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"Congreso Andaluz de las Enfermedades Cardiovasculares"
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NOVEDADES EN EL TRATAMIENTO FARMACOLÓGICO DE LA INSUFICIENCIA CARDÍACA

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Unidad de Insuficiencia Cardíaca
Complejo Hospitalario Universitario de Granada, Virgen de las Nieves

IMPORTANCIA DE LA INSUFICIENCIA CARDÍACA

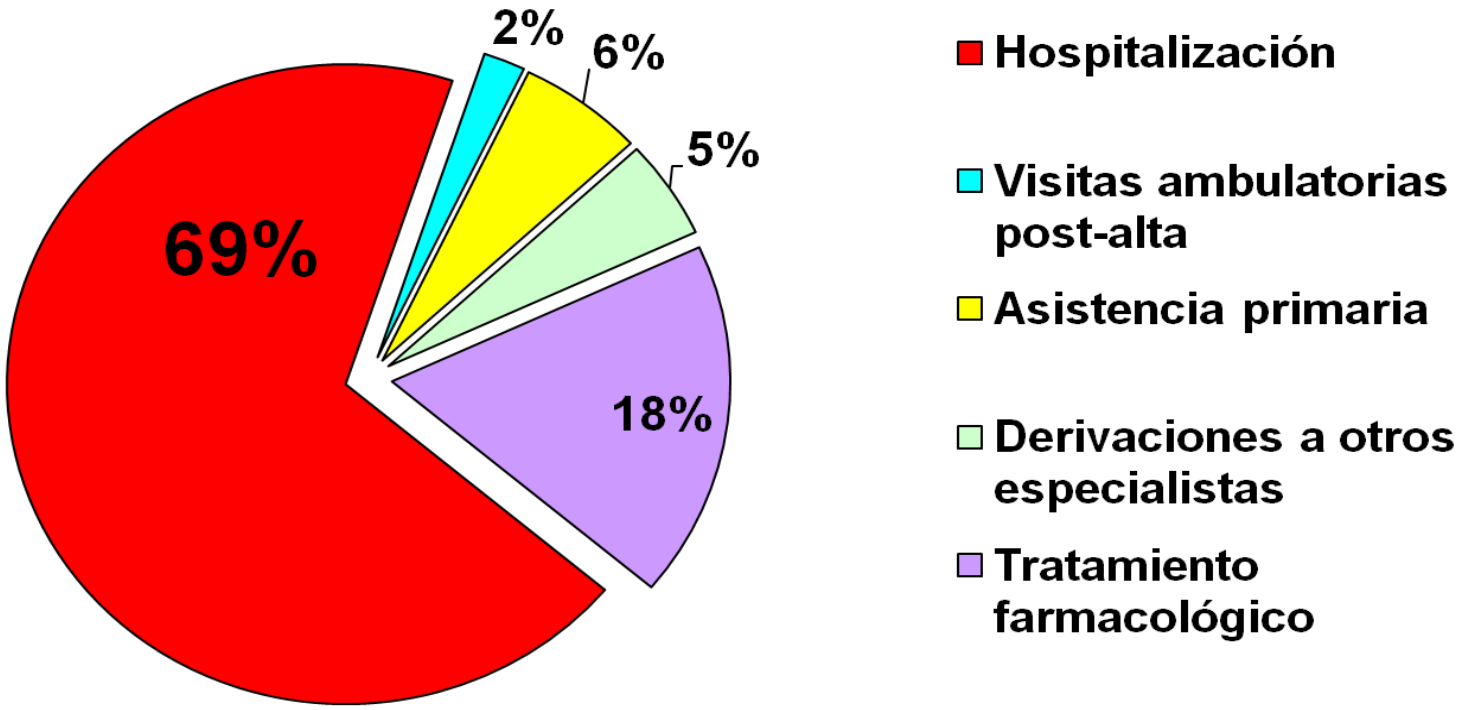
Heart failure prevalence can be estimated with the results of a specific study done in Spain (Muñiz, et al. Rev Esp Cardiol supl. 2006;6:2F-8F) and actual population data (2009 national statistics institute data). The estimated number of heart failure patients in Spain is 1.200.000.

Rango de edad	Población (Nº personas)	Prevalencia IC (%)	Prevalencia IC (Nº personas)
45-54	6.292.412	1,70%	106.971
55-64	4.935.501	3,0%	148.065
65-74	3.782.802	6,10%	230.751
75 y más	3.846.132	18,7%	719.227
Total			**1.205.014**

- A pesar del uso de terapias actuales en la IC:
  - Alta tasa de mortalidad: 50% de pacientes mueren a los 4 años[1].
  - Alta tasa de morbilidad: 24% de los pacientes reingresan a los 3 meses[1]

1. Guías europeas de IC 2008.

IMPORTANCIA DE LA INSUFICIENCIA CARDÍACA



La hospitalización representa el mayor coste económico asociado a la IC. Por tanto hay un objetivo claro en la reducción de los episodios de hospitalización.

Stewart S, et al. Eur J Heart Fail. 2002;4:361-371.

PRONÓSTICO: "peor que algunas neoplasias"

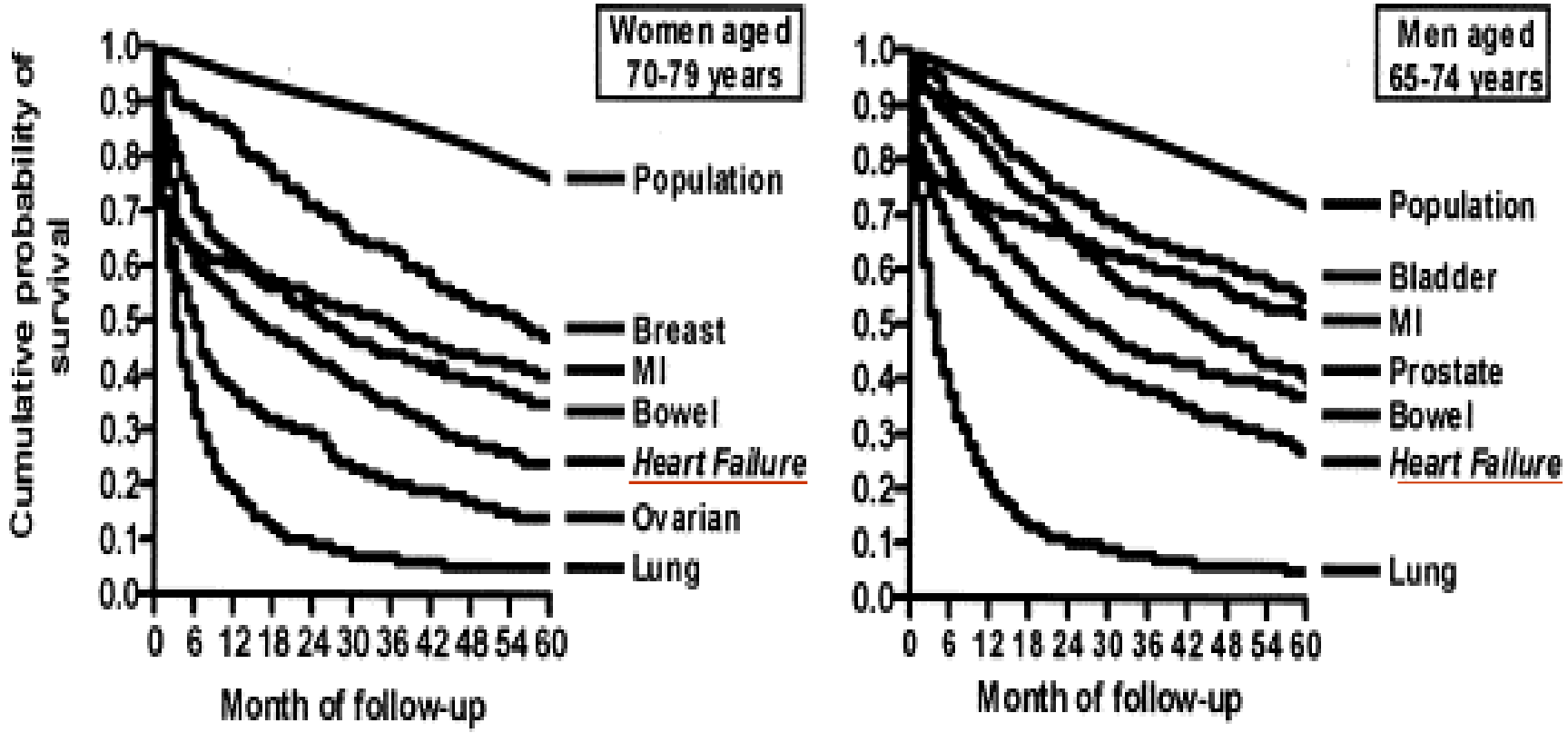
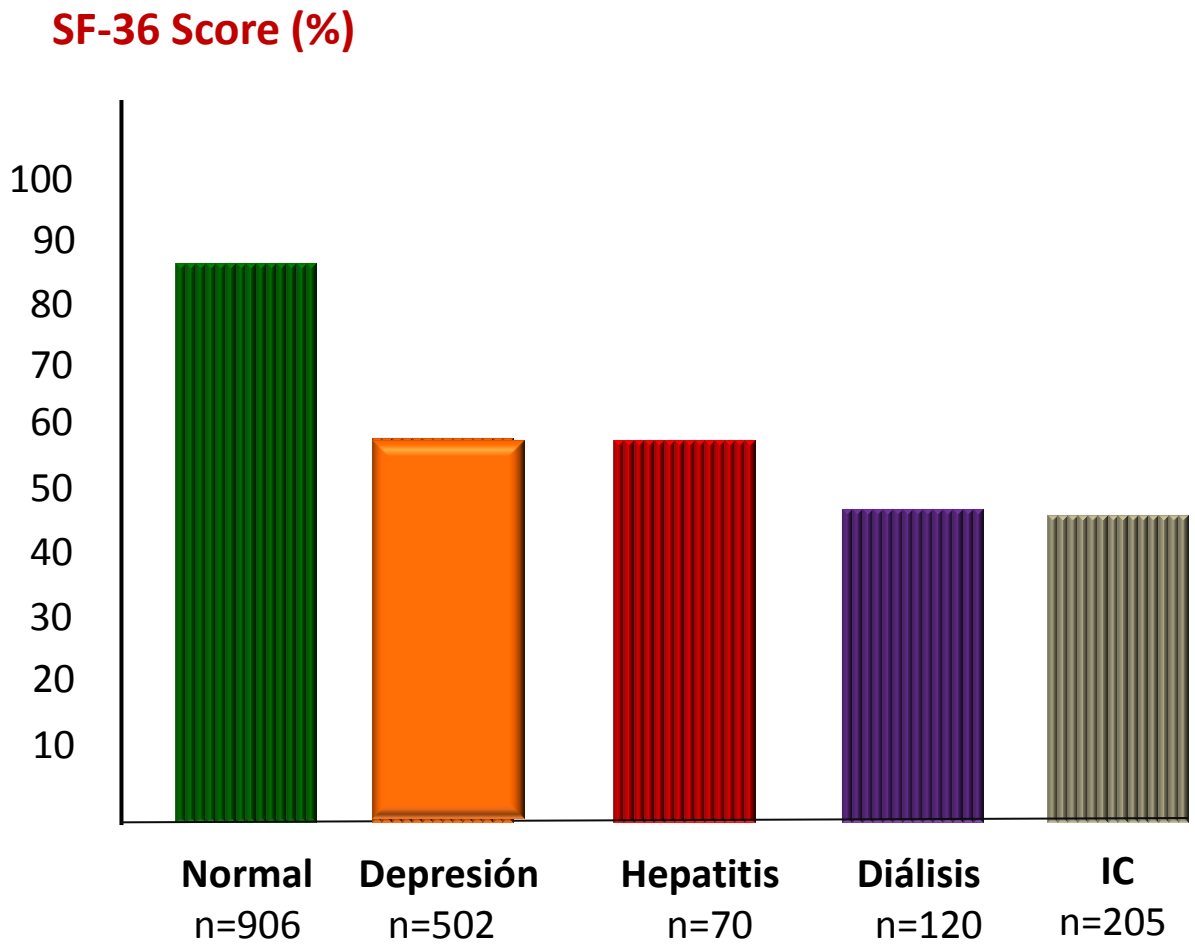


Fig. 2. Age-specific probability of survival following a first admission for heart failure, myocardial infarction and the four most common types of cancer specific to men and women relative to the overall population. Data for women aged 70–79 years (28% of the total cohort) are based on the following number of patients: heart failure (*n*=1167), myocardial infarction (*n*=1600) and cancer of the lung (*n*=475), breast (*n*=441), bowel (*n*=369) and ovary (*n*=108). Similarly data for men aged 65–74 years (26% of the total cohort) are based on the following numbers of patients: heart failure (*n*=1063), myocardial infarction (*n*=2083) and cancer of the lung (*n*=1064), bowel (*n*=485), prostate (*n*=452) and bladder (*n*=264). ***Stewart et al. Eur J Heart Failure; 2001:3:315-222***

Calidad de vida en pacientes con IC crónica: "peor que en hemodiálisis"

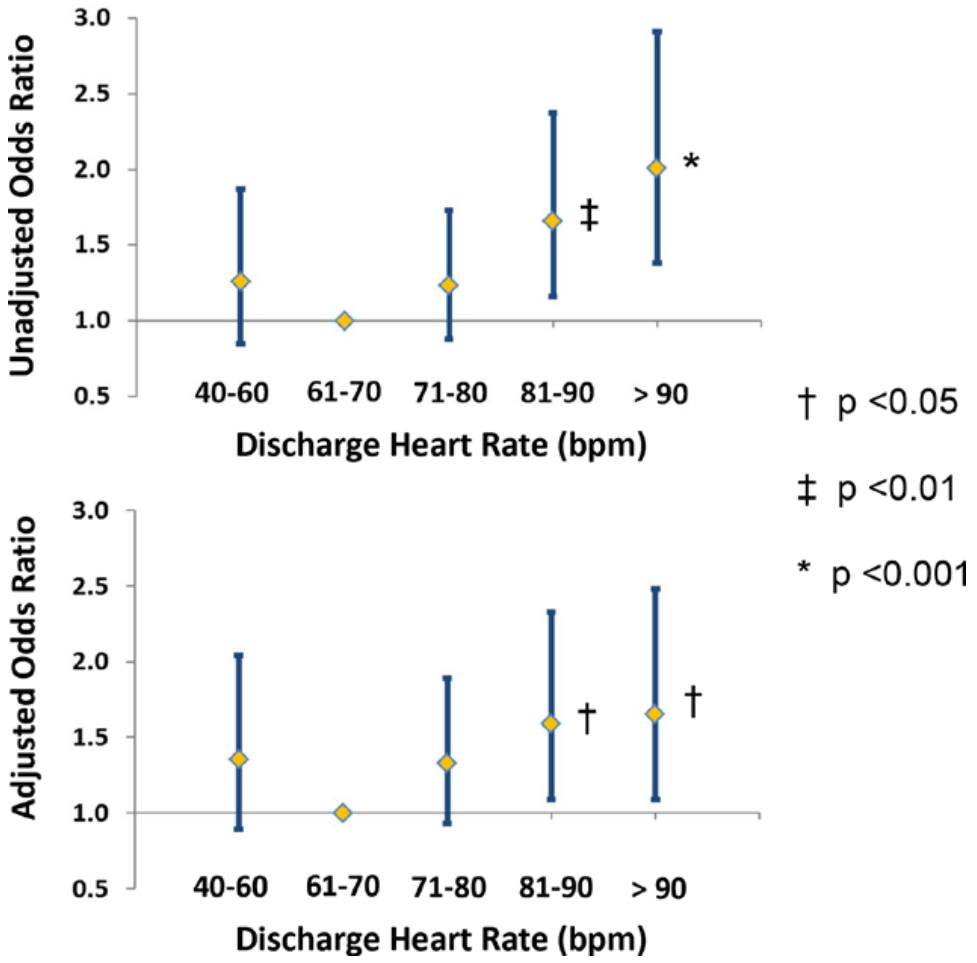


Juenger J, et al. Heart. 2002;87:235-241.

Guías ESC 2012/AHA 2013: Modelo terapéutico actual: inhibición neurohormonal +/- dispositivos: CRT-DAI

EN UNA COHORTE DE MAS DE 9000 PACIENTES LA FC AL ALTA FUE MARCADOR PRONOSTICO DE MORTALIDAD CARDIOVASCULAR

FC al alta y Mortalidad Cardiovascular a los 30 días

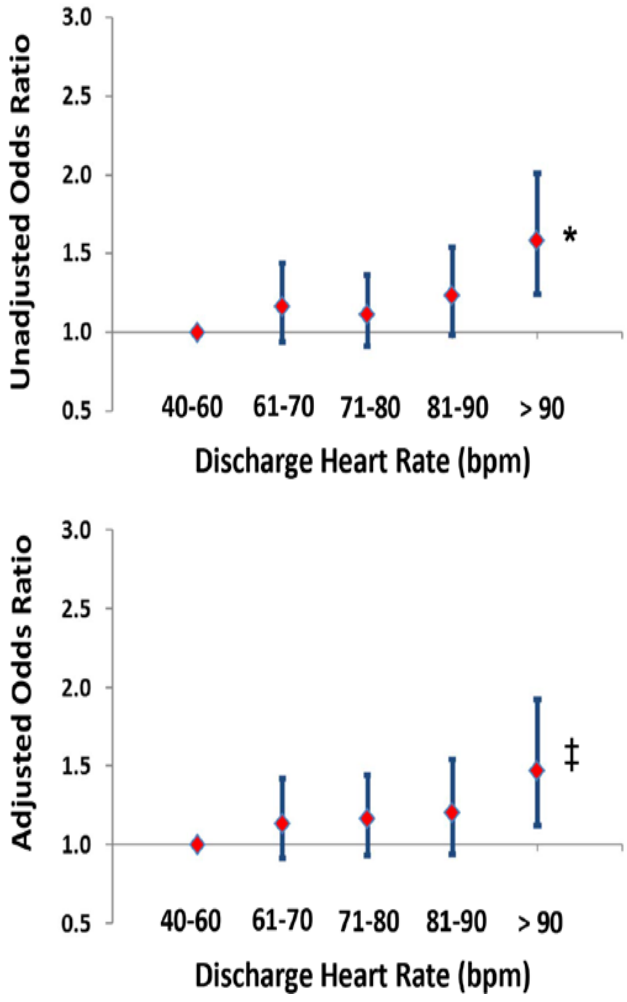


† p <0.05

‡ p <0.01

* p <0.001

FC al alta y Mortalidad Cardiovascular al año



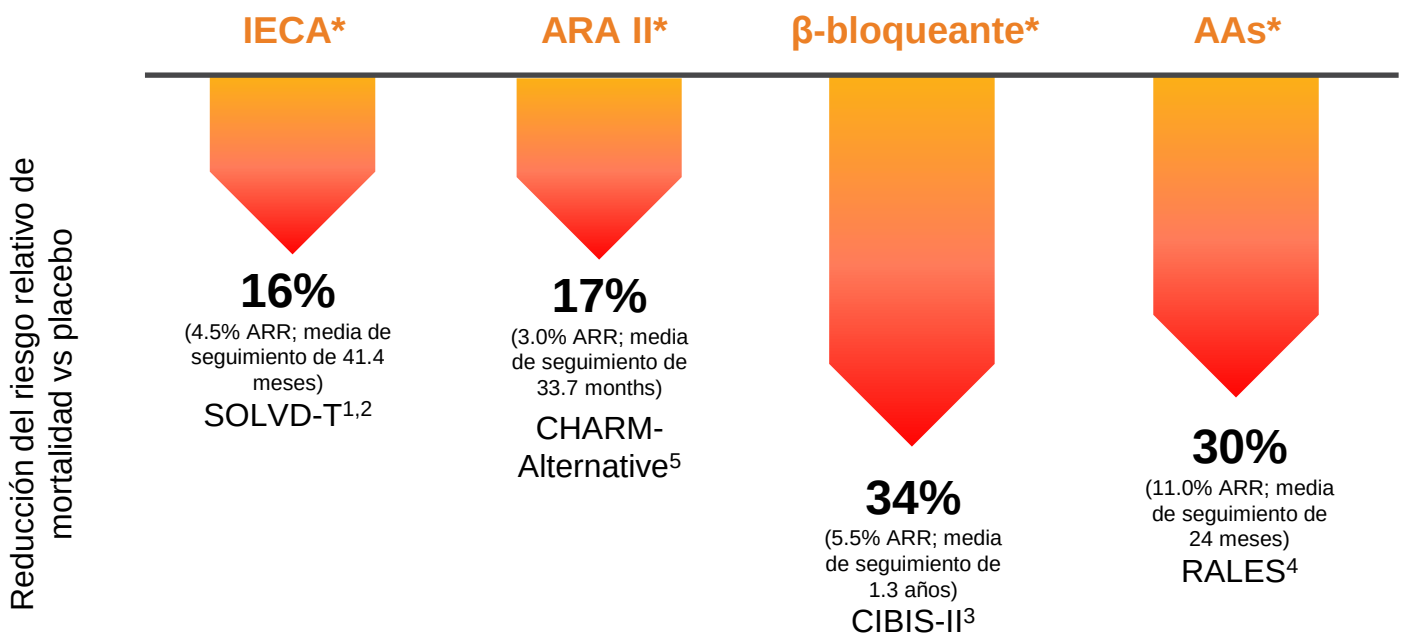
‡ p <0.01

* p <0.001

Habal, et al .Circ Heart Fail. 2014;7:12-20

Evolución de la terapia farmacológica en I Cardíaca

- **Las tasas de supervivencia en IC crónica han mejorado con la introducción de nuevas terapias**



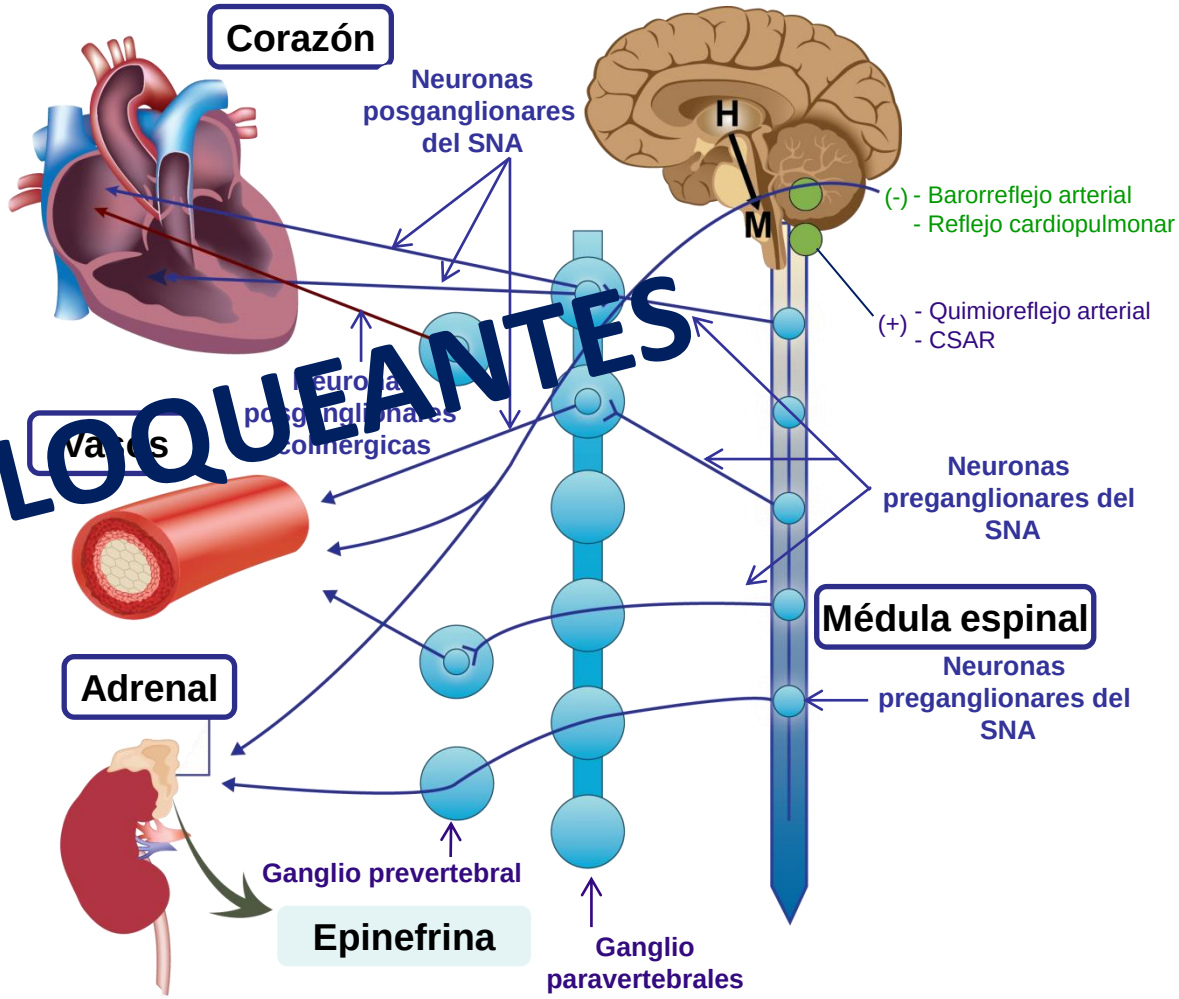
Sin embargo…

se mantiene una mortalidad significativa: ~50% de pacientes muere a los 5 años del diagnóstico[1–3]

1 Go et al. Circulation 2014;129:e28-e292; 2. Yancy et al. Circulation 2013;128:e240–327; 3. Levy et al. N Engl J Med 2002;347:1397–402

Sistema Nervioso Simpático (o adrenal)

- El SNS ejerce una amplia variedad de efectos cardiovasculares:
  - **Aceleración del ritmo cardiaco**
  - **Aumento de la contractilidad cardiaca**
  - **Vasoconstricción periférica**



BETABLOQUEANTES

SNA: sistema nervioso autónomo; CSAR: reflejo cardiaco aferente simpático; SNS: sistema nervioso simpático

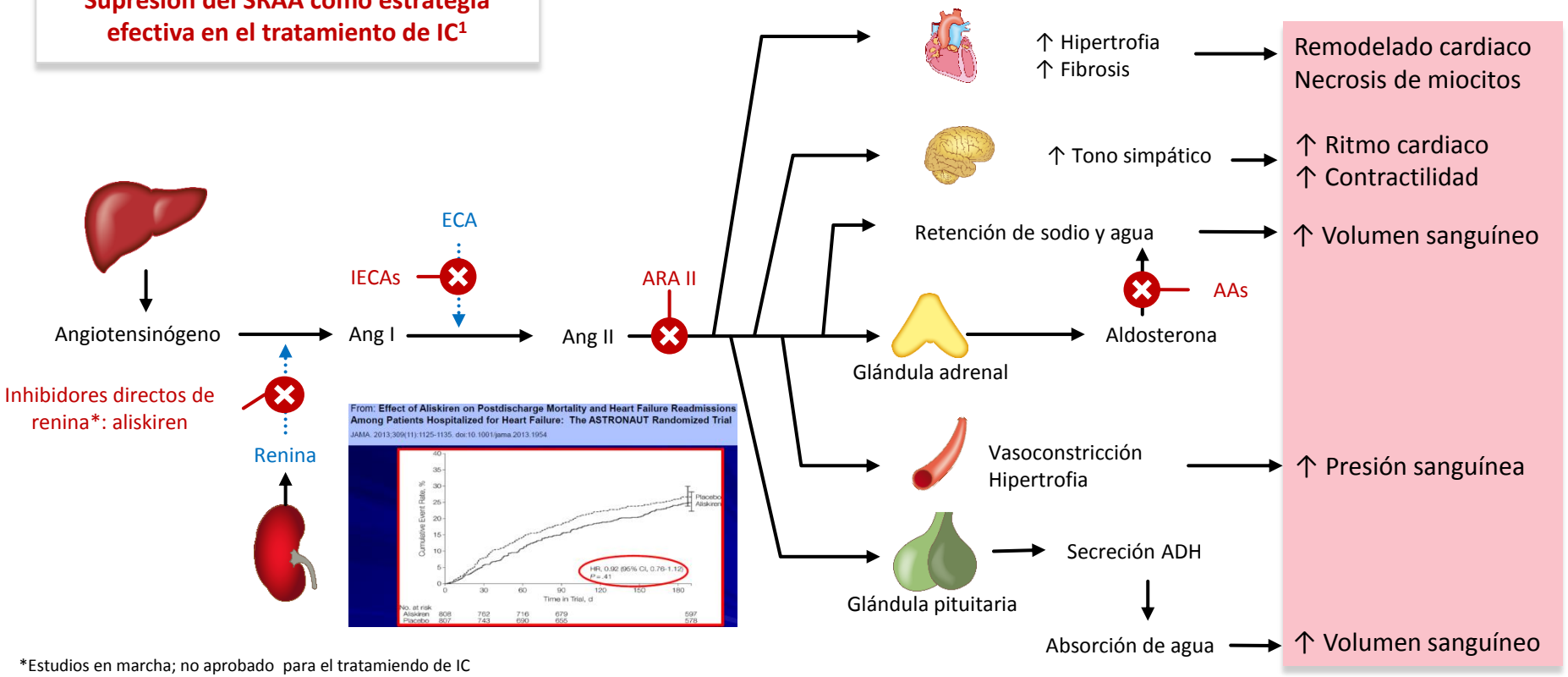
Lymperopoulos et al. Circ Res 2013;113:739–53

La activación prolongada del SRAA tiene un efecto nocivo en IC

La disfunción cardiaca lleva a la activación del SRAA…

…la activación prolongada pone mayor presión en el corazón ya debilitado, creando un círculo vicioso

Supresión del SRAA como estrategia efectiva en el tratamiento de IC[1]



*Estudios en marcha; no aprobado para el tratamiendo de IC

ECA=enzima convertidora de angiotensina; IECA=inhibidor de la enzima convertidora de la angiotensin; ADH=hormona antidiurética; ARA ii=antagonistas de los receptores de la angiotensina II; Ang=angiotensina; IC=insuficiencia cardiaca; AAs=antiaaldosterónicos; SRAA=sistema renina angiotensina aldosterona

Zaman et al. Nat Rev Drug Discov 2002;1:621–36
Schrier, Abraham. N Engl J Med 1999;341:577–85
Brewster et al. Am J Med Sci 2003;326:15–24
Schmeider. Am J Hypertens 2005;18: 720-30
McMurray et al. Eur Heart J 2012;33:1787–847

Novedades farmacológicas IC: 2014/2015

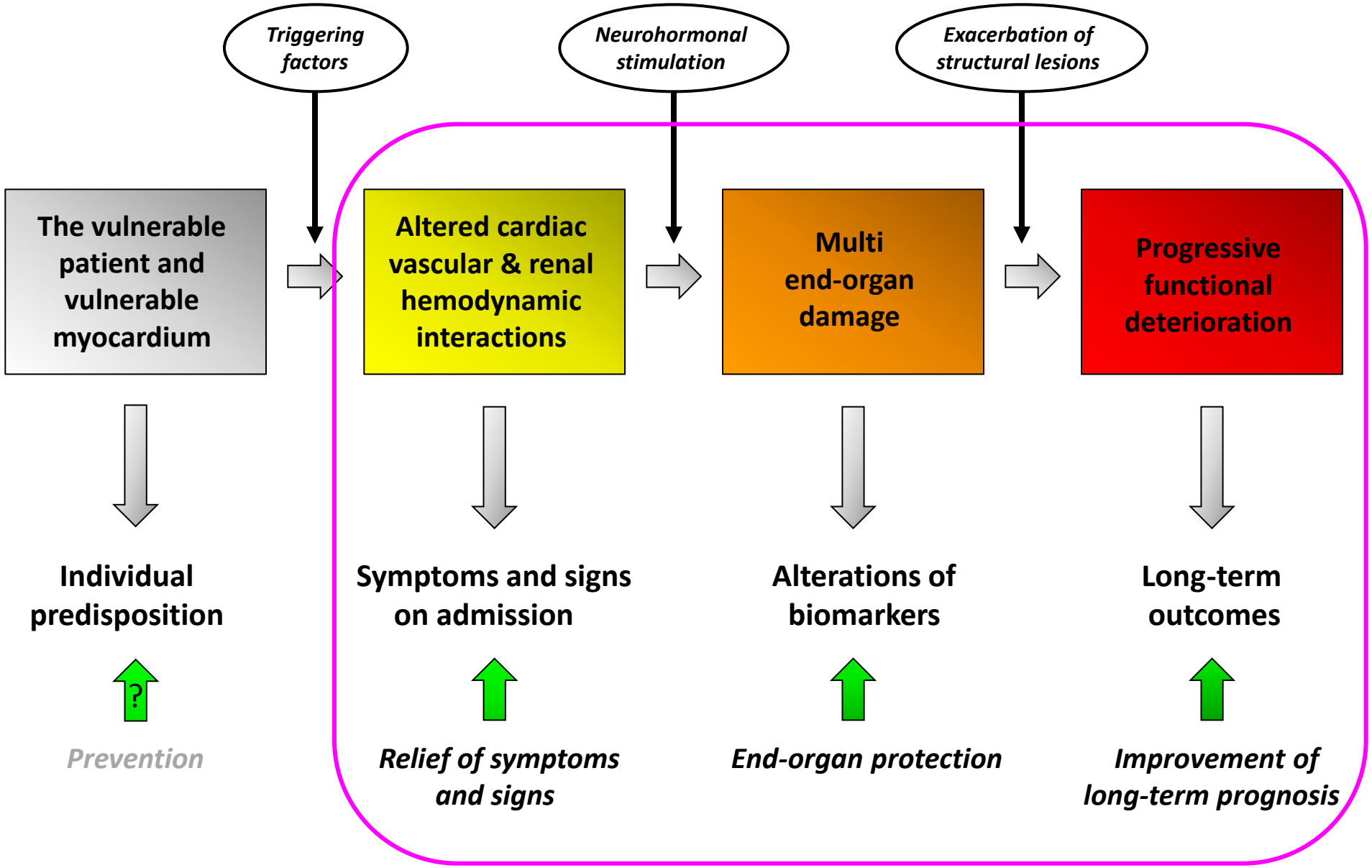
"Existe una necesidad racional de buscar "**nuevos conceptos en la terapia farmacológica"** más que de seguir redundando con nuevos fármacos en los conceptos ya establecidos"

- **Nuevos "conceptos" y fármacos para la IC aguda.**
- **Nuevos "conceptos" y fármacos para la IC crónica con FEVI reducida**
- **Nuevos "fármacos" en la IC crónica con FEVI preservada.**
  (¿¿nos faltan los "nuevos conceptos" en IC FEVI preservada??)

- 1. INSUFICIENCIA CARDÍACA AGUDA: nuevos receptores diana con una visión más "preservadora" y "holística"

- Nuevos inotropos/vasodiladores/diuréticos
- Nuevas formas de utilización de fármacos conocidos

‘Holistic’ therapy of AHF



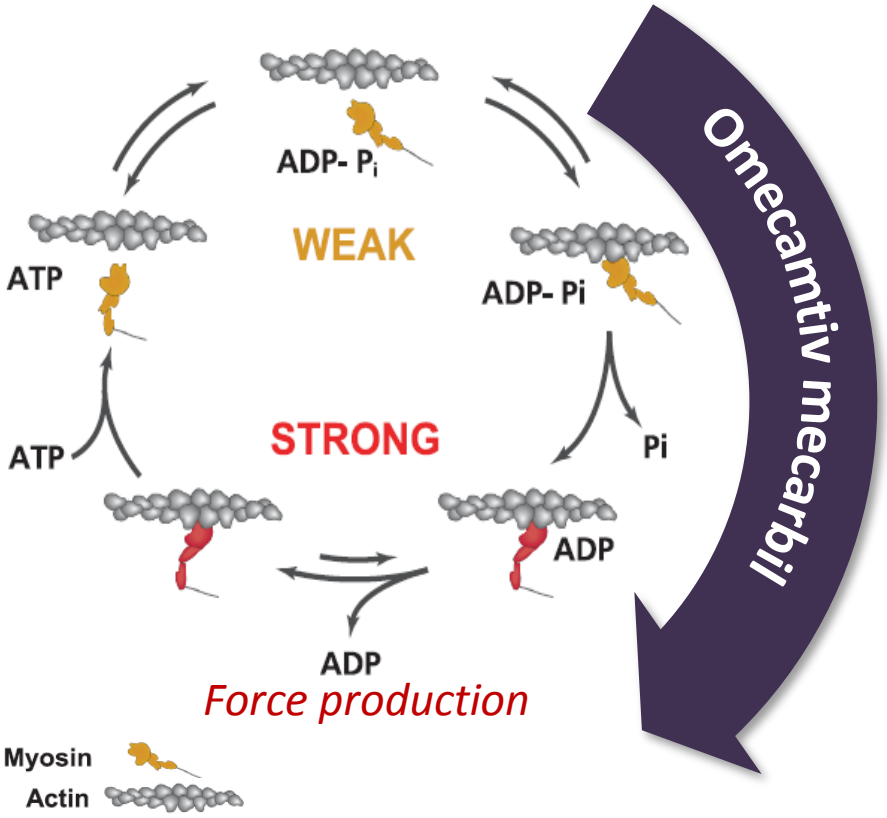
Díez J, et al. Am J Cardiovasc Drugs. 2014

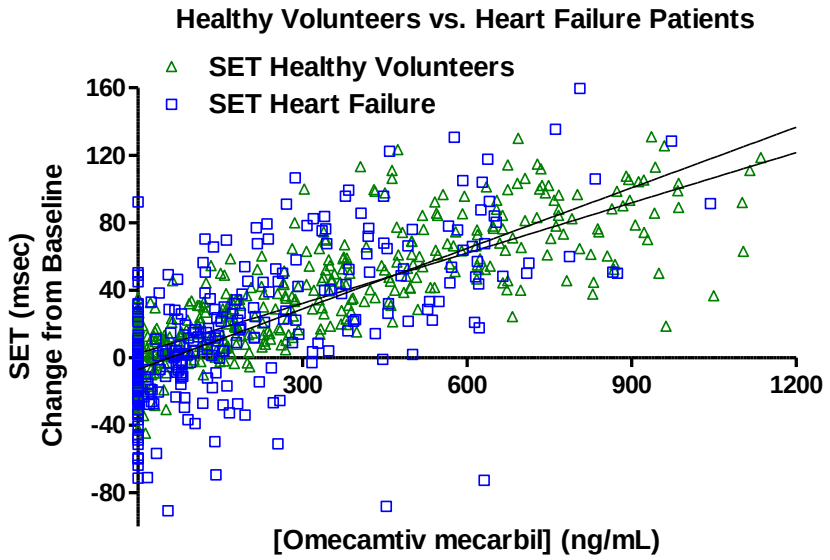
NOVEL DRUGS IN CLINICAL DEVELOPMENT FOR ACUTE HEART FAILURE

NEW TARGETS IN ACUTE HEART FAILURE		
Target & mechanism	**Molecule**	**Phase of development**
Inhibition of Na+ K+ ATPase **& increased SERCA2a ATPase activity**	Istaroxime	Phase 2
Cardiac myosin ATPase activation	**Omecamtiv Mecarbil**	Phase 2
Pro-ANP	Ularitide	Phase 3
ANP	Carperitide	Phase 2
Recombinant form of relaxin −2	**Serelaxin**	Phase 2/3
Soluble guanylate cyclase activators	Riociguat **BAY 1021189**	Phase 2

Omecamtiv Mecarbil (OM) is a Novel Selective Cardiac Myosin Activator

Omecamtiv mecarbil increases the entry rate of myosin into the tightly-bound, force-producing state with actin
"More hands pulling on the rope"





- Increases duration of systole
- Increases stroke volume
- No increase in myocyte calcium
- No change in dP/dt_{max}
- No increase in MVO_2

Mechanochemical Cycle of Myosin

Malik FI, *et al.* *Science* 2011; 331:1439-43.

ATOMIC-AHF

Acute **T**reatment with **O**mecamtiv **M**ecarbil to **I**ncrease **C**ontractility in **A**cute **H**eart **F**ailure

Objective:

- To evaluate the safety, pharmacokinetics/ pharmacodynamics, and efficacy of IV omecamtiv mecarbil (OM) in patients with acute heart failure (AHF)

Hypothesis:

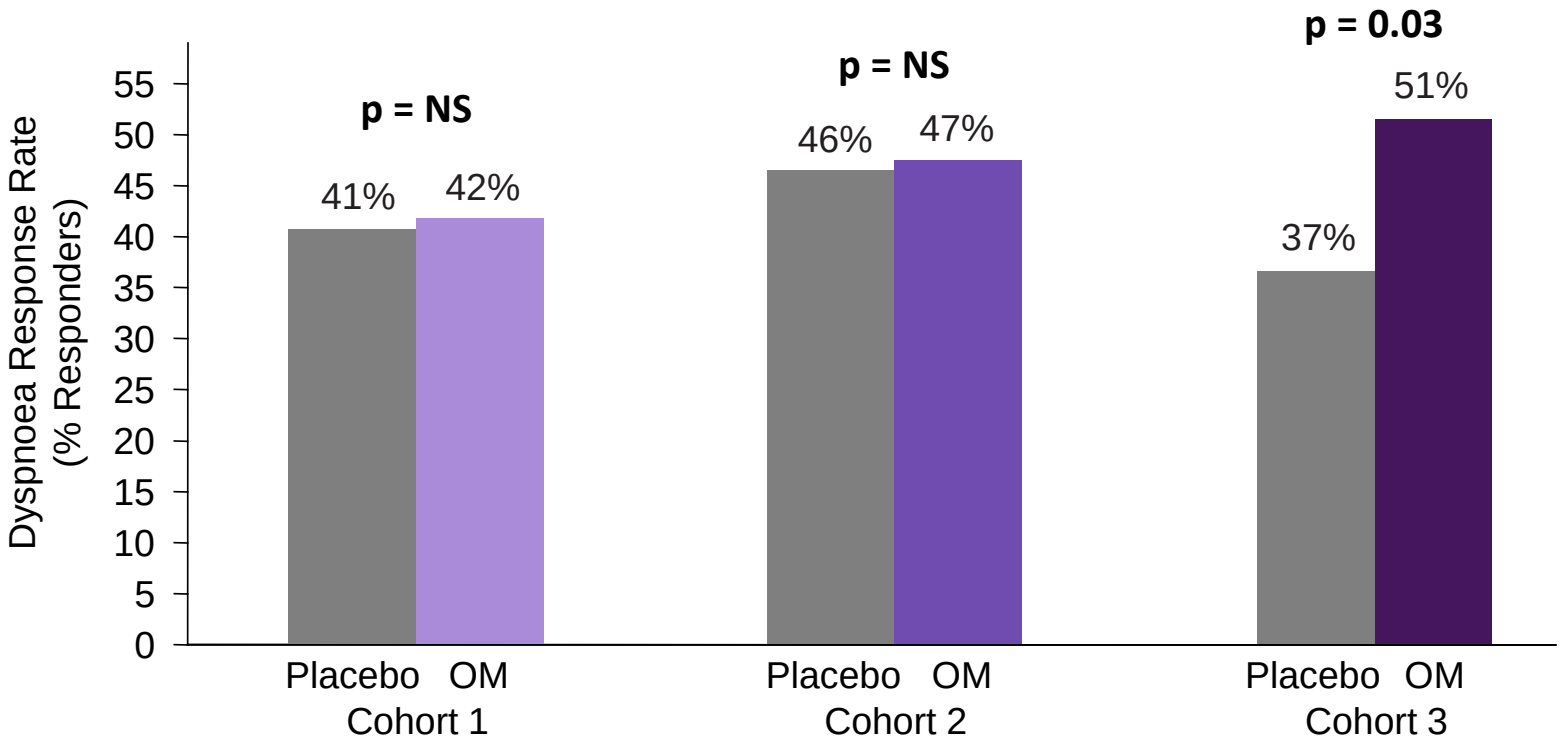
- At least 1 dose level of IV OM will be well tolerated and will result in improvement of dyspnoea in subjects with left ventricular systolic dysfunction hospitalised for AHF

Supplemental Primary Analysis:

Dyspnoea Response (Likert Scale)

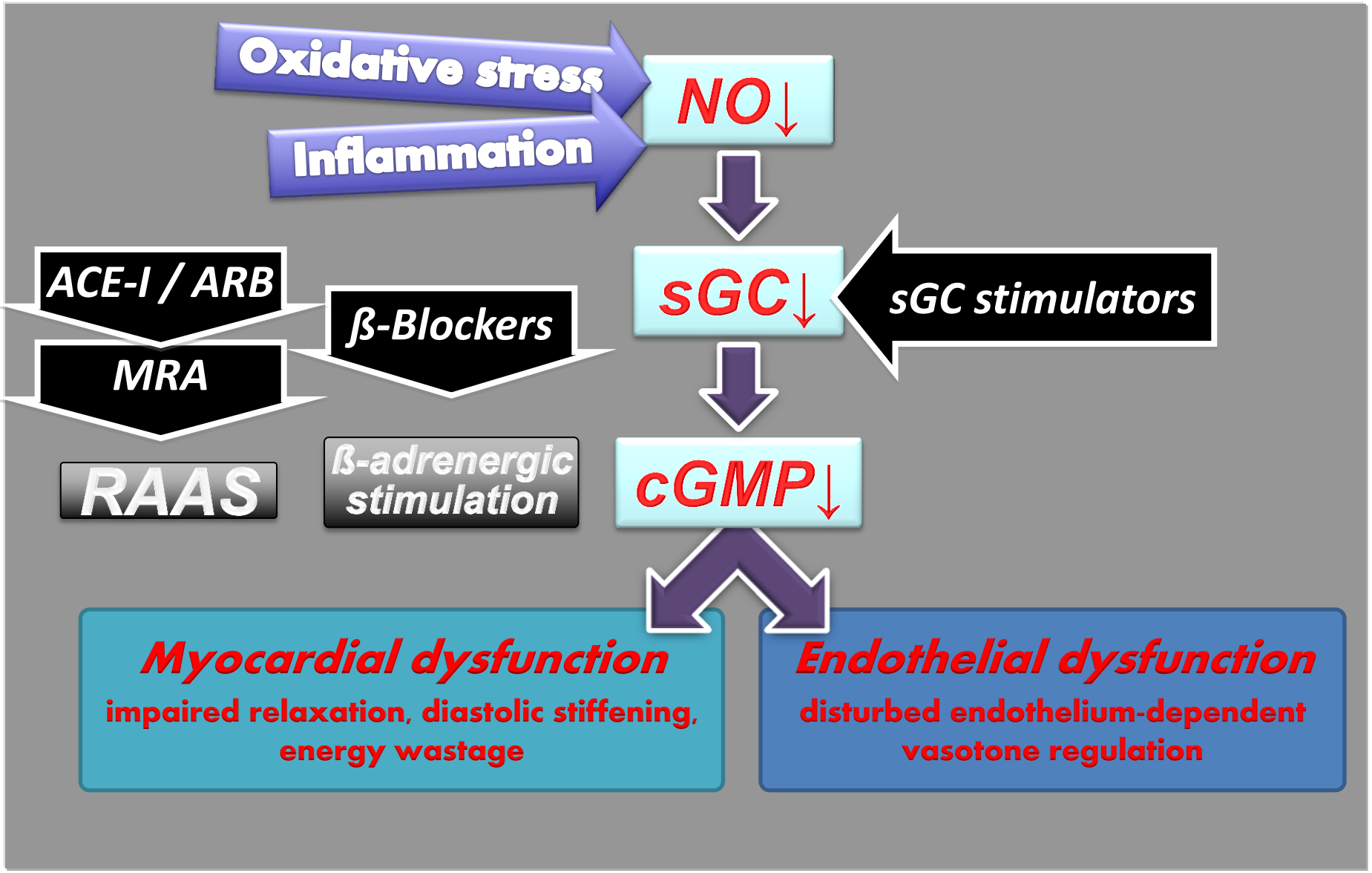
History of HF and LVEF ≤40%
Hospitalised for AHF requiring IV therapy

Paired Placebo



Response Rate Ratio	**1.02**	**1.02**	**1.41**
95% CI	**(0.74, 1.42)**	**(0.76, 1.37)**	**(1.02, 1.93)**

Insufficient soluble Guanylate Cyclase (sGC): A Novel Target in Heart Failure: Riociguat



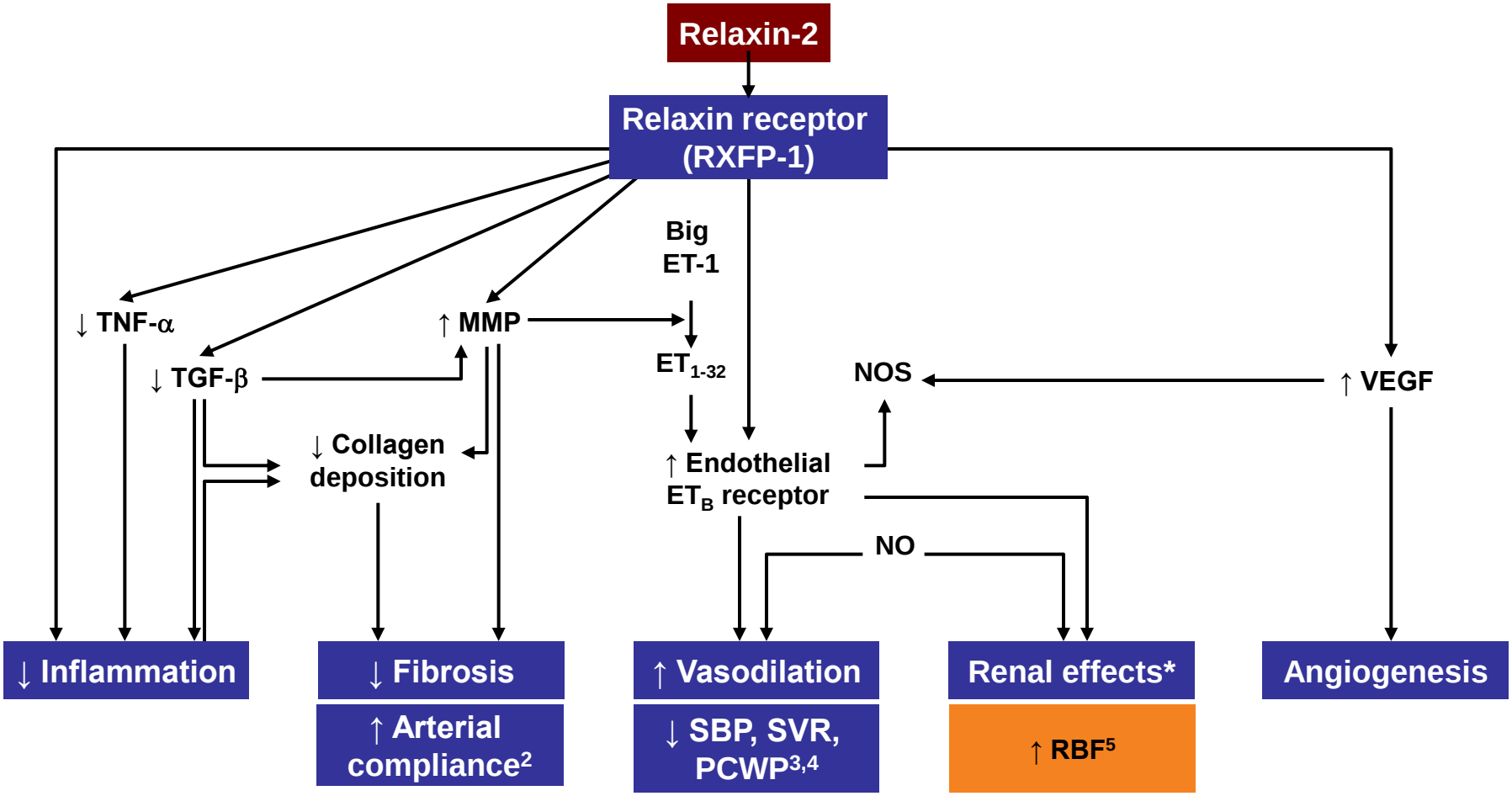
Soluble GC stimulator for heart failure study – SOCRATES (Fase II)

Population	**Worsening chronic HF with hospitalization for HF with treatment initiation upon clinical stabilization**	
	reduced ejection fraction (**HFrEF**, **SOCRATES-REDUCED**) LVEF <45%	preserved ejection fraction (**HFpEF**, **SOCRATES-PRESERVED**) LVEF ≥45%
Objective	Identify the optimal dose of the oral sGC stimulator BAY 1021189 in addition to standard HF therapy (HFrEF) or diuretic & comorbidity treatment (HFpEF) by characterizing safety, tolerability, pharmacodynamic effects and pharmacokinetics in patients with worsening chronic HFrEF / HFpEF	
Design	Prospective, randomized, placebo-controlled, double-blind, 5 parallel arm (2 continuous doses and 2 dose titration regimens of BAY 1021189 vs. placebo), multi-center dose finding phase II trial	
Treatment	12 weeks duration	
Number of subjects	513 subjects will be screened and 410 randomized	588 subjects will be screened and 470 randomized

Eur J Heart Fail. 2014 Sep;16(9):1026-38

Serelaxina: forma recombinante de Relaxin-2

Summary of the main cellular and vascular effects



Adapted from Teichman et al. 2010; 1. Teichman et al. Curr Heart Fail Rep 2010;7:75–82;
2. Conrad et al. Endocrinology 2004;145:3289–96; 3. Teerlink et al. Lancet 2009;373:1429–39;
4. Dschietzig et al. J Card Failure 2009;15:182–90; 5. Smith et al. J Am Soc Nephrol 2006;17:3192–7;
6. Schneider et al. Annu Rev Pharmacol Toxicol 2007;47:731–759; 7. Goddard et al. Circulation 2004;109:1186–1193.

RELAX-AHF

Serelaxin in patients with AHF

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

Phase III
Serelaxin vs Placebo (1:1)

N=1.160

Inclusión: AHF

Dispnea, Chest RX congestion, high NP, Renal Insuf mild-mod and SBP ≥125 mmhg

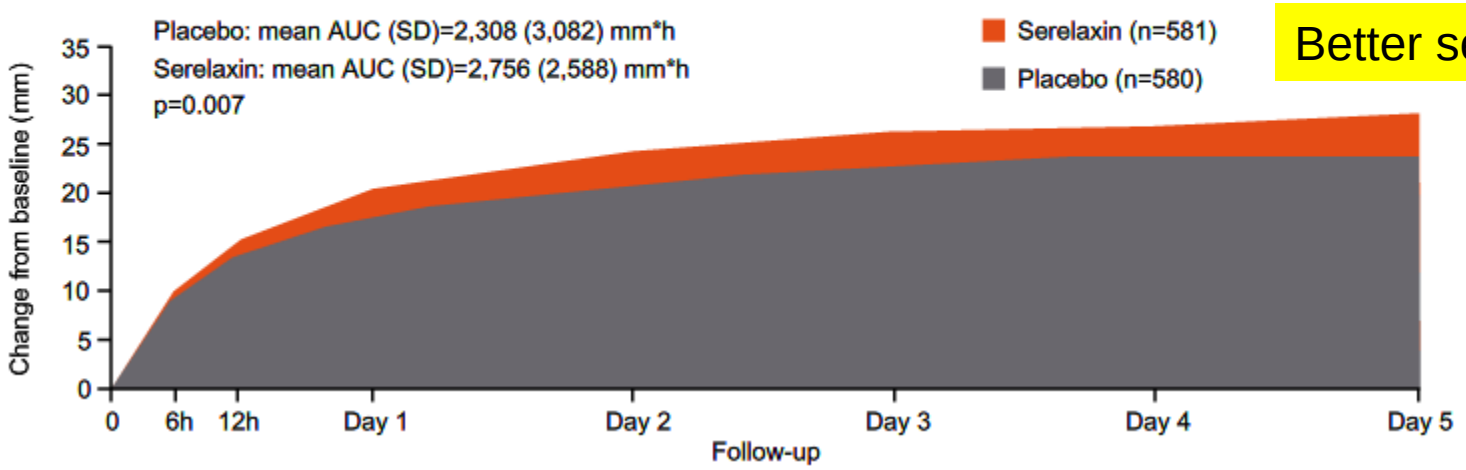
Randomization (first 16h): serelaxina iv 48 h vs placebo

Primay endpoint : **Dyspnea** at 24h and 5 days

Teerlink JR et al. Lancet 2012; 381: 29-39

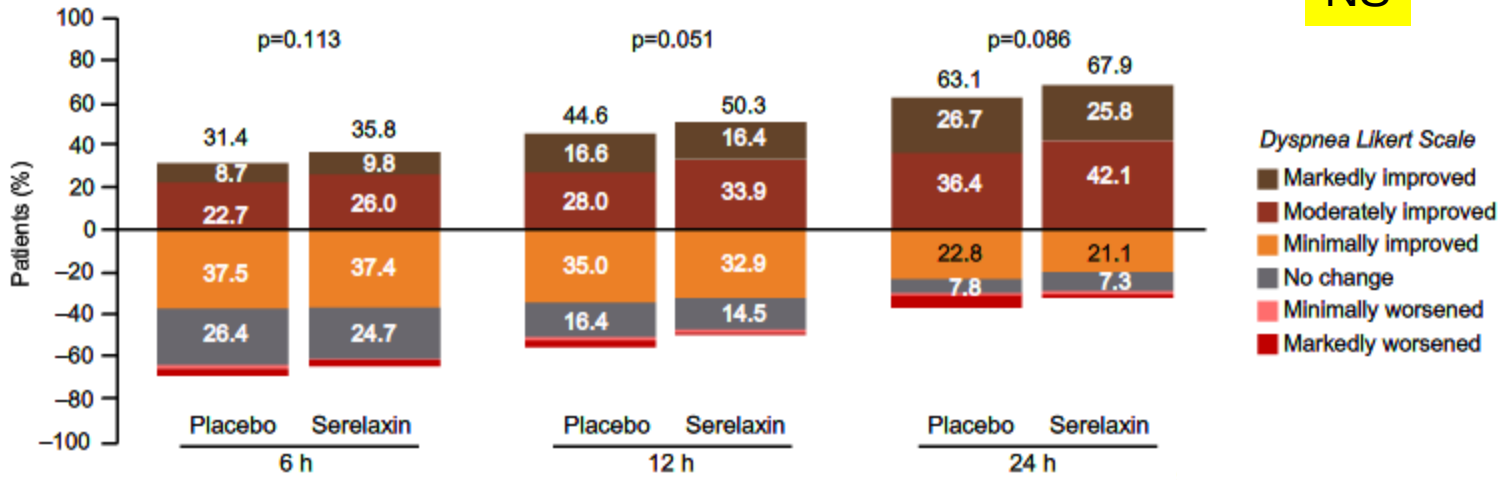
Serelaxin - RELAX-AHF

1e Primary Endpoint: Change in dyspnea with VAS



Better serelaxin

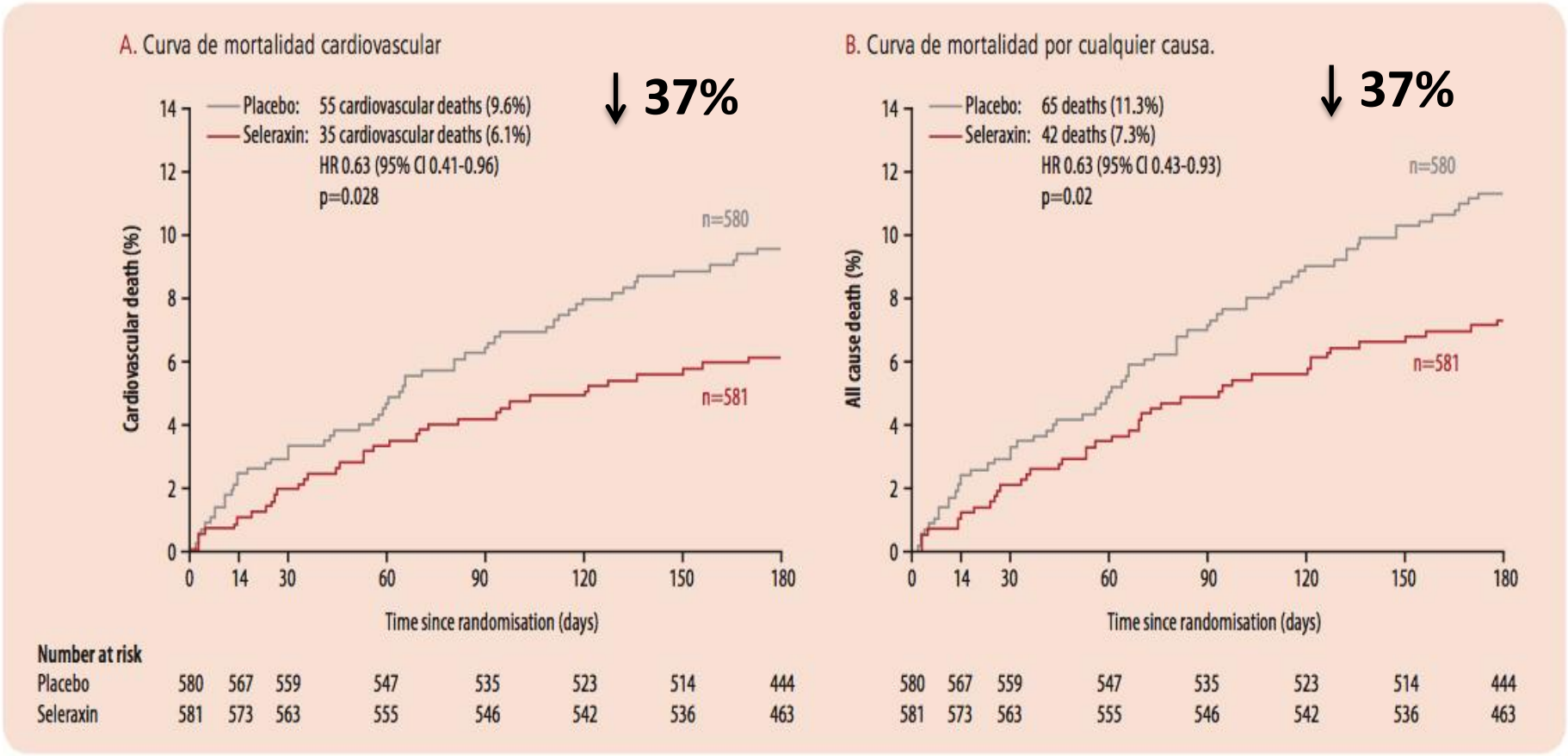
2e Primary Endpoint: Change in dyspnea with Likert



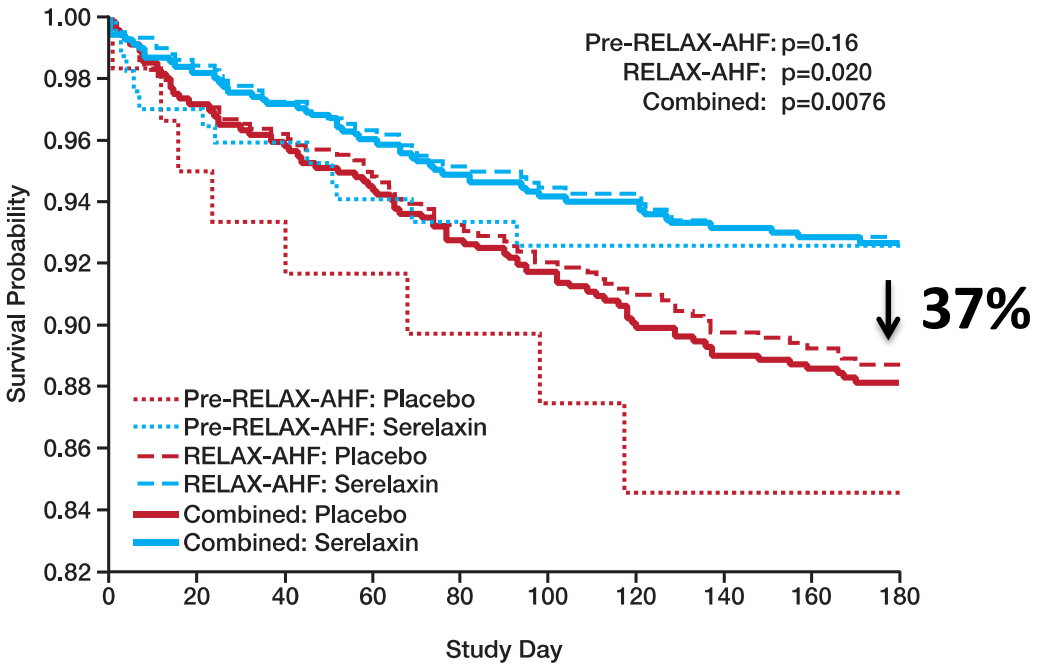
NS

Teerlink JR et al. Lancet 2012; 381: 29-39

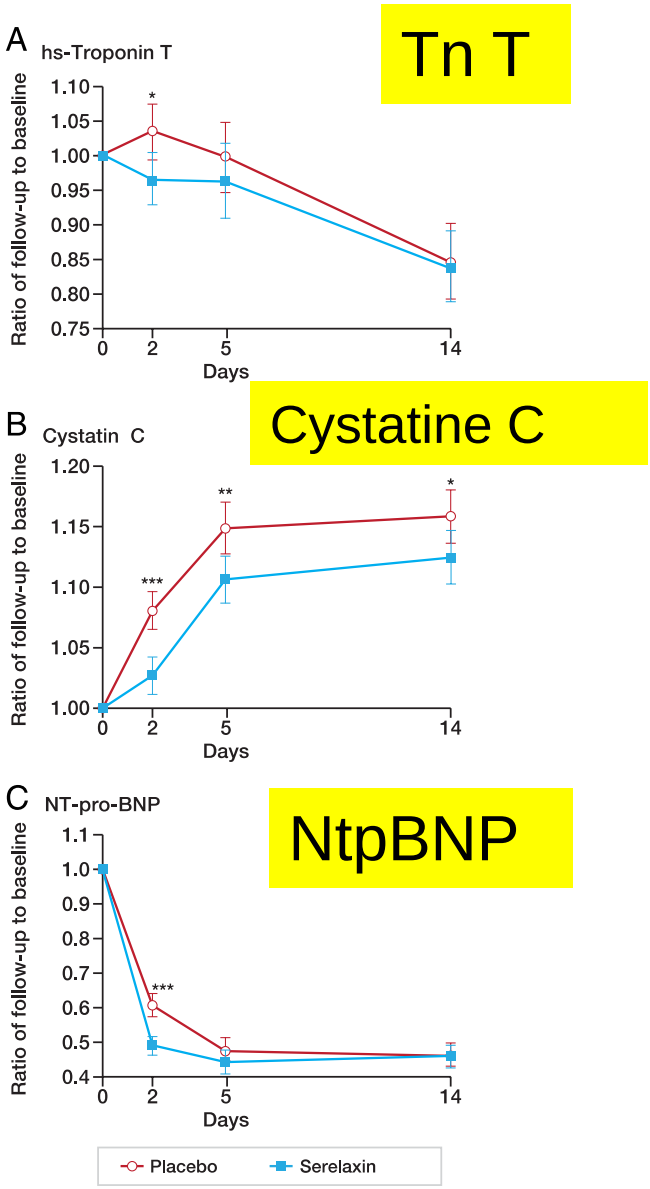
Serelaxin - RELAX-AHF



RELAX-AHF Biomarkers



Early administration of serelaxin was associated with a reduction of 180-day mortality, and this occurred with fewer signs of organ damage and more rapid relief of congestion during the first days after admission.



Metra M, JACC 2013; 61: 196-206

DOS ESTUDIOS EN MARCHA (RECLUTAMIENTO) PROSPECTIVOS RANDOMIZADOS MULTICÉNTRICOS
ENFOCADOS EN:

-1. MORTALIDAD COMO OBJETIVO PRIMARIO: RELAX-AHF-2

- 2. MEJORÍA DE SÍNTOMAS DE IC INTRAHOSPITALARIA LOS 5 DÍAS
+/- BIOMARCADORES: RELAX-AHF-EU

A multicenter, prospective, randomized, open label study to assess the effect of serelaxin versus standard of care in acute heart failure (AHF) patients

RESULTADOS PROXIMAMENTE…2017

Ensayos clínicos randomizados en IC AVANZADA con LEVOSIMENDÁN FORMA INTERMITENTE en pacientes ambulatorios:

Inodilatador

- **LION-HEART** (NCT01536132) (6h)
- **LEVOREPT Study Europeo (6h)**
- **LAICA** (24h)
- **ELEVATE** (NCT 01290146)

European Journal of Heart Failure (2014) **16**, 898–906
doi:10.1002/ejhf.118

Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study: a multicentre randomized trial

Aims The aim of this study was to determine whether intermittent ambulatory treatment with levosimendan would improve functional capacity, quality of life, and event-free survival in patients with advanced heart failure.

Methods and results This was a prospective, randomized, double-blind, placebo-controlled, multicentre, parallel-group trial of pulsed infusions of levosimendan in 120 outpatients with advanced heart failure (EF ≤35%, NYHA class III or IV). The study was conducted at 11 centres in Austria, Greece, and Germany. Levosimendan (0.2 μg/kg/min) or placebo was administered for 6 h at 2-week intervals over 6 weeks, in addition to standard care therapy. The primary outcome was the proportion of patients with a ≥20% improvement in the 6 min walk test and a ≥15% score increase on the Kansas City Cardiomyopathy Questionnaire at the end of the 24-week study period. Secondary outcomes included event-free survival after 24 weeks. Analyses were performed on an intention-to-treat basis. The primary endpoint was reached in 19% of patients receiving levosimendan and 15.8% of patients receiving placebo (odds ratio 1.25; 95% confidence interval 0.44–3.59; $P = 0.810$). Cardiac death (four vs. one), heart transplants (two vs. one), and acute heart failure (14 vs. nine) were more frequent with placebo as compared with levosimendan. The incidence of side effects was comparable between groups.

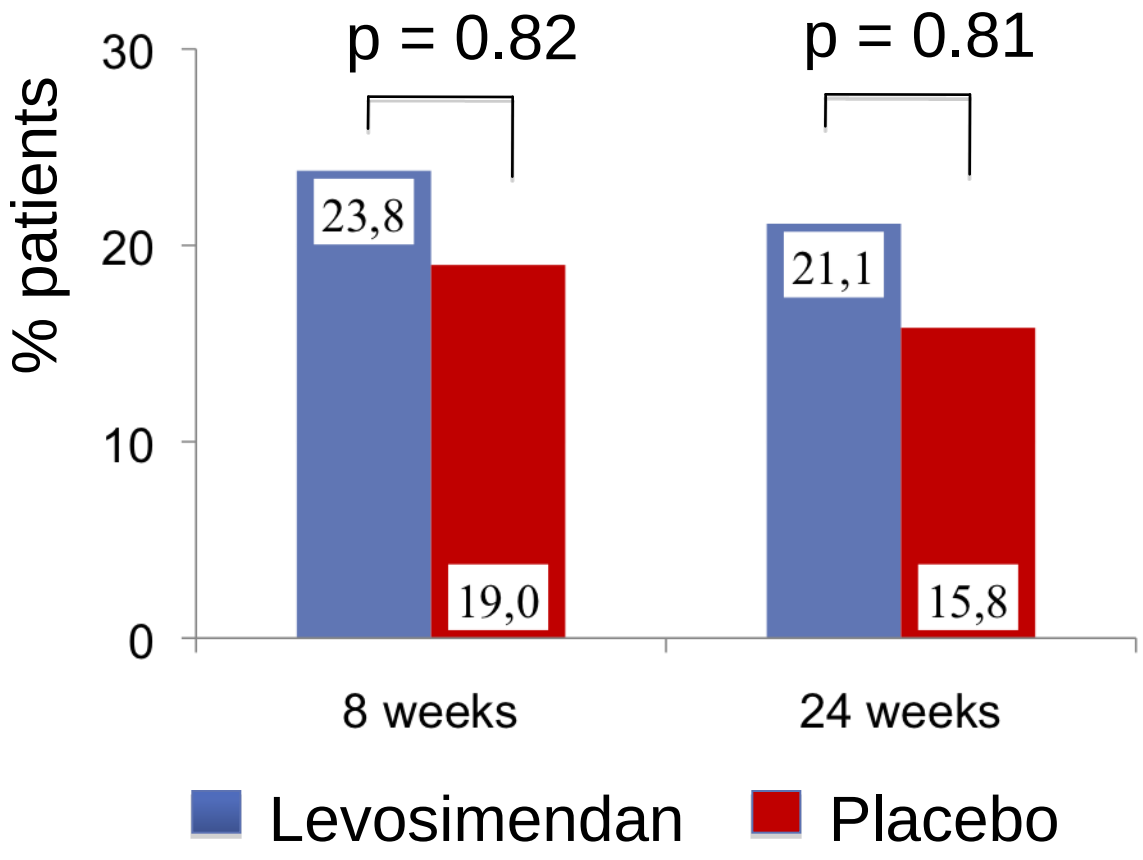
Conclusion Intermittent ambulatory treatment with levosimendan in patients with advanced heart failure did not improve significantly functional capacity or quality of life as compared with placebo. An adequately powered, event-driven trial is warranted to enlarge on our findings.

Trial registration: NCT01065194.

Keywords Levosimendan • Pulsed infusions • Advanced heart failure • Outcome • Safety • Outpatient setting

Levorept: Primary endpoint

Improvements in six min walk test ≥20% and KCCQ clinical summary score ≥15%



Altenberger J et al. Eur J Heart Fail.2014;16:898-906.

LEVOSIMENDÁN EN DOSIS INTERMITENTES EN IC AVANZADA

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Repetitive use of levosimendan for treatment of chronic advanced heart failure: Clinical evidence, practical considerations, and perspectives: An expert panel consensus

M.S. Nieminen [a,*], J. Altenberger [b], T. Ben-Gal [c], A. Böhmer [d], J. Comin-Colet [e], K. Dickstein [f], I. Édes [g], F. Fedele [h], C. Fonseca [i], M.J. García-González [j], G. Giannakoulas [k], Z. Iakobishvili [l], P. Jääskeläinen [m], A. Karavidas [n], J. Kettner [o], M. Kivikko [p], L.H. Lund [q], S.T. Matskeplishvili [r], M. Metra [s], F. Morandi [t], F. Oliva [u], A. Parkhomenko [v], J. Parissis [w], P. Pollesello [p], G. Pölzl [x], R.H.G. Schwinger [y], J. Segovia [z], M. Seidel [aa], B. Vrtovec [ab], G. Wikström [ac]

Int J Cardiol. 2014 Jun 15;174(2):360-7

LAICA ESTUDIO

Estudio Randomizado Doble Ciego y Controlado con Placebo Para Evaluar la Eficacia y Seguridad de la Administración Intermitente y a Largo Plazo de LevosimendAn en Pacientes con Insuficiencia Cardiaca Avanzada

LION-HEART.

Tipo de estudio: Estudio multicéntrico, doble ciego, al… …do con placebo para evaluar la eficacia y seguridad de la… …venosa de dosis intermitentes de levosimendán en pa… …encia cardíaca crónica avanzada.

ClinicalTrials.gov Id

LION-HEART RESULTADOS: SEMANA QUE VIENE EN LA REUNIÓN DE LA SECCIÓN- CONGRESO EUROPEO DE IC EN SEVILLA

- 2. NOVEDADES en INSUFICIENCIA CARDÍACA CRÓNICA CON FEVI REDUCIDA

FASE II: ESTUDIO ARTS : BAY 94-8862 (Finerenona)

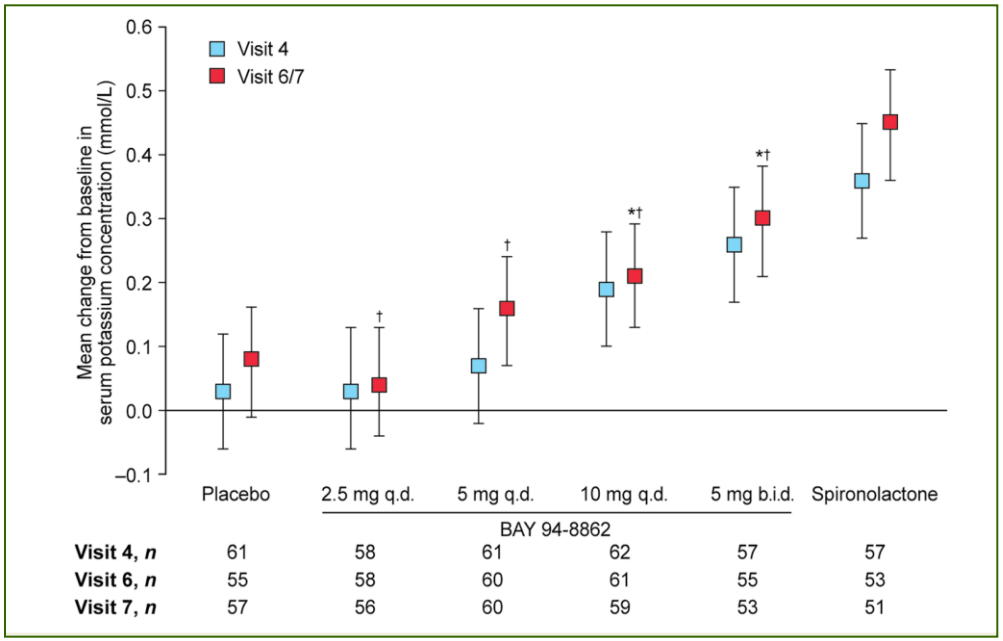
Nuevo MRA no esteroideo en ICFEr y disfunción renal ligera-moderada

Parte A: Seguridad y tolerabilidad

BAY 94-8862: 2,5, 5, 10 mg/día vs placebo (1:1:1:1)

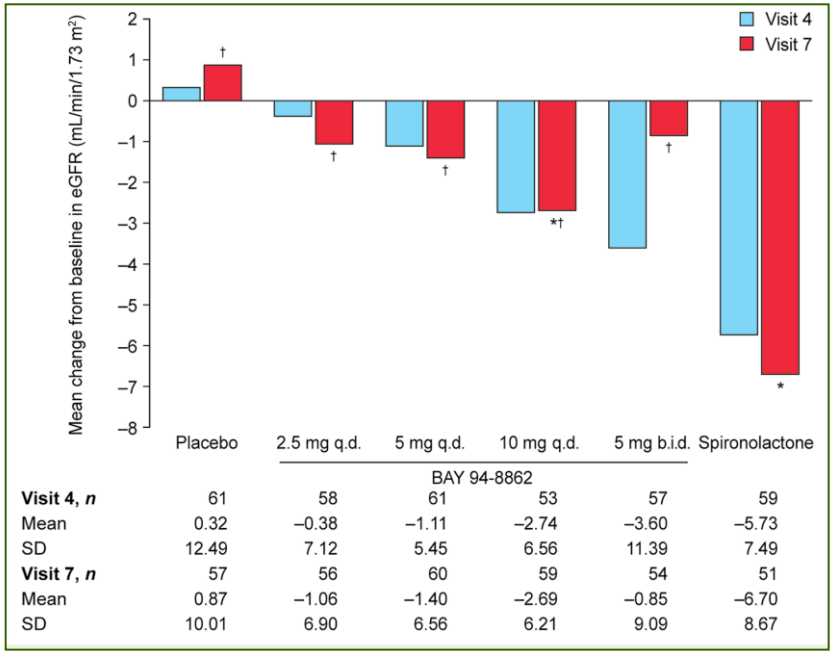
Parte B: Cambio en K sérico (basal)

BAY 94-8862: 2,5, 5, 10 mg/día, 5 mg/12h, espironolactona 25-50 (1:1:1:1:1:1)



	Placebo	2.5 mg q.d.	5 mg q.d.	10 mg q.d.	5 mg b.i.d.	Spironolactone
Visit 4, *n*	61	58	61	62	57	57
Visit 6, *n*	55	58	60	61	55	53
Visit 7, *n*	57	56	60	59	53	51

Cambio K+ sérico basal vs visita 4 y visita 7 (30 días)



	Placebo	2.5 mg q.d.	5 mg q.d.	10 mg q.d.	5 mg b.i.d.	Spironolactone
Visit 4, *n*	61	58	61	53	57	59
Mean	0.32	−0.38	−1.11	−2.74	−3.60	−5.73
SD	12.49	7.12	5.45	6.56	11.39	7.49
Visit 7, *n*	57	56	60	59	54	51
Mean	0.87	−1.06	−1.40	−2.69	−0.85	−6.70
SD	10.01	6.90	6.56	6.21	9.09	8.67

Cambio eGFR entre basal y visita 4 y visita 7 (30 días)

Pitt, B etl al. Eur Heart J. 2013 August ;34(31):2453-2463.

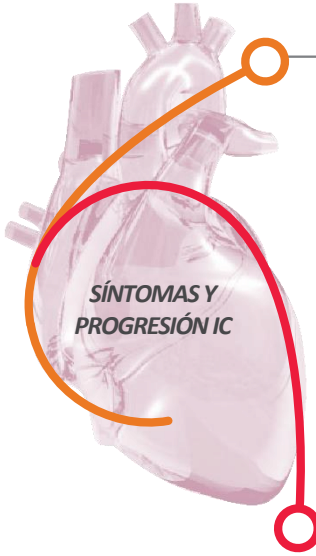
A

FASE IIb: ESTUDIOS PENDIENTES DE RESULTADOS CON FINERENONA

Rank	Status	Study
1	Completed	Phase IIb Safety and Efficacy Study of BAY94-8862 in Subjects With Worsening Chronic Heart Failure and Left Ventricular Systolic Dysfunction and Either Type 2 Diabetes Mellitus With or Without Chronic Kidney Disease or Moderate Chronic Kidney Disease Alone **Condition:** Heart Failure **Interventions:** Drug: BAY94-8862; Drug: Eplerenone; Drug: Placebo
2	Completed	BAY94-8862 Dose Finding Trial in Subjects With Chronic Heart Failure and Mild (Part A) or Moderate (Part B) Chronic Kidney Disease **Condition:** Heart Failure **Interventions:** Drug: BAY94-8862; Drug: Placebo; Drug: Spironolactone
3	Completed	Phase IIb Safety and Efficacy Study of Different Oral Doses of BAY94-8862 in Subjects With Worsening Chronic Heart Failure and Left Ventricular Systolic Dysfunction and Either Type 2 Diabetes Mellitus With or Without Chronic Kidney Disease or Chronic Kidney Disease Alone **Condition:** Heart Failure **Interventions:** Drug: Finerenone (BAY94-8862); Drug: Placebo; Drug: Inspra (eplerenone)

ClinicalTrials.gov

La disminución de la función sistólica activa dos grandes sistemas neurohormonales



SNS ✕ — **β-bloqueantes**

Epinefrina
Norepinefrina → Receptores α_1, β_1, β_2

Vasoconstricción
- Actividad SRAA ↑
- Vasopresina ↑
- Frecuencia cardiaca ↑
- Contractilidad ↑

SRAA ✕ — **Inhibidores del SRAA(IECA, ARA II, AAs)**

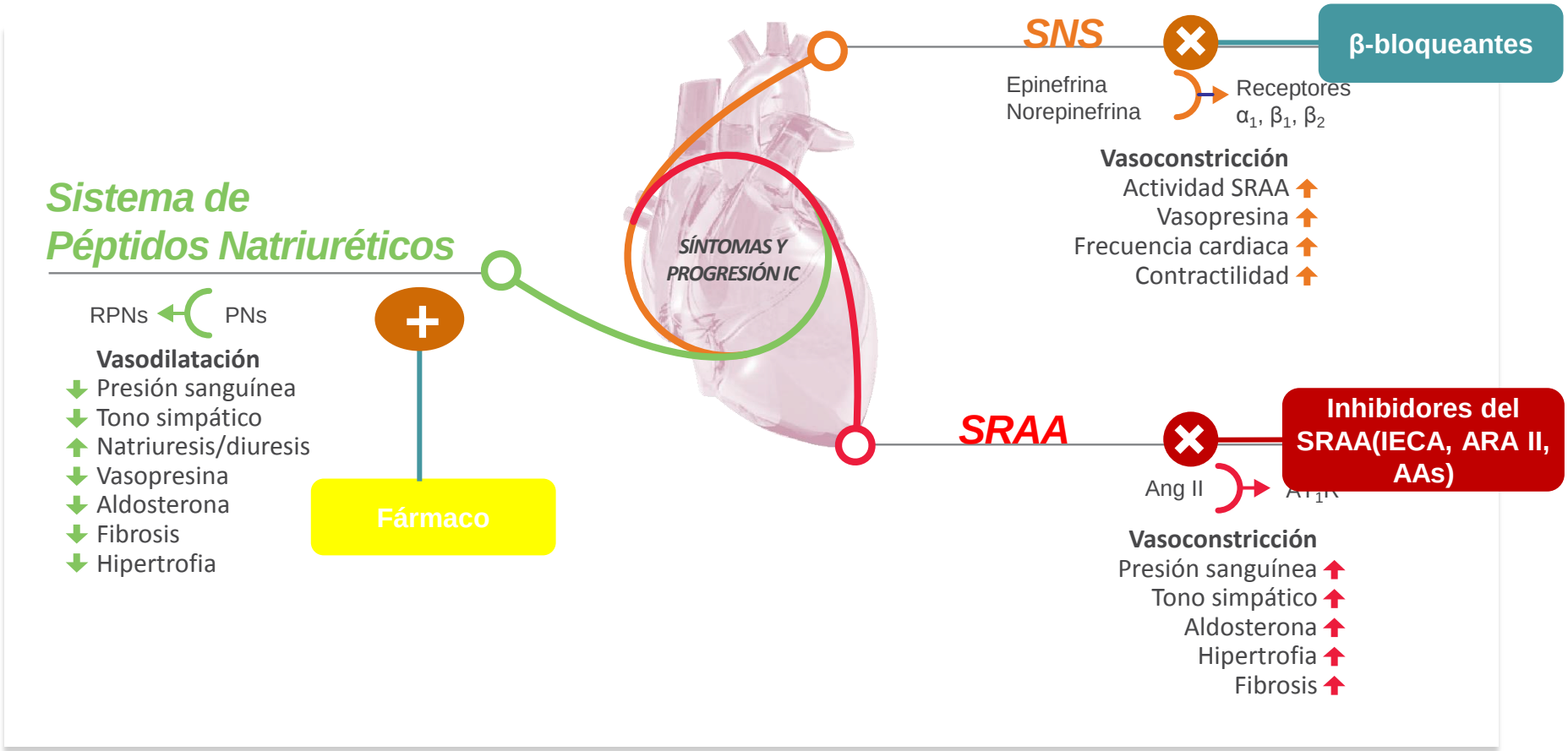
Ang II → AT_1R

Vasoconstricción
- Presión sanguínea ↑
- Tono simpático ↑
- Aldosterona ↑
- Hipertrofia ↑
- Fibrosis ↑

La regulación del SRAA y del SNS es la base de la terapia actual, pero…

McMurray et al. Eur Heart J 2012;33:1787–847
Figure references: Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42; Kemp & Conte. Cardiovascular Pathology 2012;365–371;
Schrier & Abraham. N Engl J Med 1999;341:577–85

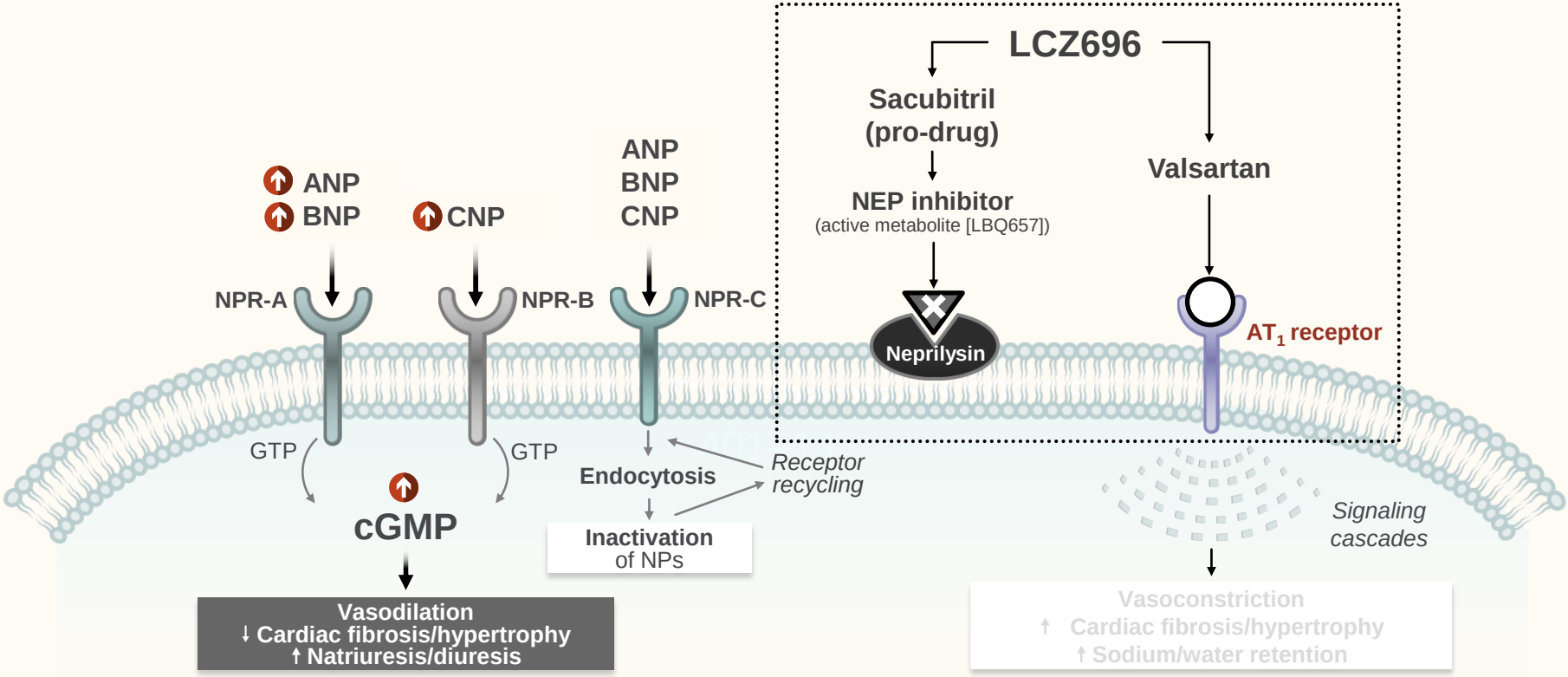
El corazón actúa como órgano endocrino, liberando PNs en respuesta a la elongación mecánica, contrarrestando algunos efectos del SRAA

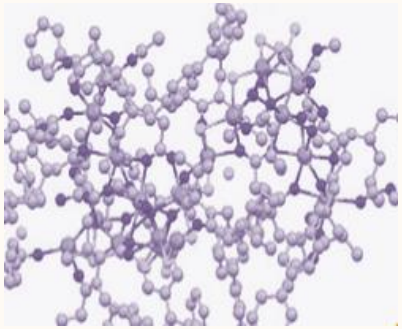


Ang=angiotensina; AT_1R=receptor de angiotensina II tipo 1; PNs=péptidos natriuréticos; RPNs=receptores de péptidos natriuréticos

Levin et al. N Engl J Med 1998;339:321–8;
Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42;
Kemp & Conte. Cardiovascular Pathology 2012;365–371;
Schrier & Abraham. N Engl J Med 2009;341:577–85

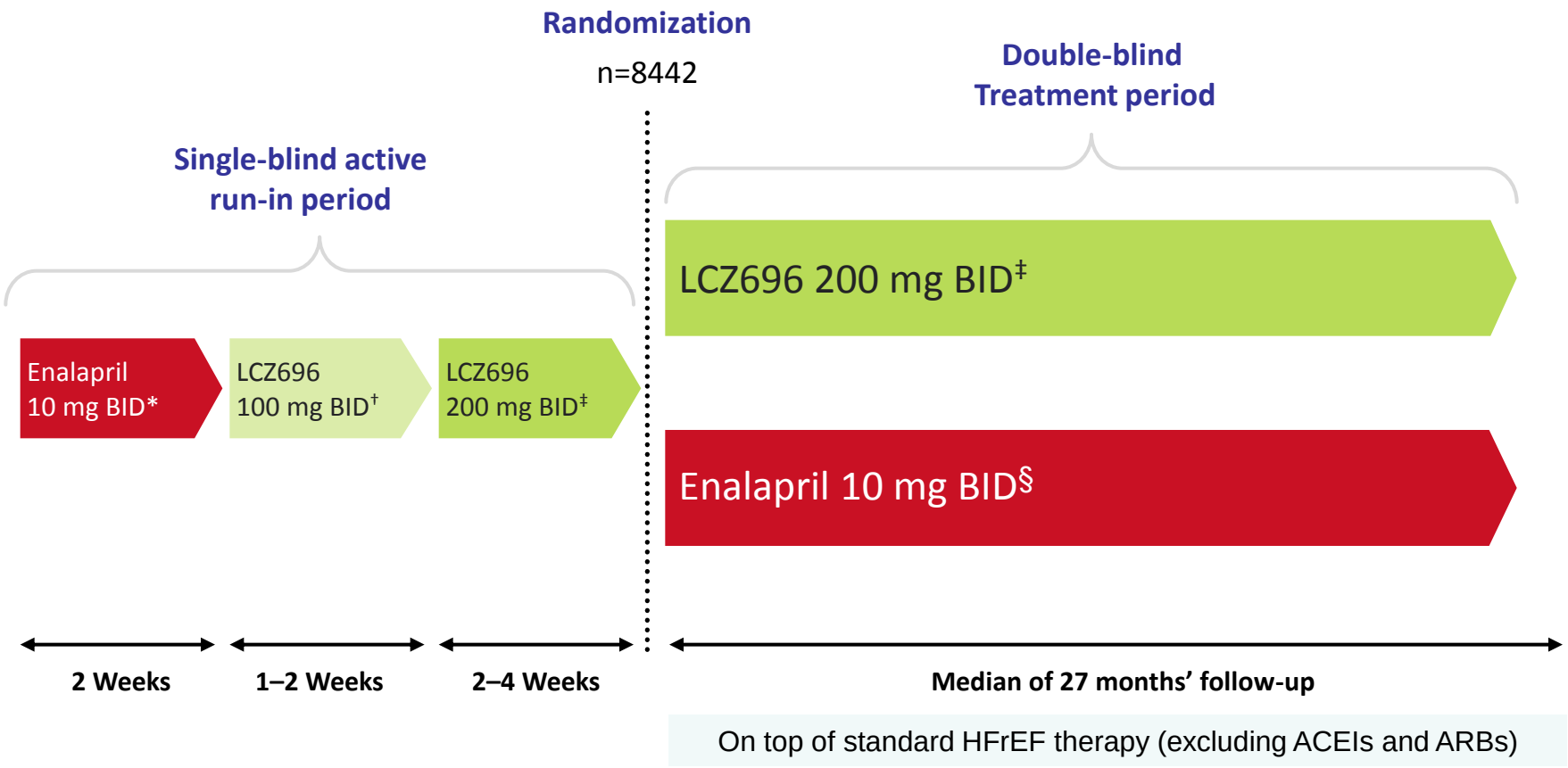
LCZ696 simultáneamente potencia el efecto beneficioso de los péptidos natriurético y bloquea el efecto deletéreo de la activación del Sistema RAA





1. Gu et al. J Clin Pharmacol 2010;50:401–14

PARADIGM-HF: Study design



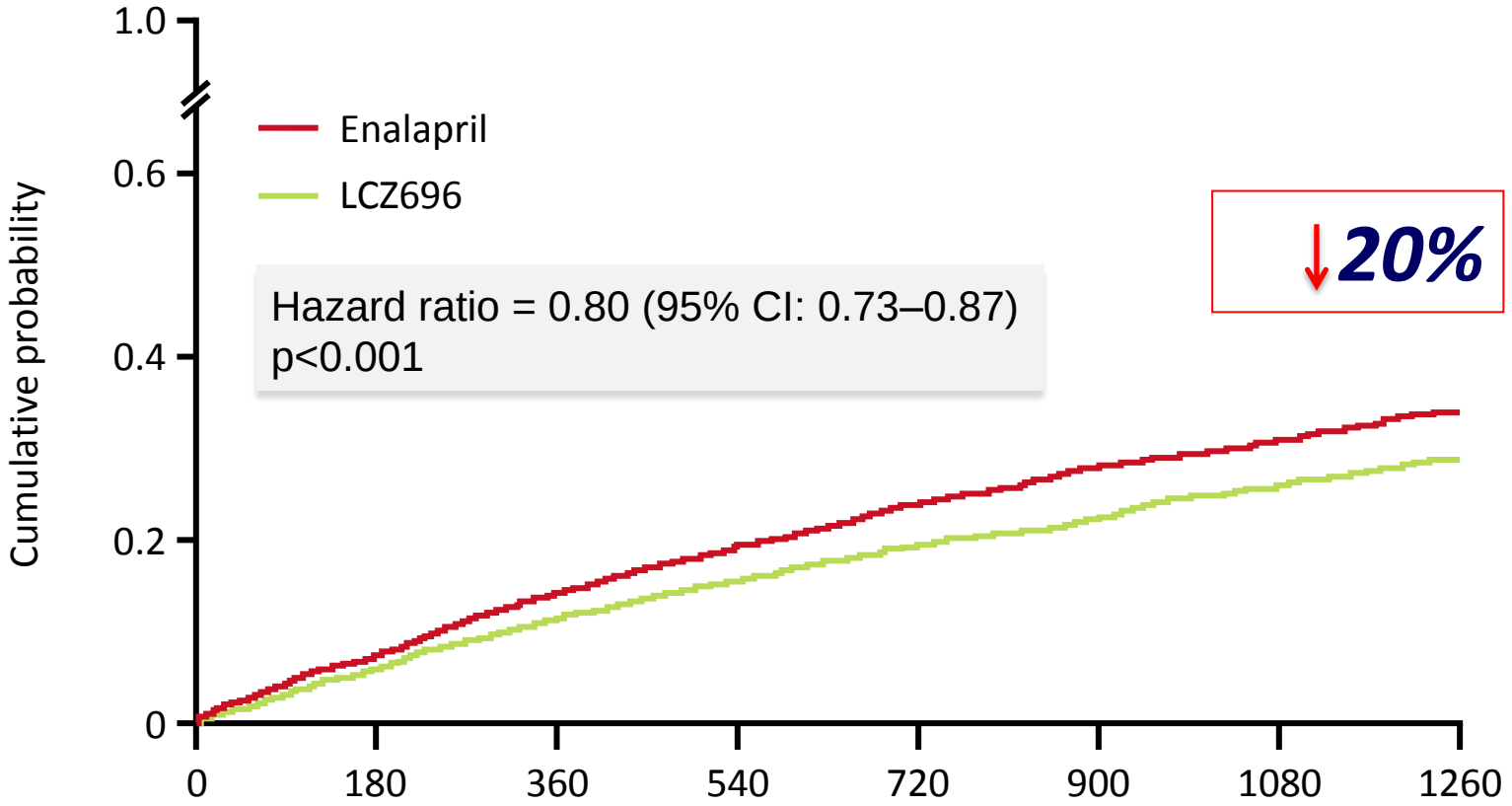
*Enalapril 5 mg BID (10 mg TDD) for 1–2 weeks followed by enalapril 10 mg BID (20 mg TDD) as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEI; †200 mg TDD; ‡400 mg TDD; §20 mg TDD.

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; ePub ahead of print: DOI: 10.1056/NEJMoa1409077.

PARADIGM-HF

Primary endpoint:

Death from CV causes or first hospitalization for HF

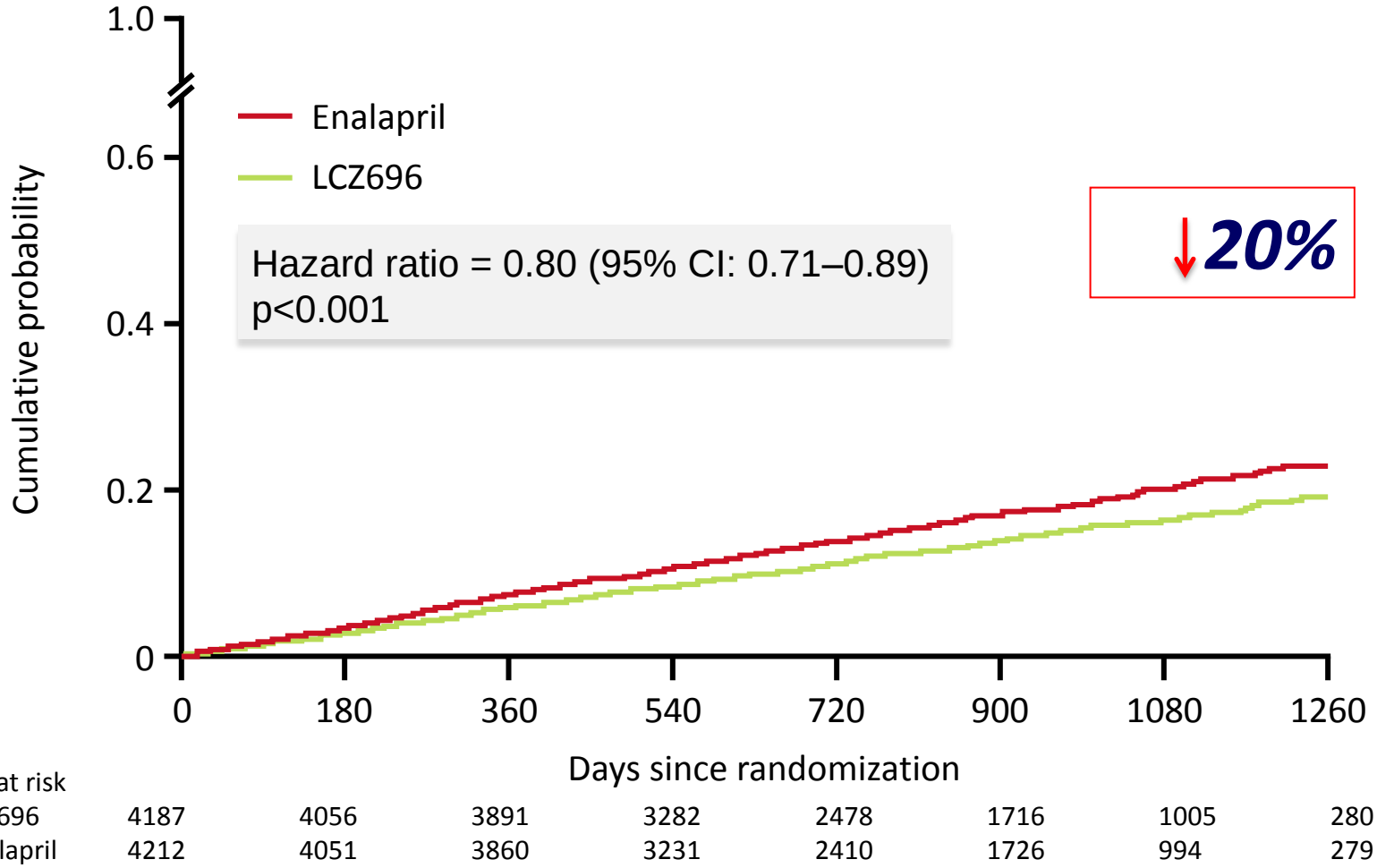


No at risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

McMurray J, et al. N Engl J Med 2014. 11;371: 993-1004

PARADIGM-HF

Components of primary endpoint: Death from CV causes

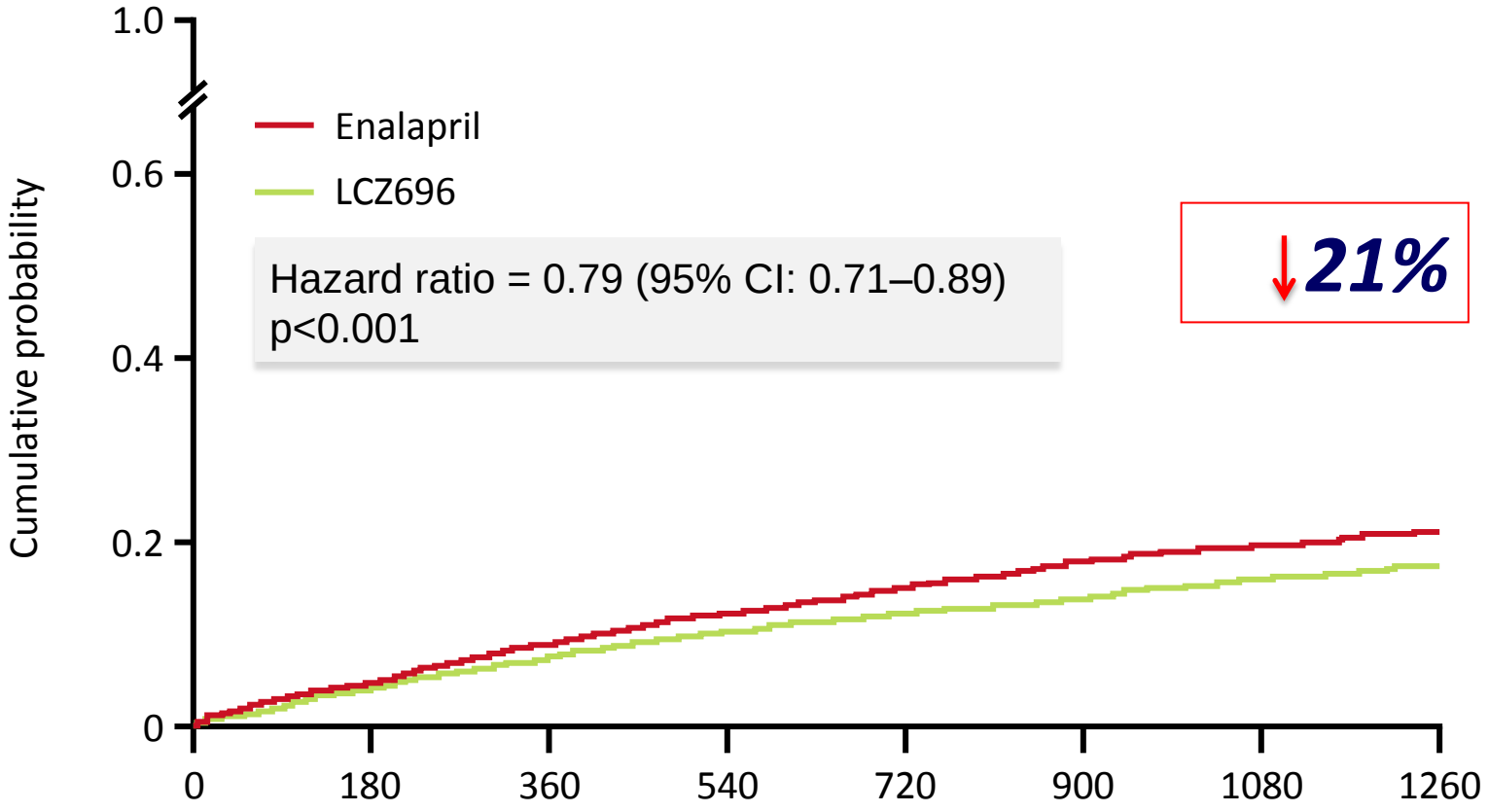


No at risk								
LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

McMurray J, et al. N Engl J Med 2014. 11;371: 993-1004

PARADIGM-HF

Components of primary endpoint: First hospitalization for HF

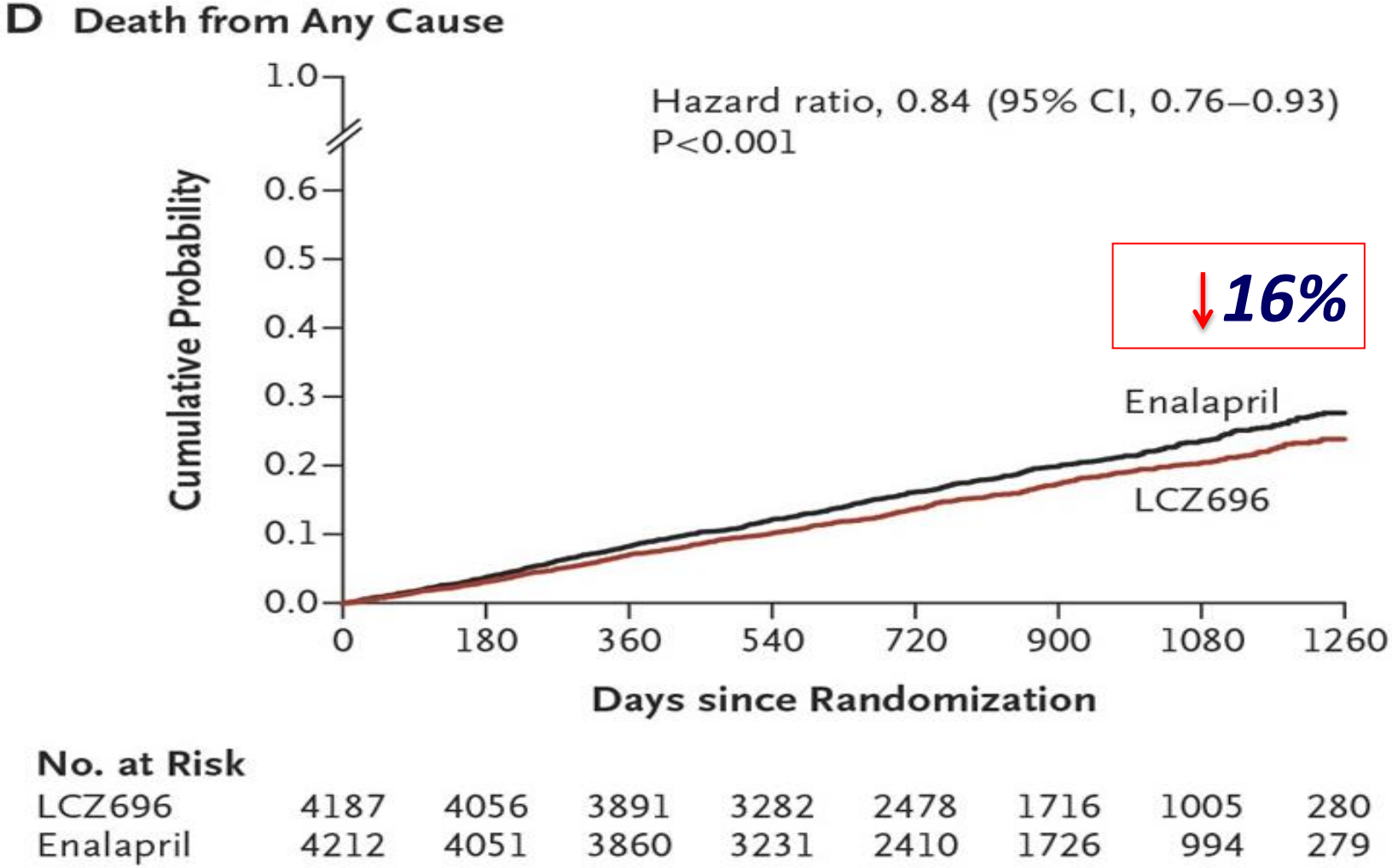


No at risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

McMurray J, et al. N Engl J Med 2014. 11;371: 993-1004

PARADIGM-HF

Death from any cause



McMurray J, et al. N Engl J Med 2014. 11;371: 993-1004

Prospectively defined safety events

Event, n (%)	LCZ696 (n=4187)	Enalapril (n=4212)	p-value‡
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with SBP <90 mmHg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dL	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dL	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/L	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/L	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema (adjudicated by a blinded expert committee)			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalized without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	---

- Fewer patients in the LCZ696 group than in the enalapril group stopped their study medication because of an AE (10.7 vs 12.3%, p=0.03)

McMurray J, et al. N Engl J Med 2014. 11;371: 993-1004

"CONFIRM-HF" CONFIRMA UN NUEVO CONCEPTO: LA FERROPENIA SÍ IMPORTA

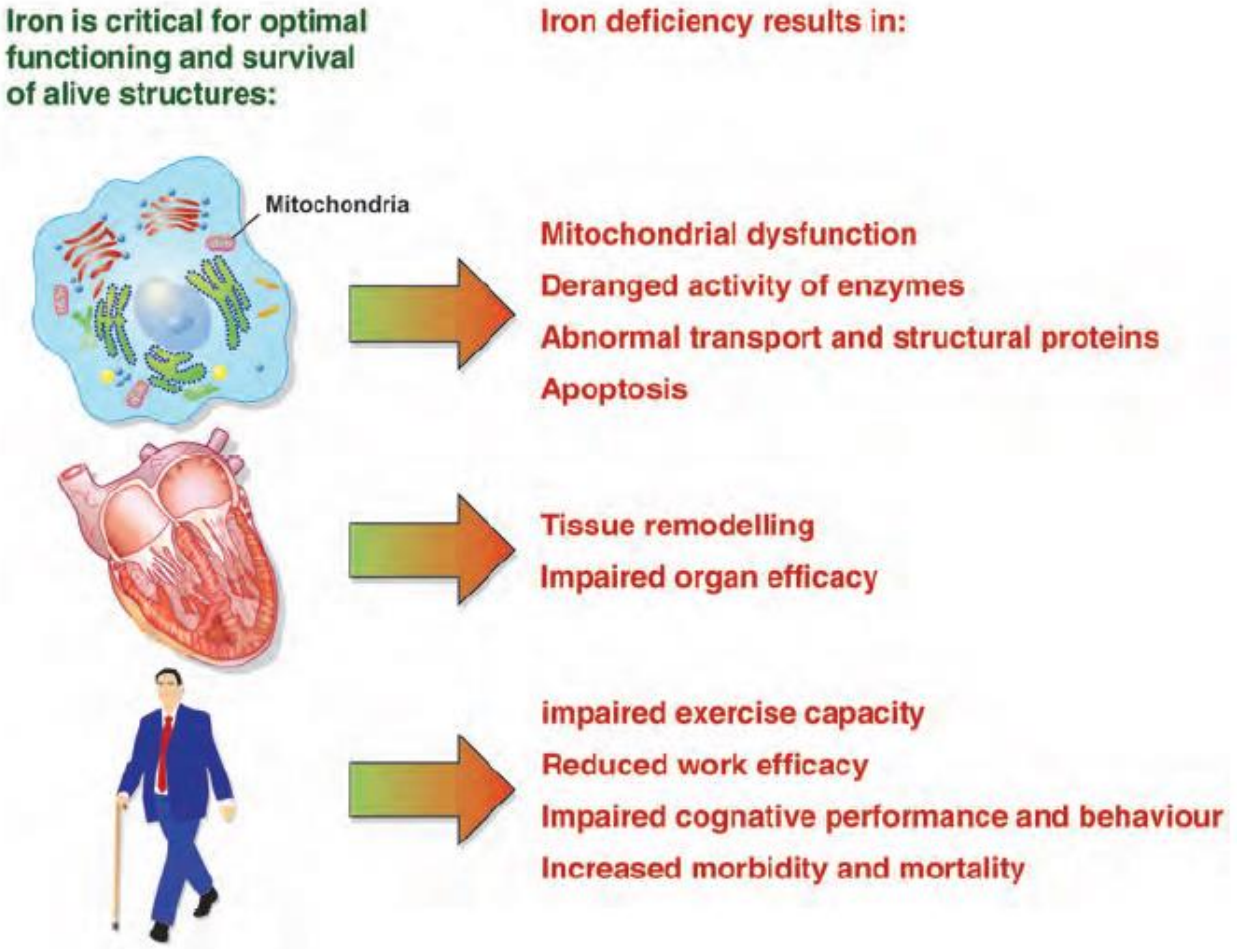


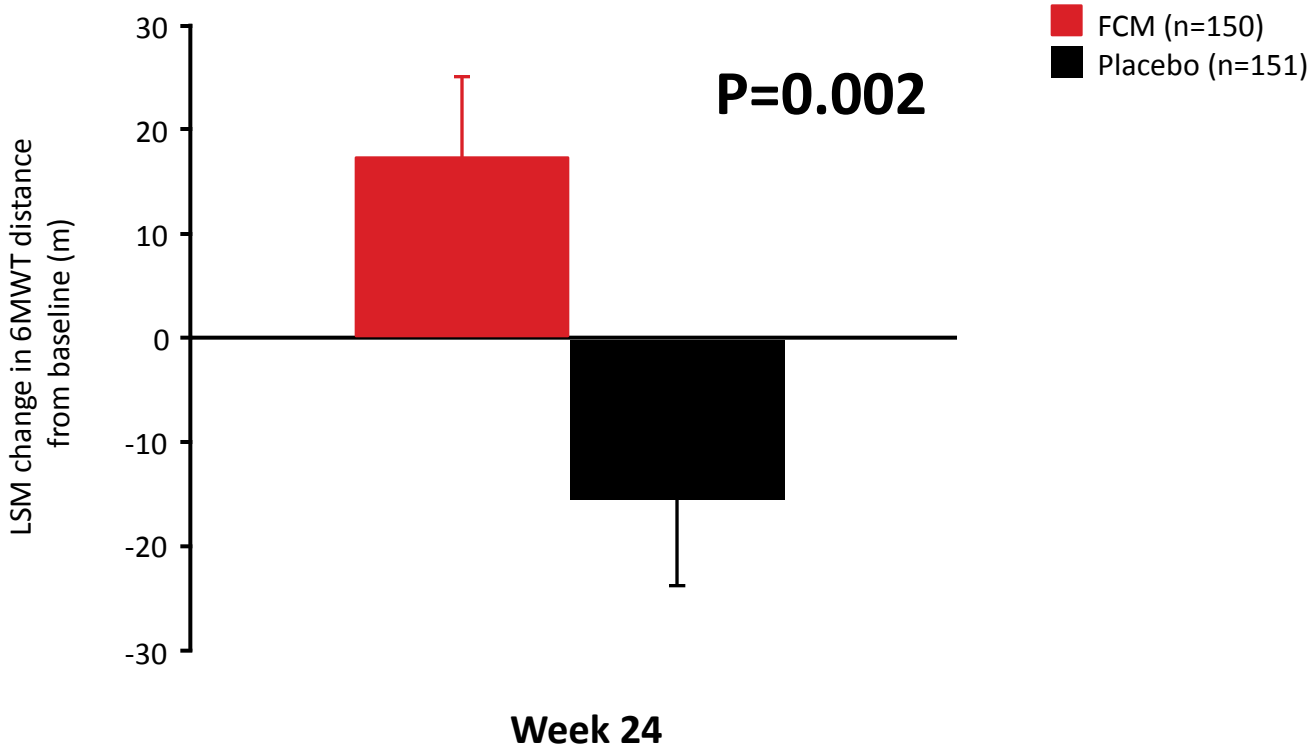
Figure 1 Importance of iron for functioning and survival across all levels of complexity of living structures.

European Heart Journal (2013) **34**, 816–826

CONFIRM-HF Primary endpoint: 6-minutes walking distance at week 24w

Iron deficiency: serum ferritin <100 ng/mL or 100-300 ng/mL if TSAT <20% with and without anaemia. 304 pts carboximaltosa férrica vs placebo, 52 weeks

- FCM improved 6MWT at week 24:
- FCM vs placebo: 33 ± 11 m (least squares mean ± standard error)



Ponikowski P et al. *ESC Heart Fail J* 2014

Secondary end-point: Outcome events

CONFIRM-HF

	FCM (N=150)		Placebo (N=151)			
End-point or event	**Total events (n)**	**Incidence/ (100 patient risk-year)**	**Total events (n)**	**Incidence/ (100 patient risk-year**	**Time to first event Hazard ratio 95% CI**	**P-value**
Death	12	12 (8.9)	14	14 (9.9)	0.89 (0.41 – 1.93)	0.77
Death for any CV reason	11	11 (8.1)	12	12 (8.5)	0.96 (0.42 – 2.16)	0.91
Hospitalisation	46	32 (26.3)	69	44 (37.0)	0.71 (0.45 – 1.12)	0.14
Hospitalisation for any CV reason	26	21 (16.6)	51	33 (26.3)	0.63 (0.37 – 1.09)	0.097
Hospitalisation due to worsening HF	**10**	**10 (7.6)**	**32**	**25 (19.4)**	**0.39 (0.19 – 0.82)**	**0.009**

FCM reduced the risk of recurrent hospitalisations due to worsening HF (post-hoc):

Incidence Rate Ratio (95% CI) – 0.30 (0.14-0.64), p=0.0019

Ponikowski P et al. *ESC Heart Fail J* 2014

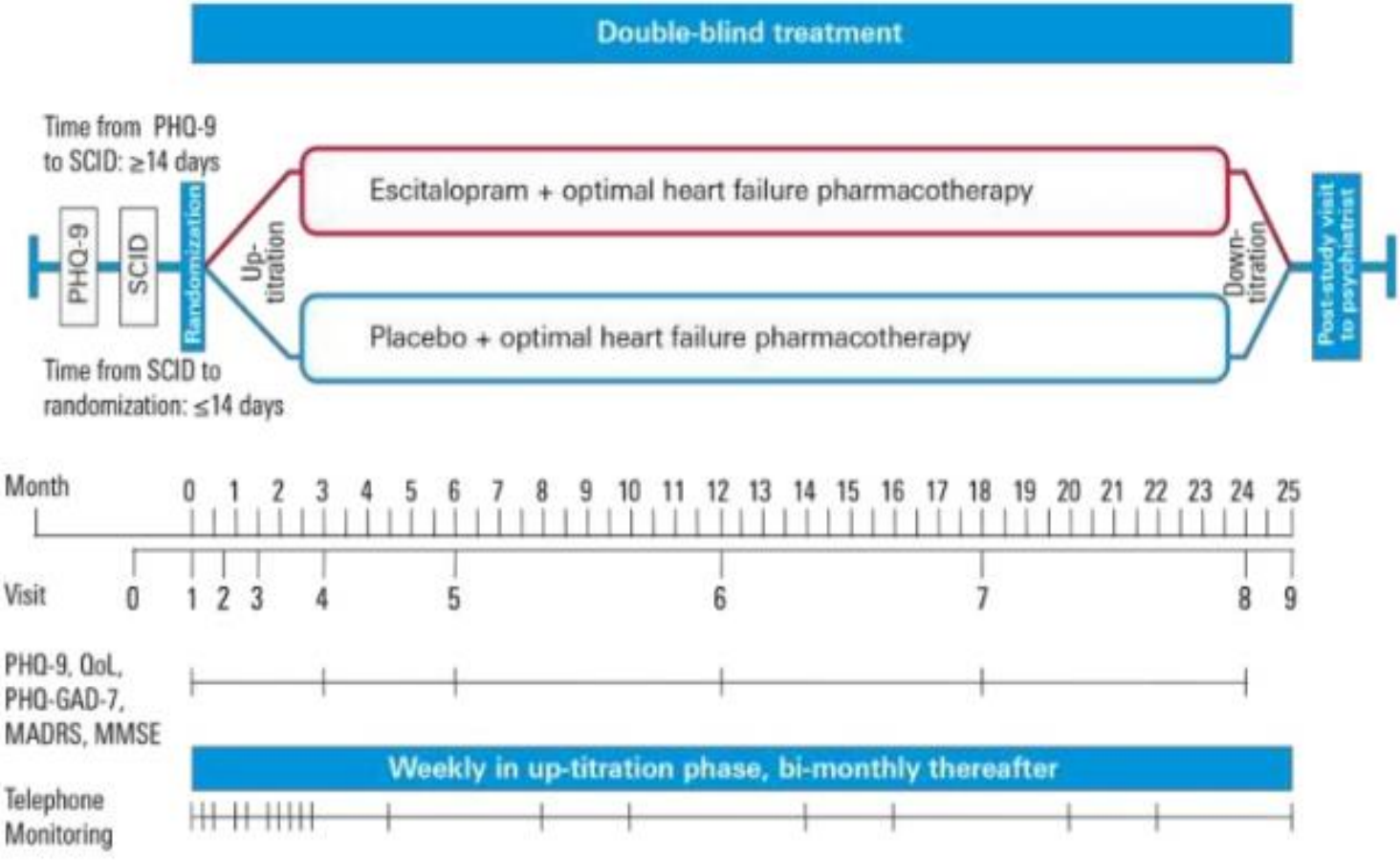
MOOD-HF Trial

ACC CONGRESS 2015 CHICAGO

Effects of selective serotonin re-uptake inhibition on **MO**rtality, m**O**rbidity and mood in **D**epressed **H**eart **F**ailure patients

Age ≥18 y, stable symptomatic systolic HF (NYHA II – IV), LV ejection fraction <45%. Current episode of major depression diagnosed by Structured Clinical Interview (SCID)

235 PTS, FU: 24 MONTHS



MOOD-HF Trial

ACC CONGRESS 2015 CHICAGO

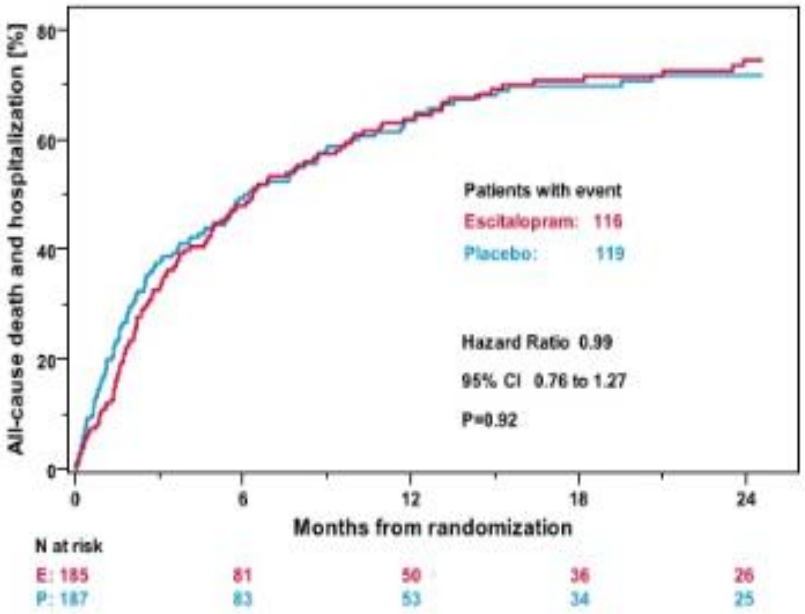
Effects of selective serotonin re-uptake inhibition on **MO**rtality, m**O**rbidity and mood in **D**epressed **H**eart **F**ailure patients

Total number of enrollees: 235

Follow-up: 24 months

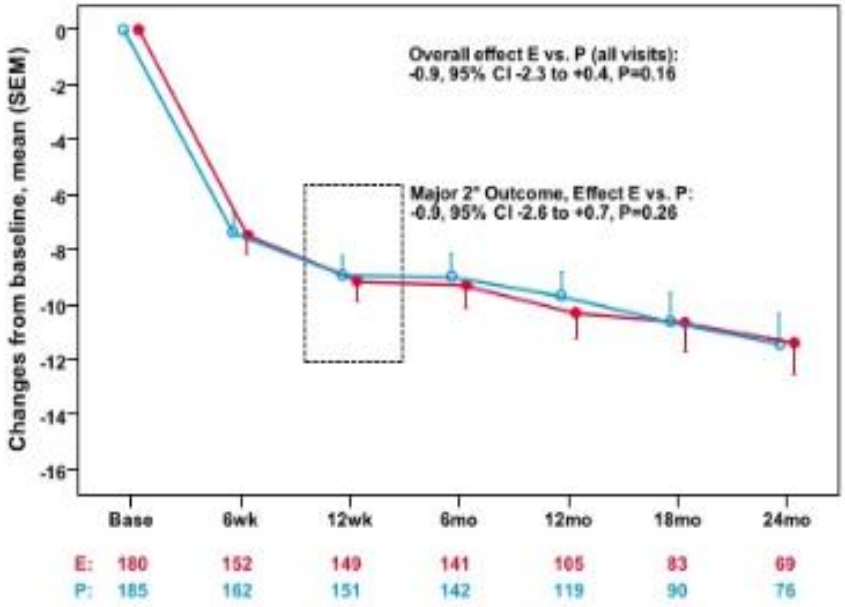
Primary Outcome

Time to all-cause death or hospitalization

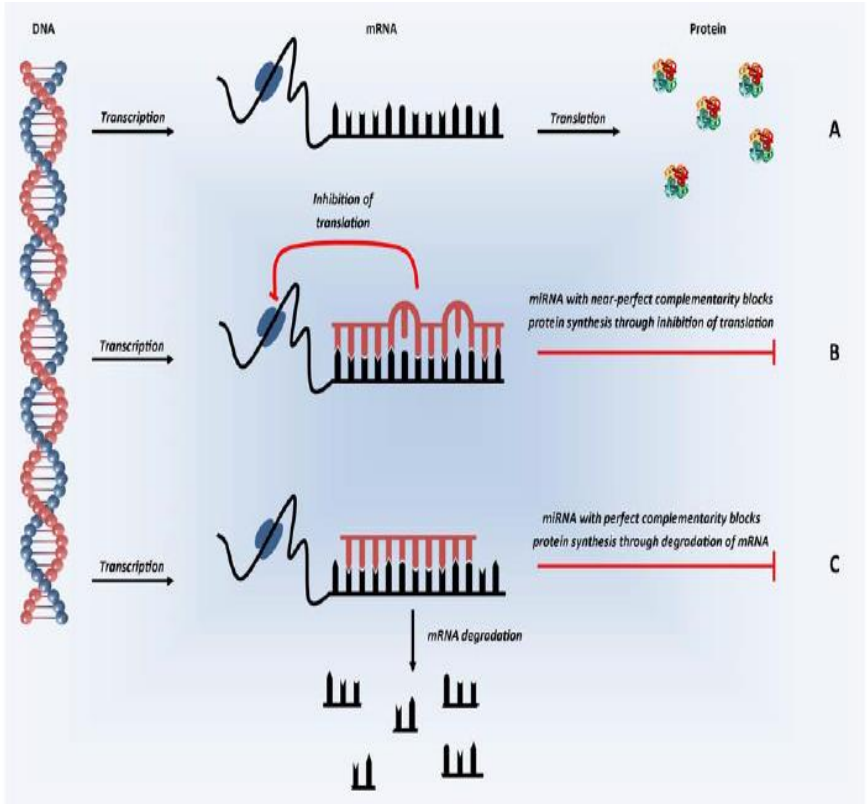


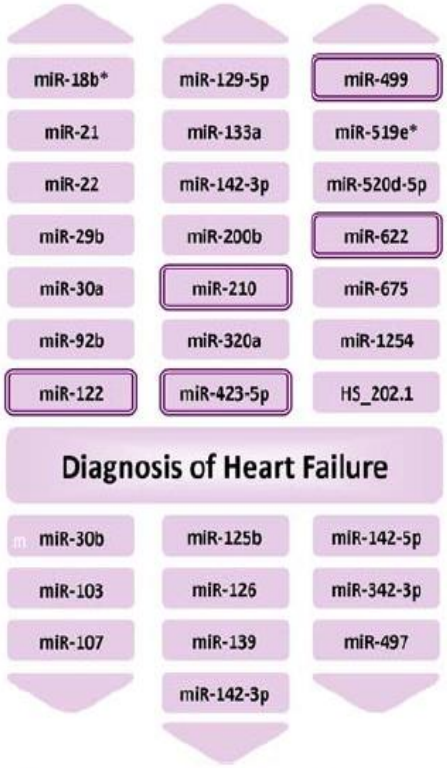
Major Secondary Outcome

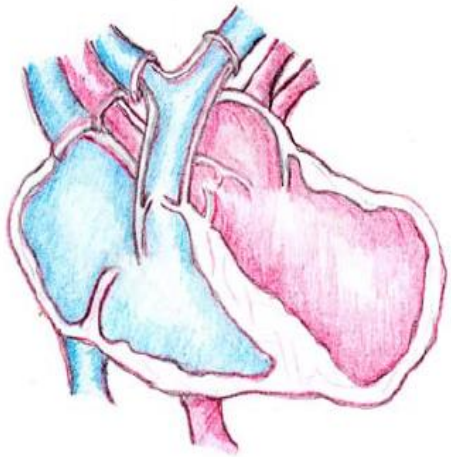
10- item Montgomery–Åsberg Depression Rating Scale



Nuevos conceptos prometedores aún no en la clínica: **Micro-RNAs**







Heart Failure

with a diagnosis of heart failure. MicroRNAs with a double border have been linked to heart failure I

Heart Online First, published on April 9, 2015 as 10.1136/heartjnl-2013-305402

Review

OPEN ACCESS

MicroRNAs in cardiovascular disease: an introduction for clinicians

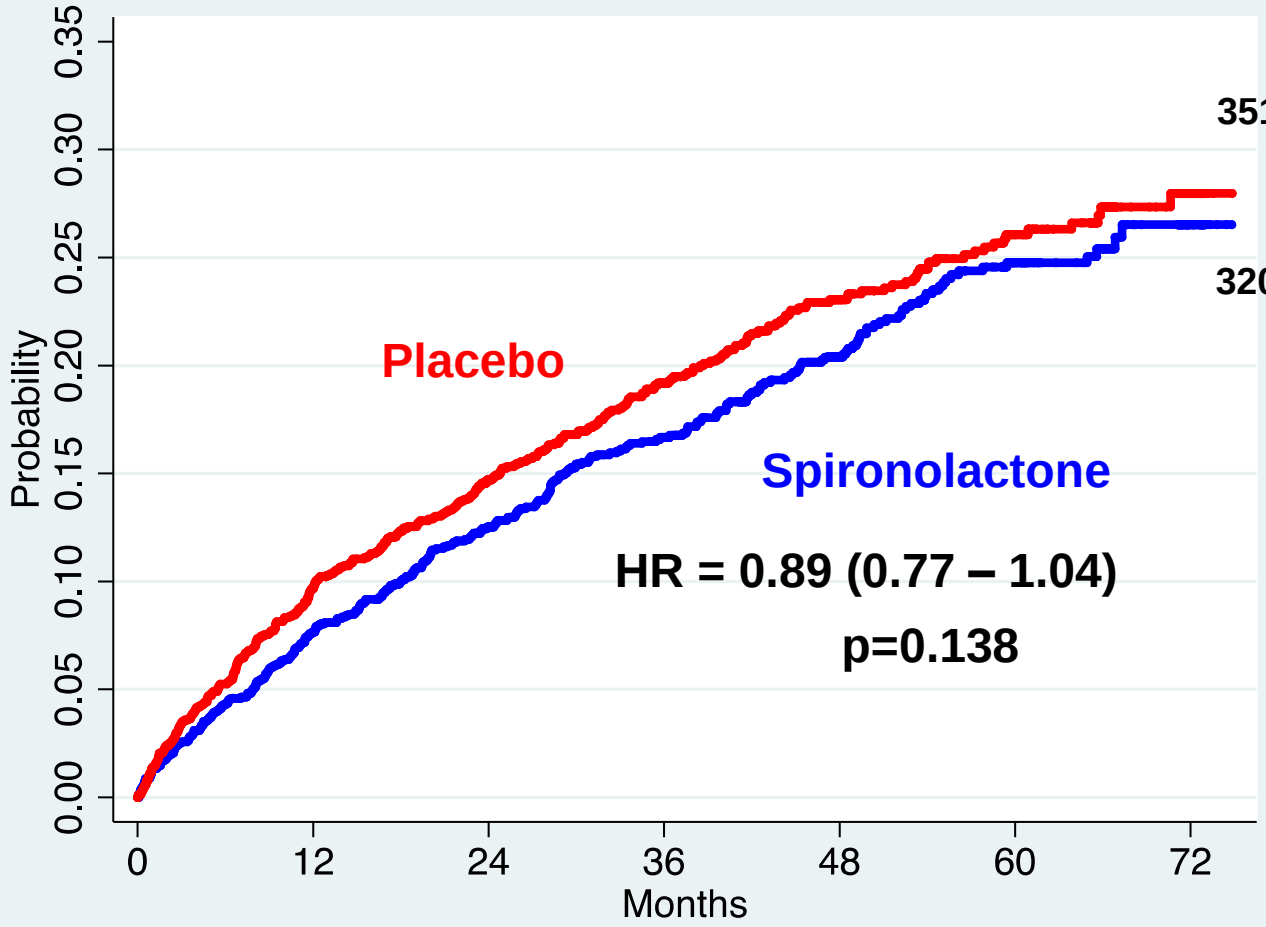
Simon P R Romaine,[1] Maciej Tomaszewski,[1,2] Gianluigi Condorelli,[1,2,3] Nilesh J Samani[1,2]

- 3. INSUFICIENCIA CARDÍACA CON FEVI PRESERVADA:

- Nuevos estudios neutros/negativos
- Nuevos conceptos:
* tipo de población diana "adecuada"
* nuevos conceptos fisiopatólogicos:
" *Coronariopatía y asincronía en HFPEF*"
- Estudios pendientes de Resultados

1° Outcome
(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)

TOPCAT
Funded by the NHLBI



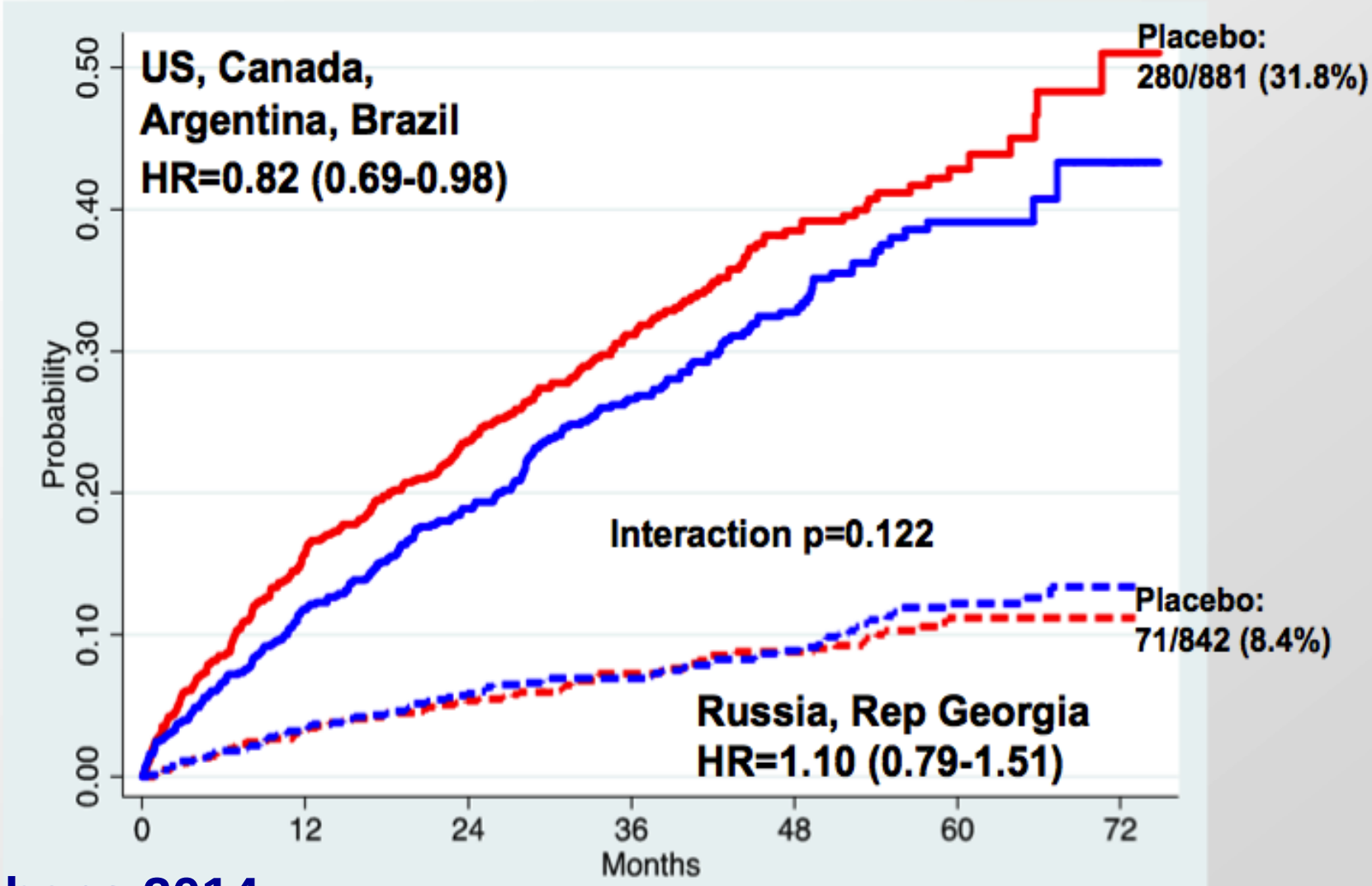
Number at risk

Spiro	1722	1502	1168	870	614	330	53
Placebo	1723	1462	1145	834	581	331	53

AHA 2013

Exploratory (post-hoc): Placebo vs. Spiro by region

TOPCAT
Funded by the NHLBI



Soluble GC stimulator for heart failure study – SOCRATES (Fase II)

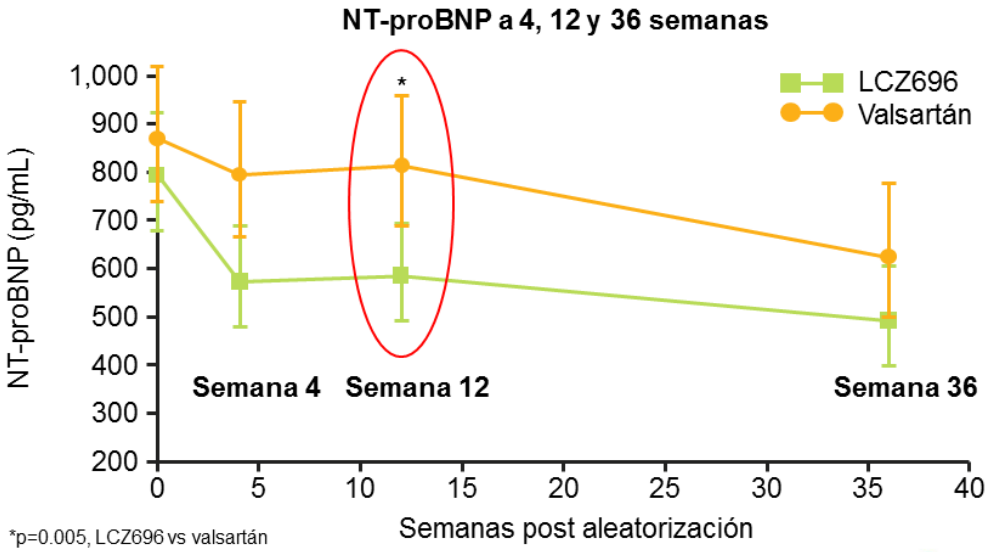
Population	**Worsening chronic HF with hospitalization for HF with treatment initiation upon clinical stabilization**	
	reduced ejection fraction (**HFrEF**, **SOCRATES-REDUCED**) LVEF <45%	preserved ejection fraction (**HFpEF**, **SOCRATES-PRESERVED**) LVEF ≥45%
Objective	Identify the optimal dose of the oral sGC stimulator BAY 1021189 in addition to standard HF therapy (HFrEF) or diuretic & comorbidity treatment (HFpEF) by characterizing safety, tolerability, pharmacodynamic effects and pharmacokinetics in patients with worsening chronic HFrEF / HFpEF	
Design	Prospective, randomized, placebo-controlled, double-blind, 5 parallel arm (2 continuous doses and 2 dose titration regimens of BAY 1021189 vs. placebo), multi-center dose finding phase II trial	
Treatment	12 weeks duration	
Number of subjects	513 subjects will be screened and 410 randomized	588 subjects will be screened and 470 randomized

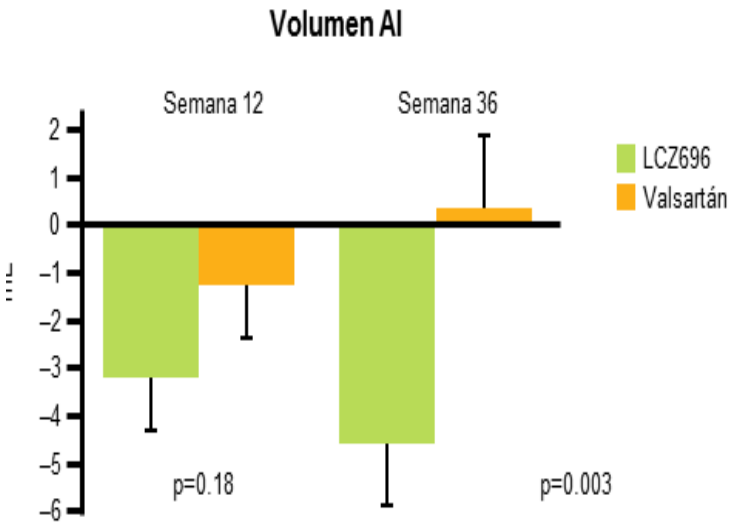
Eur J Heart Fail. 2014 Sep;16(9):1026-38

PARAMOUNT-HF: LCZ696 comparado con valsartán en pacientes con insuficiencia cardíaca crónica y fracción de eyección del ventrículo izquierdo **preservada (IC diastólica)**

n=308, 12 semanas

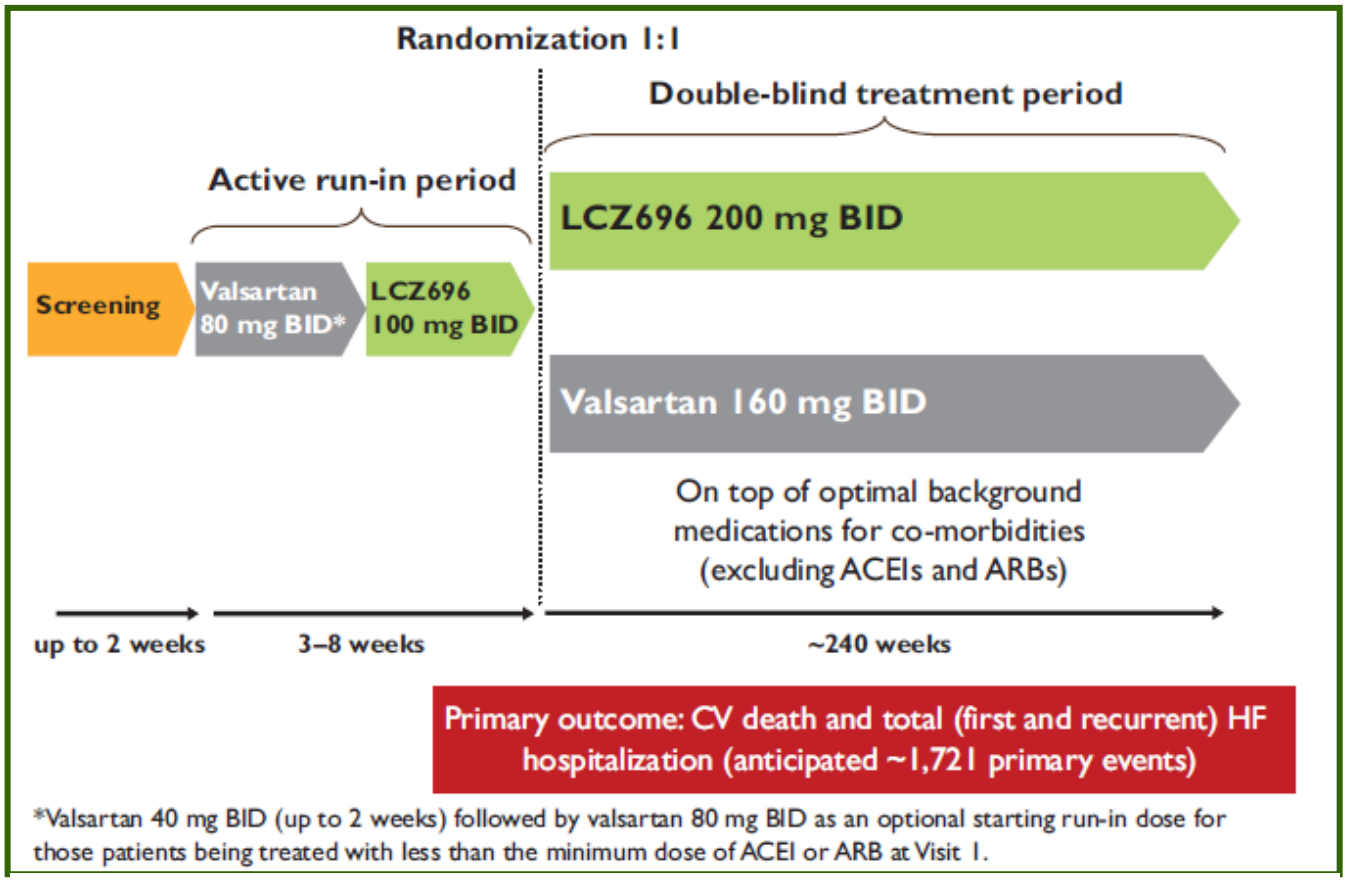
PARAMOUNT: reducción mantenida de NT-proBNP con LCZ696 a la Semana 36





Solomon et al. Lancet 2012;380:1387–95

PARAGONHF



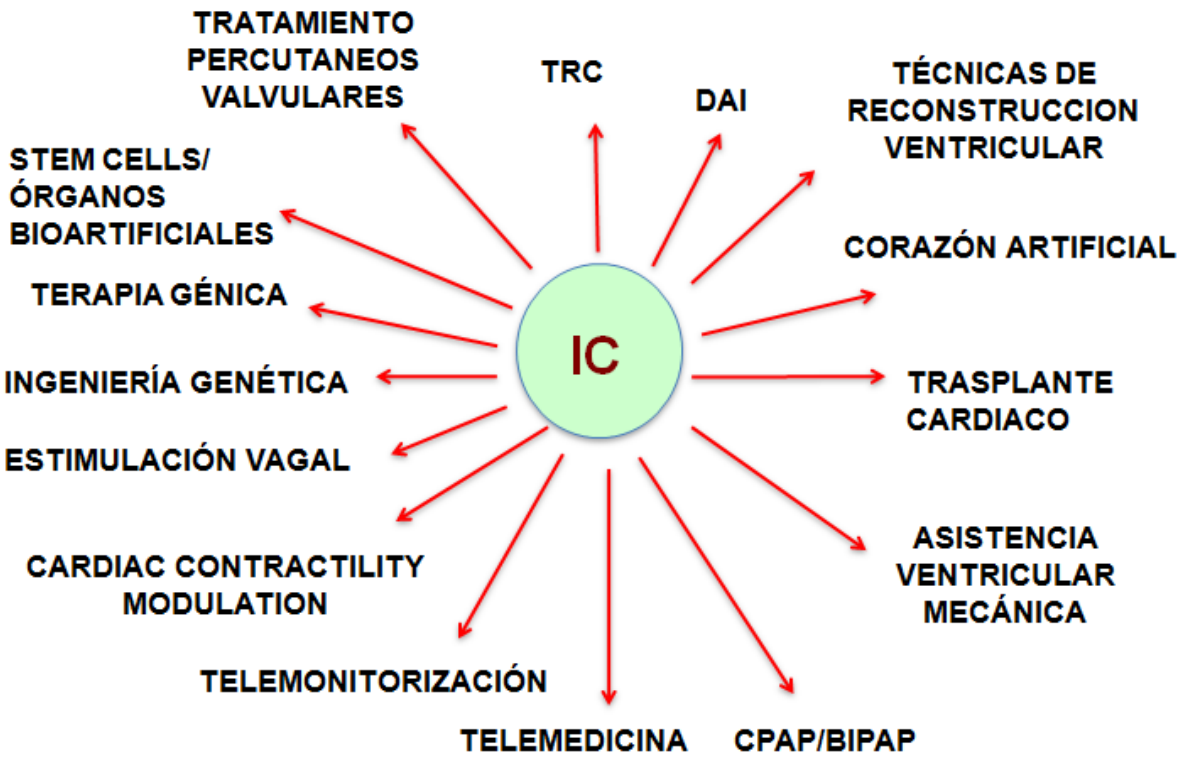
Primary objective

- The primary objective of this trial is to compare LCZ696 to valsartan in reducing the rate of the composite endpoint of CV death and total (first and recurrent) HF hospitalizations, in HF patients (NYHA Class II-IV) with preserved EF (left ventricular ejection fraction [LVEF] ≥45%).

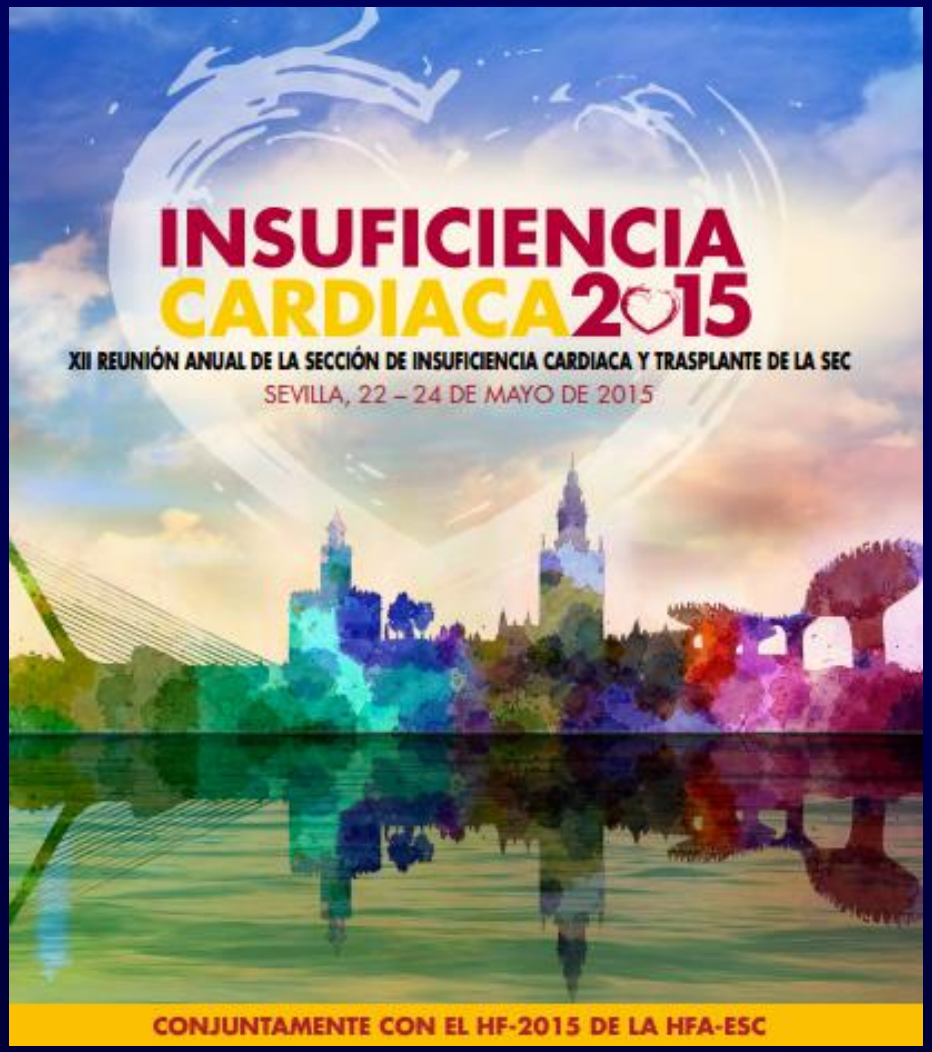
CONCLUSIONES: Novedades farmacológicas IC:

Muchas novedades en conceptos, dianas terapéuticas y fármacos…

…muchos avances tecnológicos en desarrollo…

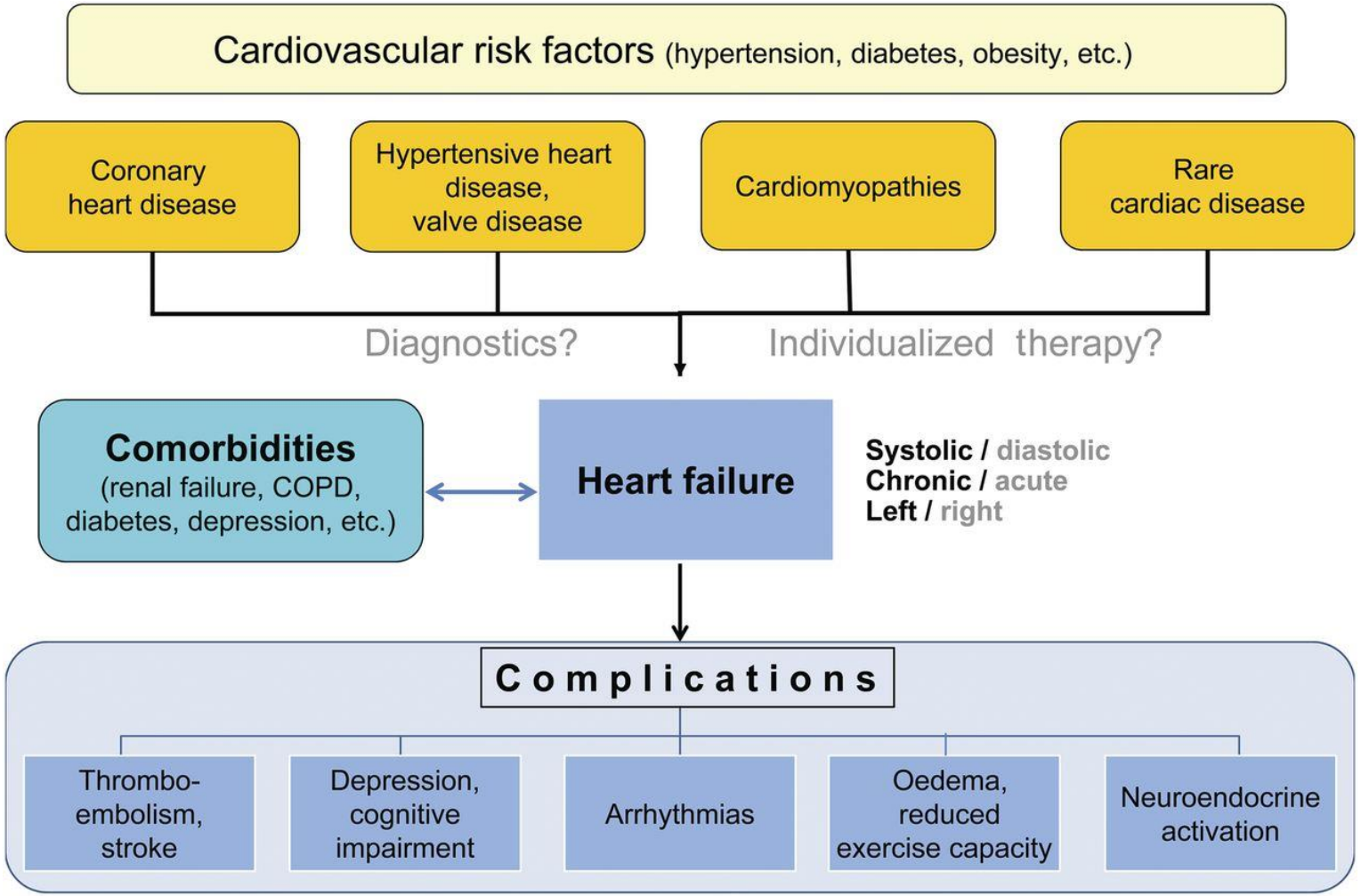


CONCLUSIONES: Novedades farmacológicas IC:



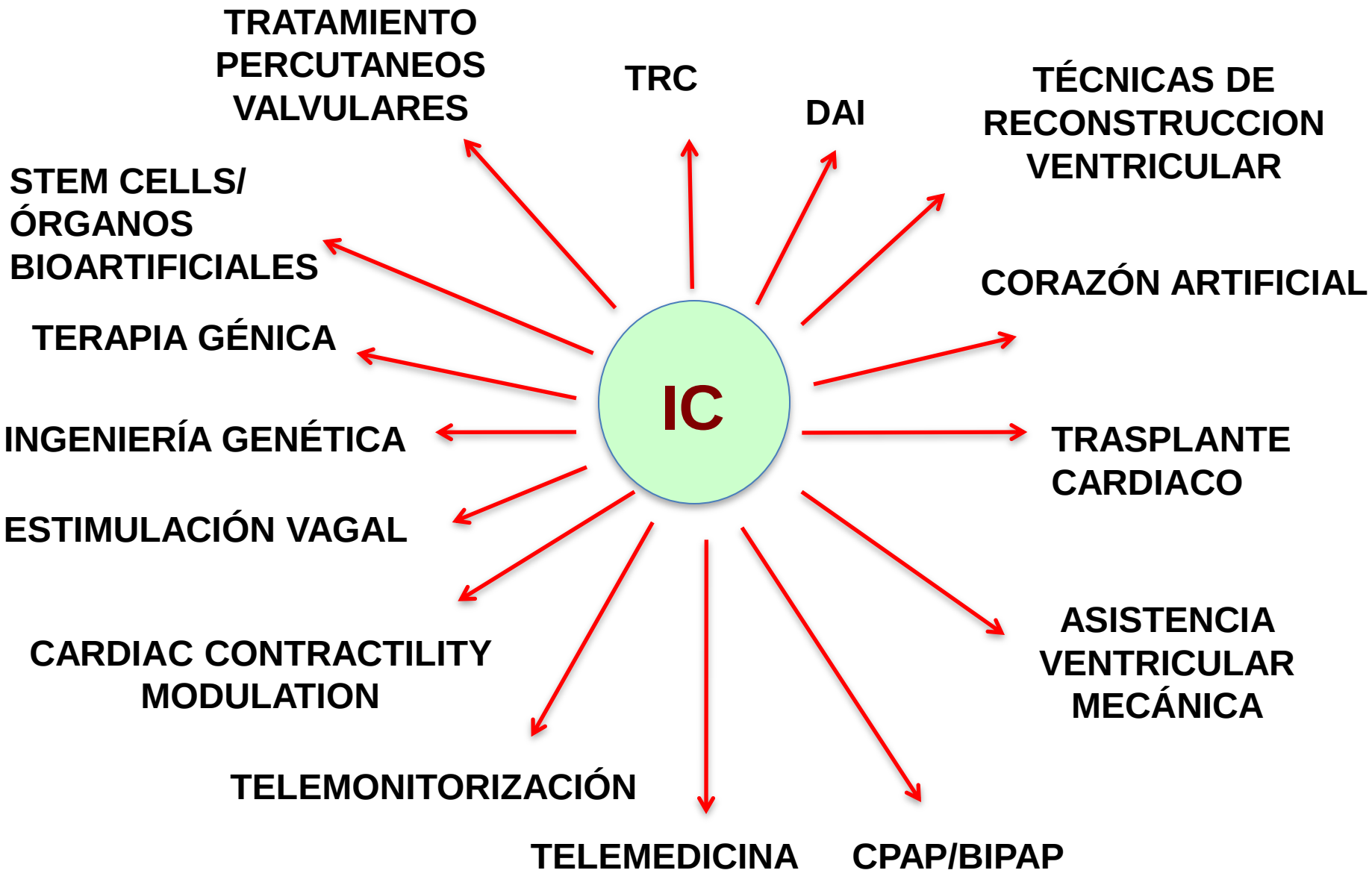
Os esperamos en Sevilla!

Patients may develop heart failure on the basis of various cardiovascular risk factors and heart diseases.



Georg Ertl, Frank Ruschitzka Eur Heart J 2014

AVANCES TECNOLÓGICOS EN INSUFICIENCIA CARDÍACA



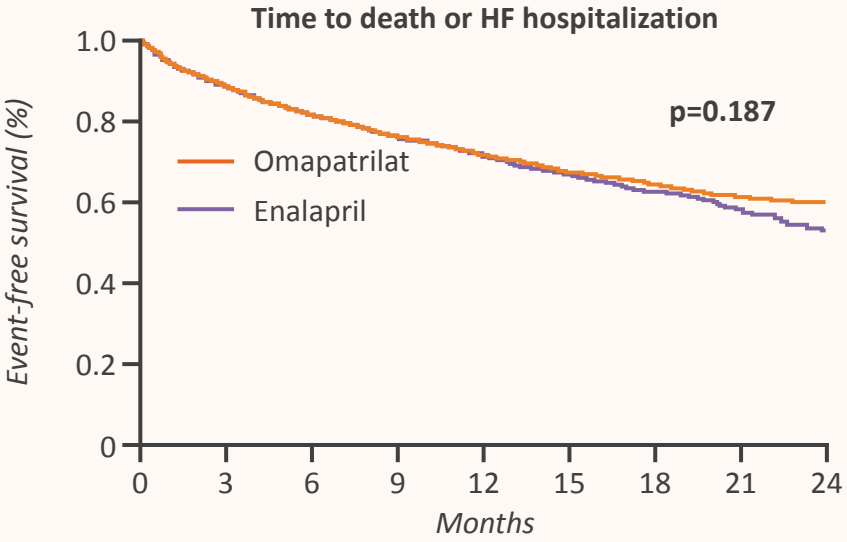
BCN Bio HF calculator es software para dispositivos móviles y para su ejecución es necesaria la siguiente configuración:

Para dispositivos con iOS: Necesario el Sistema Operativo iOS 7.0 o superior con conexión a Internet.

Para dispositivos Android: Necesario el Sistema Operativo Android 3.2 o superior con conexión a Internet.

OVERTURE study shows trends towards efficacy with dual NEP-ACEI but raises significant safety concerns (1/2)

In the OVERTURE study, the dual NEP-ACE inhibitor omapatrilat was compared with the ACEI enalapril in 5,770 patients with HFrEF for a mean of 14.5 months*

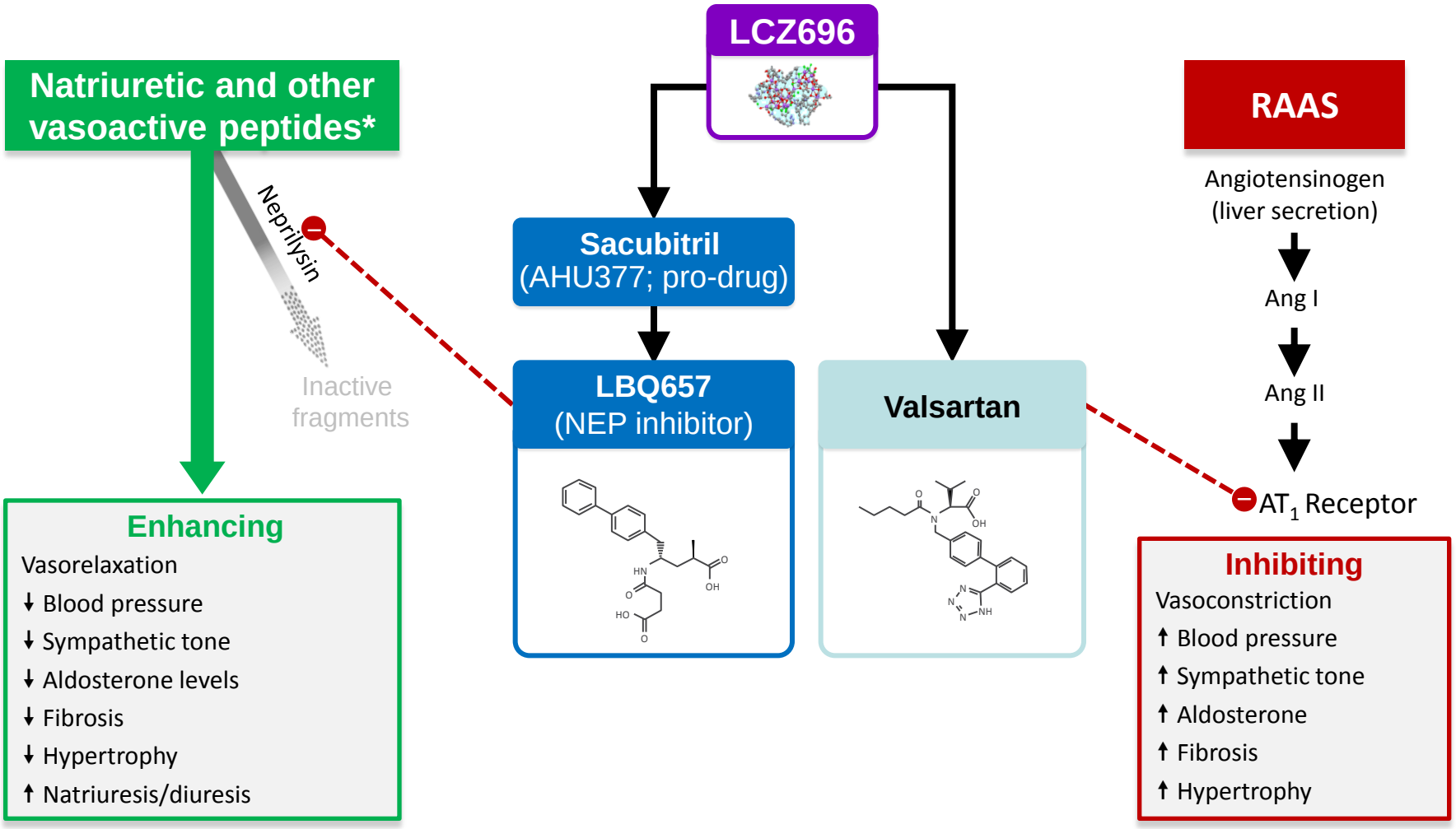


Development of omapatrilat was discontinued due to:

Lack of efficacy (see figure)
attributed to sub-optimal NEP and ACE inhibition over 24 hours due to the once-daily dosing regimen

Safety concern
unacceptable risk of angioedema (24 patients [0.8%] vs 14 patients [0.5%] for omapatrilat and enalapril, respectively). This was attributed to simultaneous NEP and ACE inhibition leading to elevated bradykinin levels, which are associated with cough and angioedema

LCZ696 simultaneously inhibits NEP (via LBQ657) and blocks the AT_1 receptor (via valsartan)



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

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

Fisiopatología de IC sistólica

El daño en miocitos cardiacos y matriz extracelular provoca cambios en el tamaño, la forma y la función del corazón y estrés en la pared cardíaca

↓

Sobreactivación del sistema neurohormonal

↓

Vasoconstricción, fibrosis, apoptosis, hipertrofia, alteraciones celulares y moleculares, miotoxicidad

↓

Remodelado inadecuado y empeoramiento progresivo de la función VI ↔ Alteraciones hemodinámicas, retención de sal y agua

↓

Morbilidad y mortalidad: arritmias, fallo de bomba ↔ **CÍRCULO VICIOSO FISIOPATOLÓGICO** ↔ **Síntomas IC:** disnea, edema, fatiga

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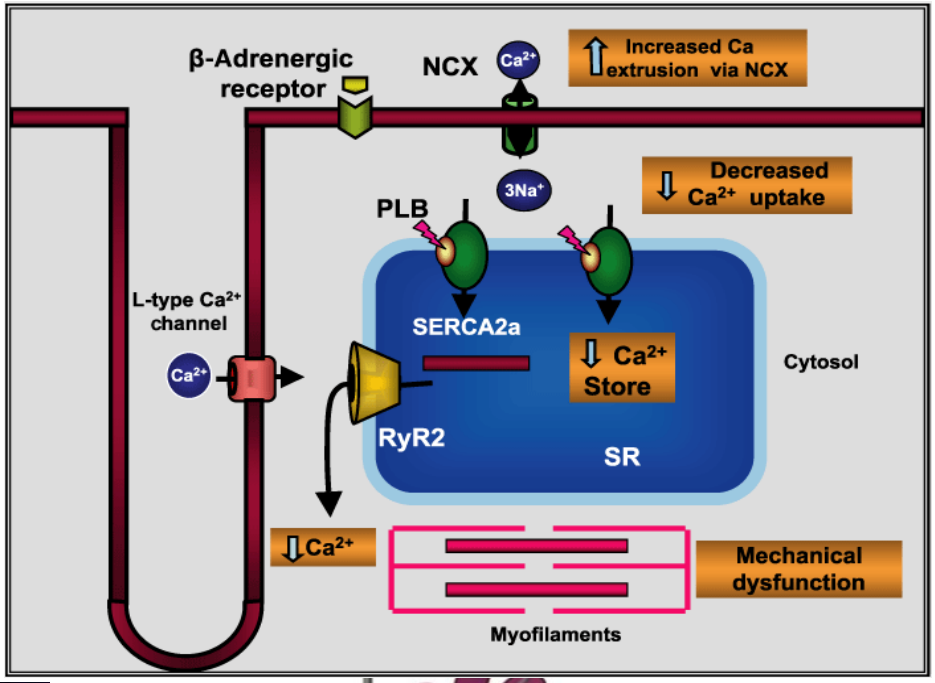
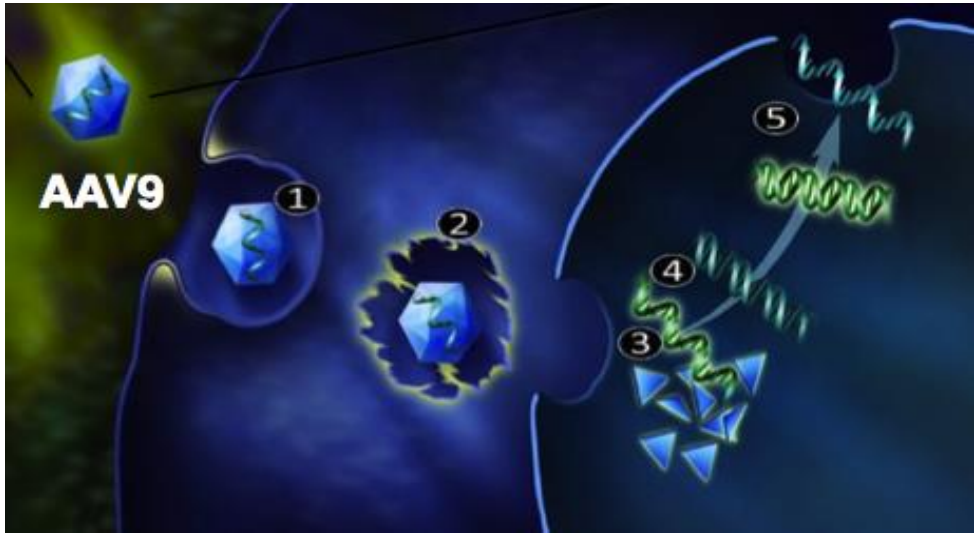
NEW TARGETS, NEW APPROACHES : CALCIUM REGULATION

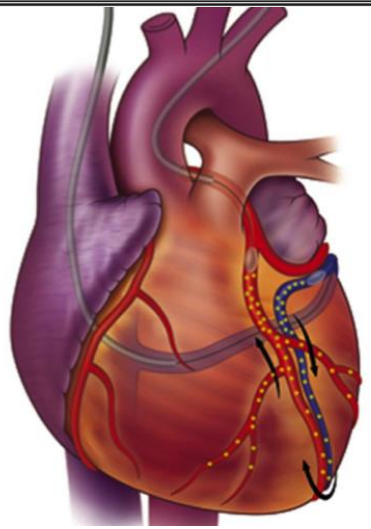
Sarcoplasmic reticulum Ca21-ATPase (SERCA2a).

-In HF, the level and the activity of SERCA2a is decreased, contributing directly to impaired cardiac contraction and relaxation.

- It has been shown that increasing the activity of SERCA2a via gene transfer increases contractility in isolated failing human cardiac
myocytes and leads to an improvement in cardiac function and metabolism in animal models of HF







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Design of a Phase 2b Trial of Intracoronary Administration of AAV1/SERCA2a in Patients With Advanced Heart Failure

The CUPID 2 Trial (Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease Phase 2b)

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Resultados: 2015