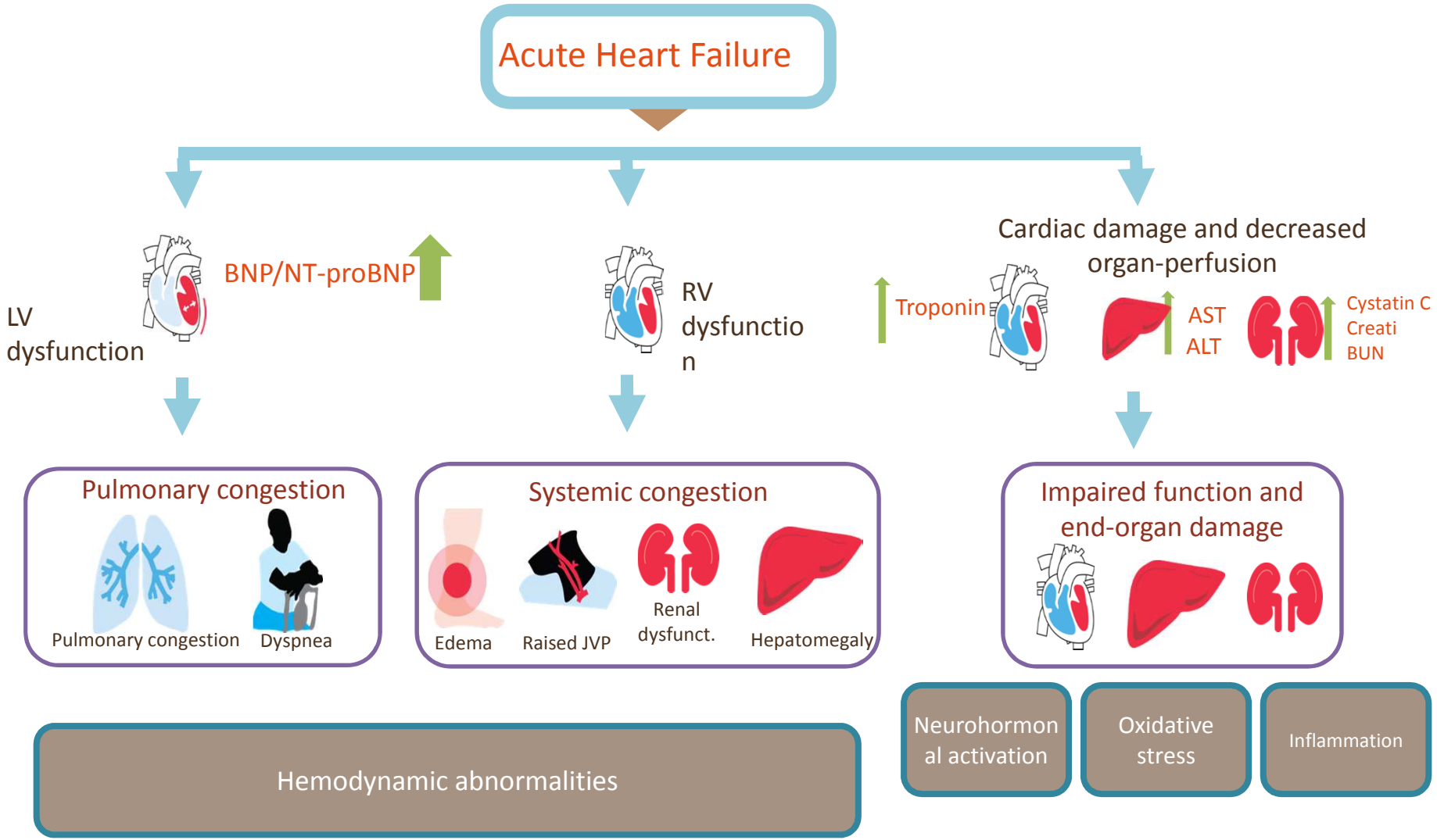
Renoprotección en la insuficiencia cardiaca aguda: papel de la serelaxina

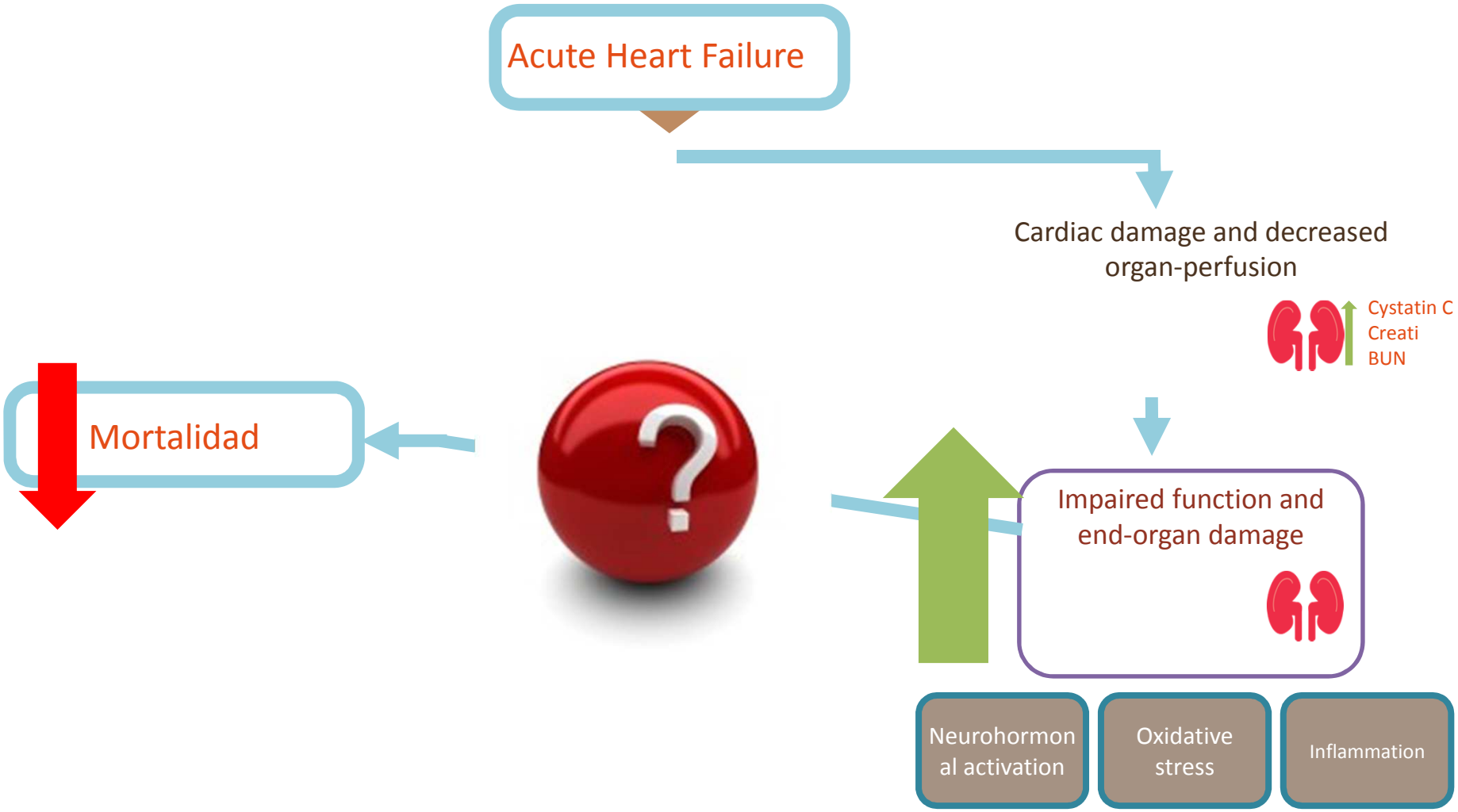
Jesús Casado Cerrada

Servicio de Medicina Interna.

RELACION IR-ICA



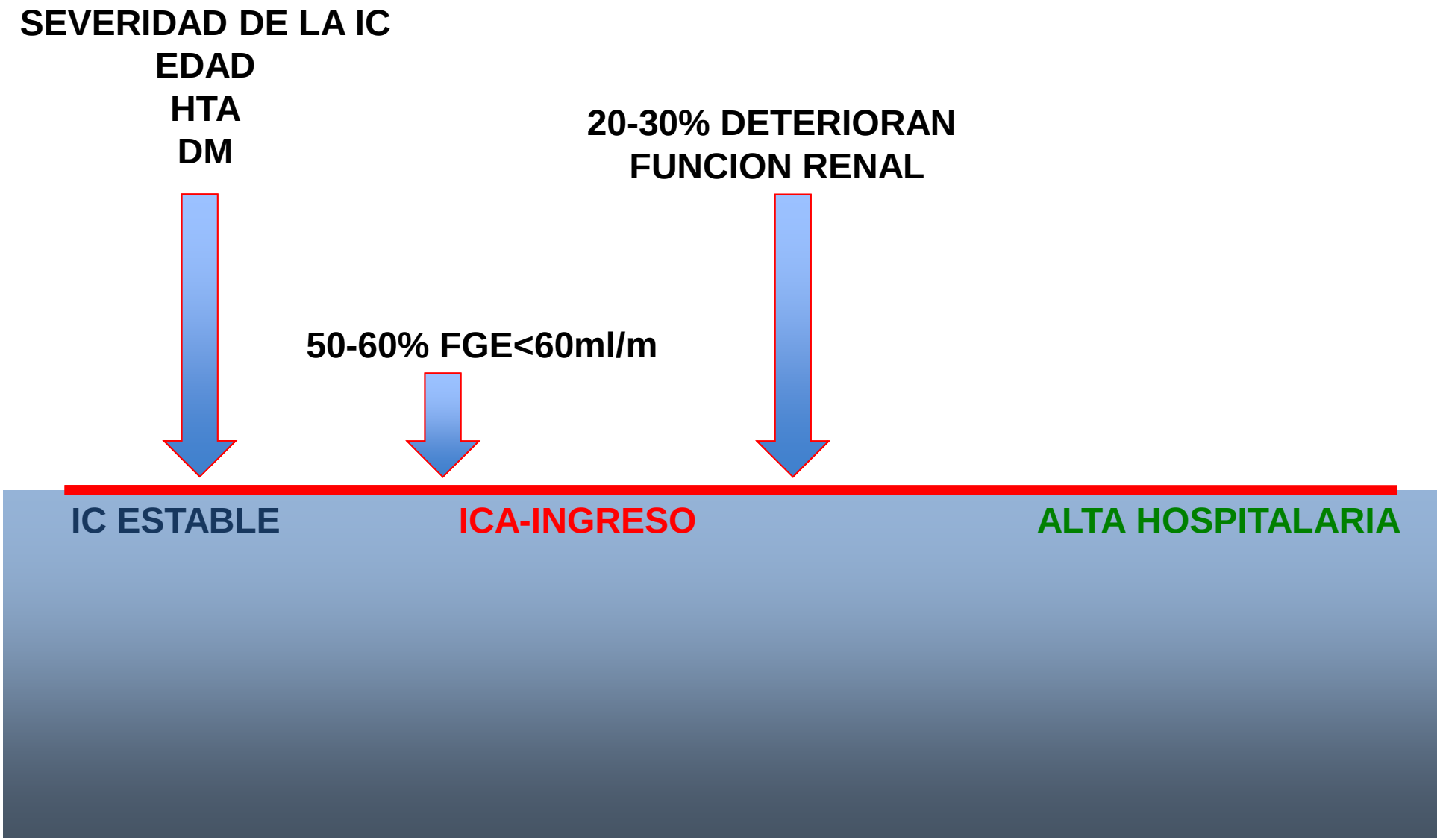
RELACION IR-ICA



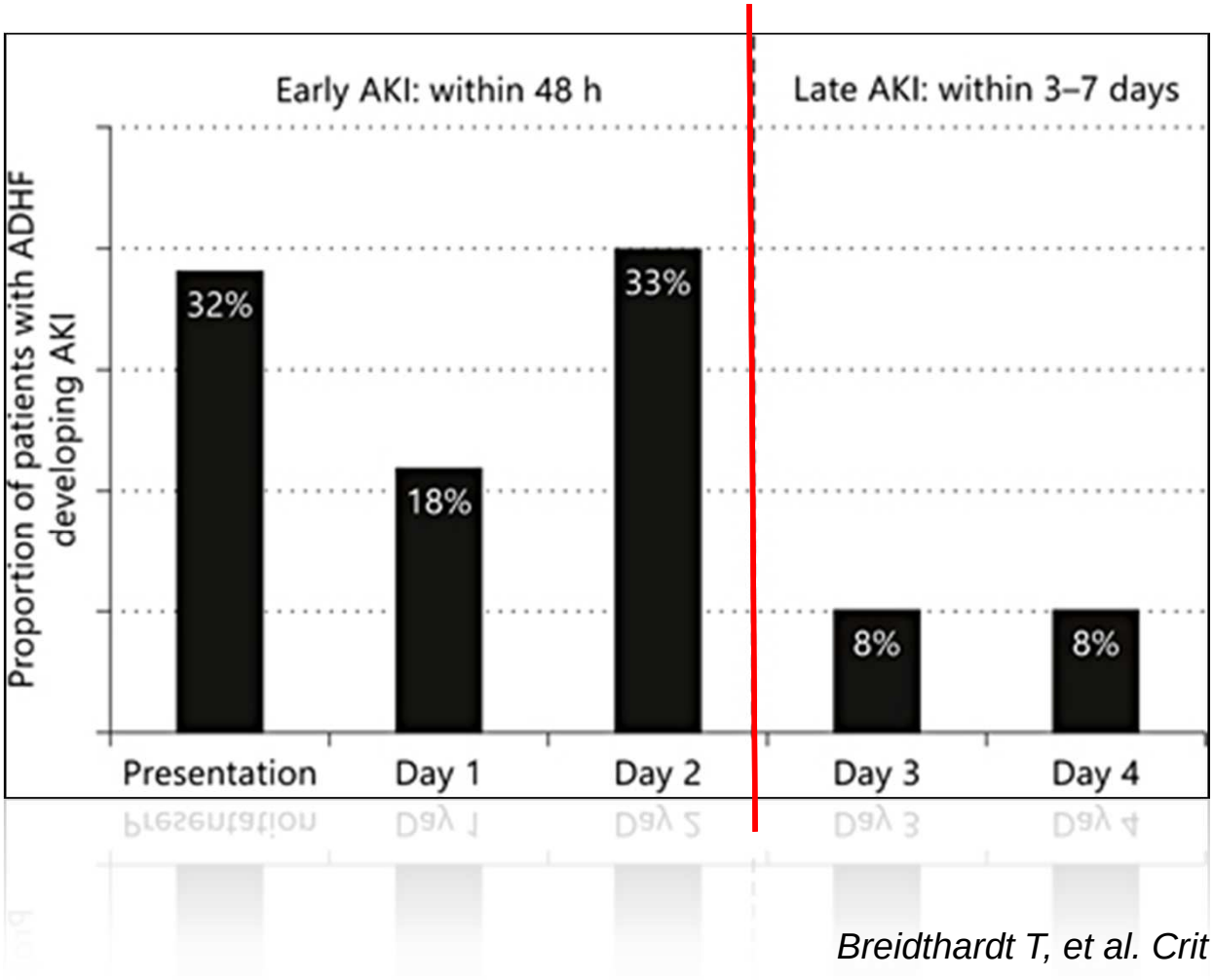
GRUPO DE INSUFICIENCIA CARDIACA

PREVALENCIA IR-ICA

PREVALENCIA IR-ICA



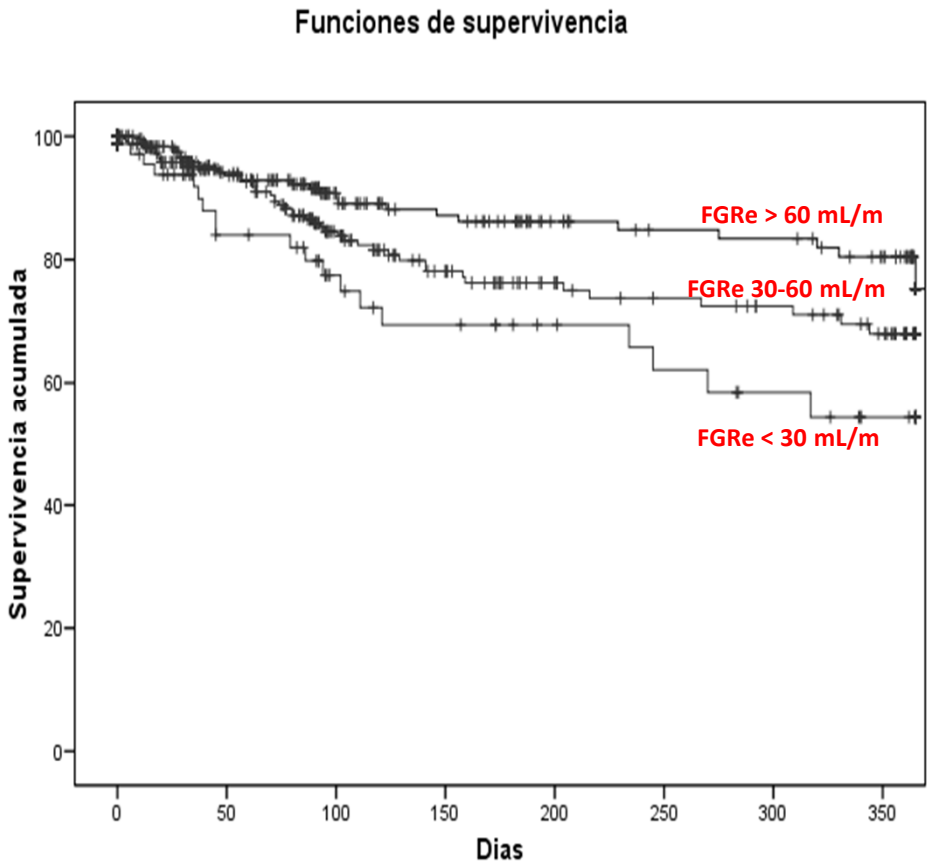
El daño renal se produce los primeros días de ingreso en la mayoría de pacientes con ICA

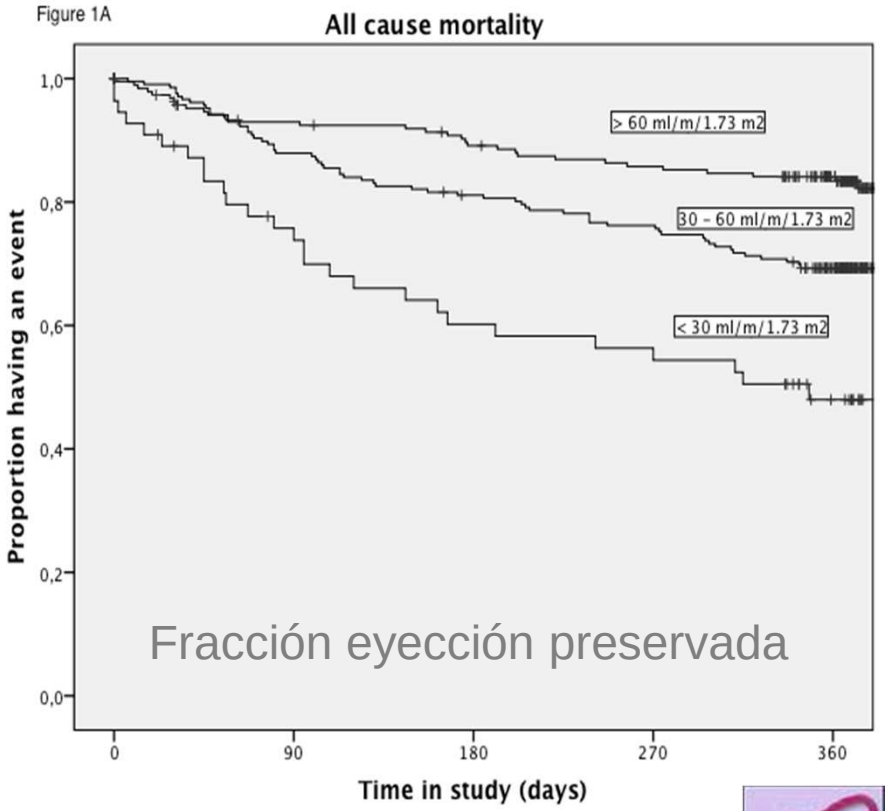


Breidthardt T, et al. Crit Care 2012;16:R2.

INFLUENCIA DE LA IR EN EL PRONOSTICO DE LA ICA

FUNCION RENAL AL INGRESO DE ICA

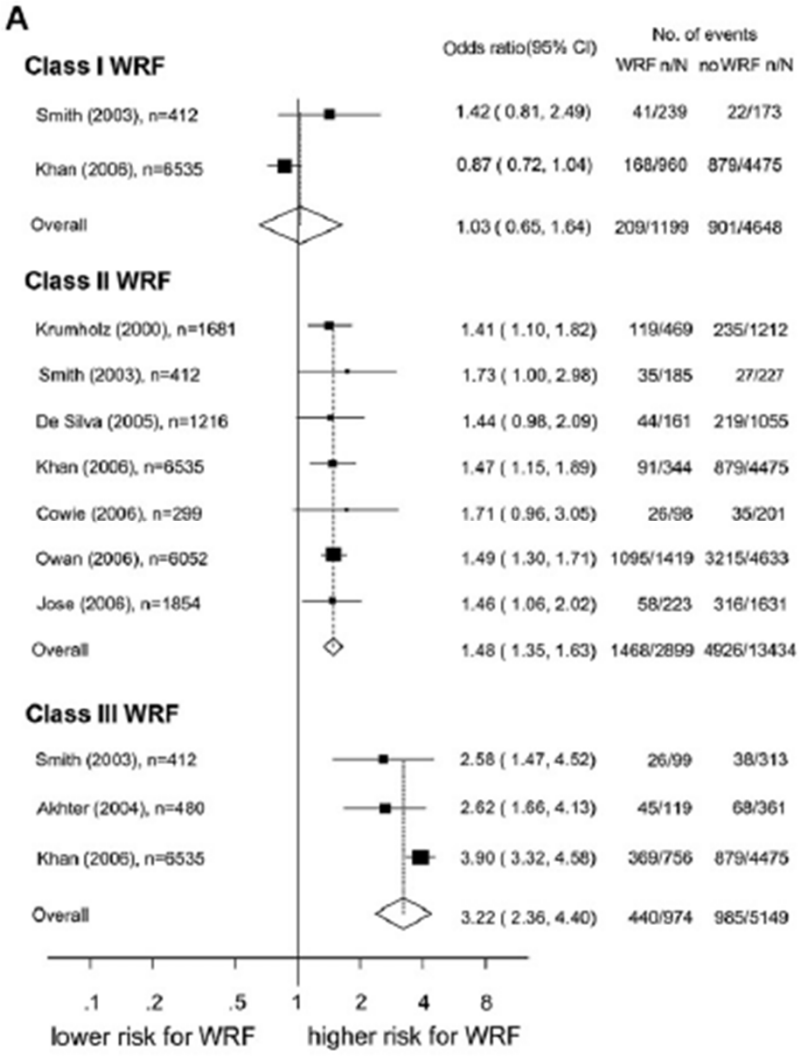




Casado J et al. Rev Clin Esp. 2012;212:119-126; Casado J et al. Eur J Intern Med 2013;24:677–683

INFLUENCIA DE LA IR EN EL PRONOSTICO DE LA ICA

DETERIORO DE LA FUNCION RENAL DURANTE INGRESO POR ICA



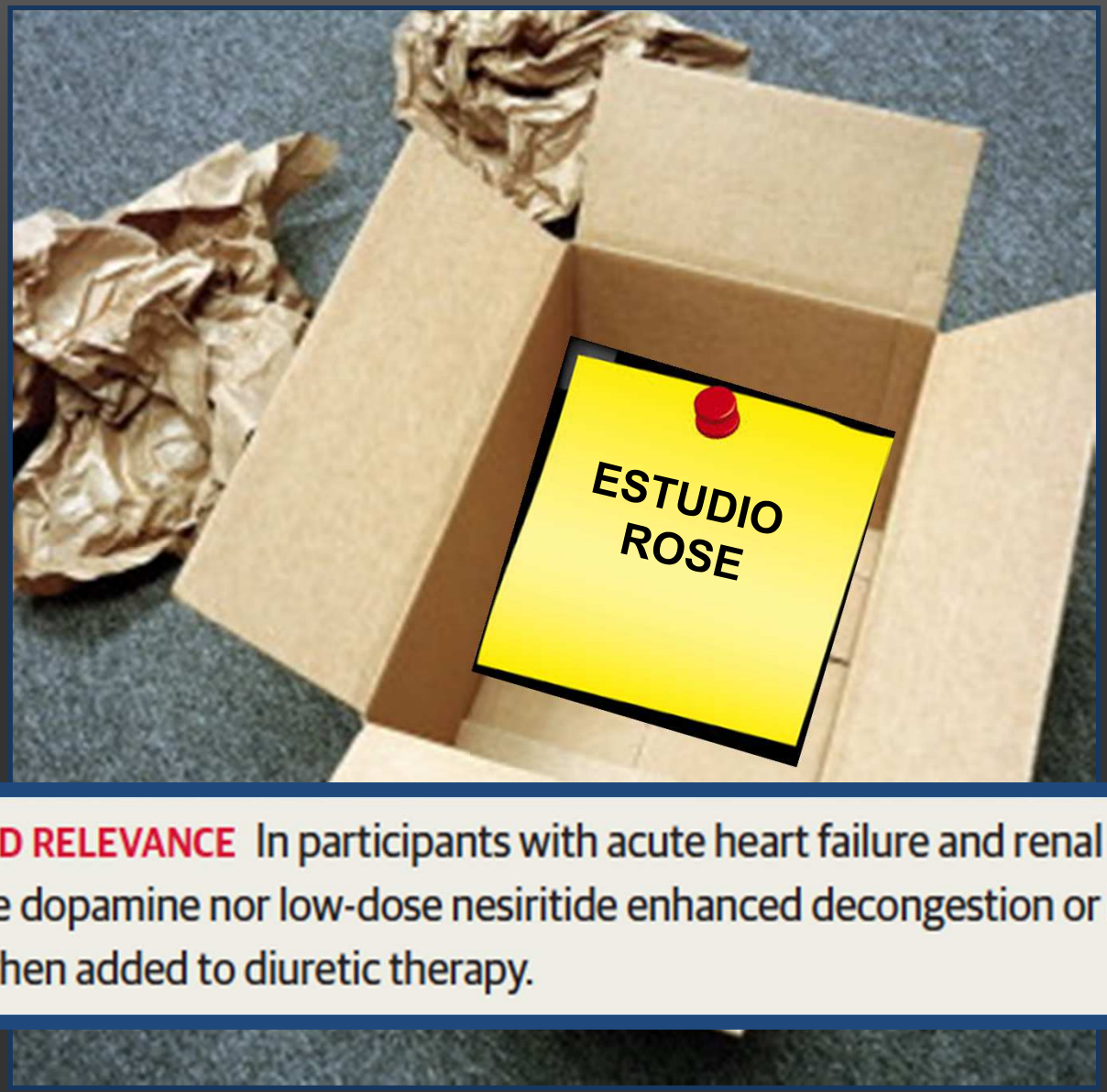
Class I WRF: Aumento de Cr 0.2-0.3 mg/dL o descenso eGFR 5-10 mL/m

Class II WRF: Aumento de Cr 0,3-0,5 mg/dL o descenso eGFR 11-15 mL/m

Class III: Aumento de Cr >0,5mg/dL o descenso eGFR >15 mL/m

Damman et al. J Cardiac Fail 2007;13:599-608

PROTECCIÓN RENAL MEJORARÍA EL PRONOSTICO DE LA ICA?



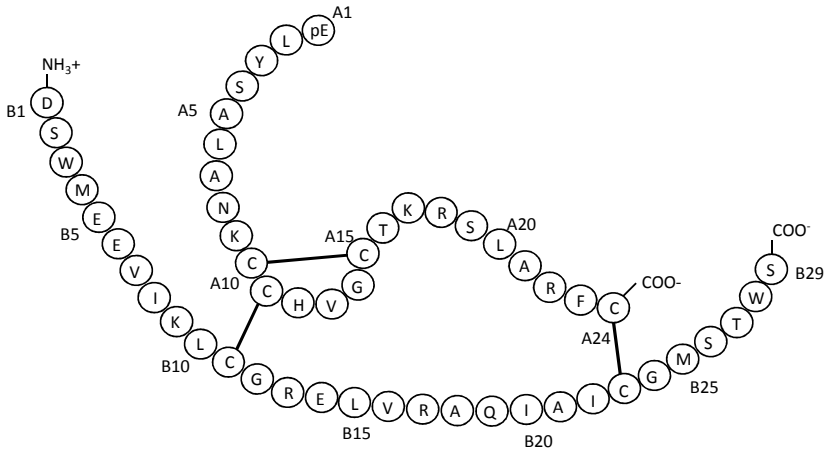
CONCLUSION AND RELEVANCE In participants with acute heart failure and renal dysfunction, neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or improved renal function when added to diuretic therapy.

GRUPO DE INSUFICIENCIA CARDIACA

POCOS AVANCES EN TRATAMIENTO DE ICA

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

SERELAXINA. INTRO



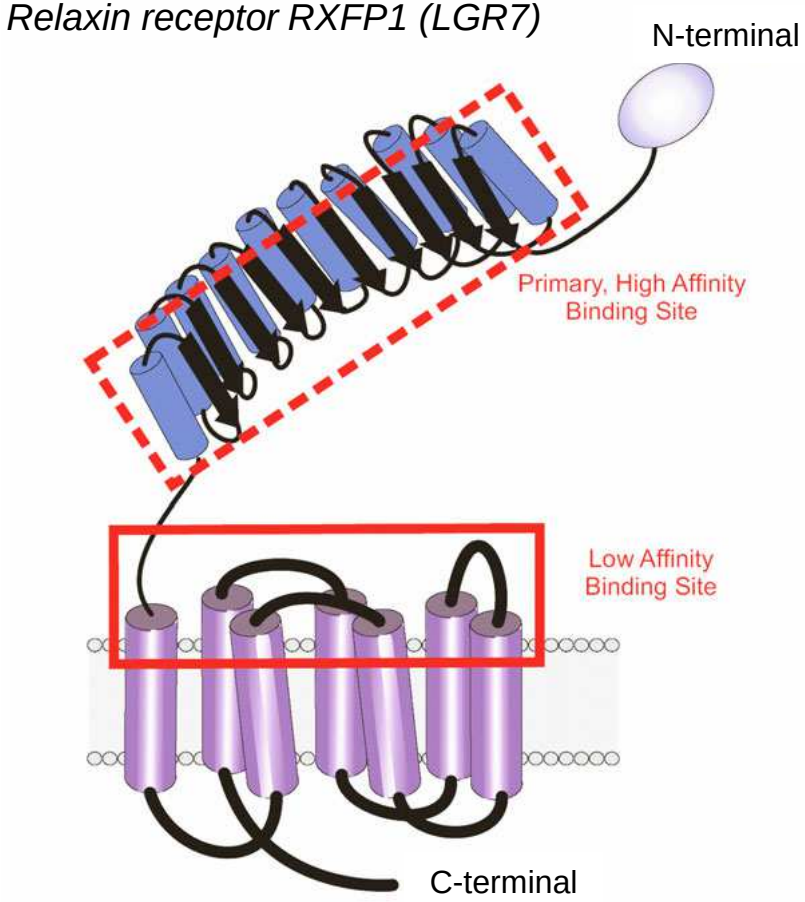
RELAXINA-2

- **Hormona peptidica que interviene en los cambios sistémicos hemodinámicos y la adaptación renal durante la gestación.**
- **Estructura: 53 aminoácidos (2 cadenas conectadas por dos puentes disulfuros)**
- **Es una de los siete péptidos de la familia de hormonas relaxinicas**
- **Cada uno de estos siete péptidos es estructuralmente y funcionalmente distinta.**

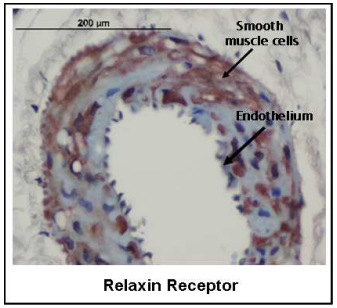
Teichman et al. Heart Fail Rev 2009;14:321–9;
Jeyabalan et al. Adv Exp Med Biol 2007;612:65–87
Kong et al. Moll Cell Endocrinol 2010;320:1–15

SERELAXINA. INTRO

Relaxin receptor RXFP1 (LGR7)



- La Relaxina-2 ejerce sus efectos a través de su unión con dos receptores de membrana específicos.
- Receptores: RXFP1 (LGR7) and RXFP2 (LGR8). Cada receptor tiene dos puntos de unión: de alta y baja afinidad.
- Estos receptores se encuentran en endotelio vascular de multitud de vasos sanguineos.



Teichman et al. Heart Fail Rev 2009;14:321–9; Dschietzig et al. Pharmacol Therap 2006;112:38–56; Bathgate et al. Pharmacol Rev 2006;58:7–31; Kong et al. Moll Cell Endocrinol 2010;320:1–15; Svendsen et al. Mol cell Endocrinol 2008;296:10–17; Halls et al. J Pharmacol Exp Ther 2005;313:677–87

SERELAXINA. INTRO

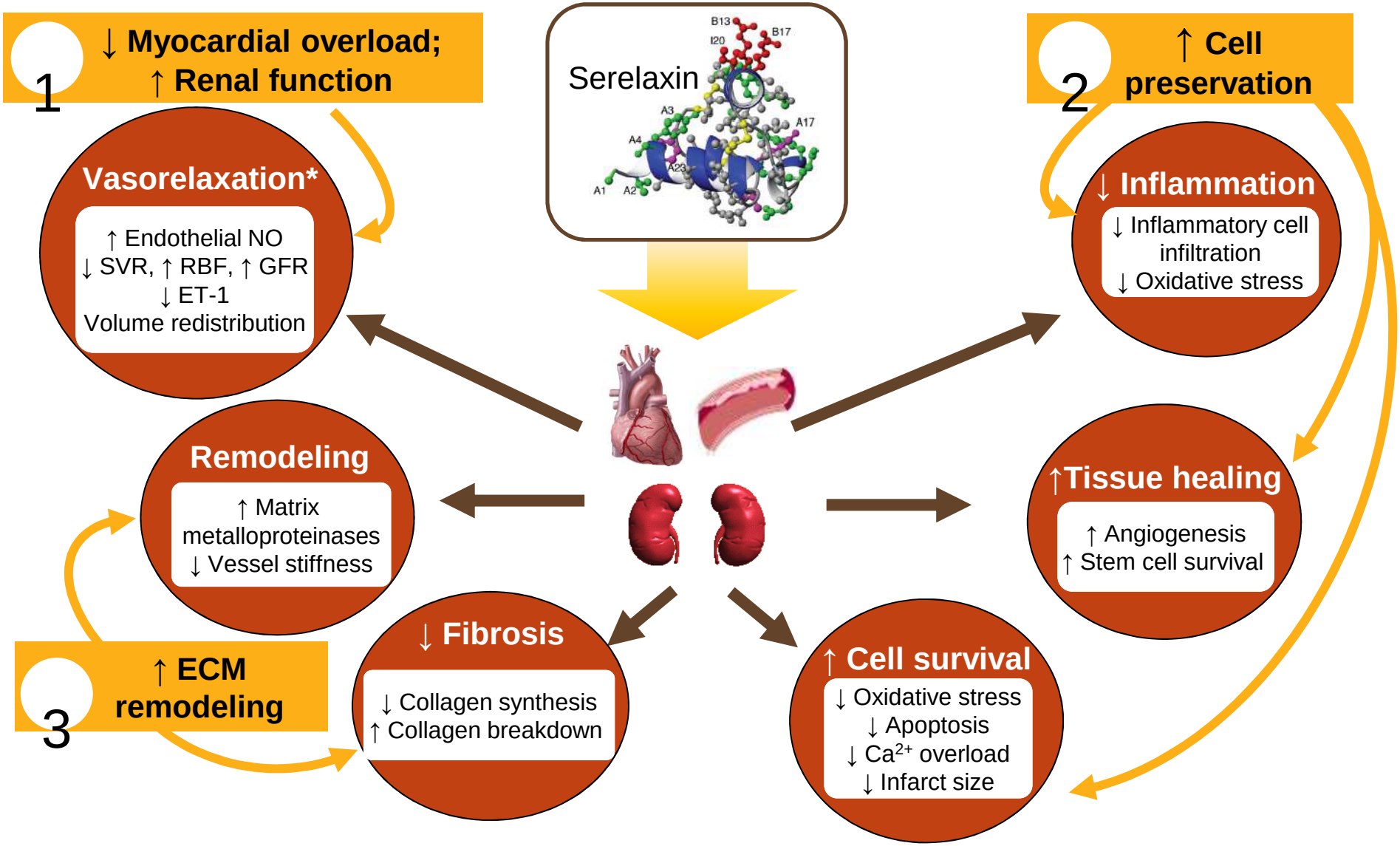
- Modificaciones hemodinamicas y renales relacionadas con la actividad de la Relaxina-2 durante la gestación:

Parametro	Embarazo
Volumen minuto (L/min)	Incrementa 20%
Resistencia Vascular Sistémica (dyn.s.cm^2)	Disminuye 30%
Compliance Arterial Global (mL/mmHg)	Incrementa 30%
Aclaramiento de Creatinina (mL/min)	Incrementa 45%

- Sus niveles se incrementan en la circulación sistémica a partir del primer trimestre del embarazo.

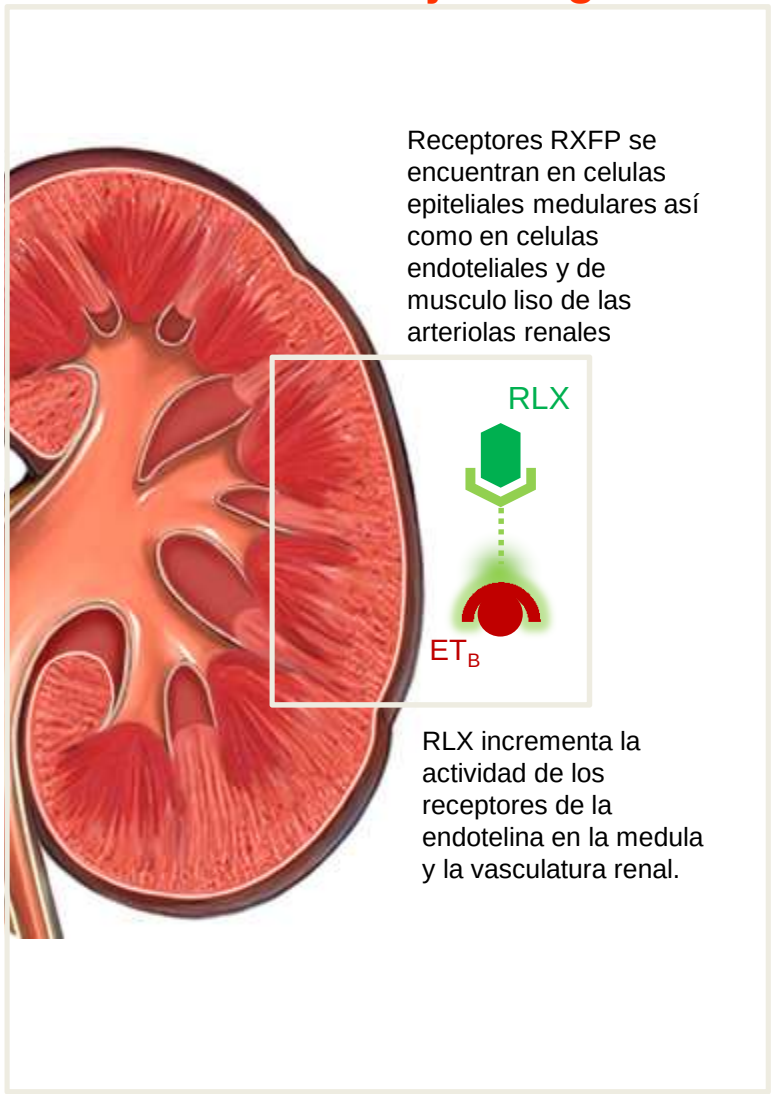
Teichman et al. Heart Fail Rev 2009;14:321–9; Jeyabalan et al. Adv Exp Med Biol 2007;612:65–87; Sherwood. The Physiology of Reproduction. Acad Press 1994; 61–1009

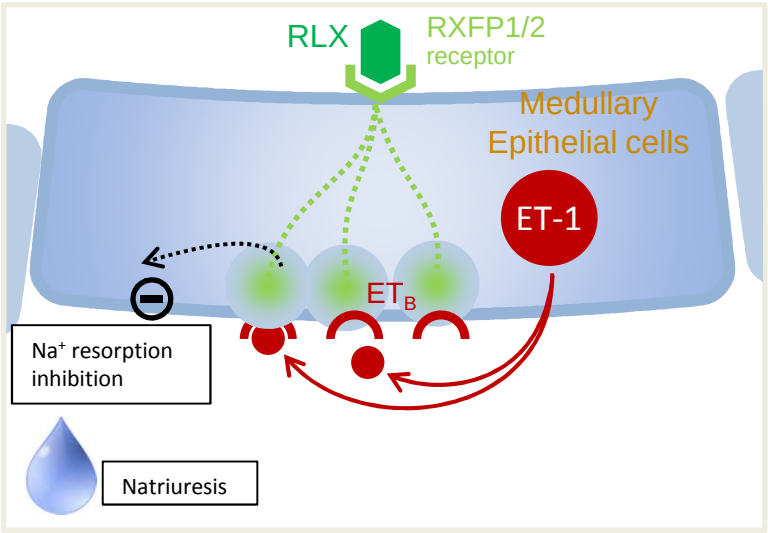
SERELAXINA. INTRO

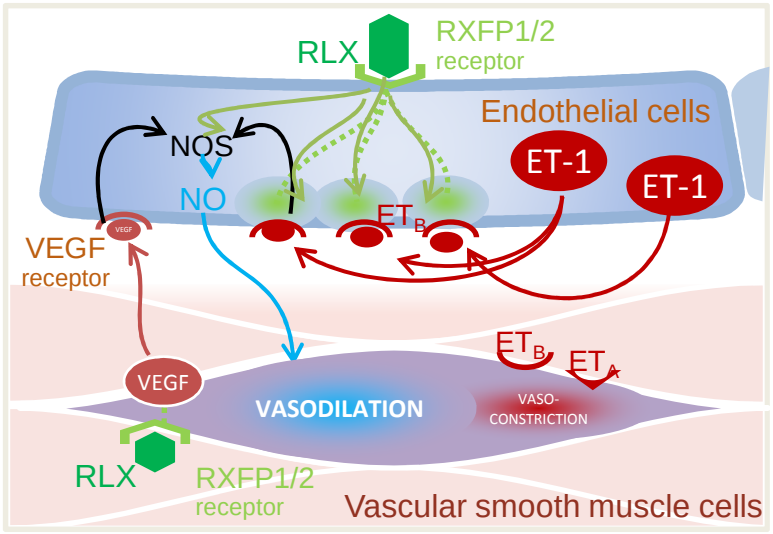


Adapted from Du et al. Nat Rev Cardiol 2010;7:48–58

Incremento de flujo sanguineo renal estimulando diuresis y natriuresis







Teichman et al. Curr Heart Fail Rep 2010;7:75–82. *Schneider et al. Ann Rev Pharmacol Toxicol 2007;47:731–59*


Pérez, nos hemos quedado sin ratas en el laboratorio, así que póngase esto y venga con nosotros!!
www.megustaestarbien.com

Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multicentre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study

Prof John R Teerlink MD a, Prof Marco Metra MD b, G Michael Felker MD c, Prof Piotr Ponikowski MD d, Adriaan A Voors MD e, Beth Davison Weatherley PhD f, Prof Alon Marmor MD g, Prof Amos Katz MD h, Jacek Grzybowski MD i, Elaine Unemori PhD j, Sam L Teichman MD j, Gad Cotter MD f

Lancet 2009; 373: 1429–39

Fase II
234 pacientes
Sugiere mejoría en disnea
Sugiere reducción mortalidad

Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial

John R Teerlink, Gad Cotter, Beth A Davison, G Michael Felker, Gerasimos Filippatos, Barry H Greenberg, Piotr Ponikowski, Elaine Unemori, Adriaan A Voors, Kirkwood F Adams Jr, Maria I Dorobantu, Liliana R Grinfeld, Guillaume Jondeau, Alon Marmor, Josep Masip, Peter S Pang, Karl Werdan, Sam L Teichman, Angelo Trapani, Christopher A Bush, Rajnish Saini, Christoph Schumacher, Thomas M Severin, Marco Metra, for the RELAXin in Acute Heart Failure (RELAX-AHF) Investigators

Lancet 2013; 381: 29–39

Fase III
1161 pacientes
Confirma mejoría en disnea
Sugiere reducción mortalidad

Effect of Serelaxin on Cardiac, Renal, and Hepatic Biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) Development Program

Correlation With Outcomes

Marco Metra, MD,* Gad Cotter, MD,† Beth A. Davison, PHD,† G. Michael Felker, MD, MHS,‡ Gerasimos Filippatos, MD,§ Barry H. Greenberg, MD,‖ Piotr Ponikowski, MD, PHD,¶

J Am Coll Cardiol 2013;61:196–206

Subanalisis de RELAX
Efecto de serelaxina en lesión orgánica

NEXT

Objetivo mortalidad

Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial

METODOS

Estudio multicéntrico, internacional, doble ciego controlado con placebo.

Pacientes ingresados por ICA

Aleatorizados 1:1 a 48h de infusión IV de serelaxina 30 mcgr/Kg/día o placebo dentro de las primeras 16 horas del ingreso.

CRITERIOS DE INCLUSION

Disnea de reposo o mínimos
Rx compatible
NT-proBNP>1400 ng/L
FGe 30-75 mL/m
PAs>125mmHg
Furosemida >40mg IV

OBJETIVOS

Primario. Eficacia. Disnea

Cambio en la percepción de disnea, evaluado por área bajo la curva de la Escala analógica visual (VAS; 0-100mm) al ingreso y al día 5.

Proporción de pacientes con mejoría significativa o moderada de la disnea utilizando la Escala Likert 7 a las 6h, 12h, y 24h.

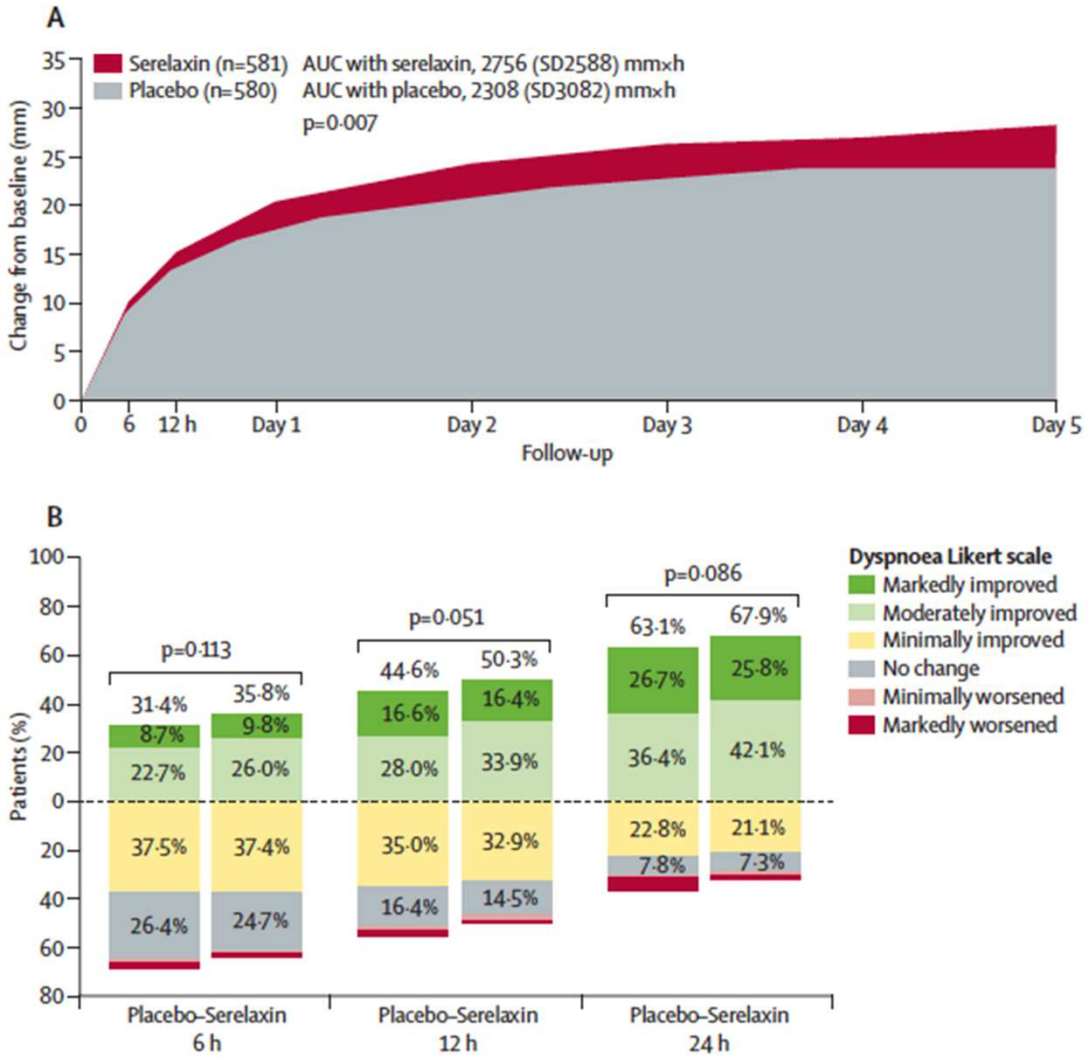
Secundario. Seguridad. Mortalidad. Reingresos.

Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial

	PLACEBO	SERELAXINA
EDAD	72,5	71,6
VARONES	67%	63%
FEVI	38,6%	38,7%
FEVI<40%	55%	55%
CARDIOP. ISQUEMICA	53%	51%
FA	53%	51%
HTA	88%	85%
DM	47%	48%
FGe	53,3%	53,7%

Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial

RESULTADOS. DISNEA

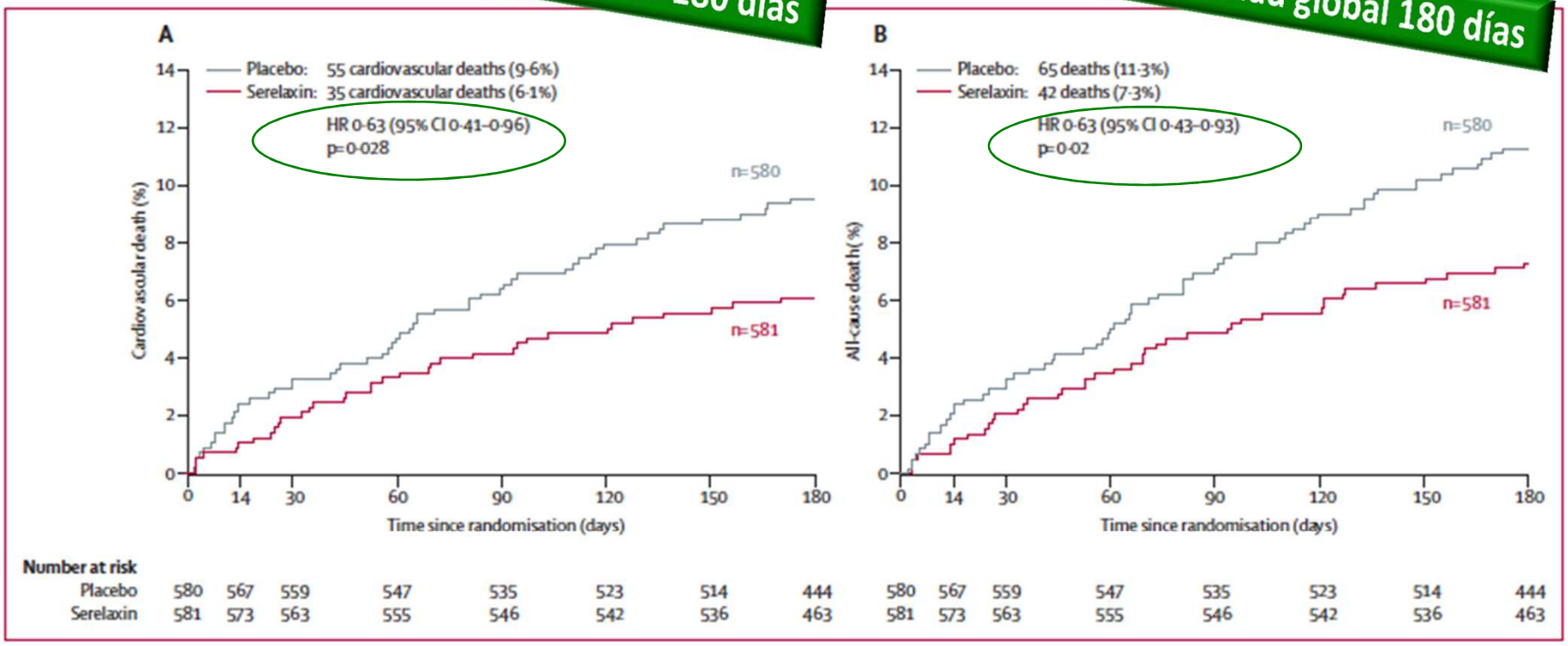


Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial

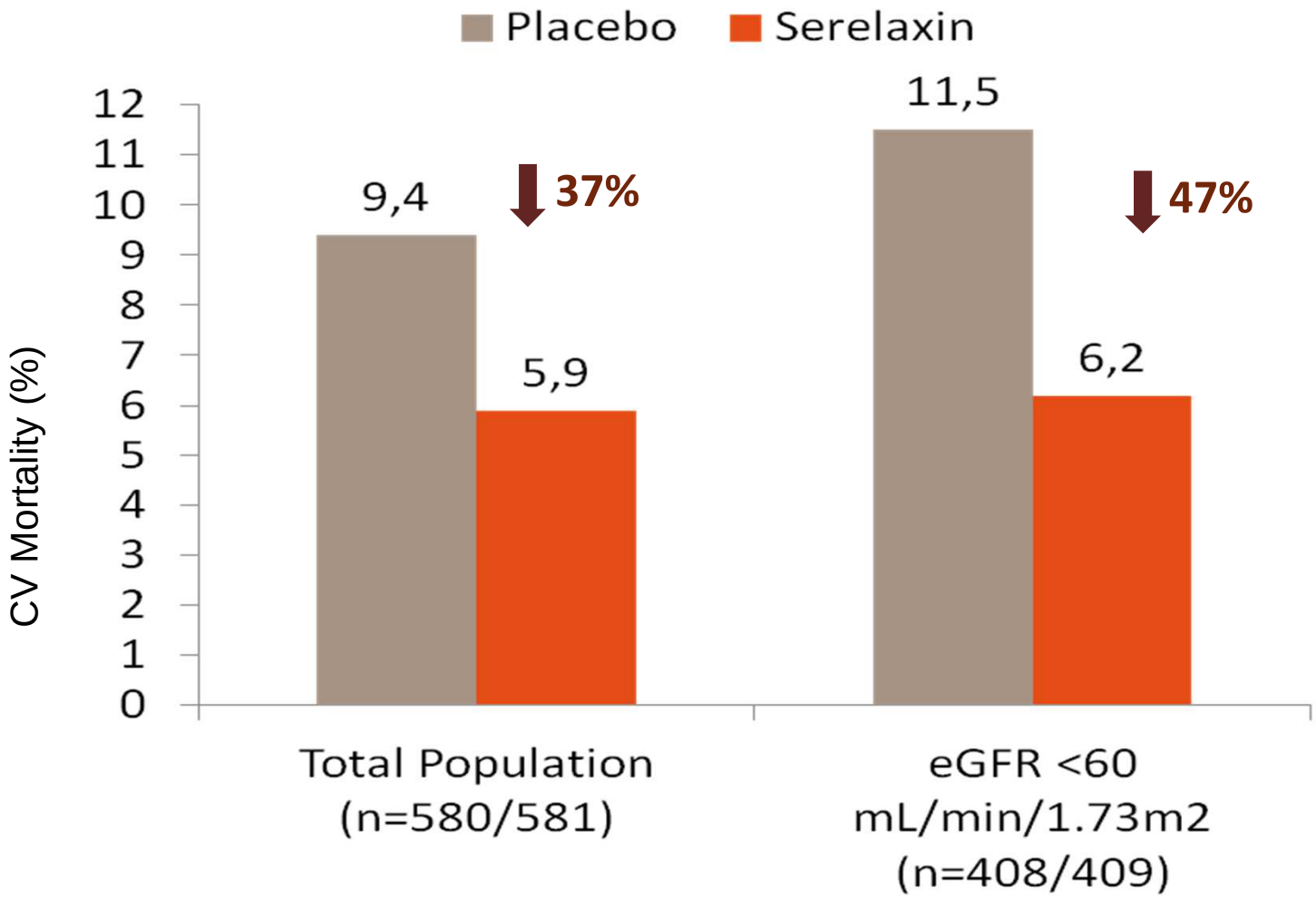
RESULTADOS. MORTALIDAD

Mortalidad cdv 180 días

Mortalidad global 180 días



ANALISIS DE SUBGRUPOS



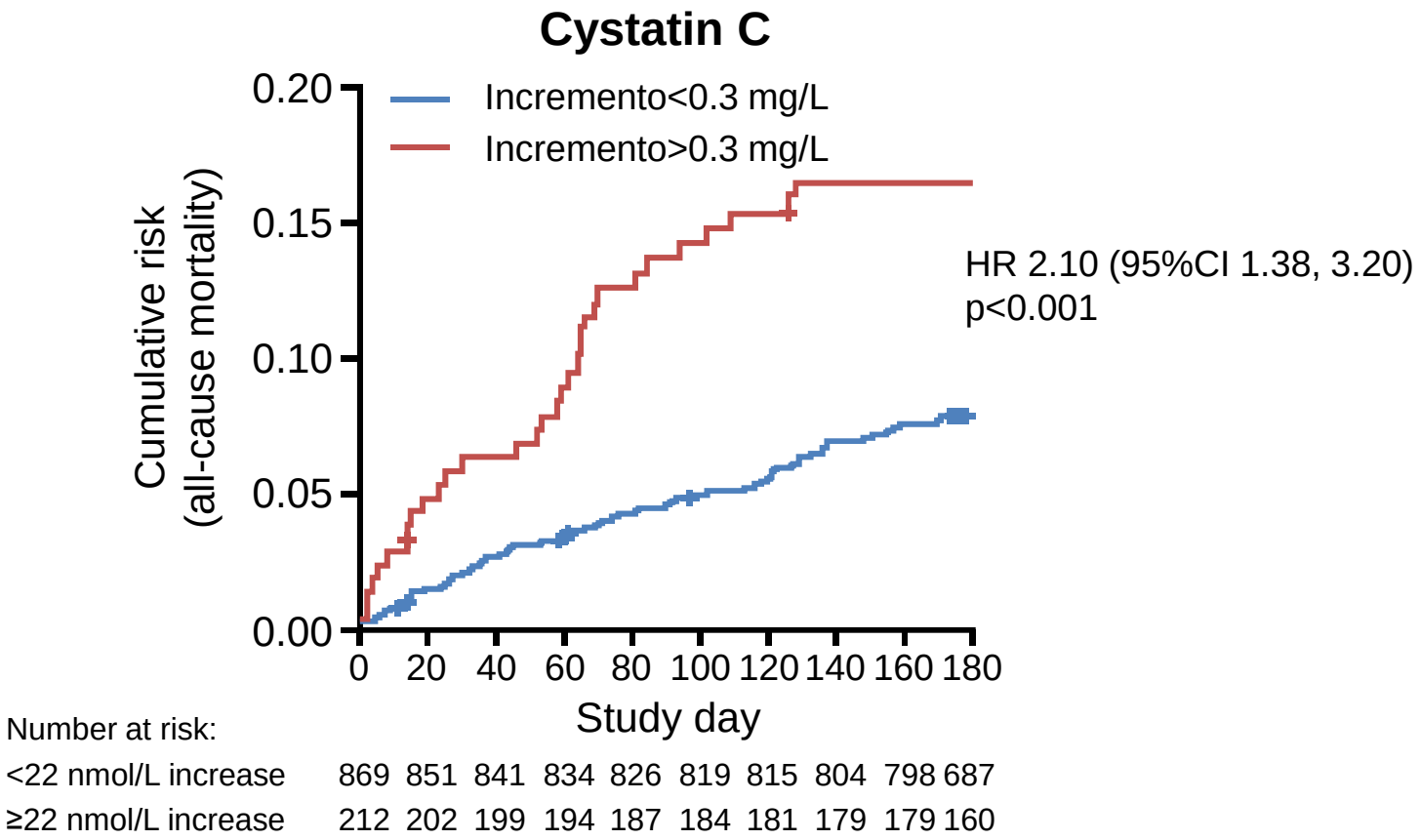
El deterioro de la función renal incrementa el riesgo de mortalidad global a los 180 días.

Table 3 Association of Substantial Biomarker Changes at 48 h From Randomization With 180-Day Mortality in the Relaxin in Acute Heart Failure Study

	Death Through Day 180			
Biomarker Change From Baseline to Day 2	No	Yes	HR (95% CI)	p Value
Troponin (≥20% increase)	62/825	30/231	1.80 (1.16–2.777)	0.0076
	7.6 (6.0–9.6)	13.1 (9.3–18.2)		
Creatinine (≥27 μmol/l [0.3 mg/dl] increase)	75/919	23/167	1.76 (1.11–2.82)	0.016
	8.2 (6.6–10.2)	13.8 (9.4–20.0)		
Cystatin-C (≥22 nmol/l [0.3 mg/l] increase)	66/869	32/212	2.10 (1.38–3.20)	0.0004
	7.7 (6.1–9.7)	15.2 (11.0–20.7)		
AST (≥20% increase)	73/906	13/99	1.66 (0.92–3.00)	0.099
	8.1 (6.5–10.1)	13.4 (8.0–22.0)		
ALT (≥20% increase)	79/970	15/99	1.96 (1.13–3.40)	0.015
	8.2 (6.6–10.1)	15.3 (9.5–24.1)		
NT-proBNP (≥30% decrease)	53/395	45/686	0.47 (0.31–0.69)	0.0001
	13.5 (10.5–17.4)	6.6 (5.0–8.8)		

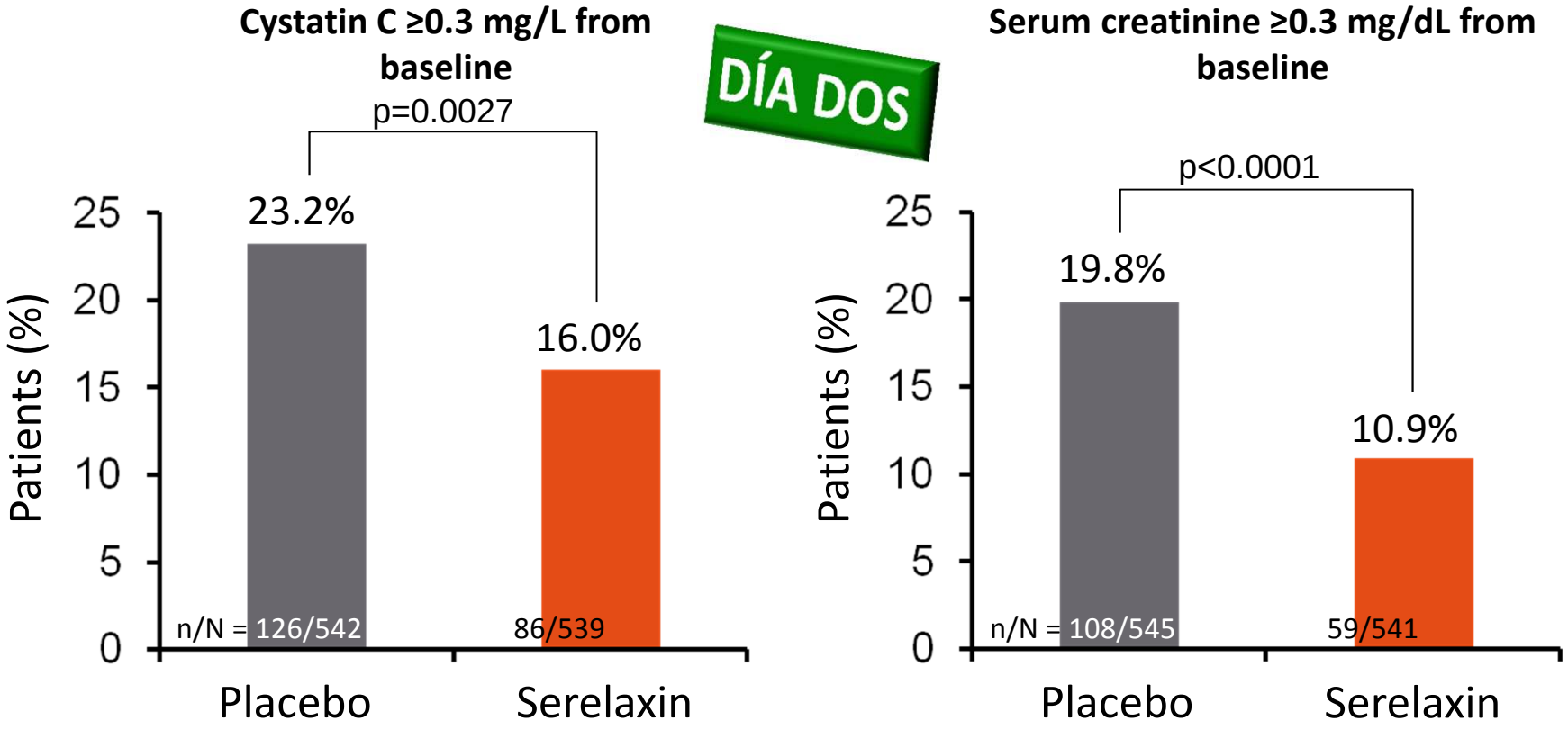
Metra et al. J Am Coll Cardiol 2013;61:196–206

El deterioro de la función renal incrementa el riesgo de mortalidad global a los 180 días.



Metra et al. J Am Coll Cardiol 2013;61:196–206

Serelaxina reduce la incidencia de deterioro de función renal



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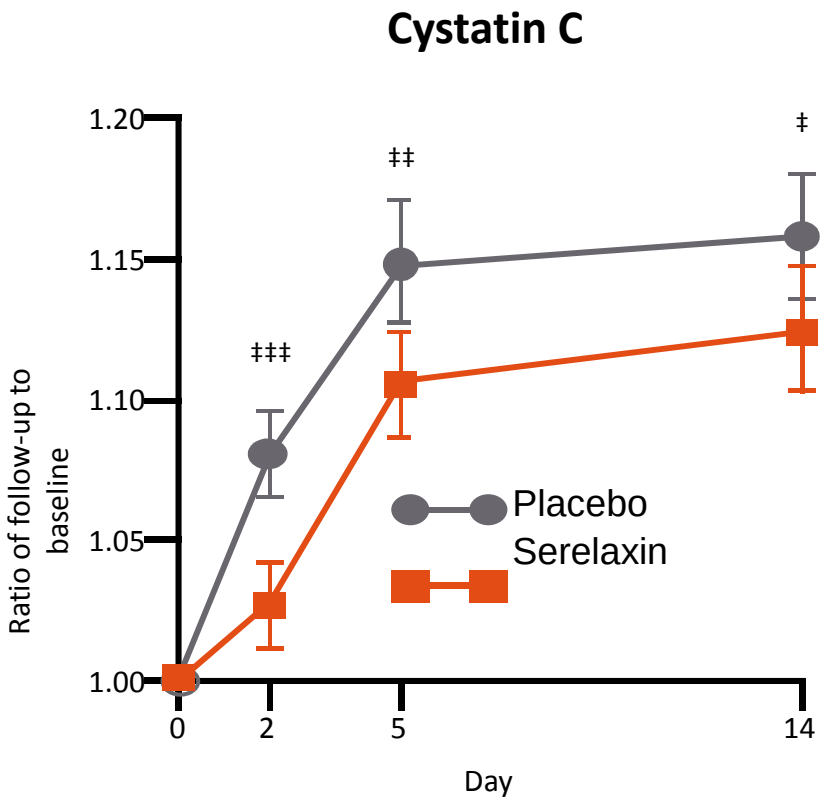
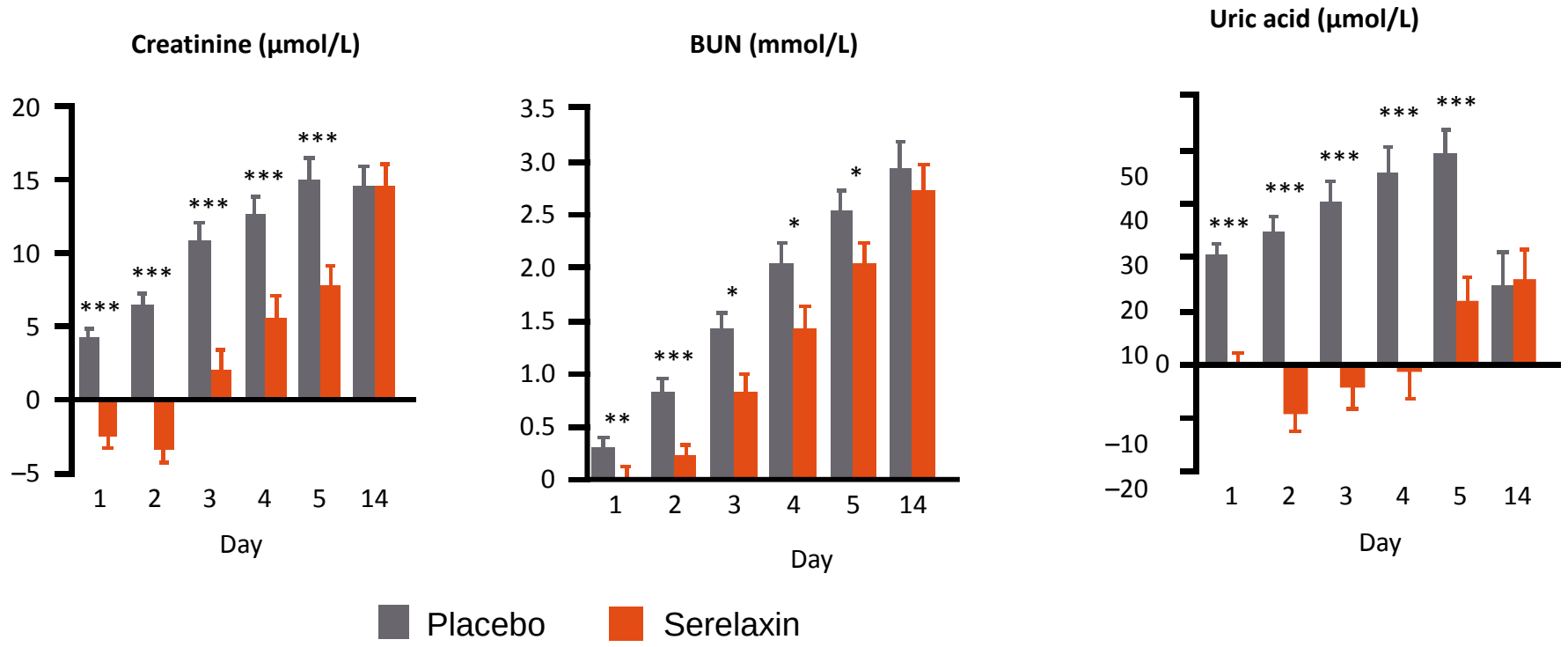
Serelaxina reduce la incidencia de deterioro de función renal



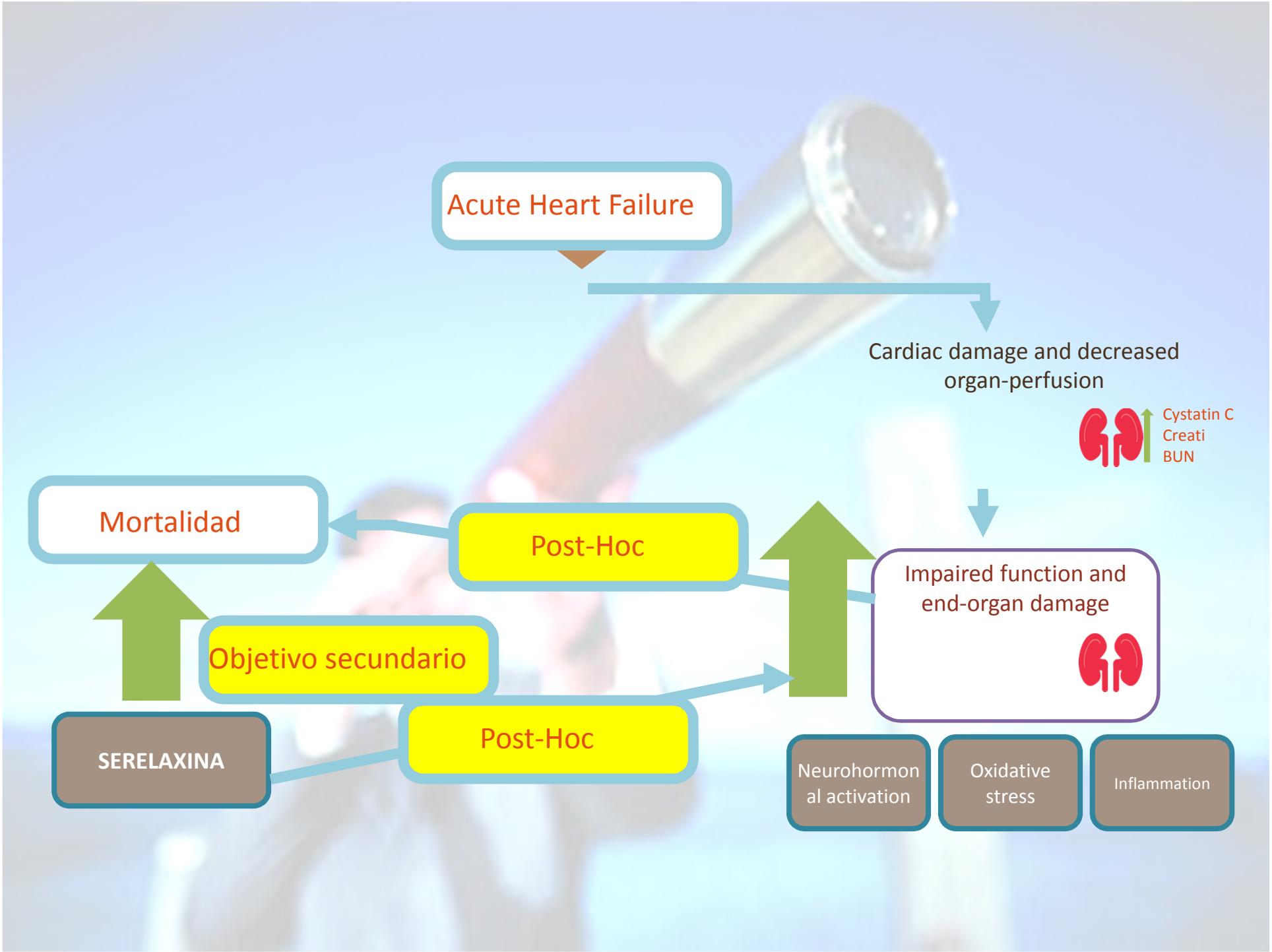
Metra et al. J Am Coll Cardiol 2013;61:196–206

SUBANALISIS LESION ORGÁNICA

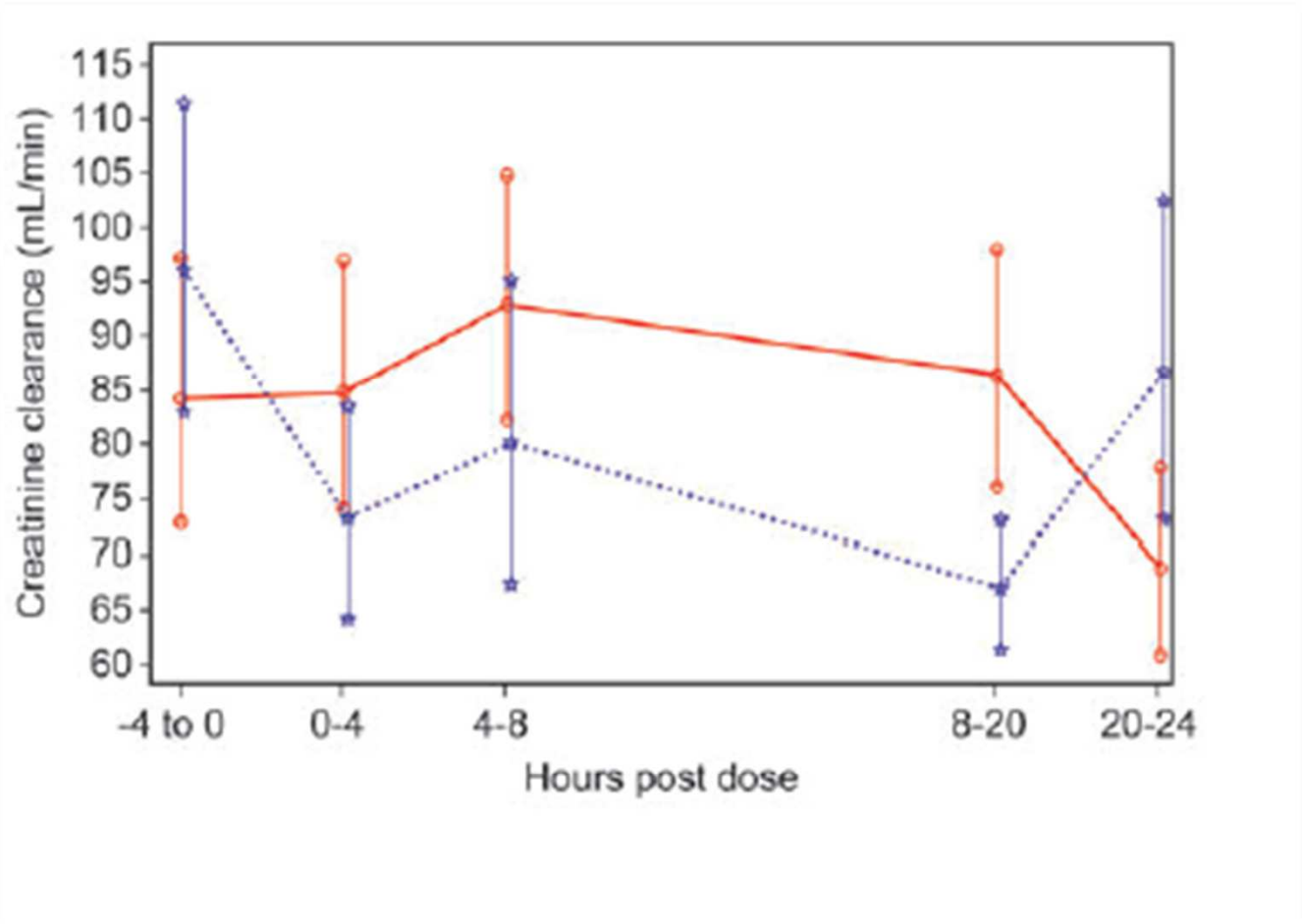


*p<0.05; **p<0.005; ***p<0.001 vs. placebo (two-sided two sample t-test)
‡p<0.05; ‡‡p<0.005; ‡‡‡p<0.001 by repeated measures analysis of variance with adjustment for baseline value

Metra et al. J Am Coll Cardiol 2013;61:196–206


Acute Heart Failure
Cardiac damage and decreased organ-perfusion
Cystatin C
Creati
BUN
Mortalidad
Post-Hoc
Objetivo secundario
Post-Hoc
SERELAXINA
Impaired function and end-organ damage
Neurohormonal activation
Oxidative stress
Inflammation

ESTUDIO DE PARAMETROS HEMODINÁMICOS



Doble ciego, multicéntrico

71 pacientes con ICA

Objetivo: evaluar cambios hemodinámicos en 1ª 48h

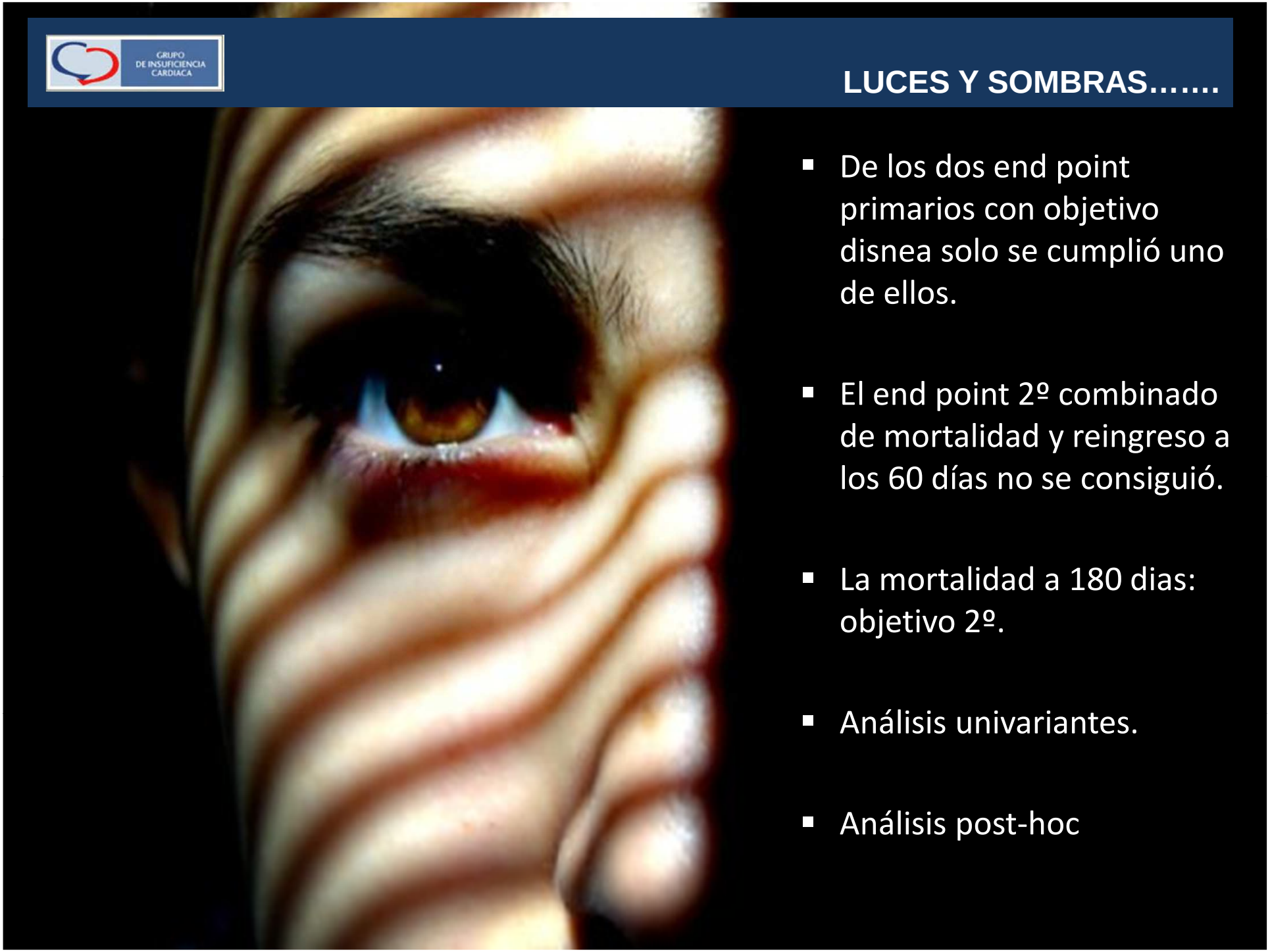
Dosis de RELAX-HF

Ponikowski et al. *European Heart Journal (2014) 35, 431–441*

Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial

- **Hipotensión arterial**
  - **Grupo serelaxina precisó reducción de tratamiento a la mitad por hipoTA hasta en un 13%. Placebo 7%**
  - **Grupo serelaxina hubo que retirar tratamiento por hipoTA en un 19%. Placebo 12%.**
- **Deterioro de la función renal**
  - **9% en placebo y 6 % en serelaxina**

LUCES Y SOMBRAS…….



- De los dos end point primarios con objetivo disnea solo se cumplió uno de ellos.
- El end point 2º combinado de mortalidad y reingreso a los 60 días no se consiguió.
- La mortalidad a 180 dias: objetivo 2º.
- Análisis univariantes.
- Análisis post-hoc

Gracias