Levosimendan e Nitroprussiato sodico:protocolli gestionali medico-infermieristici

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Torino 15 Ottobre 2009

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM)

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European Heart Journal
doi:10.1093/eurheartj/ehn309

European Journal of Heart Failure
doi:10.1016/j.ejheart.2008.08.005

Table 3 Definition of heart failure

Heart failure is a clinical syndrome in which patients have the following features:

- **Symptoms typical of heart failure**
  (breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling)

  and

- **Signs typical of heart failure**
  (tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral oedema, hepatomegaly)

  and

- **Objective evidence of a structural or functional abnormality of the heart at rest**
  (cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic peptide concentration)

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Clinical classification

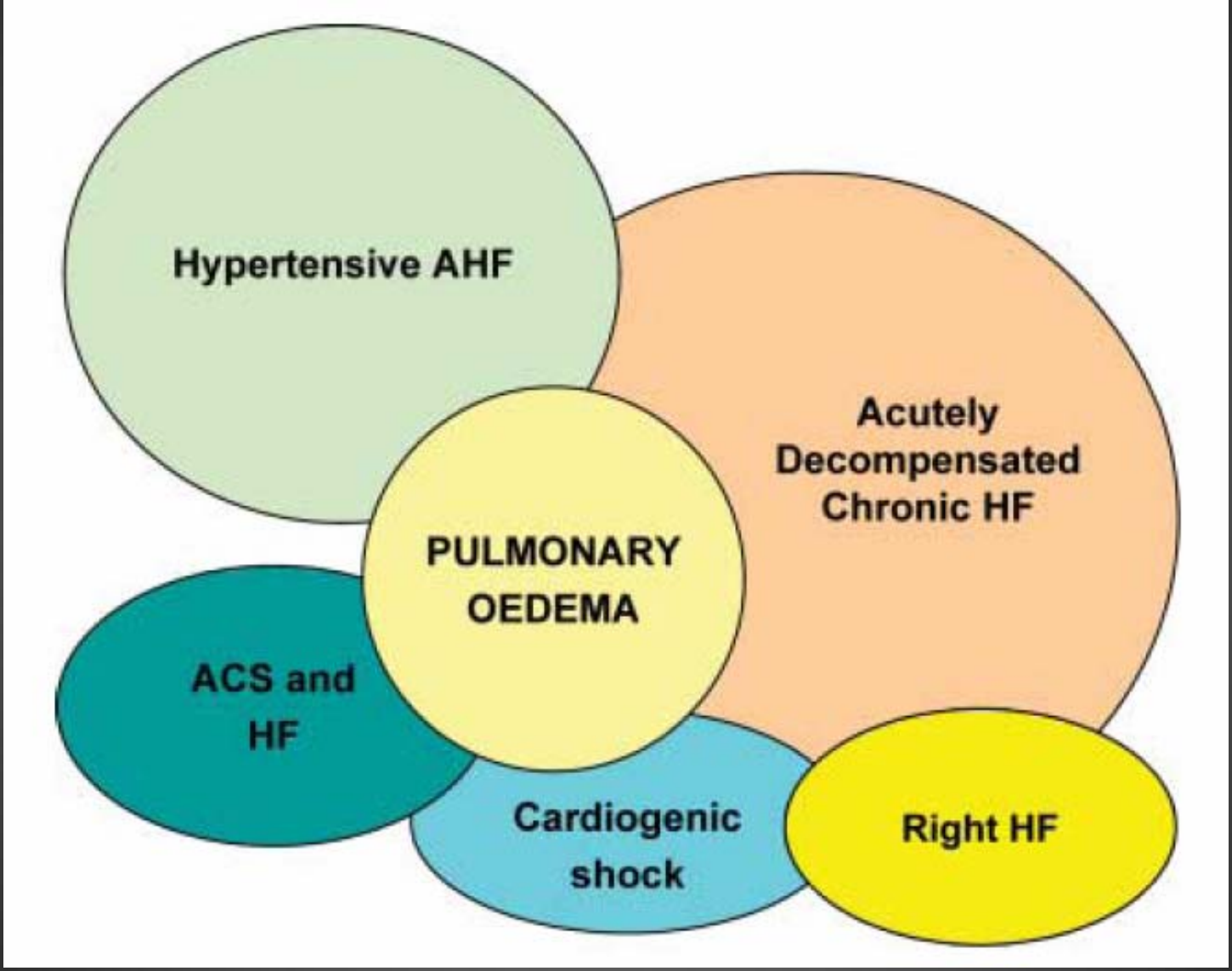

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Table 27 Goals of treatment in acute heart failure

- **Immediate (ED/ICU/CCU)**
  - Improve symptoms
  - Restore oxygenation
  - Improve organ perfusion and haemodynamics
  - Limit cardiac/renal damage
  - Minimize ICU length of stay
- **Intermediate (in hospital)**
  - Stabilize patient and optimize treatment strategy
  - Initiate appropriate (life-saving) pharmacological therapy
  - Consider device therapy in appropriate patients
  - Minimize hospital length of stay
- **Long-term and pre-discharge management**
  - Plan follow-up strategy
  - Educate and initiate appropriate lifestyle adjustments
  - Provide adequate secondary prophylaxis
  - Prevent early readmission
  - Improve quality of life and survival

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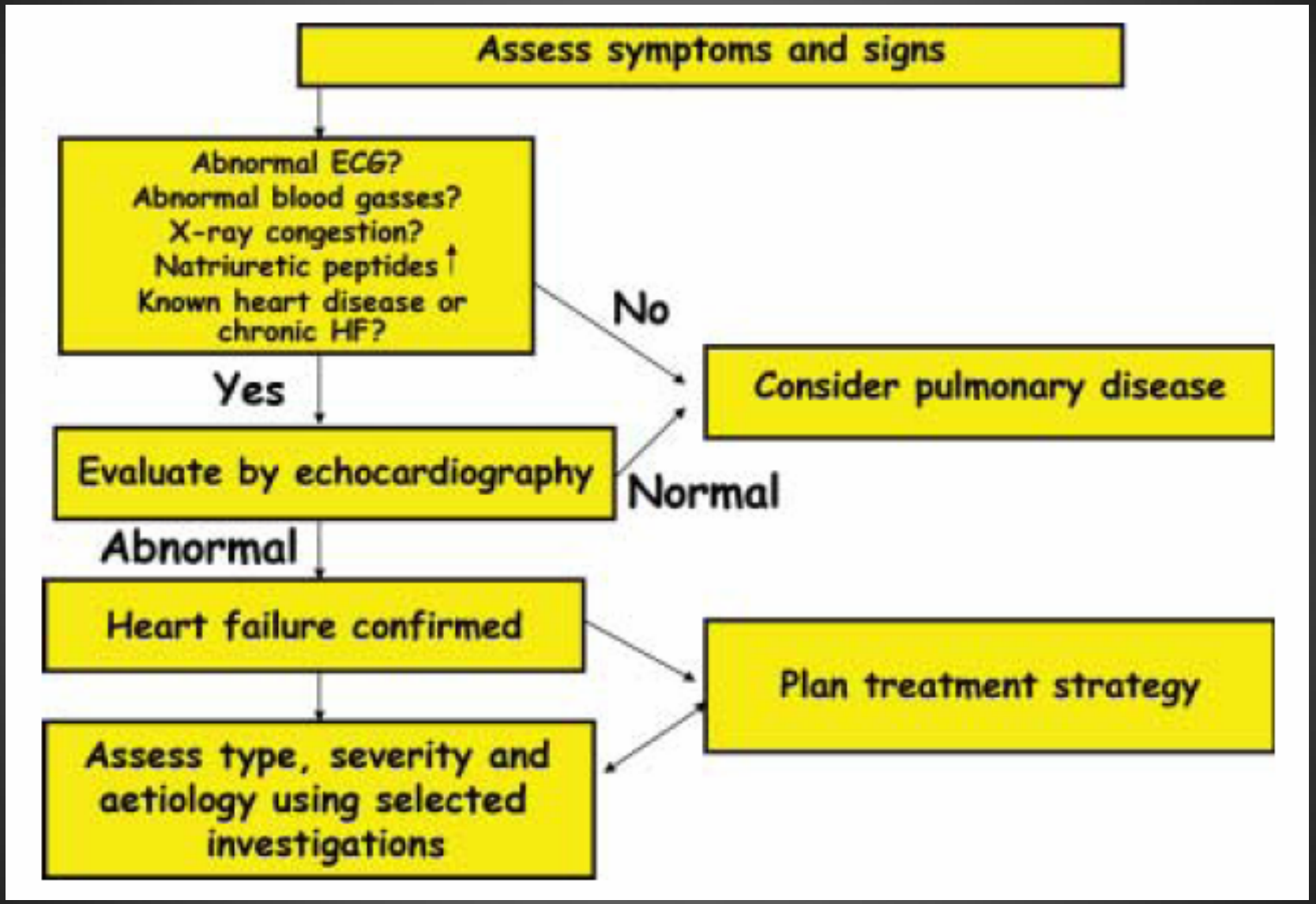
Diagnosis of acute HF



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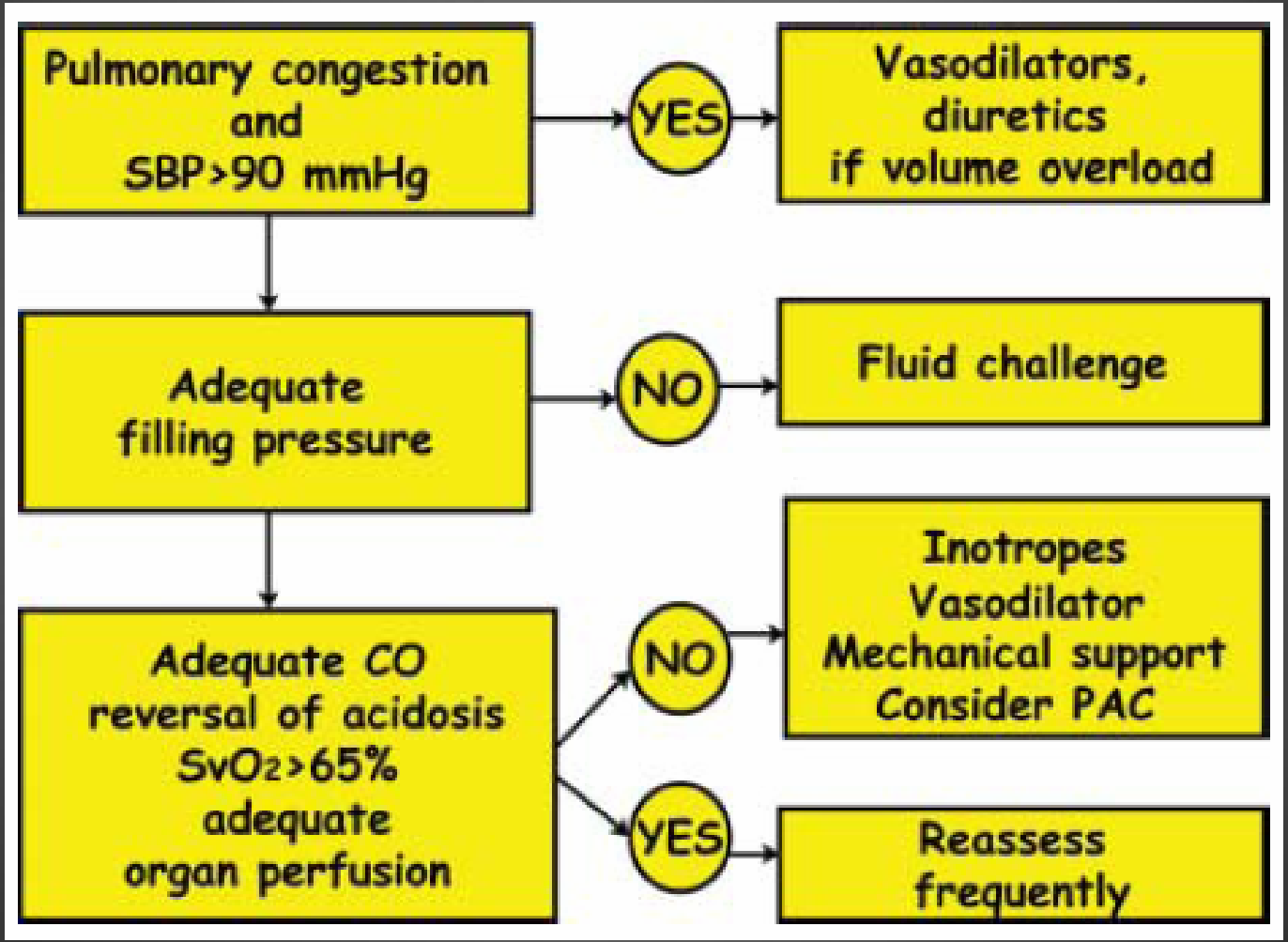
AHF treatment according to LV filling pressure



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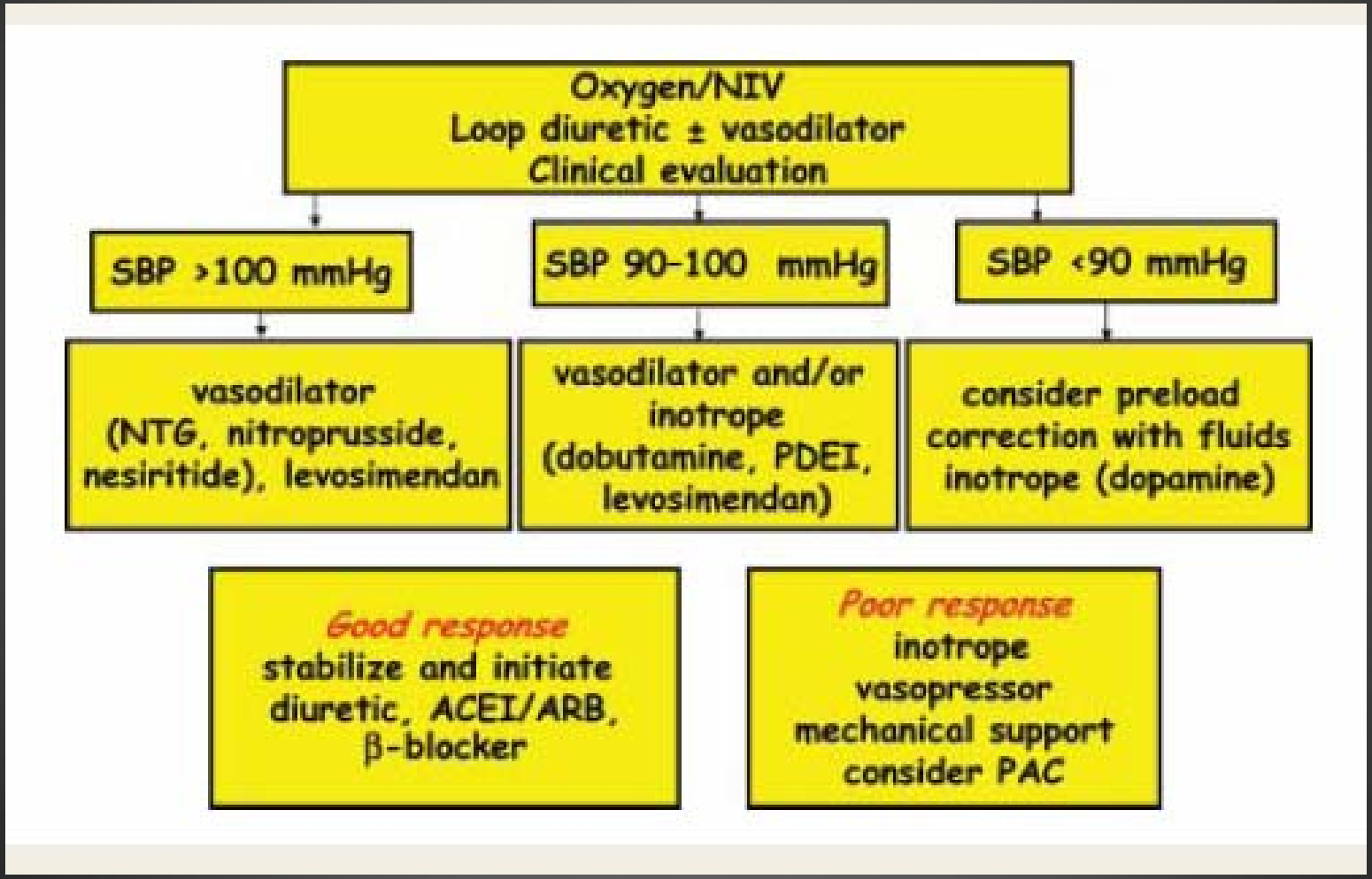
AHF treatment according to SBP



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Indications and dosing of i.v. vasodilatators

Vasodilator	Indication	Dosing	Main side-effects	Other
Nitroglycerine	Pulmonary congestion/oedema BP >90 mmHg	Start 10–20 μg/min, increase up to 200 μg/min	Hypotension, headache	Tolerance on continuous use
Isosorbide dinitrate	Pulmonary congestion/oedema BP >90 mmHg	Start with 1 mg/h, increase up to 10 μg/h	Hypotension, headache	Tolerance on continuous use
Nitroprusside	Hypertensive HF congestion/ oedema BP >90 mmHg	Start with 0.3 μg/kg/min and increase up to 5 μg/kg/min	Hypotension, isocyanate toxicity	Light sensitive
Nesiritide*	Pulmonary congestion/oedema BP >90 mmHg	Bolus 2 μg/kg + infusion 0.015–0.03 μg/kg/min	Hypotension	

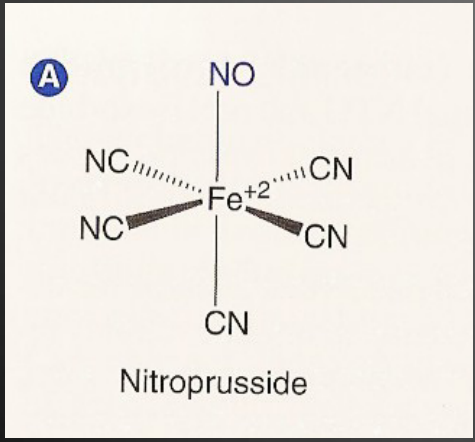
*Not available in many ESC countries.

Class of recommendation IIa, level of evidence B

Sodium Nitroprusside

Potent and rapid (1-2 min) artero-venodilator

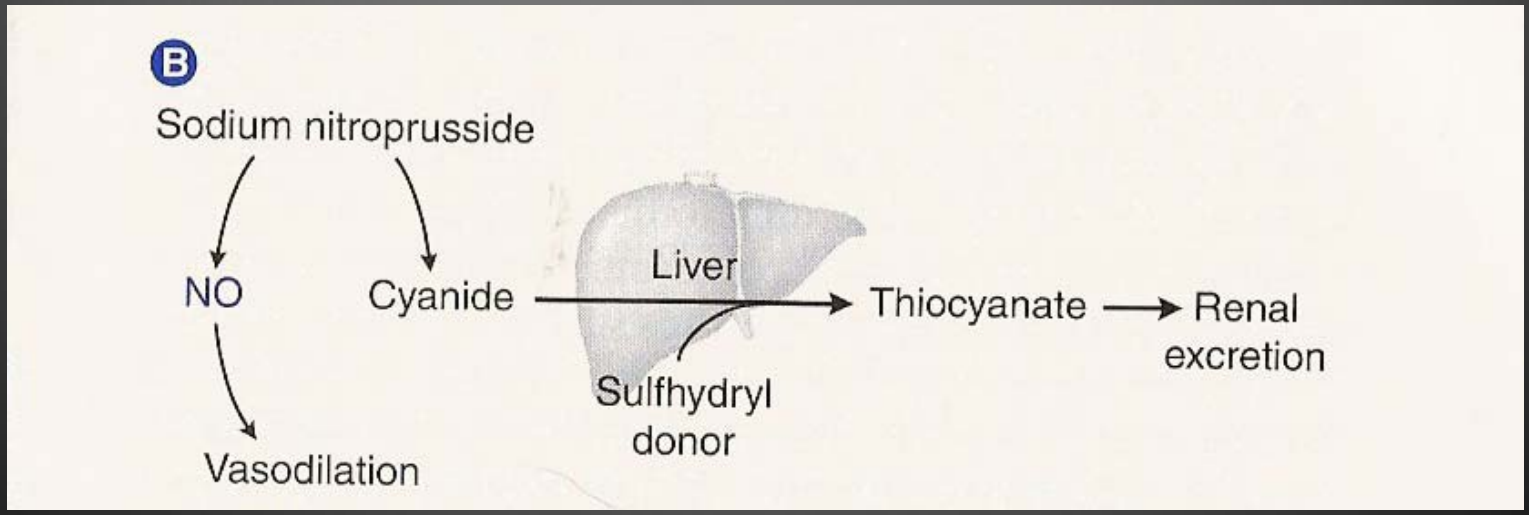
EFFECTS:
-increase in cardiac output
-reduction of ventricular filling pressures and mitral regurgitation
-improved organ blood supply



Sodium Nitroprusside

RISKS:

1.hypotension
2.cyamide toxicity (liver dysfunction): lactic acidosis and methemoglobinemia-thiocynate toxicity (renal dysfunction): nausea, confusion, tremor, rarely coma (halflife 3-7 days).



ELSEVIER

European Journal of Heart Failure 3 (2001) 601–610

The European Journal of Heart Failure

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Chronic infusion of dobutamine and nitroprusside in patients with end-stage heart failure awaiting heart transplantation: safety and clinical outcome

Soccorso Capomolla[a,*], Oreste Febo[a], Cristina Opasich[b], Giampaolo Guazzotti[a], Angelo Caporotondi[a], Maria Teresa La Rovere[a], Marco Gnemmi[a], Andrea Mortara[c], Margherita Vona[a], Gian Domenico Pinna[a], Roberto Maestri[a], Franco Cobelli[a]

AGE	**53±7 years**
LVEF	**18.5%**
CI	**1.95 L/min/m2**
PCWP	**26.5 mmHg**

SNP

N. 70

0.76γ/Kg/min for 12h/day for 23-24 days

Dobutamine

N.73

7 γ/Kg/min for 12h/day for 28-29 days

Capomolla S, Eur J of Heart Failure 2001; 3: 601

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Follow-up 337±264days	Dobutamine	SNP	
Mortality + Transplantation	84%	51%	
Hospitalitazion for severing HF	86%	58%	
Improvement in NYHA class	14%	43%	p 0.008

Capomolla S, Eur J of Heart Failure 2001; 3: 601

Sodium Nitroprusside for Advanced Low-Output Heart Failure

Wilfried Mullens, MD, Zuheir Abrahams, MD, PHD, Gary S. Francis, MD, FACC, Hadi N. Skouri, MD, Randall C. Starling, MD, MPH, FACC, James B. Young, MD, FACC, David O. Taylor, MD, FACC, W. H. Wilson Tang, MD, FACC

Cleveland, Ohio

Retrospective, single-center, nonrandomized (first recent database)

78 patients with a Cardiac Index ≤ 2l/min/m2 vs Control Patients (n=97)

<u>Sodium Nitroprusside infusion protocol (24-72h)</u>
continuous infusion at a dose of 10 to 400 μg/min (without bolus) as tolerated to achieve targetin MAP 65 to 70 mmHg
To wean off: ↓ infusion gradually as tolerated while maintaining MAP goals and initiating/increasing oral vasodilators

Mullen s et al, JACC 2008; 52: 200-7

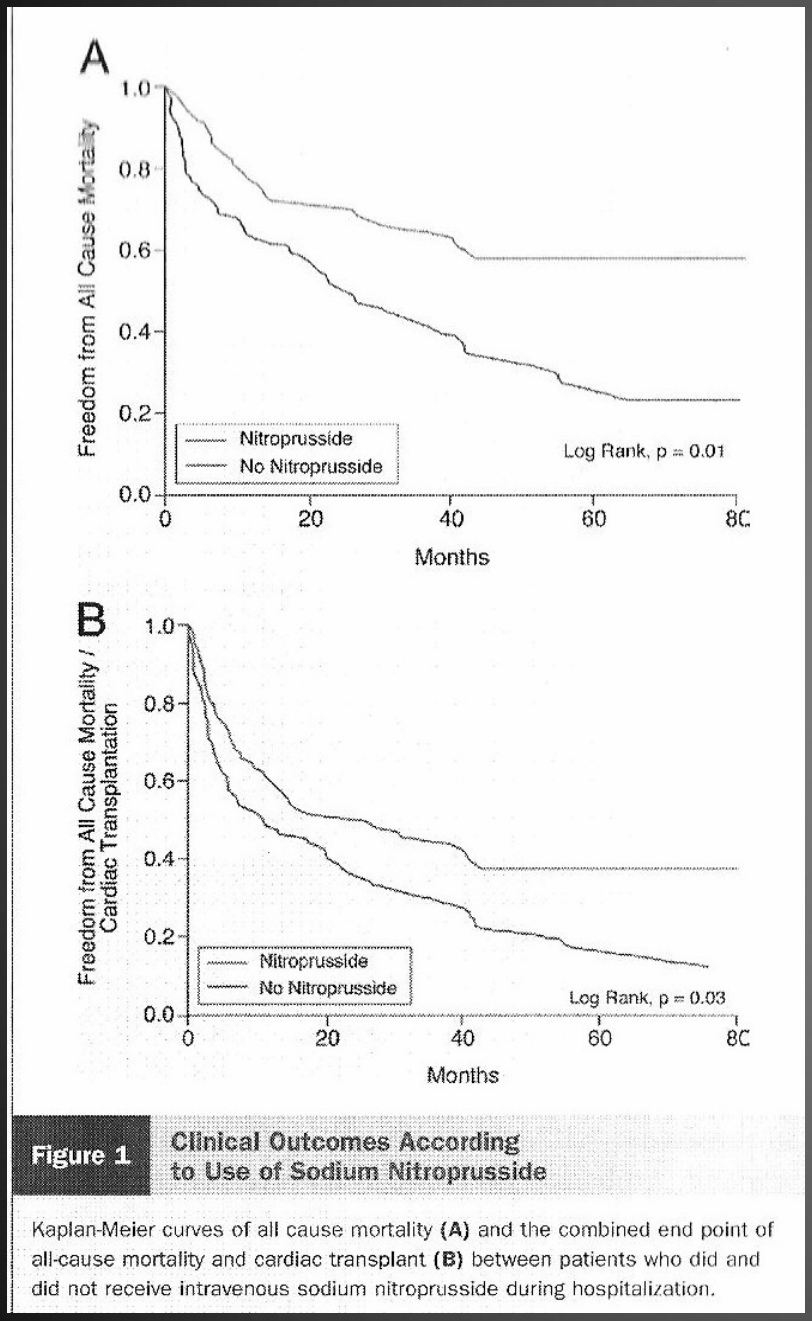


Figure 1 **Clinical Outcomes According to Use of Sodium Nitroprusside**

Kaplan-Meier curves of all cause mortality **(A)** and the combined end point of all-cause mortality and cardiac transplant **(B)** between patients who did and did not receive intravenous sodium nitroprusside during hospitalization.

Treatment with SNP was associated with lower all-cause mortality (29% vs 44%; p. 0.01) and all-cause mortality/cardiac transplant

Mullen s et al, JACC 2008; 52: 200-7

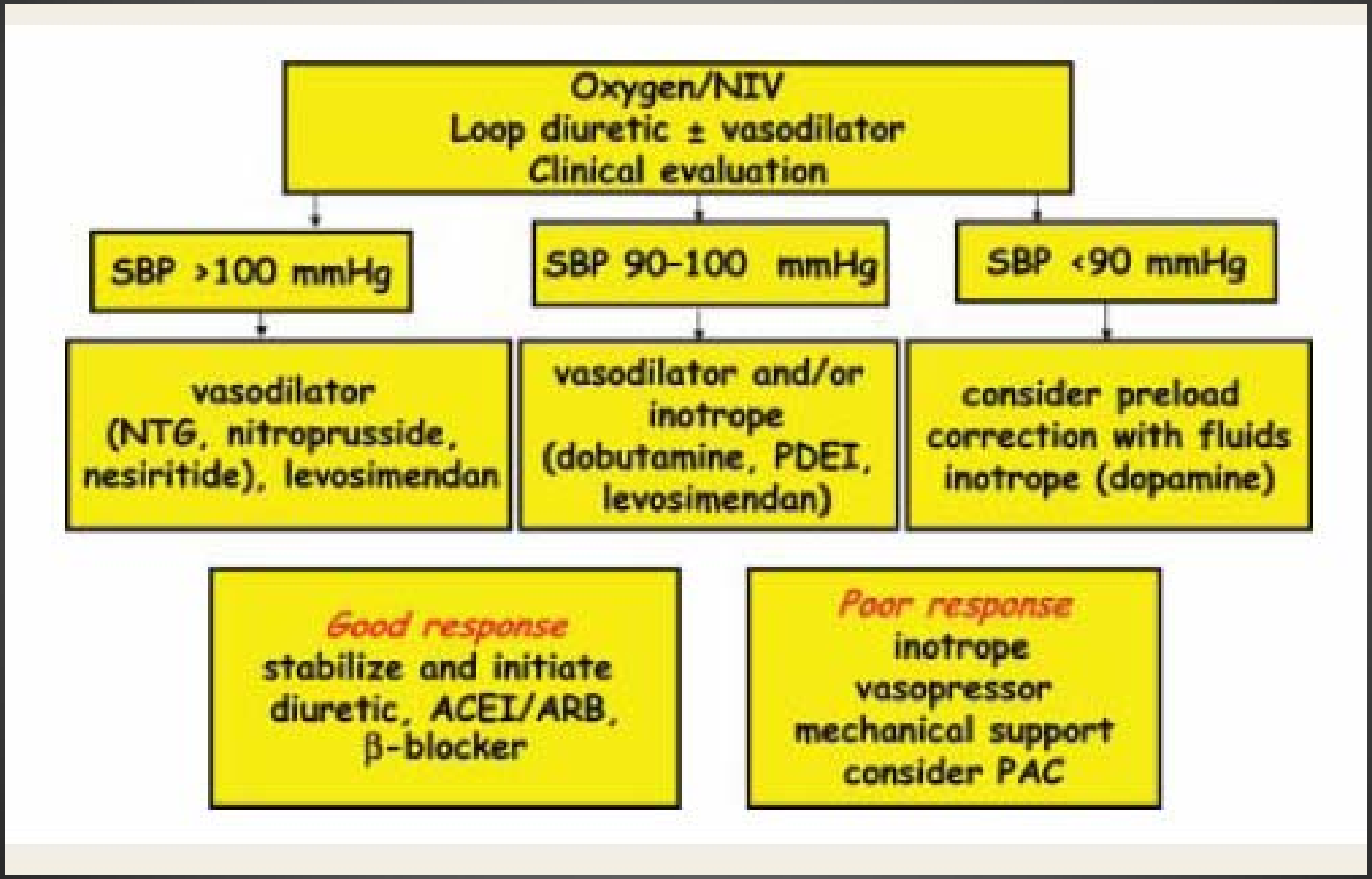
Vasodilator Therapy for Decompensated Heart Failure

"What was once old is now new again"

- Data supporting SNP from "consensus opinion" and not from clinical trial (no randomized multicenter data)
- Process of care delivery systems are very center specific
- Not a reasonable noninvasive alternative to right heart catheterization
- The Escape study data dissuading routine use of right heart catheterization

C.W. Yancy JACC 2008; 52 (3): 208-10

AHF treatment according to SBP



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Dosing of positive inotropic agents in AHF

	Bolus	Infusion rate
Dobutamine	No	2–20 μg/kg/min (β+)
Dopamine	No	<3 μg/kg/min: renal effect (δ+) 3–5 μg/kg/min: inotropic (β+) >5 μg/kg/min: (β+), vasopressor (α+)
Milrinone	25–75 μg/kg over 10-20 min	0.375–0.75 μg/kg/min
Enoximone	0.25–0.75 mg/kg	1.25–7.5 μg/kg/min
Levosimendan*	12 μg/kg over 10 min (optional)**	0.1 μg/kg/min which can be decreased to 0.05 or increased to 0.2 μg/kg/min
Norepinephrine	No	0.2–1.0 μg/kg/min
Epinephrine	Bolus: 1 mg can be given i.v. during resuscitation, repeated every 3–5 min	0.05–0.5 μg/kg/min

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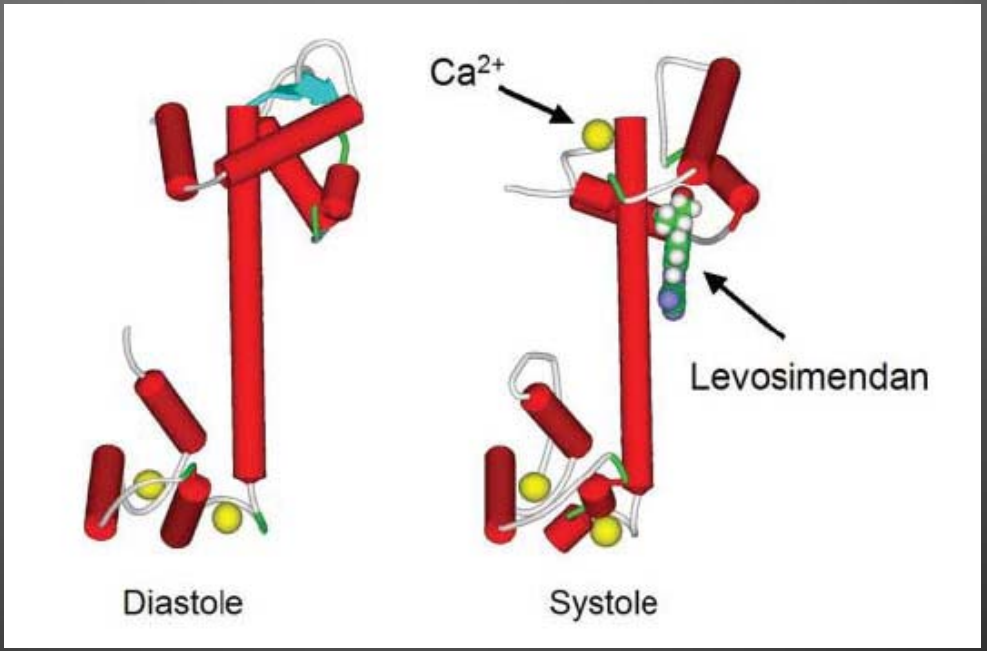
Levosimendan (1)

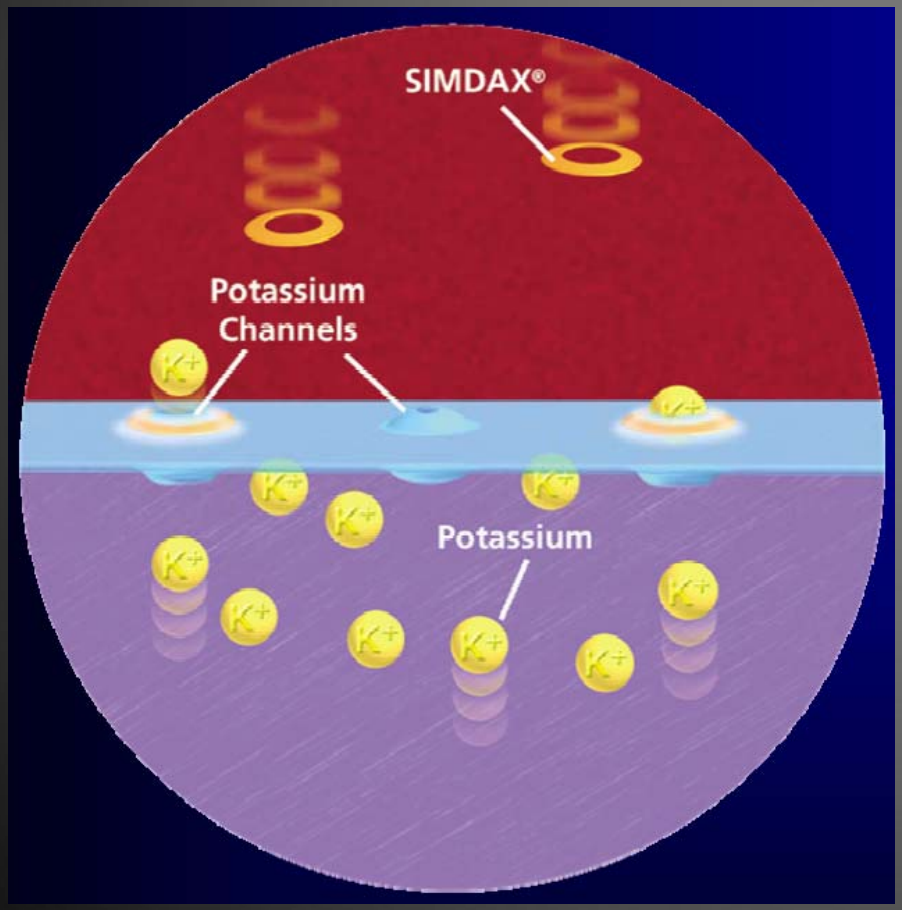
CALCIUM SENSITIZING AGENT

- Positive inotropic action by increasing the sensitivity of the contractile apparatus to Ca2+ (binding to N-terminal domain of Troponin C)
- No increase in intracellular cAMP or Ca2+
- Increase of force at costant Ca2+
- Favourable relation between force production / Ca2+
- No impairment in relaxation
- No increase in diastolic Ca2+



Levosimendan (2)

Opening of ATP-sensitive potassium channels
Iperpolarization →vasodilation



↑CARDIAC OUTPUT

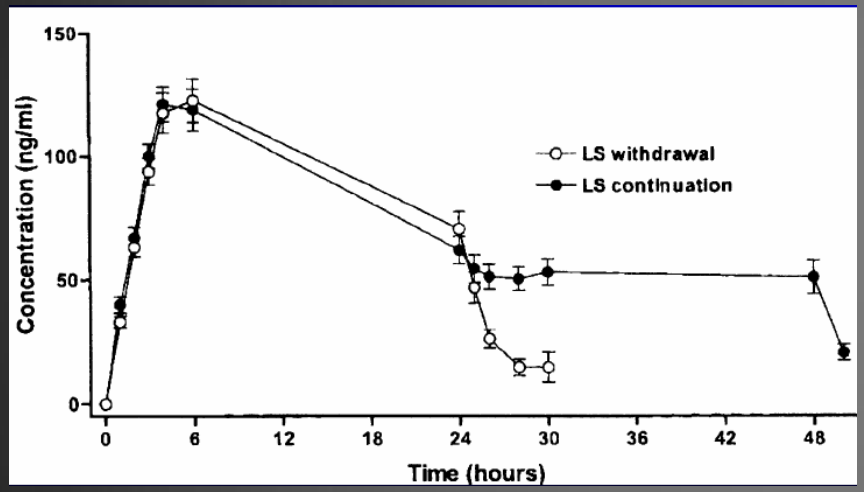
↓PCWP

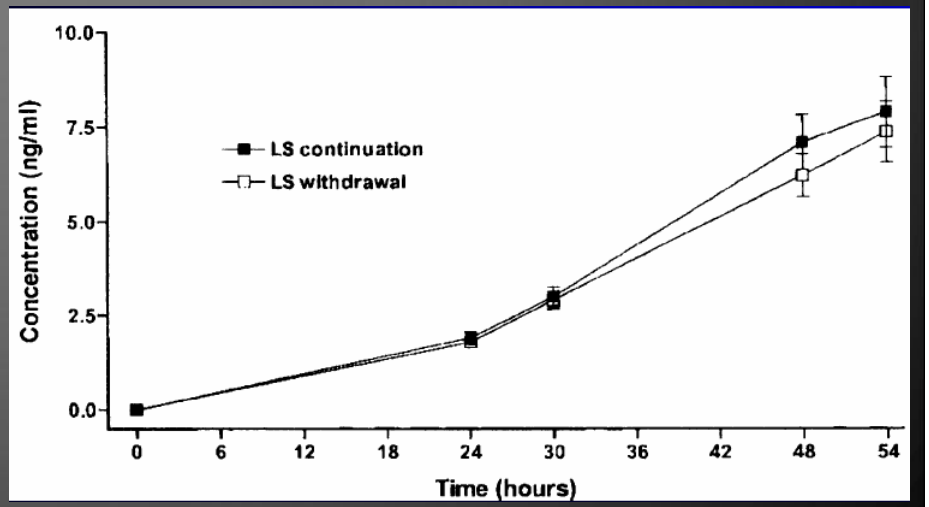
↓PULMONARY CONGESTION

↓PRE-AFTER LOAD

Levosimendan (3)

Half-life of Levosimendan is short (~ 1 hour) but metabolites (OR-1855) are active for ~ 7 days





Kivikko M, Circulation 2003; 107: 81-6

Levosimendan (4)

Practical advice (1)

- ***Loading dose**: 6-12-24 µg/Kg in 10 min according to the urgency of the clinical need and the monitoring setting.*

If an immediate effect is not needed or the patient is hypotensive, the loading dose should be avoided

- ***Maintenance dose**: 0.05-0.1-0.2 µg/Kg/ min reconsidered every 2-3 hours (half life of the drug ~ 1 hour) according to the hemodynamic changes*

Infusion: 24 hours, no longer because active metabolite accumulates.

Levosimendan (5)

Practical advice (2)

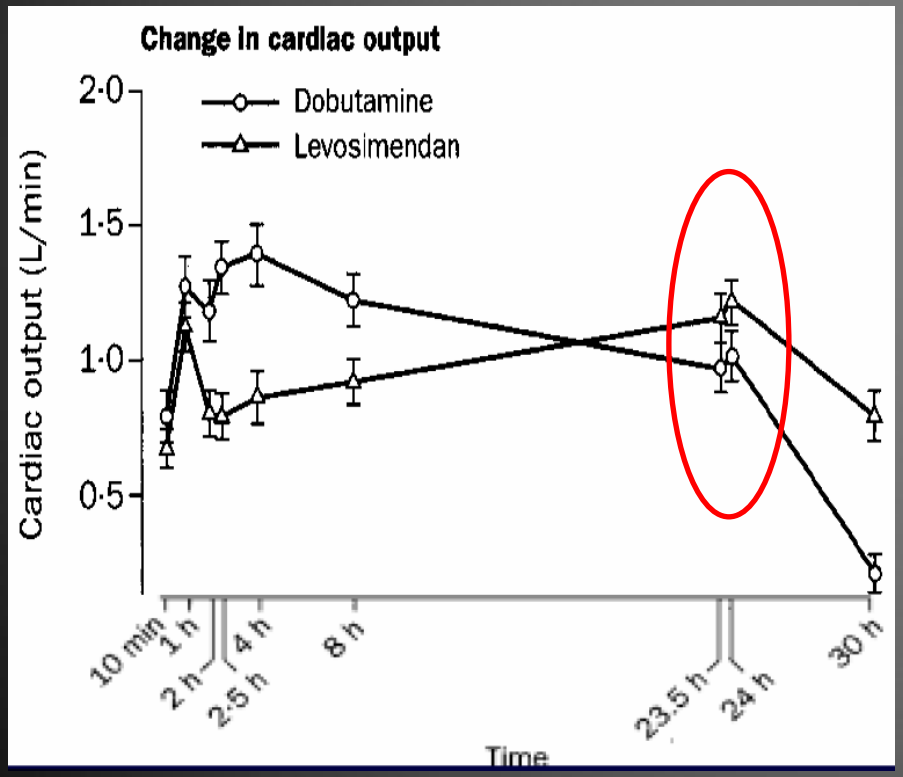
- *Use of diuretics: keep the present dose (do not increase) and stop diuretics i.v. If needed, small repeated doses are preferable.*

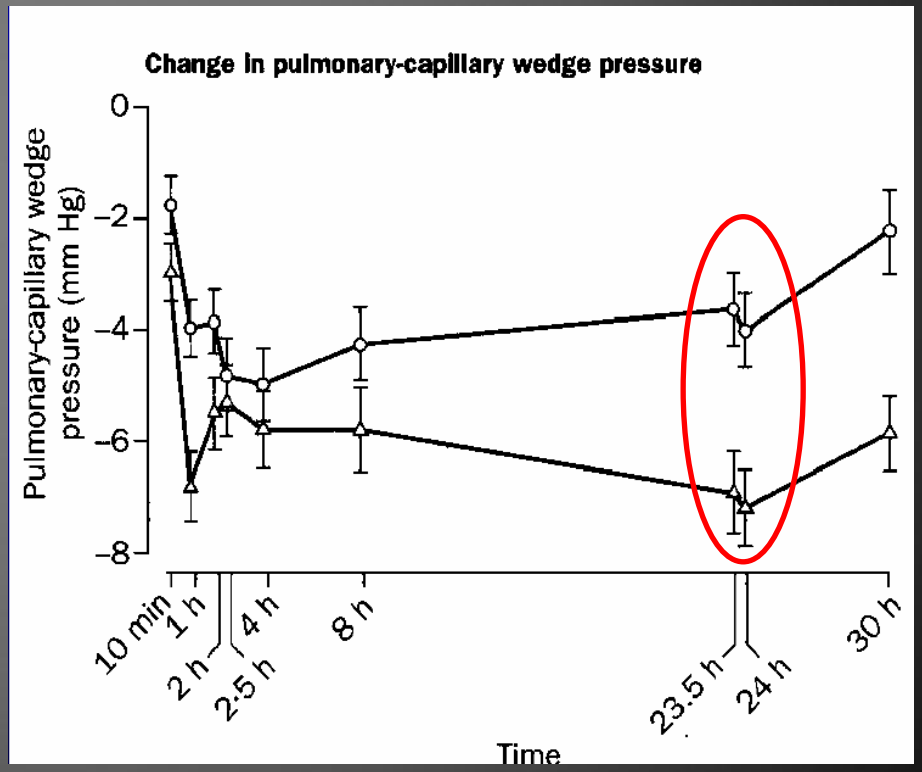
- *Associations with vasopressors: levosimendan can be associated with vasopressors. Large experience with norepinephrine in non-cardiac Intensive Units.*

- *Invasive monitoring: in first patients to become familiar with the drug. Afterwards only in severe, unstable patients*

LIDO Study

StudyResponders (↑30% CO + ↓25%PCWP at 24 h):
Levosimendan 28%vs Dobutamine15%, p=0.022

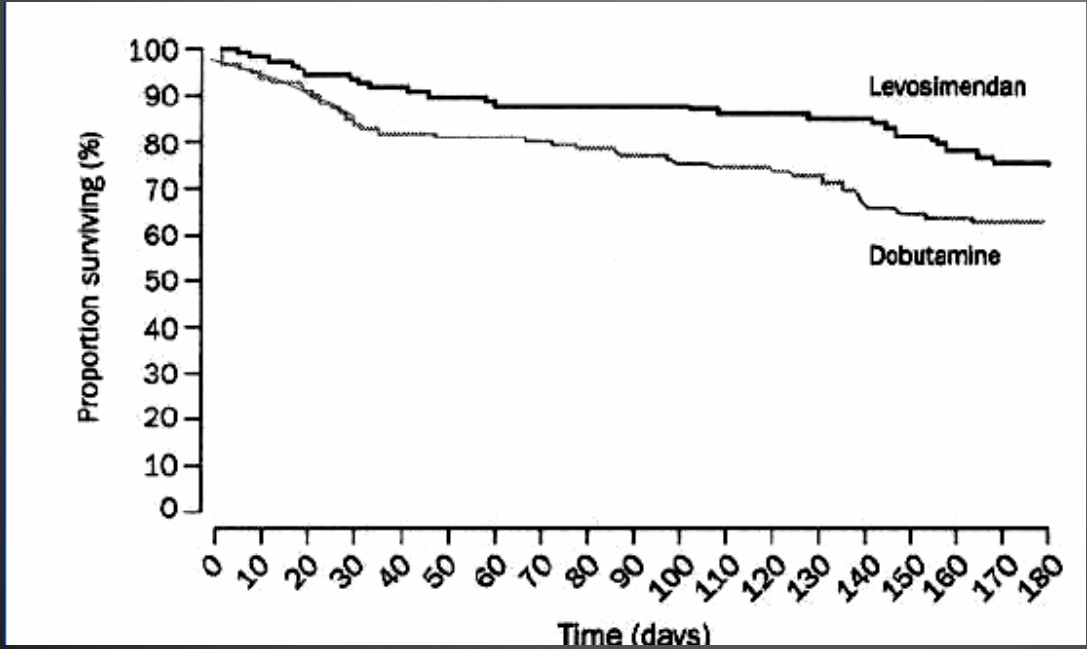




Follath et al,Lancet 2002; 360: 196-202

LIDO Study

	Dobutamine	Levosindeman	p
Arrhytmias	13	4	0.023
Myocardial Ischemia	7	0	0.013
Hypotension	4	9	NS
Headache	5	14	NS



Mortality (30 days)
levo 8% vs dobut 7%
p =0.049
HR: 0.43 (0.18-1.00)

Mortality (180 days)
levo 26% vs dobut 38%
p =0.029
HR: 0.57 (0.34-0.95)

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

CASINO study

299 patients low-output HF, levo vs. dobut vs. placebo.

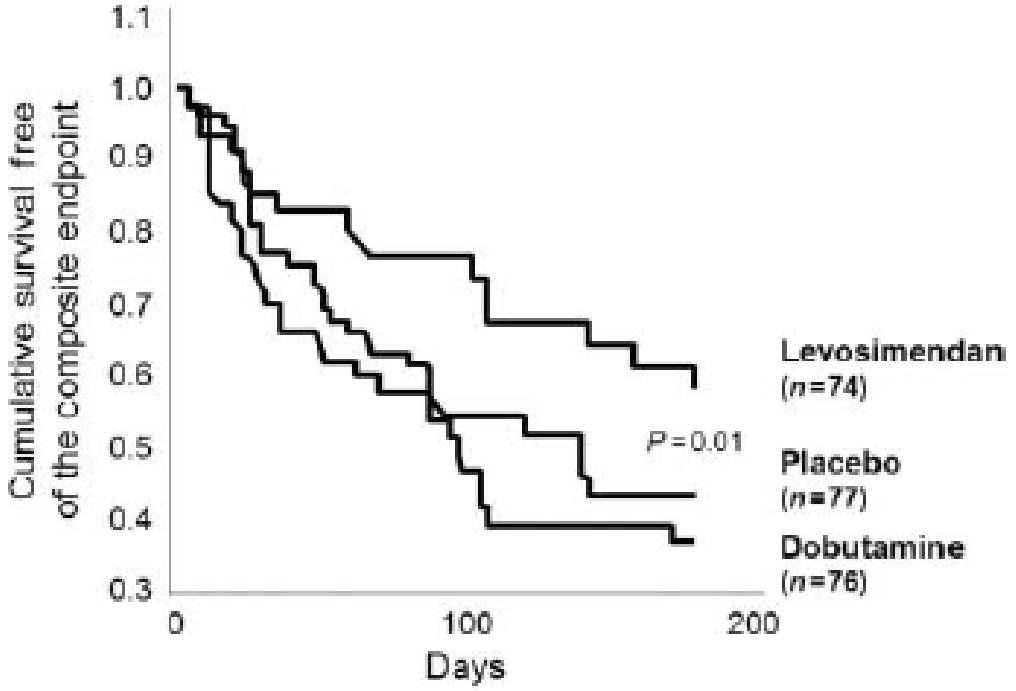
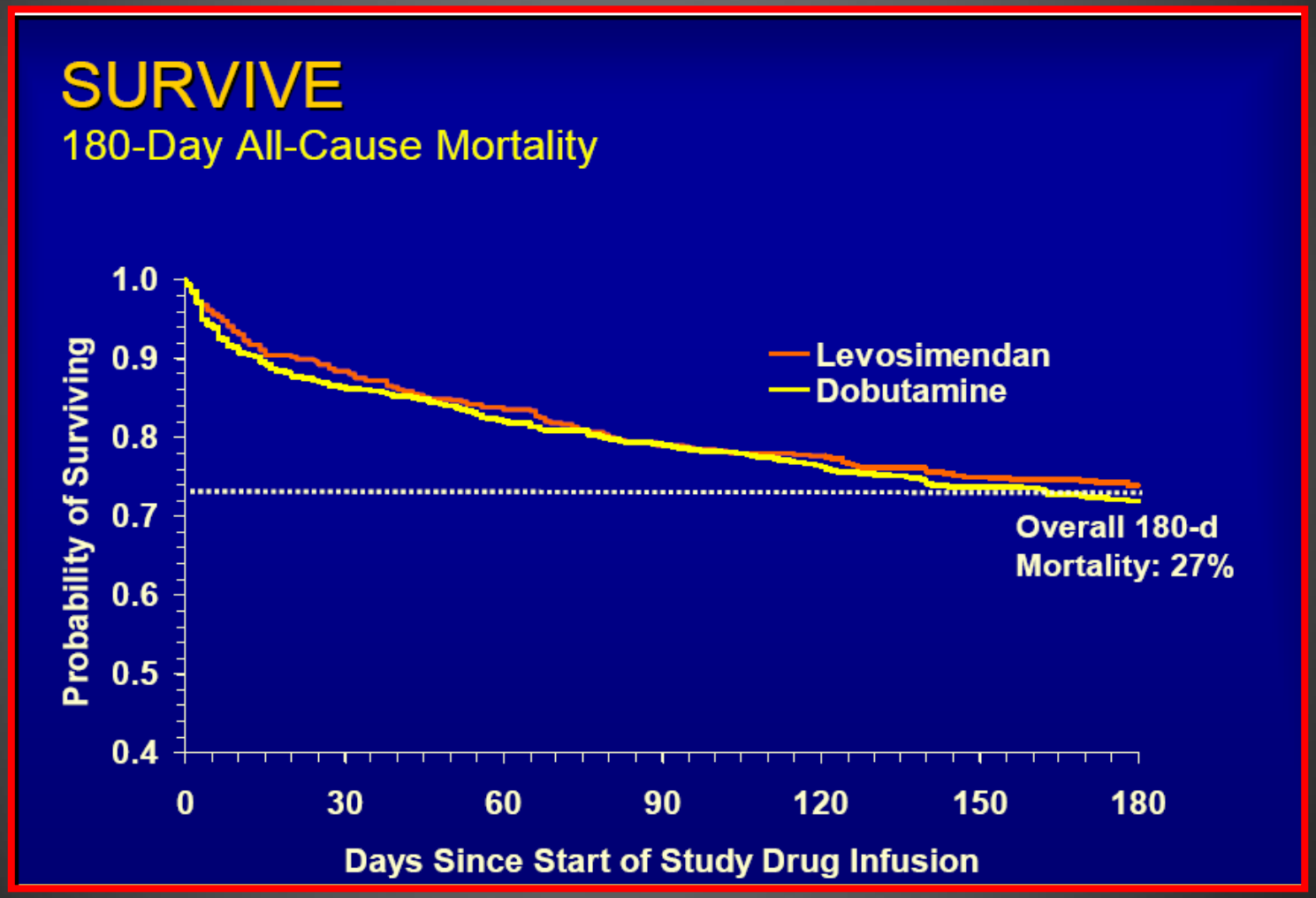


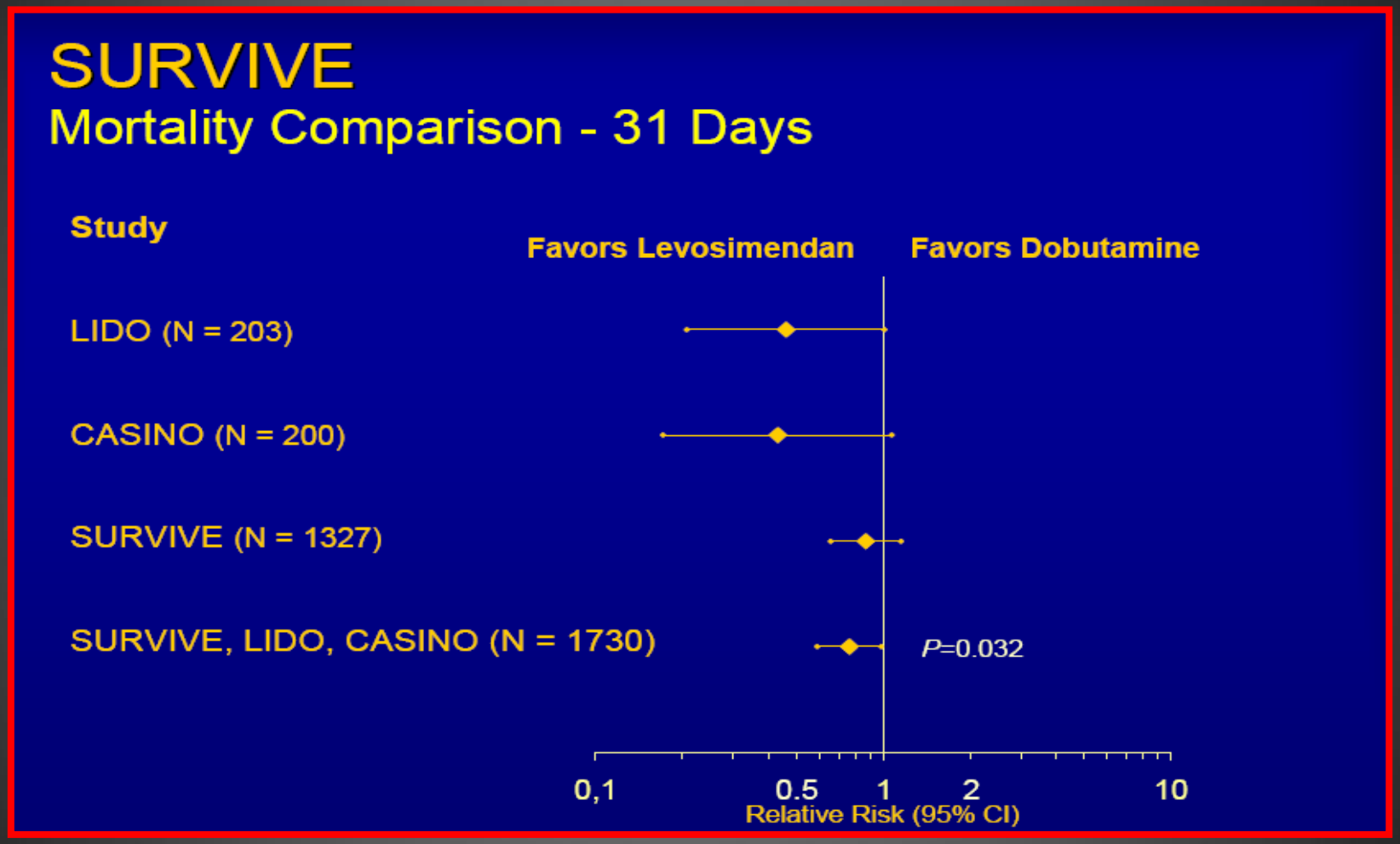
Figure 4 Survival curves for the three treatment arms of the CASINO study before complete follow-up of patients.[50]

SURVIVE study



JAMA 2007; 297: 1883-91

SURVIVE study



JAMA 2007; 297: 1883-91

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

- Levosimendan vs placebo: no increase in mortality (6 studies, 1578 patients, RR 0.83, IC 95% 0.62-1.10, p: 0.02)

- Levosimendan vs Dobutamine: survival increase (8 studies, 1979 patients, RR 0,75, IC 95% 0.61-0.92, p: 0.005)

Int J Cardiol, inn press

Table 27 Goals of treatment in acute heart failure

- **Immediate (ED/ICU/CCU)**
  - Improve symptoms
  - Restore oxygenation
  - Improve organ perfusion and haemodynamics
  - Limit cardiac/renal damage
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  - Educate and initiate appropriate lifestyle adjustments
  - Provide adequate secondary prophylaxis
  - Prevent early readmission
  - Improve quality of life and survival

GRAZIE PER L'ATTENZIONE!