

**XVII REUNIÓN DE INSUFICIENCIA CARDIACA
Y
FIBRILACIÓN AURICULAR**

16-17 de abril de 2015



Universidad
Zaragoza

1542



Hospital Clínico Universitario
"Lozano Blesa" de Zaragoza



Juan Ignacio Pérez Calvo

Novedades y controversias en insuficiencia cardiaca y sus comorbilidades

La inhibición de la neprilisina: un nuevo “target” en el tratamiento de la IC crónica

Moderadores:

F. Formiga
P. Bettencourt



Conflicto de intereses



Oficina de Transferencia de Resultados de Investigación (OTRI)



INDICE



EL DESENLACE

ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H.,
Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D.,
Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D.,
Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D.,
for the PARADIGM-HF Investigators and Committees*

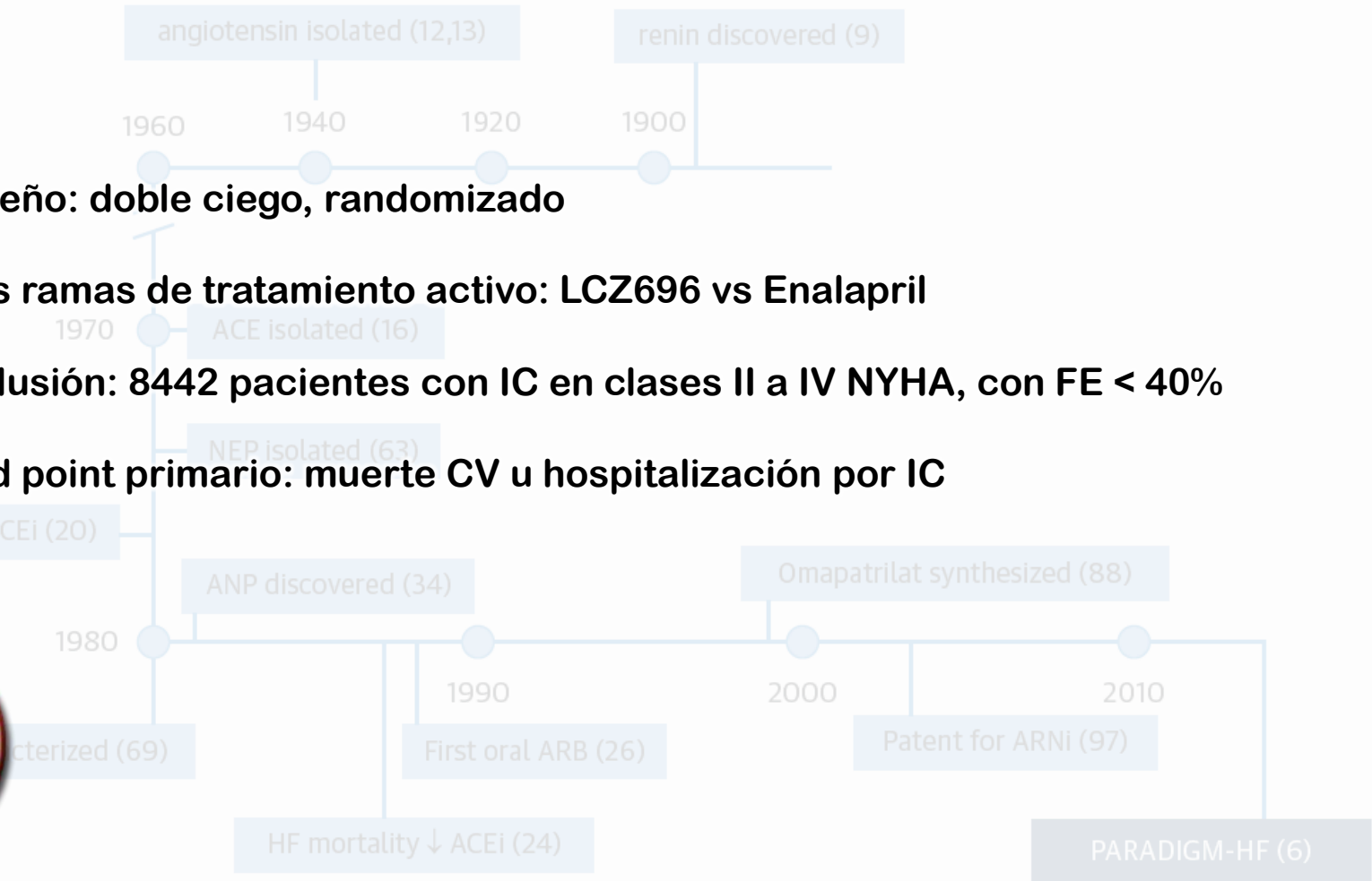
ESTUDIO PARADIGM-HF

Diseño: doble ciego, randomizado

Dos ramas de tratamiento activo: LCZ696 vs Enalapril

Inclusión: 8442 pacientes con IC en clases II a IV NYHA, con FE < 40%

End point primario: muerte CV u hospitalización por IC



ESTUDIO PARADIGM-HF

Tratamiento de las ramas del estudio

Characteristic	LCZ696 (N= 4187)	Enalapril (N= 4212)
Treatments at randomization — no. (%)		
Diuretic	3363 (80.3)	3375 (80.1)
Digitalis	1223 (29.2)	1316 (31.2)
Beta-blocker	3899 (93.1)	3912 (92.9)
Mineralocorticoid antagonist	2271 (54.2)	2400 (57.0)
Implantable cardioverter–defibrillator	623 (14.9)	620 (14.7)
Cardiac resynchronization therapy	292 (7.0)	282 (6.7)

ESTUDIO PARADIGM-HF

Resultados

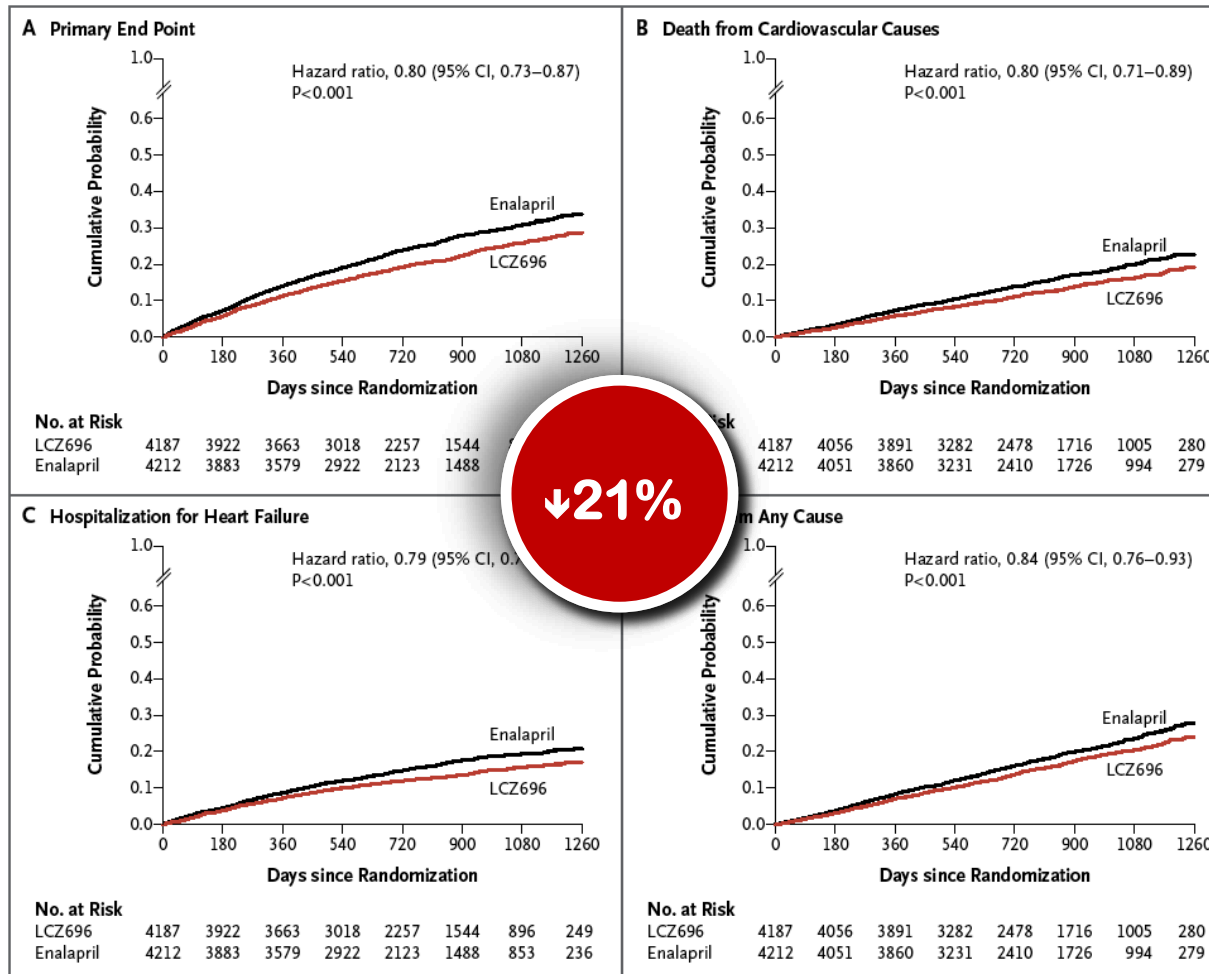
Table 2. Primary and Secondary Outcomes.*

Outcome	LCZ696 (N=4187)	Enalapril (N=4212)	Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome — no. (%)				
Death from cardiovascular causes or first hospitalization for worsening heart failure	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from cardiovascular causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalization for worsening heart failure	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001
Secondary outcomes — no. (%)				
Death from any cause	711 (17.0)	835 (19.8)	0.84 (0.76–0.93)	<0.001
Change in KCCQ clinical summary score at 8 mo†	-2.99±0.36	-4.63±0.36	1.64 (0.63–2.65)	0.001
New-onset atrial fibrillation‡	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	0.83
Decline in renal function§	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	0.28

Efectos adversos

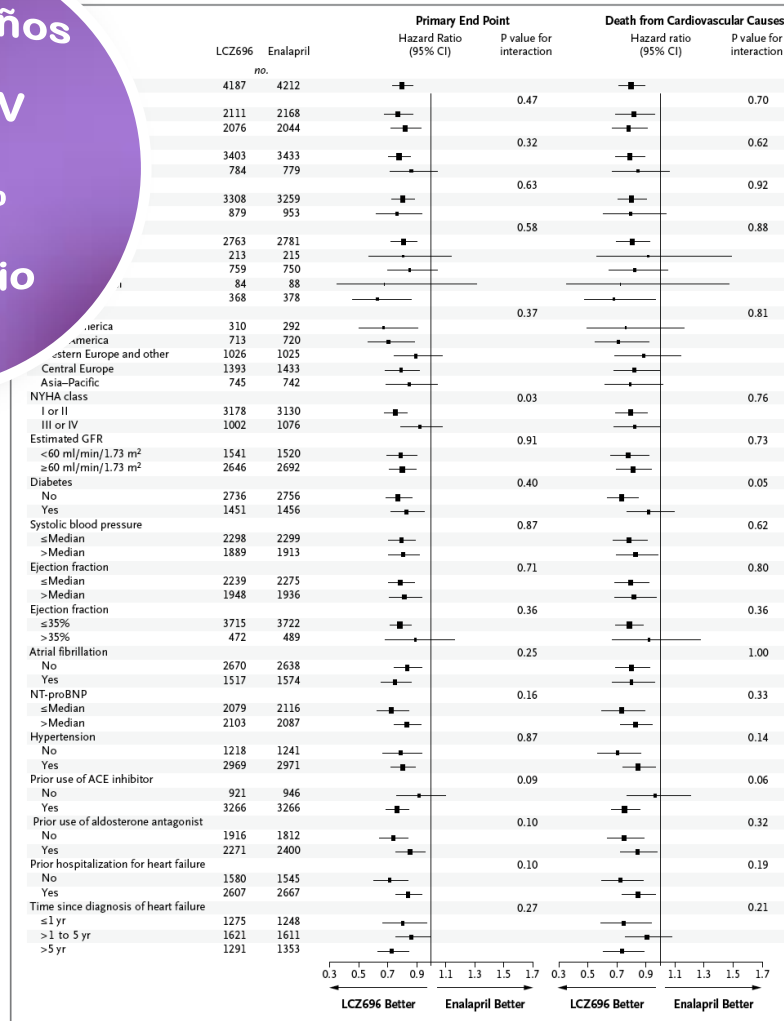
- **Hipotensión sintomática** (no discontinuación medicación)
- **Tos**
- **Elevación de creatinina y potasio**
- **Angioedema** (tendencia no significativa)

ESTUDIO PARADIGM-HF



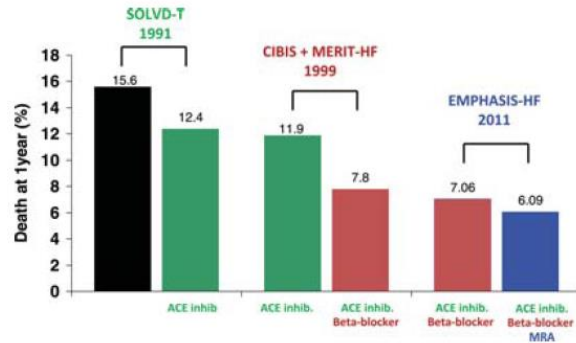
ESTUDIO PARADIGM-HF

Edad > 75 años
 Clase III-IV
 FE > 35%
 IECA previo

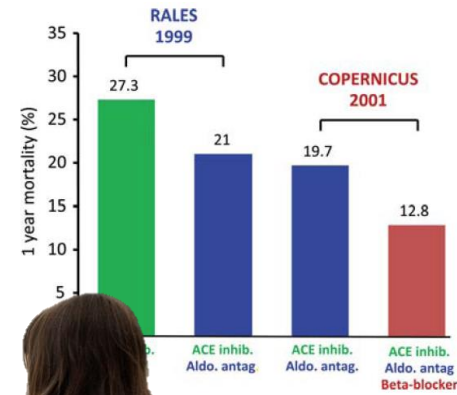


ESTUDIO PARADIGM-HF

Síntomas leve a moderados

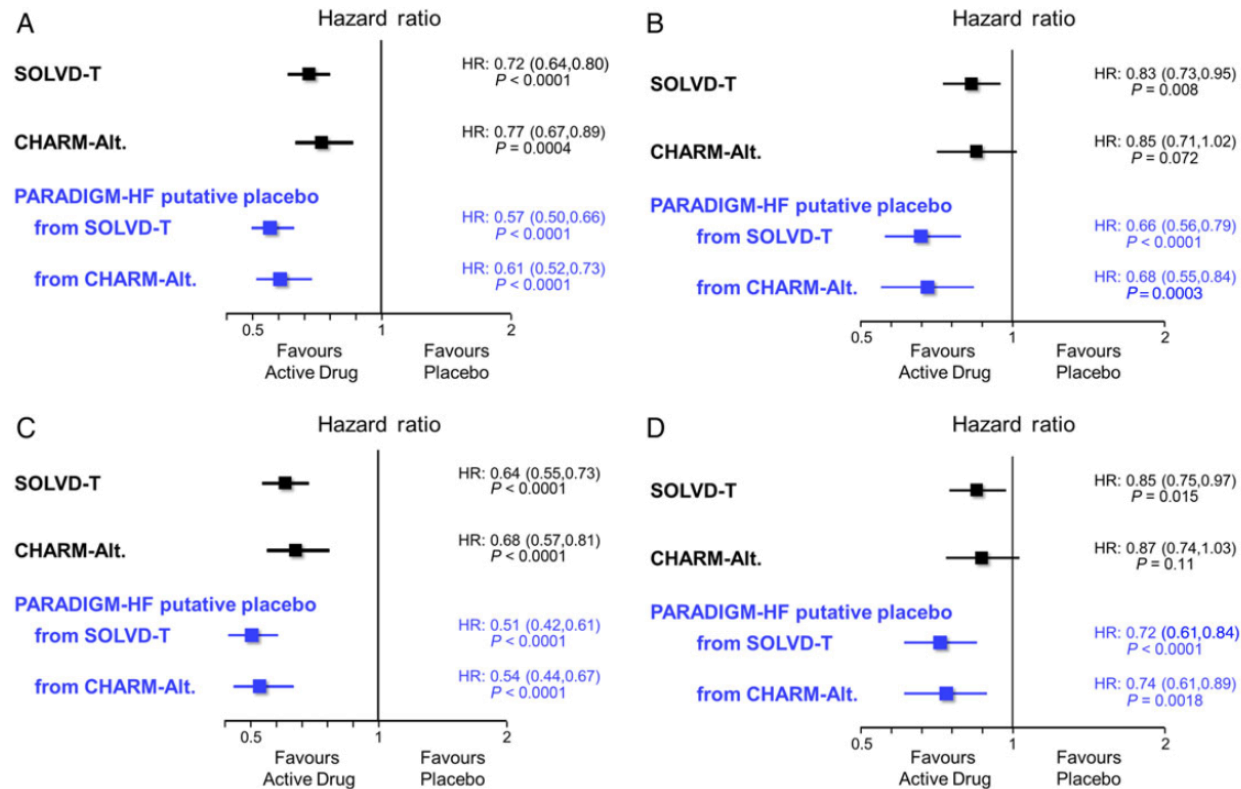


Síntomas moderado a severos



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¿Y FRENTE A PLACEBO...?



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	LCZ696 vs. Enalapril			LCZ696 vs. Candesartan		
	Reducción riesgo	IC 95%	p	Reducción riesgo	IC 95%	p
A (Muerte CV u hospitalización por IC)	43%	34-50%	< 0,0001	39%	27-48%	< 0,0001
B (Muerte CV)	34%	21-44%	< 0,0001	32%	16-45%	< 0,0001
C (hospitalización por IC)	49%	39-48%	< 0,0001	46%	33-56%	< 0,0001
D (Mortalidad por cualquier causa)	28%	15-39%	< 0,0001	26%	11-39%	< 0,0001

¿Y FRENTE A PLACEBO...?

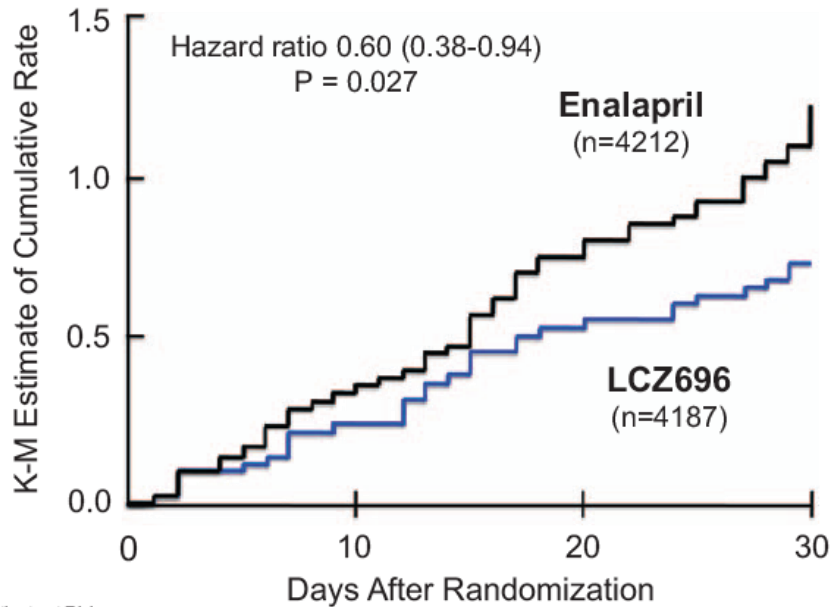
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Angiotensin Receptor Neprilysin Inhibition Compared With Enalapril on the Risk of Clinical Progression in Surviving Patients With Heart Failure

Milton Packer, MD*; John J.V. McMurray, MD*; Akshay S. Desai, MD, MPH;
Jianjian Gong, PhD; Martin P. Lefkowitz, MD; Adel R. Rizkala, PharmD; Jean L. Rouleau, MD;
Victor C. Shi, MD; Scott D. Solomon, MD; Karl Swedberg, MD, PhD; Michael Zile, MD;
Karl Andersen, MD, PhD; Juan Luis Arango, MD; J. Malcolm Arnold, MD; Jan Bělohávek, MD, PhD;
Michael Böhm, MD; Sergey Boytsov, MD; Lesley J. Burgess, MBBCh, PhD; Walter Cabrera, MD;
Carlos Calvo, MD; Chen-Huan Chen, MD; Andrej Dukat, MD; Yan Carlos Duarte, MD;
Andrejs Erglis, MD, PhD; Michael Fu, MD; Efrain Gomez, MD; Angel González-Medina, MD;
Albert A. Hagège, MD, PhD; Jun Huang, MD; Tzvetana Katova, PhD; Songsak Kiatchoosakun, MD;
Kee-Sik Kim, MD, PhD; Ömer Kozan, Prof Dr; Edmundo Bayram Llamas, MD; Felipe Martinez, MD;
Bela Merkely, MD; Iván Mendoza, MD; Arend Mosterd, MD, PhD; Marta Negrusz-Kawecka, MD, PhD;
Keijo Peuhkurinen, MD; Felix J.A. Ramires, MD, PhD; Jens Refsgaard, MD, PhD;
Arvo Rosenthal, MD, PhD; Michele Senni, MD; Antonio S. Sibulo Jr, MD; José Silva-Cardoso, MD, PhD;
Iain B. Squire, MD; Randall C. Starling, MD, MPH; John R. Teerlink, MD; Johan Vanhaecke, MD, PhD;
Dragos Vinereanu, MD, PhD; Raymond Ching-Chiew Wong, MBBS; on behalf of the PARADIGM-HF
Investigators and Coordinators†

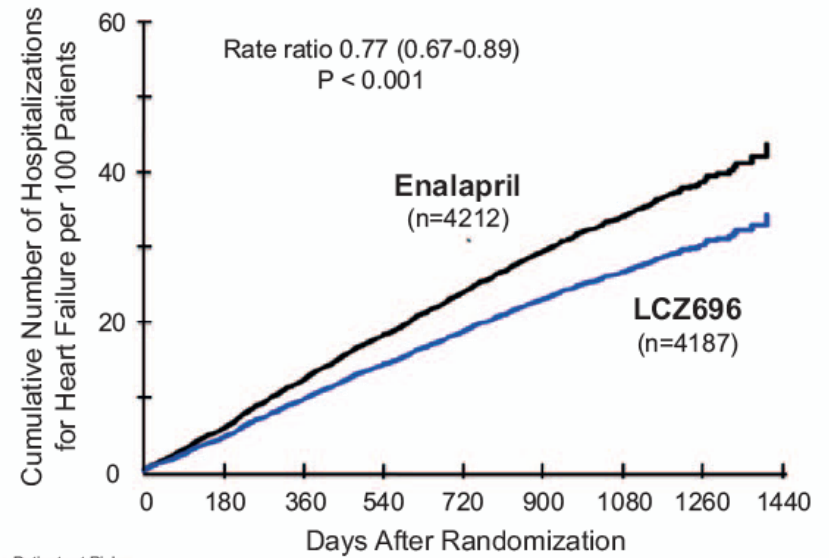


Días hasta 1ª hospitalización



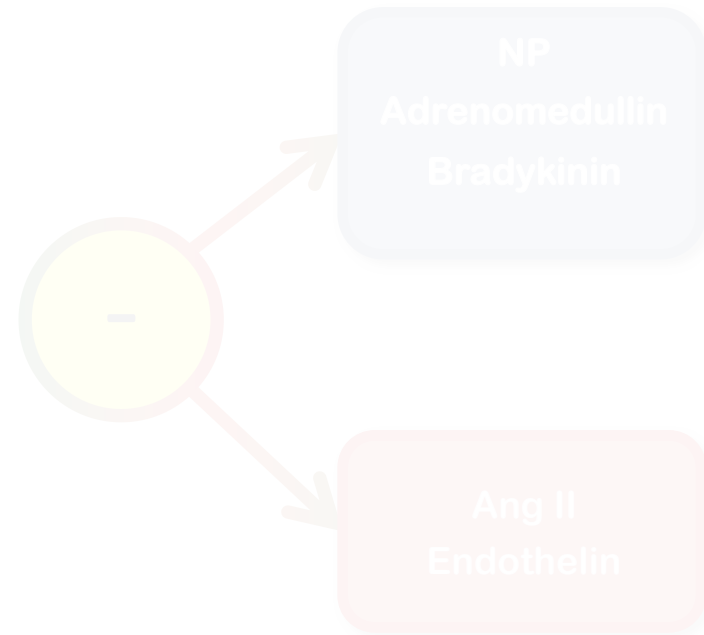
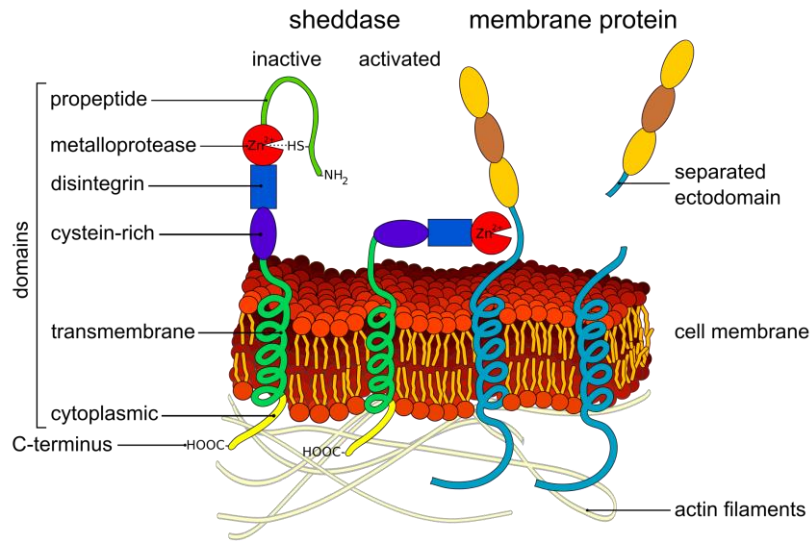
Patients at Risk					
LCZ696	4187	4174	4153	4140	
Enalapril	4212	4192	4166	4143	

Número de hospitalizaciones



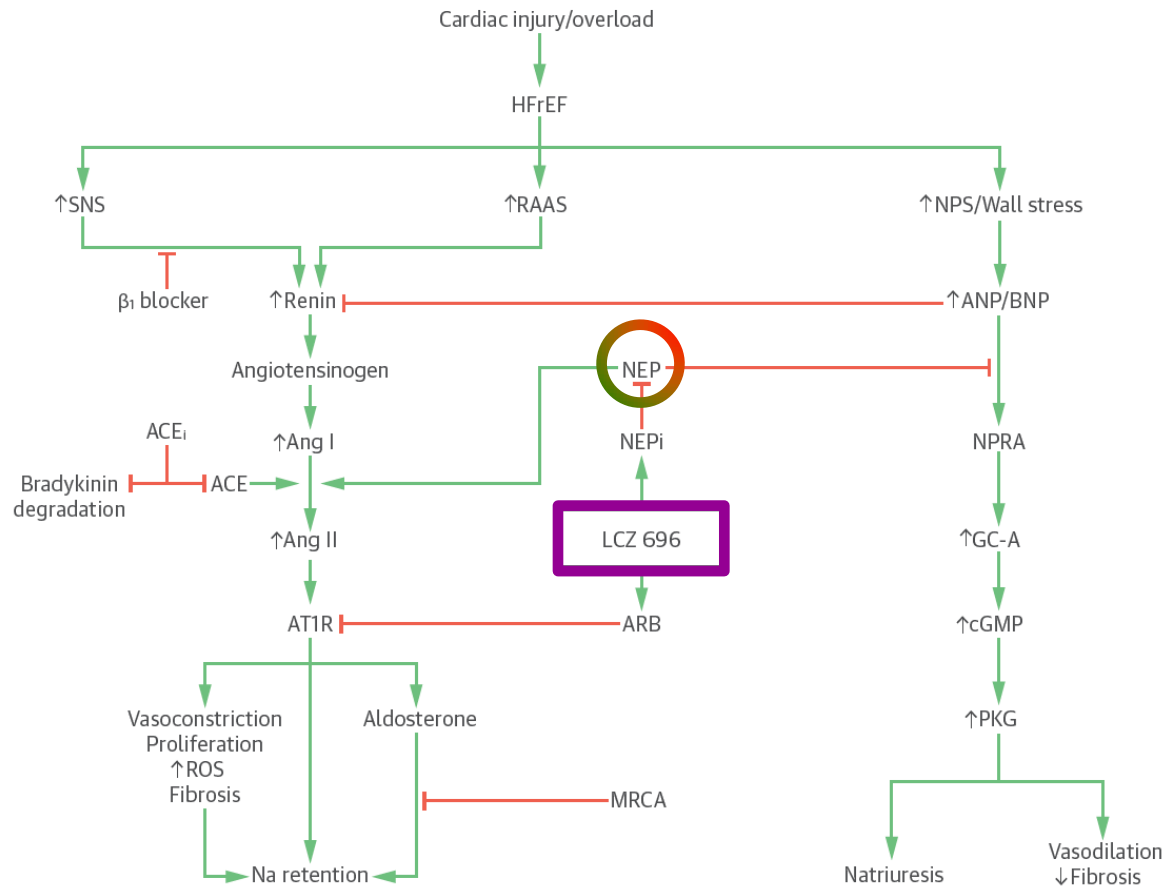
Patients at Risk										
LCZ696	4187	4054	3885	3276	2472	1710	1001	279	12	
Enalapril	4212	4049	3857	3228	2408	1724	993	278	17	

NEPRILISINA

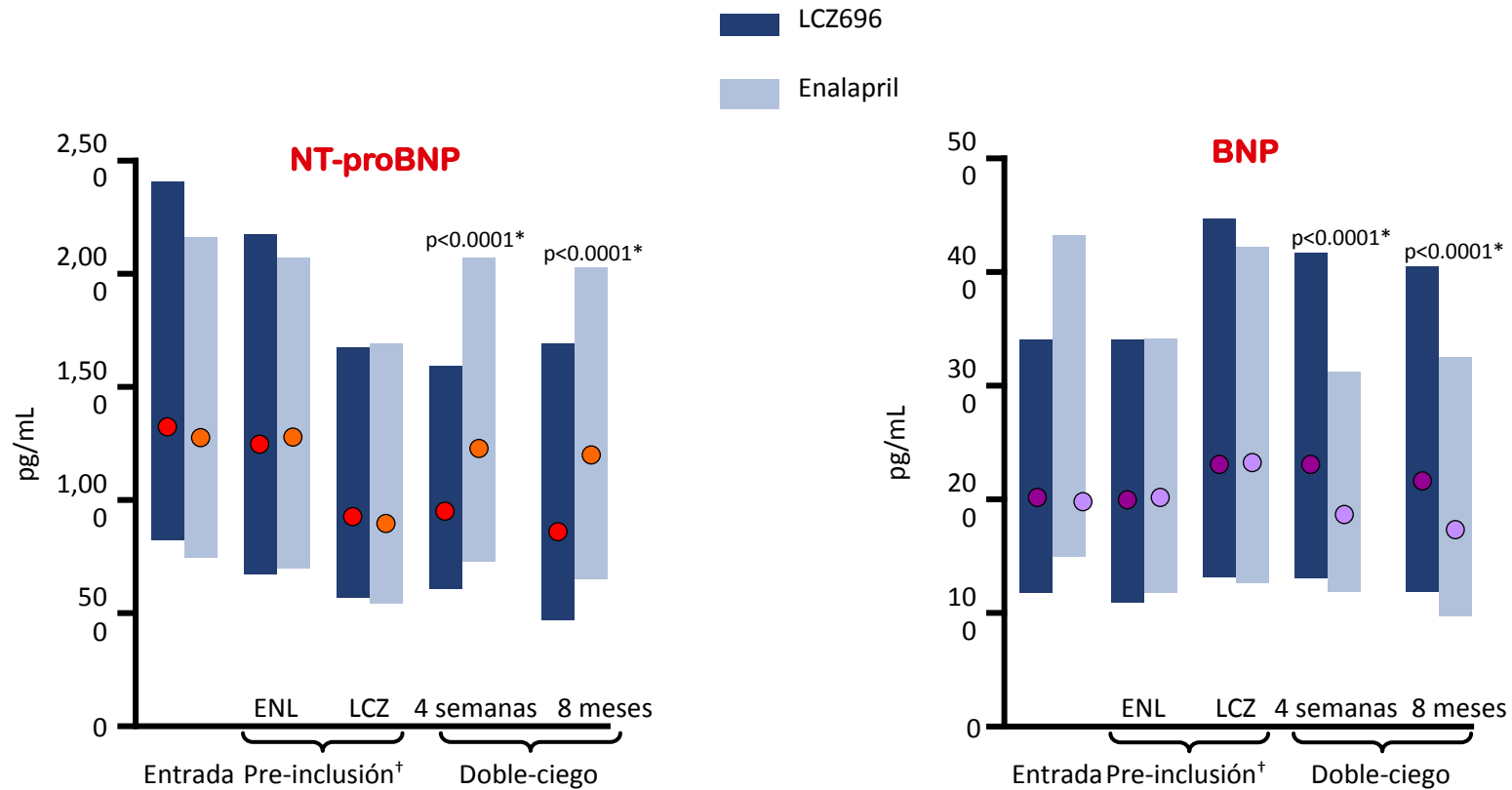


Atriopeptidase, neutral endopeptidase, EC 3.4.24.11, enkephalinase, common acute lymphoblastic leukemia antigen, CD10

BLOQUEO NEUROHUMORAL



COHORTE DE SUPERVIVIENTES

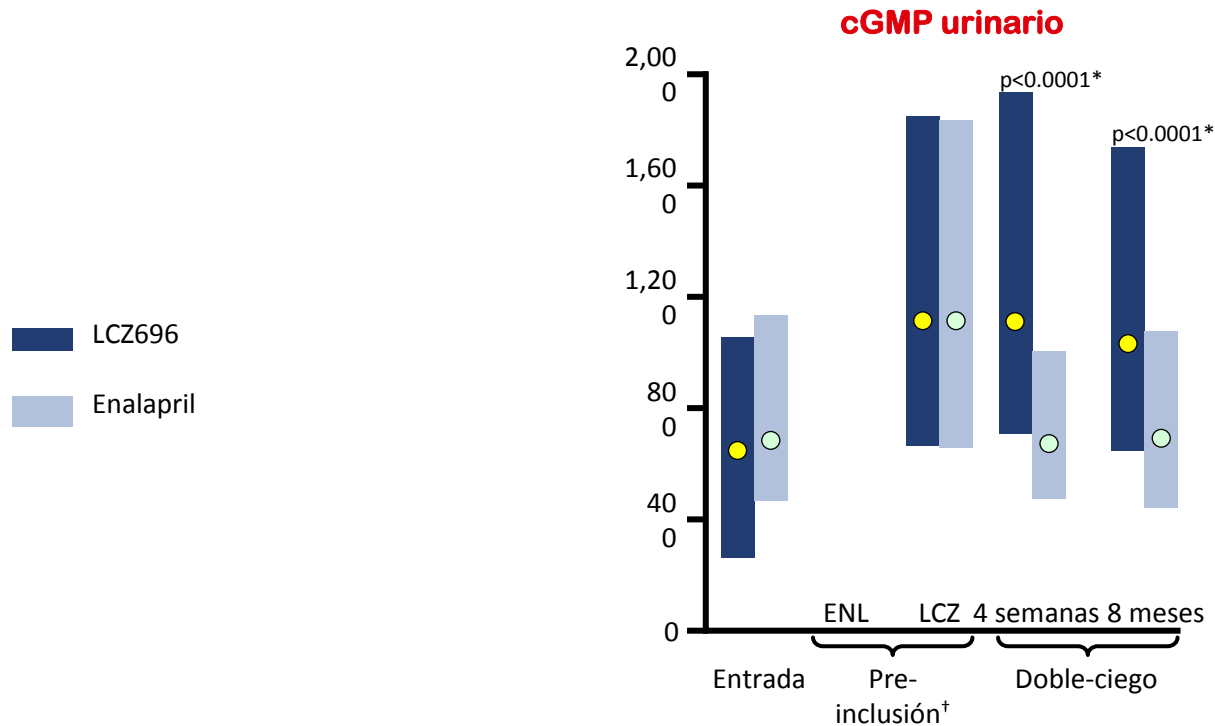


○ = mediana

Barras representan 25%/75% rango intercuartílico

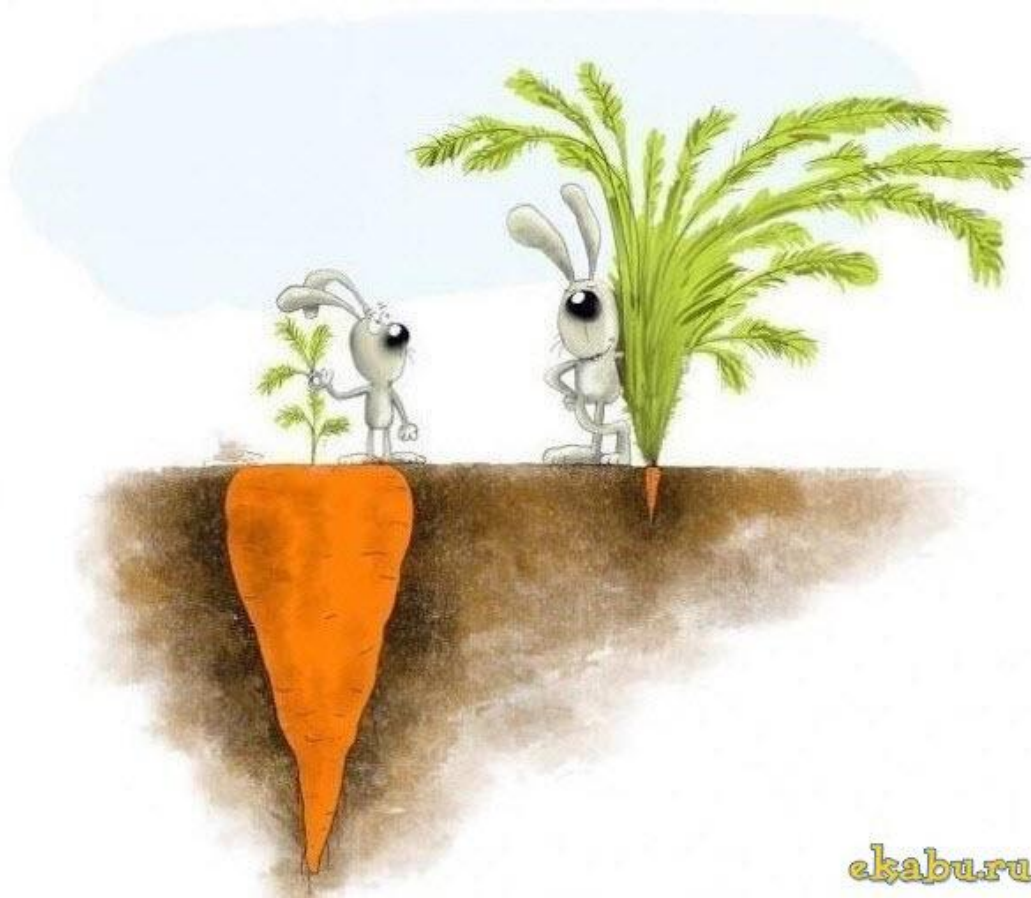


COHORTE DE SUPERVIVIENTES



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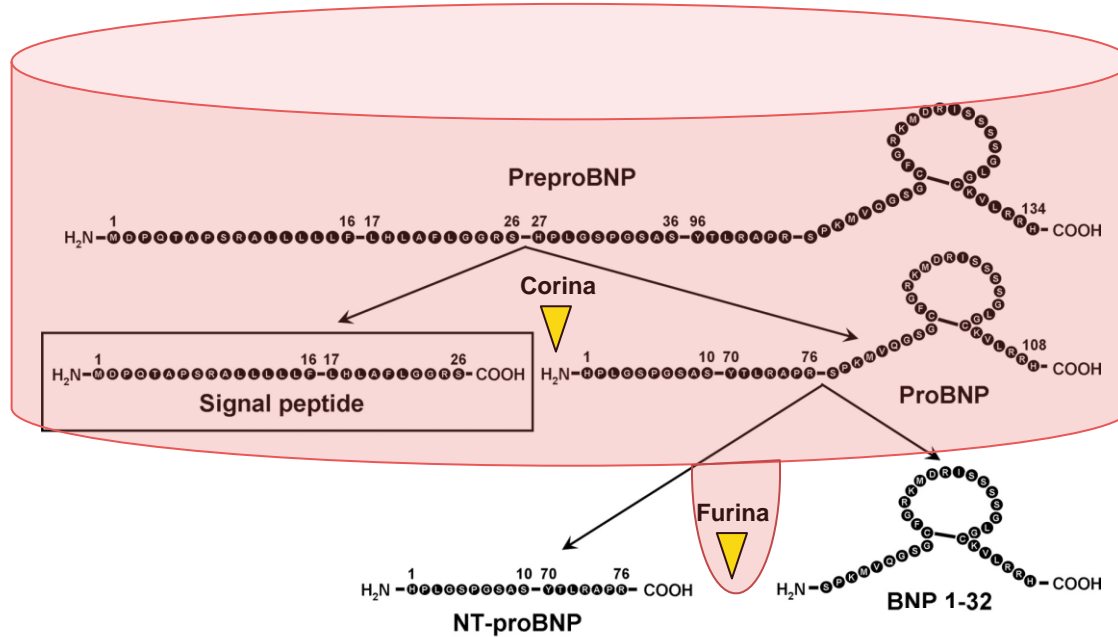
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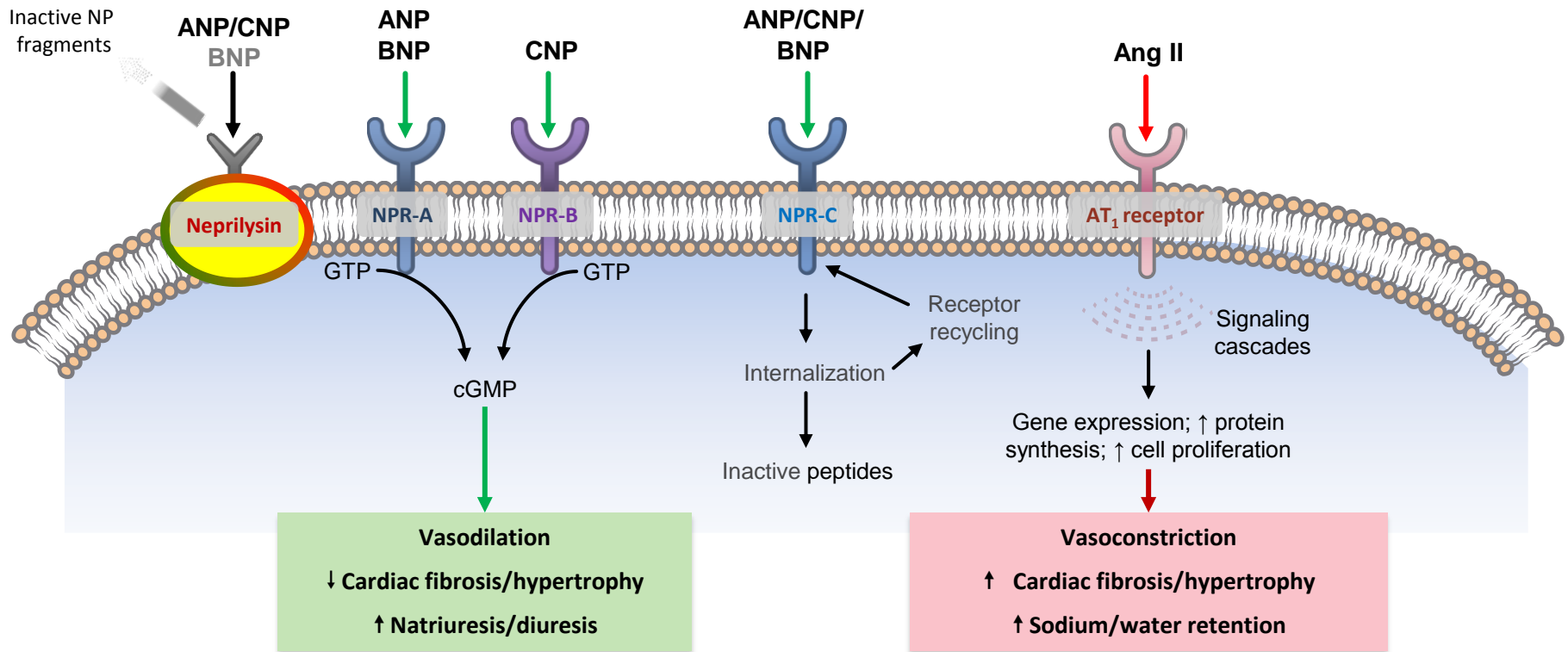
¡¡ El tamaño importa !!

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FISIOLOGÍA DE LOS PN



FISIOLOGÍA DE LOS PN



Cortesía Dr. A. Bayés



¿?



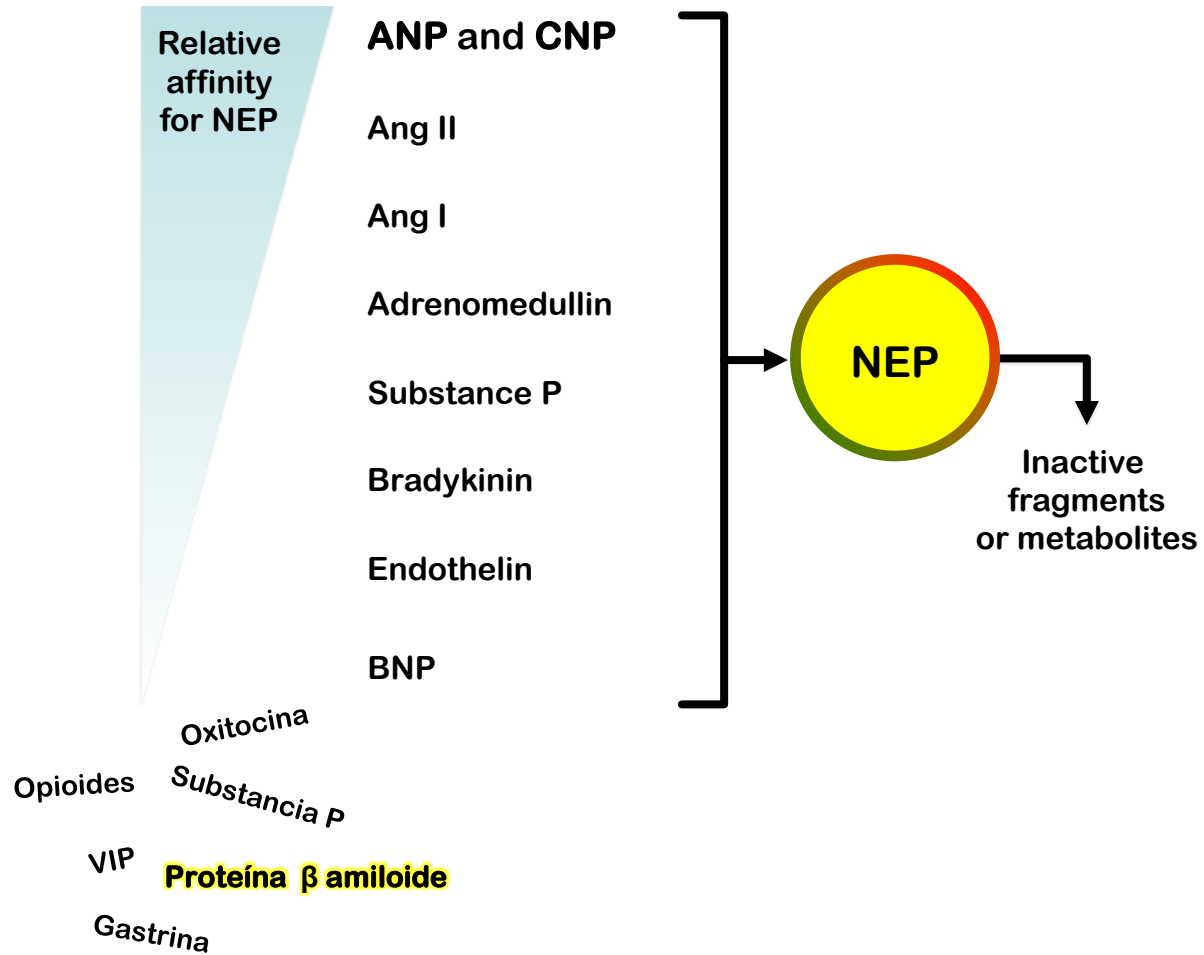
Substratos alternativos de la NEP

Acciones metabólicas de los PN

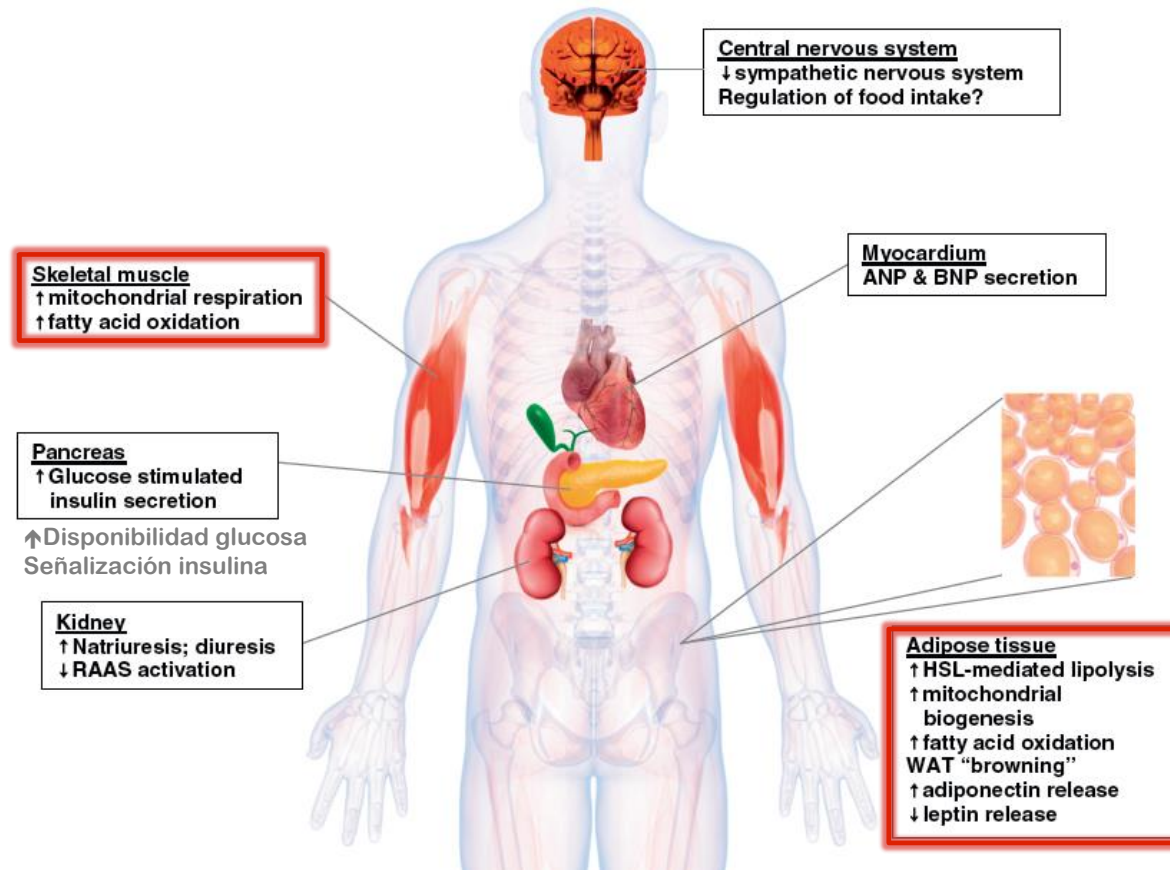
Acciones locales y péptidos relacionados

Na⁺ intersticial

SUBSTRATOS ALTERNATIVOS



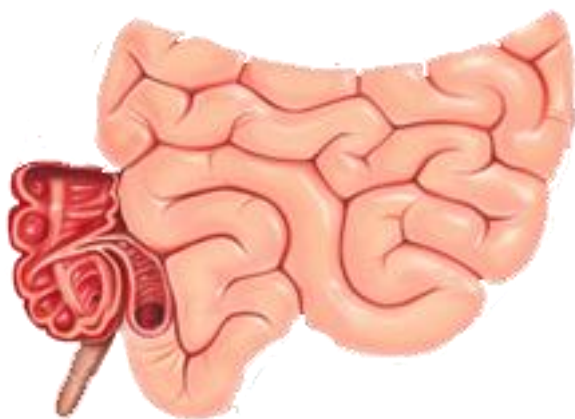
ACCIONES METABÓLICAS



Atenuación del crecimiento adipocitos
↓Citoquinas proinflamatorias del tejido adiposo

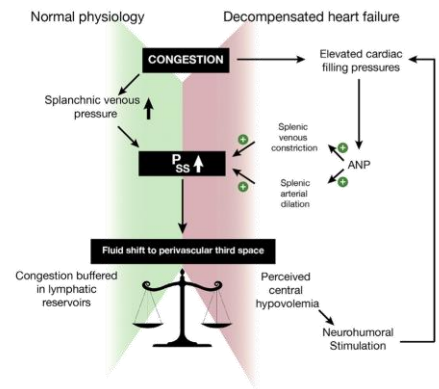
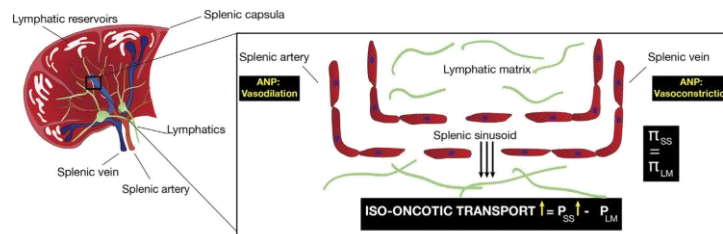
ACCIONES LOCALES

Intestino

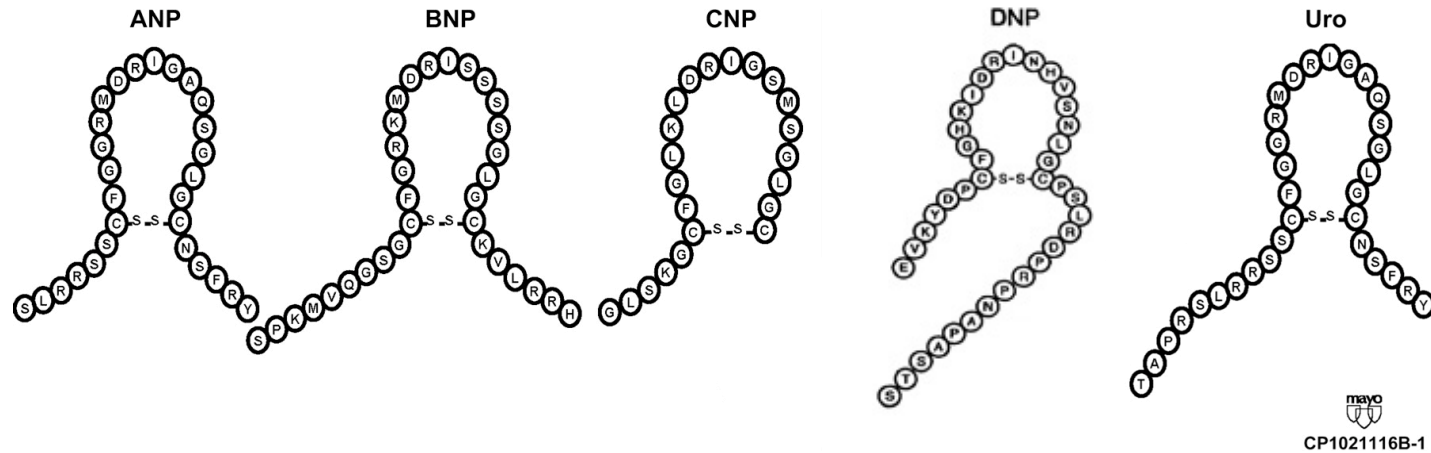


Uroguanylina
Guanylina

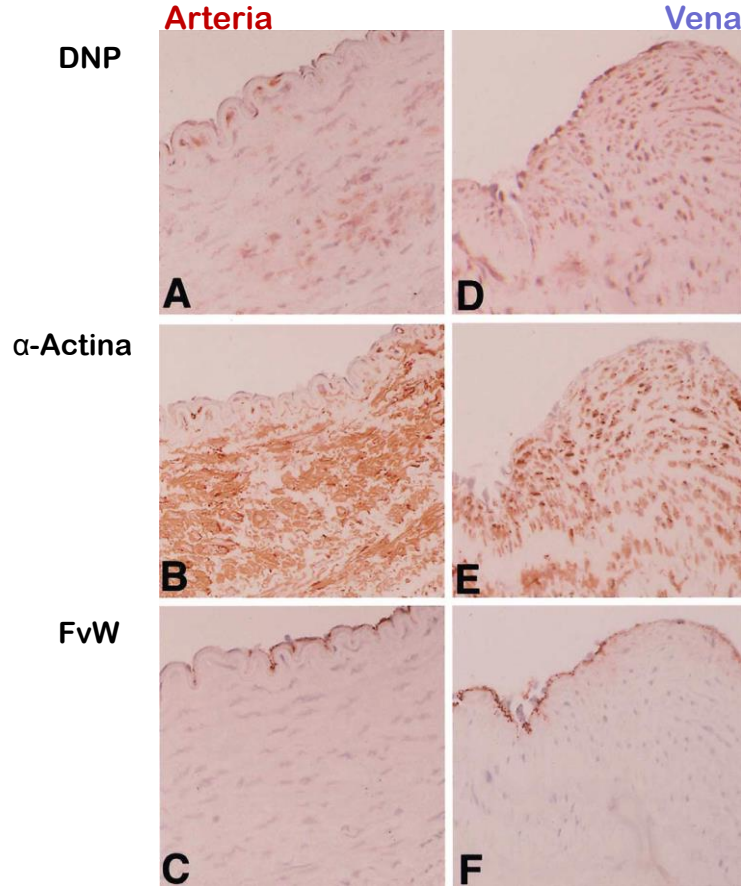
Bazo



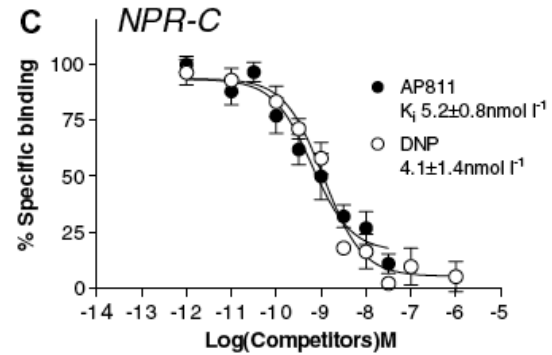
PÉPTIDOS NATRIURÉTICOS



PN RELACIONADOS

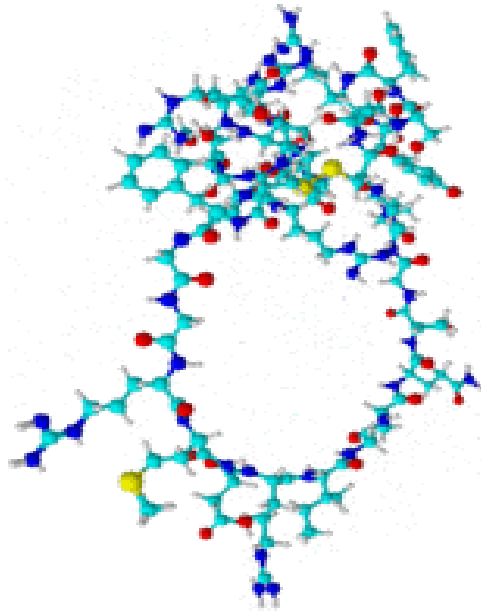


DNP

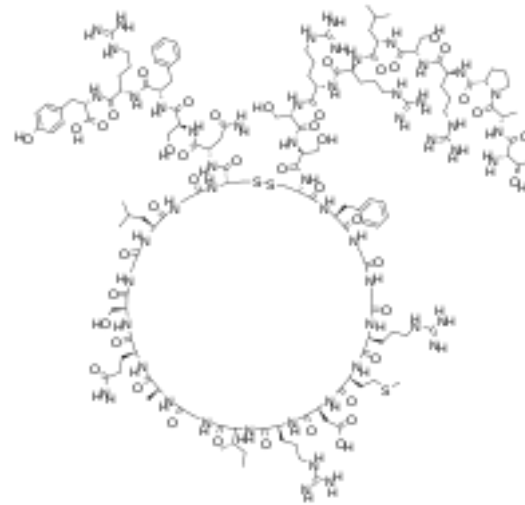


PN RELACIONADOS

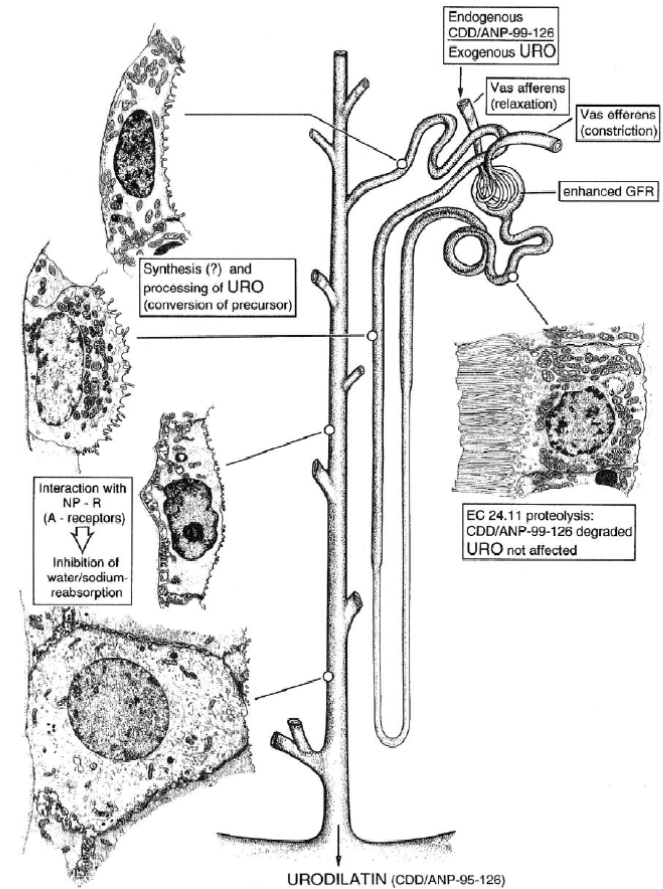
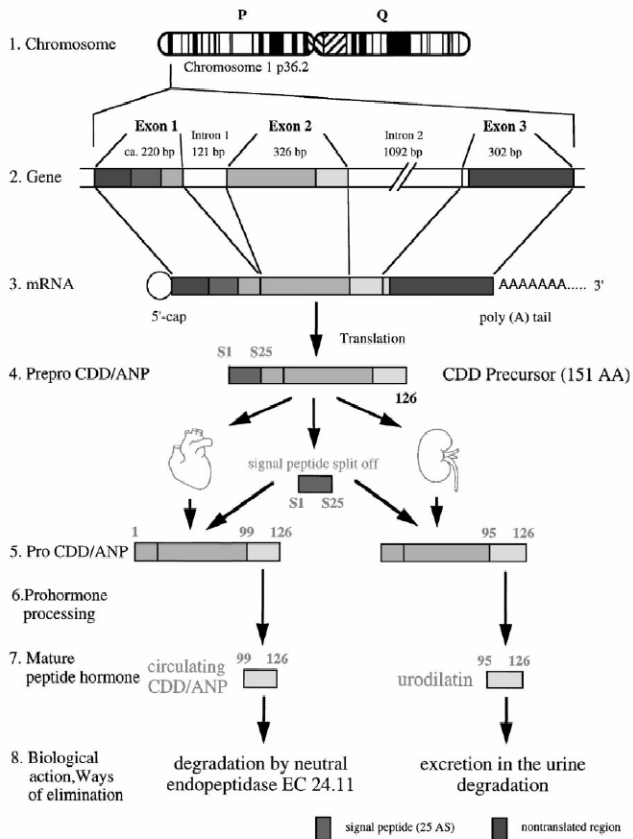
Urodilatina



www.podlabe.com

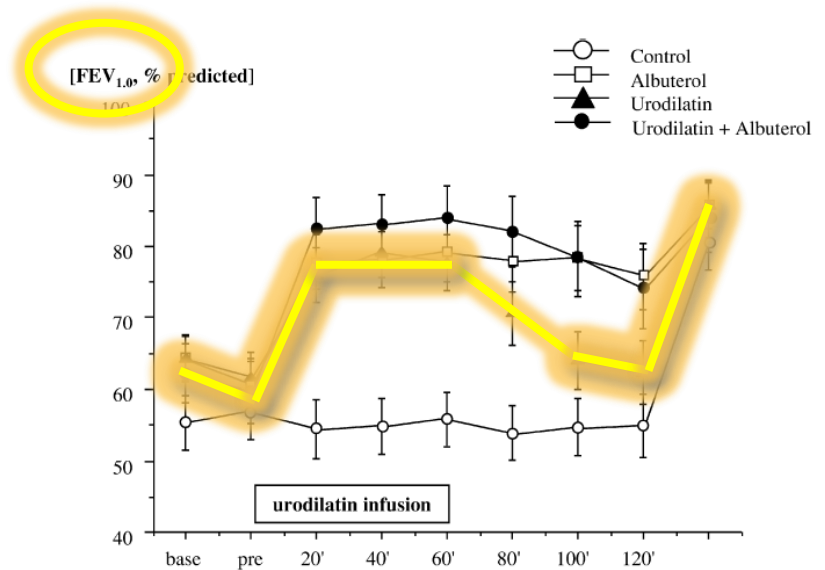
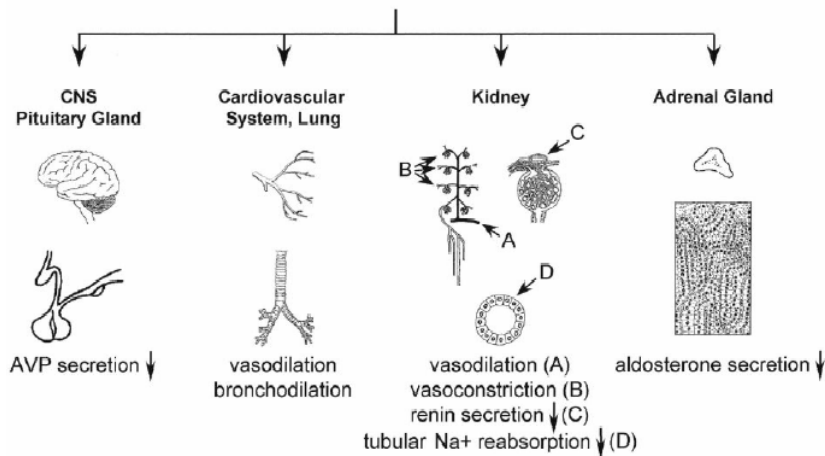


PN RELACIONADOS

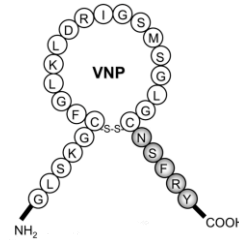


PN RELACIONADOS

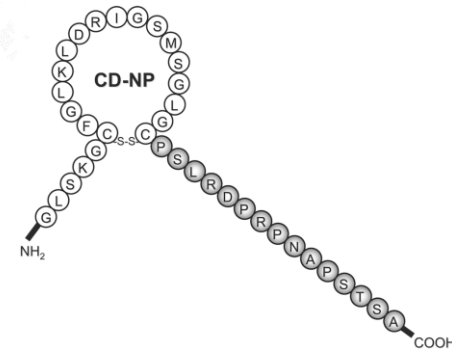
Main Effects of Natriuretic Peptides on Organ Systems



PÉPTIDOS DE DISEÑO

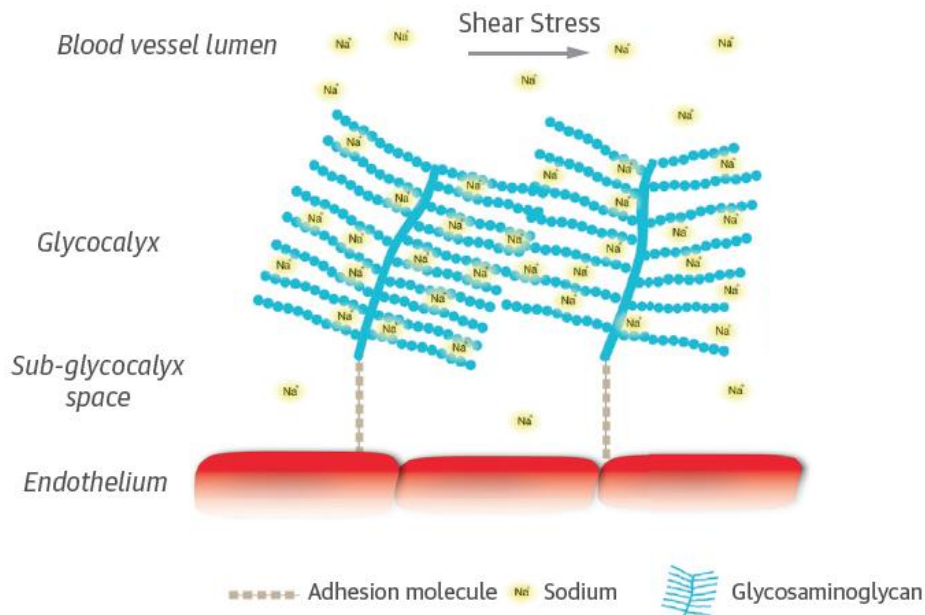


Vasonatrina



Na⁺ INTERSTICIAL

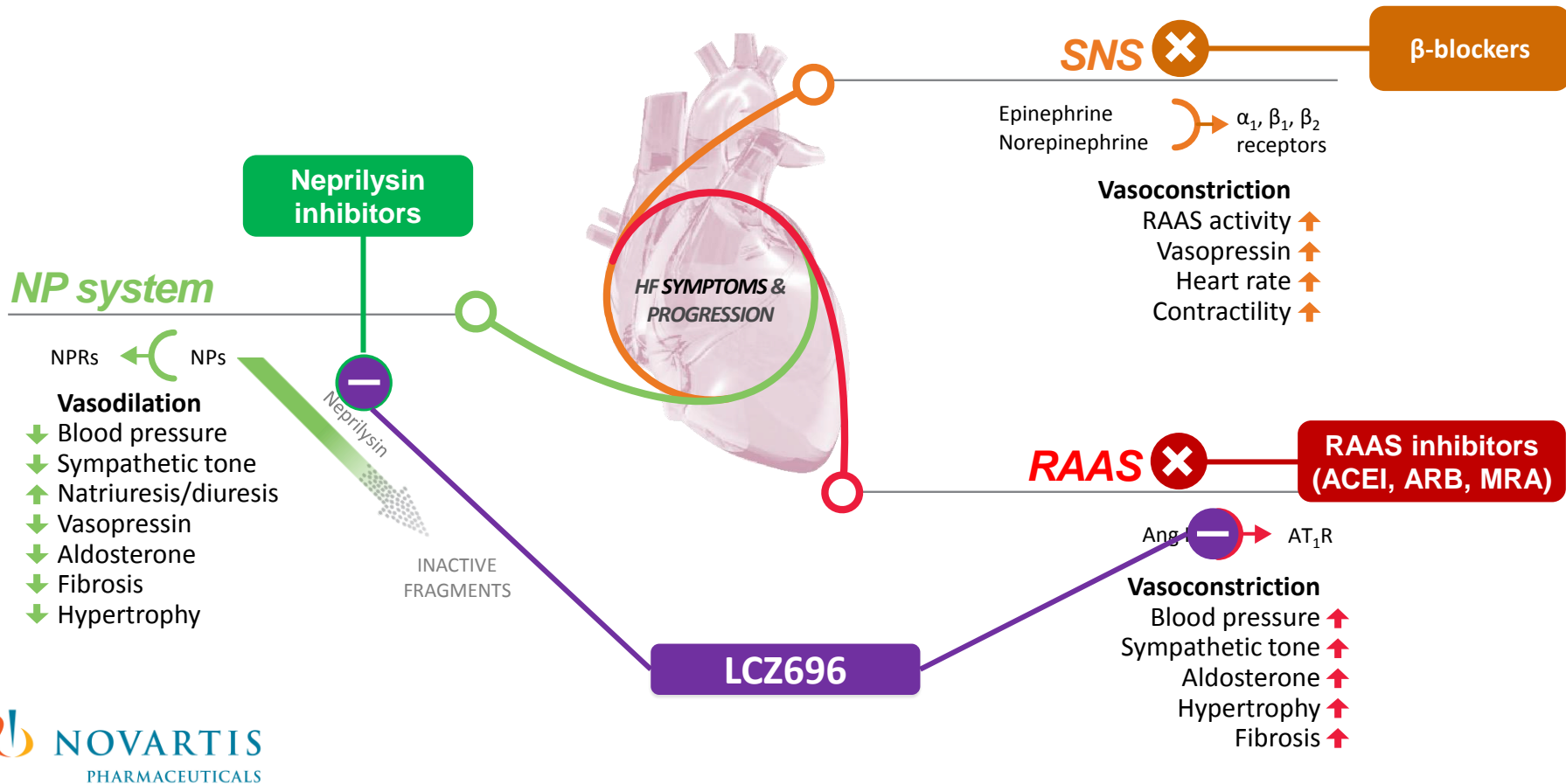
El Glicocálix endotelial



Funciones

- Protección mecánica del polo apical endotelial
- Reduce la permeabilidad vascular
- Restringe el acceso de algunas moléculas
- Evita interacción con plaquetas
- Evita interacción con leucocitos
- Tampona cambios en la concentración de Na⁺
- Mecanotransductor del “shear stress”
- Señalización intracelular endotelial
- Organización del citoesqueleto

BLOQUEO NEUROHUMORAL



Periodo de "run-in"
Terminación precoz
Desfibriladores
MP biventricular
Angioedema
Péptidos β -amiloides



European Heart Journal (2015) 36, 410–412
doi:10.1093/eurheartj/ehu501

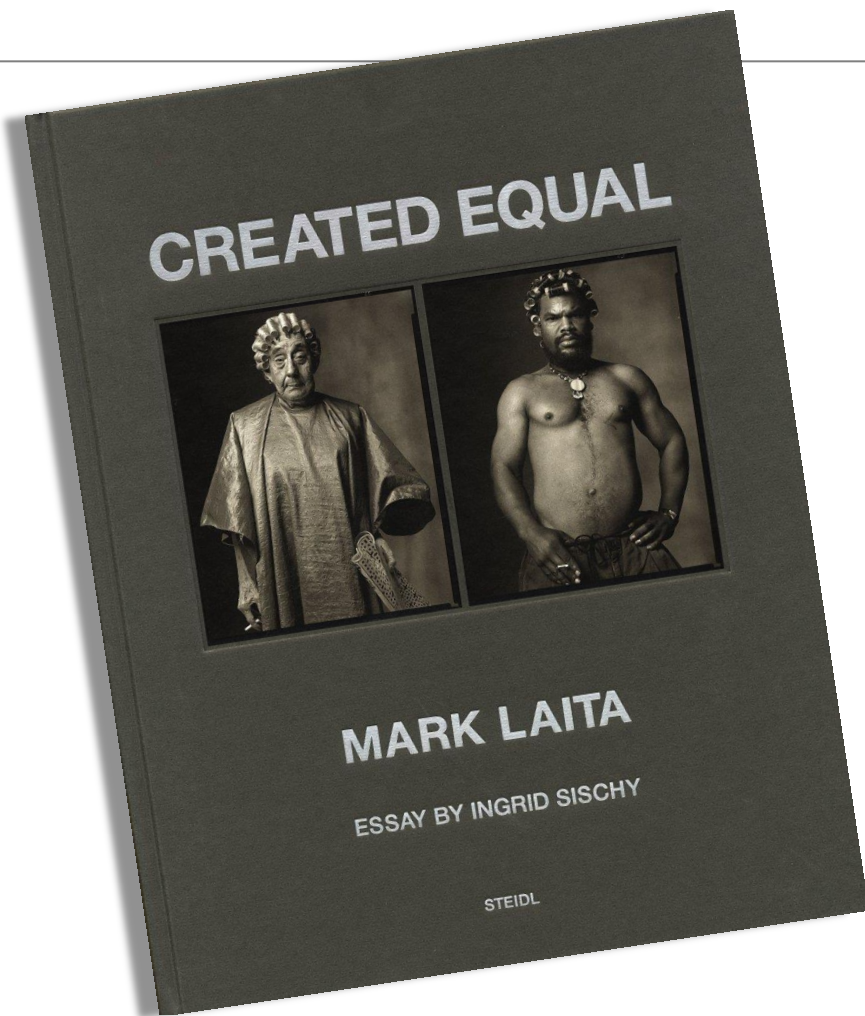
EDITORIAL

LCZ696: too good to be true?

Robert M. Califf[®]

Division of Cardiology, Department of Medicine, Duke University School of Medicine, Durham, NC, USA; and Duke Translational Medicine Institute, Durham, NC, USA

¿Substituyen IECA?
Primera línea
ICFEP
IC aguda
Insuf renal
Hipertensión



Gracias