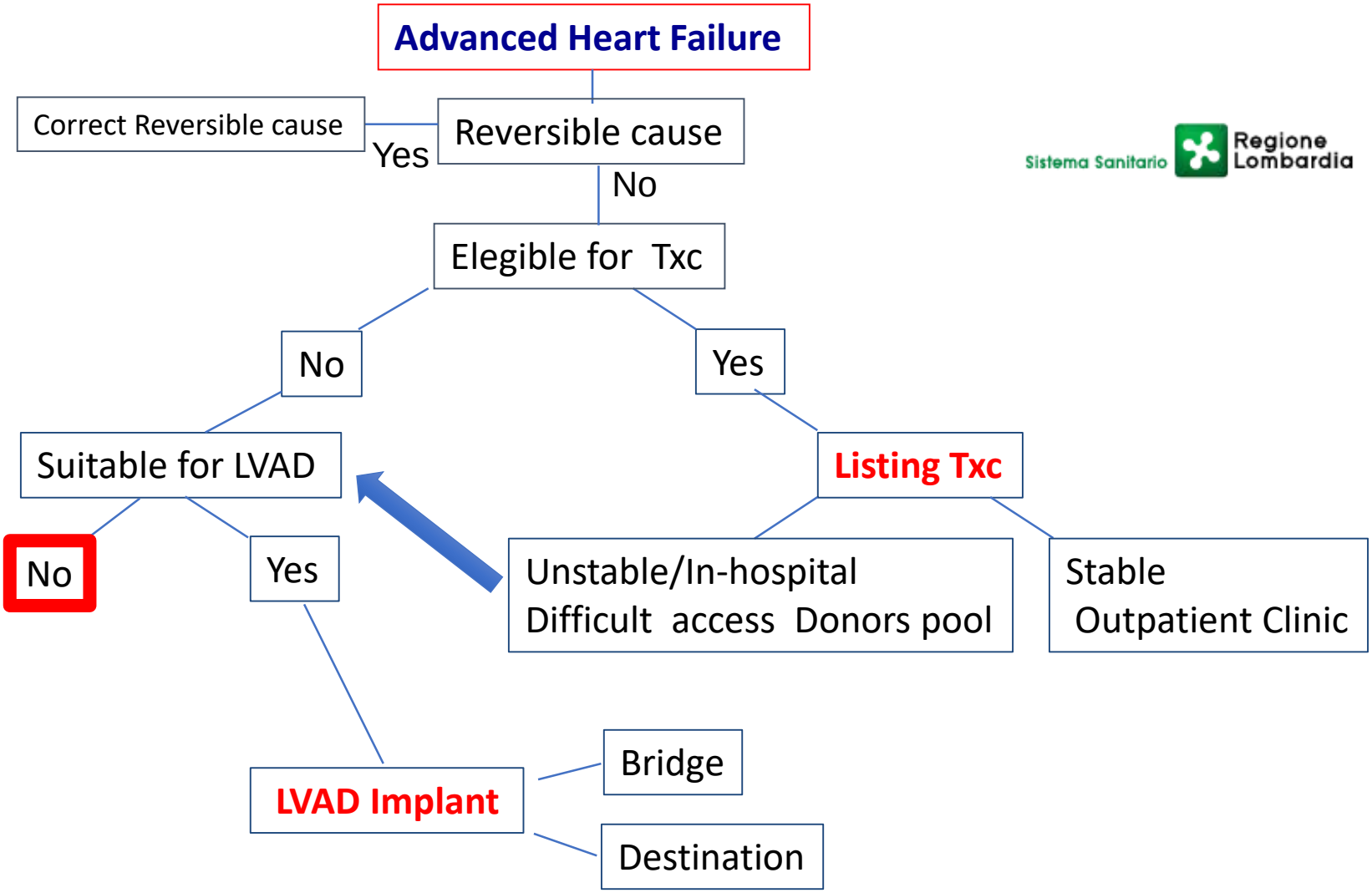
Oliva F. et al *ESC 2017*

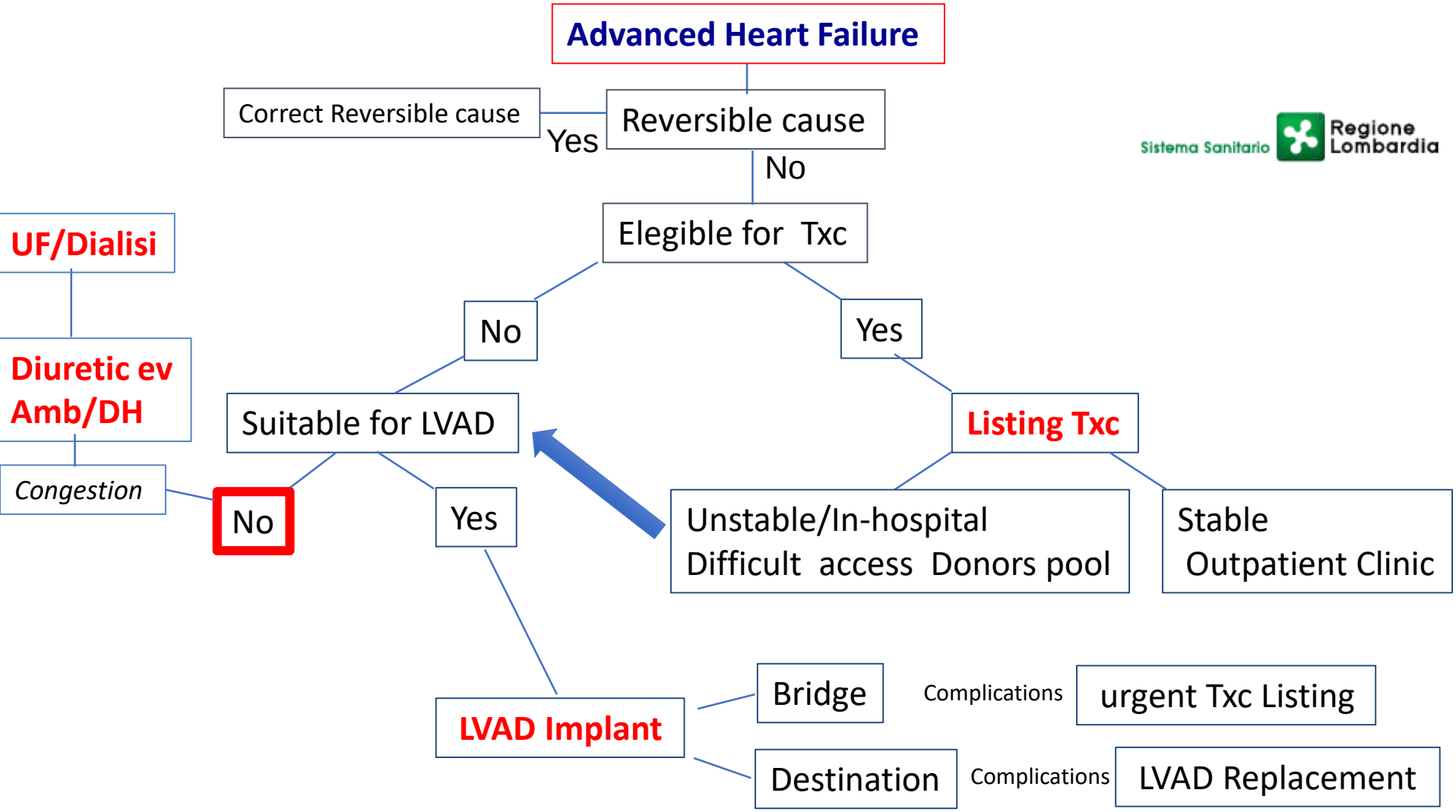
RELEVANT-HF

Median natriuretic peptides values over 6 months



Oliva F. et al *ESC 2017*


Advanced Heart Failure
Reversible cause
Correct Reversible cause
Yes
No
Elegible for Txc
No
Yes
Suitable for LVAD
Listing Txc
No
Yes
Unstable/In-hospital
Difficult access Donors pool
Stable
Outpatient Clinic
LVAD Implant
Bridge
Destination



Sistema Sanitario Regione Lombardia

Azienda Ospedaliera
Ospedale Niguarda Ca' Granda

Dipartimento Cardiotoracovascolare "A. De Gasperis"
A.O. Ospedale Niguarda Ca' Granda - Milano

Advanced Heart Failure

Reversible cause
- Yes → Correct Reversible cause
- No → Elegible for Txc

Elegible for Txc
- No → Suitable for LVAD
- Yes → **Listing Txc**

Listing Txc
- Unstable/In-hospital
  Difficult access Donors pool
- Stable
  Outpatient Clinic

Suitable for LVAD
- No
  - *Congestion* → **Diuretic ev Amb/DH** → **UF/Dialisi**
  - *Hypotension/ Low output* → Levosimendan
    - Non Responder → **Ambulatory Dobutamine**
    - Responder → **Levosimendan Rep** → Recurrent Acute HF
- Yes → **LVAD Implant**
  - Bridge → Complications → urgent Txc Listing
  - Destination → Complications → LVAD Replacement

Advanced-Refractory HF Treatment
INFERENCES

- Outpatient **inotropic therapy** may be considered as bridge or palliative therapy

- Current data suggest that intermittent/repetitive **Levosimendan** infusion can be used to maintain patient stability

- There is evidence showing improvements in haemodynamics, symptoms, rehospitalization rates, QoL and biomarkers. The issue of mortality will require further studies.

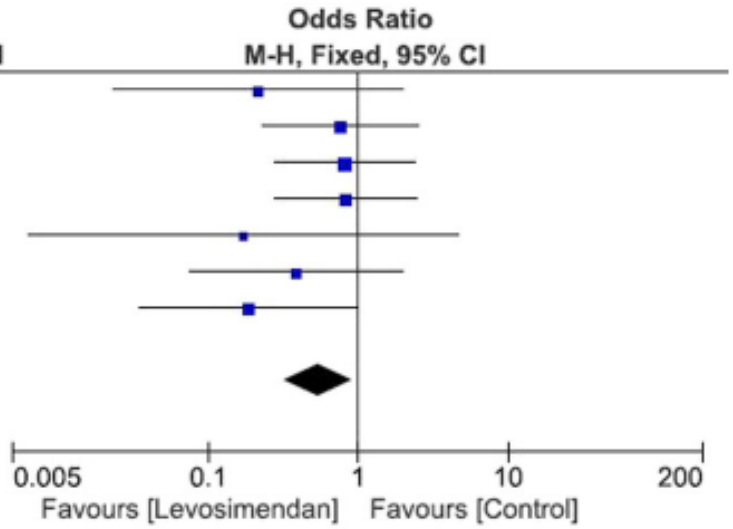
What do we know?

Meta-analysis on trials with levosimendan vs placebo, dobutamine or prostaglandins – reduction in mortality!

Study or Subgroup	Levosimendan Events	Levosimendan Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Altenberger J 2014	1	63	4	57	10.9%	0.21 [0.02, 1.97]
Berger R 2007	6	39	7	36	16.3%	0.75 [0.23, 2.50]
Bonios MJ 2012	14	42	8	21	18.8%	0.81 [0.27, 2.42]
Comin-Colét 2015	14	48	7	21	18.2%	0.82 [0.27, 2.47]
Kleber FX 2009	0	18	1	10	4.9%	0.17 [0.01, 4.62]
Malfatto G MD 2012	4	22	4	11	11.5%	0.39 [0.08, 2.00]
Mavrogeni S 2007	2	25	8	25	19.4%	0.18 [0.03, 0.98]
Total (95% CI)		**257**		**181**	**100.0%**	**0.54 [0.32, 0.91]**
Total events	41		39			

Heterogeneity: Chi² = 4.28, df = 6 (P = 0.64); I² = 0%

Test for overall effect: Z = 2.32 (P = 0.02)



Silvetti S, et al. Int J Cardiol 2016:202

LeoDOR Trial

REPETITIVE LEVOSIMENDAN IN ADVANCED HEART FAILURE

Proposal for a new study:

Rationale

LeoDOR Trial

REPETITIVE LEVOSIMENDAN IN ADVANCED HEART FAILURE

Aim of the study

To test the ***efficacy and safety of intermittent levosimendan*** therapy started during the ***vulnerable phase*** after a recent hospitalisation for heart failure

Study hypothesis

Compared with placebo, ***repetitive administration of levosimendan*** in the post-acute heart failure syndrome (AHFS) discharge period, will be associated with ***greater clinical stability*** through 14 weeks as assessed by a composite clinical endpoint consisting of mortality, acute heart failure episodes and change in natriuretic peptide levels