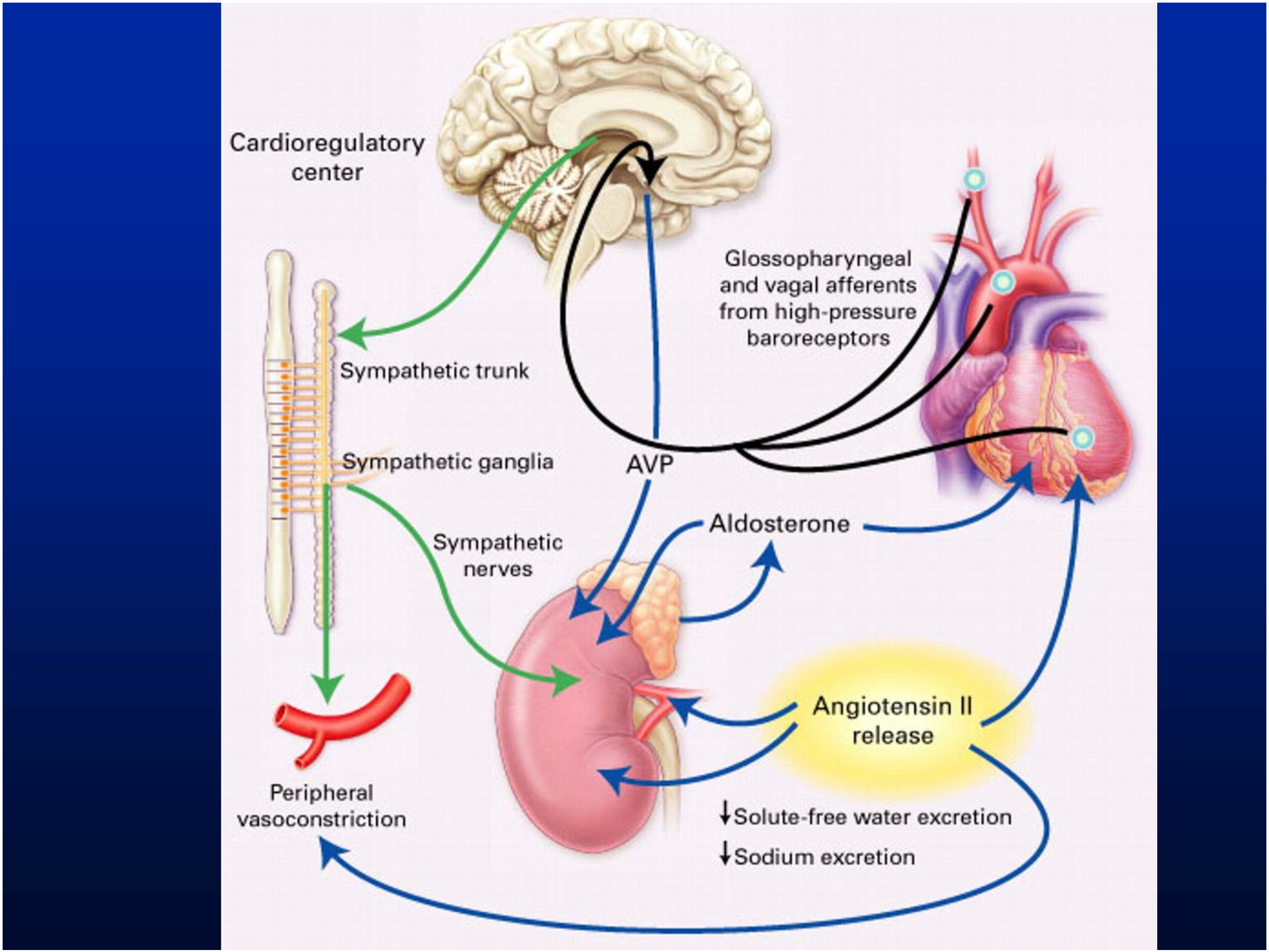
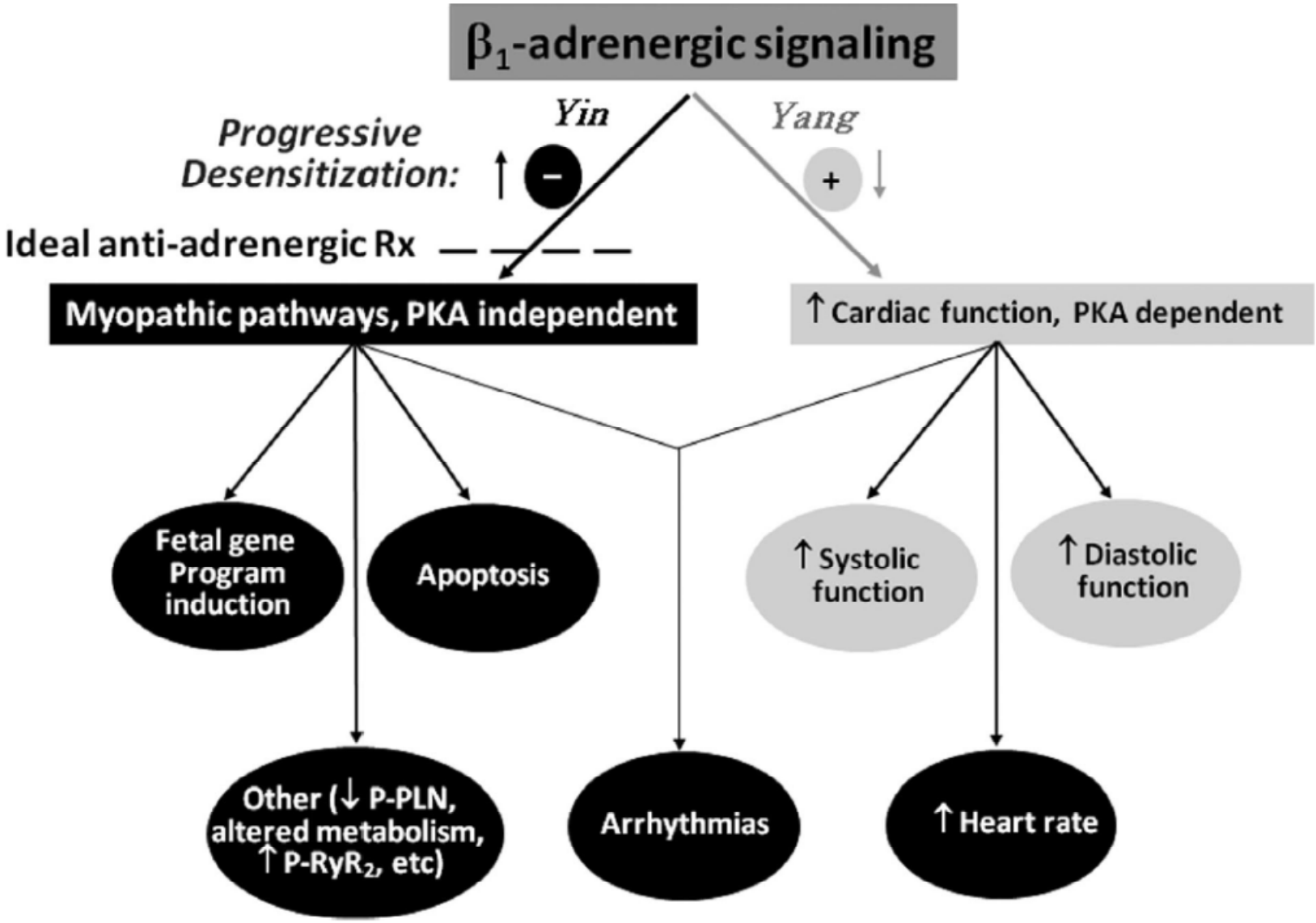
Ivabradina i Eplerenona en Insuficiència Cardíaca

Félix Pérez Villa

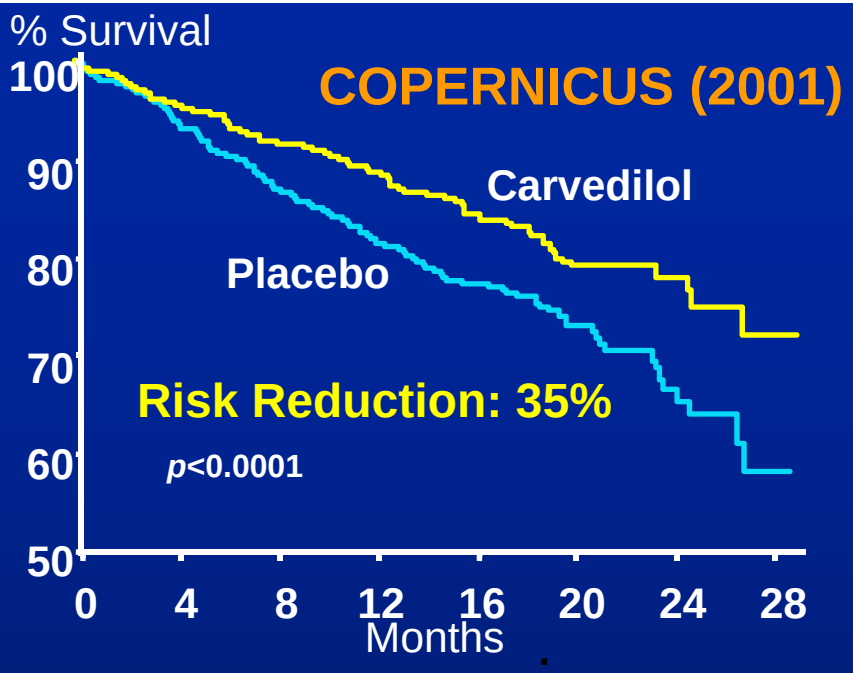
Unitat
d'Insuficiència Cardíaca

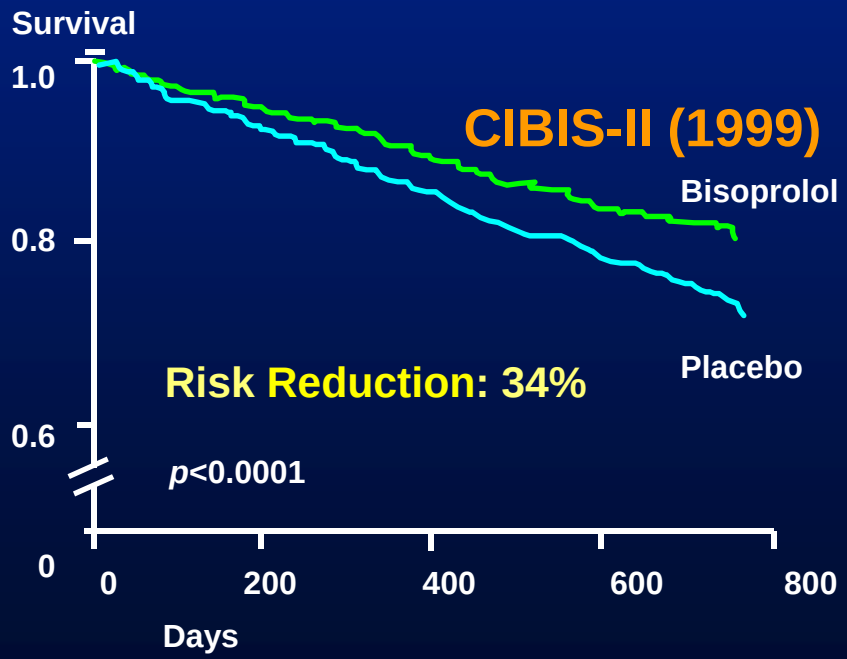
Hospital Clínic

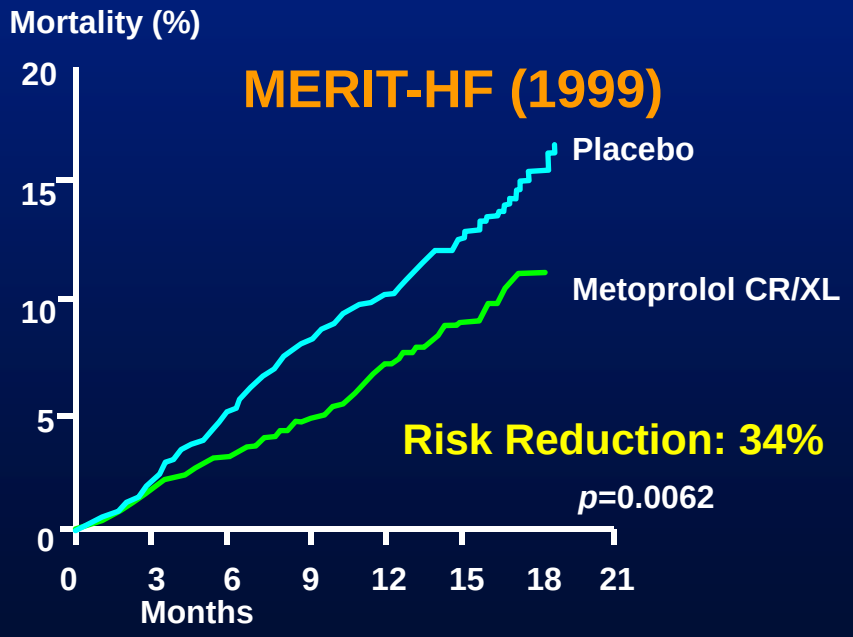

Cardioregulatory center
Glossopharyngeal and vagal afferents from high-pressure baroreceptors
Sympathetic trunk
Sympathetic ganglia
AVP
Sympathetic nerves
Aldosterone
Angiotensin II release
Peripheral vasoconstriction
↓Solute-free water excretion
↓Sodium excretion


β1-adrenergic signaling
Yin
Yang
Progressive Desensitization:
−
+
Ideal anti-adrenergic Rx
Myopathic pathways, PKA independent
↑ Cardiac function, PKA dependent
Fetal gene Program induction
Apoptosis
↑ Systolic function
↑ Diastolic function
Other (↓ P-PLN, altered metabolism, ↑ P-RyR2, etc)
Arrhythmias
↑ Heart rate

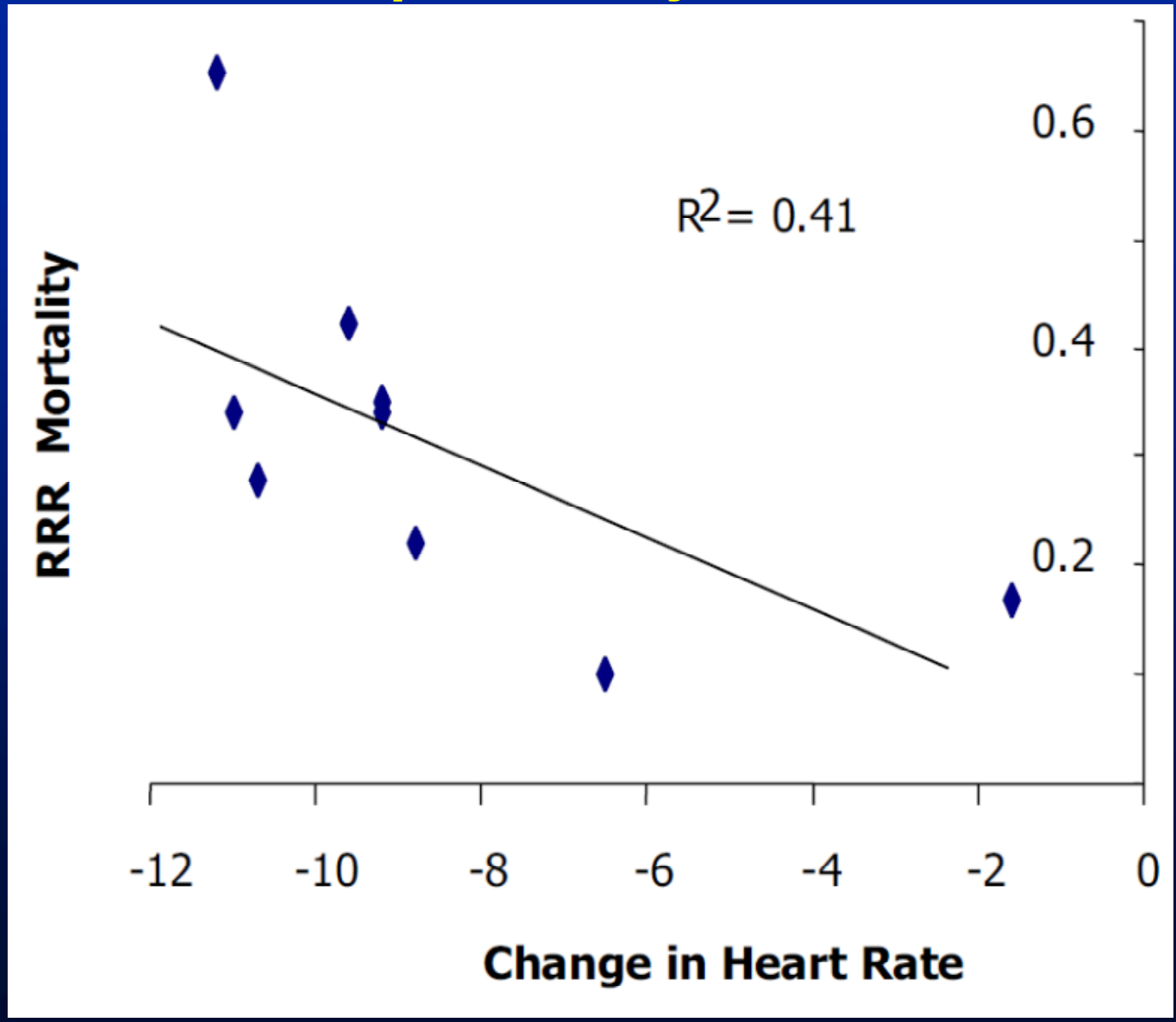
β blockers in HF
All-cause Mortality





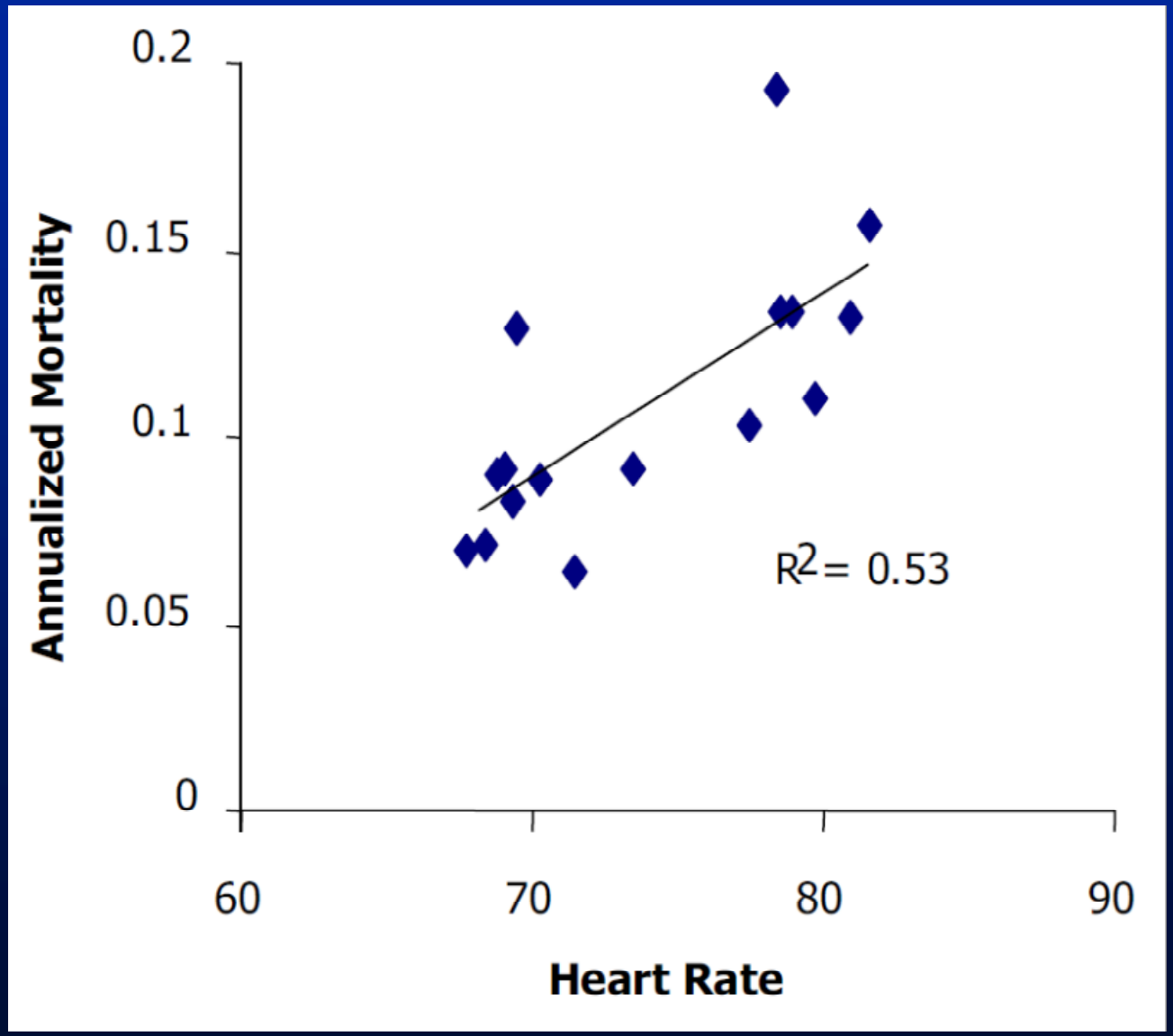


Correlación entre cambio en FC con Betabloqueantes y Mortalidad



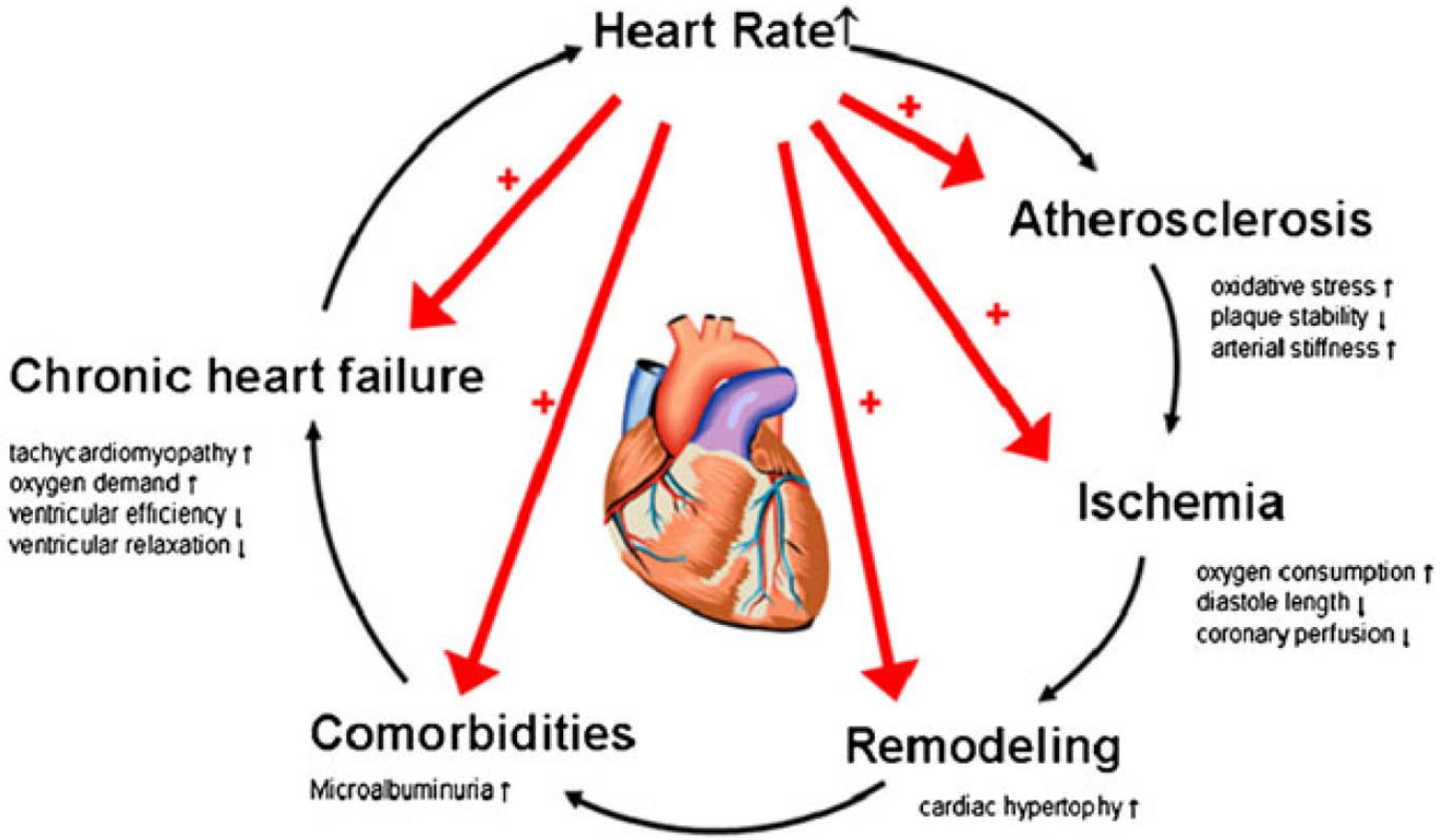
Flannery. Am J Cardiol 2008

Correlación entre FC con Betabloqueantes y Mortalidad



Flannery. Am J Cardiol 2008

Heart Rate in Cardiovascular Pathophysiology



Clin Res Cardiol 2011;100:11

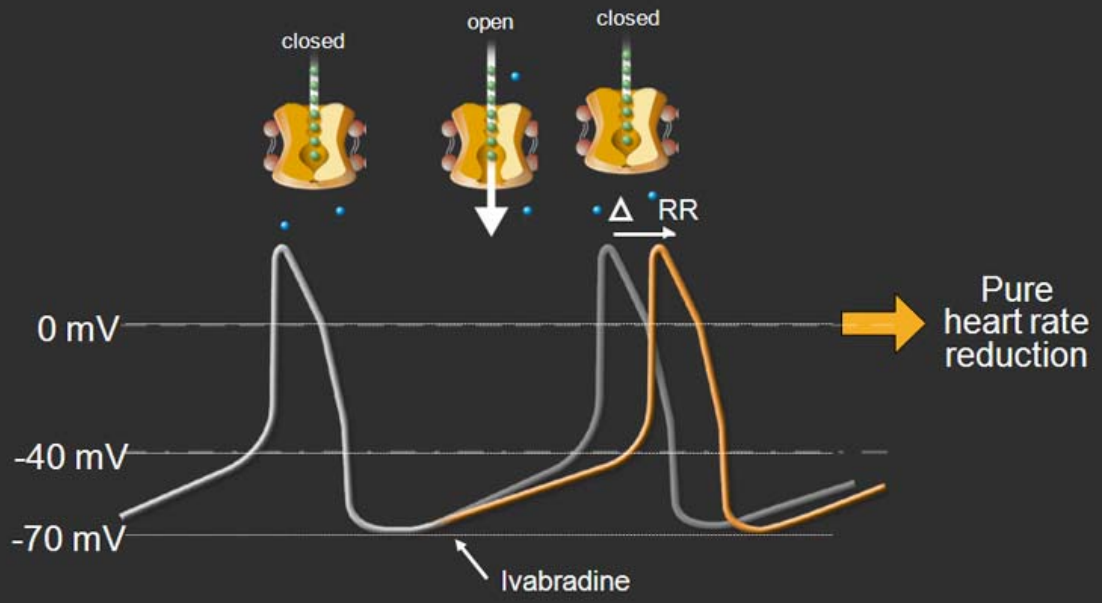
Concepto:

- **“La Frecuencia Cardiaca no es un marcador de riesgo, sino un factor de riesgo en Insuficiencia Cardiaca”**

Hipótesis:

- **“Reducir exclusivamente la Frecuencia Cardiaca mejora el pronóstico en Insuficiencia Cardiaca”**

Ivabradine: pure heart rate reduction



I_f inhibition reduces the diastolic depolarization slope, and thereby lowers heart rate

Thollon C. *Brit J Pharmacol*. 1994;112:37-42.

Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

*Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators**

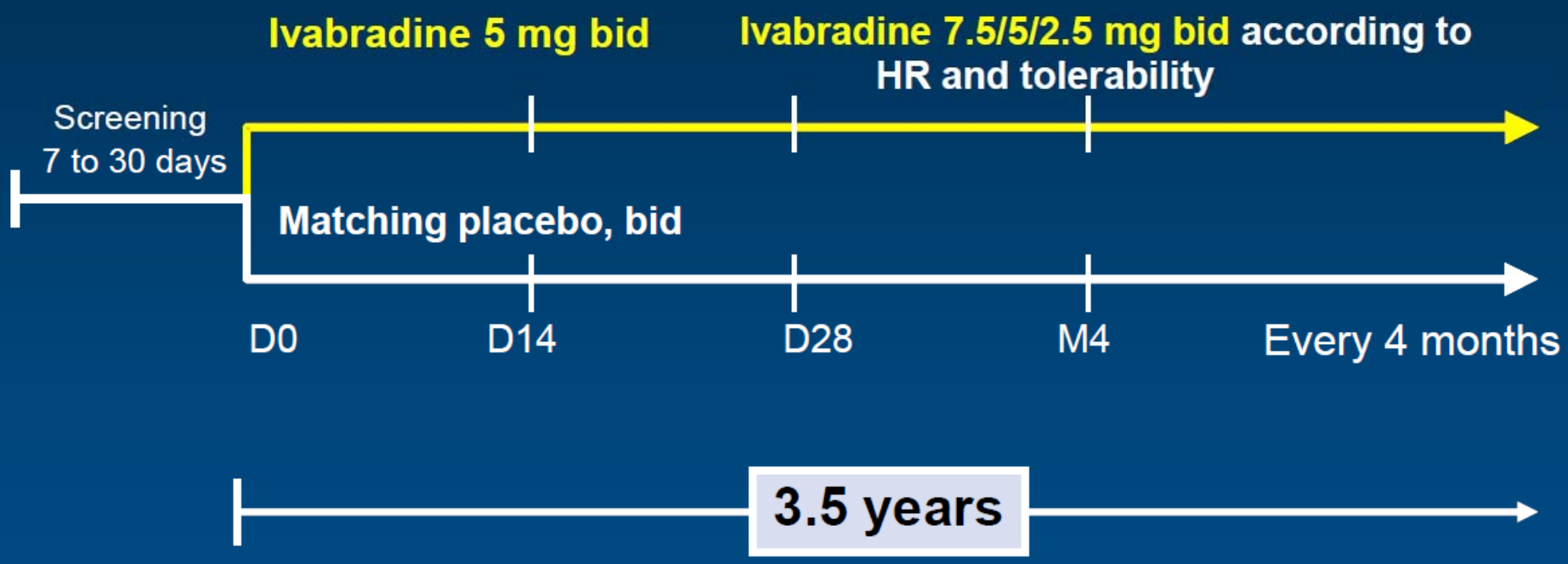
Lancet 2010; 376: 875–85

Inclusion criteria

- ≥18 years
- Class II to IV NYHA heart failure
- Ischaemic/non-ischaemic aetiology
- LV systolic dysfunction (EF ≤35%)
- Heart rate ≥70 bpm
- Sinus rhythm
- Documented hospital admission for worsening heart failure ≤12 months

Swedberg K, et al. *Eur J Heart Fail.* 2010;12:75-81.

Study design

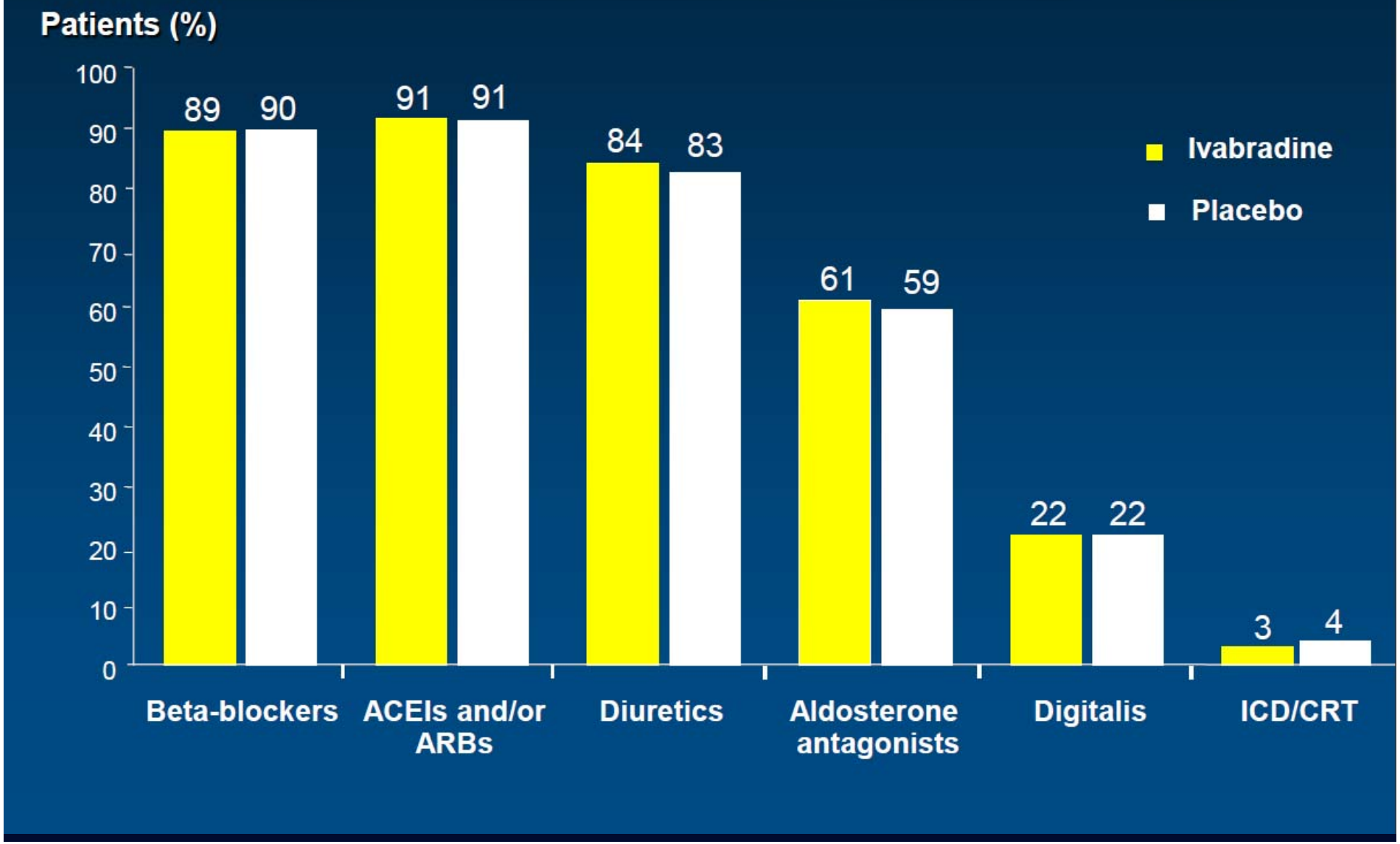


Swedberg K, et al. *Eur J Heart Fail.* 2010;12:75-81.

Baseline characteristics

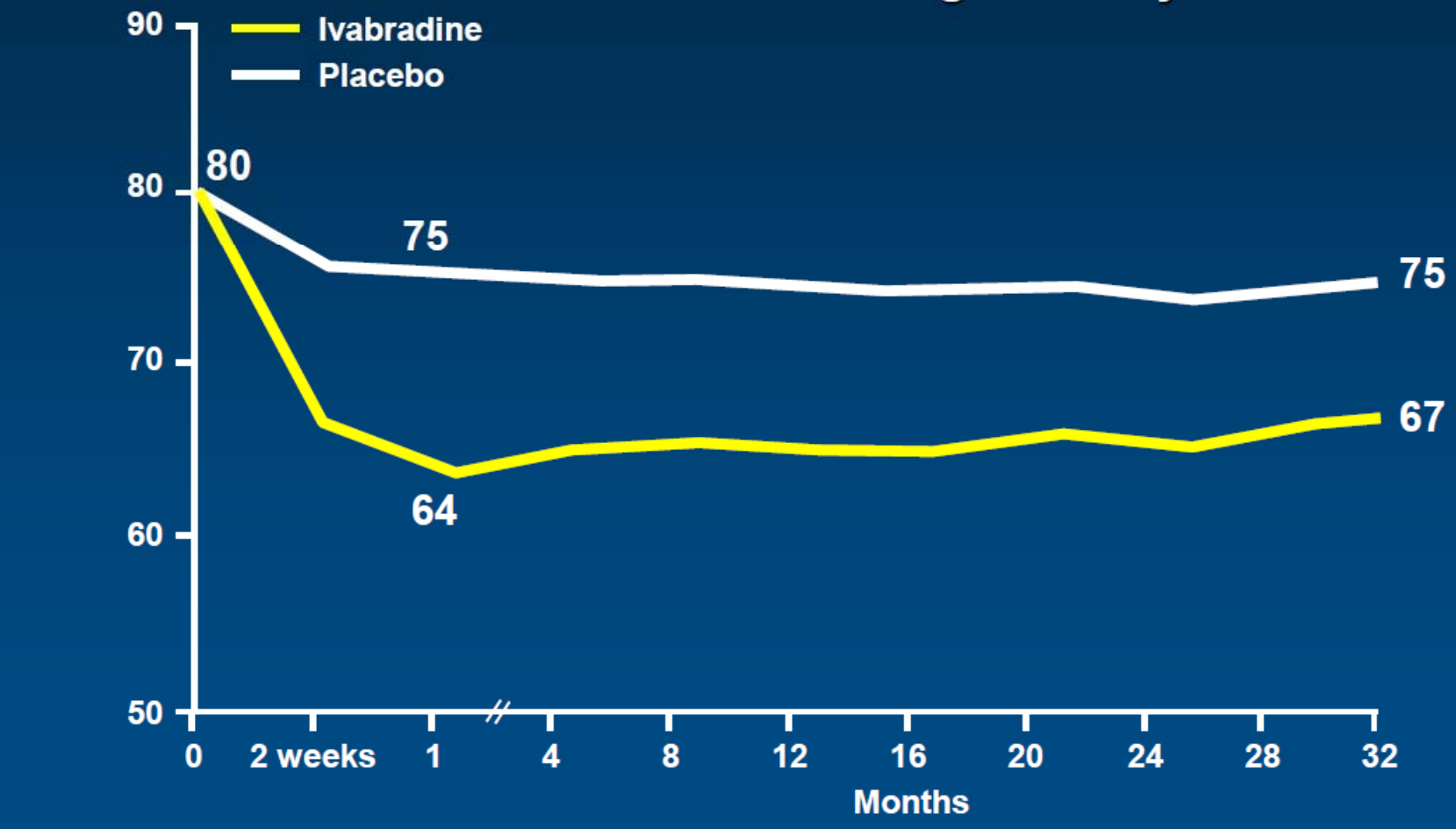
	Ivabradine	Placebo
	3241	3264
Mean age, y	60.7	60.1
Male, %	76	77
Ischaemic aetiology, %	68	67
NYHA II, %	49	49
NYHA III/IV, %	51	51
Previous MI, %	56	56
Diabetes, %	30	31
Hypertension, %	67	66

SHIFT Chronic HF background treatment



Mean heart rate reduction

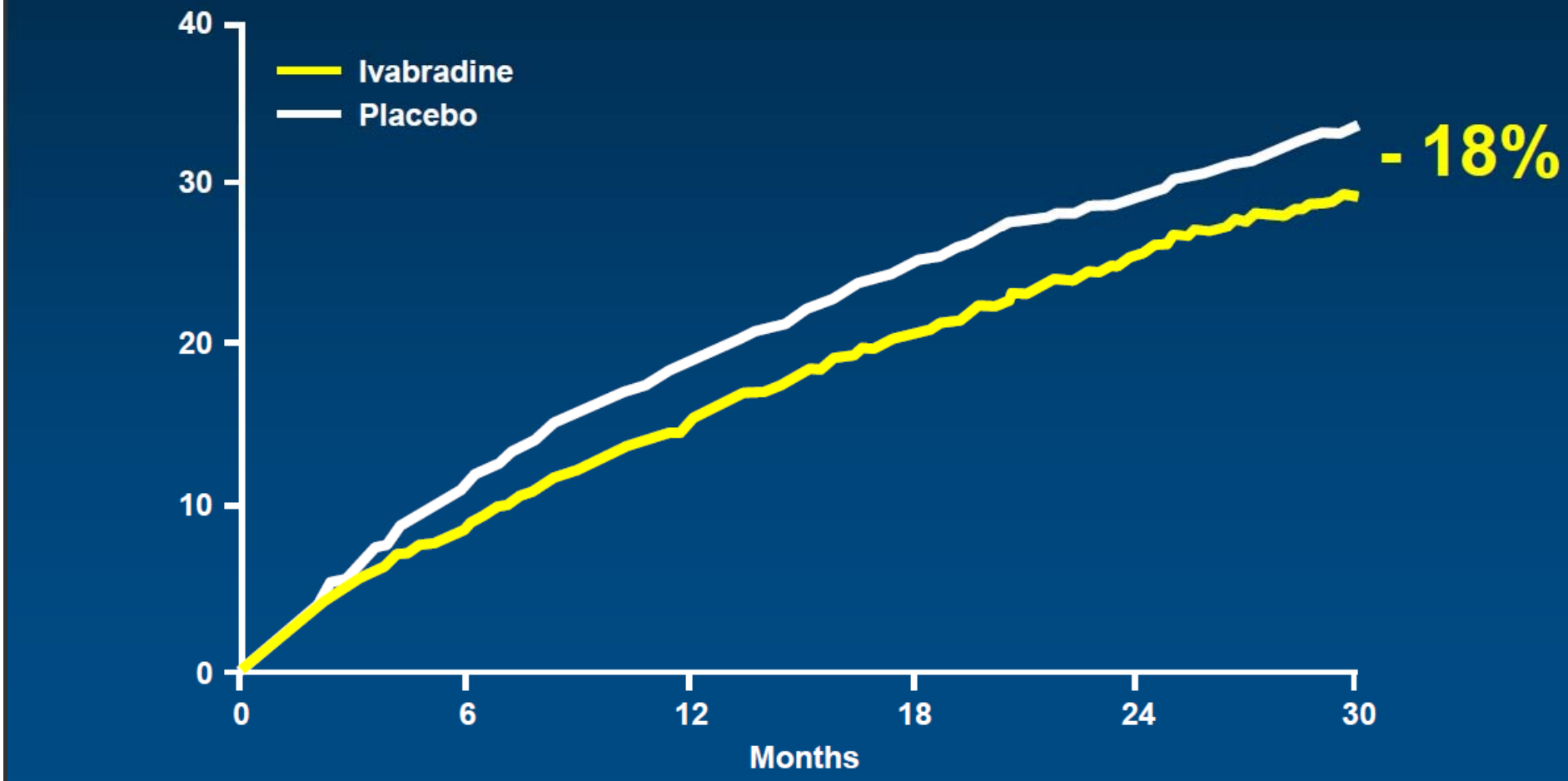
Mean ivabradine dose: 6.4 mg bid at 1 month
6.5 mg bid at 1 year



Primary composite endpoint

Ivabradine n=793 (14.5%PY) Placebo n=937 (17.7%PY)

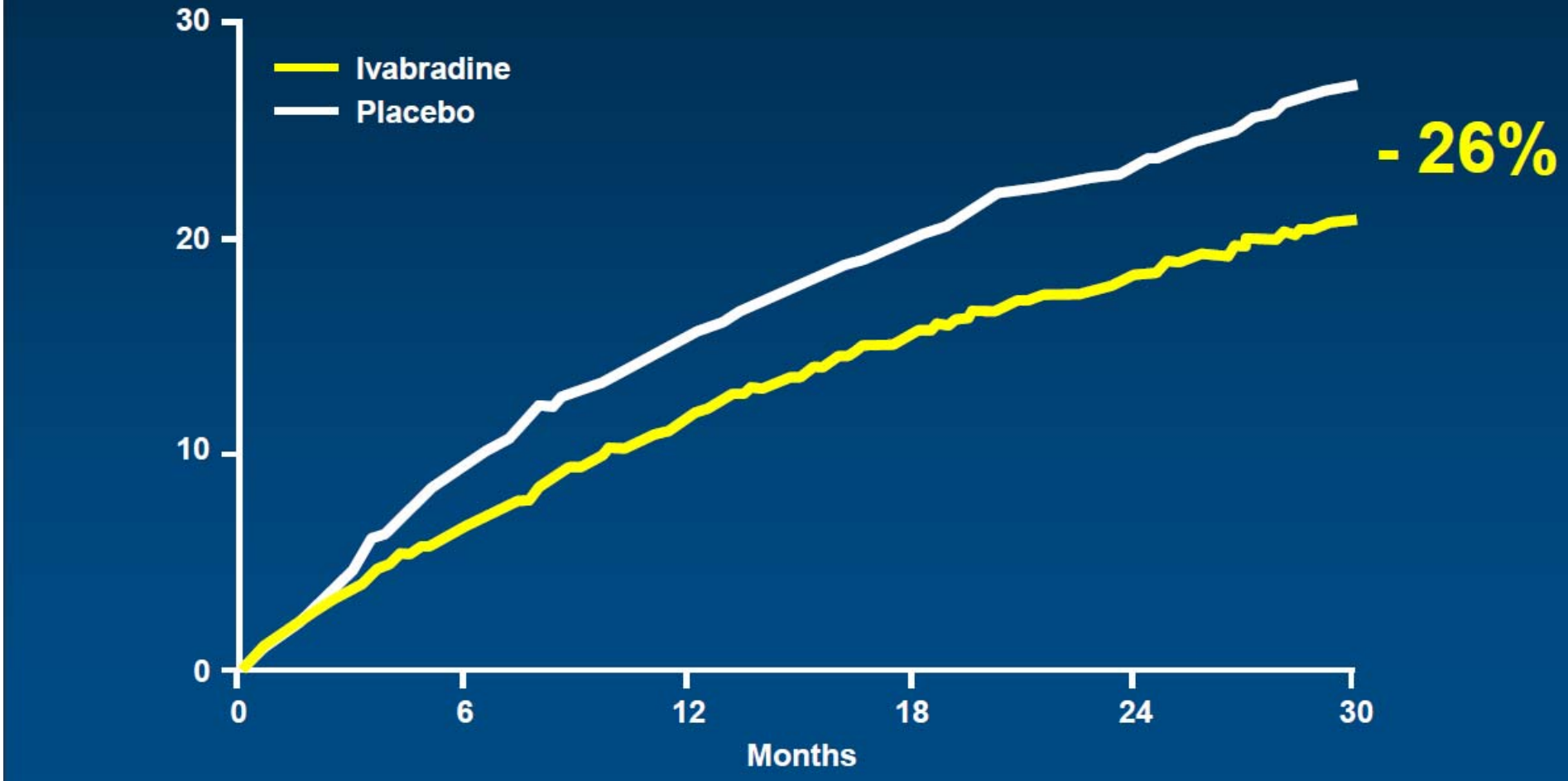
HR = 0.82 [95% CI 0.75-0.90] $p<0.0001$



Hospitalization for heart failure

Ivabradine n=514 (9.4%PY) Placebo n=672 (12.7%PY)

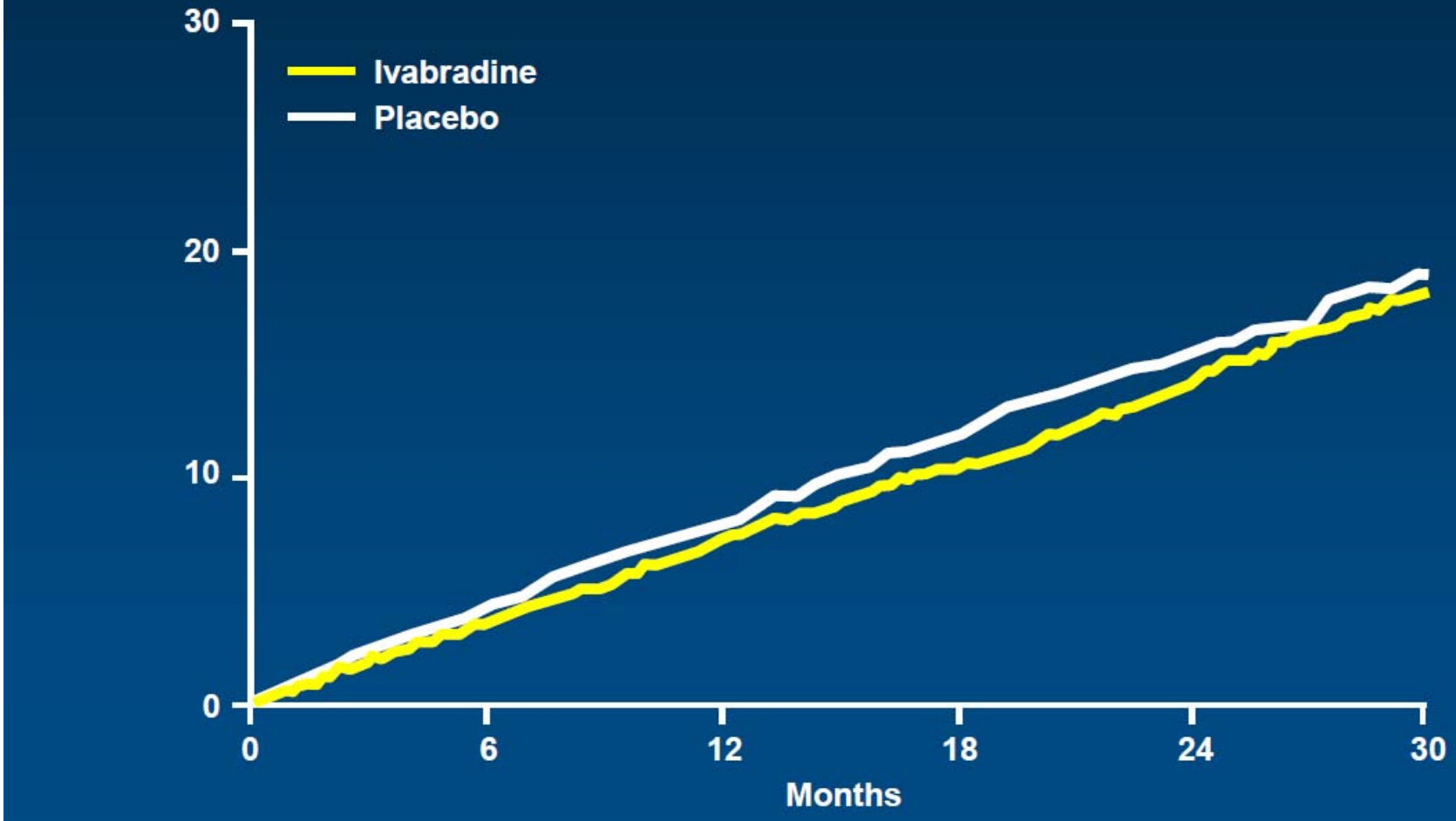
HR = 0.74 [95% CI 0.66-0.83] $p<0.0001$



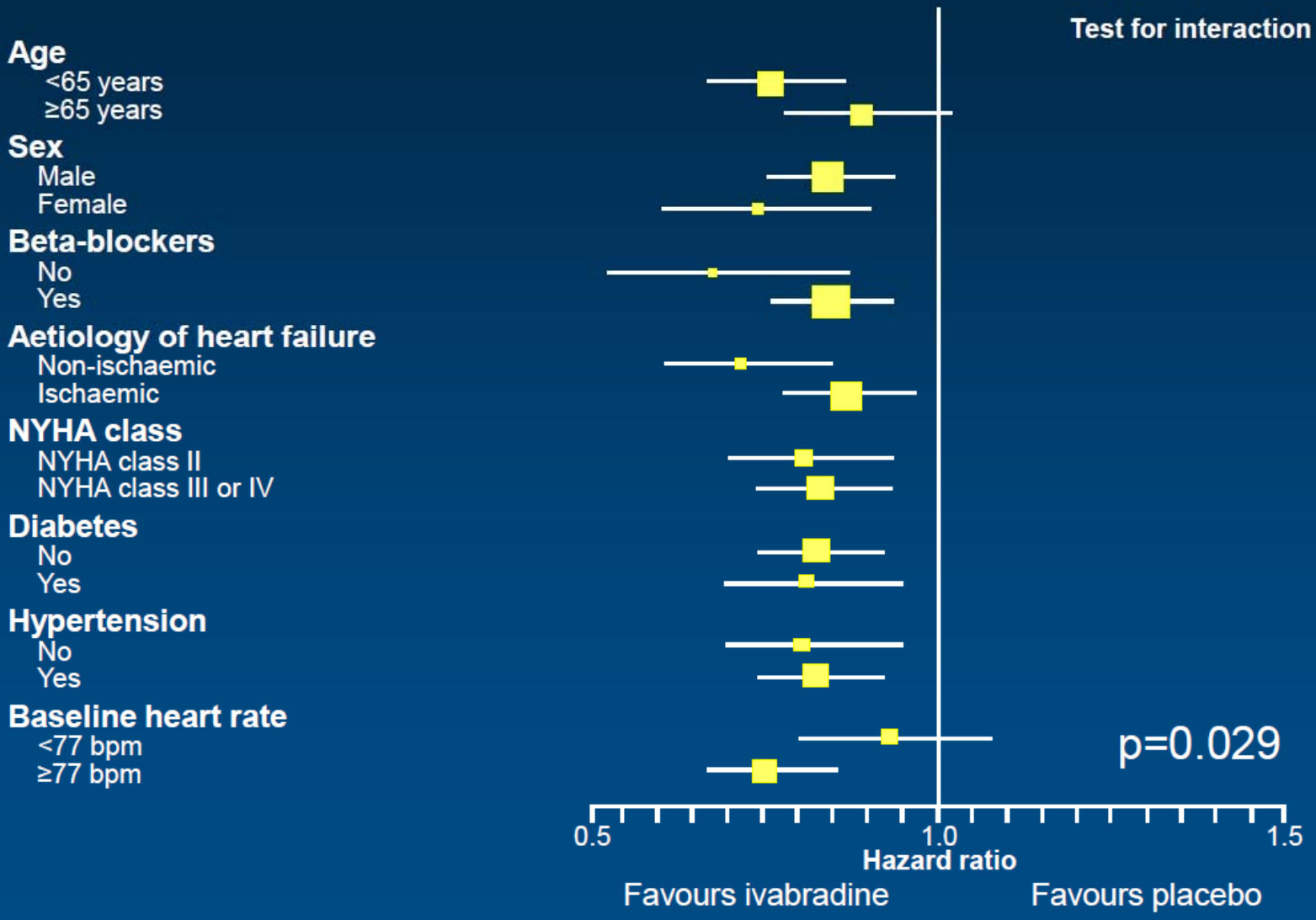
Cardiovascular death

Ivabradine n=449 (7.5%PY) Placebo n=491 (8.3%PY)

HR = 0.91 *p*=0.128



Effect of ivabradine in prespecified subgroups



Incidence of selected adverse events (N = 6492)

	Patients with an event		
	Ivabradine N=3232, % (n)	Placebo N=3260, % (n)	*p* value
All serious adverse events	**45%** (1450)	**48%** (1553)	**0.025**
All adverse events	**75%** (2439)	**74%** (2423)	**0.303**
Heart failure	**25%** (804)	**29%** (937)	**=0.0005**
Symptomatic bradycardia	**5%** (150)	**1%** (32%)	**<0.0001**
Asymptomatic bradycardia	**6%** (184)	**1%** (48)	**<0.0001**
Atrial fibrillation	**9%** (306)	**8%** (251)	**0.012**
Phosphenes	**3%** (89)	**1%** (17)	**<0.0001**
Blurred vision	**1%** (17)	**0.2%** (7)	**0.042**

SHIFT

Available now online
European Heart Journal

EUROPEAN SOCIETY OF CARDIOLOGY®

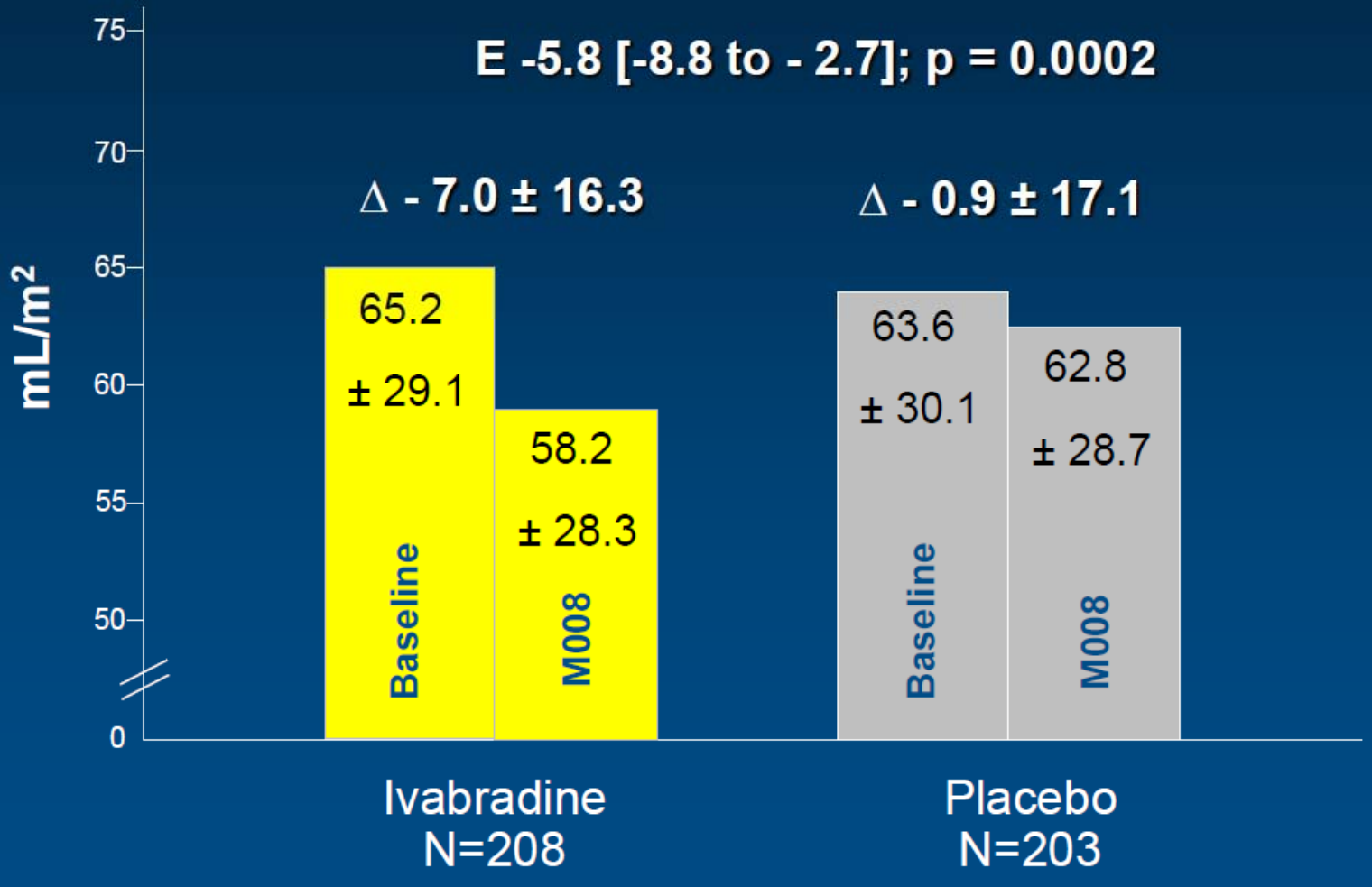
European Heart Journal
doi:10.1093/eurheartj/ehr311

FASTTRACK
ESC CLINICAL TRIAL UPDATE

Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy

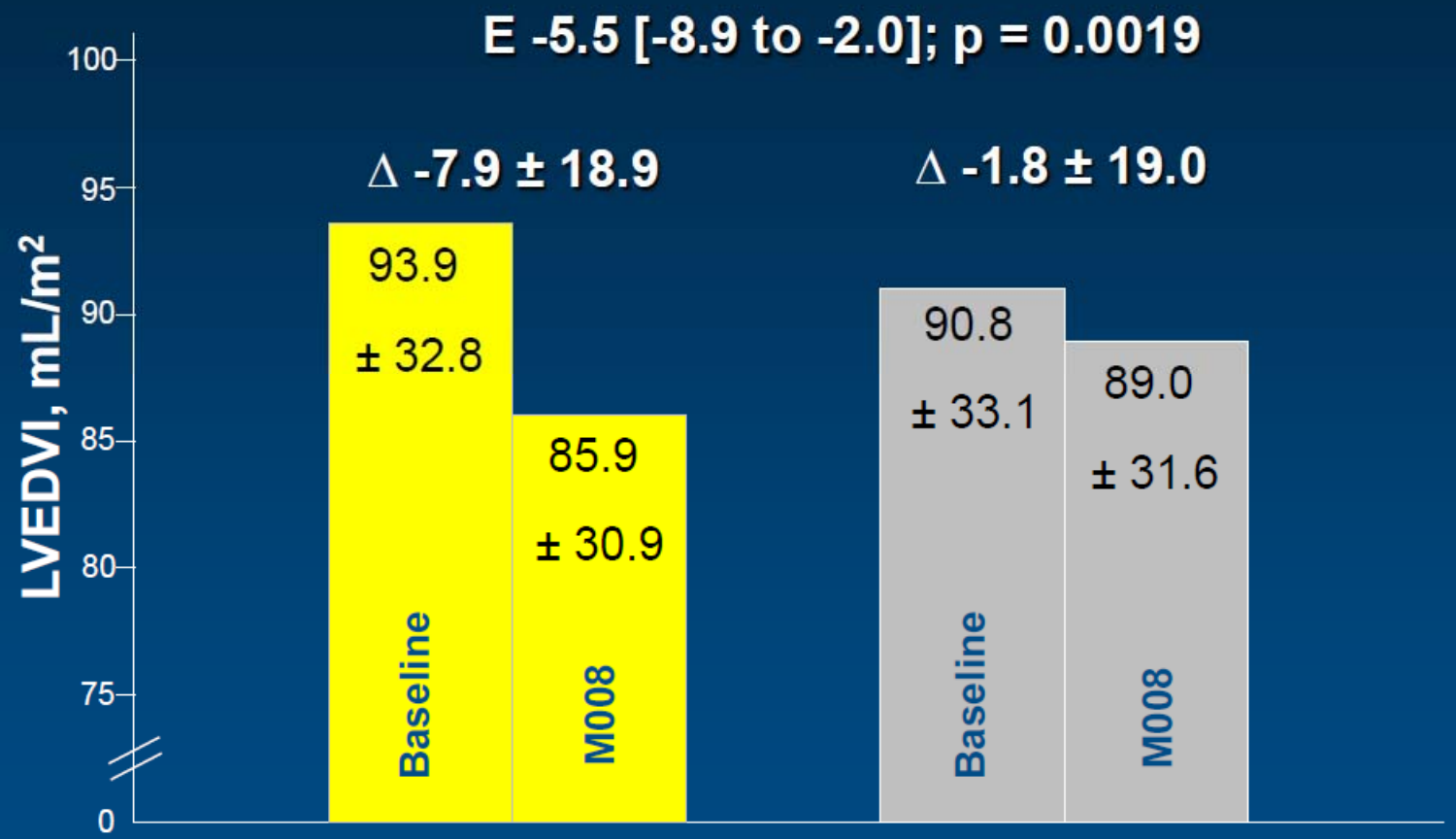
Jean-Claude Tardif[1]*, Eileen O'Meara[1], Michel Komajda[2], Michael Böhm[3], Jeffrey S. Borer[4], Ian Ford[5], Luigi Tavazzi[6], and Karl Swedberg[7], on behalf of the SHIFT Investigators

Primary endpoint: change in LVESVI from baseline to 8 months



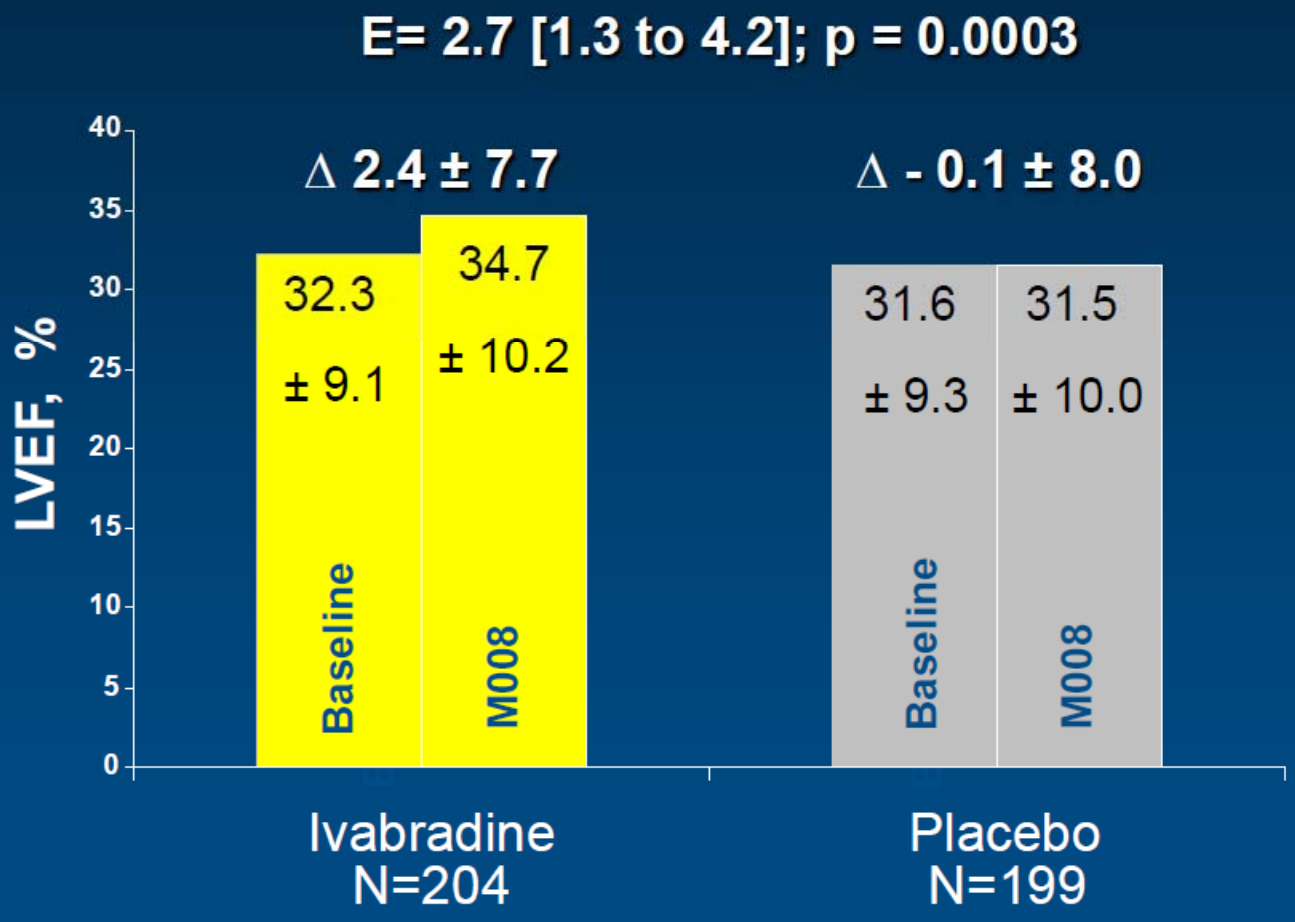
LVESVI: Left ventricular end-systolic volume index

Secondary endpoint: change in LVEDVI from baseline to 8 months



LVEDVI: Left ventricular end-diastolic volume index

Secondary endpoint: change in LVEF from baseline to 8 months



LVEF: Left ventricular ejection fraction

Available now online from ***European Heart Journal***

European Heart Journal
doi:10.1093/eurheartj/ehr343

FASTTRACK

ESC CLINICAL TRIAL UPDATE

Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: results from the SHIFT study

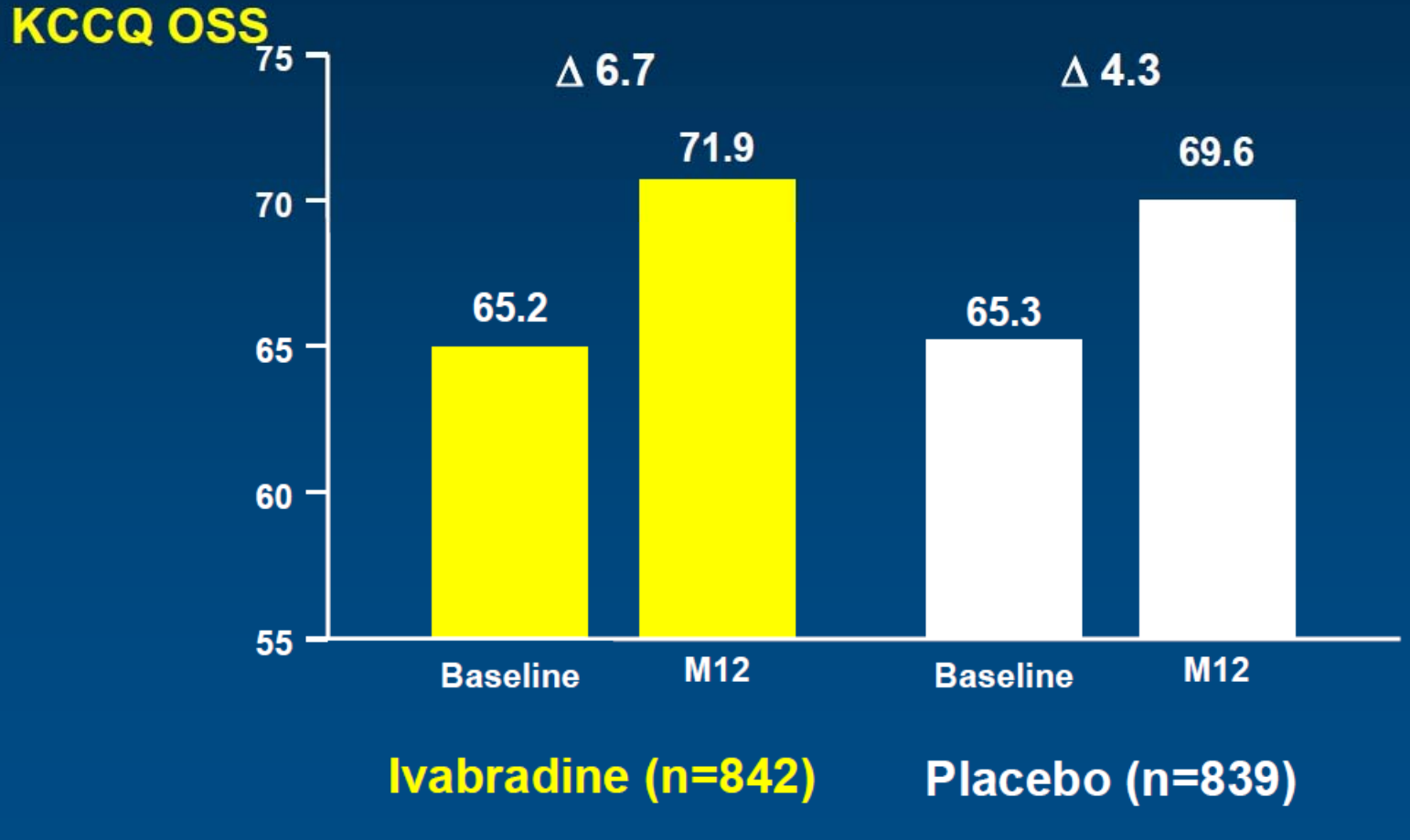
Inger Ekman[1,2*], Olivier Chassany[3,4], Michel Komajda[5,6], Michael Böhm[7], Jeffrey S. Borer[8], Ian Ford[9], Luigi Tavazzi[10], and Karl Swedberg[2,11]

http://eurheartj.oxfordjournals.org/cgi/content/full/ehr343

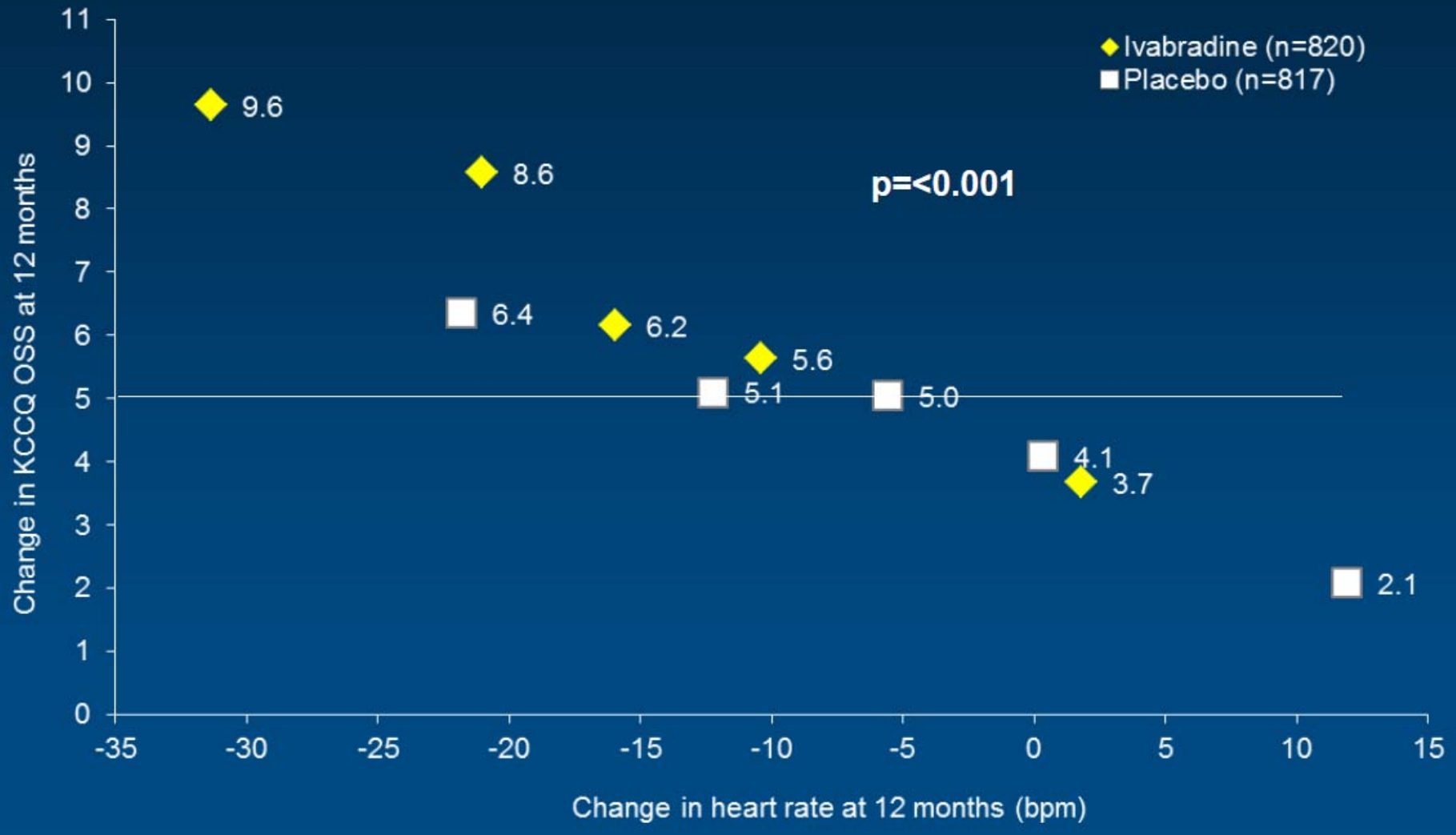
Overall summary score

Change from baseline – 12 months

Δ = 2.4, p<0.001



SHIFT Mean of change KCCQ overall score at 12 months by quintiles of HR change



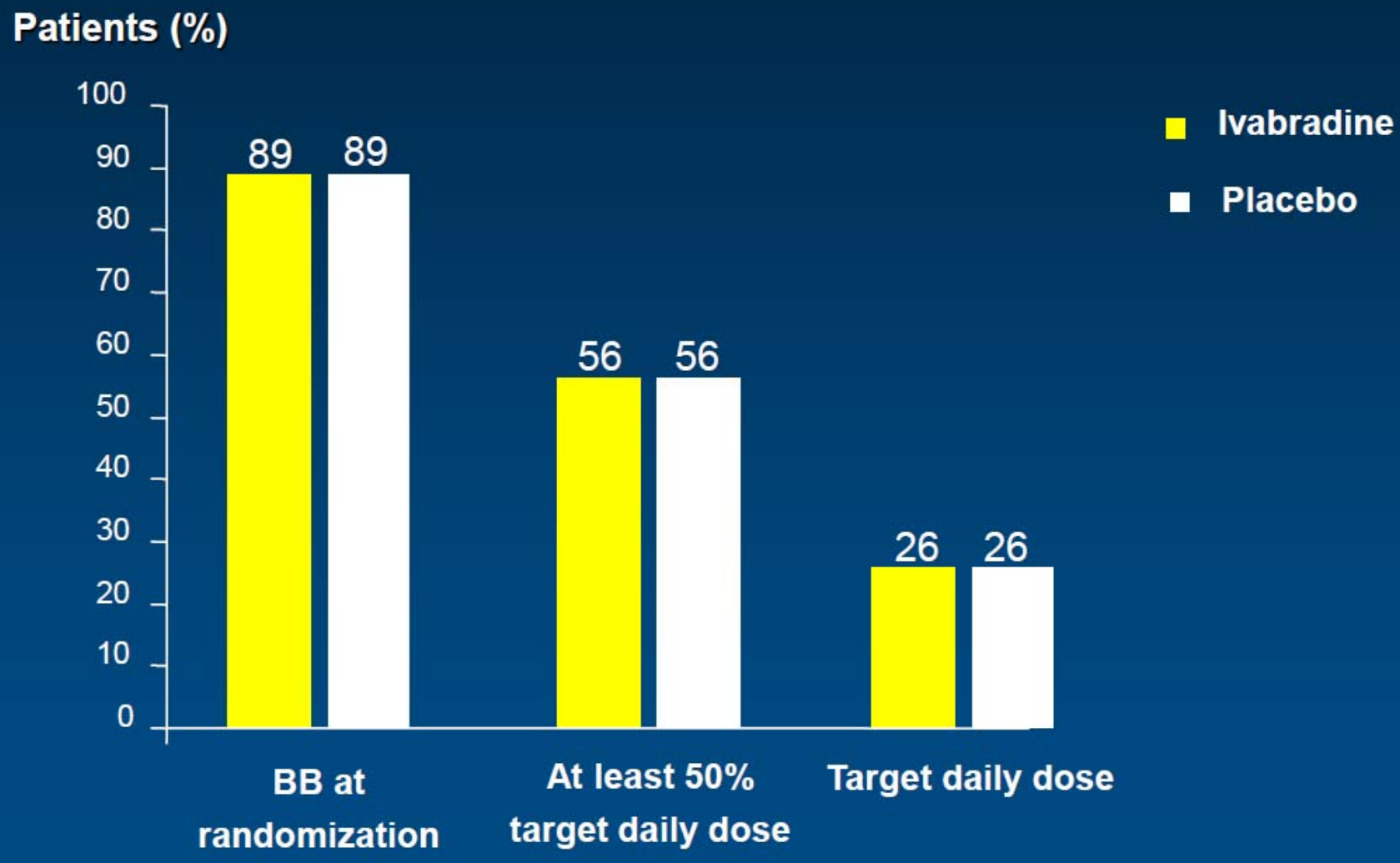
Conclusiones

- **Ivabradina reduce las hospitalizaciones por IC en un 26%.**
- **Tiene un efecto positivo sobre el remodelado ventricular.**
- **Mejora la calidad de vida en pacientes con IC.**

Pregunta:

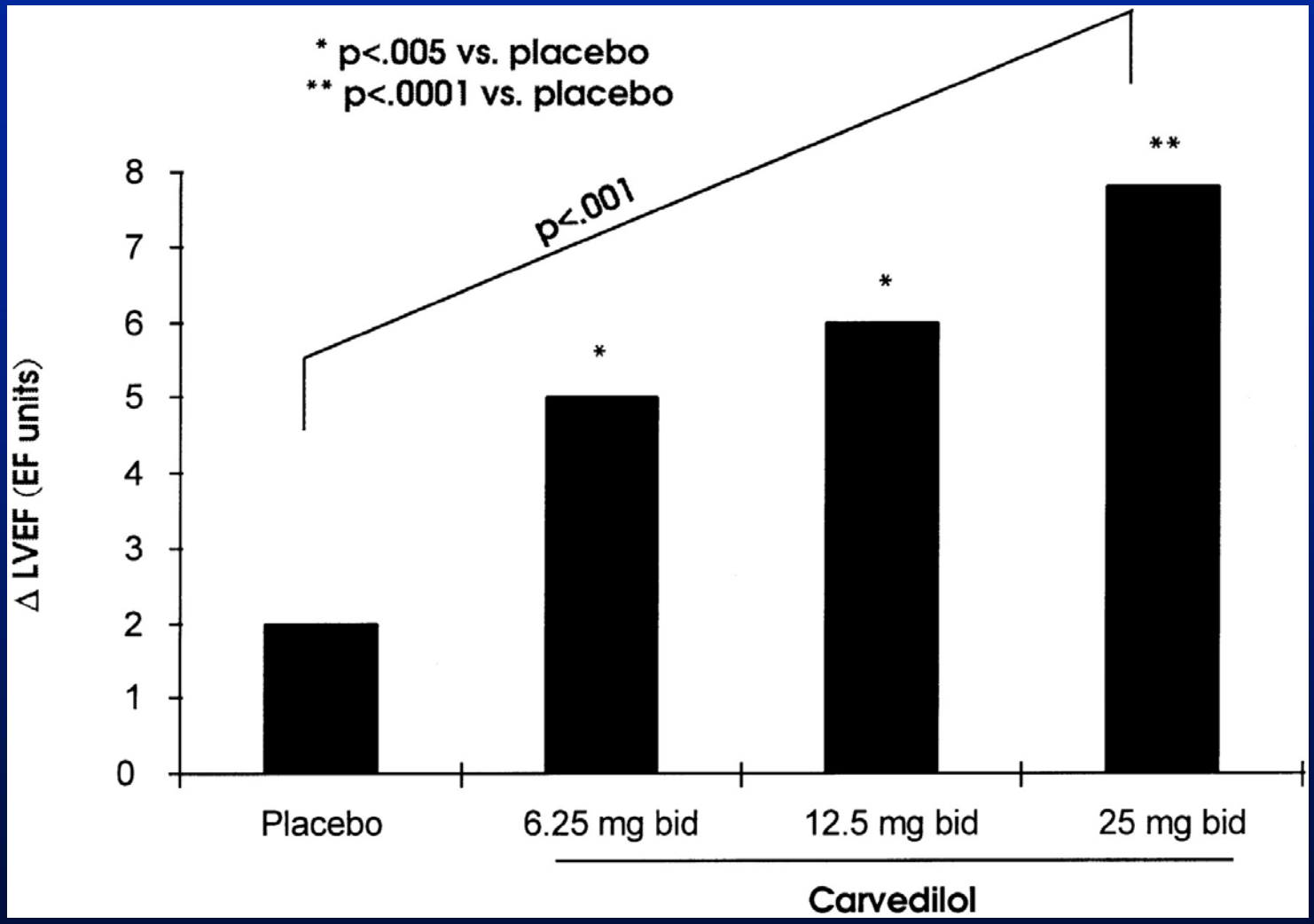
- ¿Porqué tomaban tan poco **Betabloqueador** los pacientes del SHIFT?

Background beta-blocker treatment

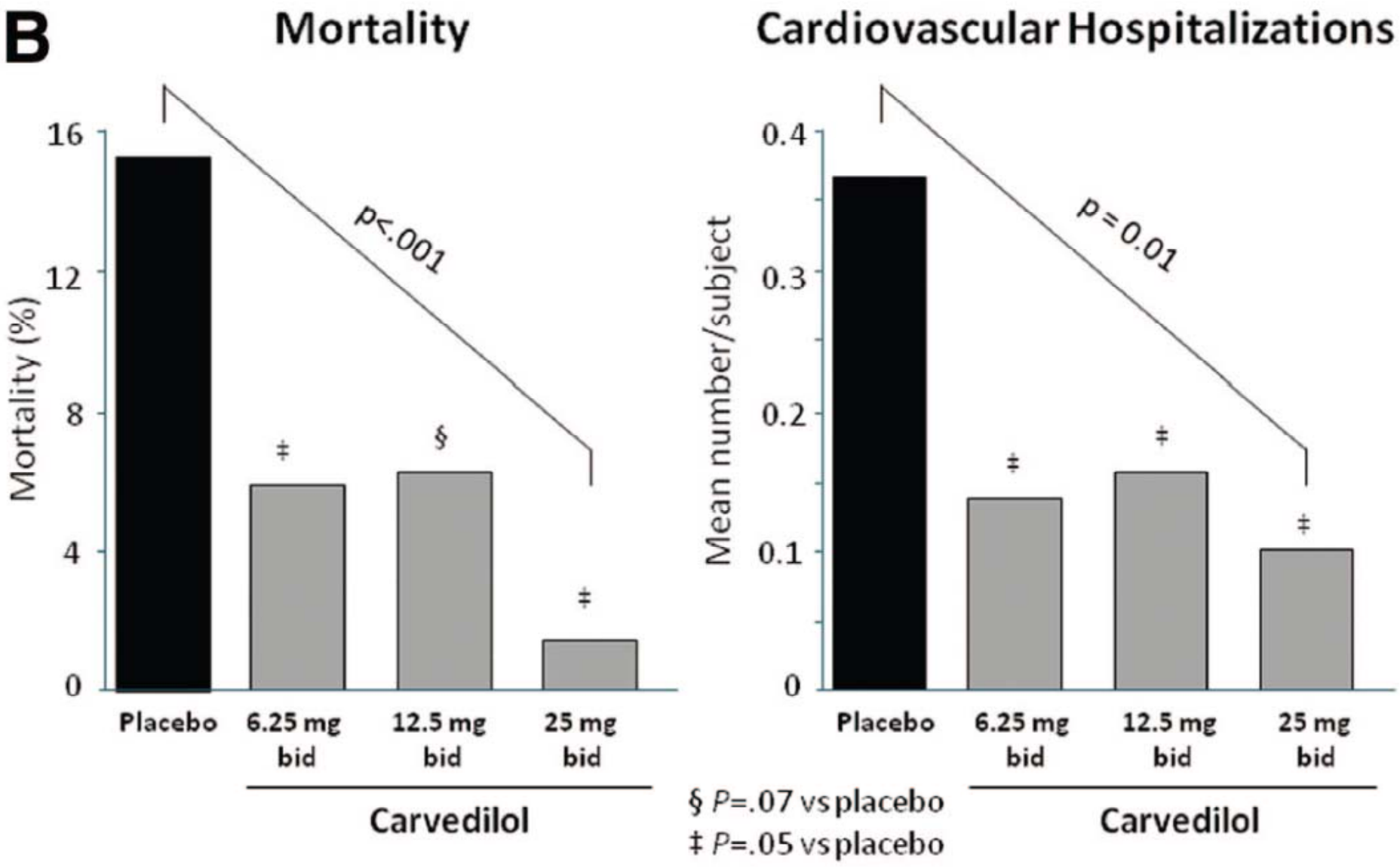


	Ivabradine group (n=3241)	Placebo group (n=3264)
Patients at target dose of β blocker*	743 (26%)	745 (26%)
Patients at ≥50% target dose of β blocker*	1581 (56%)	1600 (56%)
Reasons for failure to reach target dose*†		
Hypotension	933 (44%)	952 (45%)
Fatigue	676 (32%)	670 (32%)
Dyspnoea	284 (14%)	302 (14%)
Dizziness	267 (13%)	245 (12%)
Bradycardia	134 (6%)	125 (6%)
Other	199 (9%)	219 (10%)
Patients not receiving β blocker	344 (11%)	341 (10%)

	Ivabradine group (n=3241)	Placebo group (n=3264)
Patients at target dose of β blocker*	743 (26%)	745 (26%)
Patients at ≥50% target dose of β blocker*	1581 (56%)	1600 (56%)
Reasons for failure to reach target dose*†		
Hypotension	933 (44%)	952 (45%)
Fatigue	676 (32%)	670 (32%)
Dyspnoea	284 (14%)	302 (14%)
Dizziness	267 (13%)	245 (12%)
Cardiac parameters		
Heart rate (bpm)	79·7 (9·5)	80·1 (9·8)
SBP (mm Hg)	122·0 (16·1)	121·4 (15·9)
DBP (mm Hg)	75·7 (9·6)	75·6 (9·4)
LVEF (%)	29·0% (5·1)	29·0% (5·2)
eGFR (mL/min per 1·73 m^2)	74·6 (22·9)	74·8 (23·1)



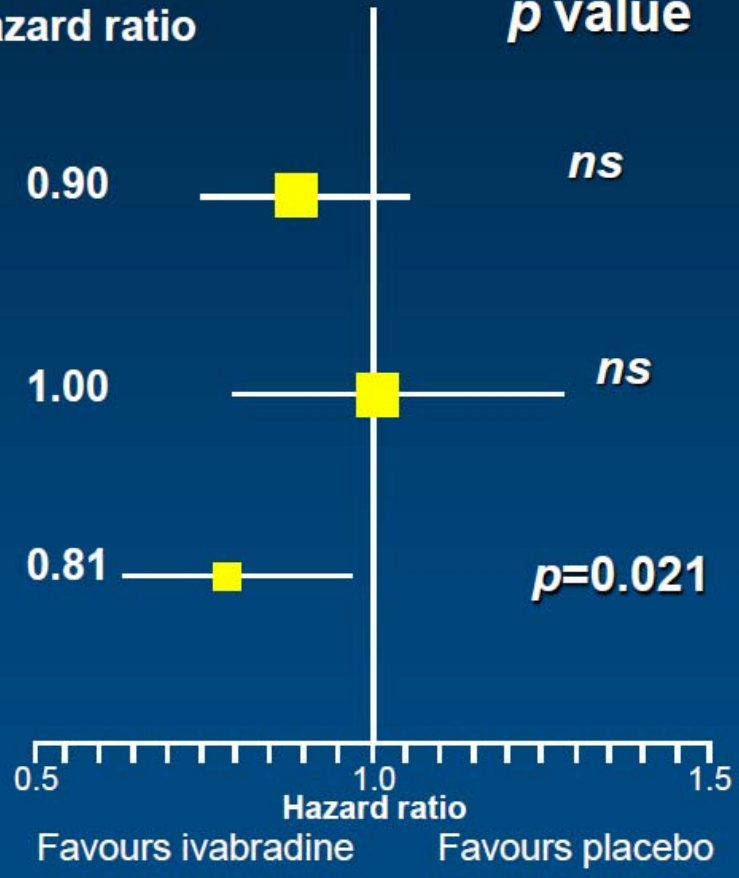
Bristow M R et al. Circulation 1996;94:2807-2816



Bristow. Circ Res. 2011

Patients with at least 50% BB target dose (n=3181)

	Ivabradine	Placebo	Hazard ratio	*p* value
Primary composite endpoint	330 (11.9 PY)	362 (13.3 PY)	0.90	*ns*
Cardiovascular death	176 (5.9 PY)	175 (5.9 PY)	1.00	*ns*
Hospitalization for worsening HF	213 (7.7 PY)	260 (9.6 PY)	0.81	*p*=0.021



Pregunta:

- ¿Es relevante el **beneficio de la Ivabradina** en los pacientes con Insuficiencia Cardiaca?

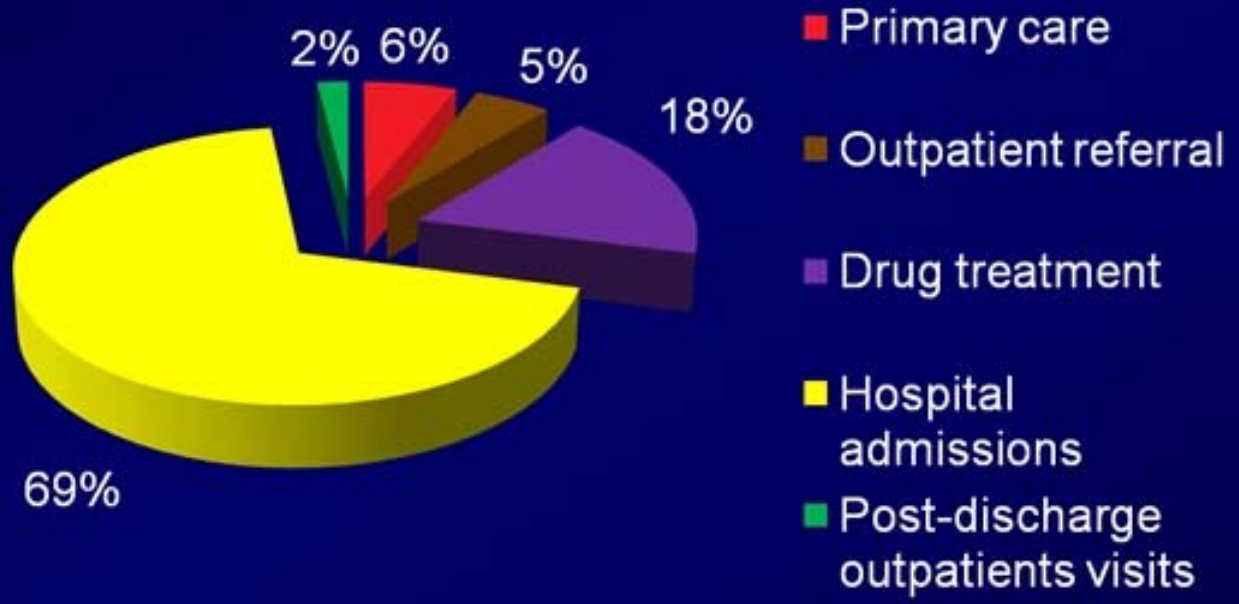
Comparison of B-blockers and Ivabradine
Relative Risk Reduction

	MERIT-HF **Metoprolol**	CIBIS-II **Bisoprolol**	COPERNICUS **Carvedilol**
All-cause Mortality	**34**	**34**	**35**
Heart Failure Death	**49**	**26**	NA
Sudden Death	**41**	**44**	**44**
Heart Failure Hospitalizations	**35**	**32**	**33**

Comparison of B-blockers and Ivabradine
Relative Risk Reduction

	MERIT-HF **Metoprolol**	CIBIS-II **Bisoprolol**	COPERNICUS **Carvedilol**	**SHIFT Ivabradine**
All-cause Mortality	**34**	**34**	**35**	**0**
Heart Failure Death	**49**	**26**	NA	**26**
Sudden Death	**41**	**44**	**44**	**0**
Heart Failure Hospitalizations	**35**	**32**	**33**	**26**

Economic burden of chronic HF: the weight of hospitalisations



Stewart S et al. *Eur J Heart Fail* 2002;4:361–71.

Conclusiones

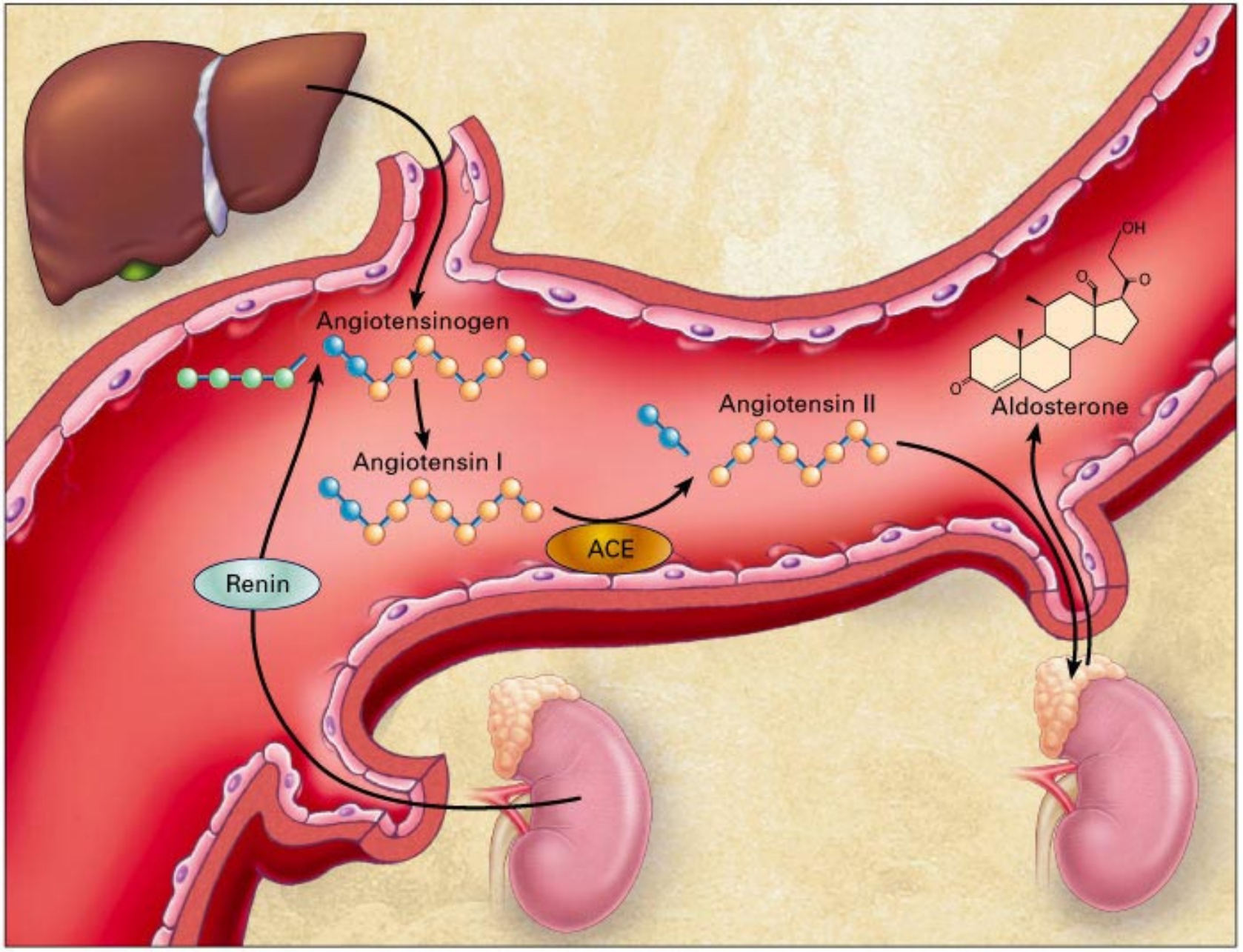
- La frecuencia cardiaca es un **marcador** de mal pronóstico y también un **factor** que empeora el pronóstico de la IC.

Conclusiones

- **Es más beneficioso reducir la frecuencia cardiaca con un Betabloqueador, porque aumenta la supervivencia y reduce las hospitalizaciones.**

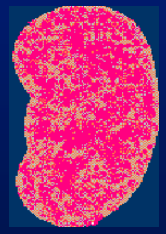
Conclusiones

- **Si fracasa el intento de aumentar Betabloqueadores, está indicado administrar Ivabradina si la FC es > 70.**

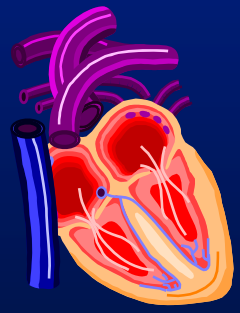

Angiotensinogen
Angiotensin I
Angiotensin II
ACE
Renin
Aldosterone
OH
O
O
O

Aldosterona

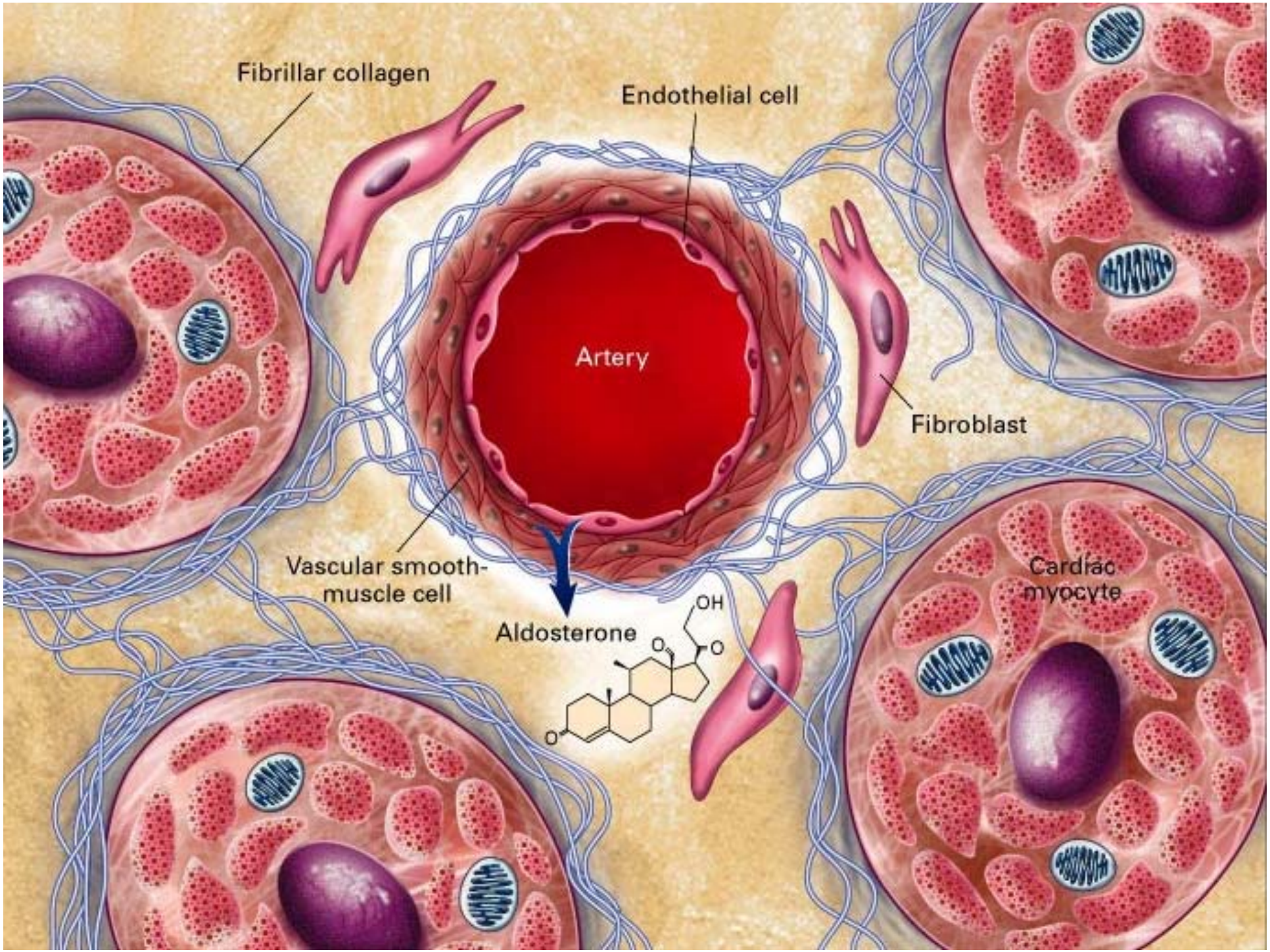
Aldosterona



Retención de Na
Retención de aigua
Excreción de K+
Excreción de Mg++

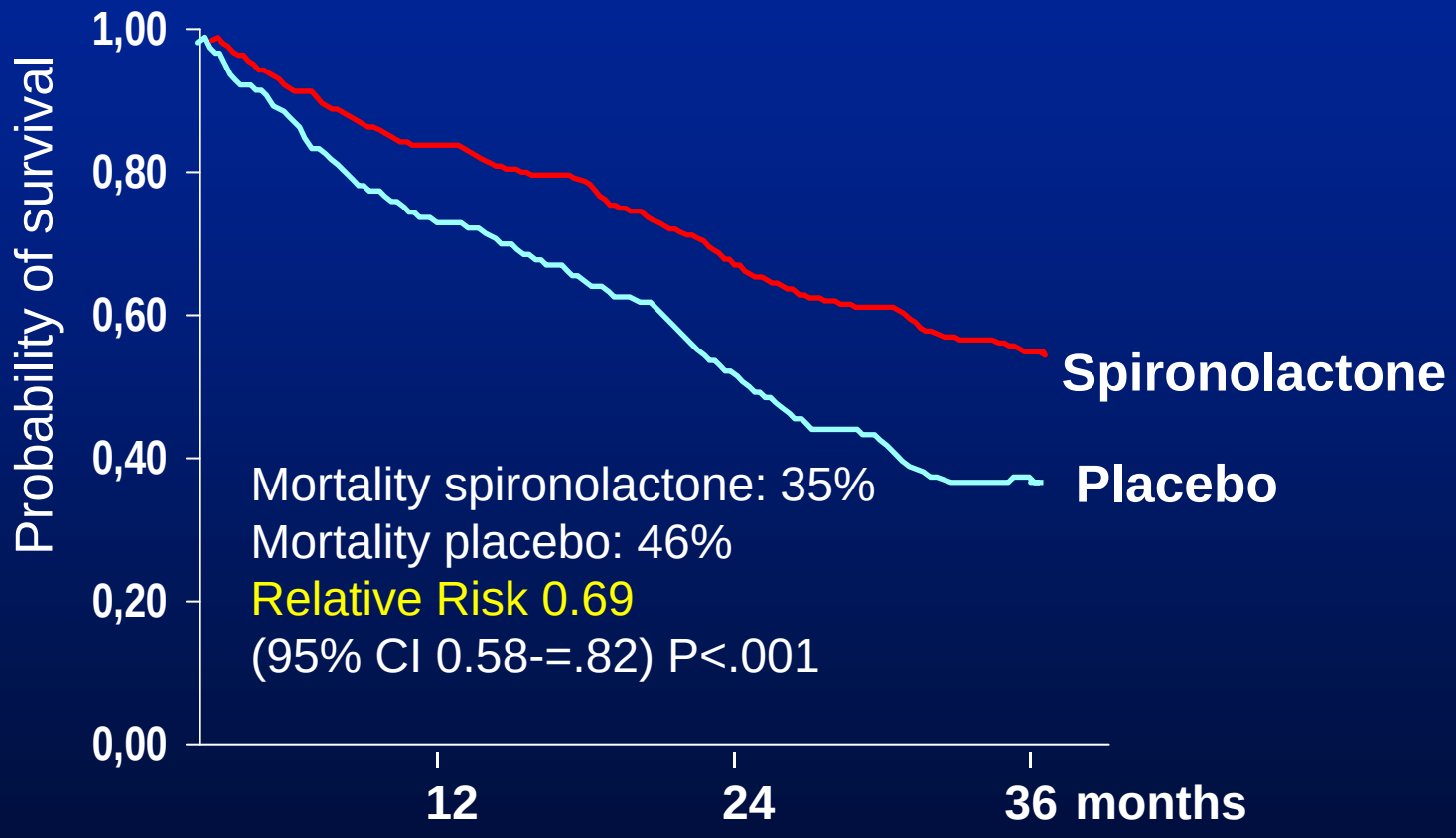


Fibrosis


Fibrillar collagen
Endothelial cell
Artery
Fibroblast
Vascular smooth-muscle cell
Aldosterone
OH
O
O
O
Cardiac myocyte

RALES: All-cause Mortality

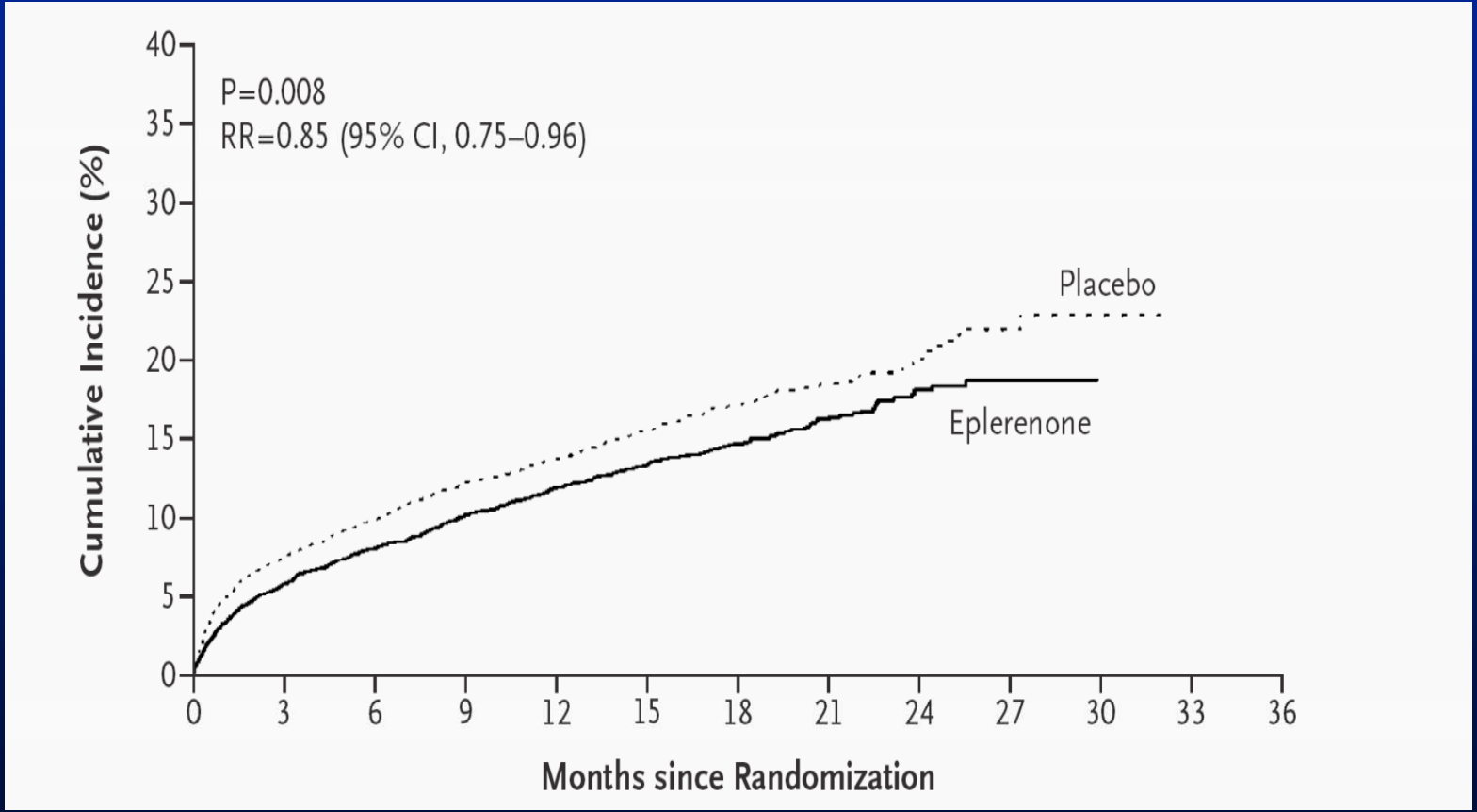
1663 pts CF III-IV; EF < 35% . Exclusion: Crea > 2,5 or K >5
Spironolactone (25 mg/d) or Placebo. Follow-up: 24 months



NEJM 1999;341:709

Eplerenone for LV dysfuncion after AMI (EPHESUS)

6642 pts 3-14 days post-AMI: EF < 40% and Heart Failure or Diabetis
Eplerenone (43 mg/d) or Placebo. Follow-up: 16 months



Mortality Eplerenone: 14.4 %
Mortality placebo: 16.7%
RR: 0.85

NEJM 2003;348:1309

ORIGINAL ARTICLE

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

EMPHASIS-HF*

Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., PhD., Dirk J. van Veldhuisen, M.D.,Ph.D., Karl Swedberg, M.D., Ph.D, Harry Shi, M.S., John Vincent, M.B., PhD., Stuart J Pocock, Ph.D. and Bertram Pitt, M.D. for the EMPHASIS-HF Study Group

ClinicalTrials.gov, NCT00232180

EMPHASIS HF

* Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure

N Engl J Med 2010.

Inclusion Criteria

- Inclusion
  - > 55 years of age
  - NYHA functional class II
  - Ejection fraction ≤ 30% (or, if between 31% and 35%, QRS >130 msec)
  - Treated with the recommended or maximally tolerated dose of ACE inhibitor (or an ARB or both) and a beta-blocker (unless contraindicated).
  - Within 6 months of hospitalization for a cardiovascular reason [or, if no such hospitalization, BNP ≥ 250 pg/ml or NT-pro-BNP ≥500 pg/ml (males) or 750 pg/ml (females)]
- Exclusion
  - Serum potassium > 5.0 mmol/L
  - eGFR < 30 ml/min/1.73 m^2
  - Need for a potassium-sparing diuretic
  - Any other significant comorbid condition

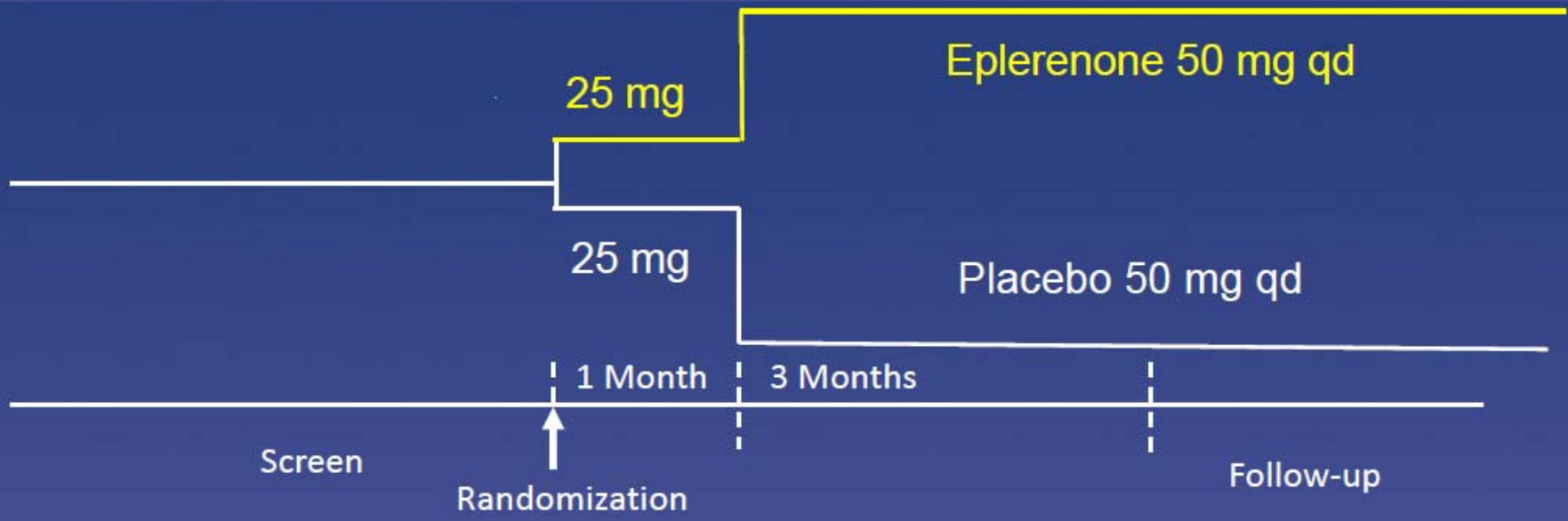
EMPHASIS HF

Inclusion Criteria

- Inclusion
  - > 55 years of age
  - NYHA functional class II
  - Ejection fraction ≤ 30% (or, if between 31% and 35%, QRS >130 msec)
  - Treated with the recommended or maximally tolerated dose of ACE inhibitor (or an ARB or both) and a beta-blocker (unless contraindicated).
  - Within 6 months of hospitalization for a cardiovascular reason [or, if no such hospitalization, BNP ≥ 250 pg/ml or NT-pro-BNP ≥500 pg/ml (males) or 750 pg/ml (females)]
- Exclusion
  - Serum potassium > 5.0 mmol/L
  - eGFR < 30 ml/min/1.73 m^2
  - Need for a potassium-sparing diuretic
  - Any other significant comorbid condition

EMPHASIS HF

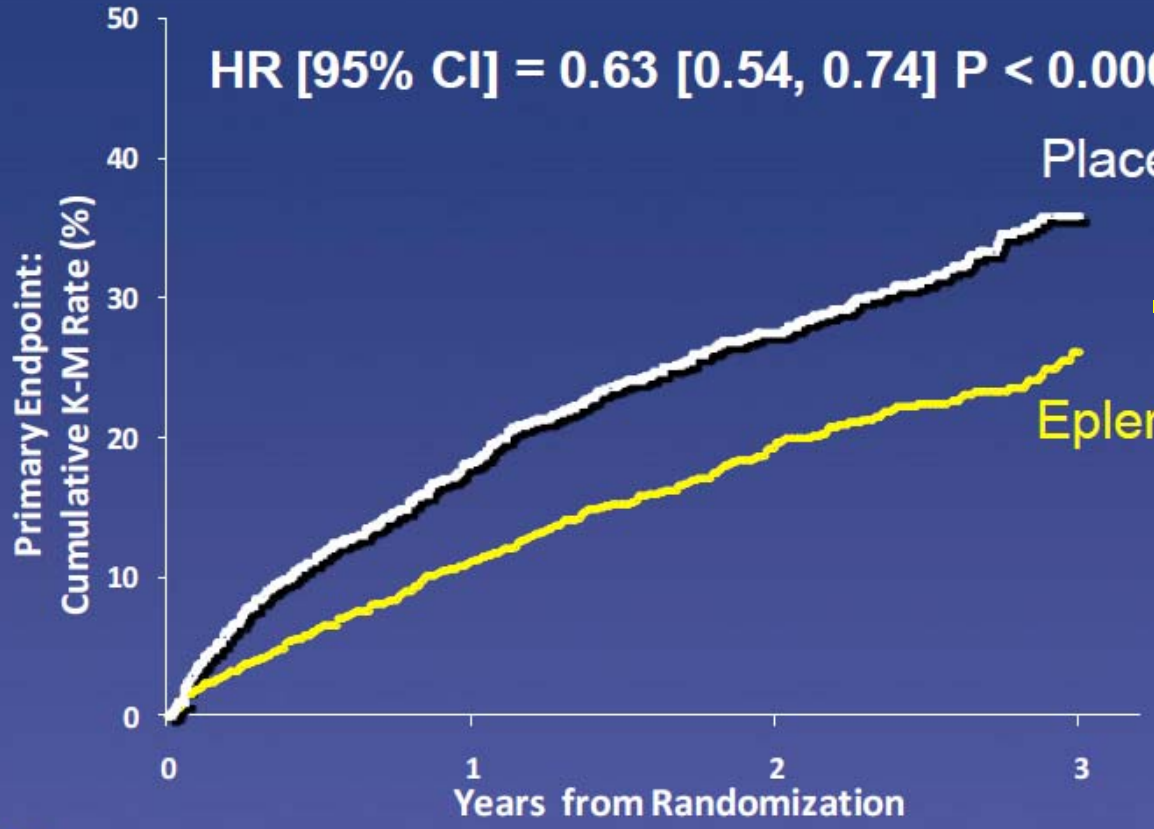
Study Design and Sample Size



- Primary endpoint: CV death or hospitalization for HF
- The initial assumptions :
  - 2584 patients,
  - annual event rate 18% in the placebo group,
  - 813 primary events in 48 months,
  - 80% power to detect an 18% risk reduction (alpha=0.05).
- In June 2009 the overall blinded event rate was lower than expected and the sample size was increased to 3100 patients

EMPHASIS HF

Primary Endpoint Cardiovascular Death or Hospitalization for HF

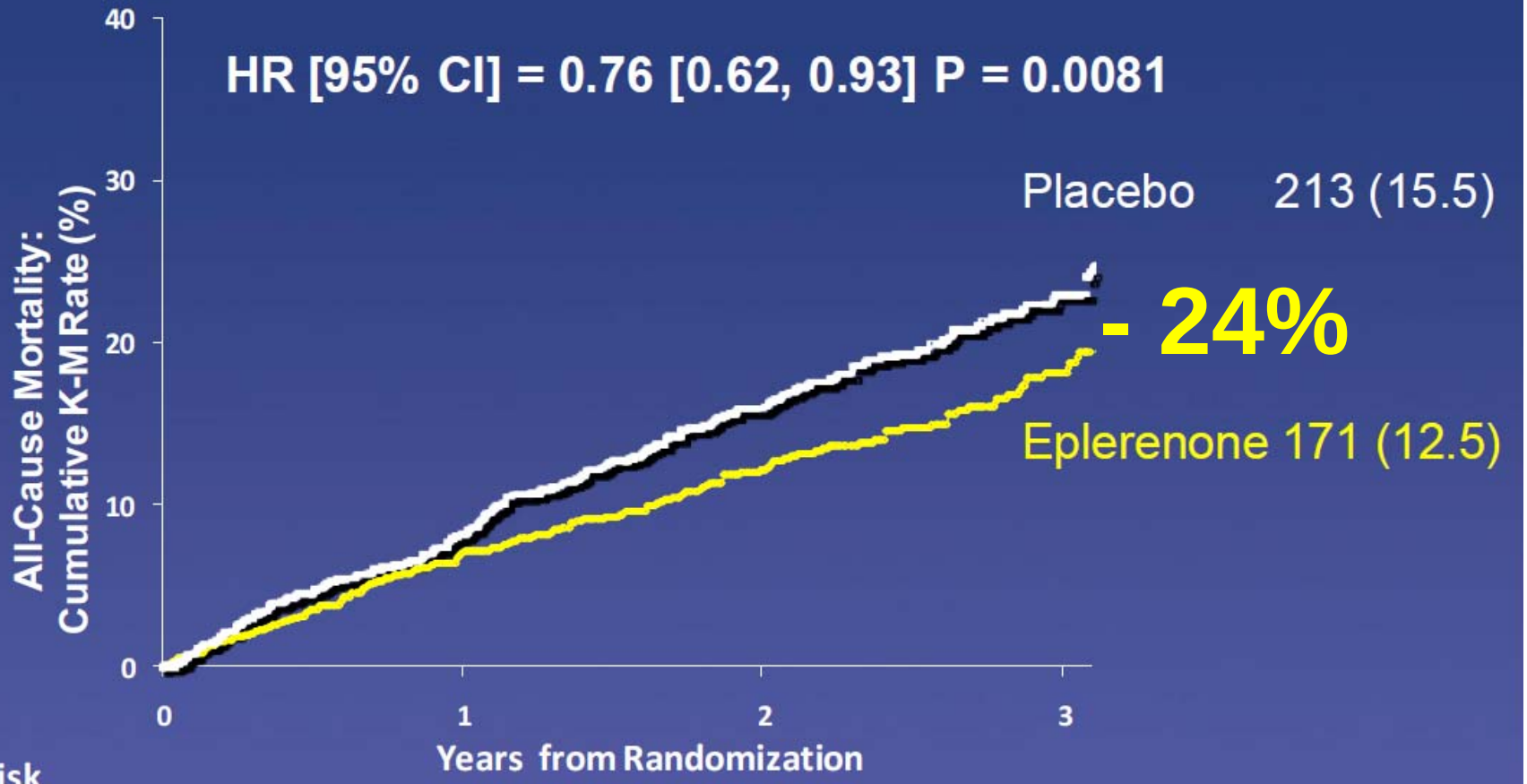


No. at Risk				
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

EMPHASIS HF

*Unadjusted HR 0.66; 0.56, 0.78; p<0.0001

Mortality From Any Cause

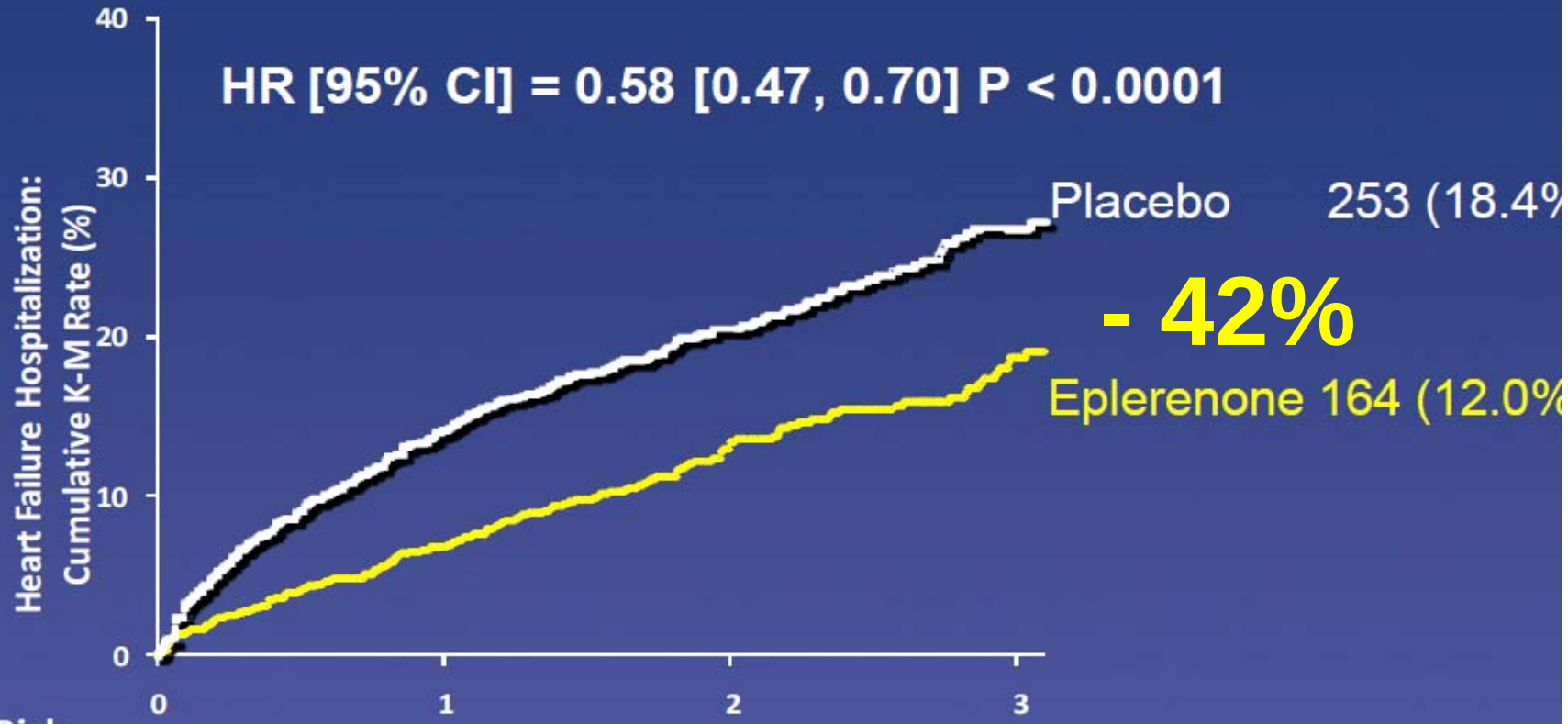


No. at Risk				
Placebo	1373	947	587	242
Eplerenone	1364	972	625	269

EMPHASIS HF

*Unadjusted HR, 0.78; 0.64, 0.95; p=0.01

Heart Failure Hospitalization

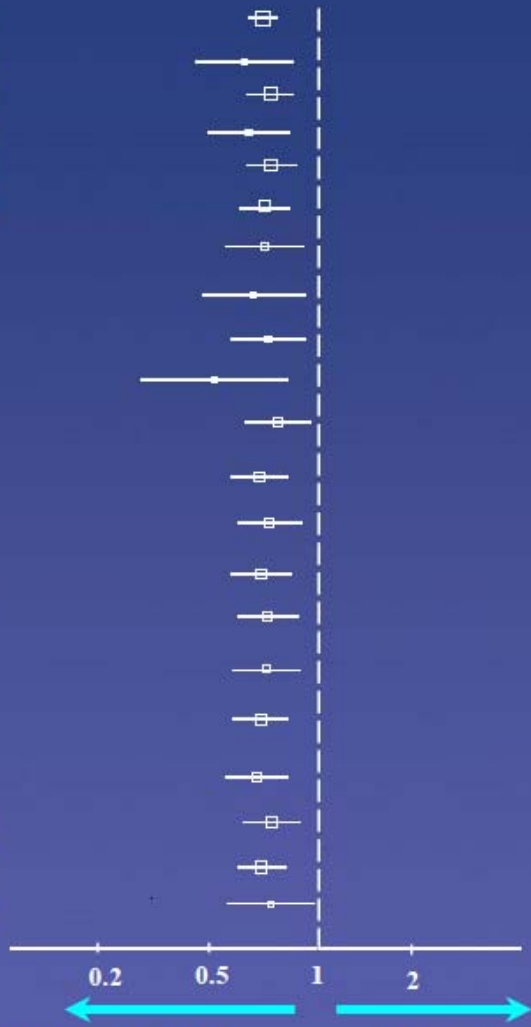


EMPHASIS HF

*Unadjusted HR, 0.61; 0.50, 0.75; p <0.0001

Subgroup Analysis – Primary Endpoint

Baseline Variable	Subgroup	No. of Patients	P-value for Interaction
Overall		2,737	
Gender	Female	610	0.36
	Male	2,127	
Age	< 65 yr	883	0.37
	>= 65 yr	1,854	
Age	< 75 yr	2,080	1.00
	>= 75 yr	657	
Region	Asia/Middle East/ Africa	380	0.46
	East Europe	911	
	South/North America	346	
	West Europe / Australia	1,100	
Systolic BP	< Median	1,352	0.65
	>= Median	1,384	
Pulse Pressure	< Median	1,272	0.75
	>= Median	1,464	
Heart Rate	< Median	1,340	0.79
	>= Median	1,383	
eGFR	< 60 ml/min/1.73m2	912	0.50
	>= 60 ml/min/1.73m2	1,821	
Primary Diagnosis	Ischaemic Heart Failure	1,886	0.73
	Non-Ischaemic Heart Failure	846	



EMPHASIS HF

Safety – Drug Discontinuation due to AEs

(Investigator reported events)

	Patients with an adverse event leading to drug withdrawal — no. (%)		
Outcome	Eplerenone (N=1360)	Placebo (N=1373)	P Value
All	188 (13.8)	222 (16.2)	0.09
Hyperkalemia	15 (1.1)	12 (0.9)	0.57
Hypokalemia	0	3 (0.2)	0.25
Renal failure	4 (0.3)	6 (0.4)	0.75
Hypotension	0	3 (0.2)	0.25
Gynecomastia and other breast disorders	2 (0.1)	2 (0.1)	1.00

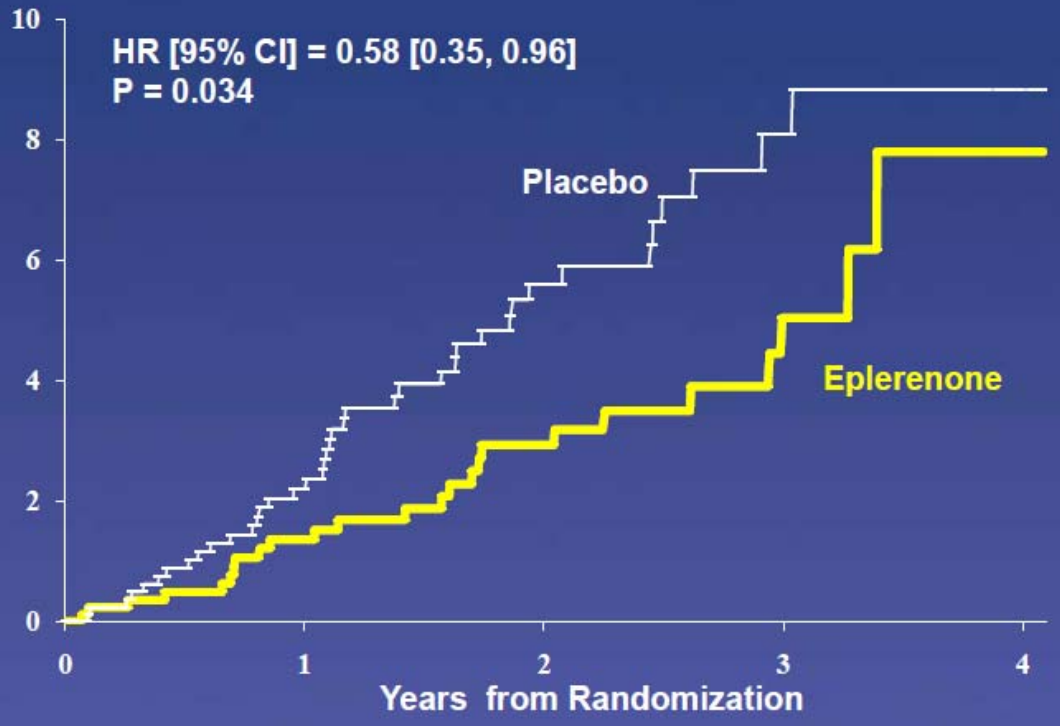
EMPHASIS HF

Safety - Potassium Related Issues

Outcome	Patients with an adverse event leading to drug withdrawal — no. (%)		
	Eplerenone (N=1360)	Placebo (N=1373)	P Value
Hyperkalemia (investigator reported AE)	109 (8)	50 (3.7)	<0.001
Hyperkalemia leading to drug discontinuation	15 (1.1)	12 (0.9)	0.57
Serum K+ > 5.5 mmol/L	158 (11.8)	96 (7.2)	<0.001
Serum K+ > 6.0 mmol/L	33 (2.5)	25 (1.9)	0.29
Hospitalization for hyperkalemia (adjudicated)	4 (0.3)	3 (0.2)	0.85

EMPHASIS HF

New Onset Atrial Fibrillation/Flutter (AFF)



No. at Risk					
Placebo	883	611	345	133	1
Eplerenone	911	627	397	162	2

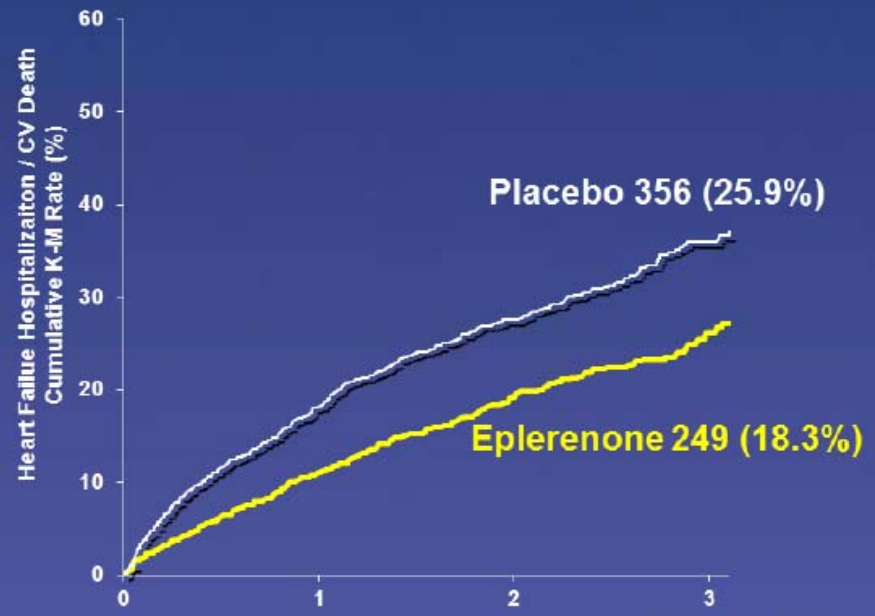
EMPHASIS HF

Swedberg at el, ESC – HF 2011

CV Death or HF Hospitalization

Overall

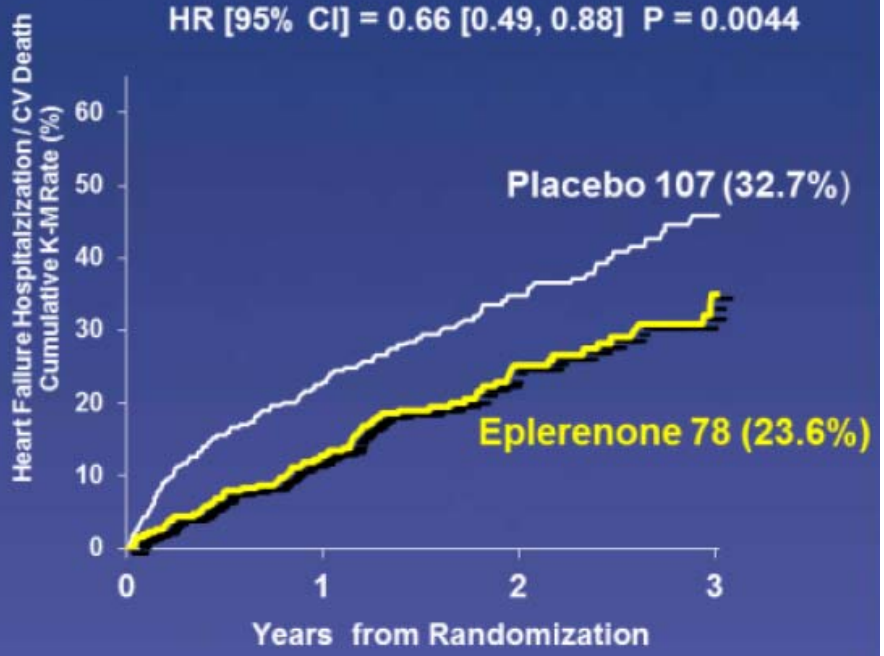
HR [95% CI] = 0.63 [0.54, 0.74] P < 0.0001



No. at Risk				
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

>=75 years

HR [95% CI] = 0.66 [0.49, 0.88] P = 0.0044



No. at Risk				
Placebo	327	188	112	39
Eplerenone	330	226	122	44

*Un-adjusted HR [95% CI] = 0.66 [0.56, 0.78] P < 0.0001

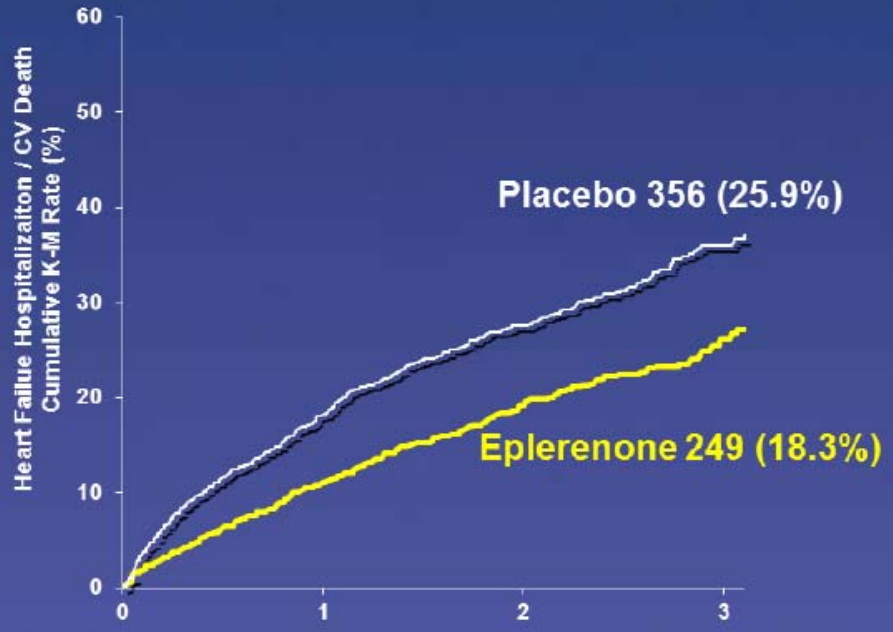
EMPHASIS HF

ESC 2011

CV Death or HF Hospitalization

Overall

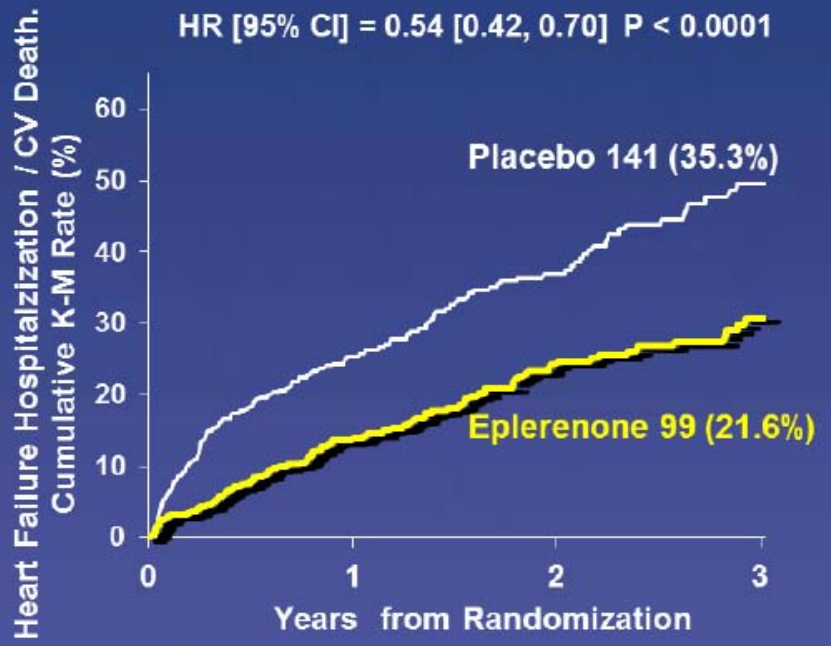
HR [95% CI] = 0.63 [0.54, 0.74] P < 0.0001



No. at Risk				
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

Diabetes Mellitus

HR [95% CI] = 0.54 [0.42, 0.70] P < 0.0001



No. at Risk				
Placebo	400	218	123	42
Eplerenone	459	294	175	74

*Un-adjusted HR [95% CI] = 0.66 [0.56, 0.78] P < 0.0001

EMPHASIS HF

CV Death or HF Hospitalization

Overall

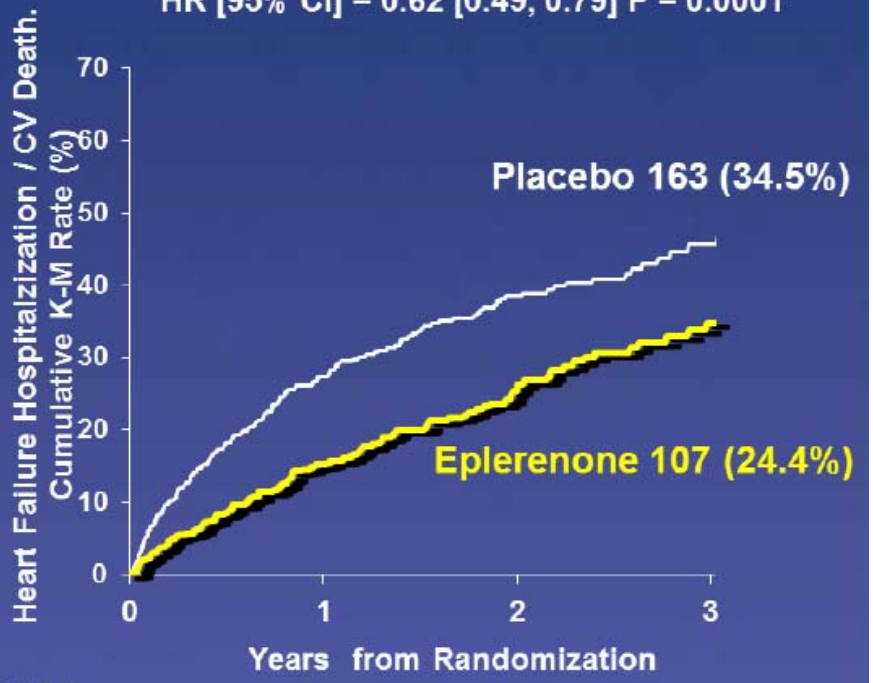
HR [95% CI] = 0.63 [0.54, 0.74] P < 0.0001

No. at Risk				
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

*Un-adjusted HR [95% CI] = 0.66 [0.56, 0.78] P < 0.0001

eGFR < 60 ml/min/1.73m^2

HR [95% CI] = 0.62 [0.49, 0.79] P = 0.0001



No. at Risk				
Placebo	473	252	146	41
Eplerenone	439	281	165	71

EMPHASIS HF

Safety Results: Serum Potassium and Renal Function - eGFR<60 ml/min/1.73m^2

Outcome	Eplerenone	Placebo	p-value
Serum K+>5.5 mmol/l	70/422 (16.6)	43/461 (9.3)	0.002
Serum K+>6.0 mmol/l	8/422 (1.9)	15/461 (3.3)	0.29
Hyperkalemia leading to treatment discontinuation	5/439 (1.1)	10/473 (2.1)	0.30
Hospitalization for hyperkalemia	1/439 (0.2)	2/473 (0.4)	0.57
Serum K+<3.5 mmol/l	26/422 (6.2)	46/461 (10.0)	0.048
Hospitalization for worsening renal function	5/439 (1.1)	8/473 (1.7)	0.32

EMPHASIS HF

Conclusiones

NYHA clase II: BB + IECA + Eplerenona

- **Reducción del 24% en Mortalidad global**
- **Reducción del 42% en Hospitalizaciones por IC**

- Riesgo de Hiperpotasemia moderado (si se controla el K^+)

¿Funciona igual Espironolactona?

Condiciones para una "Clase" de fármacos:

- **Mecanismo de acción común.**

- **Eficacia similar en ensayos clínicos con el mismo tipo de pacientes.**

Antman. Circulation 2003

	EPHESUS Early post-MI	EMPHASIS Class II +	RALES Adv III-IV
Ave LVEF	0.33	0.26	0.25
Bblockers	75%	85%	10%
1 yr mort	14% 12%	8% 7%	25% 18%
Deaths diverge	< 3 mos	≤12 mos	< 3 mos
Death CV Death	.85 .87	.76 .76	.70 .69

	EPHESUS Early post-MI	EMPHASIS Class II +	RALES Adv III-IV
Ave LVEF	0.33	0.26	0.25
Bblockers	75%	85%	10%
1 yr mort	14% 12%	8% 7%	25% 18%
Deaths diverge	< 3 mos	≤12 mos	< 3 mos
Death CV Death	.85 .87	.76 .76	.70 .69

	EPHESUS Early post-MI	EMPHASIS Class II +	RALES Adv III-IV
Ave LVEF	0.33	0.26	0.25
Bblockers	75%	85%	10%
1 yr mort	14% 12%	8% 7%	25% 18%
Deaths diverge	< 3 mos	≤12 mos	< 3 mos
Death	.85	.76	.70
CV Death	.87	.76	.69

¿Hay diferencias entre Espironolactona y Eplerenona?

Espironolactona: Acción sobre Receptores

Mineralocorticoide: Antagonista

Glucocorticoide: Antagonista

Andrógenos: Antagonista

Progesterona: Agonista

Espironolactona: Efectos secundarios

- R. Mineralocorticoide:
  - Hiper K+

- R. Glucocorticoide:
  - Aumento Cortisol
  - Aumento HbA1

- R. Andrógenos/R.Progesterona:
  - Ginecomastia (dosis i tiempo dependiente)
  - Mastodinia
  - Impotencia
  - Anomalias menstruales

Eplerenona vs. Espironolactona: Acción sobre Receptores

Mineralocorticoide: **20 veces menos afinidad**

Glucocorticoide: **10 veces menos**

Andrógenos: **200 veces menos**

Progesterona: **2000 veces menos**

Table 1. Pharmacokinetic Comparison of Eplerenone Versus Spironolactone[7,21-23]

Parameter	Eplerenone	Spironolactone
Bioavailability (%)	unknown[a]	73
Absorption with food	no change	increased
t_{max} (h)	1–2	1–2
Protein binding (%)	49	90
Metabolic pathway	hepatic (CYP3A4) to inactive metabolites	hepatic (deacetylation and dethiolation) to active and inactive metabolites
$t_{1/2}$ (h)	parent drug, 3.5–6	parent drug, 1.3–1.4 active metabolites 7-α-thiomethylspirolactone, 2.8 6-β-hydroxy-7-α-thiomethylspirolactone, 10–15 canrenone, 13–24
Excretion (%)		
urine	67	53
bile/feces	32	20

$t_{1/2}$ = half-life; t_{max} = time required to reach maximum serum concentrations.

[a]Although the package insert does not report bioavailability, others have suggested that eplerenone is well absorbed.

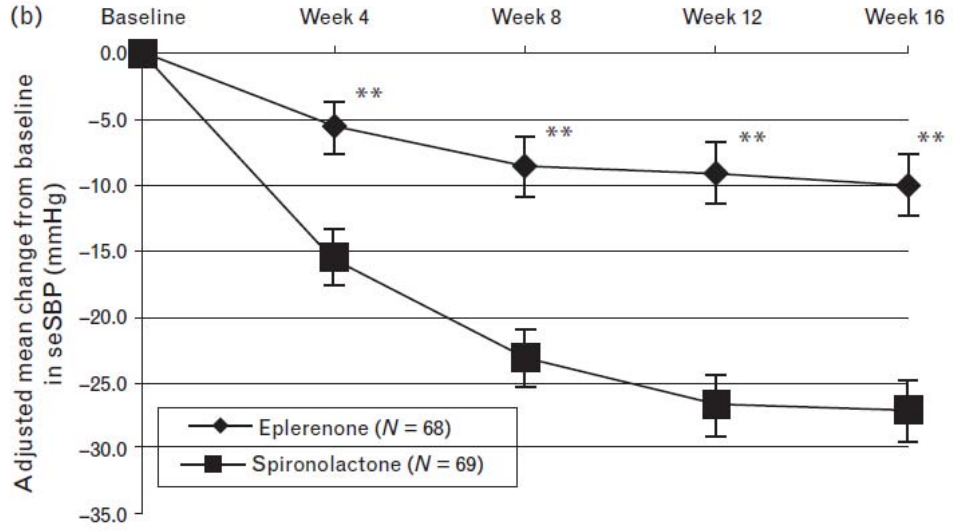
A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism

Hari K. Parthasarathy[a], Joel Ménard[b], William B. White[c], William F. Young Jr[d],

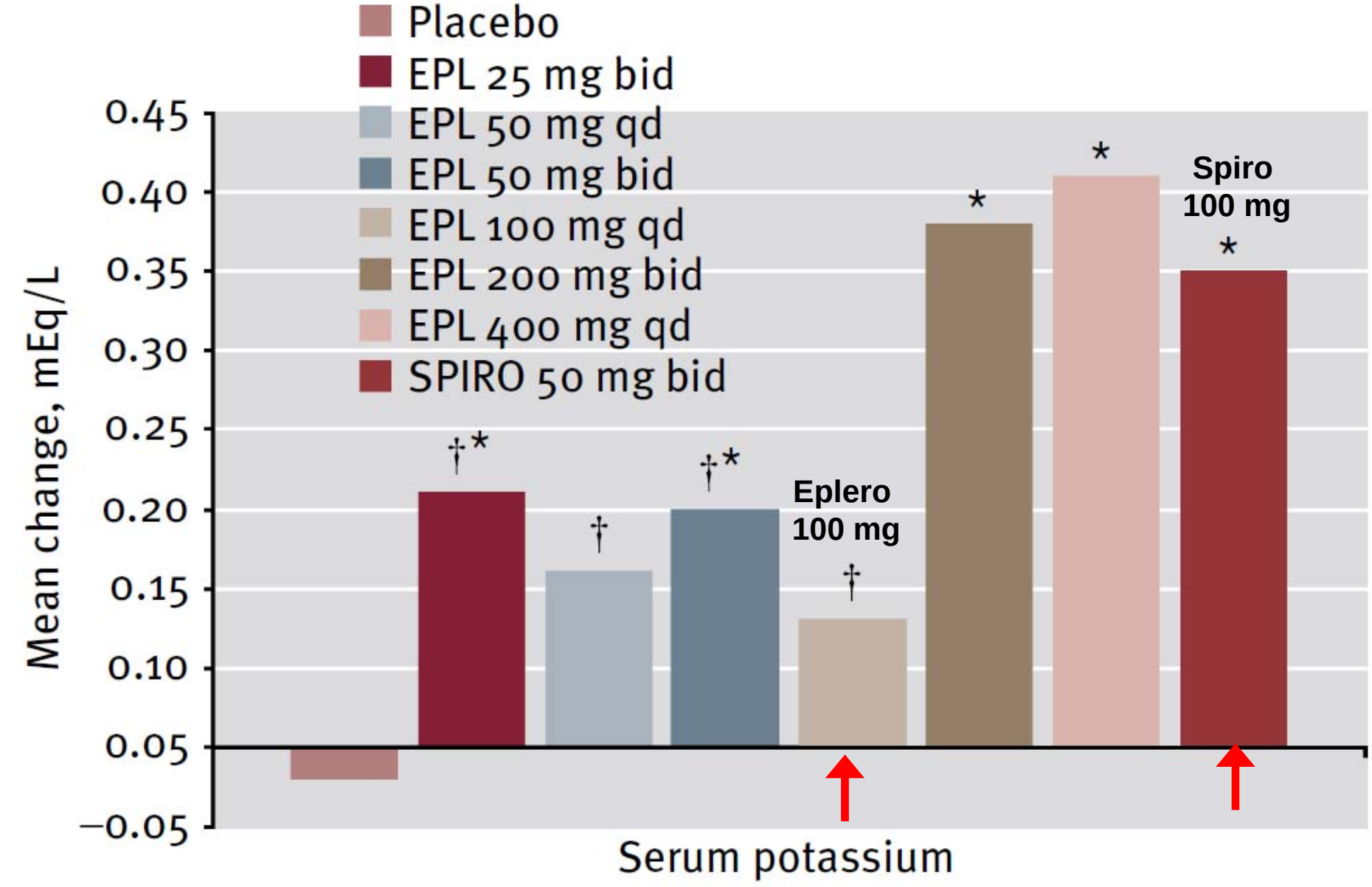
Espironolactona:

- **Más hipotensor**
- **Más Hiper K+**
- Ginecomastia (21%)
- Mastodinia fem (21%)
- Alt. Menstrual (11%)
- Impotencia (6%)

Espiro 150 mg versus Eplerenona 250 mg
Efecto en la TA sistólica (16 semanas)

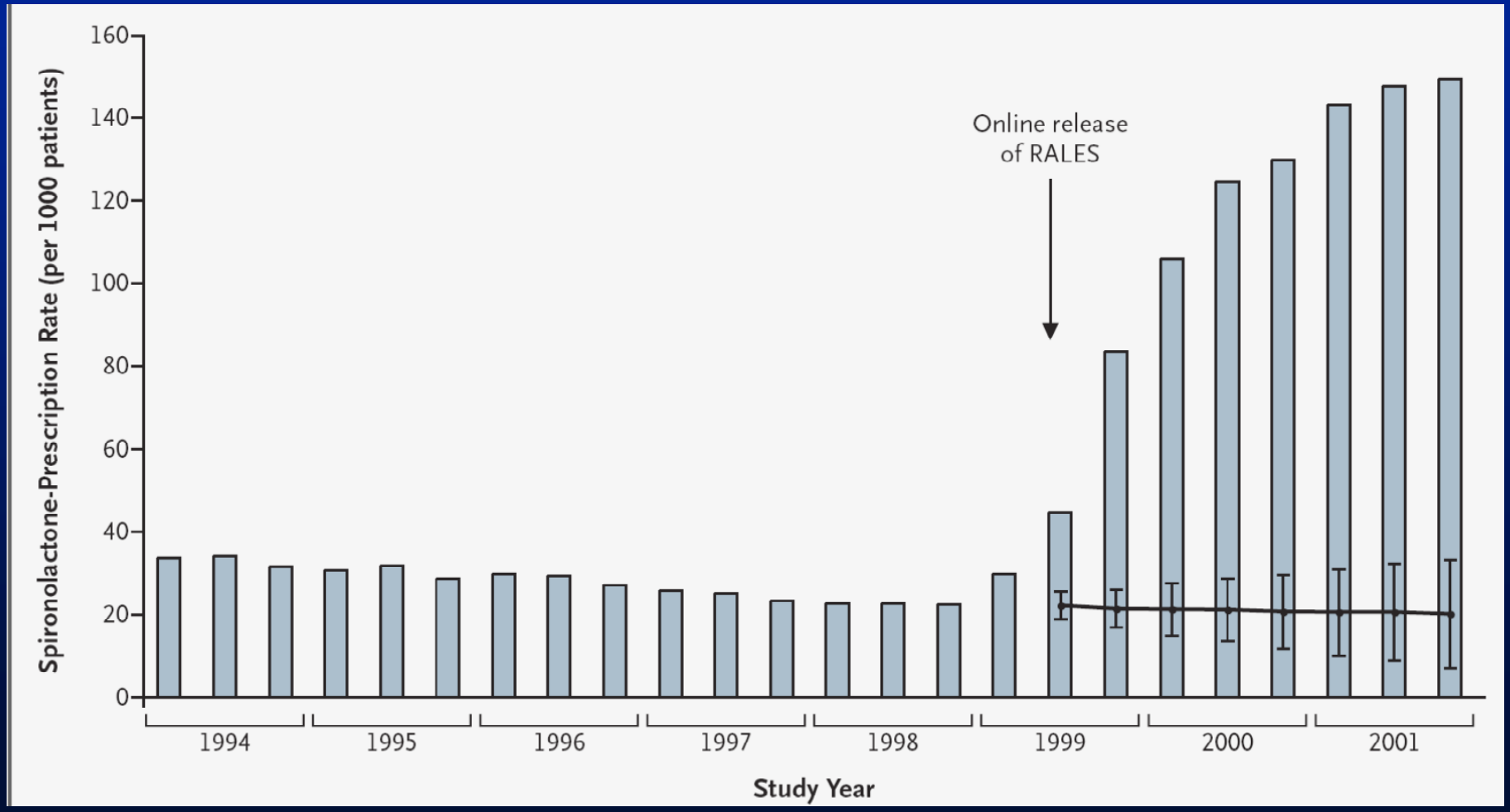


Parthasarathy. J Hypertens 2011


Placebo
EPL 25 mg bid
EPL 50 mg qd
EPL 50 mg bid
EPL 100 mg qd
EPL 200 mg bid
EPL 400 mg qd
SPIRO 50 mg bid
Mean change, mEq/L
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
−0.05
†*
†*
†
*
*
*
Eplero
100 mg
Spiro
100 mg
Serum potassium

Antialdosterónicos y Hiperpotasemia

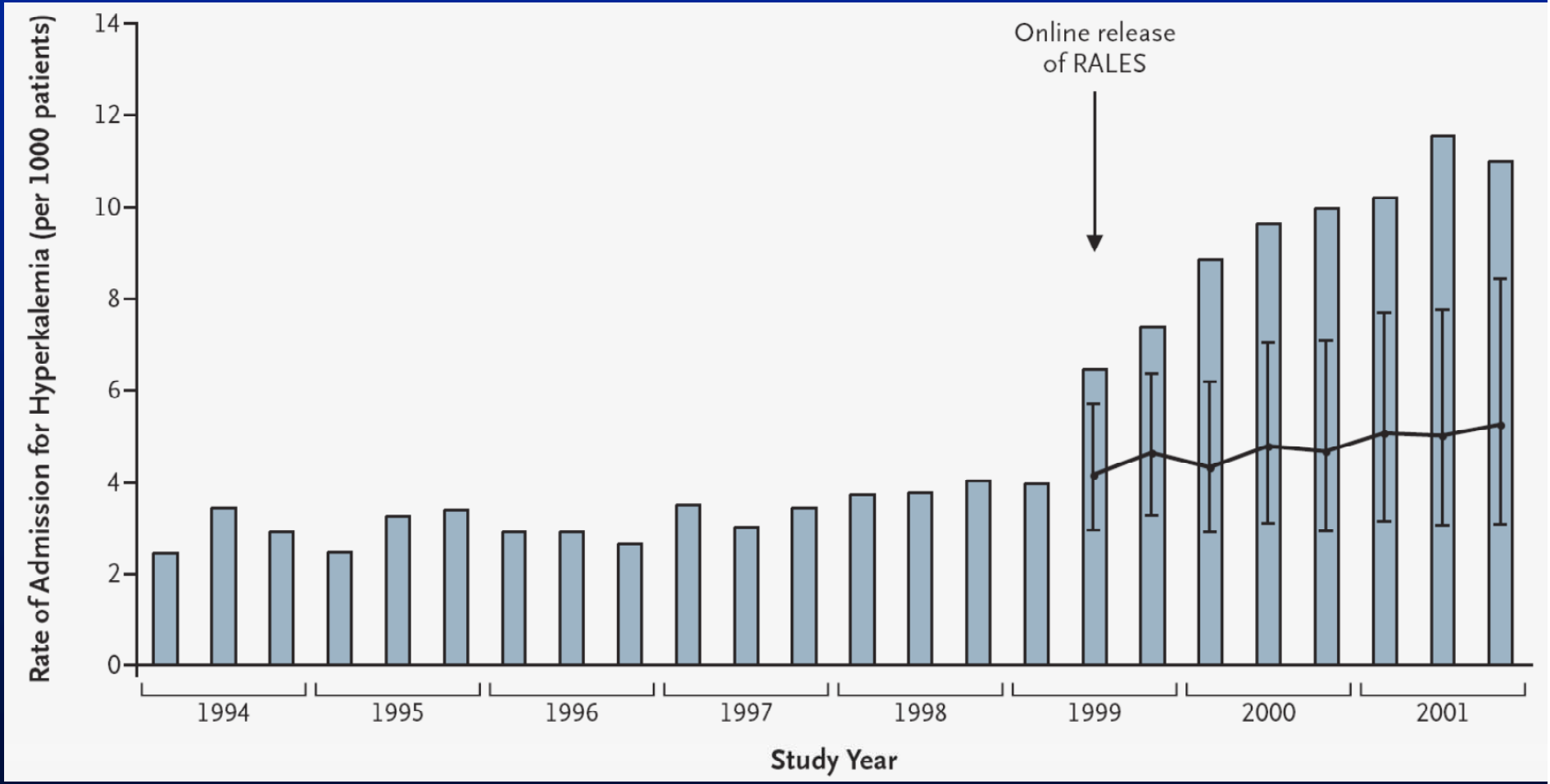
Prescripción de Espironolactona en IC



NEJM 2004;351:543

Antialdosterónicos y Hiperpotasemia

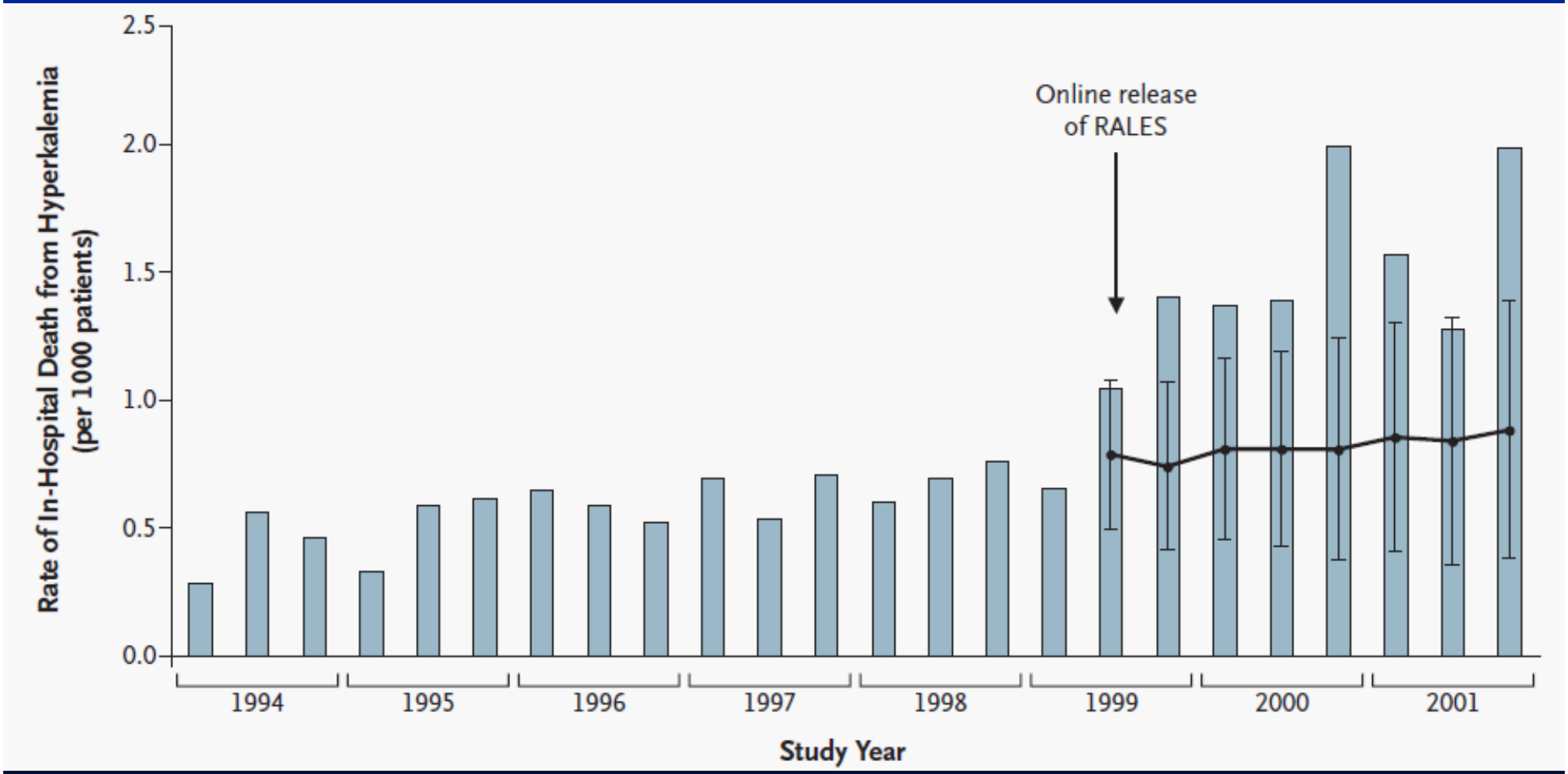
Ingresos por HiperK+



NEJM 2004;351:543

Antialdosterónicos y Hiperpotasemia

Muertes por HiperK+



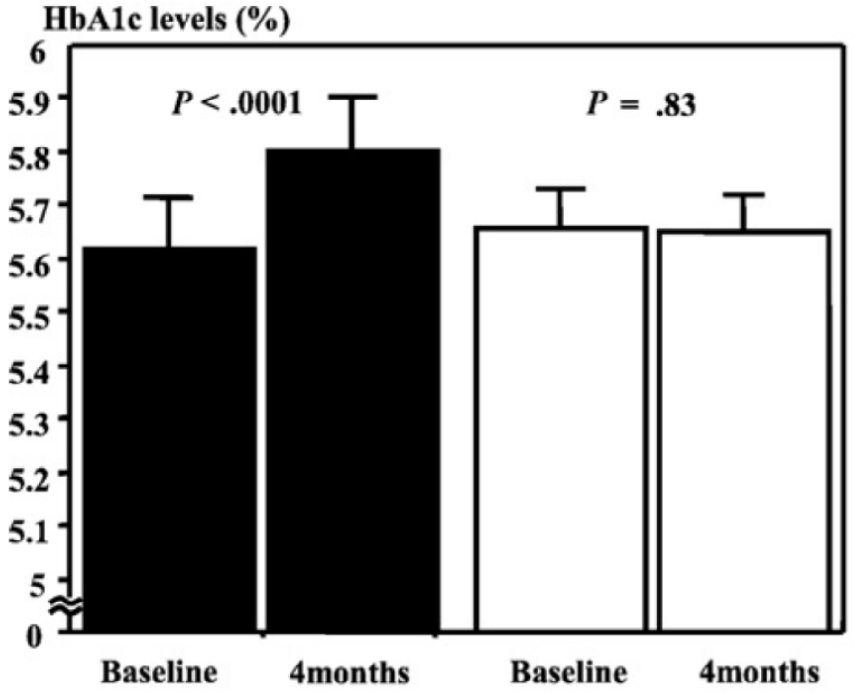
NEJM 2004;351:543

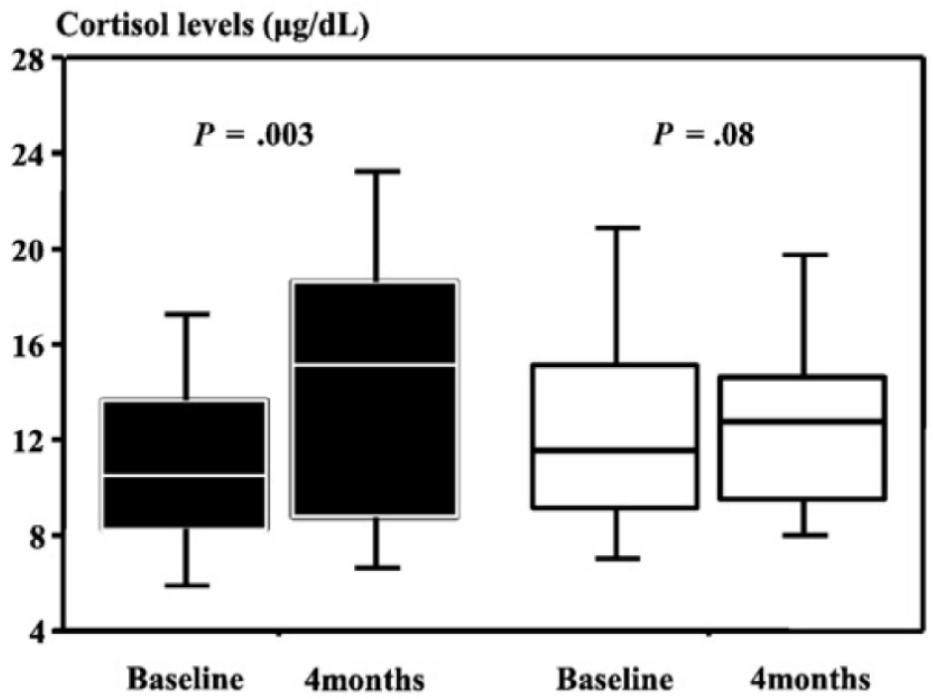
	EPHESUS Early post-MI	EMPHASIS Class II +	RALES Adv III-IV
Ave LVEF	0.33	0.26	0.25
Bblockers	75%	85%	10%
1 yr mort	14% 12%	8% 7%	25% 18%
Deaths diverge	< 3 mos	≤12 mos	< 3 mos
Death	.85	.76	.70
CV Death	.87	.76	.69

Espironolactona versus Eplerenona

Efecto en Cortisol y Hb glicada

Pacientes con IC: Espiro 25 mg vs Eplerenona 50 mg

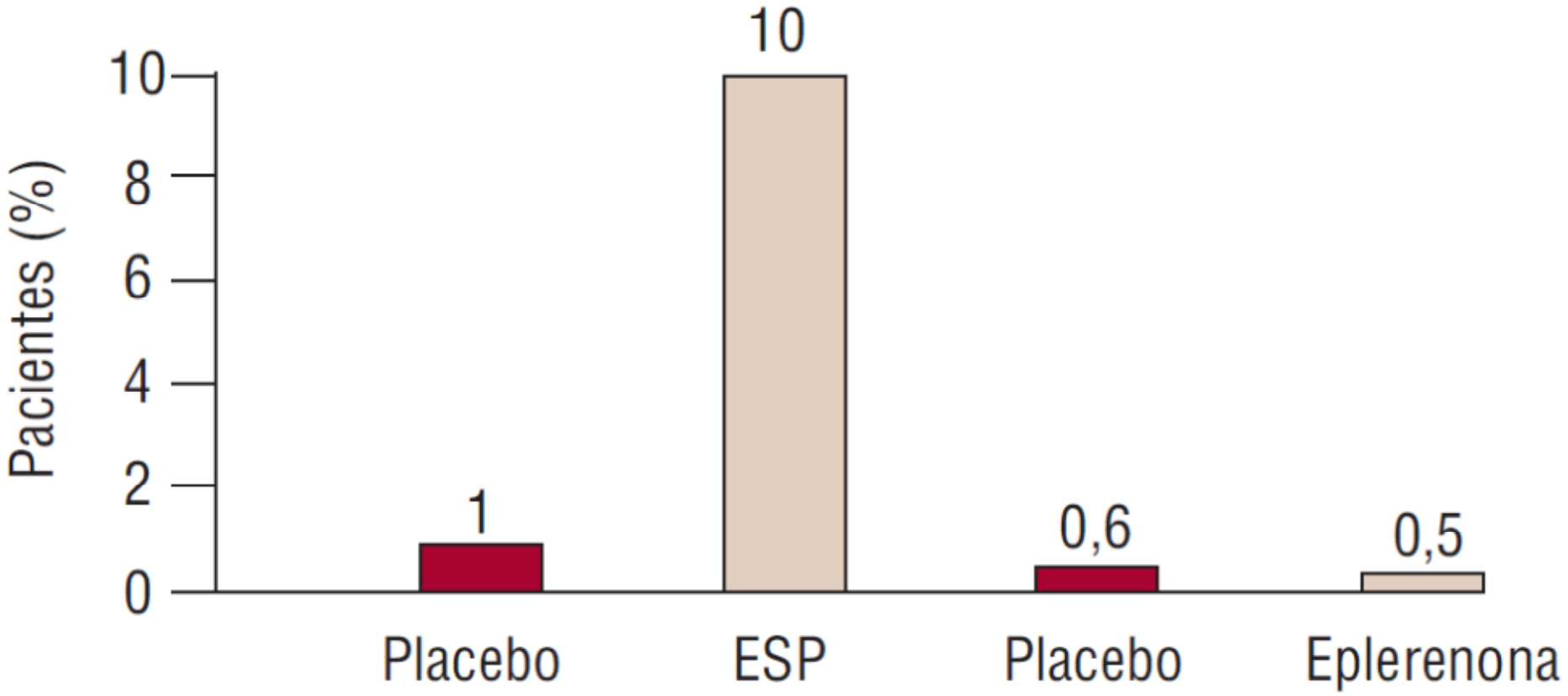




Yamaji. Am Heart J 2010

Espironolactona versus Eplerenona

Ginecomastia



Espironolactona versus Eplerenona
Antagonismo de Testosterona

ARTÍCULO ORIGINAL

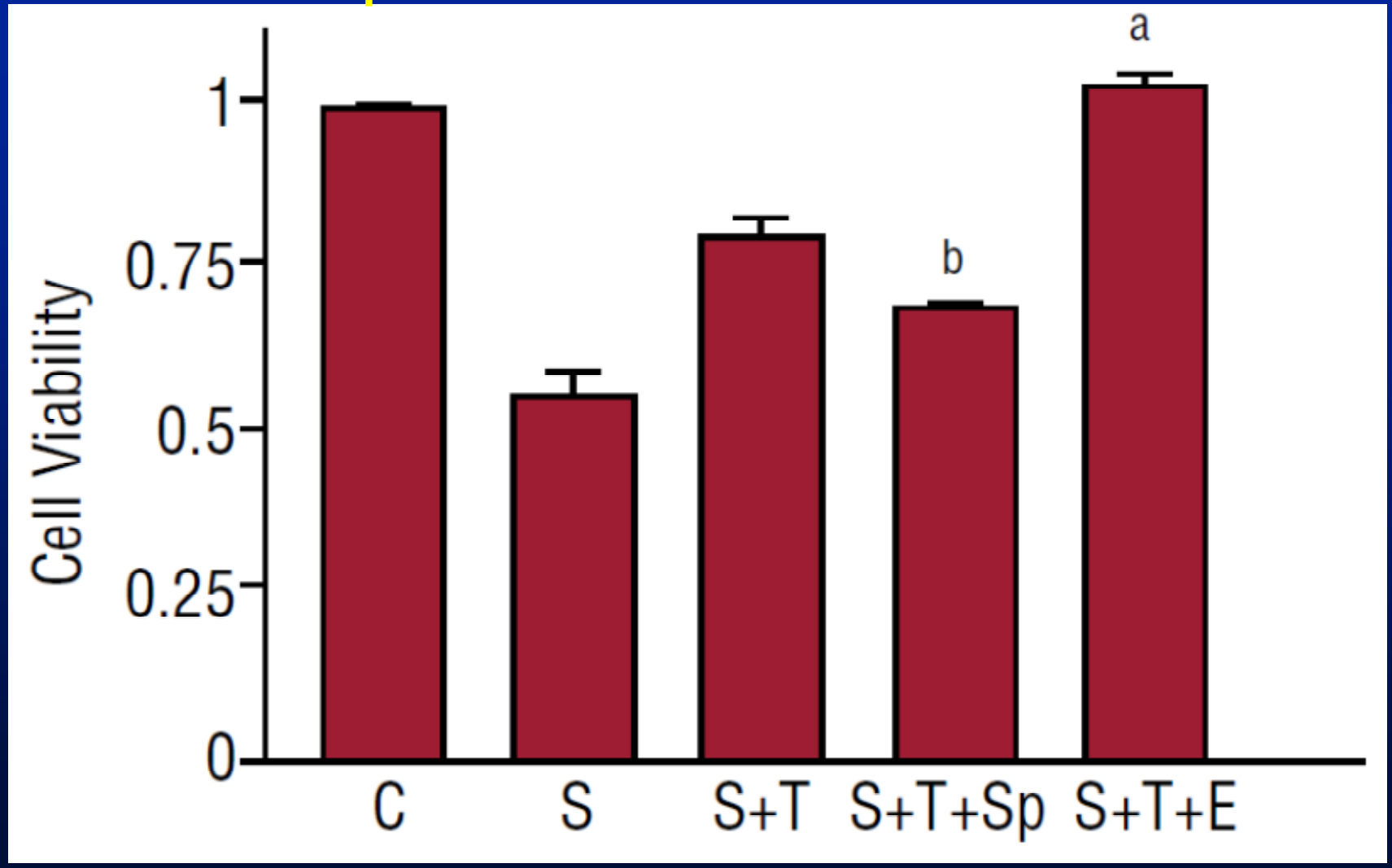
Efecto diferencial de espironolactona frente a eplerenona sobre el papel protector *in vitro* de testosterona en la apoptosis de cardiocitos

Jesús Sánchez-Más, María C. Turpín, Antonio Lax, Juan A. Ruipérez, Mariano Valdés Chávarri y Domingo A. Pascual-Figal

Rev Esp Cardiol. 2010;63(7):779-87

Espironolactona versus Eplerenona

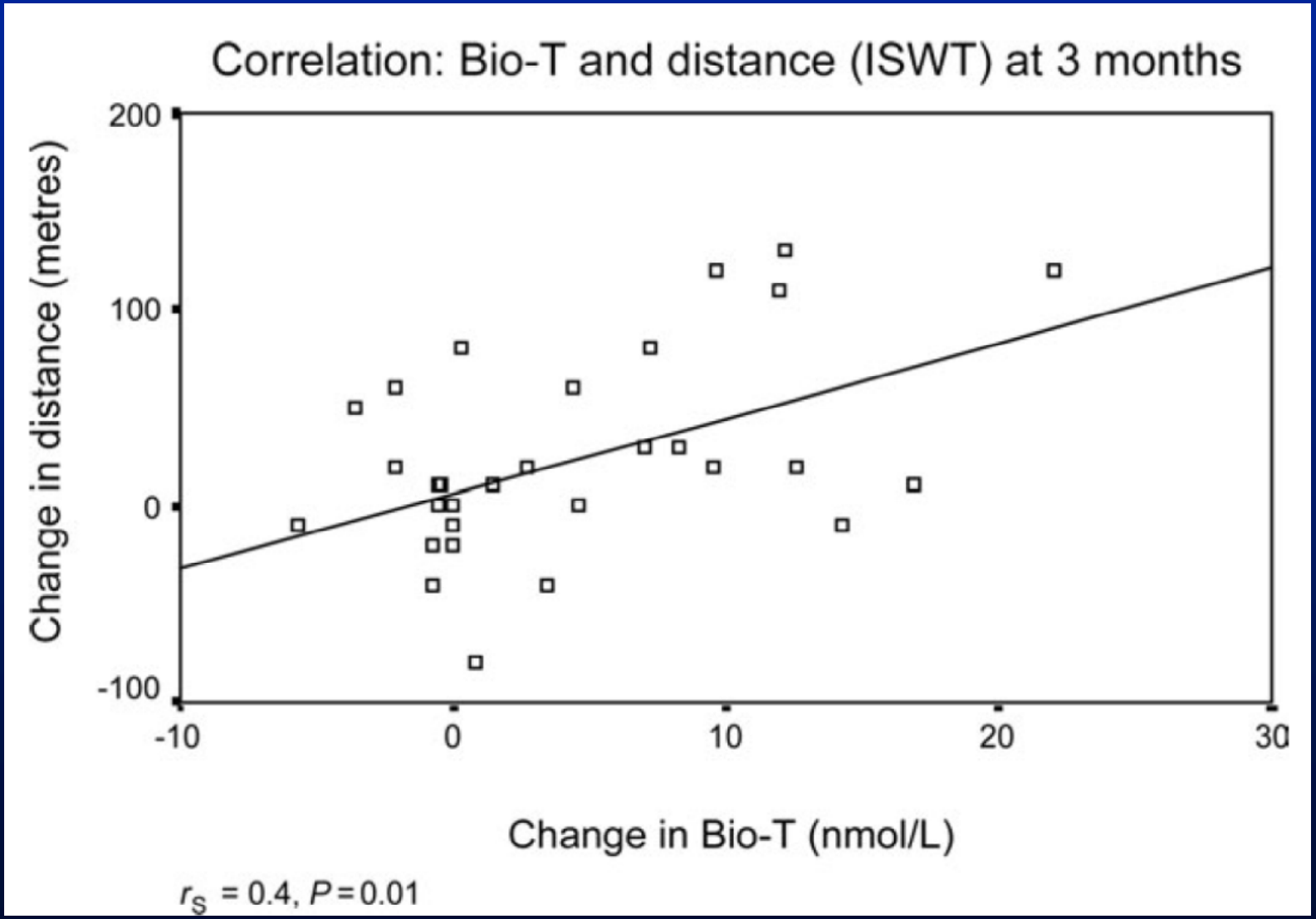
Efecto protector de Testosterona



C=Control. S=Sorbitol. T=Testosterona. Sp=Espiro. E=Eplerenona

Terapia con Testosterona en hombres con IC.

Relación entre aumento de niveles de Testosterona y mejoría en Capacidad funcional



Malkin. Eur Heart J 2006

Conclusiones

- **Espironolactona y Eplerenona tienen un mecanismo de acción común**
- **Han demostrado eficacia en ensayos clínicos, pero con poblaciones distintas de pacientes**

Conclusiones

- Tienen **mecanismos de acción diferenciales** que podrían justificar una diferencia en mortalidad si se comparasen entre ellos

Conclusiones

- ¿Si sustituimos **Eplerenona** por **Espironolactona** podemos estar seguros de obtener el mismo resultado clínico?

....

Conclusiones

- **¿Si sustituimos Eplerenona por Espironolactona podemos estar seguros de obtener el mismo resultado clínico?**

No

Tratamiento Farmacológico de la Insuficiencia Cardiaca

	Mejoran **Supervivencia**	Reducen **Ingresos Hospitalarios**
IECA	**Si**	**Si**
Beta-Bloqueadores	**Si**	**Si**
Antialdosteronicos **-Espironolactona** **-Eplerenona**	**Si**	**Si**

Tratamiento Farmacológico de la Insuficiencia Cardiaca

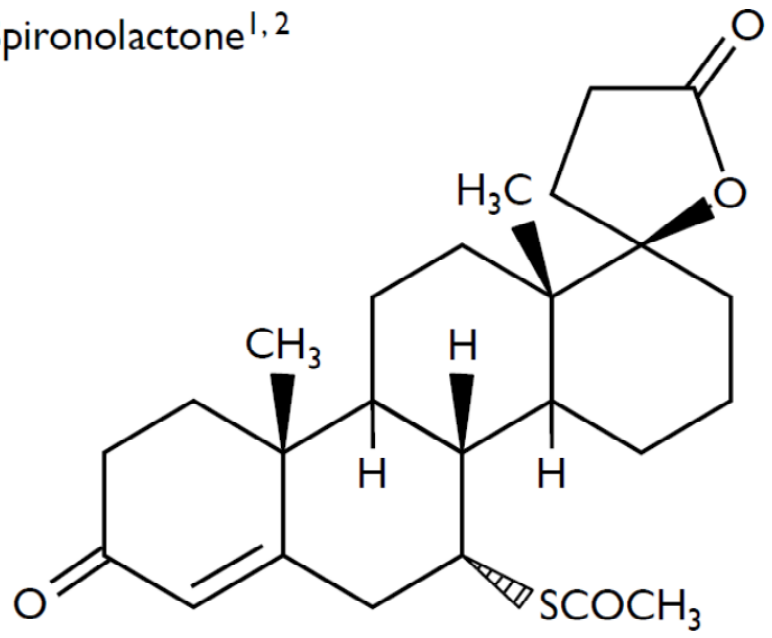
	Mejoran **Supervivencia**	Reducen **Ingresos Hospitalarios**
Ivabradina	**No**	**Si**
ARA (+IECA)	**No**	**Si**
Digoxina	**No**	**Si**

Table 1. Dosage Adjustments in EPHESUS Based on Serum Potassium

Serum Potassium, mEq/L	Dosage Adjustment
<5	Increase 25 mg QOD to 25 mg QD; increase 25 mg QD to 50 mg QD
5.0–5.4	No adjustment
5.5–5.9	Decrease 50 mg QD to 25 mg QD; decrease 25 mg QD to 25 mg QD; decrease 25 mg QOD to withhold
≥6.0	Discontinue eplerenone until serum K^+ <5.5 mEq/L

QD indicates daily; QOD, every other day.

Spironolactone[1, 2]



Eplerenone[1]