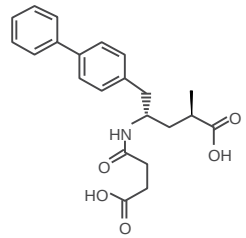
Explorando el mundo de los iSGLT2 y ARNI

Conociendo a fondo los ARNI

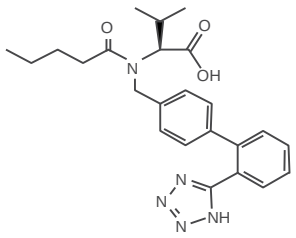
Dr. Gustavo L. Escalada Lesme FACC, FSIAC

Sacubitrilo-Valsartán

Sacubitrilat
(NEP inhibidor)



Valsartán



Número: CAS 149709-62-6

Código ATC: C09DX04

PubChem: 9811834

Nombre técnico: LCZ696

Fórmula: $C_{24}H_{29}NO5$

Peso mol: 411.49 g/mol

PEPTIDOS VASOACTIVOS*

Neprilysin

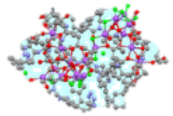
Inactive fragments

Estimula

Vasodilatación:

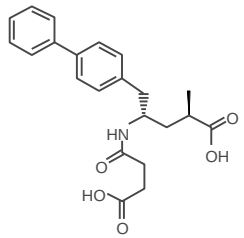
- ↓ Presión Arterial
- ↓ Tono simpático
- ↓ Niveles de aldosterona
- ↓ Fibrosis
- ↓ Hipertrofia
- ↑ Natriuresis/Diuresis

Sacubitril-Valsartán

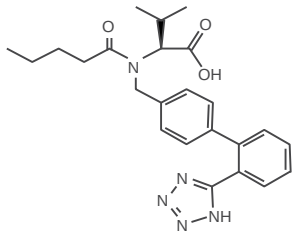


Sacubitril
(pro-droga)

Sacubitrilat
(NEP inhibidor)



Valsartán



SRAA

Angiotensinogen
(secreción hepática)

↓

Ang I

↓

Ang II

↓

AT_1 receptor

Inhibe:

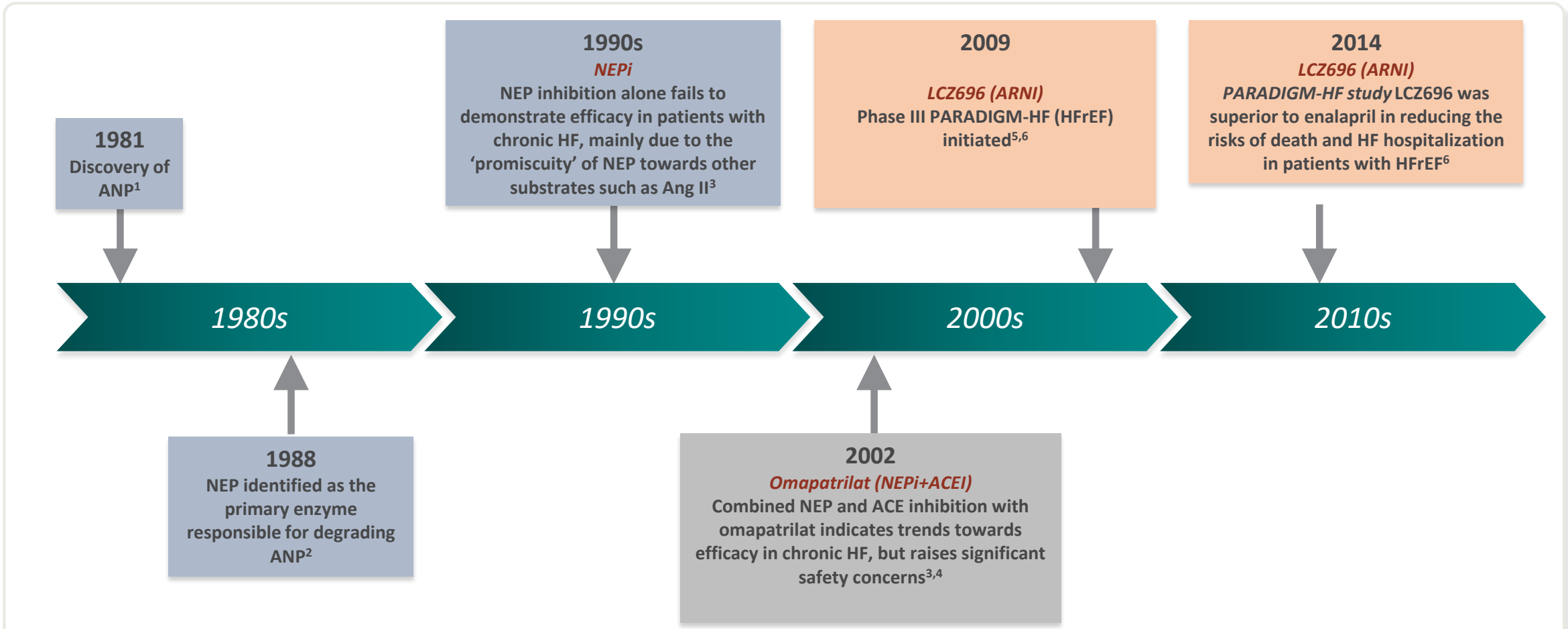
Vasoconstrictón

- ↑ Presión Arterial
- ↑ Tono simpático
- ↑ Niveles de Aldostrona
- ↑ Fibrosis
- ↑ Hipertrofia
- ↑ Natriuresis/Diuresis

**Neprilysin substrates listed in order of relative affinity for NEP: ANP, CNP, Ang II, Ang I, adrenomedullin, substance P, bradykinin, endothelin-1, BNP*

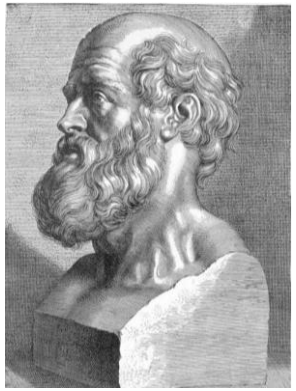
Ang: angiotensin; ANP: atrial natriuretic peptide; AT_1: angiotensin II type 1; BNP: B-type natriuretic peptide; CNP: C-type natriuretic peptide; NEP: neprilysin; RAAS: renin-angiotensin-aldosterone system

Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42; Schrier & Abraham. N Engl J Med 2009;341:577–85; Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9; Feng et al. Tetrahedron Letters 2012;53:275–6

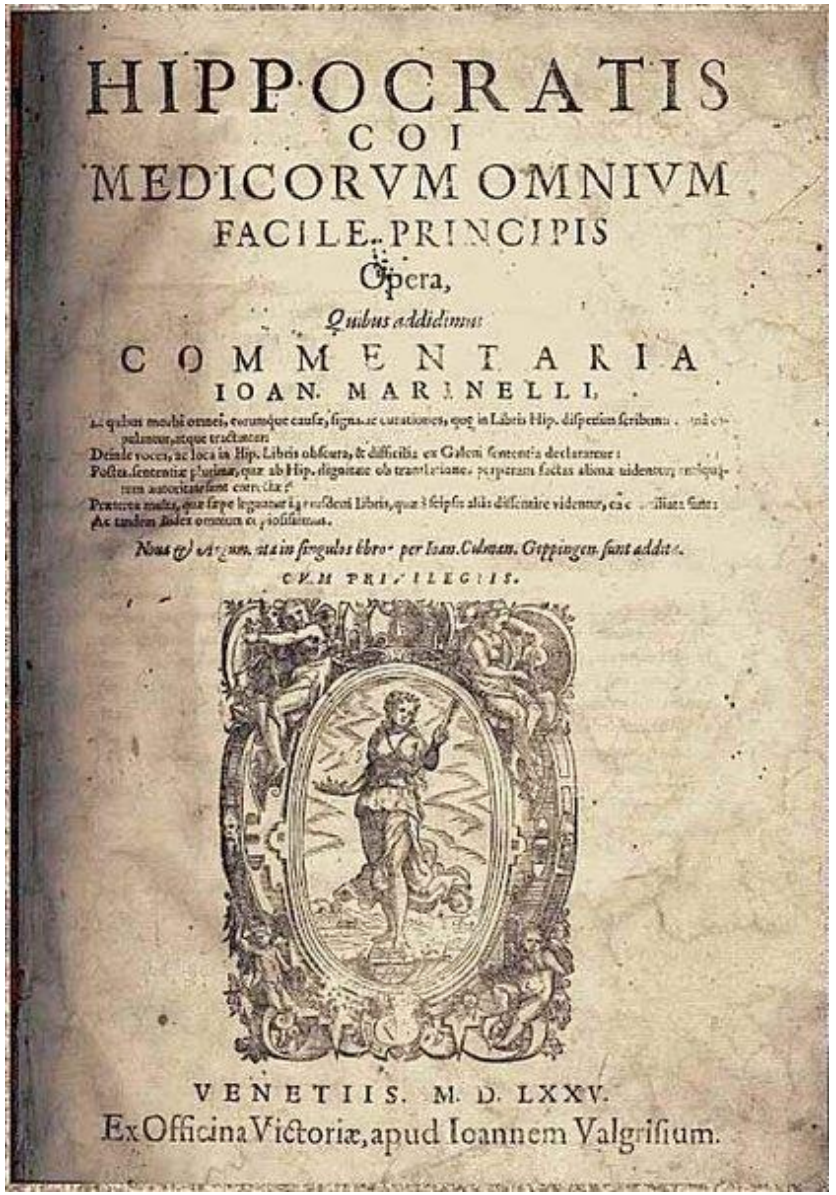


ACE: angiotensin-converting enzyme; ACEI: angiotensin-converting-enzyme inhibitor; Ang: angiotensin; ANP: atrial natriuretic peptide; ARNI: angiotensin receptor neprilysin inhibitor; AT_1R: angiotensin II type 1 receptor; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; NEP: neprilysin; NEPi: neprilysin inhibition; NP: natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

1. de Bold et al. Life Sci 1981;28:89–94; 2. Sonnenberg et al. Peptides 1988;9:173–80; 3. Von Lueder et al. Pharmacol Ther 2014;144:41–9; 4. Packer et al. Circulation 2002;106:920–6; 5. McMurray et al. Eur J Heart Fail 2013;15:1062–73; 6. McMurray et al. N Engl J Med 2014;371:993–1004

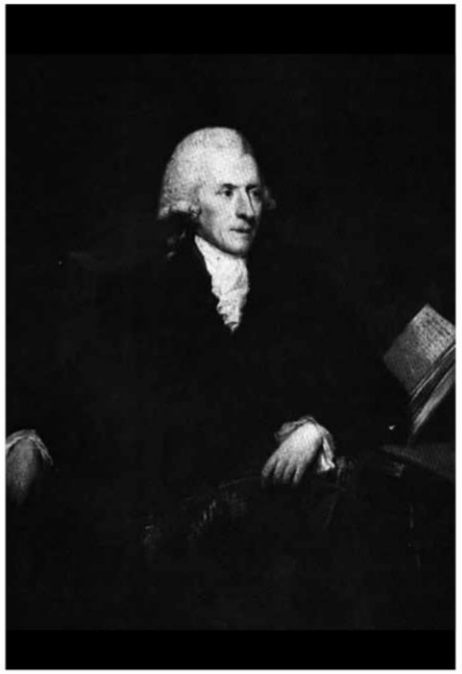


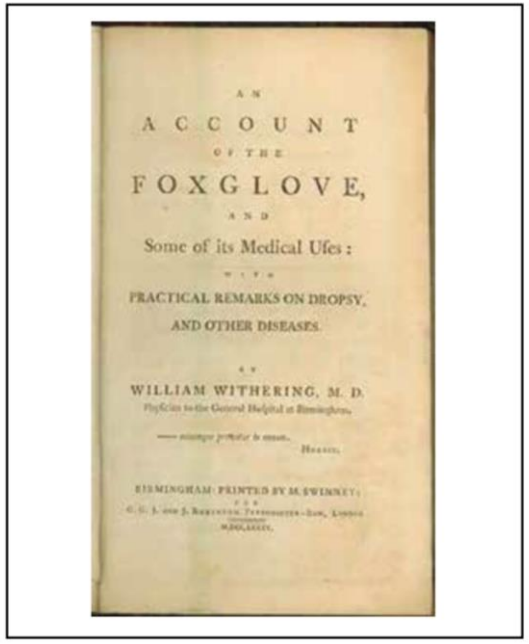
Hipócrates de Cos, griego,
Cos 460 a. C.-Tesalia c. 370 a

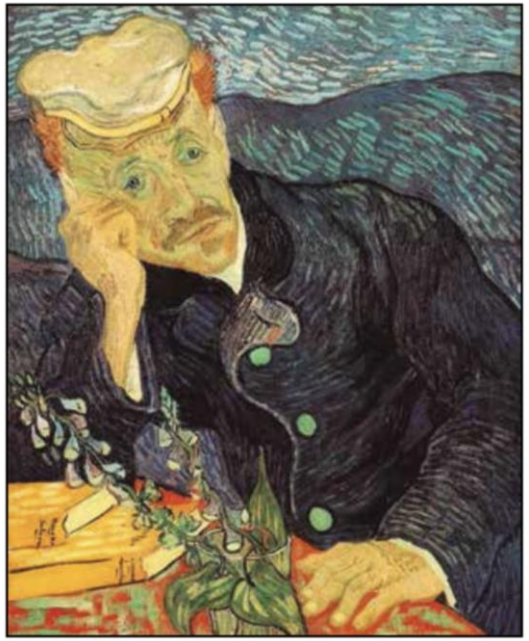


CORPUS HIPOCRÁTICO (Cuerpo Hipocrático), con gran experiencia y utilizando su sentido común, ha dejado una detallada descripción de los signos y síntomas de la IC, distinguiendo la acumulación de líquido, el edema, la ascitis llamándola *"la hidropesia"*, a la cual se refería diciendo: ***"Los musculos se convierten en agua. El abdomen se llena de agua. Los pies y las piernas se hinchan, y los hombros y las clavículas se derriten."***, constituyendo una descripción de la anasarca y la caquexia cardíaca.

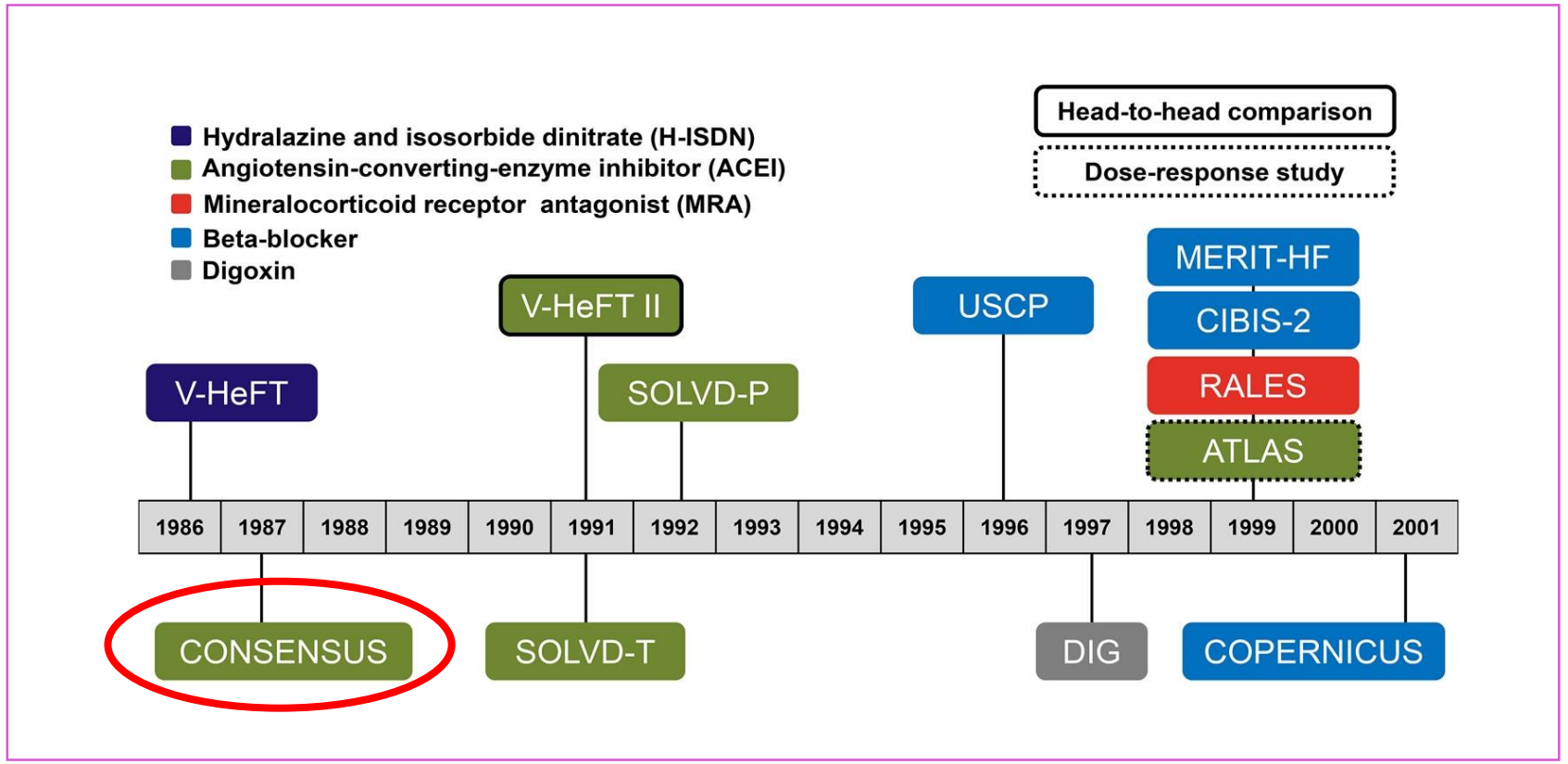
También se refirió a los estertores o rales como sigue: ***"Cuando el oído se lleva al pecho y se escucha por algún tiempo, puede ser escuchado que hierven en el interior como un punto de ebullición de vinagre".***

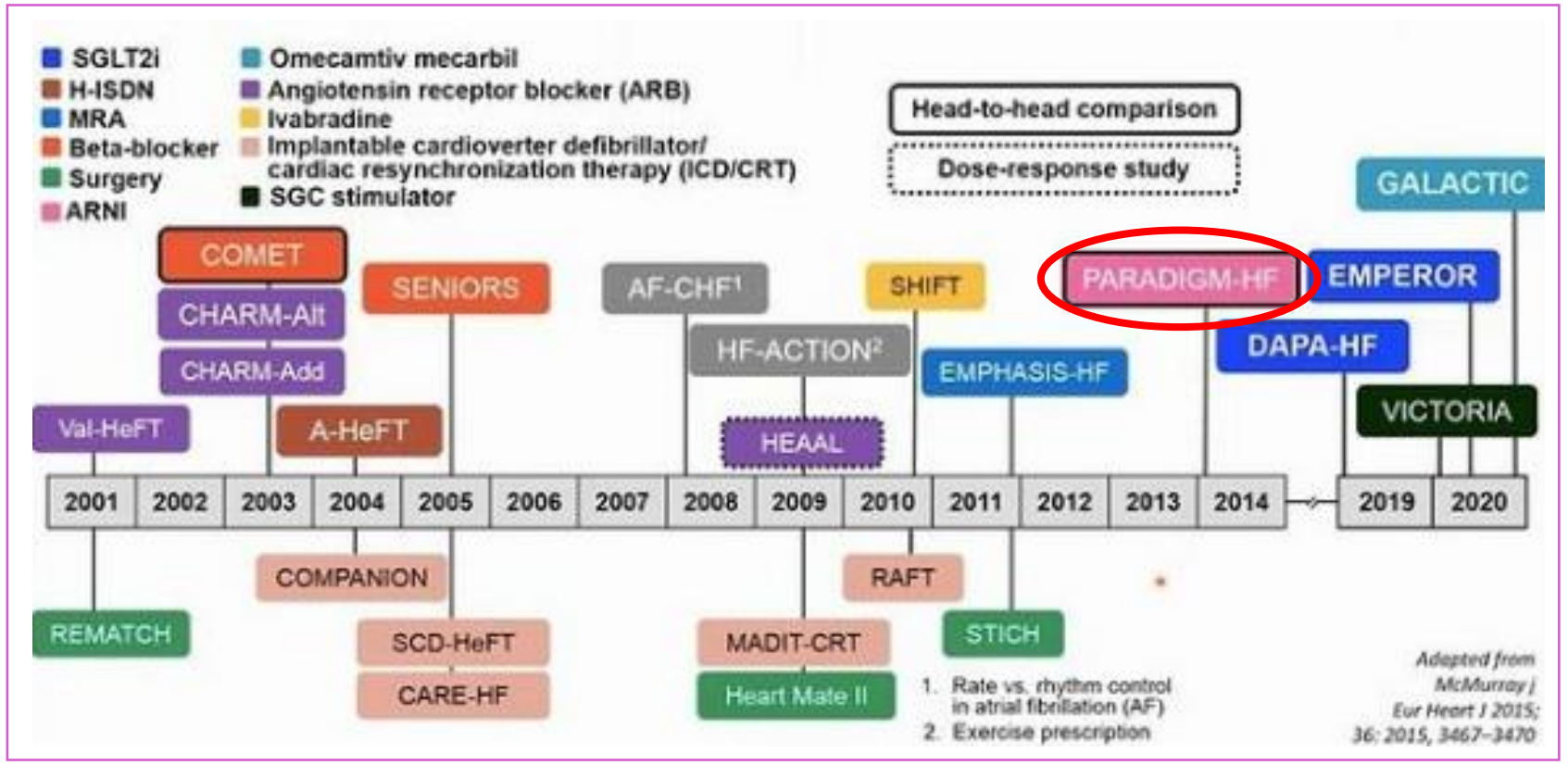




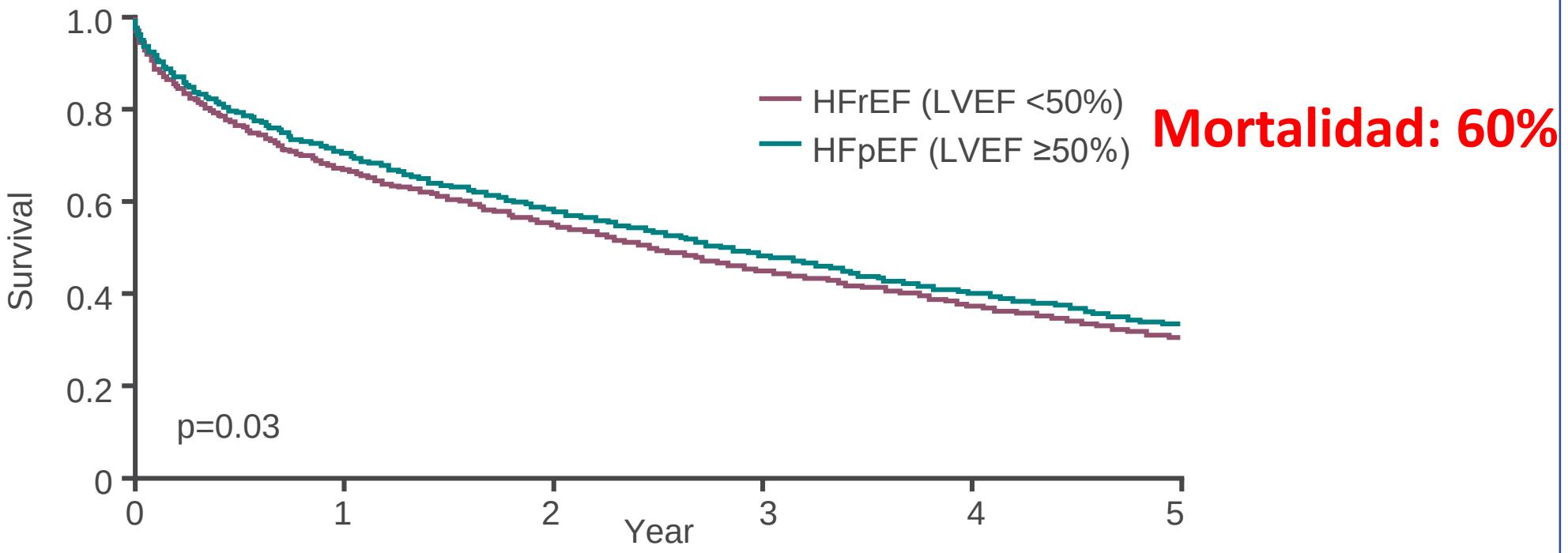


Si bien las hojas de digital purpúrea *(Digitalis purpurea)* se empleaban desde el año 500 D.C., fue el Dr. William Whitering, de Inglaterra, quien investigó sus propiedades y en 1785 escribió un libro que ingresó entre los clásicos de la historia de la medicina: *An account of the foxglove and some of its medical uses, with practical remarks on dropsy and other diseases*.


Hydralazine and isosorbide dinitrate (H-ISDN)
Angiotensin-converting-enzyme inhibitor (ACEI)
Mineralocorticoid receptor antagonist (MRA)
Beta-blocker
Digoxin
Head-to-head comparison
Dose-response study
V-HeFT
V-HeFT II
SOLVD-P
USCP
MERIT-HF
CIBIS-2
RALES
ATLAS
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
CONSENSUS
SOLVD-T
DIG
COPERNICUS


SGLT2i
H-ISDN
MRA
Beta-blocker
Surgery
ARNI
Omecamtiv mecarbil
Angiotensin receptor blocker (ARB)
Ivabradine
Implantable cardioverter defibrillator/ cardiac resynchronization therapy (ICD/CRT)
SGC stimulator
Head-to-head comparison
Dose-response study
COMET
CHARM-Alt
CHARM-Add
Val-HeFT
A-HeFT
SENIORS
AF-CHF[1]
HF-ACTION[2]
HEAAL
SHIFT
EMPHASIS-HF
PARADIGM-HF
DAPA-HF
GALACTIC
EMPEROR
VICTORIA
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2019
2020
COMPANION
RAFT
REMATCH
SCD-HeFT
CARE-HF
MADIT-CRT
Heart Mate II
STICH
1. Rate vs. rhythm control in atrial fibrillation (AF)
2. Exercise prescription
Adapted from McMurray J Eur Heart J 2015; 36: 2015, 3467–3470

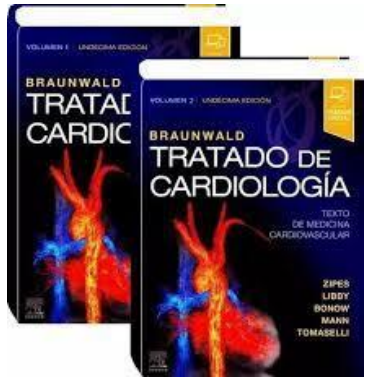
- Survival rate among patients with a discharge diagnosis of HF in the USA was slightly higher among patients with HFpEF than those with HFrEF between 1987–2001[1]
  - respective mortality rates were 29% and 32% at 1 year and 65% and 68% at 5 years



- HFpEF is associated with significant morbidity and mortality, despite having a slightly higher survival rate compared with HFrEF[2,3]

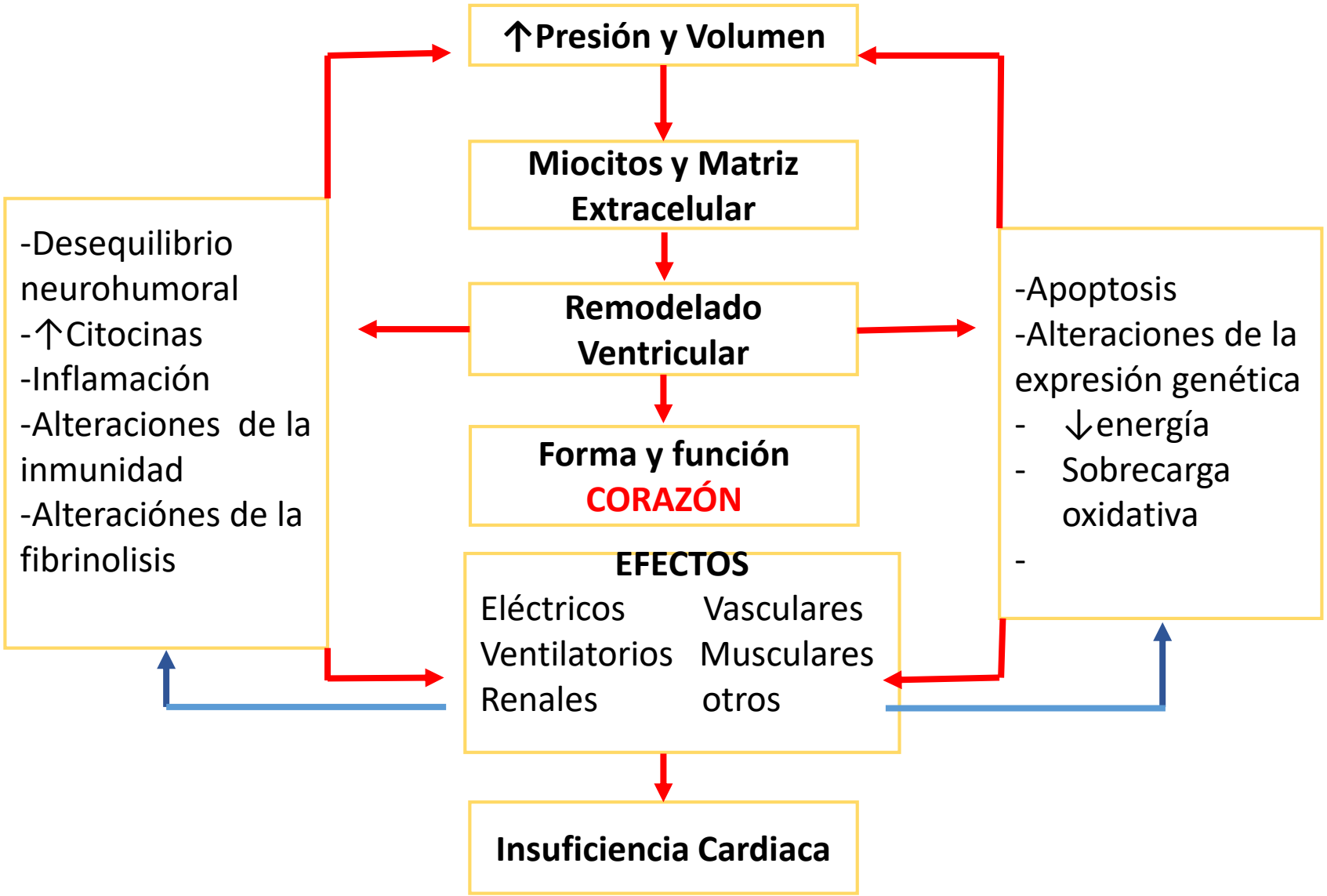
HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; USA: United States of America

1. Owan et al. N Engl J Med 2006;355:251–9; 2. Blanche et al. Swiss Med Wkly 2010;140:66–72; 3. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). Eur Heart J 2012;33:1750–7

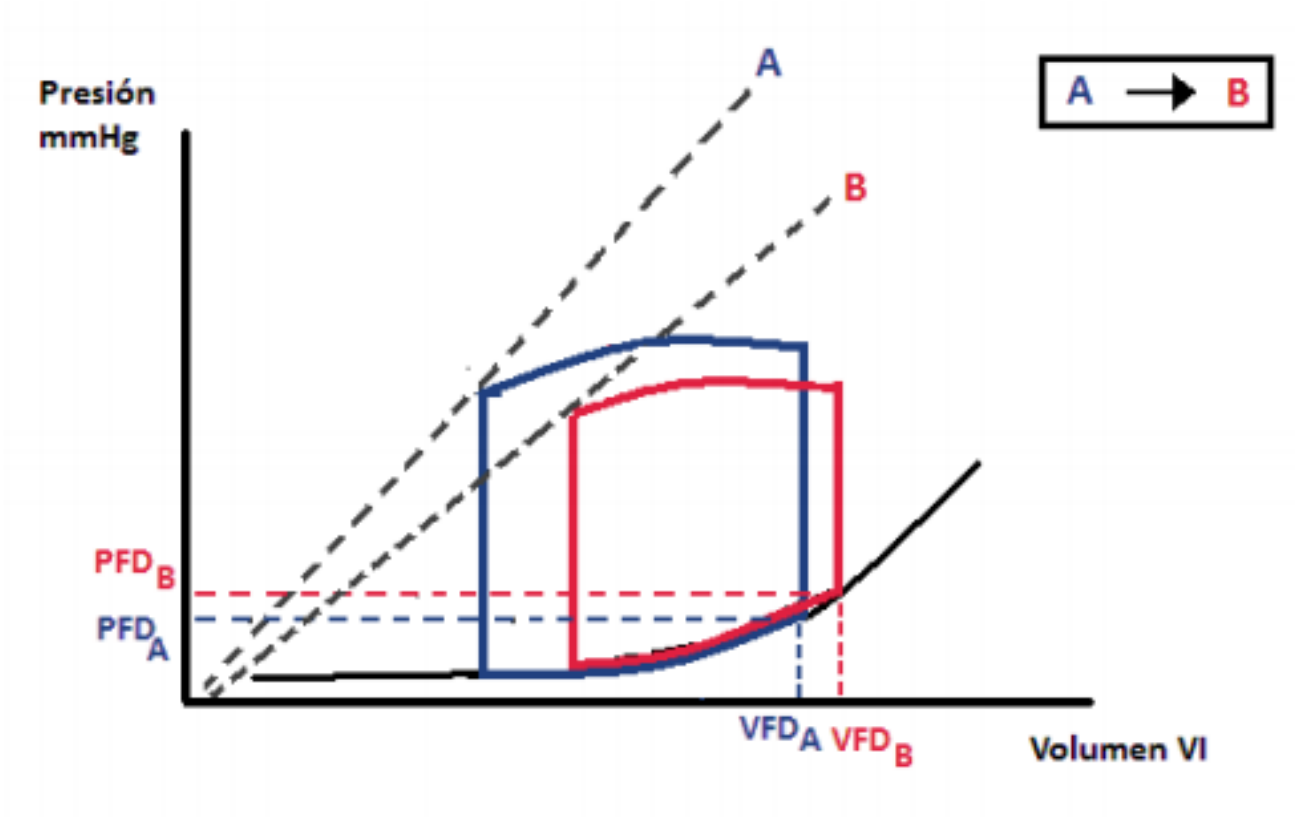


Insuficiencia Cardiaca: es la incapacidad del corazón de ***bombear sangre a volúmenes adecuados*** para mantener el *metabolismo de los tejidos periféricos* o si lo hace es a expensas de un ***aumento de las presiones*** intra cámara tras una serie de ***mecanismos neurohumorales***.

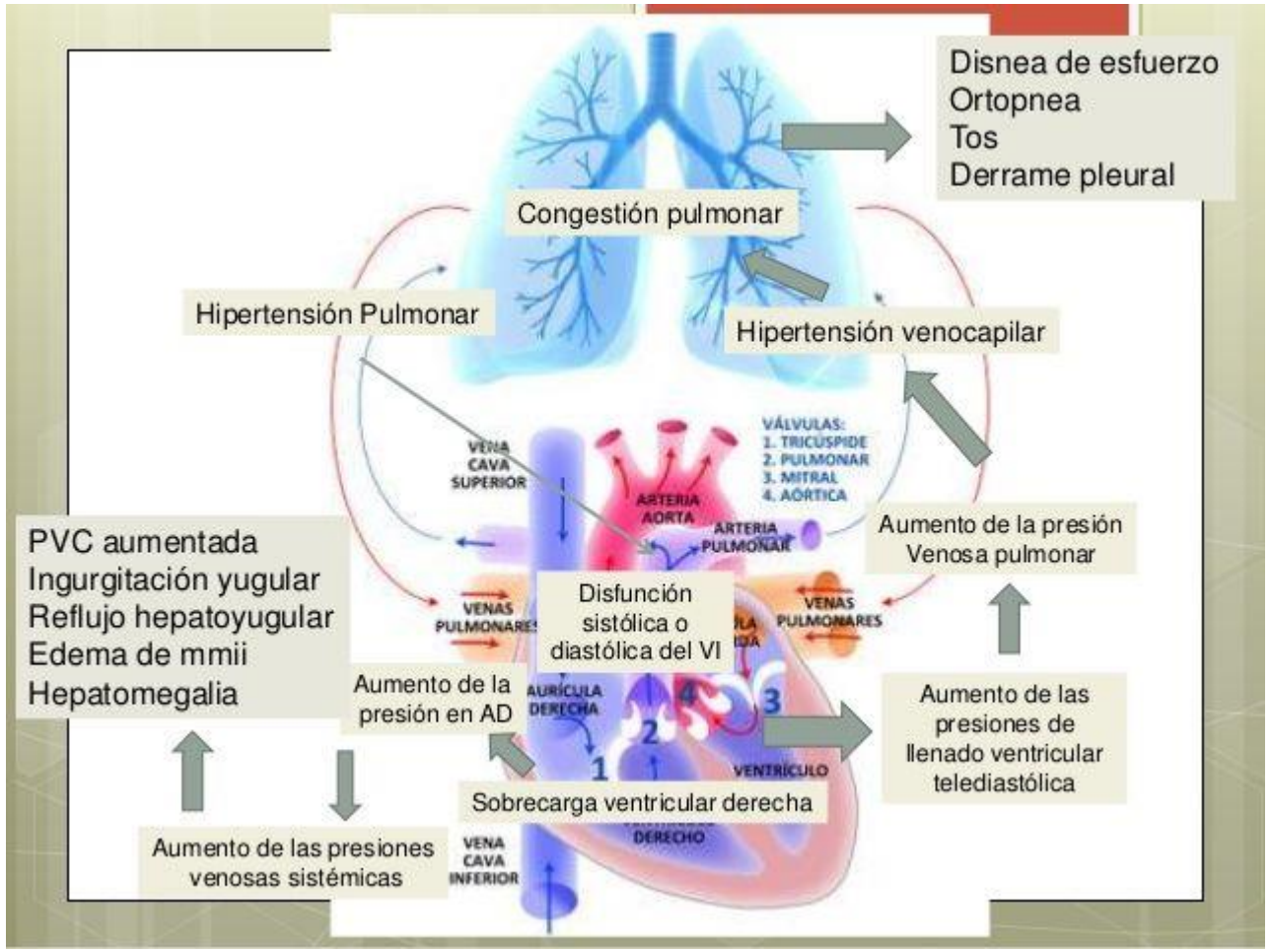
Braunwald. *Modificado*


↑Presión y Volumen
Miocitos y Matriz Extracelular
Remodelado Ventricular
Forma y función
CORAZÓN
EFECTOS
Eléctricos
Vasculares
Ventilatorios
Musculares
Renales
otros
Insuficiencia Cardiaca
-Desequilibrio neurohumoral
-↑Citocinas
-Inflamación
-Alteraciones de la inmunidad
-Alteraciónes de la fibrinolisis
-Apoptosis
-Alteraciones de la expresión genética
- ↓energía
- Sobrecarga oxidativa
-

CURVA PRESIÓN VOLUMEN



SINTOMAS Y SIGNOS DE IC



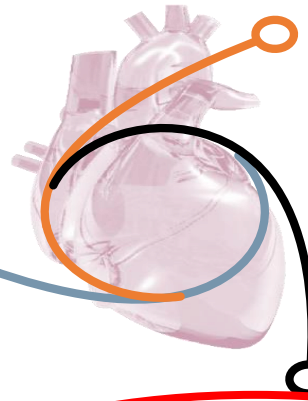
NEUROHUMORAL

SISTEMA NERVIOSO SIMPATICO

α_1, β_1, β_2 receptors ← Adrenalina, Noradrenalina

Vasoconstriction

- ↑ Actividad SRAA
- ↑ Vasopresina
- ↑ Frecuencia Cardiaca
- ↑ Contractilidad



SISTEMA DEL PEPTIDO NATRIURETICO

RPNs ← PN

VASODILATACIÓN

- ↓ Presión arterial
- ↓ Tono simpatico
- ↑ Natriuresis/diuresis
- ↓ Vasopresina
- ↓ Aldosterona
- ↓ Fibrosis
- ↓ Hipertrofia

SISTEMA RENINA-ANGIOTENSINA -ALDOSTERONA

Receptores AT1 ← Angiotnesina II

VASOCONTRICCIÓN

- ↑ Presión arterial
- ↑ Tono simpatico
- ↑ Aldosterona
- ↑ Hipertrofia
- ↑ Fibrosis

1-Levin E, *et al*. N Engl J Med 1998;339:321–8.
2. Nathisuwan and Talbert. Pharmacotherapy. 2002;22:27–42.
3. Schrier and Abraham. N Engl J Med. 1999;341:577–85.
4. Langenickel TH, Dole WP. Drug Discov Today: Ther Strateg. 2012;9:e131–9.
5. Feng *et al*. Tetrahedron Letters. 2012;53:275–6.

PARADIGM-HF: el estudio geograficamente diverso en pacientes con HFrEF

- 8,442 pacientes fueron randomizados en 985 sitios, en 47 paises[1,2]

ACEI: angiotensin-converting-enzyme inhibitor; ARNI: angiotensin receptor neprilysin inhibitor; HFrEF: heart failure with reduced ejection fraction; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

1. McMurray et al. Eur J Heart Fail 2014;16:817–25; 2. McMurray et al. Eur J Heart Fail 2013;15:1062–73

PARADIGM-HF : diseño del estudio

Criterios de Inclusión:

- IC crónica NYHA CF II-IV con FSVI ≤ **40%**
- BNP (o NT- ProBNP) niveles:

  ≥150 (or ≥600 pg/mL)

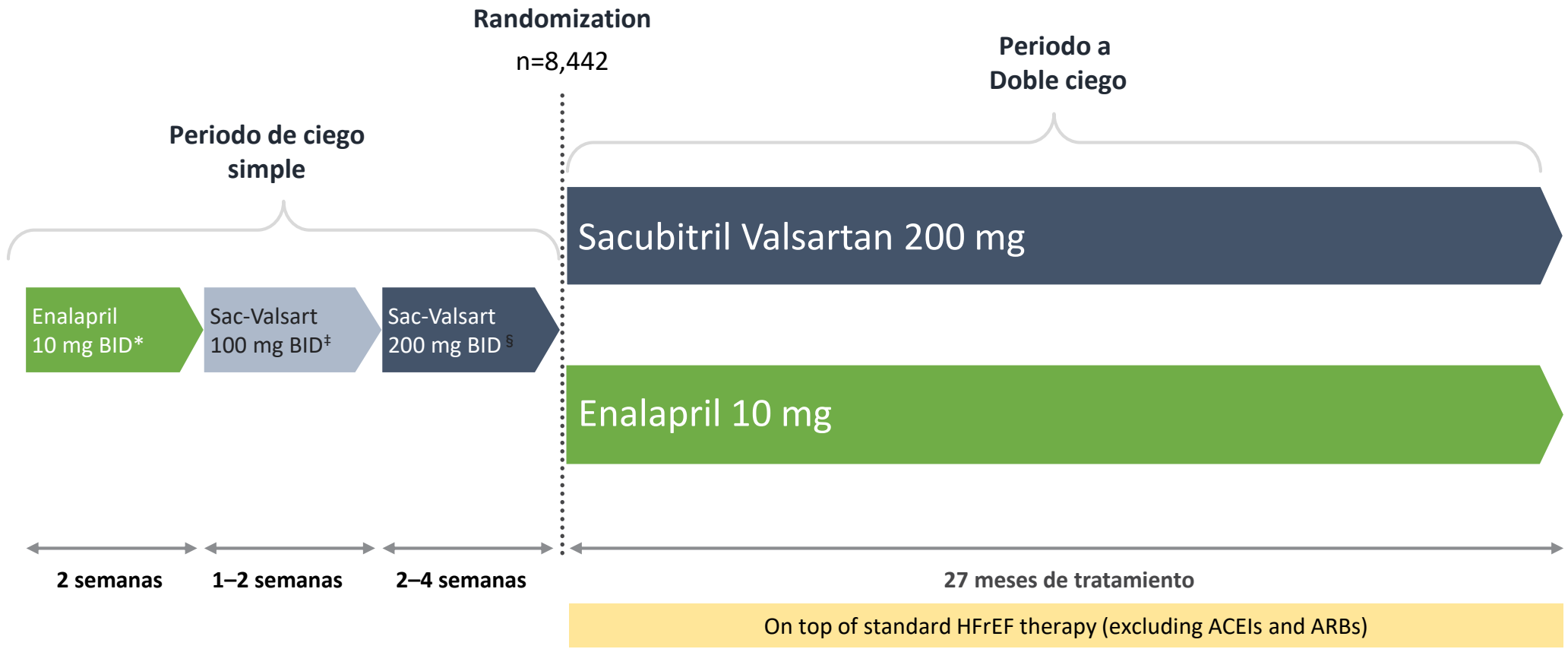
  ≥100 (or ≥400 pg/mL)
- Hospitalización por IC FE_r dentro de los últimos 12 meses.
- Más de 4 semanas de tratamiento estable con IECA /ARA II/BB/Aldosterona

**The ejection fraction entry criteria was lowered to ≤35% in a protocol amendment; #Dosage equivalent to enalapril ≥10 mg/day*

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BNP: B-type natriuretic peptide; FC: functional class; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

McMurray et al. Eur J Heart Fail. 2013;15:1062–7

PARADIGM-HF : diseño del estudio



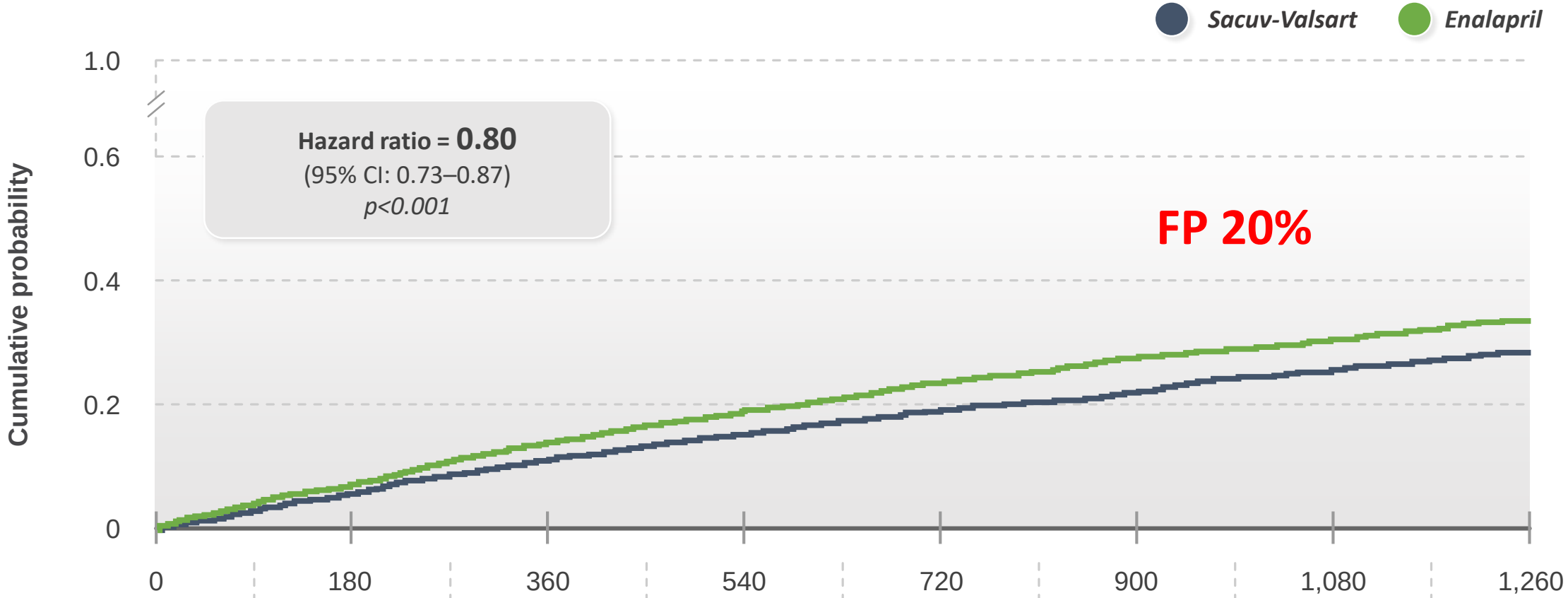
Enalapril 5 mg BID (10 mg TDD) for 1–2 weeks followed by enalapril 10 mg BID (20 mg TDD) as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEI; ‡200 mg TDD; §400 mg TDD; #20 mg TDD

ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BID: twice daily; HFrEF: heart failure with reduced ejection fraction; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; TDD: total daily dose

McMurray et al. Eur J Heart Fail. 2013;15:1062–73; McMurray et al. Eur J Heart Fail 2014;16:817–25; McMurray et al. N Engl J Med 2014;371:993–1004

PARADIGM-HF

Objetivo Primario: causas de *Muerte CV* o primera hospitalización por *IC*



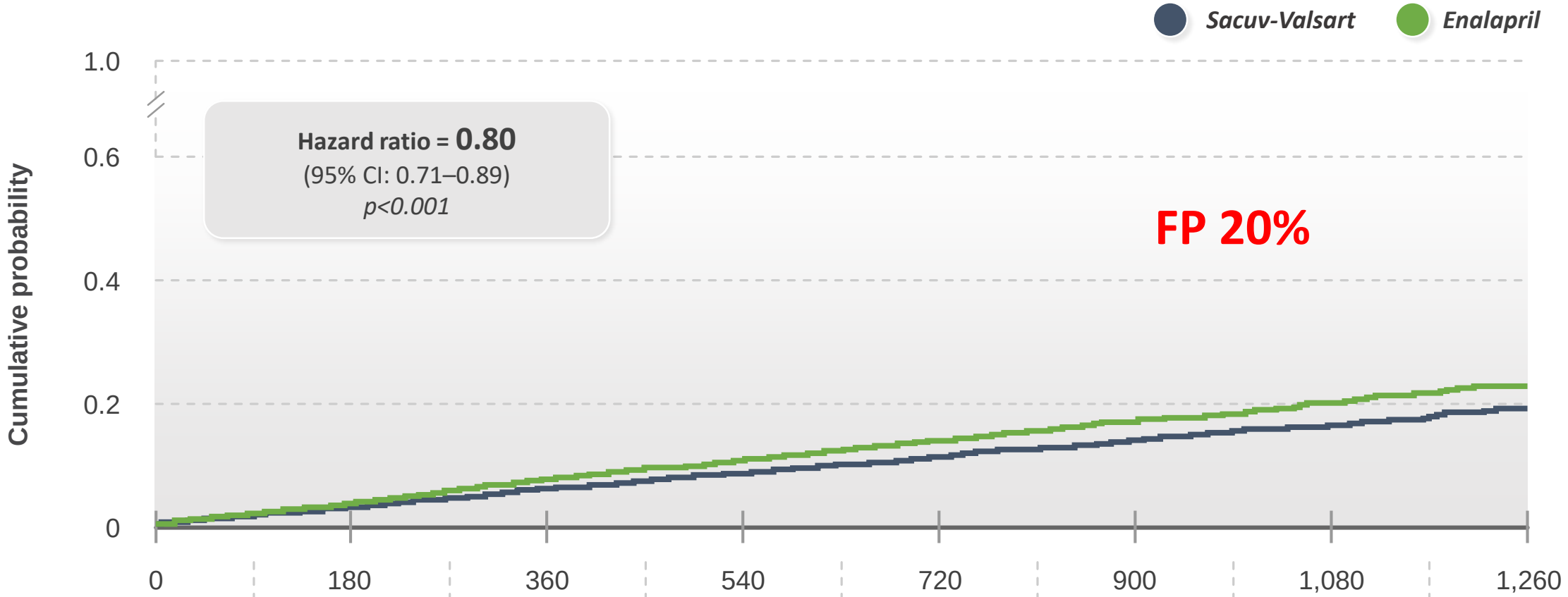
No. at risk								
Sacuvit-vals	4,187	3,922	3,663	3,018	2,257	1,544	896	249
Enalapril	4,212	3,883	3,579	2,922	2,123	1,488	853	236

CI: confidence interval; CV: cardiovascular; HF: heart failure

McMurray et al. N Engl Med 2014;371:993–1004.

PARADIGM-HF

Muerte causa *CV*



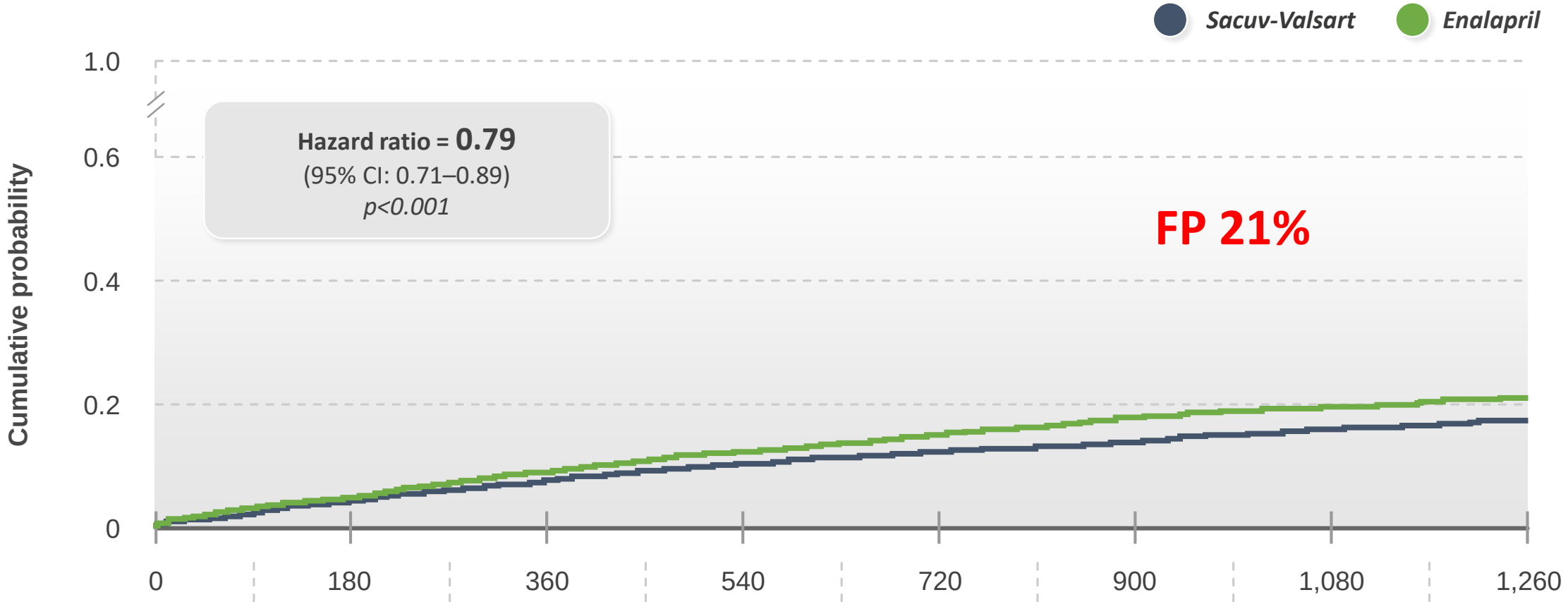
No. at risk								
Entresto®	4,187	4,056	3,891	3,282	2,478	1,716	1,005	280
Enalapril	4,212	4,051	3,860	3,231	2,410	1,726	994	279

CI: confidence interval; CV: cardiovascular; HF: heart failure

McMurray et al. N Engl Med 2014;371:993–1004.

PARADIGM-HF

Primera hospitalización por *IC*



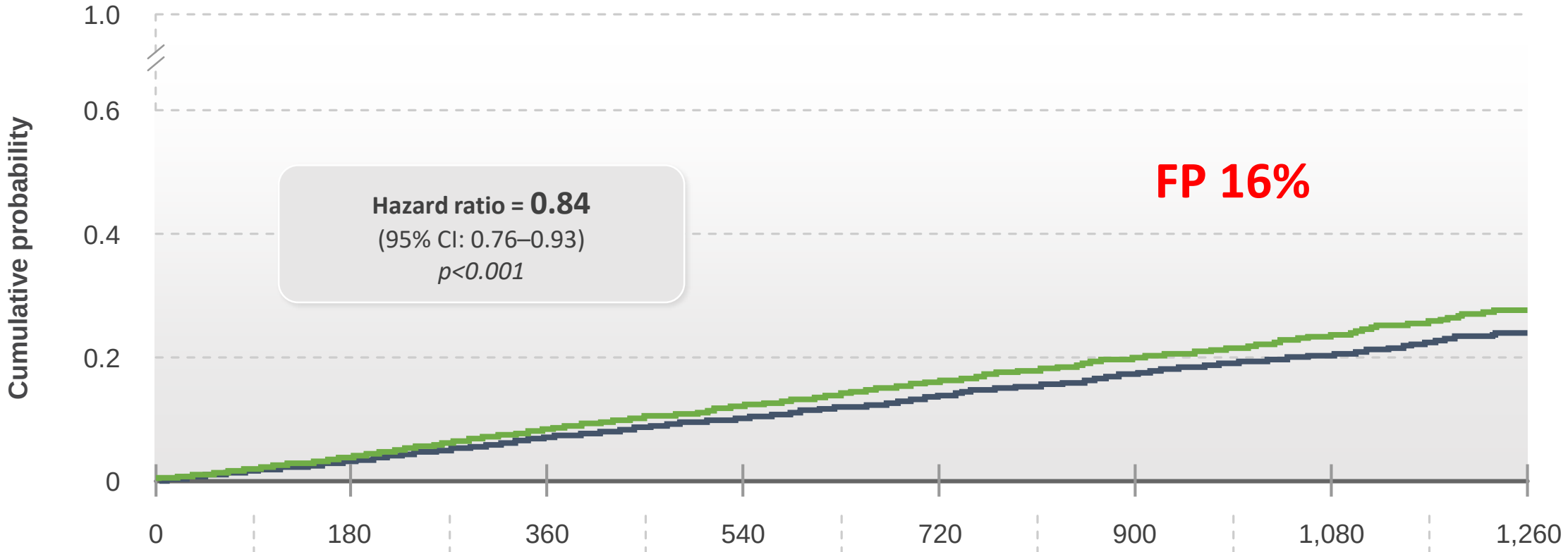
No. at risk								
Sacuvit-vals	4,187	3,922	3,663	3,018	2,257	1,544	896	249
Enalapril	4,212	3,883	3,579	2,922	2,123	1,488	853	236

CI: confidence interval; CV: cardiovascular; HF: heart failure

McMurray et al. N Engl Med 2014;371:993–1004.

PARADIGM-HF

Muerte por *cualquier causa*



No. at risk								
Sacuvit-vals	4,187	4,056	3,891	3,282	2,478	1,716	1,005	280
Enalapril	4,212	4,051	3,860	3,231	2,410	1,726	994	279

CI: confidence interval

McMurray et al. N Engl Med 2014;371:993–1004.

PARADIGM-HF

Eventos de seguridad definidos prospectivamente

Eventos (%)	Sacuvit-valsart (n=4,187)	Enalapril (n=4,212)
Hypotensión		
Sintomaticos	588 (14.0)	388 (9.2)
Sintomaticos con PA <90 mmHg	112 (2.7)	59 (1.4)
Elevación de la creatinine sérica		
≥2.5 mg/dL	139 (3.3)	188 (4.5)
≥3.0 mg/dL	63 (1.5)	83 (2.0)
Elevación potasio sérico		
>5.5 mmol/L	674 (16.1)	727 (17.3)
>6.0 mmol/L	181 (4.3)	236 (5.6)
Tós	474 (11.3)	601 (14.3)
Angioedema (adjudicated by a blinded expert committee)		
Sin treatamiento o uso de antihistaminicos solamente	10 (0.2)	5 (0.1)
Catecolaminas o glucocorticoides sin hospitalización	6 (0.1)	4 (0.1)
Hospitalizados sin compromiso de vias aéreas	3 (0.1)	1 (<0.1)
Compromiso de vías aéreas	0	0

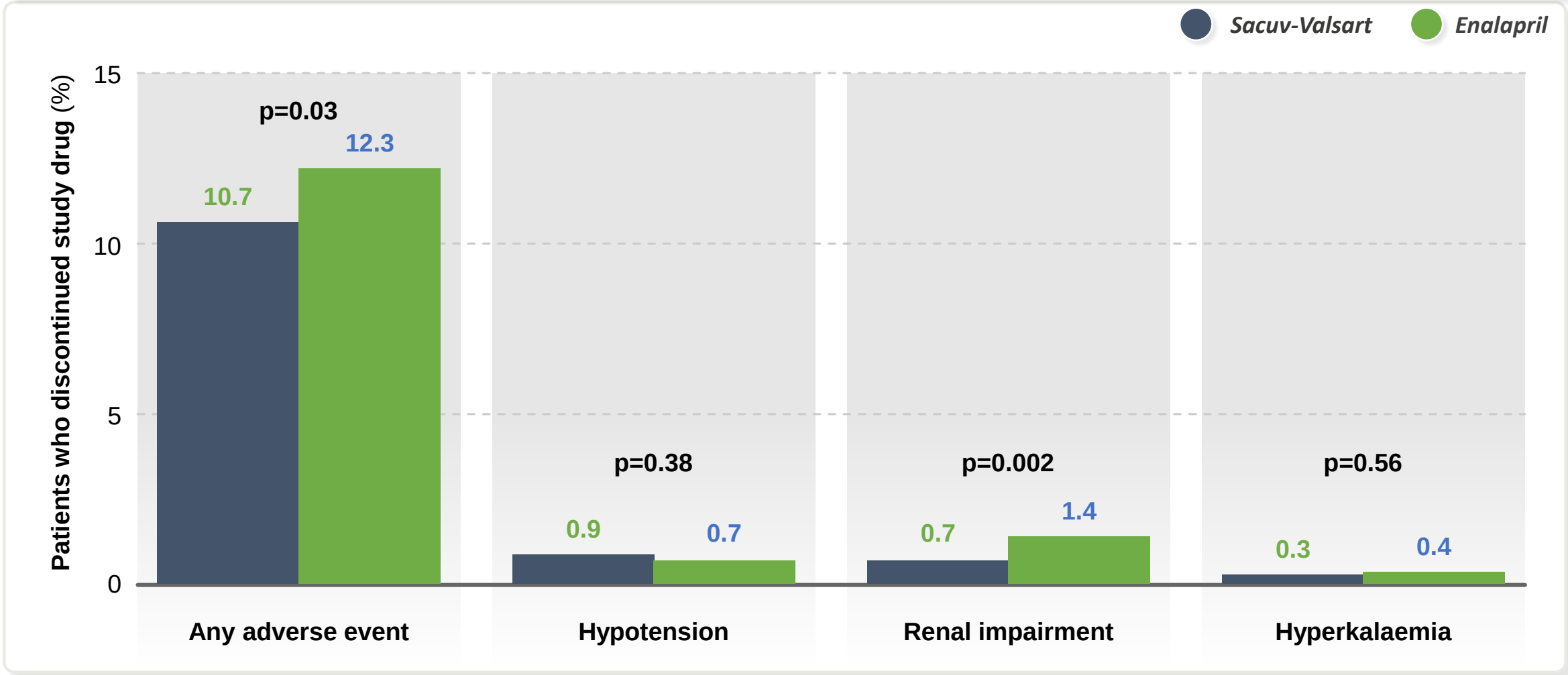
- Fewer patients in the Entresto® group than in the enalapril group stopped their study medication because of an AE (10.7 vs 12.3%, p=0.03)

AE: adverse events; SBP: systolic blood pressure; McMurray et al. N Engl J Med 2014;371:993–1004

PARADIGM-HF

Eventos adversos que llevaron a la discontinuación del Sacuv-Valsart Enalapril

- Fewer patients in the Entresto® group than in the enalapril group discontinued study drug due to an adverse event (10.7 vs 12.3%; p=0.03)



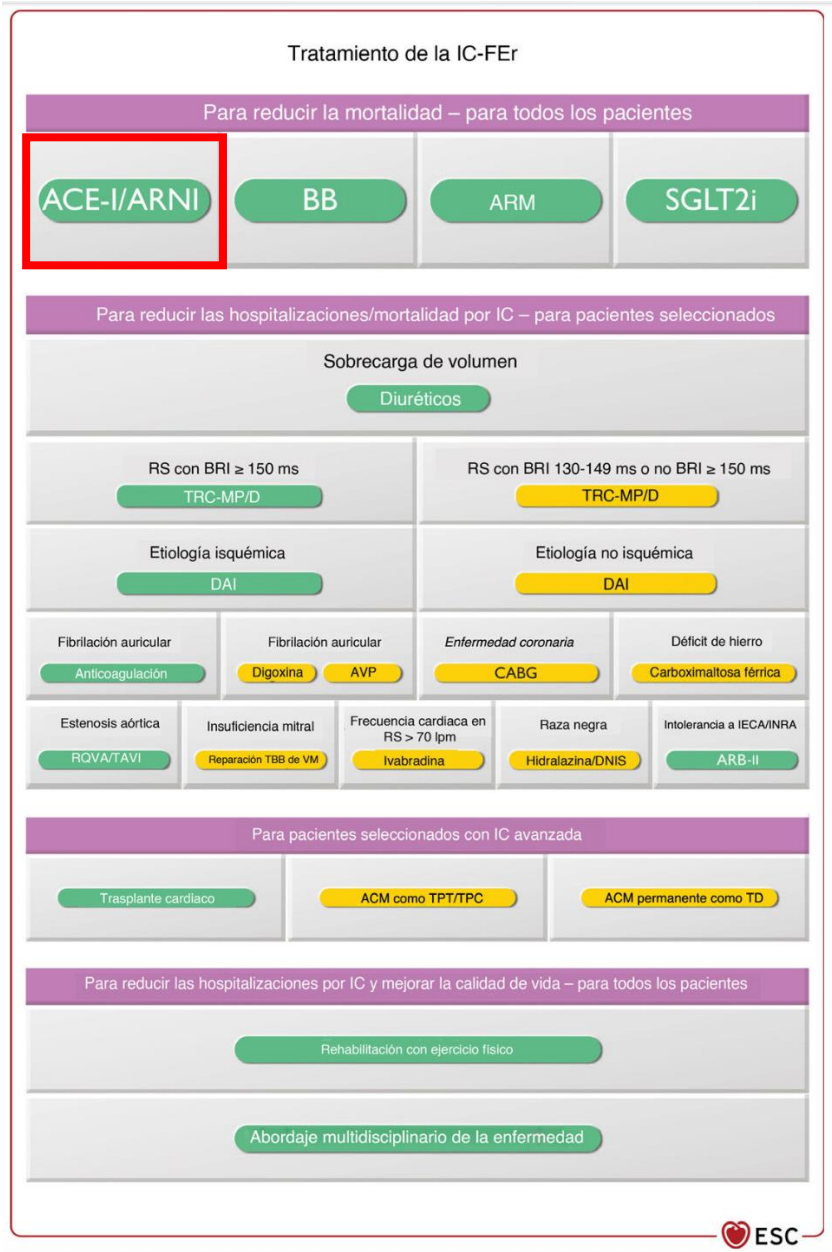
McMurray et al. N Engl J Med 2014;371:993–1004

Guía ESC 2021 sobre el diagnóstico y tratamiento de la insuficiencia cardiaca aguda y crónica

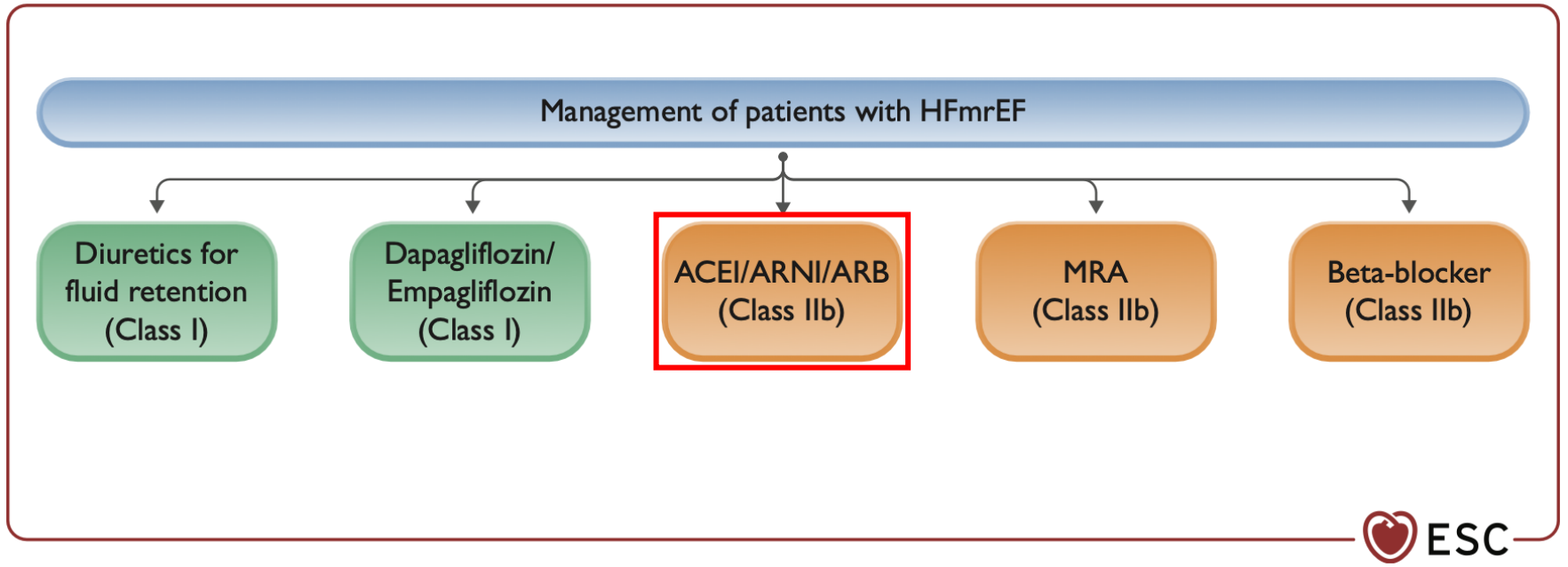
Grupo de Trabajo de la Sociedad Europea de Cardiología (ESC) de diagnóstico y tratamiento de la insuficiencia cardiaca aguda y crónica

Desarrollada con la colaboración especial de la *Heart Failure Association* (HFA) de la ESC

Rev Esp Cardiol. 2022;75(6):523.e1–523.e114



2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure



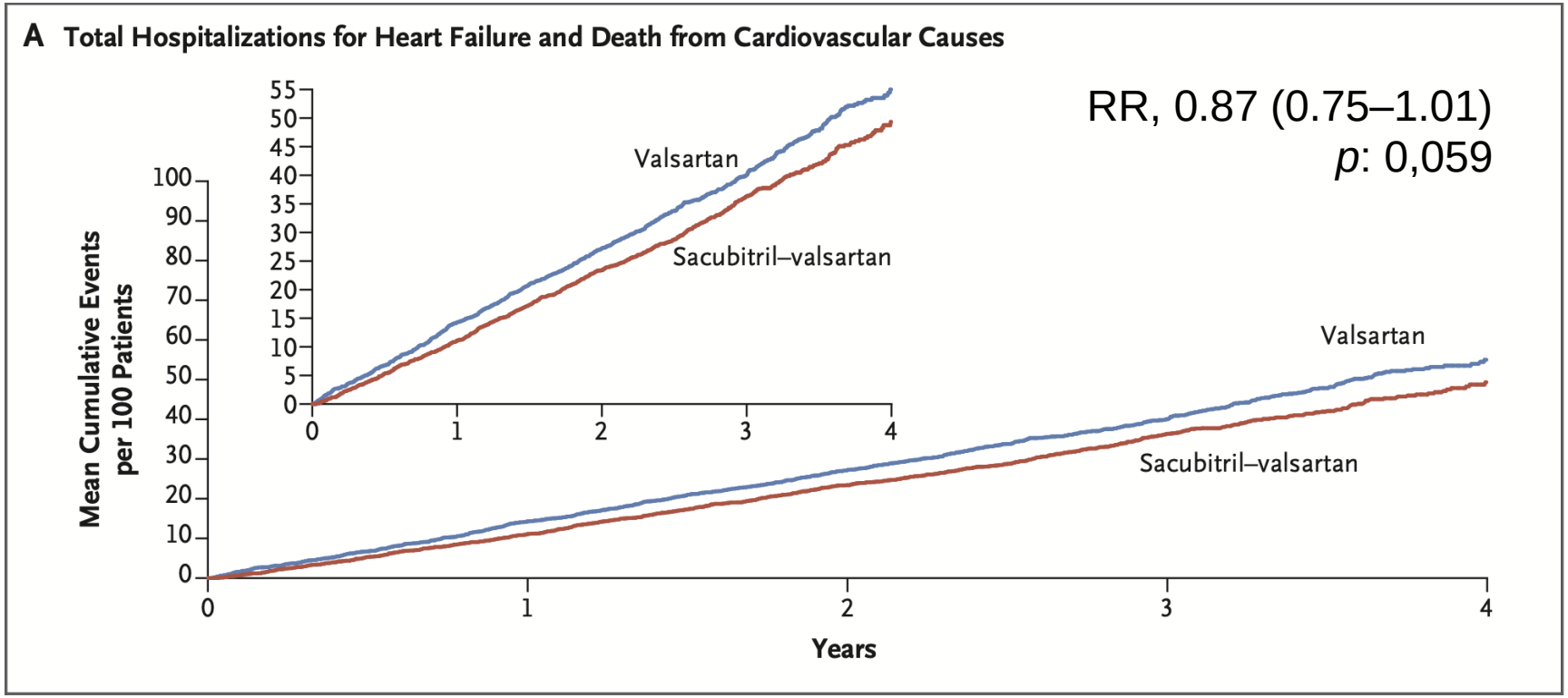
Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction, and preserved ejection fraction

Type of HF		HFrEF	HFmrEF	HFpEF
Criteria	1	Symptoms ± signs[a]	Symptoms ± signs[a]	Symptoms ± signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

European Heart Journal (2023) **00**, 1–13

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

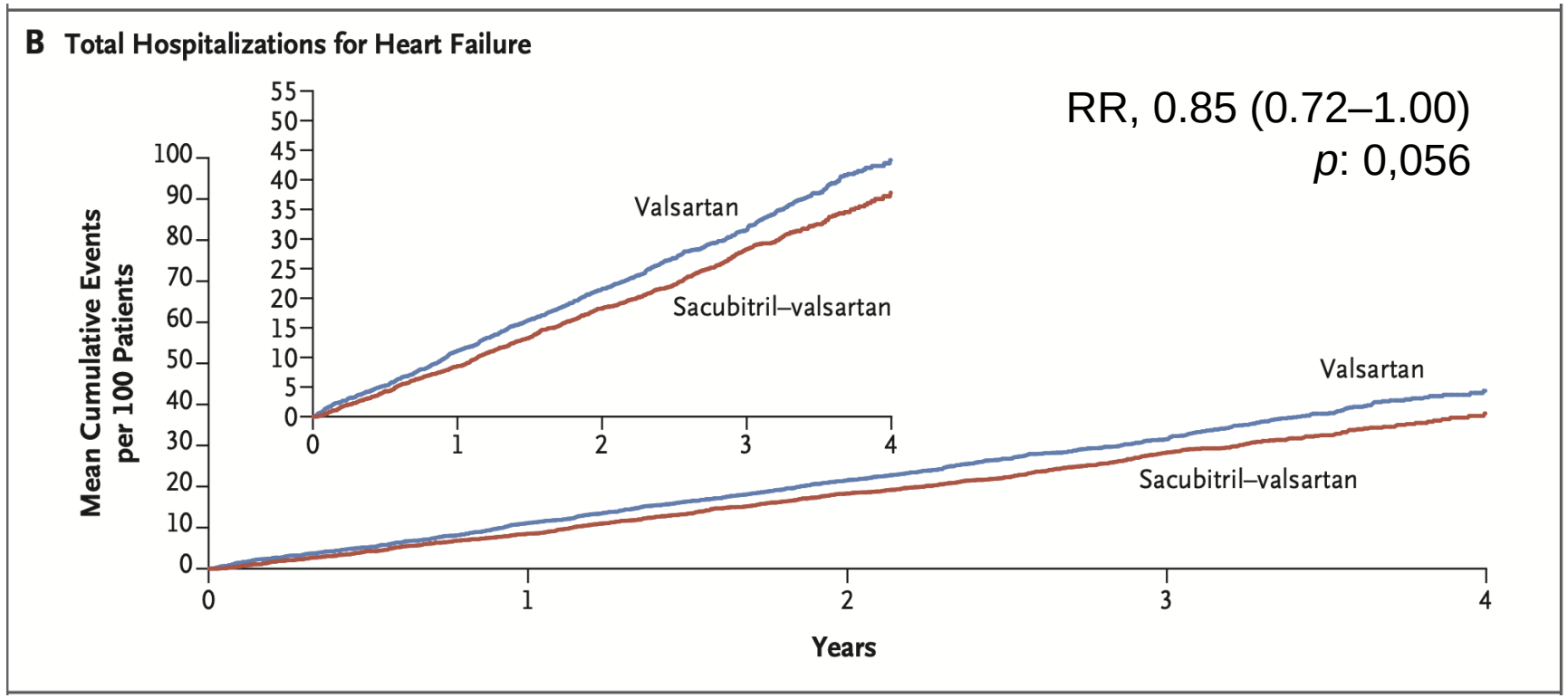
PARAGON-HF



N Engl J Med 2019;381:1609-20.

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

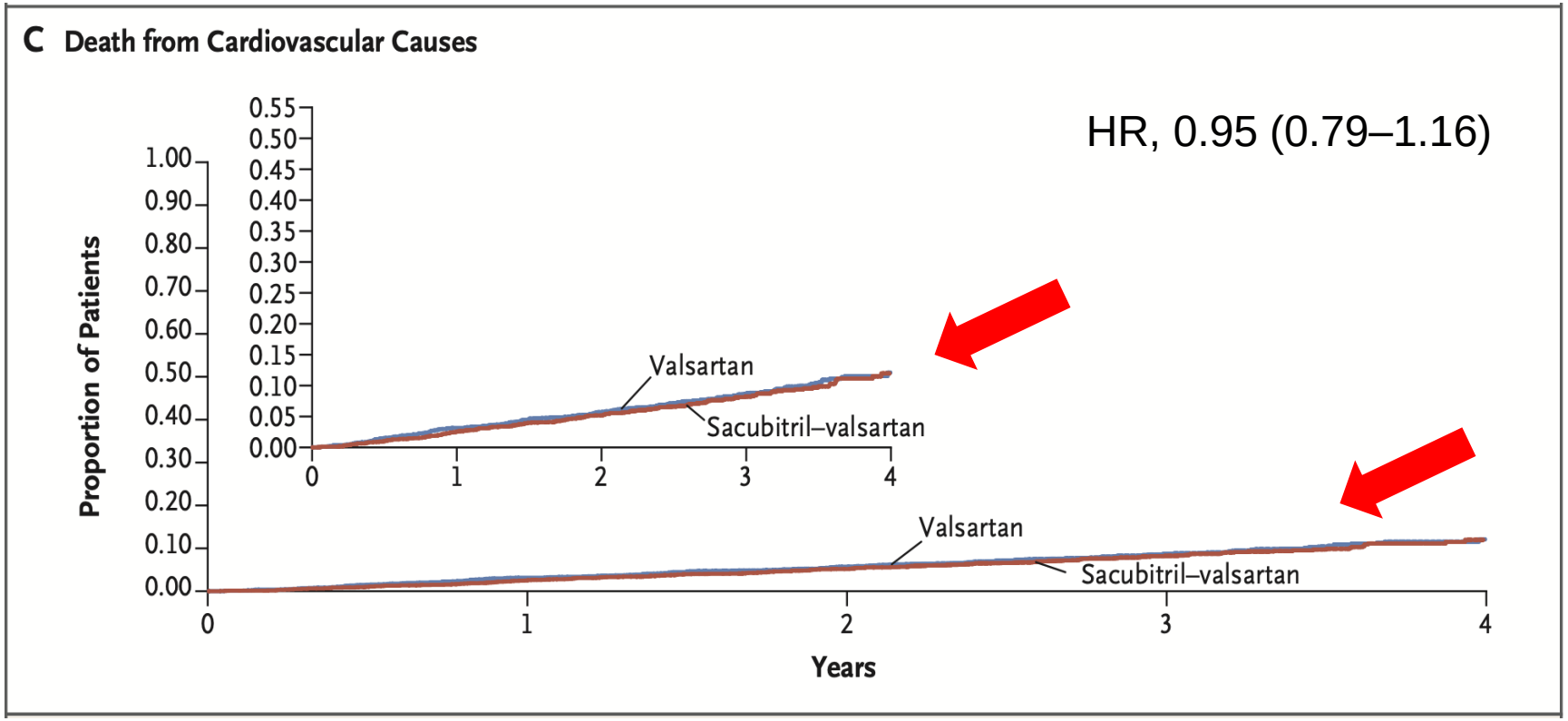
PARAGON-HF



N Engl J Med 2019;381:1609-20.

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

PARAGON-HF



N Engl J Med 2019;381:1609-20.

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

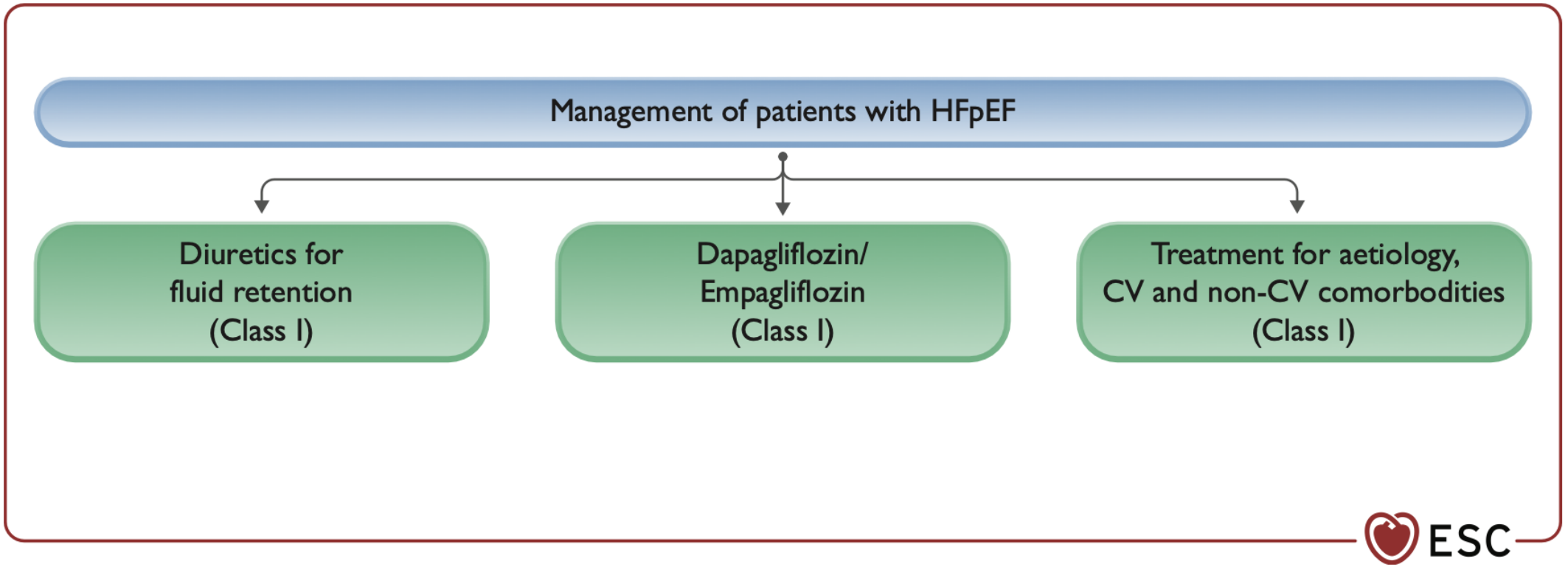
PARAGON-HF

Table 3. Adverse Events during Randomized Treatment.

Event	Sacubitril–Valsartan (N=2407)	Valsartan (N=2389)	P Value
Hypotension with systolic blood pressure <100 mm Hg — no. (%)	380 (15.8)	257 (10.8)	<0.001
Elevated serum creatinine — no. (%)			
≥2.0 mg/dl	261 (10.8)	328 (13.7)	0.002
≥2.5 mg/dl	97 (4.0)	109 (4.6)	0.36
≥3.0 mg/dl	38 (1.6)	40 (1.7)	0.79
Elevated serum potassium — no./total no. (%)			
>5.5 mmol/liter	316/2386 (13.2)	361/2367 (15.3)	0.048
>6.0 mmol/liter	75/2386 (3.1)	101/2367 (4.3)	0.04
Angioedema — no. (%)	14 (0.6)	4 (0.2)	0.02
Liver-related adverse event — no. (%)	151 (6.3)	178 (7.5)	0.11

N Engl J Med 2019;381:1609-20.

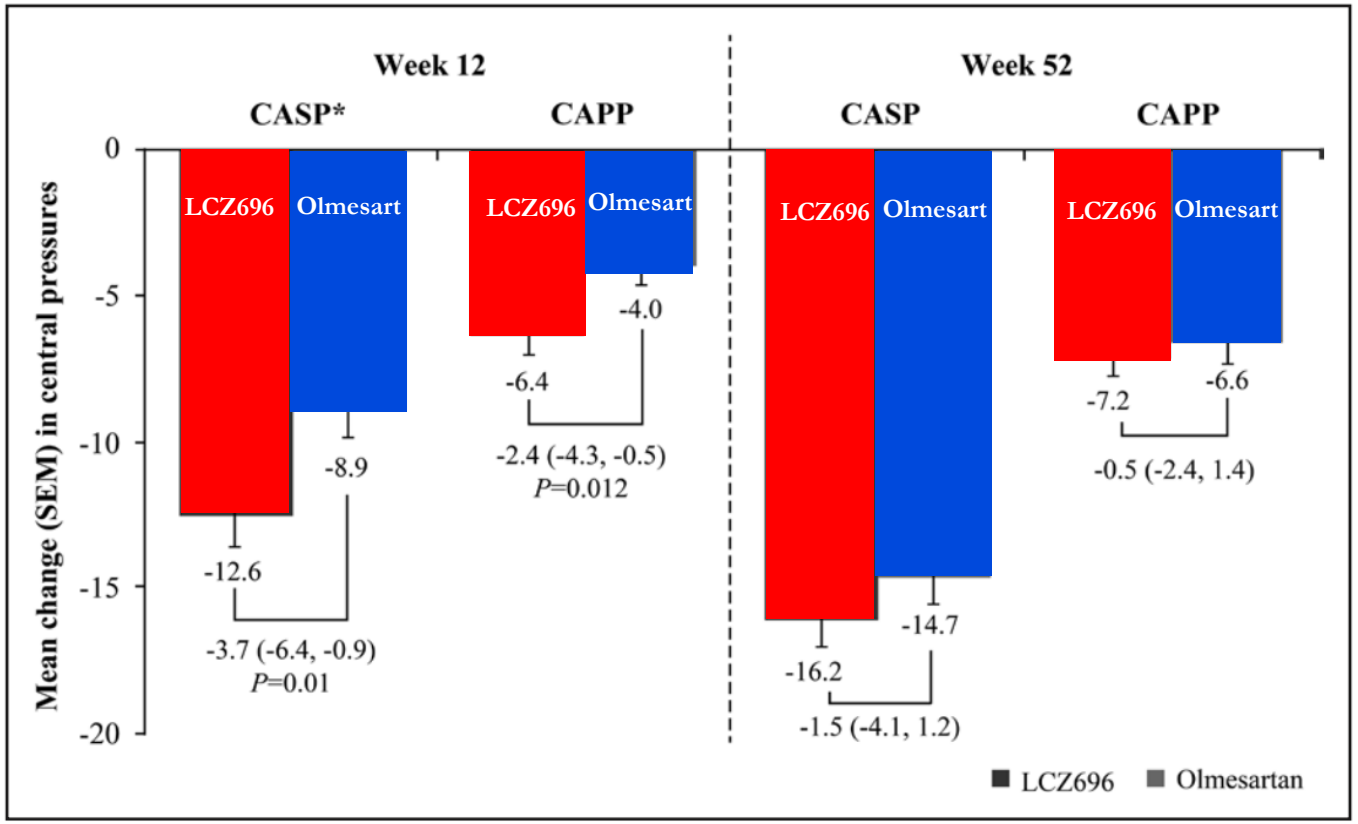
2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure



European Heart Journal (2023) **00**, 1–13

Effects of Sacubitril/Valsartan Versus Olmesartan on Central Hemodynamics in the Elderly With Systolic Hypertension
The PARAMETER Study

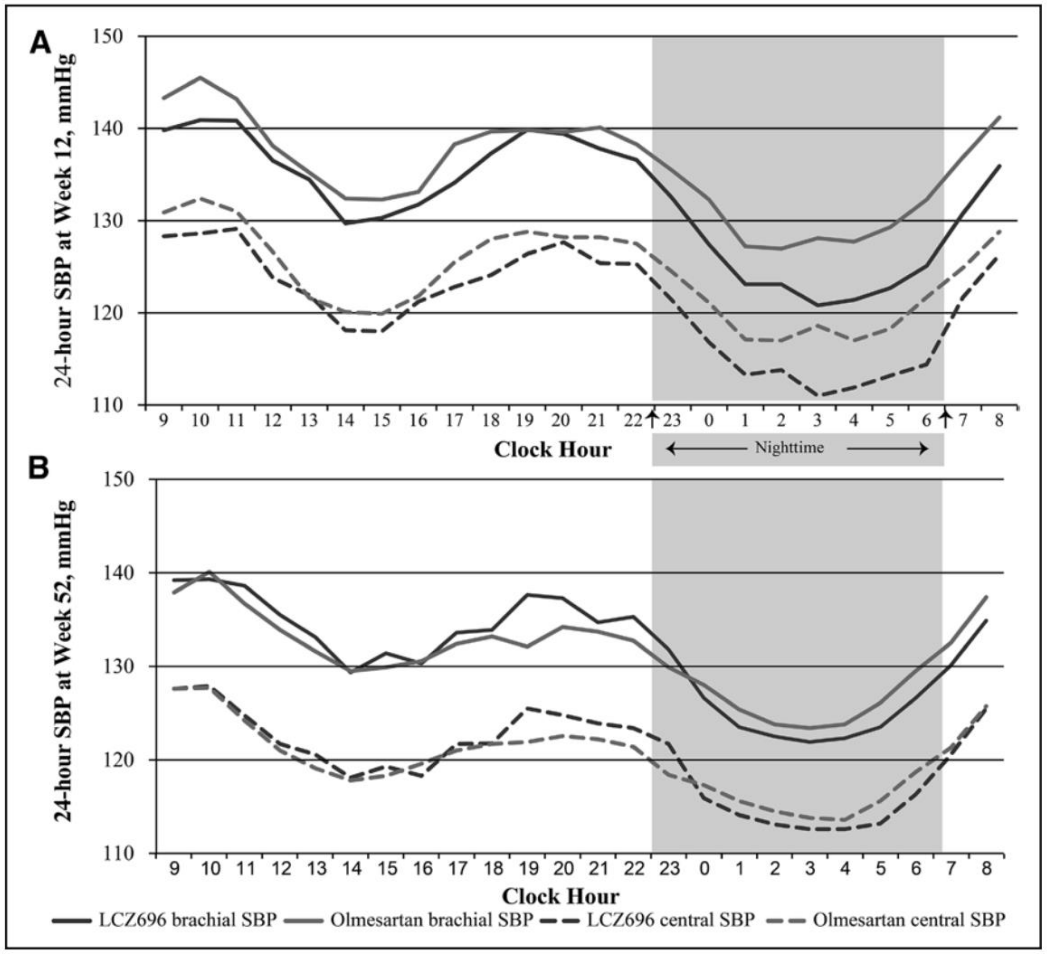
PARAMETER-HF



Hypertension. 2017;69:411-420

Effects of Sacubitril/Valsartan Versus Olmesartan on Central Hemodynamics in the Elderly With Systolic Hypertension

PARAMETER-HF



Hypertension. 2017;69:411-420

Angiotensin Receptor–Neprilysin Inhibition in Acute Myocardial Infarction

PARADISE-HF

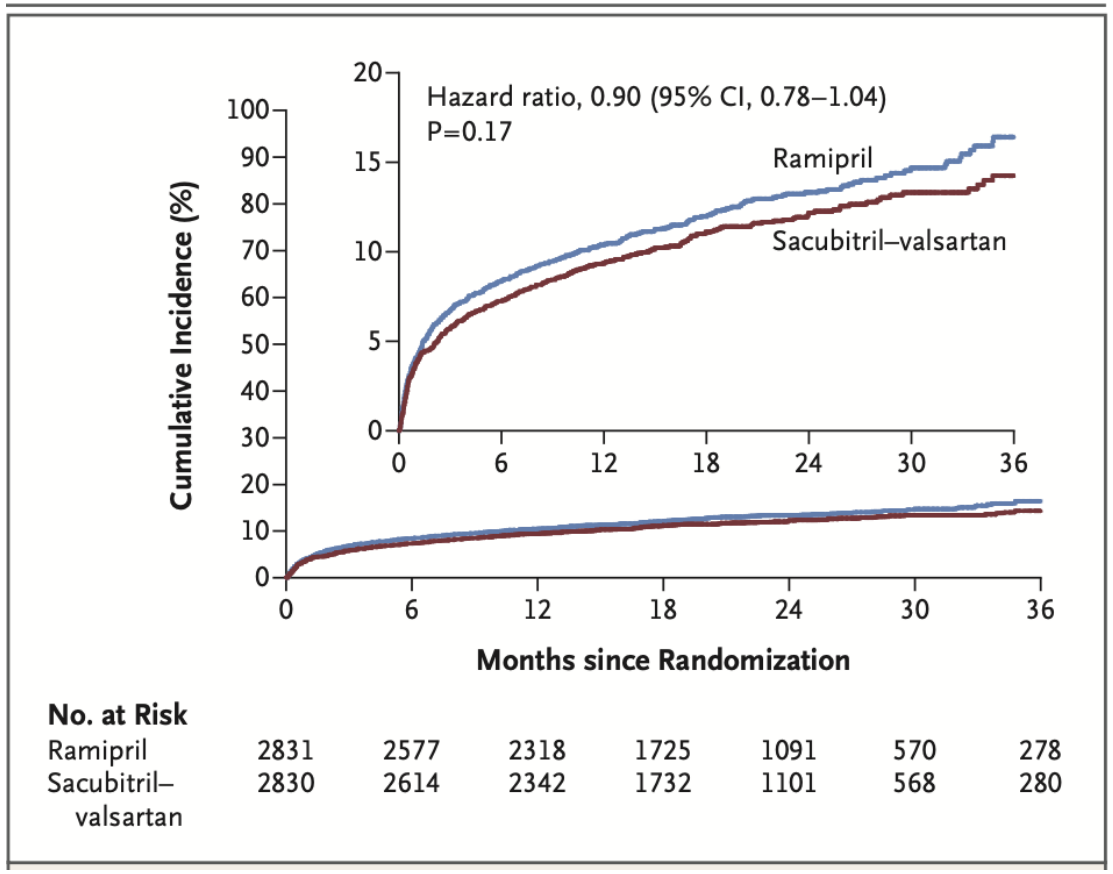


Table 2. Primary and Secondary Outcomes.

Outcome	Sacubitril–Valsartan (N=2830)	Ramipril (N=2831)	Hazard Ratio or Rate Ratio (95% CI)*	P Value
Primary composite outcome — no. (%)†	338 (11.9)	373 (13.2)	0.90 (0.78–1.04)	0.17
Components of primary outcome — no./total no. (%)‡				
Death from cardiovascular causes	137/338 (40.5)	136/373 (36.5)		
Hospitalization for heart failure	164/338 (48.5)	187/373 (50.1)		
Outpatient episode of symptomatic heart failure	37/338 (10.9)	50/373 (13.4)		
Secondary outcomes				
Death from cardiovascular causes or hospitalization for heart failure — no. (%)	308 (10.9)	335 (11.8)	0.91 (0.78–1.07)	
Hospitalization for heart failure or outpatient heart failure — no. (%)	201 (7.1)	237 (8.4)	0.84 (0.70–1.02)	
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke — no. (%)	315 (11.1)	349 (12.3)	0.90 (0.77–1.05)	
Deaths from cardiovascular causes and total hospitalizations for heart failure, myocardial infarction, or stroke — no.§	591	682	0.84 (0.70–1.00)¶	
Death from cardiovascular causes — no. (%)§‖	168 (5.9)	191 (6.7)	0.87 (0.71–1.08)	
Death from any cause — no. (%)	213 (7.5)	242 (8.5)	0.88 (0.73–1.05)	

N Engl J Med 2021;385:1845-55.


IC FE r
ARNI
I-ECA/ARA II
B-Bloq.
ARM
I SLGT2
20% (+)
17-35% / 29%
29-33%
30-35%
16-26%
Ivabradina
Digoxina
Diuréticos

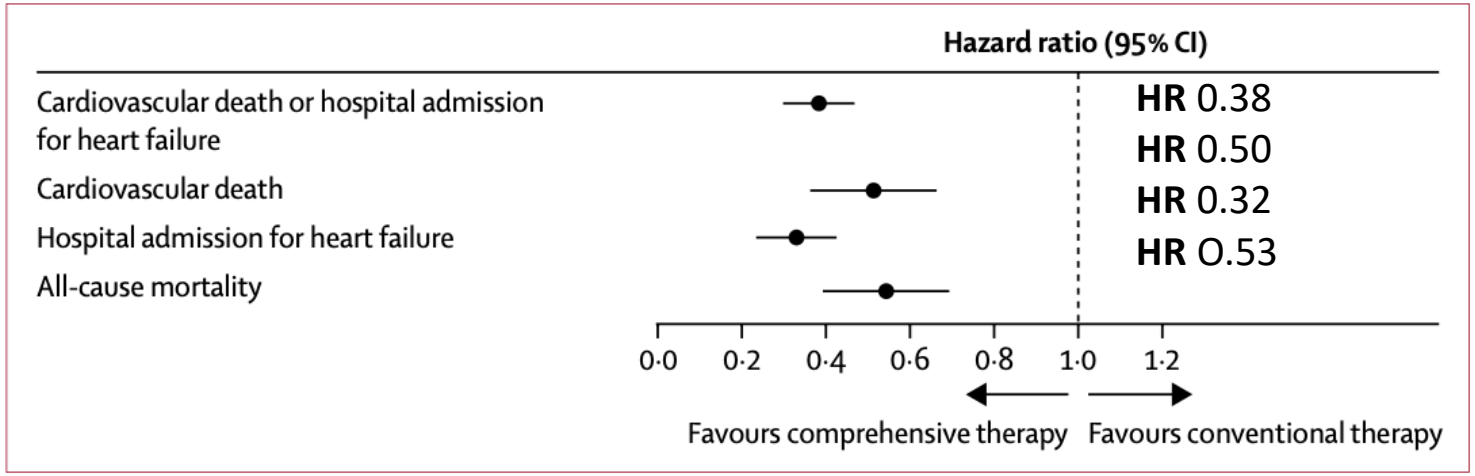
Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials

Muthiah Vaduganathan, Brian L Claggett, Pardeep S Jhund, Jonathan W Cunningham, João Pedro Ferreira, Faiez Zannad, Milton Packer, Gregg C Fonarow, John J V McMurray, Scott D Solomon

Terapia integral
ARNI + ISGLT2 + ARM

VS

Terapia convencional
IECA/ARA II + BB



www.thelancet.com **Published online May 21, 2020**

Objetivo Primario:

Sobrevida libre de eventos

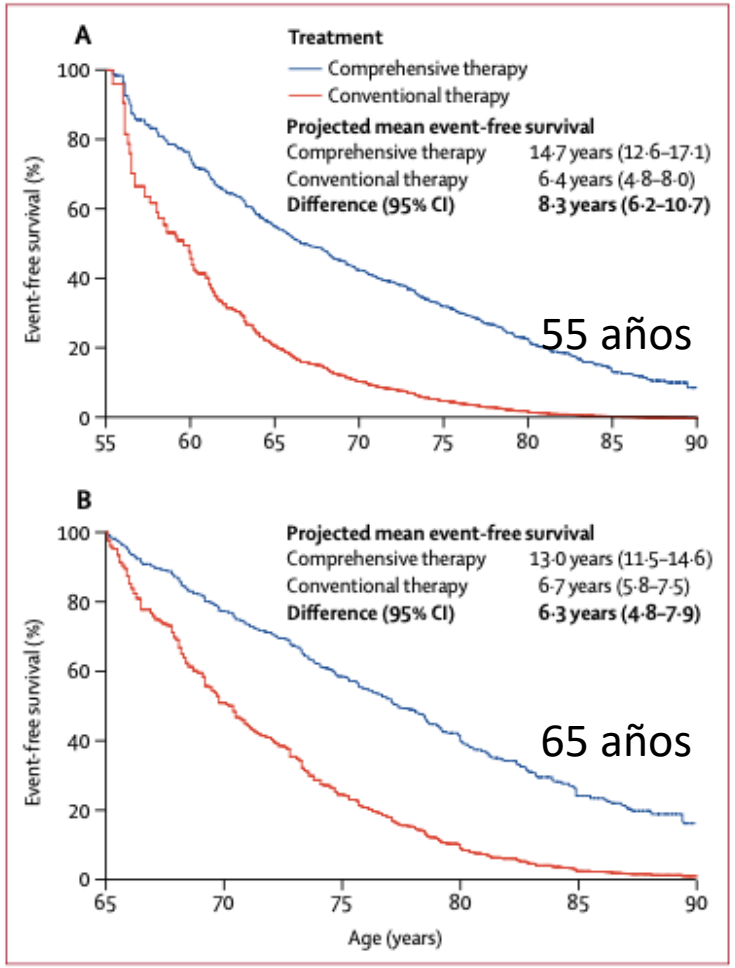


Figure 2: Event-free survival with comprehensive disease-modifying therapy *vs* conventional therapy

Sobrevida Promedio

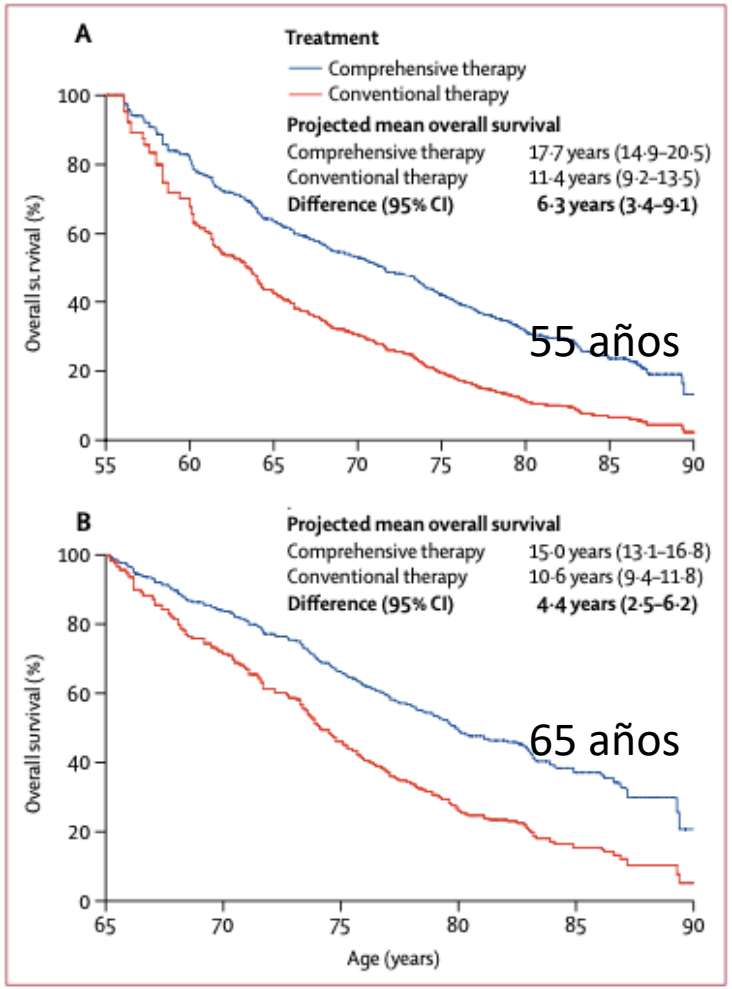


Figure 3: Long-term overall survival with comprehensive disease-modifying therapy *vs* conventional therapy

AMERICAN COLLEGE of CARDIOLOGY

DOSIS OBJETIVO

	Starting Dose	Target Dose
Beta-Blockers		
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily for weight <85 kg and 50 mg twice daily for weight ≥85 kg
Metoprolol succinate	12.5–25 mg daily	200 mg daily
ARNIs		
Sacubitril/valsartan	24/26 mg–49/51 mg twice daily	97/103 mg twice daily
ACEIs		
Captopril	6.25 mg 3× daily	50 mg 3× daily
Enalapril	2.5 mg twice daily	10–20 mg twice daily
Lisinopril	2.5–5 mg daily	20–40 mg daily
Ramipril	1.25 mg daily	10 mg daily
ARBs		
Candesartan	4–8 mg daily	32 mg daily
Losartan	25–50 mg daily	150 mg daily
Valsartan	40 mg twice daily	160 mg twice daily
Aldosterone antagonists		
Eplerenone	25 mg daily	50 mg daily
Spironolactone	12.5–25 mg daily	25–50 mg daily
SGLT2 inhibitors		
Dapagliflozin	10 mg daily	10 mg daily
Empagliflozin	10 mg daily	10 mg daily
Vasodilators		
Hydralazine	25 mg 3× daily	75 mg 3× daily
Isosorbide dinitrate†	20 mg 3× daily	40 mg 3× daily
Fixed-dose combination isosorbide dinitrate/hydralazine‡	20 mg/37.5 mg (1 tab) 3× daily	2 tabs 3× daily
Ivabradine		
Ivabradine	2.5–5 mg twice daily	Titrate to heart rate 50–60 beats/min. Maximum dose 7.5 mg twice daily

JACC VOL. 77, NO. 6, 2021 Maddox et al.
FEBRUARY 16, 2021:772–810

AMERICAN COLLEGE of CARDIOLOGY

DOSIS OPTIMA

TABLE 3 Dose Adjustments of Sacubitril/Valsartan for Specific Patient Populations

Population	Initial Dose
High-dose ACEI *> Enalapril 10-mg total daily dose or therapeutically equivalent dose of another ACEI*	**49/51 mg twice daily**
High-dose ARB *> Valsartan 160-mg total daily dose or therapeutically equivalent dose of another ARB*	

TABLE 3 Dose Adjustments of Sacubitril/Valsartan for Specific Patient Populations

De novo initiation of ARNI *Low- or medium-dose ACEI* *≤ Enalapril 10-mg total daily dose or therapeutically equivalent dose of another ACEI*	**24/26 mg twice daily**
Low- or medium-dose ARB *≤ Valsartan 160-mg total daily dose or therapeutically equivalent dose of another ARB*	
ACEI/ARB naive	
*Severe renal impairment** (*eGFR <30 mL/min/1.73 m²*)	
Moderate hepatic impairment (Child-Pugh Class B)	
Elderly (age ≥75 years)	

JACC VOL. 77, NO. 6, 2021 Maddox et al.
FEBRUARY 16, 2021: 772–810

AMERICAN COLLEGE of CARDIOLOGY

Si previamente se administro I-ECA, esperar 36 hs para su inicio

Seleccionar el inicio de dosis:

Si el paciente consumía el equivalente :
≤ 10mg de enalapril
≤ 160mg de Valsartán
S-V 24/26mg c/12hs

Si el paciente consumía el equivalente :
≥ 10mg de enalapril
≥ 160mg de Valsartán
S-V 49/51mg c/12hs

En 2 semanas evaluar la tolerabilidad
Aumentar la dosis hacia el objetivo terapeutico
Monitorear: a) PA b) electrolitos) Función renal durante la titulación

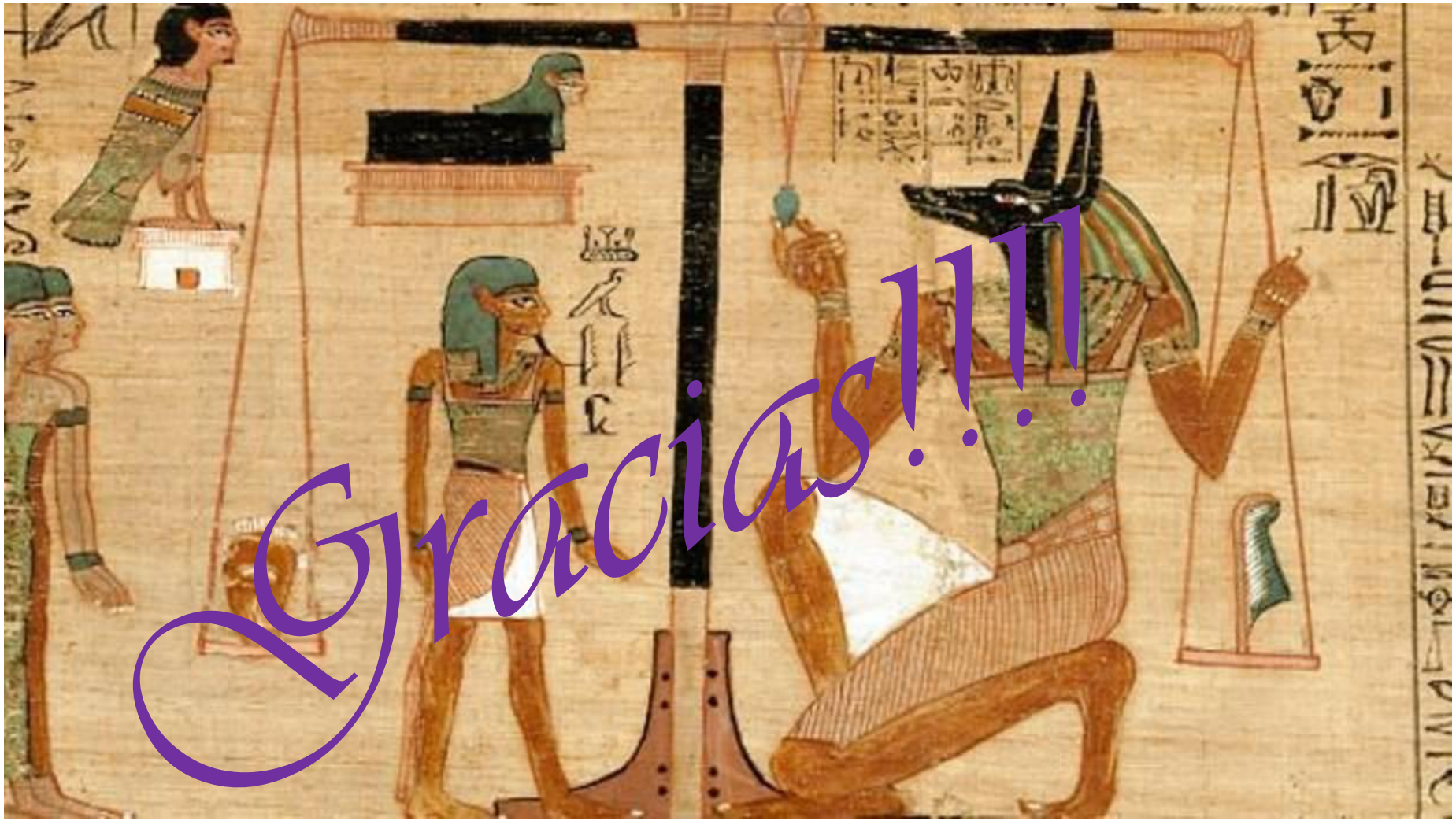
JACC VOL. 77, NO. 6, 2021 Maddox et al.
FEBRUARY 16, 2021:772–810

Conclusiones:

El Sacubitril-Valsartán en IC reducida (*Fey<40%*)

- **Mayor reducción del combinado mortalidad/ internación (21,8%)**
- **Mayor disminución en el número de internaciones (21%)**
- **Mayor reducción de la mortalidad por todas las causas (17%)**
- **Mayor reducción de la mortalidad por causas cardiovasculares (13%)**

Juicio de Osiris



Los egipcios pensaban que el corazón era el órgano más importante, porque allí confluían todos los fluídos y se encontraba la sede del pensamiento.