Levosimendan en la Insuficiencia Cardiaca Aguda

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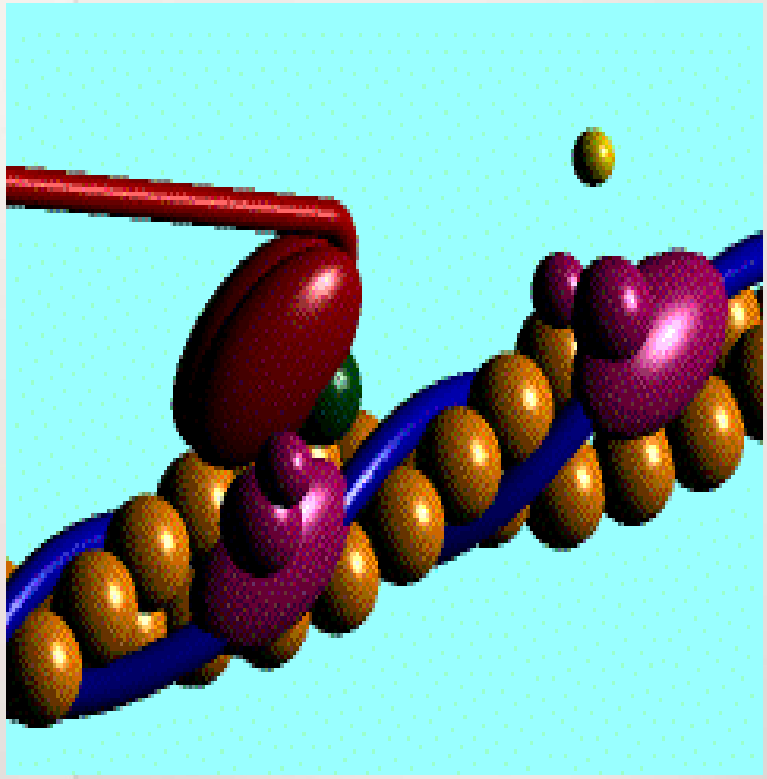
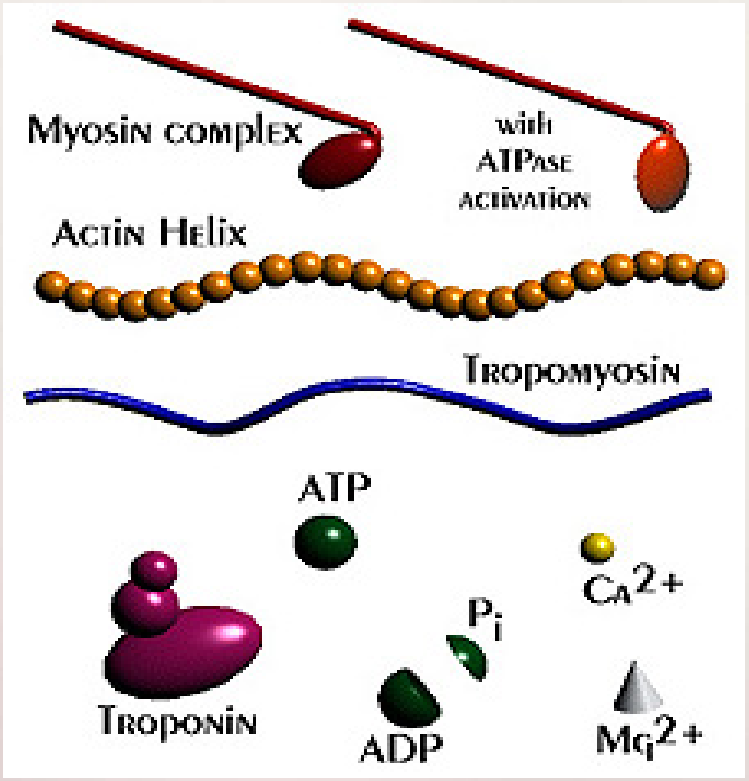
Inotropos

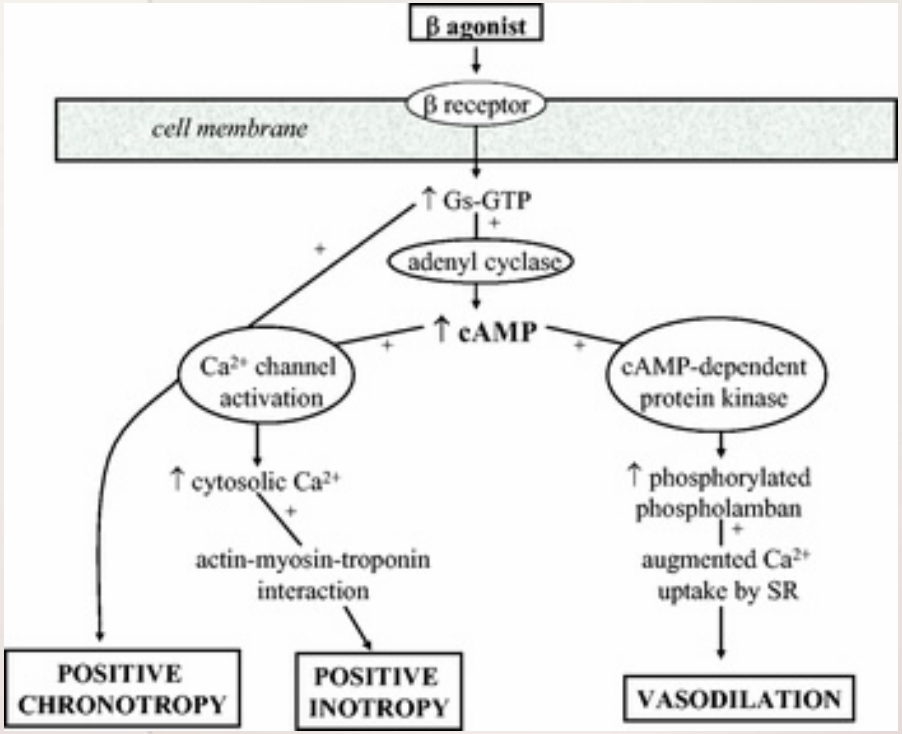
- Acciones a nivel muscular y músculo liso vascular; Metabólico, SNC, SNA
- Se administran en situaciones clínicas críticas para aumentar el GC o el tono vascular como puente a recuperación
- Eficacia clínica: Hemodinámica
- Práctica clínica: Opiniones de expertos, estudios randomizados, preferencia del médico

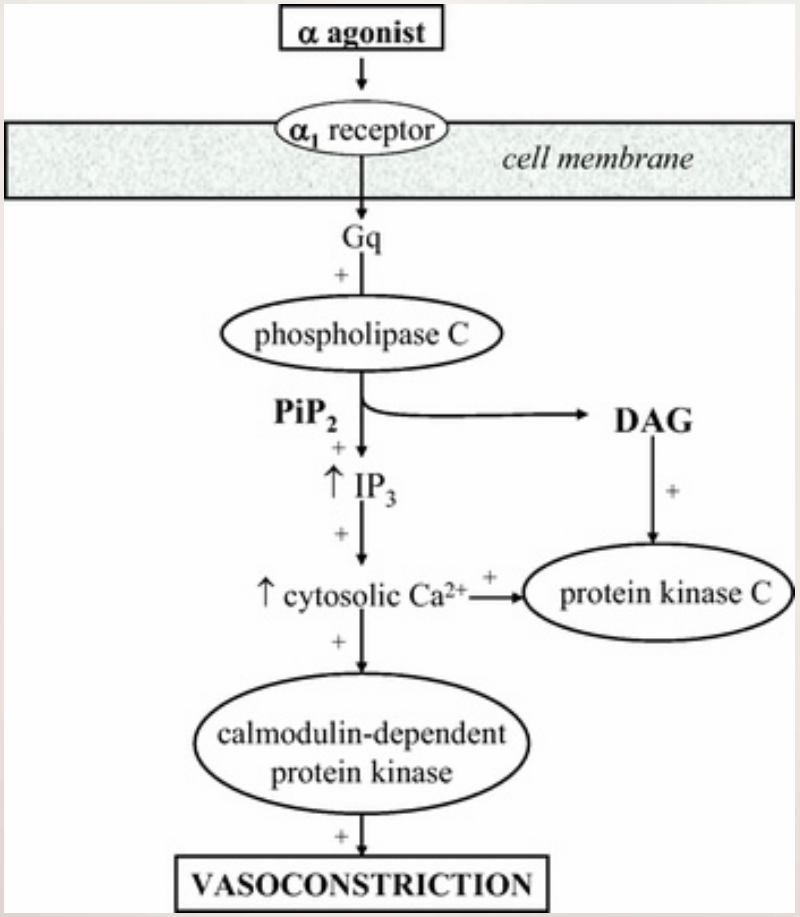
Contracción músculo cardiaco





Receptores catecolaminérgicos





- Receptores D1 y D2: Vasodilatación renal y mesentérica

Overgaard, Circulation 2008;118:1047

Fármacos catecolaminérgicos

Droga	Indicación	Dosis	Receptor α1	β1	β2	DA
Dopamina	Shock (vasodilación/ Cardiogénico) IC (**IIb/C**) Bradicardia	2-20 ug/kg/min	+++	++++	++	+++++
Dobutamina	Bajo GC (shock car/ disf mioc en sepsis) IC (**IIa/B**) Bradicardia	2-20 ug/kg/min	+	+++++	+++	N/A
Norepinefrina	Shock (vasodilatado/ cardiogénico) **IIb/C**	0,01-3 ug/kg/min	+++++	+++	++	N/A
Epinefrina	Paro cardiaco **IIb/C**	1 mg/3-5 min	+++++	++++	+++	N/A
Isoproterenol	Bradiarritmias Sde. Brugada	2-10 ug/min	0	+++++	+++++	N/A
Fenilefrina	Hipotensión Eao+hipoTA MHO con gradiente	0,4-9 ug/kg/min	+++++	0	0	N/A

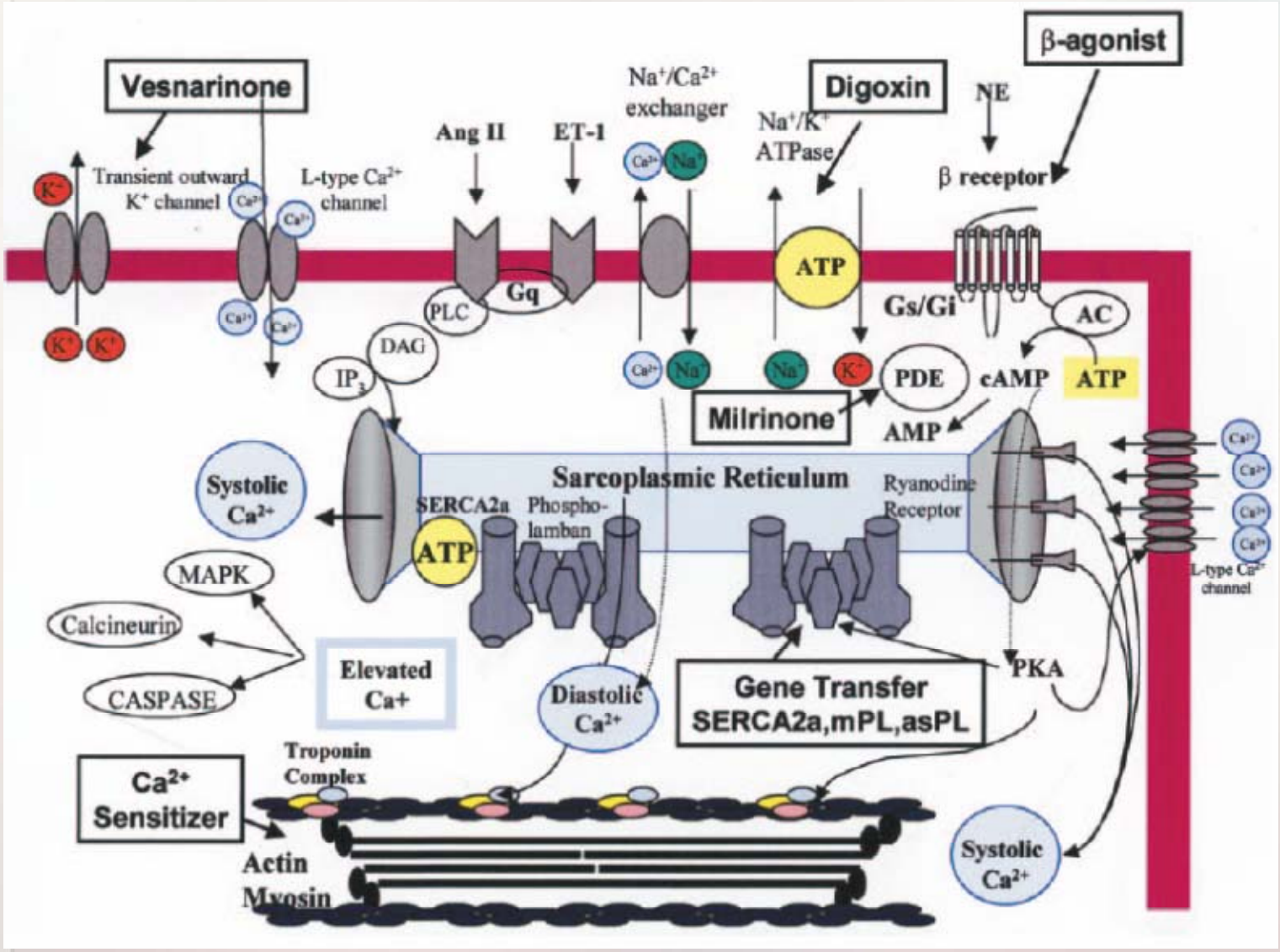
Overgaard, Circulation 2008;118:1047

Problemas fármacos catecolaminérgicos

- Aumento de la demanda de oxígeno
- Arritmias supraventriculares y ventriculares
- Vasoconstricción coronaria
- Expansión del infarto
- Desensibilización y disminución de los receptores beta en IC crónica

Overgaard, Circulation 2008;118:1047

Otros inotropos



Stevenson LW. Circulation 2003;108:367

Milrinona

- Acción inotropa, vasodilatadora y lusitrópica
- Vida media 2-4 h
- Útil en contexto de tto Bbloq

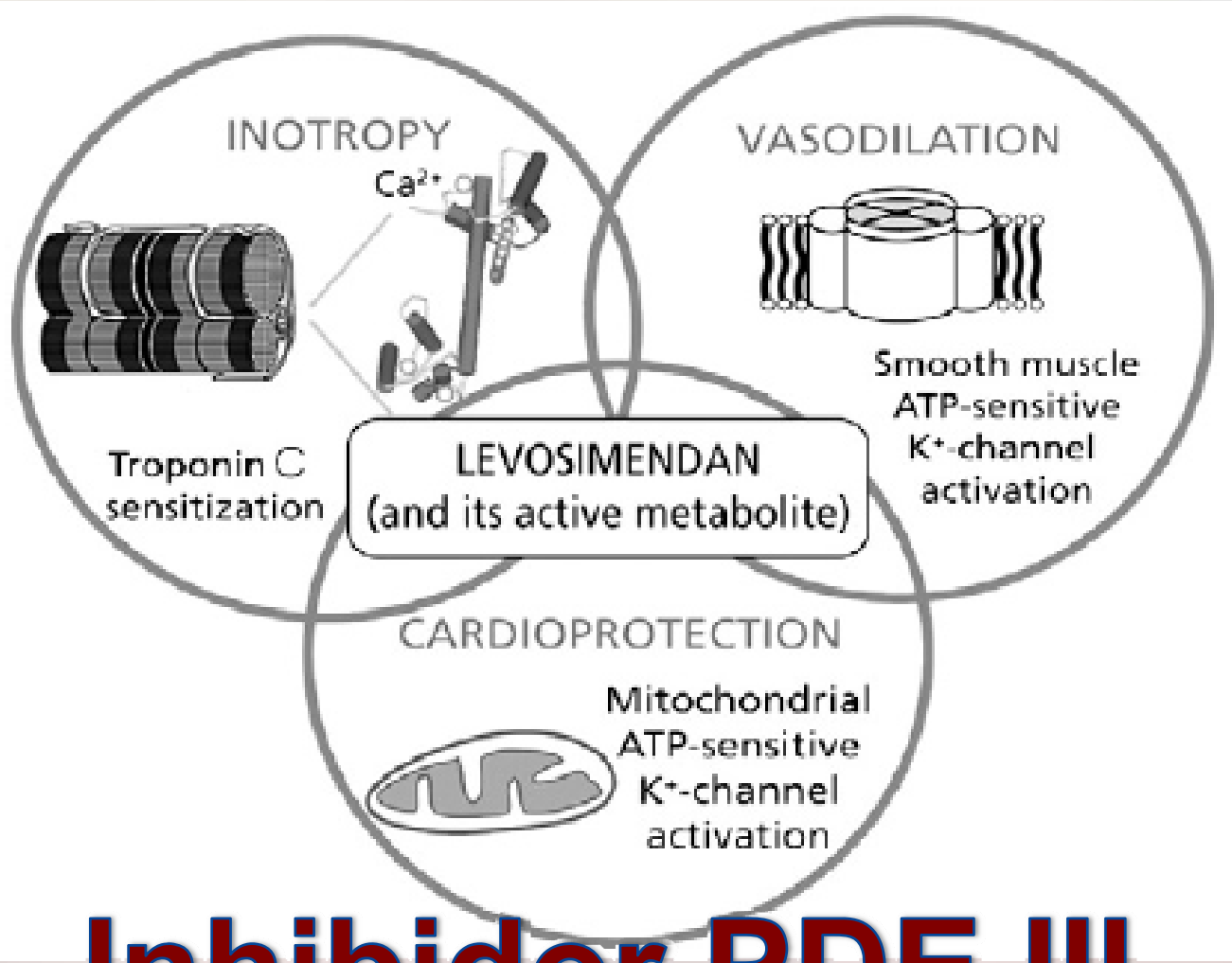
Table 6. Adverse Events and Mortality*

Adverse Event, No. (%)	Placebo (n = 472)	Milrinone (n = 477)	*P* Value
Treatment failure cause at 48 hours	43/466 (9.2)	97/470 (20.6)	<.001
Progression of heart failure	6.8	7.9	.54
Adverse event	2.1	12.6	<.001
Events during index hospitalization			
Myocardial infarction	2 (0.4)	7 (1.5)	.18
New atrial fibrillation or flutter	7 (1.5)	22 (4.6)	.004
Ventricular tachycardia or fibrillation†	7 (1.5)	16 (3.4)	.06
Sustained hypotension‡	15 (3.2)	51 (10.7)	<.001
Death	11 (2.3)	18 (3.8)	.19
Events within 60 days			
Myocardial infarction	5/448 (1.1)	10/462 (2.2)	.21
New atrial fibrillation or flutter	16/446 (3.6)	26/462 (5.6)	.14
Ventricular tachycardia or fibrillation	20/446 (4.5)	23/461 (5.0)	.72
Death	41/463 (8.9)	49/474 (10.3)	.41

OPTIME-CHF Cuffe et al. JAMA 2002;287:1541

Levosimendan: Mecanismos de acción

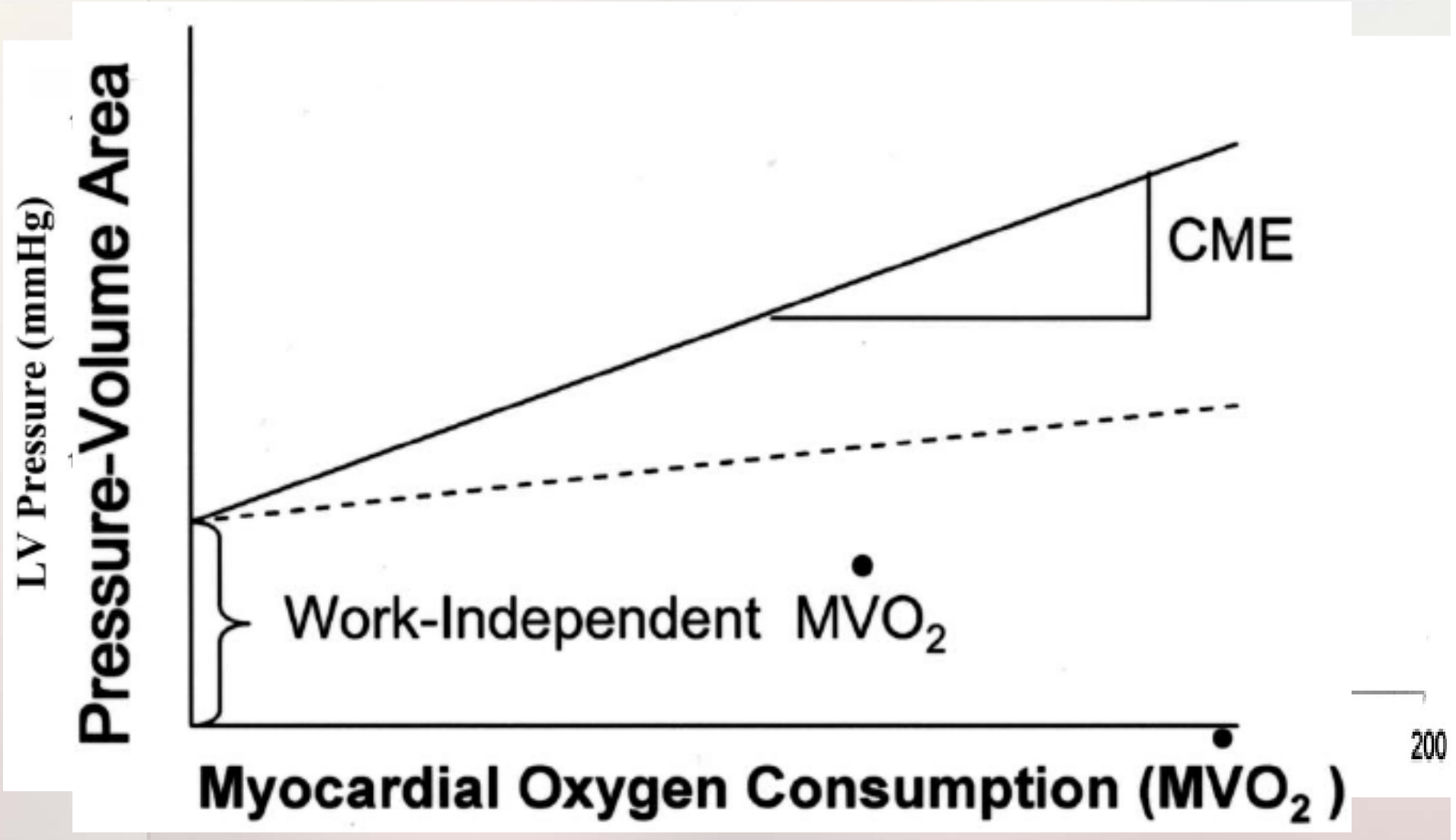
- Levo no
- Acet o
- OR-1



Inhibidor PDE III

Papp et al. Int J Cardiol 2012; 159:82

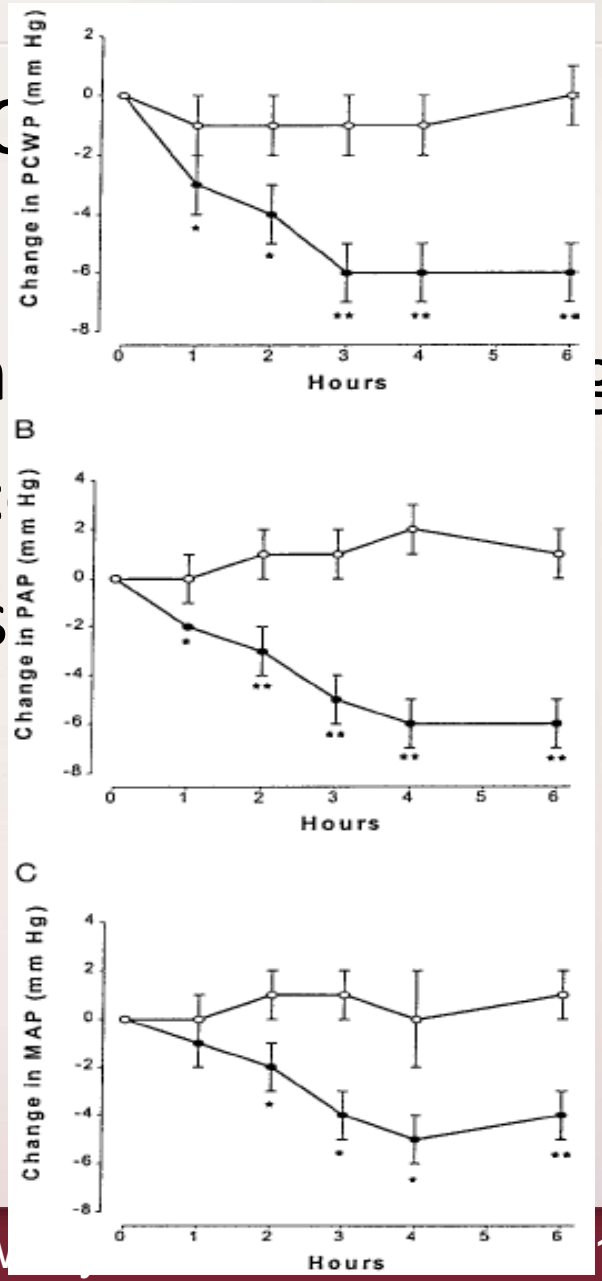
Efectos hemodinámicos

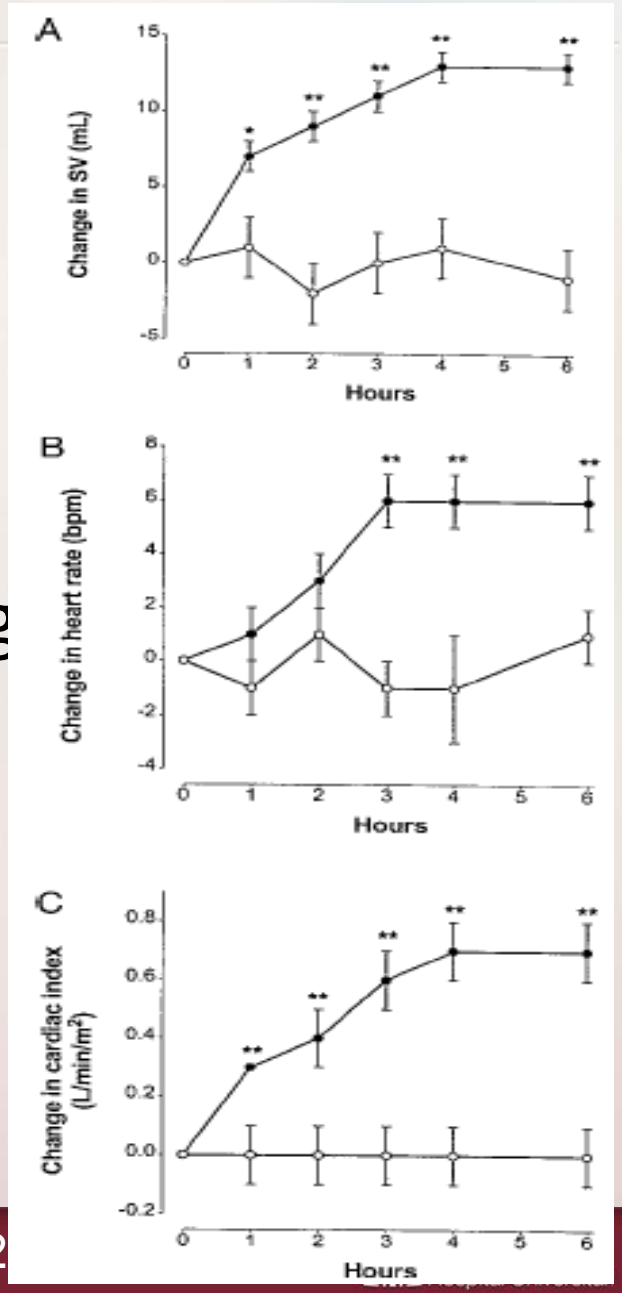


Kass et al. Circulation 2006; 113:305

Efectos hemodinámicos in vivo

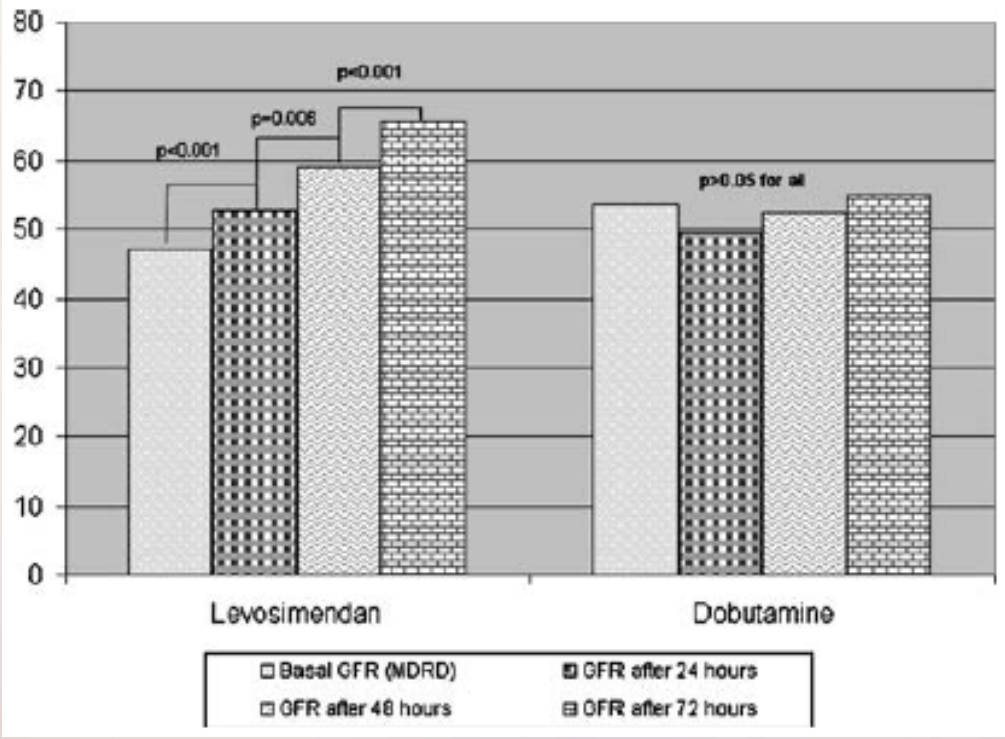
- N=146 con IC
- FEVI=21%
- IC<2,5 L/min
- Levo vs. plac
- Bolus + infus
  hora





Otros efectos Levosimendan

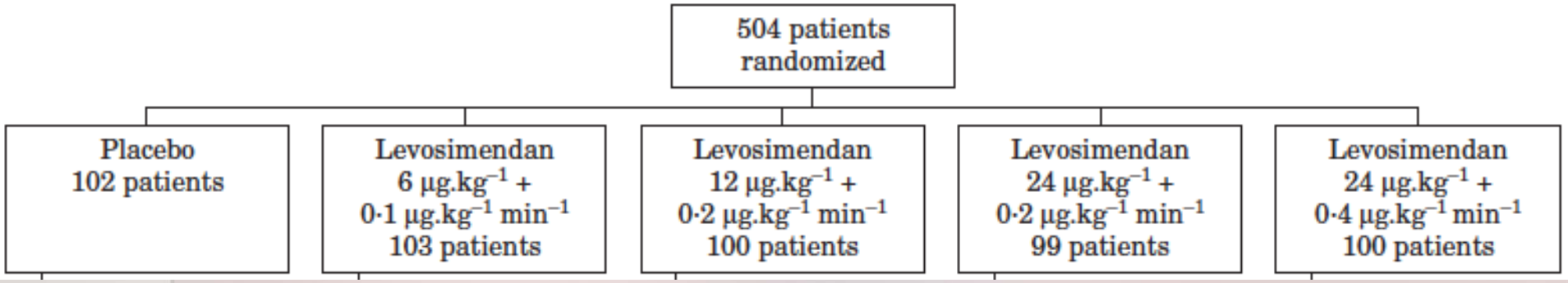
- Inhibe agregación plaquetar
- Vasodilatación coronaria
- Efectos lusitrópicos en pacientes con hipertrofia VI



Kaptan Am J Hematol 2008; Yilmaz Cardiovasc Drugs Ther 2007
Michaels Circulation 2005; Jorgensen Circulation 2008

RUSSLAN

- N=504 pacientes post-IAM: Seguridad
- Criterios inclusión:
  - Signos IC en RX tórax
  - Necesidad clínica de inotropo
- Criterios exclusión:
  - PAS<90 mm Hg
  - Arritmias



Moiseyev et al. Eur Heart J 2002;23:1422

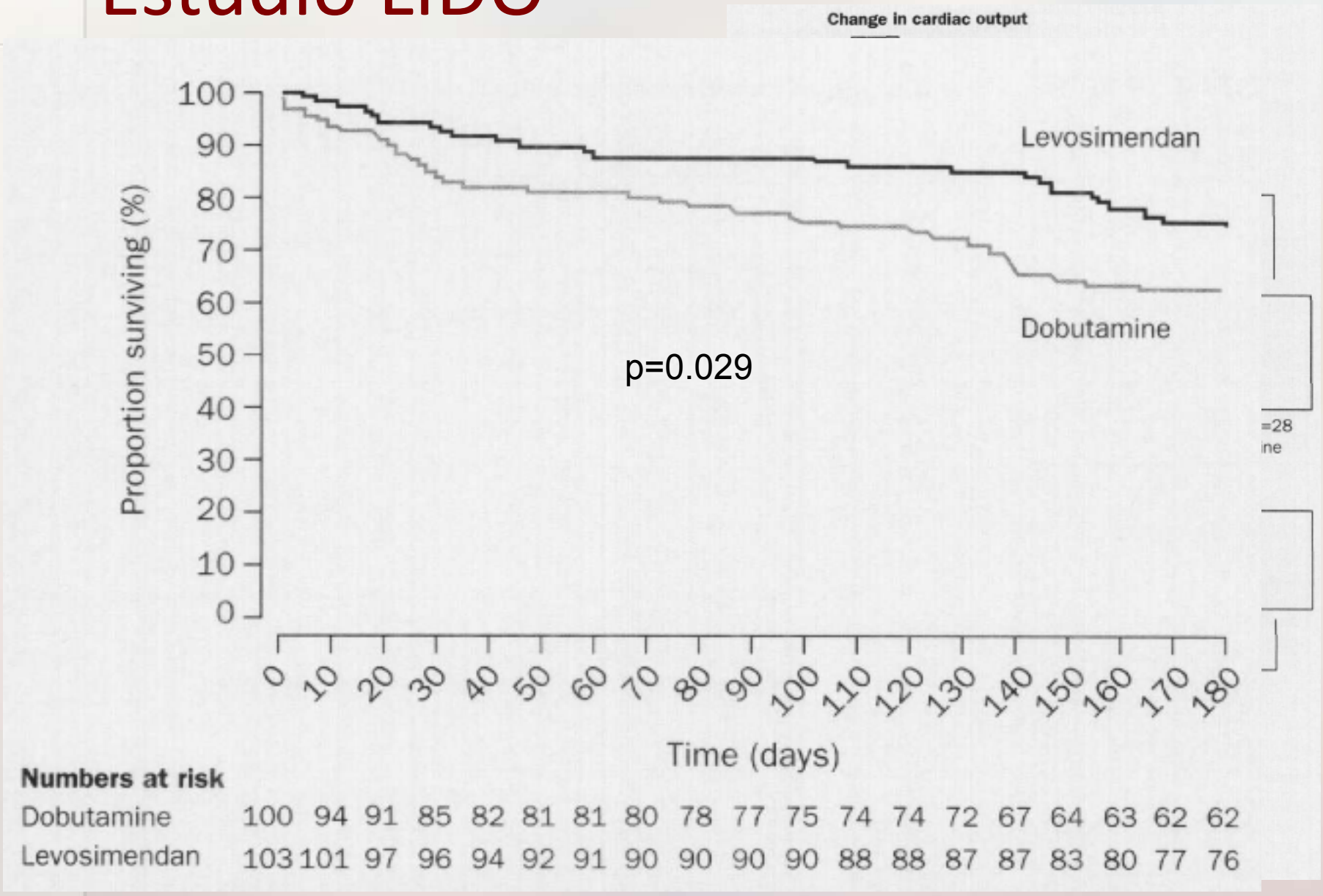
RUSSLAN

	Placebo (n=102)	Levosimendan 6 µg . kg^{-1}+ 0·1 µg . kg^{-1} . min^{-1} (n=103)
Thrombolytics (%)	15·7	17·5
Cardiac glycosides (%)	12·6	10·8
Dopamine (%)	13·6	14·7
Intravenous inotropes (others than cardiac glycosides and dopamine) (%)	6·8	9·8
Diuretics (%)	69·9	75·5
ACE-inhibitors (%)	44·7	46·1
Beta-blockers (%)	40·8	42·2
Calcium channel blockers (%)	14·6	10·8
Nitrates (%)	94·2	97·1
Antiarrhythmics (%)	30·1	22·5
Analgesics (%)	79·6	84·3
Acetylsalicylic acid (%)	88·3	90·2
Heparin/heparin analogues (%)	77·7	88·2

¿FEVI?

Moiseyev et al. Eur Heart J 2002;23:1422

Estudio LIDO



Follath et al. Lancet 2002;360:196

CASINO

- Estudio randomizado, doble ciego en 600 pacientes con ICA (FEVI<35%)
- Levo vs DBT vs Placebo durante 24 horas
- ¡¡No publicado!!
- Stop prematuro tras 300 pacientes por mortalidad a 6 meses:
  - Levo 18%
  - DBT 42%
  - Placebo 28%

Cleland JG et al. Eur J Heart Fail 2006;8:104

REVIVE

- Estudio randomizado doble ciego
- N=600 pacientes con IC descompensada CF IV que precisaban diurético ev
- [redacted] ¡¡No publicado!! [redacted] ien tolerada subir a 0,2 ug/kg/min 23 horas
- Mejoría clínica con Levo a los 5 días
- Tendencia a incremento mortalidad con Levo (15%) vs placebo (11,6%) a 90 días:
  - Hipotensión arterial y arritmias ventriculares

Petersen et al. Crit Care Med 2008;36Suppl:S106

SURVIVE

- N=1327; Randomizado, doble ciego
- ICA + FE<30%; Insuficiente respuesta a diuréticos/vasodilatadores y uno de:
  - Disnea en reposo o IOT
  - Oliguria sin hipovolemia
  - PCP>18 y/o IC<2,2
- Bolus Levosimendán (12 ug/kg) + infusión 0,1 ug/kg/min y 0,2 ug/kg/min en 1 hora hasta 24 h
- Dobutamina a 5 ug/kg/min e incrementos hasta 40 ug/kg/min y retirar según clínica

Mebazaa et al. JAMA 2007;297:1883

SURVIVE

Figure 4. Mean Change From Baseline in Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate Through 5 Days by Treatment Group

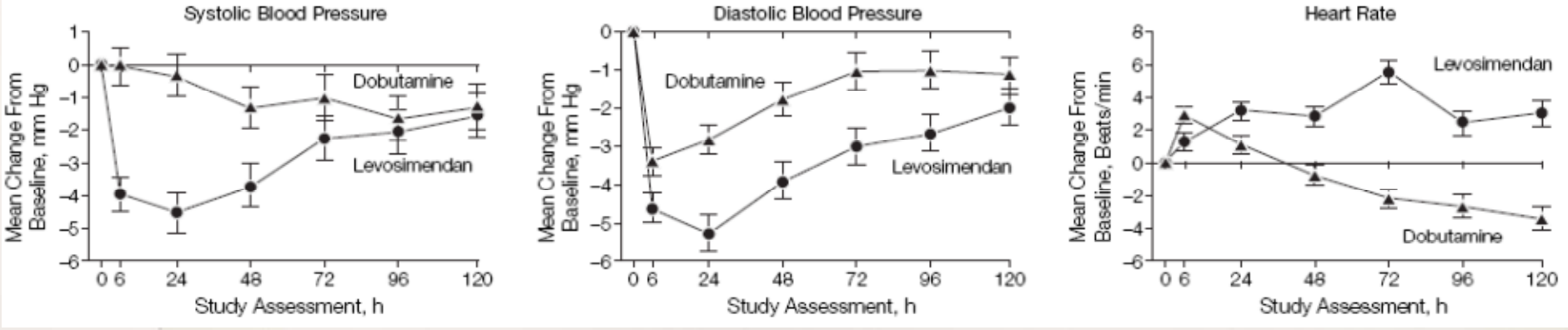


Figure 3. Mean Change From Baseline in B-Type Natriuretic Peptide Levels at 1, 3, and 5 Days by Treatment Group

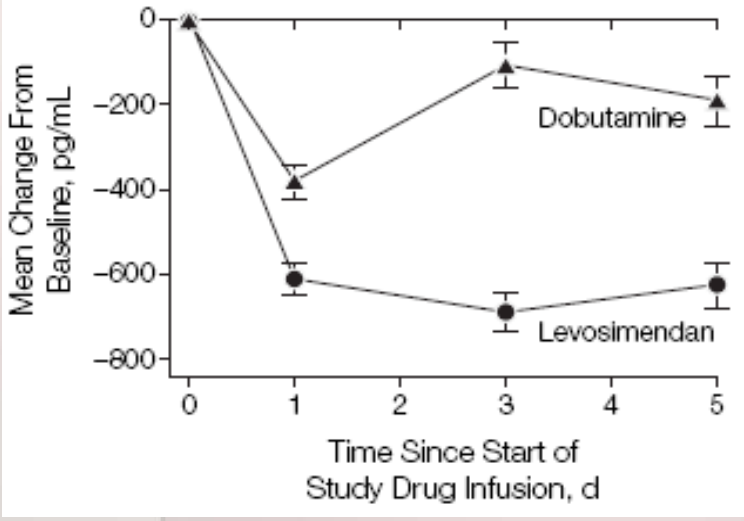
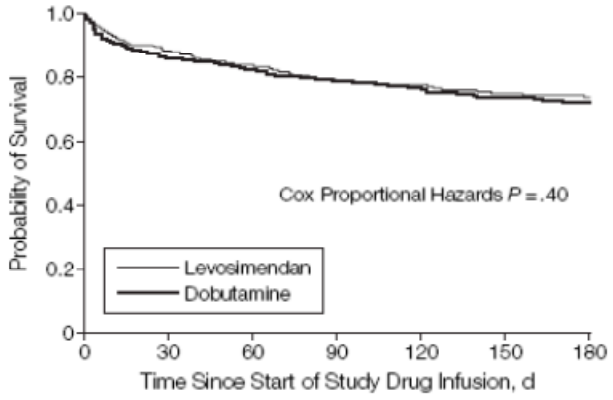


Figure 2. Effect of Dobutamine and Levosimendan Treatment on All-Cause Mortality During 180 Days Following the Start of Study Drug Infusion



No. at Risk

Levosimendan	664	608	586	525	462
Dobutamine	663	596	568	519	454

Mebazaa et al. JAMA 2007;297:1883

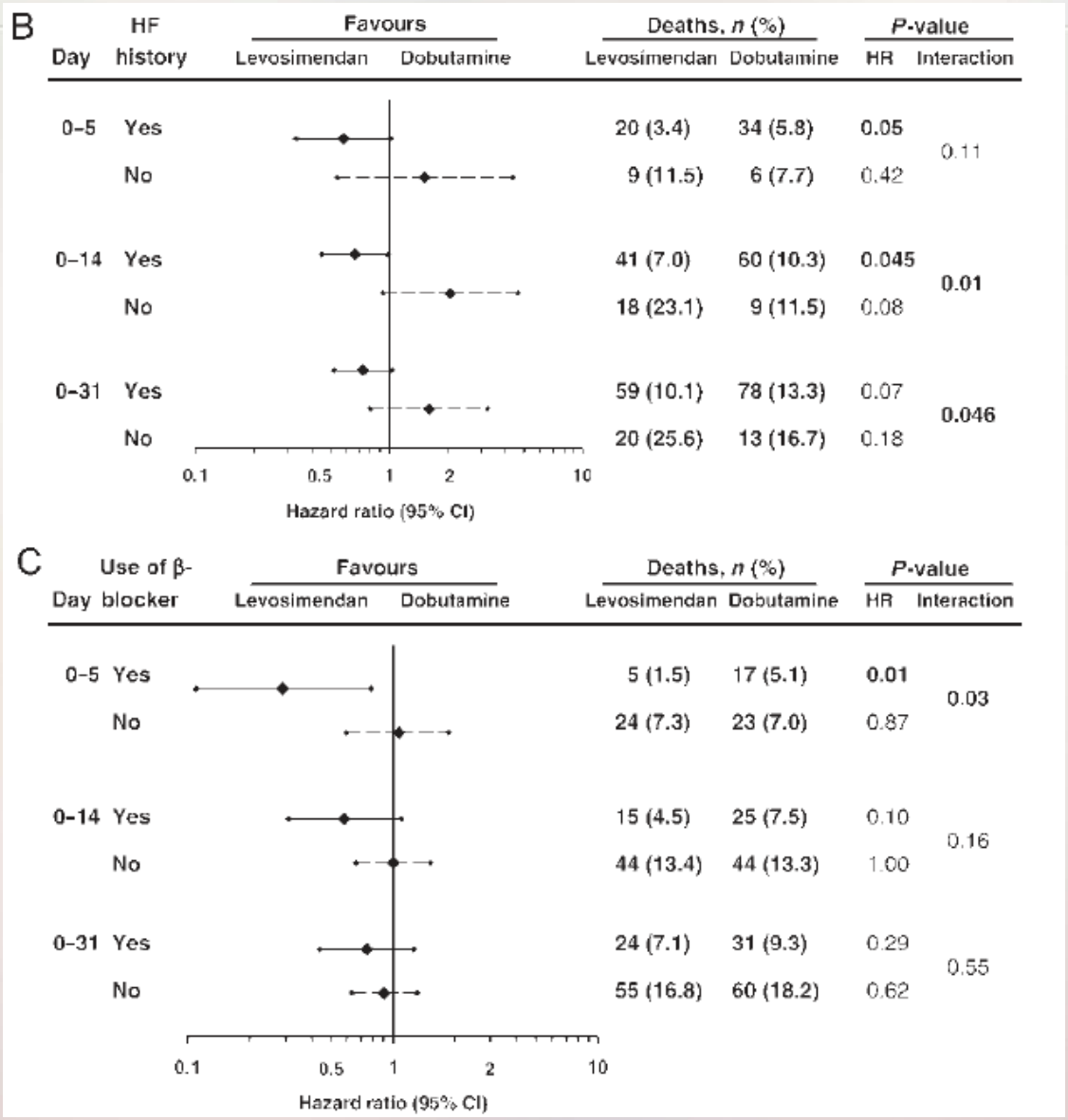
SURVIVE

Table 5. Treatment-Emergent Adverse Events*

	No. (%) of Patients		
	Levosimedan (n = 660)	Dobutamine (n = 660)	*P* Value†
Any adverse event	518 (78.5)	502 (76.1)	.32
Any serious adverse event‡	195 (29.5)	217 (32.9)	.21
Hypotension	102 (15.5)	92 (13.9)	.48
Cardiac failure§	81 (12.3)	112 (17.0)	.02
Hypokalemia	62 (9.4)	39 (5.9)	.02
Atrial fibrillation	60 (9.1)	40 (6.1)	.05
Headache	55 (8.3)	31 (4.7)	.01
Ventricular tachycardia	52 (7.9)	48 (7.3)	.76
Nausea	45 (6.8)	49 (7.4)	.75
Ventricular extrasystoles	40 (6.1)	24 (3.6)	.05
Insomnia	37 (5.6)	29 (4.4)	.38
Tachycardia	33 (5.0)	33 (5.0)	>.99
Chest pain	32 (4.8)	47 (7.1)	.10

Mebazaa et al. JAMA 2007;297:1883

Posible beneficio en subgrupos



Mebazaa et al. Eur J Heart Fail 2009;11:304

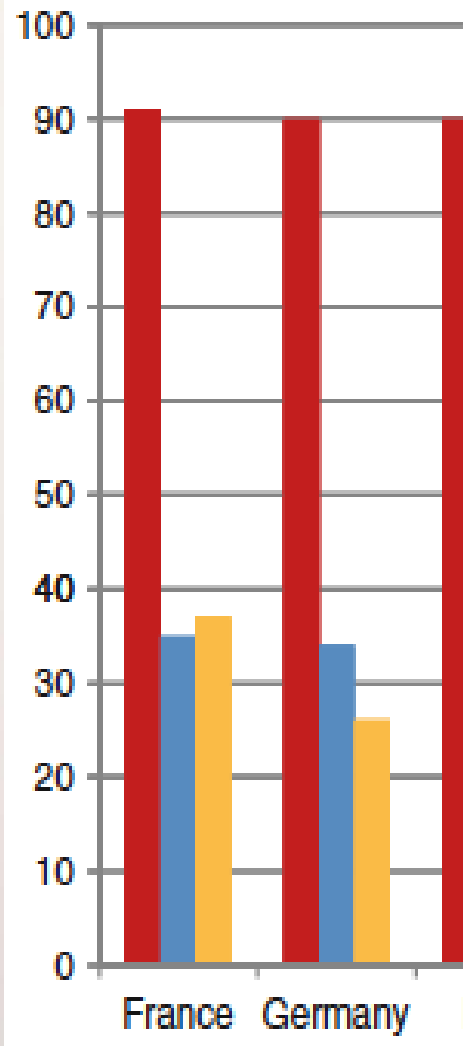
Guías IC

Recommendations	Class[a]	Level[b]
Patients with pulmonary congestion/oedema without shock		
An i.v. loop diuretic is recommended to improve breathlessness and relieve congestion. Symptoms, urine output, renal function, and electrolytes should be monitored regularly during use of i.v. diuretic.	I	B
High-flow oxygen is recommended in patients with a capillary oxygen saturation <90% or PaO_2 <60 mmHg (8.0 kPa) to correct hypoxaemia.	I	C
Thrombo-embolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism.	I	A
Non-invasive ventilation (e.g. CPAP) should be considered in dyspnoeic patients with pulmonary oedema and a respiratory rate >20 breaths/min to improve breathlessness and reduce hypercapnia and acidosis. Non-invasive ventilation can reduce blood pressure and should not generally be used in patients with a systolic blood pressure <85 mmHg (and blood pressure should be monitored regularly when this treatment is used).	IIa	B
An i.v. opiate (along with an antiemetic) should be considered in particularly anxious, restless, or distressed patients to relieve these symptoms and improve breathlessness. Alertness and ventilatory effort should be monitored frequently after administration because opiates can depress respiration.	IIa	C
An i.v. infusion of a nitrate should be considered in patients with pulmonary congestion/oedema and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Nitrates may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitrates.	IIa	B
An i.v. infusion of sodium nitroprusside may be considered in patients with pulmonary congestion/oedema and a systolic blood pressure >110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Caution is recommended in patients with acute myocardial infarction. Nitroprusside may also relieve dyspnoea and congestion. Symptoms and blood pressure should be monitored frequently during administration of i.v. nitroprusside.	IIb	B
Inotropic agents are NOT recommended unless the patient is hypotensive (systolic blood pressure <85 mmHg), hypoperfused, or shocked because of safety concerns (atrial and ventricular arrhythmias, myocardial ischaemia, and death).	III	C

Guías IC

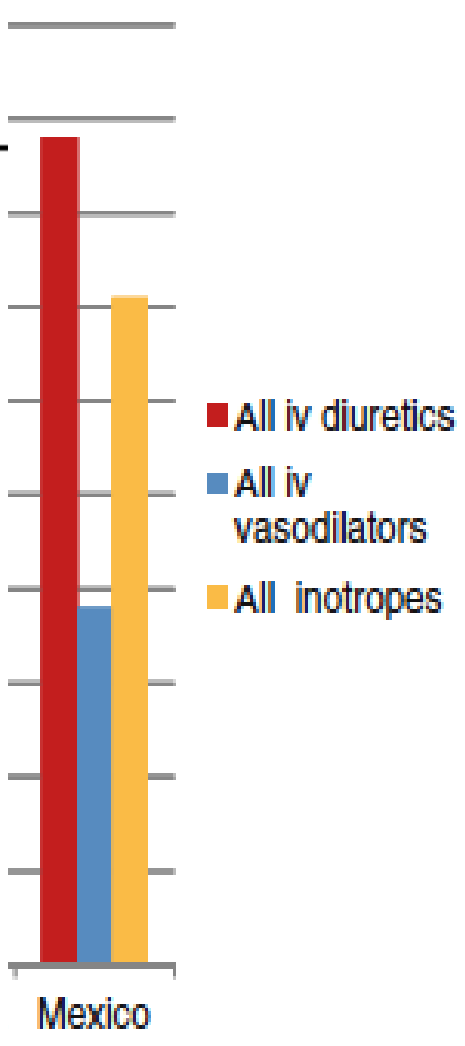
Patients with hypotension, hypoperfusion or shock		
Electrical cardioversion is recommended if an atrial or ventricular arrhythmia is thought to be contributing to the patient's haemodynamic compromise in order to restore sinus rhythm and improve the patient's clinical condition.	I	C
An i.v. infusion of an inotrope (e.g. dobutamine) should be considered in patients with hypotension (systolic blood pressure <85 mmHg) and/or hypoperfusion to increase cardiac output, increase blood pressure, and improve peripheral perfusion. The ECG should be monitored continuously because inotropic agents can cause arrhythmias and myocardial ischaemia.	IIa	C
Short-term mechanical circulatory support should be considered (as a 'bridge to recovery') in patients remaining severely hypoperfused despite inotropic therapy and with a potentially reversible cause (e.g. viral myocarditis) or a potentially surgically correctable cause (e.g. acute interventricular septal rupture).	IIa	C
An i.v. infusion of levosimendan (or a phosphodiesterase inhibitor) may be considered to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypoperfusion. The ECG should be monitored continuously because inotropic agents can cause arrhythmias and myocardial ischaemia, and, as these agents are also vasodilators, blood pressure should be monitored carefully.	IIb	C
A vasopressor (e.g. dopamine or norepinephrine) may be considered in patients who have cardiogenic shock, despite treatment with an inotrope, to increase blood pressure and vital organ perfusion. The ECG should be monitored as these agents can cause arrhythmias and/or myocardial ischaemia. Intra-arterial blood pressure measurement should be considered.	IIb	C
Short-term mechanical circulatory support may be considered (as a 'bridge to decision') in patients deteriorating rapidly before a full diagnostic and clinical evaluation can be made.	IIb	C

ALARM-HF



Treatment performed

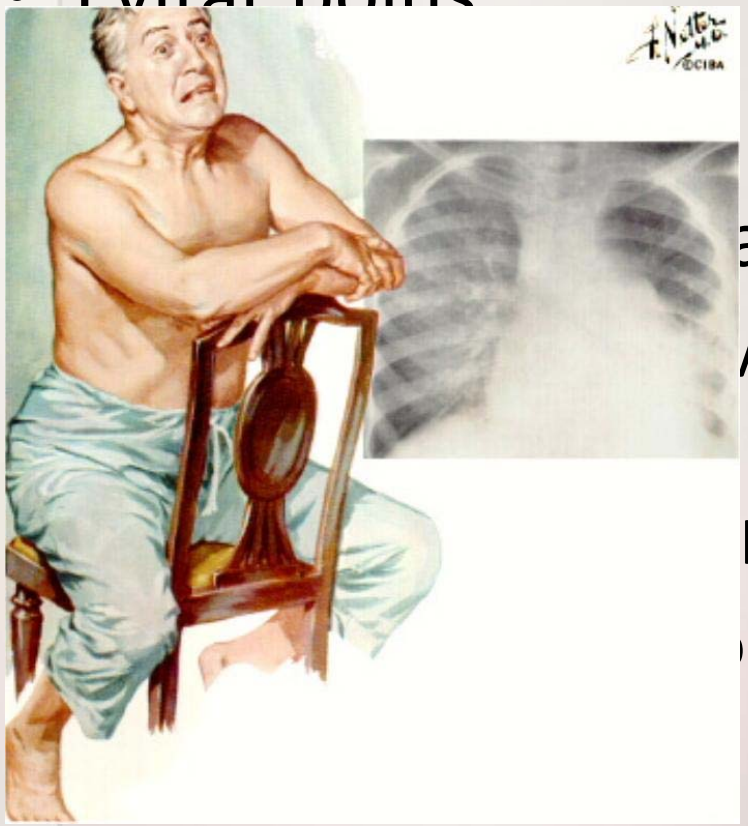
	All, $n = 4,953$ (%)
CPAP	9.6
Mechanical ventilation	16.2
Oral diuretic	60.5
IV diuretic	89.7
Oral spironolactone/eplerenone	27.5
IV nitrate	41.1
Beta-blocker	37.8
IV inotrope	
Adrenaline	3.6
Dobutamine	22.3
Dopamine	13.0
Levosimendan	6.4
Noradrenaline	4.2
Amiodarone	2.6
Heparin (UFH)	2.0
LMWH	1.0
PCI	12.8
CABG	3.0
IABP	4.8
Pacemaker	2.5
ICD	1.7
Valvular surgery	3.5
Cardioversion	7.8



Follath et al. Intensive Care Med 2011;37:619

Levosimendan en la práctica

- Evitar bolus



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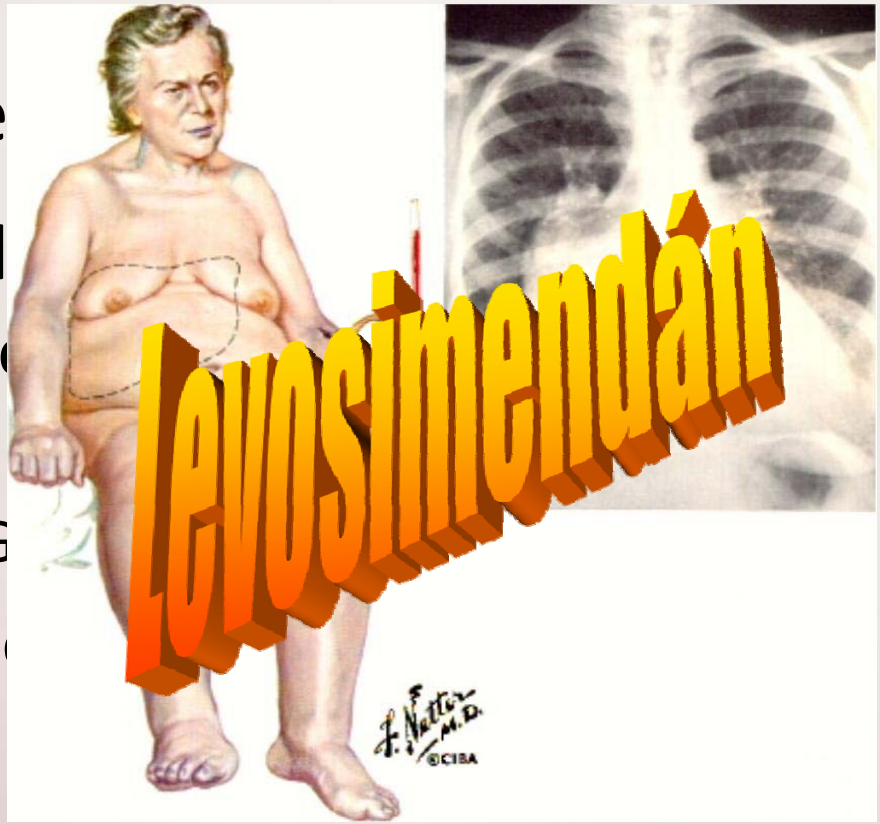
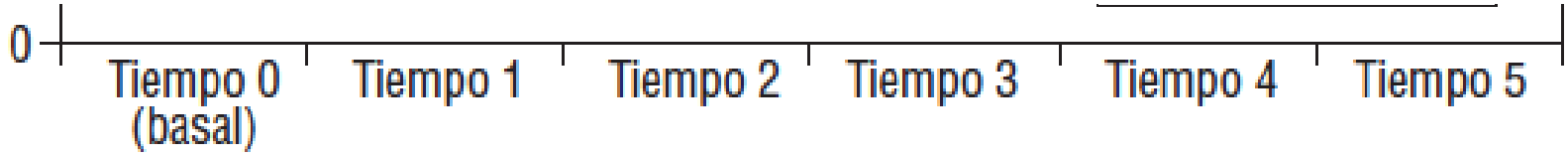
  - Predominio IC derecha



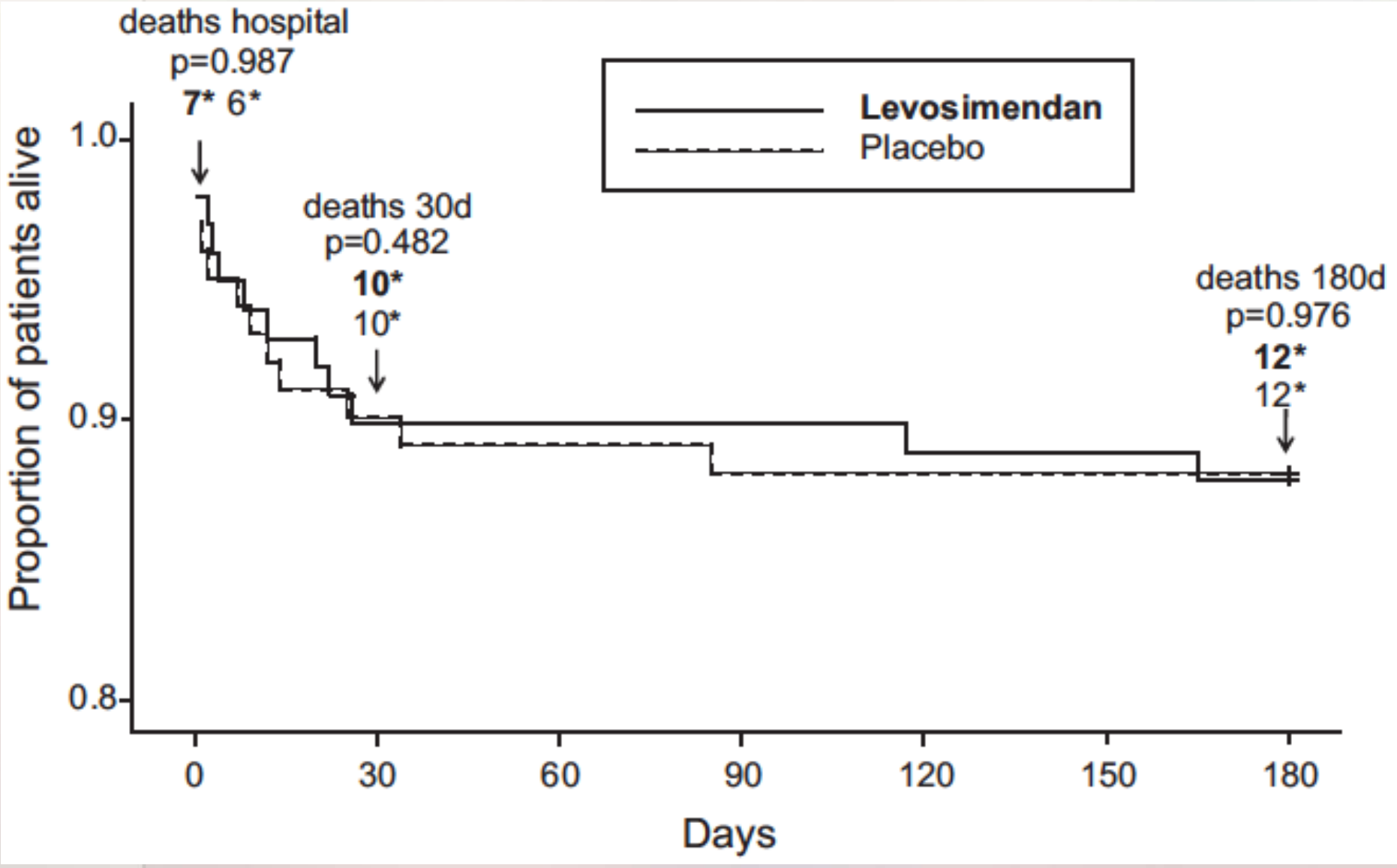
Otros usos: Levo en CCA

Complicación	Levosimendán (n = 69), n (%)	Dobutamina (n = 68), n (%)	p
Infarto perioperatorio	1 (1,4)	8 (11,8)	< 0,05
Vasoplejía	1 (1,4)	9 (13,2)	< 0,05
Insuficiencia renal aguda	5 (7,2)	21 (30,9)	< 0,05
Necesidad de diálisis	2 (2,9)	8 (11,8)	NS
Fibrilación auricular	15 (21,7)	27 (39,7)	NS
Arritmia ventricular	3 (4,3)	12 (17,6)	< 0,05
Disnea	1 (1,4)	4 (5,8)	NS
Neumonía	4 (5,8)	10 (14,7)	NS
Síndrome de respuesta inflamatoria	4 (5,8)	15 (22,1)	< 0,05
Sepsis	1 (1,4)	9 (13,2)	< 0,05
Asistencia ventilatoria prolongada	6 (8,7)	22 (32,3)	< 0,05
Accidente cerebrovascular	2 (2,9)	6 (8,8)	NS
Mortalidad	6 (8,7)	17 (25)	< 0,05



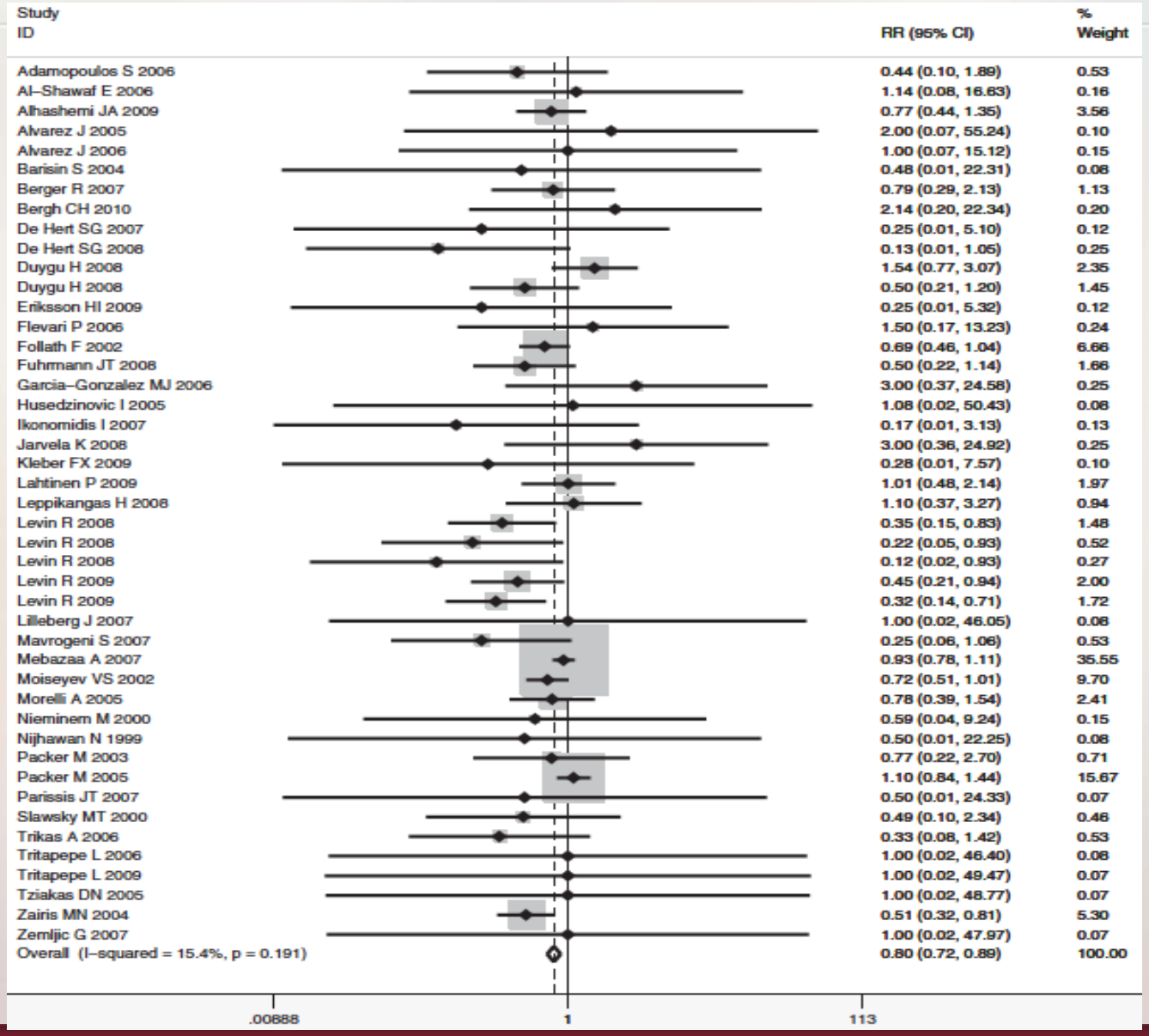
Levin et al. Rev Esp Cardiol 2008;61(5):471

Levo pre-CCA



Lahtinen et al. Crit Care Med 2011;39:2263

Meta-análisis Levosimendan



Landoni et al. Crit Care Med 2012;40:634

Otros usos

- Tako-tsubo
- Sobredosis de antagonistas del calcio
- Disfunción primaria del injerto

De Santis Ann Int Medicine 2008; Varpula Anesth Analg 2009
Weis et al. J Heart Lung Transplant 2009

Conclusión

- Levosimendan es un inodilatador efectivo
- Uso limitado por hipoTA y arritmogénesis
- Indicado en un perfil de paciente con ICC descompensada:
  - No responde a tto vasodilatador y deplectivo:
    - Oliguria
    - Empeoramiento del FG
  - Tto previo con Bbloqueantes
  - PAS>90 mm Hg
  - Predominio IC derecha

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