INSUFICIENCIA CARDIACA CON FRACCIÓN DE EYECCIÓN VENTRICULAR PRESERVADA

SEMI
SOCIEDAD ESPAÑOLA DE MEDICINA INTERNA

GRUPO DE INSUFICIENCIA CARDIACA

TRATAMIENTO

Oscar Aramburu
B

XI Reunión de Insuficiencia Cardiaca
26-28 de Marzo . 2009 Murcia

TRATAMIENTO de la IC con FEP

- ¿De qué pacientes hablamos?
- IC con FED y FEP: ¿son poblaciones diferentes?
- ¿Cómo la estamos tratando?
- ¿Qué dicen las Guías?
- Evidencias científicas
- Conclusiones

¿De qué pacientes hablamos?

EUROPEAN SOCIETY OF CARDIOLOGY

2007

How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology

European Heart Journal (2007) **28**, 2539–2550

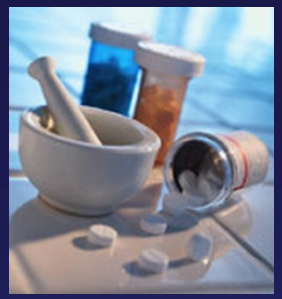
Síntomas o Signos de IC

+

FEVI > 50% y IVTDVI < 97 mL/m^2

+

Evidencia de disfunción diastólica



Ensayos clínicos en IC - FEP

Pacientes con...

Síntomas o Signos de IC, en clase NYHA ...

+

FEVI mayor de .... 35%, 40%, 45%, 50%...

ECR en pacientes con

IC - FED

FEVI es < 35 - 40%

Dónde incluimos los pacientes con

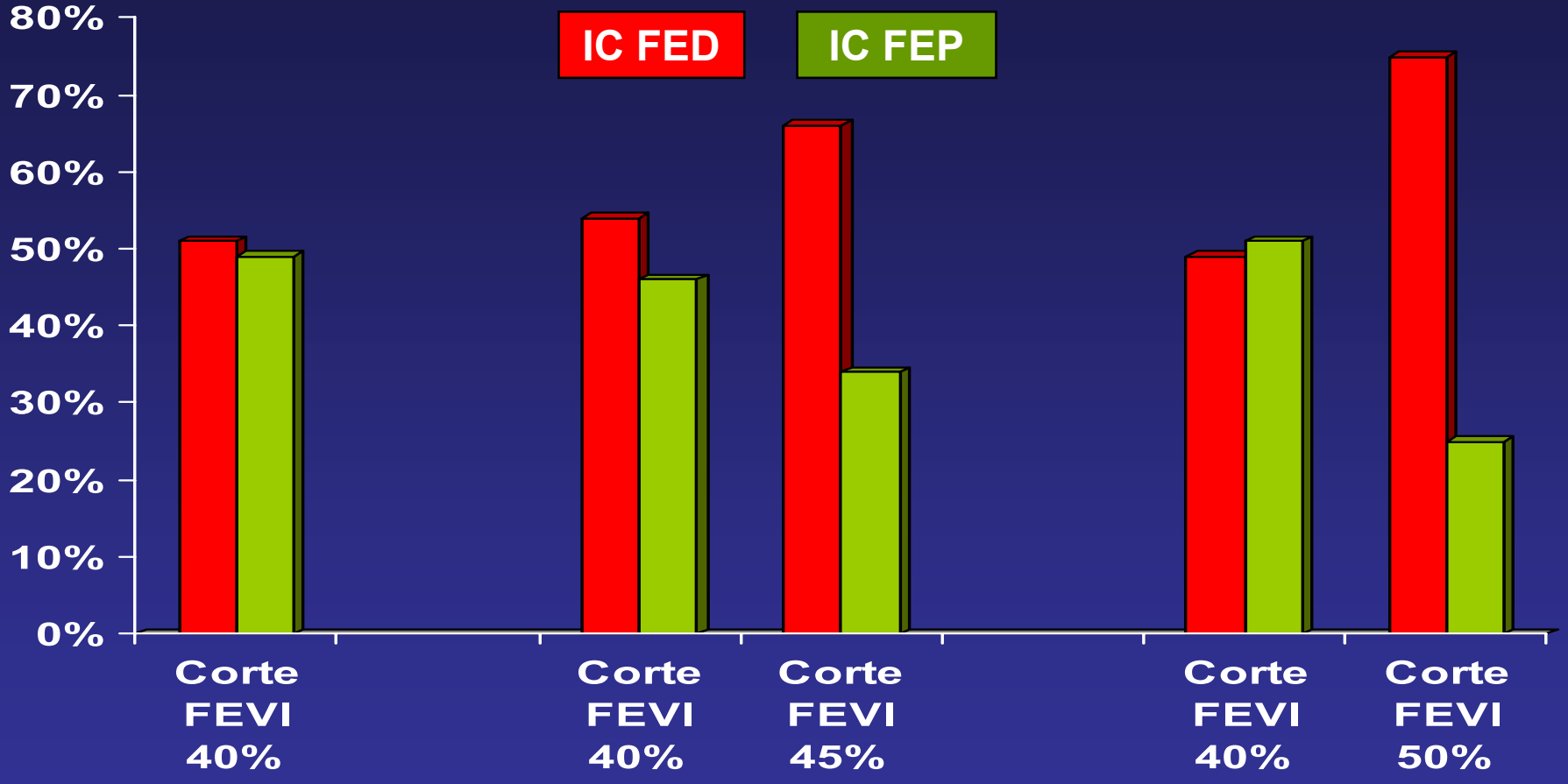
FEVI de 40 a 50 %

Definición de

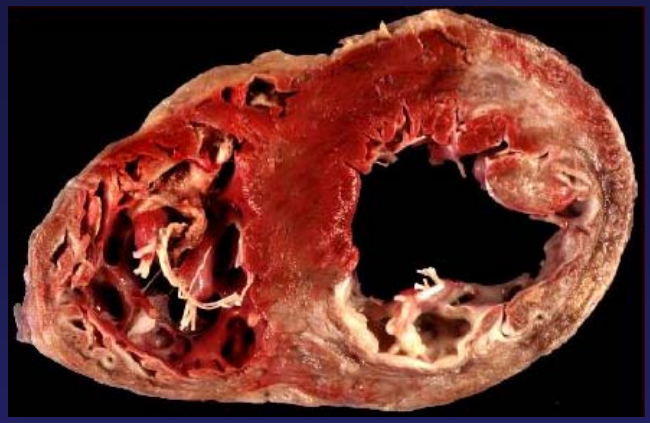
IC - FEP

FEVI > 50%

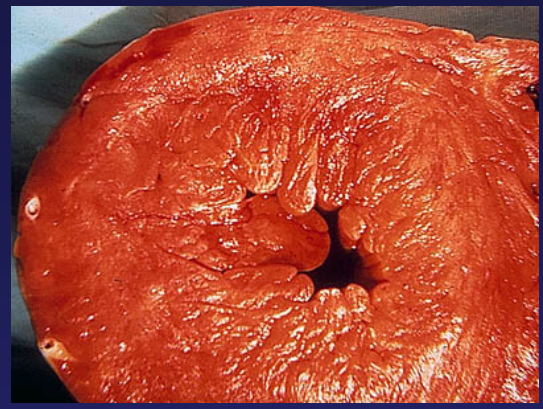
Proporción de Pacientes con FED y FEP en diferentes REGISTROS de IC



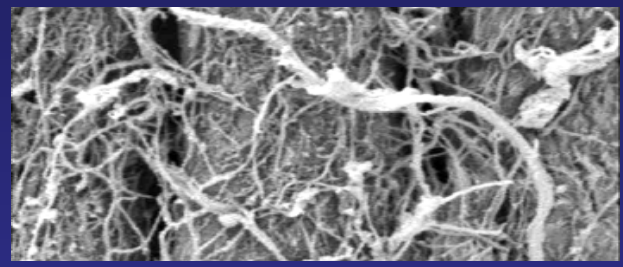
IC con FED y FEP
¿Son poblaciones diferentes?



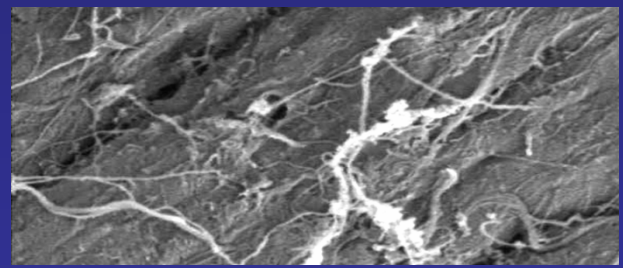
Diferencias morfológicas



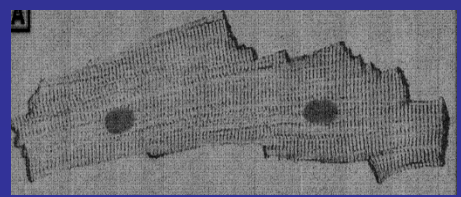
Normal

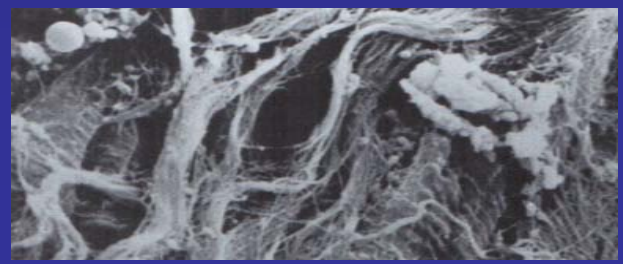


Insuficiencia cardiaca sistólica (MCD)



Insuficiencia cardiaca diastólica (MCH)



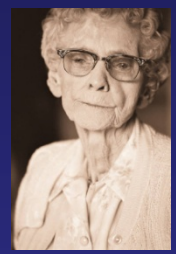


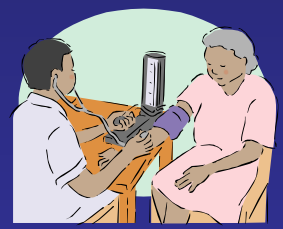
Aurigemma y cols., Circulation 2005

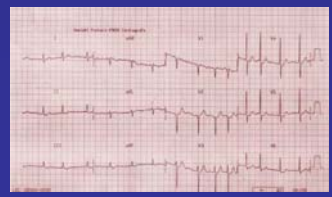
EURO HEART SURVEY

Características de los pacientes con IC

	FS Depr. (n = 3.658)	FS Pres. (n = 3.148)	p
Edad (media, SD)	67 ± 13	71 ± 12	< 0,001
Mujeres (%)	29	55	< 0,001
Hombres < 70 años (%)	26	21	< 0,001
Mujeres > 70 años (%)	17	35	< 0,001
Comorbilidad			
Hipertensión (%)	50	59	< 0,001
Diabetes mellitus (%)	28	26	0,09
Cardiopatía isquémica	69	59	< 0,001
Revascularización previa (%)	18	12	< 0,001
Insuficiencia renal (%)	6	5	0,05
Ictus previo (%)	14	16	0,02
Fibrilación auricular crónica (%)	23	25	0,01
FEVI (media, SD)	33 ± 10,9	56 ± 9,8	< 0,001







Eur Heart J 2004; 25: 1214-20.

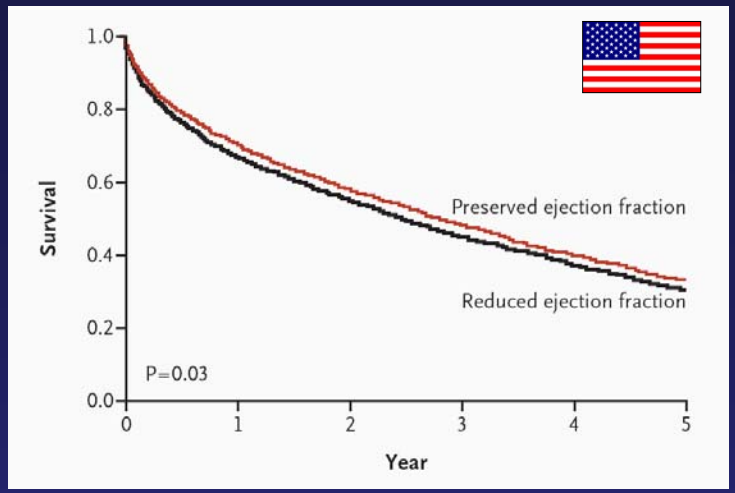
Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction

Theophilus E. Owan, M.D., David O. Hodge, M.S., Regina M. Herges, B.S., Steven J. Jacobsen, M.D., Ph.D., Veronique L. Roger, M.D., M.P.H., and Margaret M. Redfield, M.D.

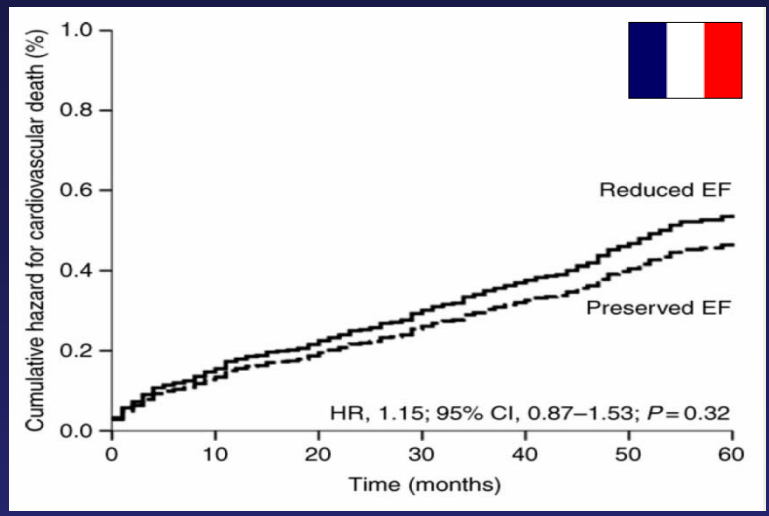
Table 1. Characteristics of Patients with Heart Failure and Preserved or Reduced Ejection Fraction.*

Characteristic	Reduced Ejection Fraction (N=2429)	Preserved Ejection Fraction (N=2167)	P Value	Adjusted P Value†
Age (yr)	71.7±12.1	74.4±14.4 ◀	<0.001	NA
Male sex (% of patients)	65.4	44.3 ◀	<0.001	<0.001
Body-mass index‡	28.6±7.0	29.7±7.8	0.002	0.17
Obesity (% of patients)‡§	35.5	41.4	0.007	0.002
Serum creatinine on admission (mg/dl)	1.6±1.0	1.6±1.1	0.31	0.30
Hemoglobin on admission (g/dl)	12.5±2.0	11.8±2.1	<0.001	<0.001
Hypertension (% of patients)	48.0	62.7 ◀	<0.001	<0.001
Coronary artery disease (% of patients)	63.7	52.9	<0.001	<0.001
Atrial fibrillation (% of patients)	28.5	41.3 ◀	<0.001	<0.001
Diabetes (% of patients)	34.3	33.1	0.42	0.61
Substantial valve disease (% of patients)	6.5	2.6	<0.001	0.05
Ejection fraction (%)	29±10	61±7	<0.001	NA

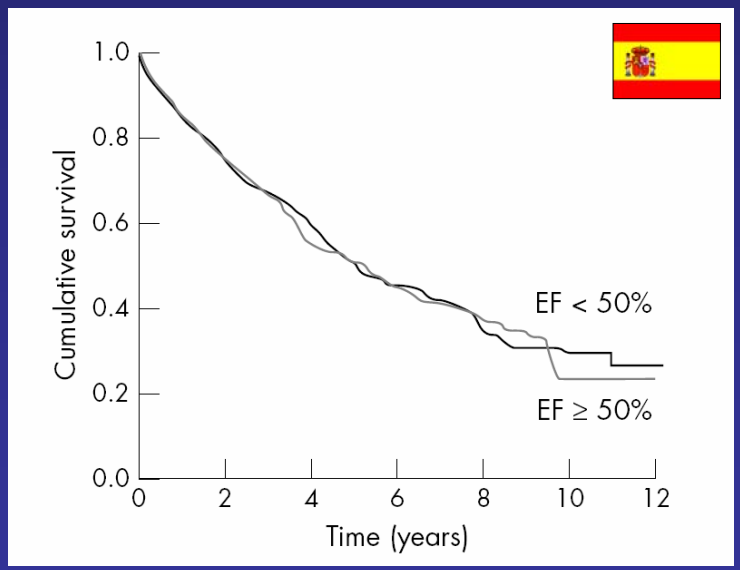
NEJM 2006; 355:251-9.



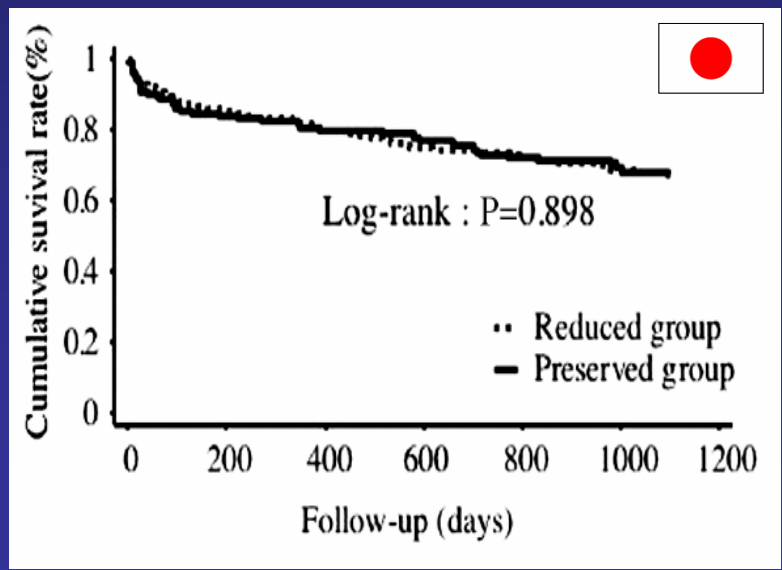
Owan et al. NEJM 2006; 355:251-9



Tribouilloy et al. Eur Heart J 2008; 29:339-47

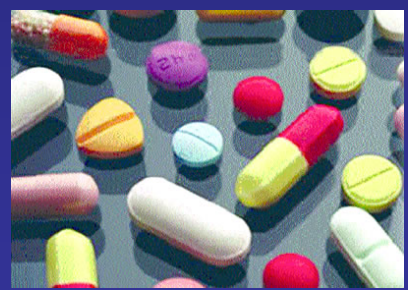


Varela-Román et al. Heart 2005; 91:489-94



Mayagishima et al. Circ J 2009; 73:92-99

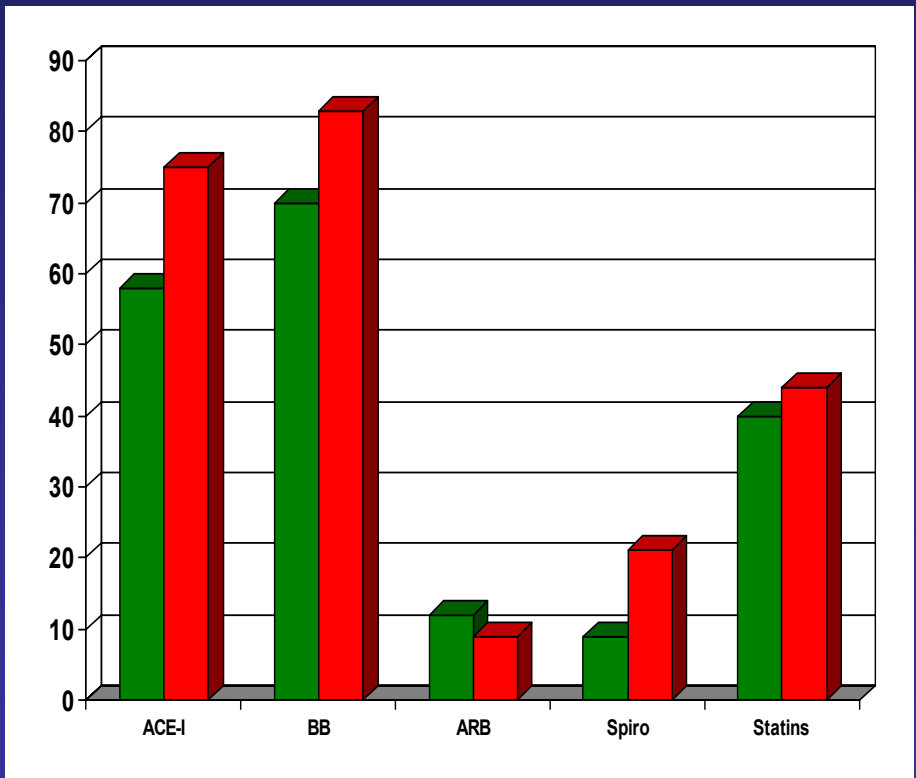
¿Cómo estamos tratando la IC-FEP?

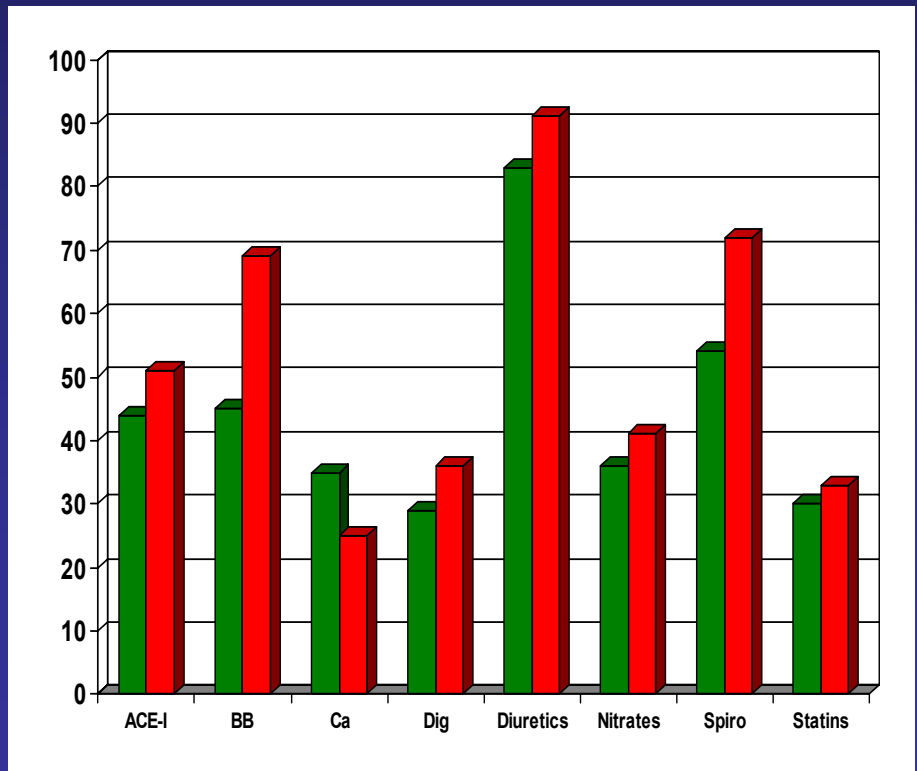


Tratamiento Médico

IC FEP vs **IC FED**

OPTIMIZE-HF

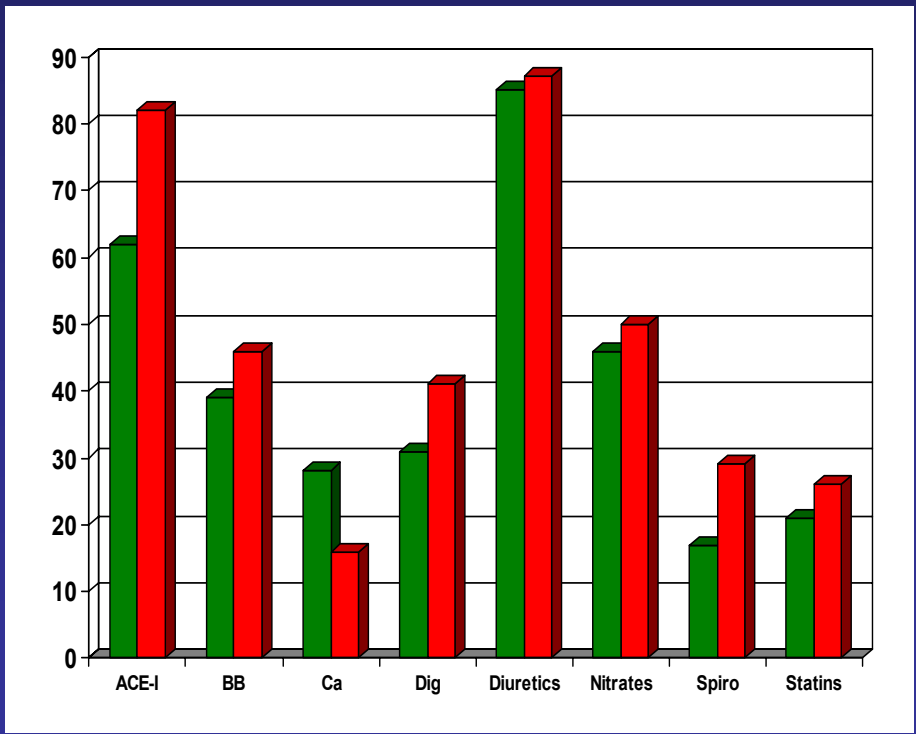




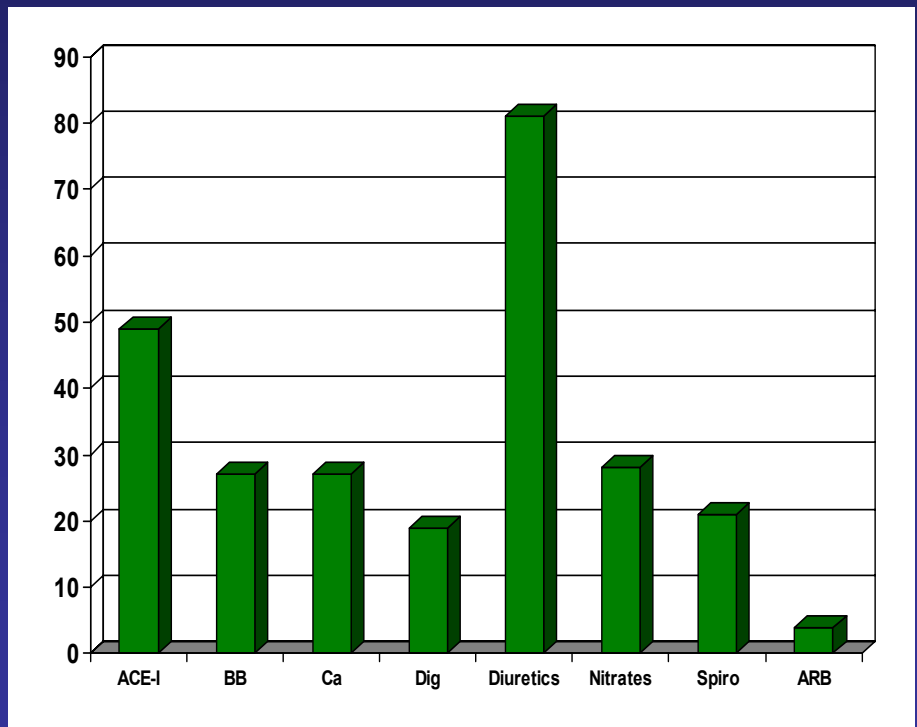
Tratamiento Médico

IC FEP vs **IC FED**

EURO HEART SURVEY

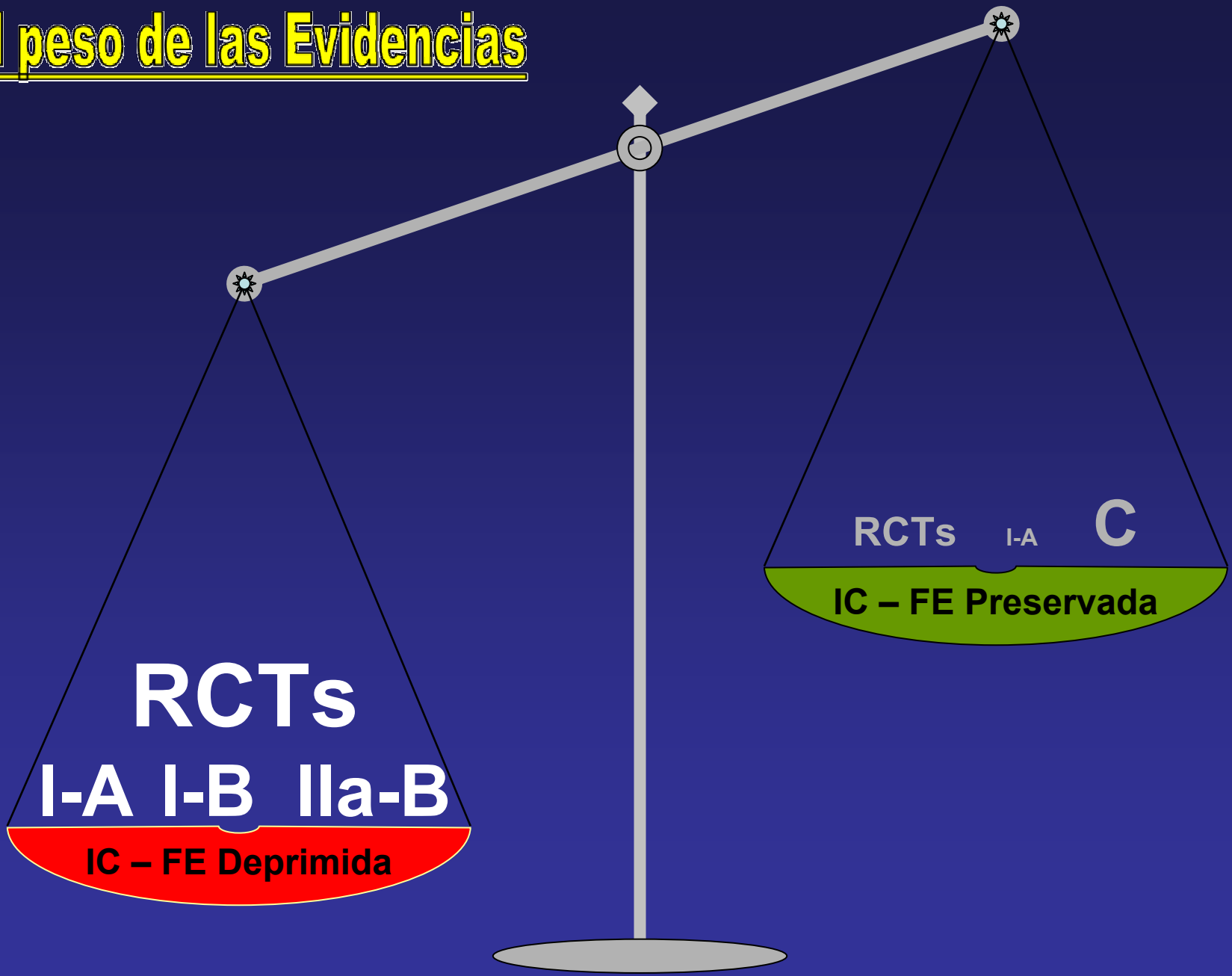


ETICS study



¿Qué dicen las Guías?

El peso de las Evidencias



59 páginas ...

SIGN

Scottish Intercollegiate Guidelines Network

NHS Quality Improvement Scotland

95

Management of chronic heart failure

A national clinical guideline

February 2007

4.9 HYDRALAZINE AND ISOSORBIDE DINITRATE

The combination of hydralazine and isosorbide dinitrate (H-ISDN) was shown to reduce mortality in patients with heart failure before ACE inhibitors were introduced.[52] It was found to be less effective than an ACE inhibitor in a subsequent head-to-head comparison with enalapril (28% mortality reduction in favour of enalapril, p=0.016).[53] Hydralazine and isosorbide dinitrate have been shown to reduce symptoms and the risk of death and hospital admissions for heart failure when added to standard treatment (which included ACE inhibitors, ARBs, beta-blockers for at least three months before randomisation, digoxin, spironolactone, and diuretics) in African-Americans with NYHA class III or IV CHF (absolute survival benefit 4.0%, hazard ratio for all cause mortality 0.57; p=0.01).[54] In Caucasian patients the main indication for H-ISDN is intolerance of an ACE inhibitor and ARB due to renal dysfunction or hyperkalaemia. Vasodilator adverse effects are common and, rarely, hydralazine can cause a lupus-like syndrome.[55,56] 1++ 1+

A **African-American patients with advanced heart failure due to left ventricular systolic dysfunction should be considered for treatment with hydralazine and isosorbide dinitrate in addition to standard therapy.**

B **Patients who are intolerant of an angiotensin converting enzyme inhibitor and an angiotensin II receptor blocker due to renal dysfunction or hyperkalaemia should be considered for treatment with a combination of hydralazine and isosorbide dinitrate.**

4.10 PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION

Not all patients with heart failure have LVSD. Patients with clinical heart failure but normal LV systolic function are described as having 'heart failure with preserved LV systolic function. The proportion of heart failure patients with preserved LV systolic function may be as high as 35-50%.[57]

Heart failure with preserved LV systolic function often occurs along with myocardial ischaemia, hypertension, myocardial hypertrophy or even myocardial/pericardial constriction. Consideration should be given as to whether these entities may be present and contribute to the clinical picture in heart failure patients with preserved LV systolic function. If present, they should be identified and treated in their own right. An additional contributory factor could be tachy-arrhythmias; if so, rate control is likely to be beneficial.

The evidence on how to treat heart failure with preserved LV systolic function is limited. The best evidence comes from the CHARM Preserved study where candasartan had favourable, but not significant, effects on the endpoint of cardiovascular mortality or heart failure hospitalisations.[58] 1++

No good evidence was identified for the benefit of diuretics, ACE inhibitors,[59] beta blockers, aldosterone antagonists or calcium antagonists in these patients. In practice, diuretics are often used to reduce and then prevent fluid overload. ARBs are also now often used because of the favourable trends in the CHARM Preserved trial.[58] Beta blockers and rate limiting calcium antagonists are also often used although the evidence base is not robust enough to recommend any of these treatments.

4.11 HEART FAILURE AND GOUT

Loop diuretics can cause an elevated urate level and may precipitate gout.[50] 4

No evidence was identified on how best to treat gout in patients with heart failure. Current practice in the management of acute gout is to use colchicine to suppress the inflammation and pain.[51] This requires careful consideration or monitoring. Another alternative is a short course of prednisolone. 1-

Once the pain is under control, consideration should be given to starting prophylactic antagonist therapy and stopping colchicine.

ASSOCIATION MÉDICALE CANADIENNE — CANADIAN MEDICAL ASSOCIATION

22 páginas ...

GUIDELINES & PROTOCOLS

ADVISORY COMMITTEE

Heart Failure Care

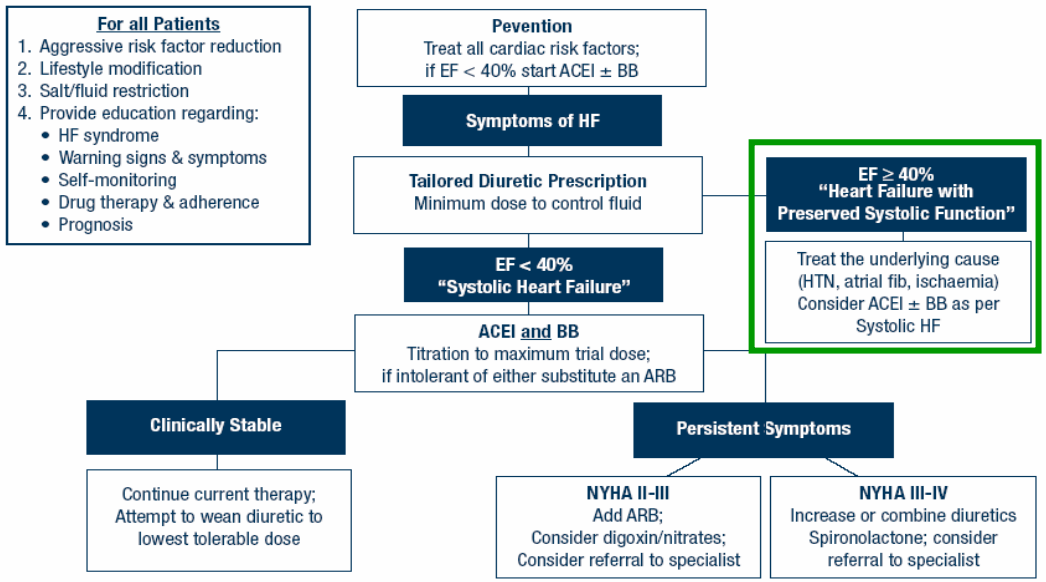
Effective Date: February 15, 2008

RECOMMENDATION 4 **Pharmacotherapy for Heart Failure**

In general, research evidence for treatment is best established for systolic HF, although the underlying principles and pharmacotherapy also apply to HF with PSF. However, when treating HF with PSF, extra caution is required with ACE-I, vasodilators and diuretics to prevent symptomatic hypotension or pre-renal failure as LV filling pressures are volume dependent.

- It is important to treat the following underlying cause where possible, especially in the case of HF with PSF:
  - Hypertension (goal is blood pressure <140/90 mmHg)
  - Ischemic heart disease
  - Atrial fibrillation (goal ventricular rate between 60-80 at rest and <110 with exercise)
  - Hypertrophic cardiomyopathy (consider referral to specialist)

Figure 2. Management



Heart Failure Society of America

38 páginas ...

Executive Summary: HFSA 2006 Comprehensive Heart Failure Practice Guideline

Table 1 Heart Failure Society of America Practice Guidelines for the management of patients with HF-PEF

Recommendations	Strength of evidence
Evaluation for ischemic heart disease and inducible ischemia is recommended for patients with HF-PEF	C
Aggressive BP monitoring is recommended	C
Counseling on low-sodium diet is recommended	C
Diuretics are recommended for patients with clinical evidence of volume overload. Treatment may be started with a thiazide or loop diuretic. Excessive diuresis may lead to orthostatic changes in BP and worsening renal function	C
ARBs or ACEI should be considered in patients with HF-PEF	ARBs: B, ACEIs: C
ACEIs (ARBs if ACEI-intolerant) should be considered in all patients with HF-PEF who have symptomatic atherosclerotic cardiovascular disease or diabetes and one additional risk factor	C
β-Blockers are recommended in patients with HF-PEF who have	
Prior MI	A
Hypertension	B
Atrial fibrillation requiring control of ventricular rate	B
Calcium channel blockers should be considered in	
Atrial fibrillation requiring control of ventricular rate in which β-blockers have proven inadequate because of intolerance. In these patients diltiazem or verapamil should be considered	C
Symptom limiting angina	A
Hypertension: amlodipine should be considered	C
Measures to restore and maintain sinus rhythm should be considered in patients with symptomatic atrial flutter–fibrillation, but this decision should be individualized	C

ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure)

American Heart Association®
Learn and Live℠

83 páginas ...

Table 8. Recommendations for Treatment of Patients With Heart Failure and Normal Left Ventricular Ejection Fraction

Recommendation	Class	Level of Evidence
Physicians should control systolic and diastolic hypertension, in accordance with published guidelines.	I	A
Physicians should control ventricular rate in patients with atrial fibrillation.	I	C
Physicians should use diuretics to control pulmonary congestion and peripheral edema.	I	C
Coronary revascularization is reasonable in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to be having an adverse effect on cardiac function.	IIa	C
Restoration and maintenance of sinus rhythm in patients with atrial fibrillation might be useful to improve symptoms.	IIb	C
The use of beta-adrenergic blocking agents, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, or calcium antagonists in patients with controlled hypertension might be effective to minimize symptoms of heart failure.	IIb	C
The use of digitalis to minimize symptoms of heart failure is not well established.	IIb	C

European Heart Journal (2008) **29**, 2388–2442
doi:10.1093/eurheartj/ehn309

ESC GUIDELINES

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008

55 páginas ...

Class of recommendation IIb, level of evidence B

Key evidence

- Most trials with statins excluded patients with HF. Only one trial, CORONA, specifically studied a statin in patients with symptomatic HF, ischaemic aetiology, and reduced EF. Rosuvastatin did not reduce the primary end-point (cardiovascular death, MI, or stroke) or all-cause mortality. The number of hospitalizations for cardiovascular causes was reduced significantly.[127]
- The value of statins in HF patients with a non-ischaemic aetiology is unknown.

Management of patients with heart failure and preserved left ventricular ejection fraction (HFPEF)

- No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HFPEF. Diuretics are used to control sodium and water retention and relieve breathlessness and oedema. Adequate treatment of hypertension and myocardial ischaemia is also considered to be important, as is control of the ventricular rate in patients with AF. Two very small studies (<30 patients each) have shown that the heart rate-limiting calcium channel blocker verapamil may improve exercise capacity and symptoms in these patients.[128,129]
- The 3023 patient Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved trial did not show a significant reduction in the risk of the primary composite end-point (adjudicated death from cardiovascular causes or admission with HF) but did show a significant reduction in the risk of investigator-reported admissions for HF.[130] The 850 patient Perindopril for Elderly People with Chronic Heart failure (PEP-CHF) study failed to show a reduction in this composite primary end-point over the total duration of the trial, but showed a significant reduction in cardiovascular death and HF hospitalization at 1 year.[131]

Devices and surgery

Revascularization procedures, valvular and ventricular surgery

- If clinical symptoms of HF are present, surgically correctable conditions should be detected and corrected if indicated.
- CAD is the most common cause of HF and is present in 60–70% of patients with HF and impaired LVEF.[132,133] In HFPEF, CAD is less frequent but still may be detected in up to half of these patients.[99] Ischaemic aetiology is associated with a higher risk of mortality and morbidity.

Revascularization in patients with heart failure

Both a coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) should be considered in selected HF patients with CAD. Decisions regarding the choice of the method of revascularization should be based on a careful evaluation of co-morbidities, procedural risk, coronary anatomy and evidence of the extent of viable myocardium in the area to be revascularized, LV function, and the presence of haemodynamically significant valvular disease.

Key evidence

There are no data from multicentre trials assessing the value of revascularization procedures for the relief of HF symptoms. However, single-centre, observational studies on HF of ischaemic origin suggest that revascularization may lead to symptomatic improvement and potentially improve cardiac function. Clinical trials are ongoing that address the effect of intervention on clinical outcomes.[134]

Evaluation for coronary artery disease in heart failure patients with unknown coronary artery status

Routine coronary angiography is not recommended.

In patients at low risk for CAD: the results of non-invasive evaluation should determine the indication for subsequent angiography (exercise ECG, stress echocardiography, stress nuclear perfusion imaging).

Coronary angiography

- is recommended in patients at high risk for CAD without contraindications to establish diagnosis and plan treatment strategy.

Class of recommendation I, level of evidence C

- is recommended in patients with HF and evidence of significant valvular disease.

Class of recommendation I, level of evidence C

- should be considered in patients with HF who experience anginal symptoms despite optimal medical therapy

Class of recommendation IIa, level of evidence C

Detection of viable myocardium

As viable myocardium may be a target for revascularization, its detection should be considered in the diagnostic work-up in HF patients with CAD. Several imaging modalities with comparable diagnostic accuracy may be employed to detect dysfunctional but viable myocardium (dobutamine echocardiography, nuclear imaging by SPECT and/or by PET, MRI with dobutamine and/or with contrast agents, CT with contrast agents).[135]

Class of recommendation IIa, level of evidence C

Valvular surgery

- Valvular heart disease (VHD) may be the underlying aetiology for HF or an important aggravating factor that requires specific management.
- The ESC Guidelines on the management of valvular disease apply to most patients with HF.[136] Although impaired LVEF is

Manejo de los pacientes con IC y FEVI conservada

Hasta la fecha, con ningún tratamiento se ha demostrado de forma convincente una reducción de la morbimortalidad en pacientes con IC-FEP.

Los diuréticos se utilizan para la retención de líquidos...

Es importante tratar adecuadamente la HTA, Isquemia y controlar la FC en la FA...

El Verapamilo mejora la capacidad de ejercicio y los síntomas en este grupo de pacientes...

El Candesartán en la IC puede reducir significativamente los ingresos por IC pero no la mortalidad...

El Perindopril mostró una reducción significativa de muertes cardiovasculares y hospitalizaciones por IC durante el primer año pero no al final del estudio (3 años).

Evidencias científicas

Guía IC 2008

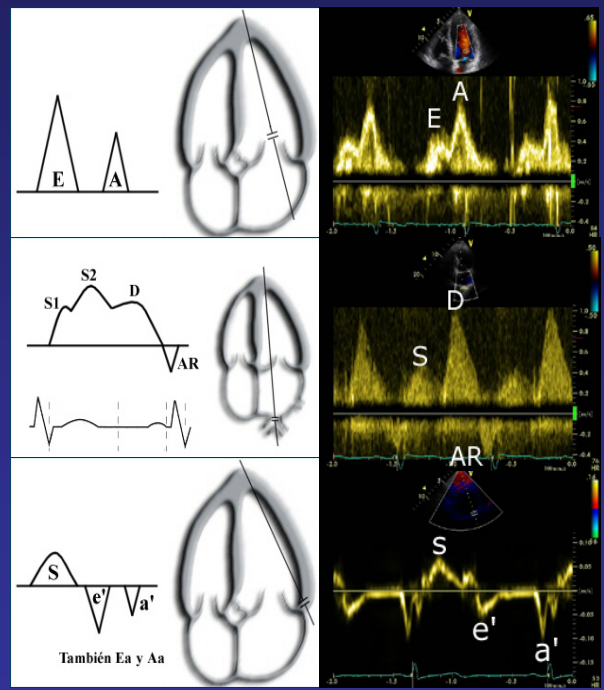
OBJETIVOS del TRATAMIENTO de la ICC

Pronóstico	Reducir la mortalidad
Morbilidad	Aliviar los síntomas y signos Mejorar la calidad de vida Eliminar edema y retención de fluidos Aumentar la capacidad de ejercicio Reducir la fatiga y la falta de aire Disminuir la necesidad de hospitalización Proporcionar cuidados al final de la vida
Prevención	Desarrollo de daño miocárdico Progresión del daño miocárdico Remodelado del miocardio Recurrencia de síntomas y retención de fluidos Hospitalización

Fisiopatológicamente, podría ser útil..

Control de la presión arterial
Reducción de la carga isquémica del miocardio

Evitar la taquicardia



Mantener el ritmo sinusal

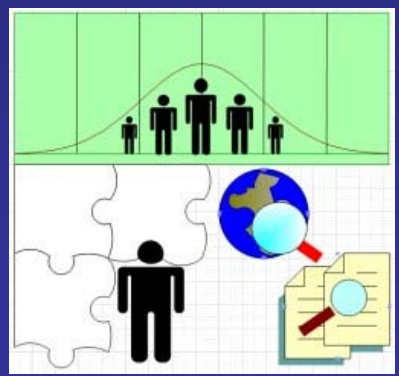
Regresar las alteraciones estructurales y funcionales del miocardio

Fisiopatológicamente, podrían ser útiles...

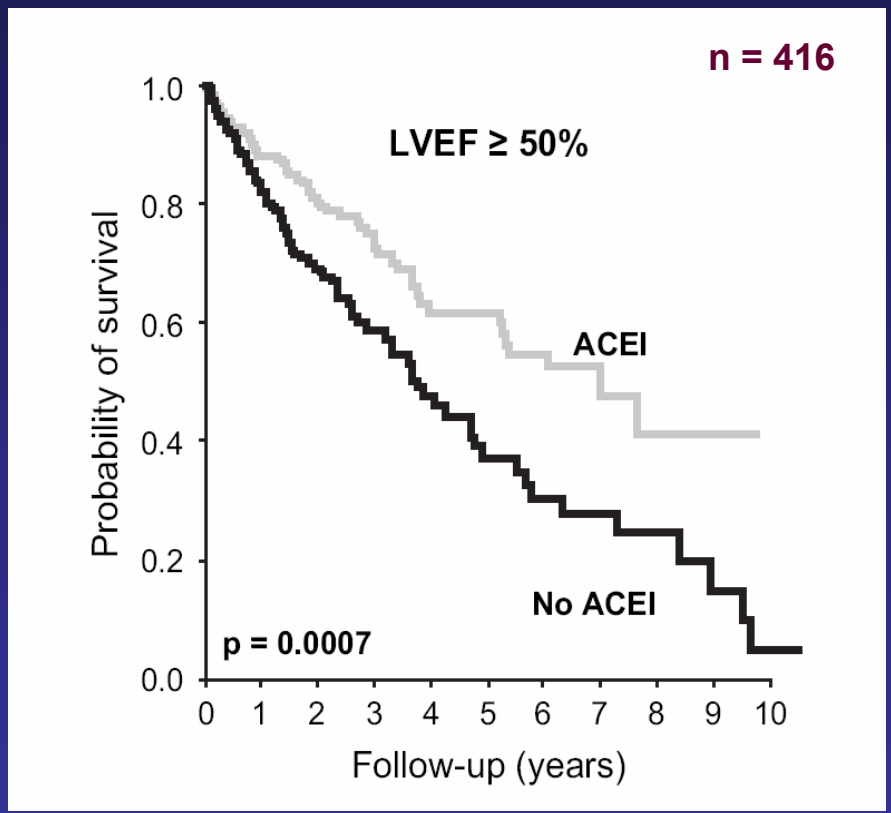
IECAs / ARA-II	Reducen la TA Reducen la HVI Mejoran la relajación del VI
β-Bloqueantes	Reducen TA Controlan taquicardia Revierten/Controlan FA Reducen HVI Reducen isquemia
Antagonistas Aldosterona	Efecto diurético Anti-fibrosis miocárdica
Digoxina	Reduce la activación neuro-hormonal Controla FC en la FA
Calcioantagonistas	Reducen la TA Reducen la HVI Mejoran la relajación del VI
Diuréticos	Deplección de Na y agua

Evidencias científicas

Estudios epidemiológicos

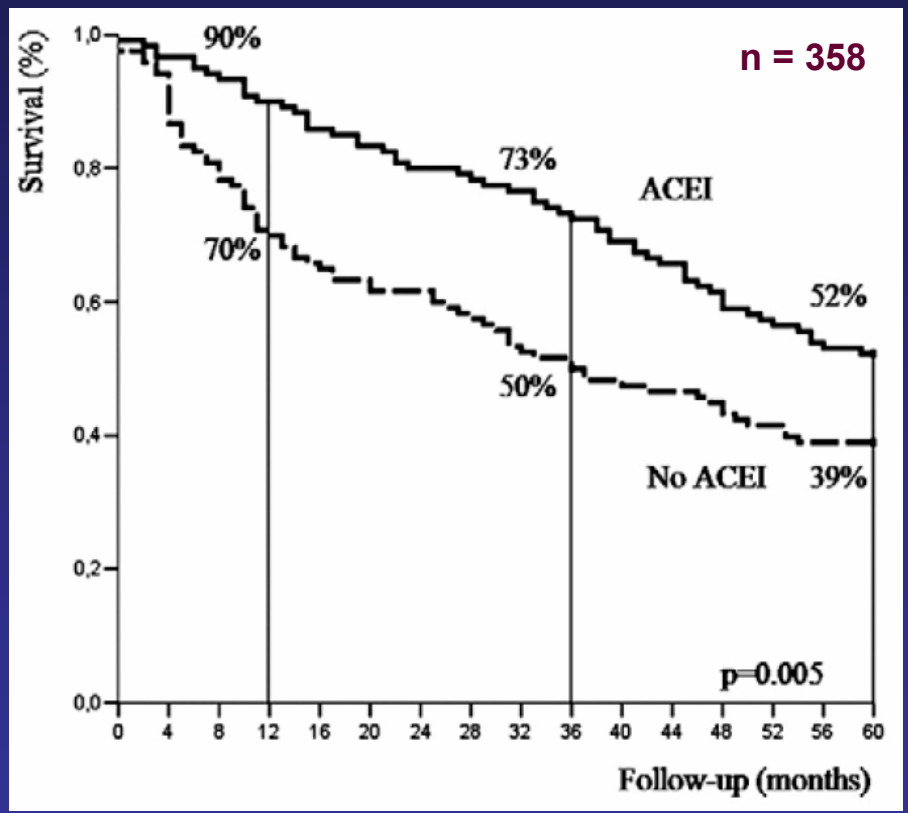


IECAs en IC-FEP
Estudios Observacionales



Santiago de Compostela - España

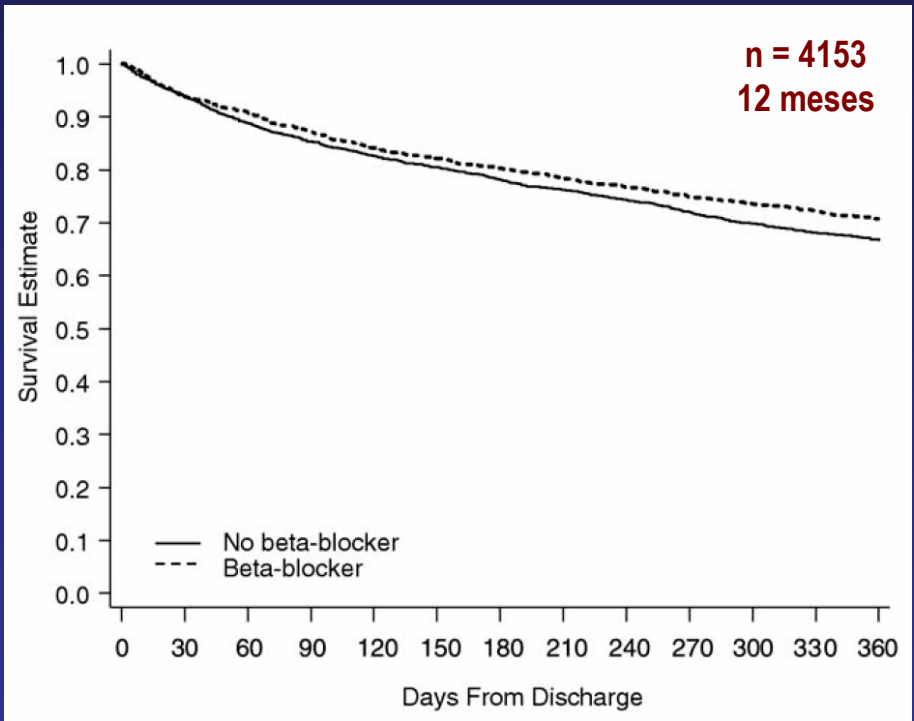
J Cardiac Fail 2006; 12: 128-133



Somme - Francia

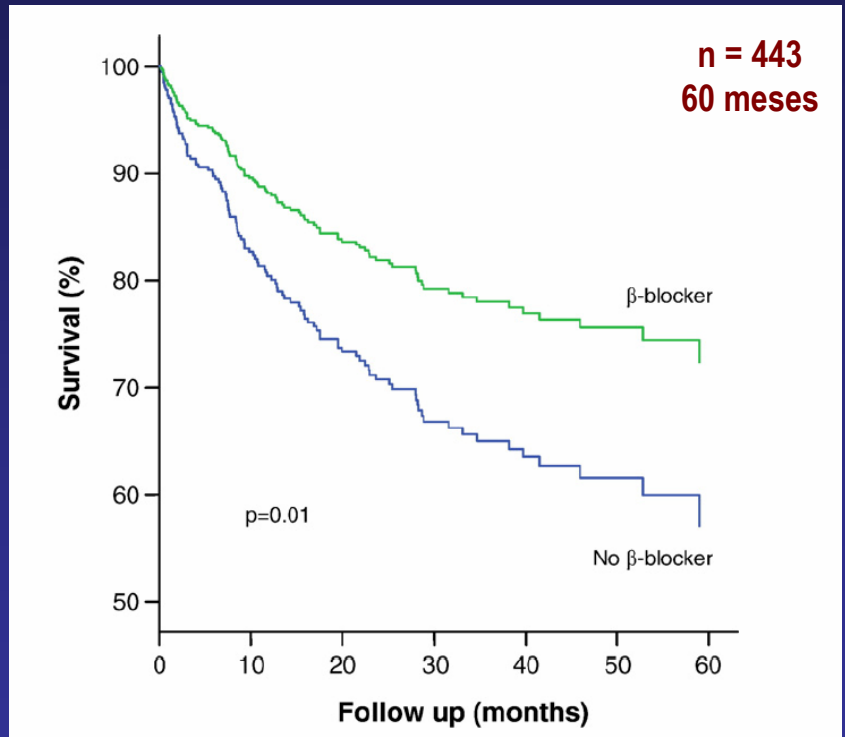
Am J Cardiol 2008; 101: 639-644

Betabloqueantes en IC-FEP
Estudios Observacionales



OPTIMIZE-HF

J Am Coll Cardiol 2009;53:184–92



Eur J Heart Fail 2007; 9: 280-6.

Diversos fármacos en IC-FEP
Estudios Observacionales

MEDICARE – USA
Pacientes: 13533
Edad > 65 años
Ingreso por IC con FEP

RR (IC 95%) de Mortalidad ajustado por variables demográficas, clínicas y para otros tratamientos.

FÁRMACO	1 AÑO		3 AÑOS	
	RR	*95% CI*	*RR*	*95% CI*
IECAs	0.88	0.82-0.95	0.93	0.89-0.98
β-Bloqueantes	0.93	0.87-1.10	0.92	0.87-0.97
Estatinas	0.88	0.82-0.95	0.88	0.82-0.95

Rahman Shah y cols. Am J Cardiol 2008

Evidencias científicas

Ensayos clínicos sobre síntomas / capacidad funcional

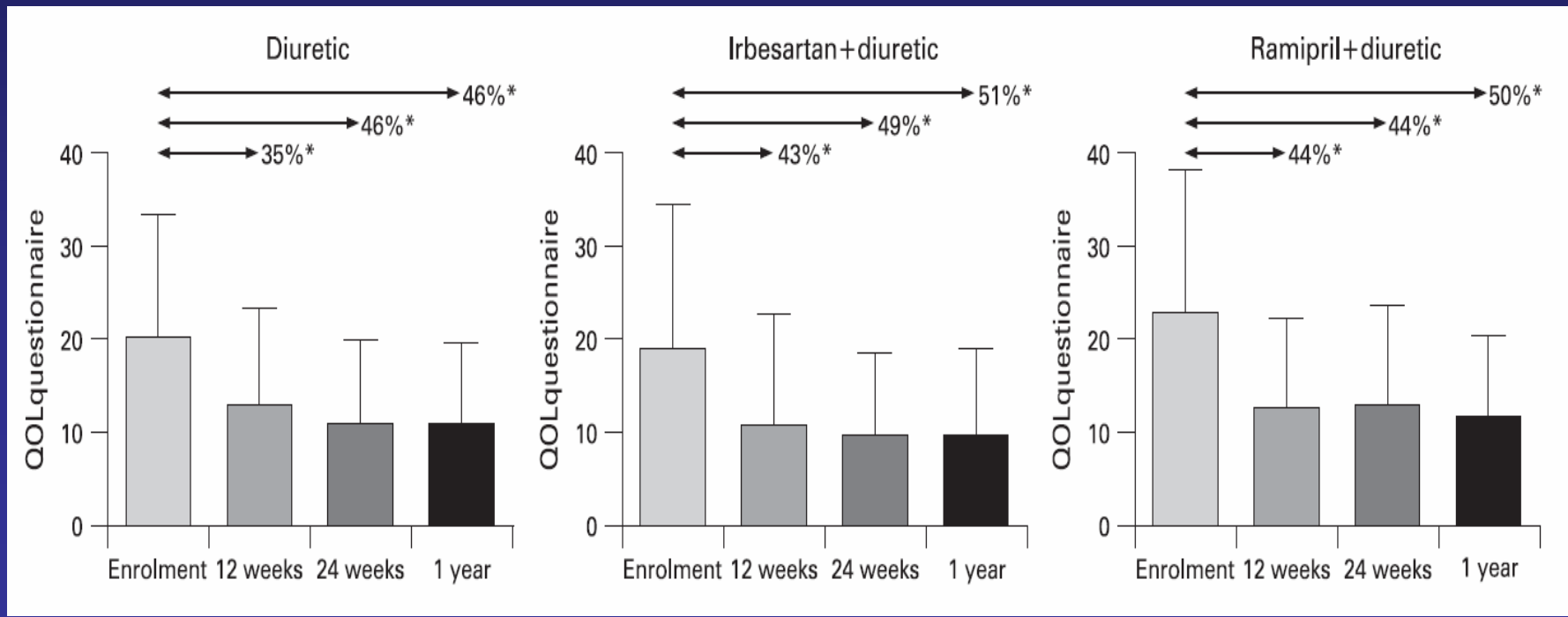
Diversos fármacos en IC-FEP
Ensayos clínicos

FÁRMACO	Pacientes	Tratamiento	Criterios de valoración	Resultados
Lisinopril Lang y cols - 1995	12	5 + 5 semanas *(E.C. Cruzado)*	Disnea - Limitación actividad física *(escala visual)*	N.S.
Enalapril Aranow y cols - 1993	21	3 meses	Clase NYHA Tiempo ejercicio (Bruce)	Mejoría de ambos P < 0.005
Quinapril Zi y cols - 2003	74	6 meses	6MWT score McMaster QoL cuestionario	N.S.
Verapamil Hung y cols - 2002	15	3 + 3 meses *(E.C. Cruzado)*	CHF score - TRIV Tiempo de ejercicio	Mejoría de todos P < 0.05
Carvedilol SWEDIC - 2004	97	6 meses	Función diastólica (4 parámetros Eco-Doppler)	Mejora Índice E:A 4P P=0.13
Carvedilol * Takeda y cols - 2004	40	12 meses	Capacidad ejercicio BNP plasmático	Mejoría de ambos P < 0.01

Diurético / Irbesartan + D / Ramipril + D en IC-FEP
Ensayo clínico

The Hong Kong DHF study - 2008

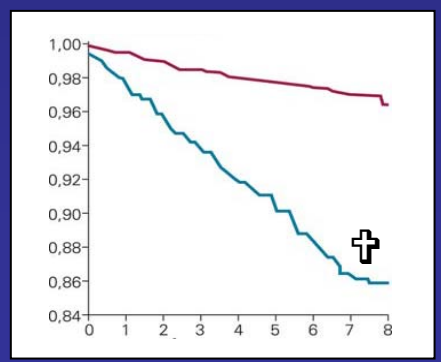
Pacientes: 150
FEVI > 45%
1 año de tto.



Heart 2008; 94: 573-580

Evidencias científicas

Ensayos clínicos de morbi-mortalidad



MBE

Heart Failure With Normal Ejection Fraction

The V-HeFT Study

Jay N. Cohn, MD, Gary Johnson, MS,
and Veterans Administration Cooperative Study Group*

Pacientes: 83 (623)
Edad $\bar{X}$: 60
FEVI ≥ 45%
Digoxina + Diur
27 meses de tto.

Tasa anual de mortalidad

Placebo	**9.0%**	
		N.S.
Hidralazina + Nitratos	**5.3%**	

Circulation 1990; 81 (Suppl III)

Effect of *Propranolol* Versus No *Propranolol* on Total Mortality Plus Nonfatal Myocardial Infarction in Older Patients With Prior Myocardial Infarction, Congestive Heart Failure, and Left Ventricular Ejection Fraction ≥40% Treated With Diuretics Plus Angiotensin-Converting Enzyme Inhibitors

Wilbert S. Aronow, MD, Chul Ahn, PhD, and Itzhak Kronzon, MD

Pacientes: 158
Edad $\bar{X}$: 81
FEVI ≥ 40%
Post-IAM
Diurético + IECA
32 meses de tto.

Incidencia de Muerte y Muerte + IAM no fatal

	Propranolol (n = 79)	No Propranolol (n = 79)
	No. (%)	No. (%)
Total mortality	44 (56)	60 (76)*
Total mortality plus nonfatal myocardial infarction	47 (59)	65 (82)†

*p = 0.007; †p = 0.002.

Am J Cardiol 1997; 80:207-9

Grandes Ensayos Clínicos en IC-FEP

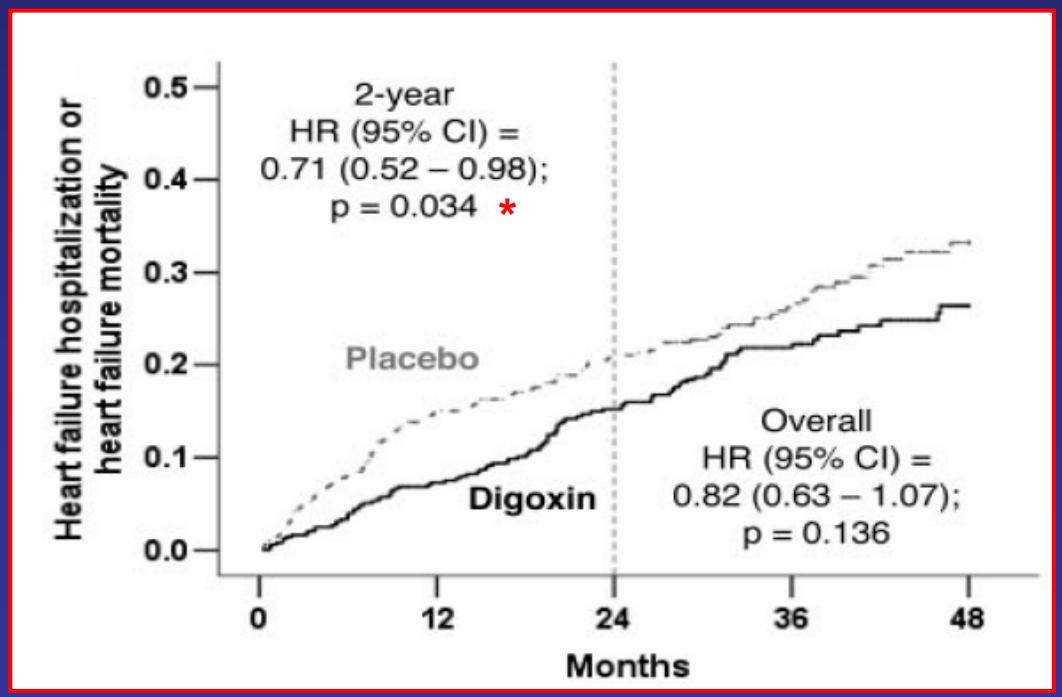
Características

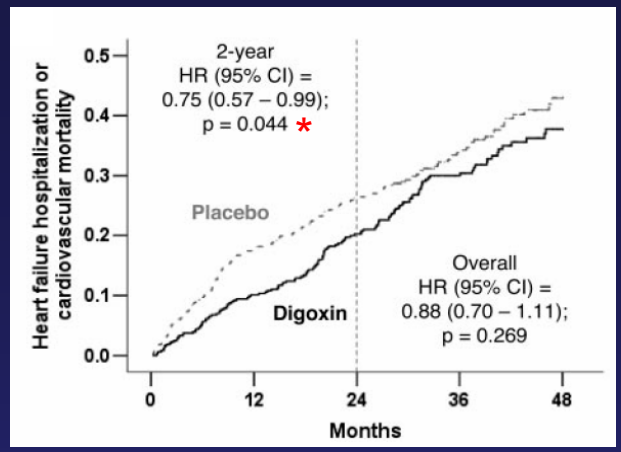
ESTUDIO	*DIG-PEF* Digoxina n = 988	*SENIORS* Nebivolol n = 2128 [752]	PEP-CHF Perindopril n = 850	CHARM-Pres Candesartan n = 3023	I-PRESERVE Irbesartan n = 4128
Edad ($\bar{X}$)	≥ 21 (67)	≥ 70 (76)	≥ 70 (75)	≥ 18 (67)	≥ 60 (72)
Mujeres %	41	37	56	40	60
FEVI ($\bar{X}$)	> 45 (55)	≤35% [> 35]	> 40 (64)	> 40 (54)	> 45 (59)
NYHA I-II / III-IV	20-58 / 21-1	3-56 / 38-2	75 / 25	0-61 / 37-2	0-21 / 76-3
Etiología: ISQ / HTA	56 / 23	? (70 EAC)	?	57 / 23	25 / 64
Seguimiento (meses)	36.6	21	26.2	37	49.5
Criterios de Inclusión	Diagnóstico de IC Clínico o Rx. NYHA I-IV Ritmo Sinusal	Historial de IC + Hospitalización por IC en 12 meses prev. ó FEVI ≤ 35% en los 6 meses previos	Hospitalización de c. cardiaca < 6 m Diuréticos > 1 sem. 3 de 9 criterios clínicos + 2 de 4 ecocardiográficos	Hospitalización de causa cardiaca. NYHA II a IV > 4 sem.	Hospitalización por IC + NYHA II-IV ó NYHA III-IV + criterios Rx, ECG o Ecocardio

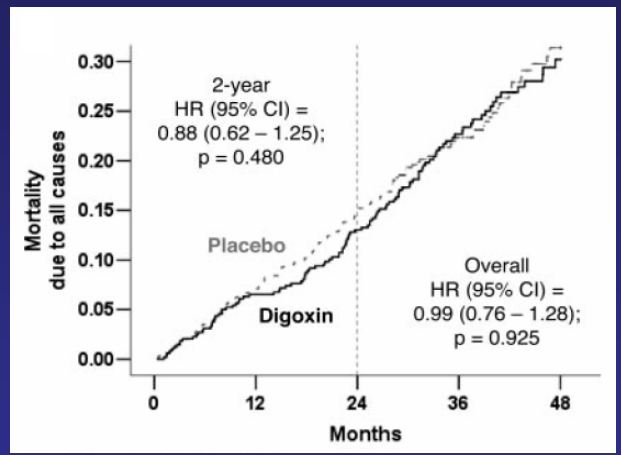
Digital en IC-FEP

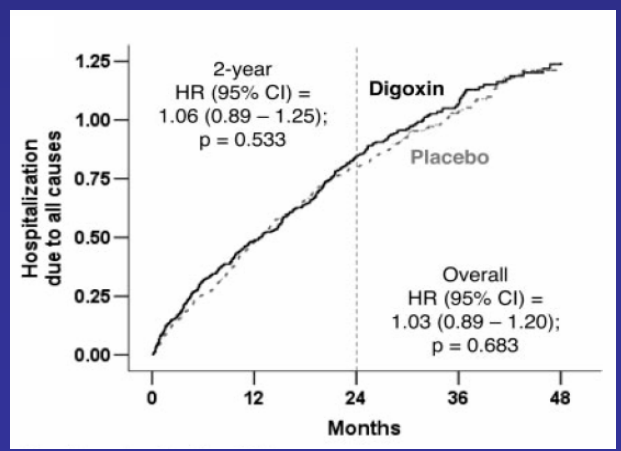
DIG-PEF: The Ancillary Digitalis Trial

Pacientes: 988
Edad $\bar{X}$: 67
FEVI > 45%
Ritmo sinusal
IECAs + Diu
3 - 4 años de tto.









Circulation. 2006; 114:397-403

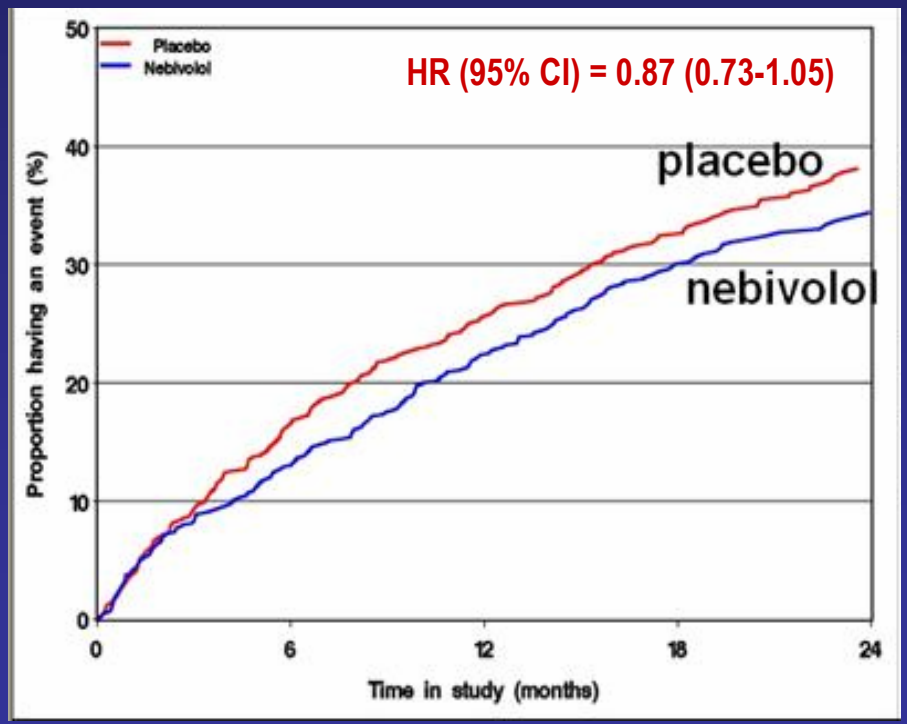
Nebivolol en IC-FEP

Estudio SENIORS

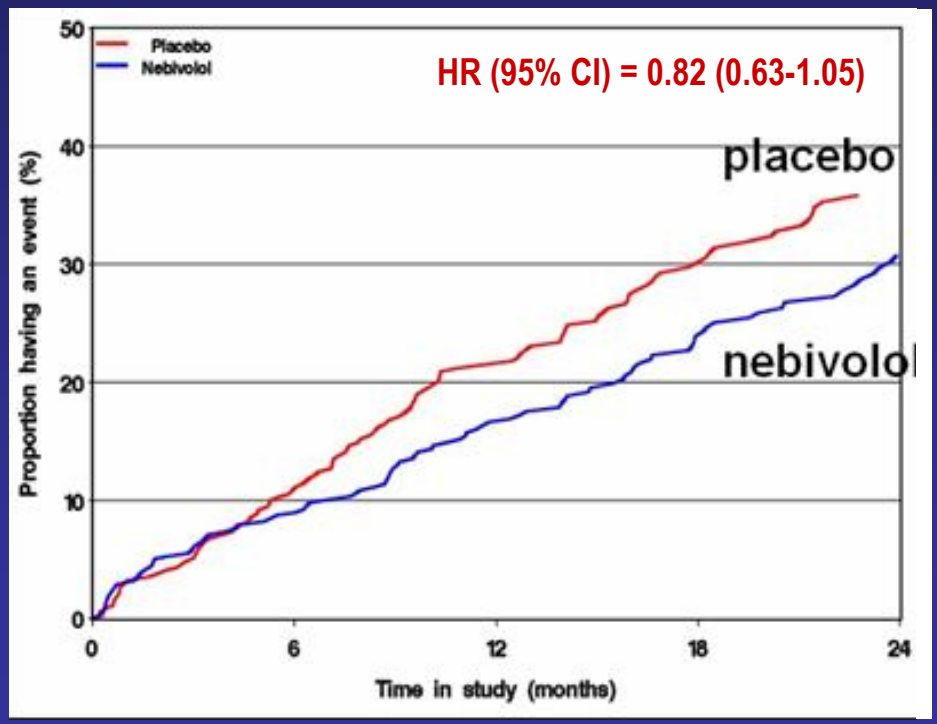
Pacientes: (2128) 752
Edad $\bar{X}$: 76
FEVI > 35
2 años de tto.

Objetivo primario : Mortalidad + Hospitalización CV → GLOBAL HR (95% CI) = 0.86 (0.74-0.99) P=0.039

FEVI ≤ 35%



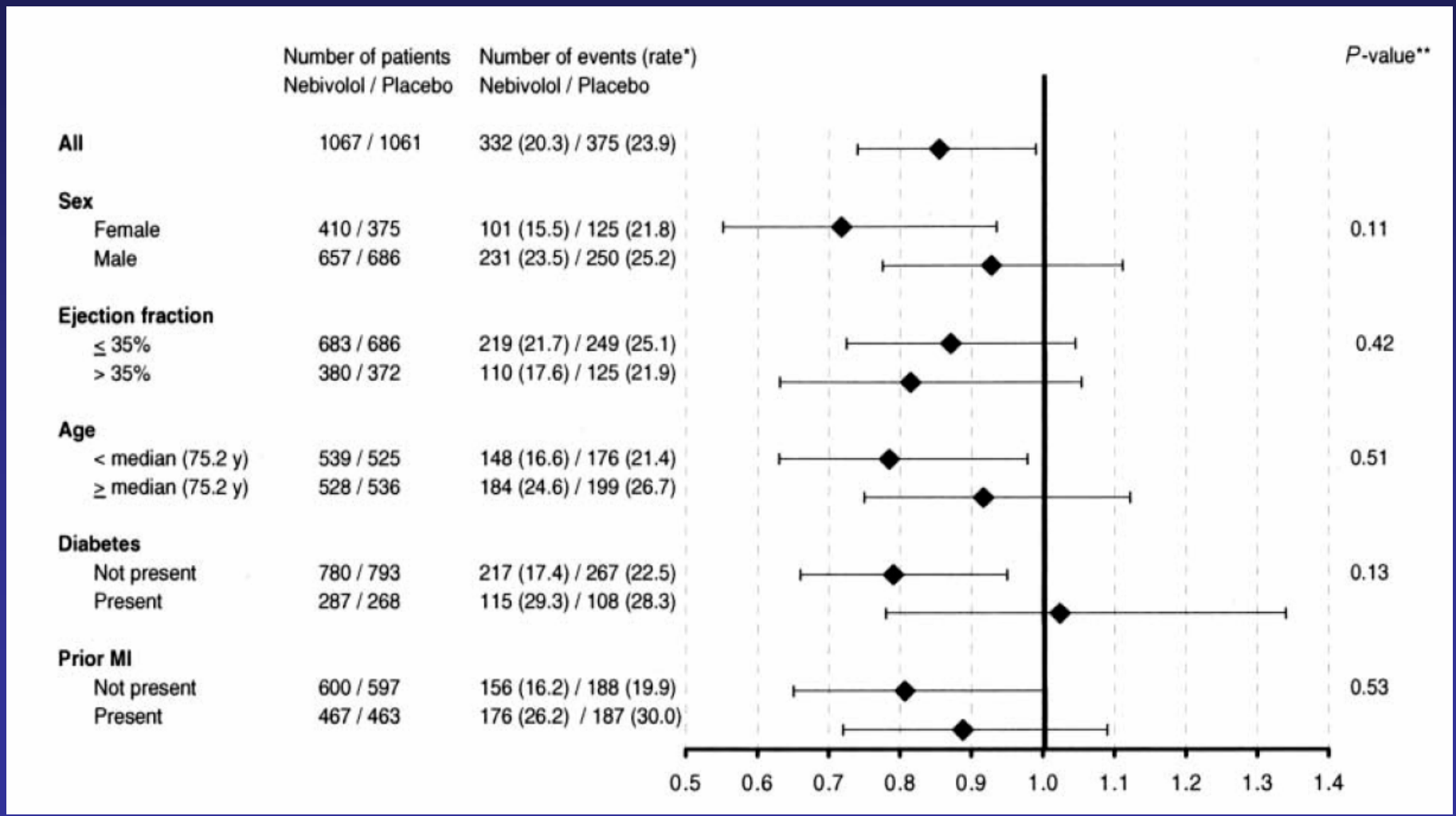
FEVI > 35%



Eur Heart J 2005; 26: 215-225

Nebivolol en IC-FEP

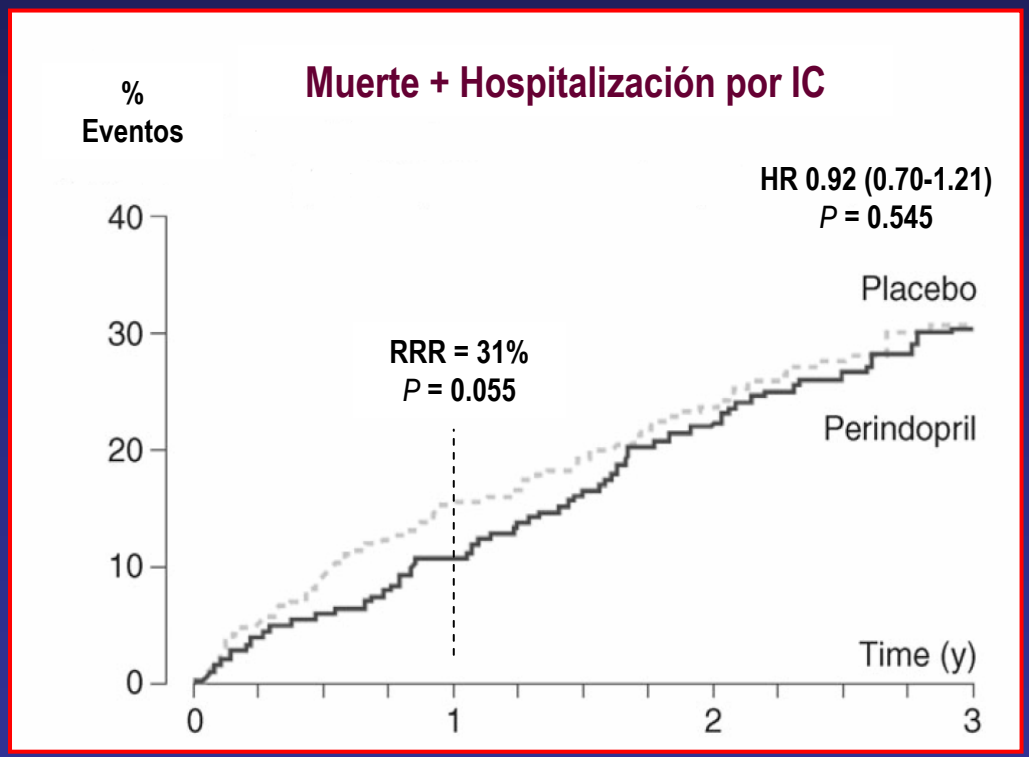
Estudio SENIORS

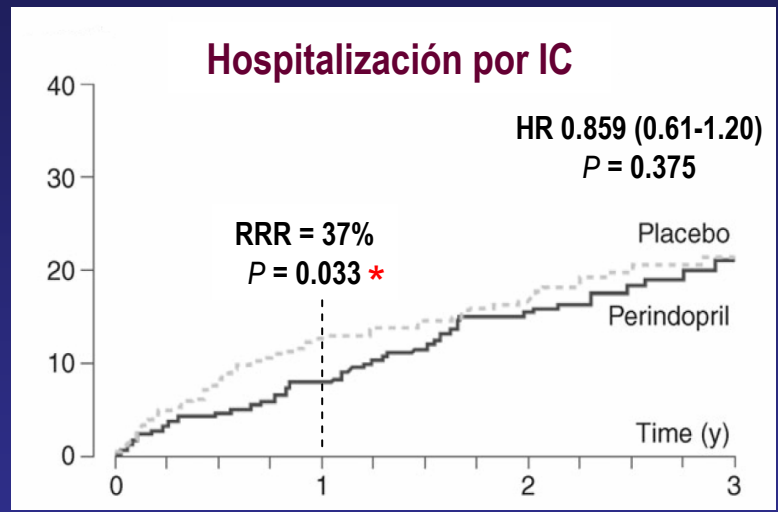


Perindopril en IC-FEP

The PEP-CHF Trial

Pacientes: 850
Edad $\bar{X}$: 75
FEVI > 40%
Diuréticos
3 años de tto.





Mejor Perindopril que Placebo:

- ✓ **Clase NYHA** (*P* = 0.030)
- ✓ **6-MWT** (*P* = 0.011)

Eur Heart J 2006; 27: 2338-45

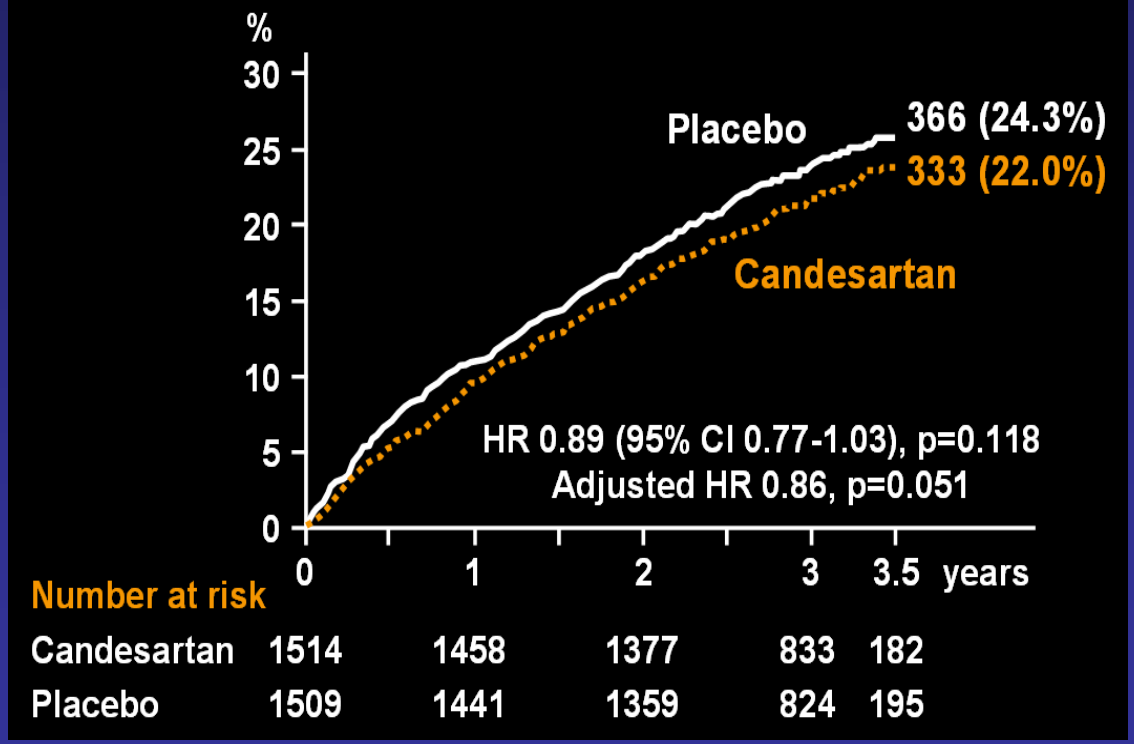
Candesartan en IC-FEP

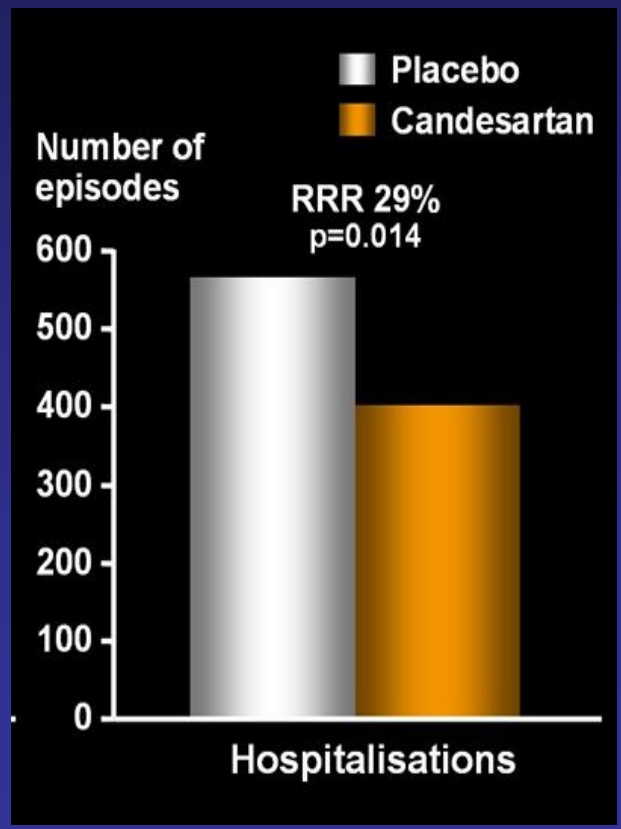
CHARM-Preserved

CHARM

Pacientes: 3023
Edad $\bar{X}$: 67
FEVI > 40%
3.5 años de tto.

Primary outcome, CV death or CHF hospitalisation





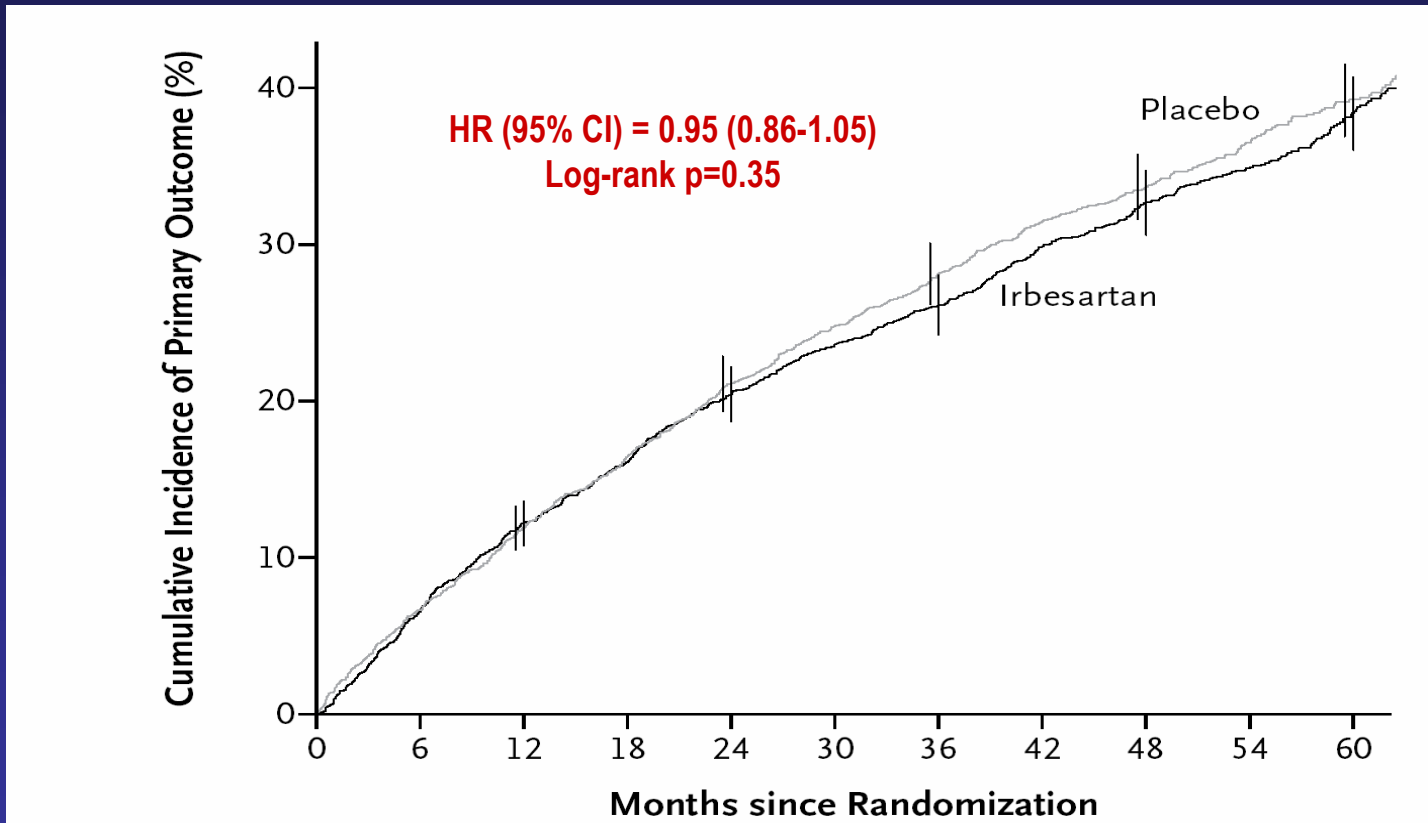
Lancet 2003; 362:777-81

Irbesartan en IC-FEP

I-PRESERVE

Pacientes: 4128
Edad $\bar{X}$: 72
FEVI ≥ 45%
4 años de tto.

Criterio principal de valoración: Muerte + Hospitalización de causa CV

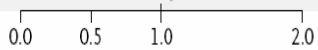


No. at Risk											
Irbesartan	2067	1929	1812	1730	1640	1569	1513	1291	1088	816	497
Placebo	2061	1921	1808	1715	1618	1539	1466	1246	1051	776	446

Irbesartan en IC-FEP

I-PRESERVE

Subgroup	Irbesartan	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients/no. of events (%)			
All patients	742/2067 (36)	763/2061 (37)	0.95 (0.86–1.06)	
Age				0.60
<65 yr	86/376 (23)	86/364 (24)	0.96 (0.71–1.30)	
65–75 yr	331/994 (33)	322/981 (33)	1.01 (0.87–1.18)	
>75 yr	325/697 (47)	355/716 (50)	0.90 (0.78–1.05)	
Sex				0.78
Female	392/1227 (32)	420/1264 (33)	0.94 (0.82–1.08)	
Male	350/840 (42)	343/797 (43)	0.96 (0.83–1.12)	
Ejection fraction				0.28
≤59%	433/1054 (41)	423/1027 (41)	0.98 (0.85–1.12)	
>59%	309/1011 (31)	339/1033 (33)	0.92 (0.79–1.07)	
Use of ACE inhibitor				0.36
No	529/1529 (35)	566/1551 (36)	0.93 (0.82–1.04)	
Yes	213/538 (40)	197/510 (39)	1.03 (0.85–1.25)	
Use of beta-blocker				0.14
No	299/842 (36)	336/859 (39)	0.87 (0.75–1.02)	
Yes	443/1225 (36)	427/1202 (36)	1.02 (0.89–1.16)	
Diabetes				0.28
No	491/1495 (33)	494/1496 (33)	0.99 (0.87–1.12)	
Yes	251/570 (44)	269/564 (48)	0.88 (0.74–1.04)	
Hospitalization for heart failure within 6 mo				0.81
No	323/1157 (28)	334/1155 (29)	0.96 (0.82–1.12)	
Yes	419/910 (46)	429/906 (47)	0.94 (0.82–1.08)	
Geographic region				0.50
Europe	518/1475 (35)	534/1464 (36)	0.95 (0.84–1.07)	
North America	87/190 (46)	99/195 (51)	0.85 (0.64–1.14)	
Other	137/402 (34)	130/402 (32)	1.07 (0.84–1.35)	



OBJETIVOS SECUNDARIOS

- -Muerte de cualquier causa
- -Hospitalización de causa CV
- -Muerte por IC + Muerte súbita + Hospitalización por IC
- -Cambios en el score del MLHFQ
- -Cambios en NTproBNP
- -Eventos CV: muerte CV + IAM no fatal + AVC no fatal
- -Muerte de causa CV.

No hubo diferencias entre los grupos tratados con Irbesartan y Placebo

Ensayos clínicos de morbi-mortalidad

Discusión (I)

- ¿Fue correcto el diagnóstico de IC con FEP?
  - *Diferentes criterios en cada estudio.*
  - *Dificultad diagnóstica por criterios hasta ahora poco claros.*
  - *Solo 2/3 de los pacientes del CHARM preservado tenían DD en ECO-Doppler y en menos de la mitad la DD fue moderada-severa*.
- ¿La dosis de los fármacos fue la adecuada?
- ¿El tiempo del seguimiento fue suficiente?
- Elevada tasa de abandonos de tratamiento (20 a 35%).

Ensayos clínicos de morbi-mortalidad

Discusión (II)

- Alta proporción de uso de otros fármacos que actúan sobre el SRAA.
  - En un escenario con tratamientos “óptimos” es difícil demostrar beneficios adicionales
- ¿Son los pacientes de los ensayos clínicos los que vemos en nuestra práctica diaria?
  - Heterogeneidad de pacientes con IC-FEP.
  - Tasas de eventos: ¿son las mismas de nuestros pacientes?
  - Fisiopatología de la IC-FEP mas compleja de lo que se pensaba, y quizás el SRAA no esté tan activado como en la IC-FE deprimida.
- En todos los ensayos hubo algún tipo de beneficio, o tendencia no significativa, del tratamiento respecto al placebo, y se aportan datos sobre la seguridad de estos fármacos en la IC-FEP.

Ensayos clínicos de morbi-mortalidad en desarrollo

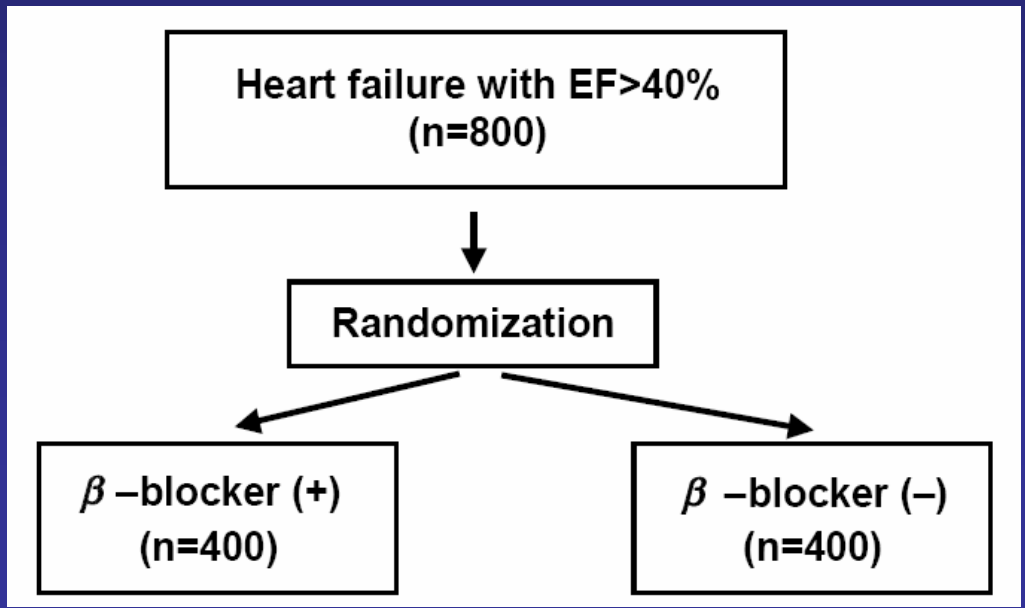
Clinical Trials Methods and Design

Rationale and Design of a Randomized Trial to Assess the Effects of β-blocker in Diastolic Heart Failure; Japanese Diastolic Heart Failure Study (J-DHF)

THE J-DHF PROGRAM COMMITTEE

Suita, Japan

Journal of Cardiac Failure Vol. 11 No. 7 2005



TRATAMIENTO STANDARD:
Diuréticos, Digital, IECAs, ARAII, Espironolactona, BCC

+

CARVEDILOL
Dosis inicial: 1.25 mgr / 12 h.
Dosis objetivo: 10 mgr / 12 h.

SEGUIMIENTO
mínimo 2 años *(¿Fin 2009?)*

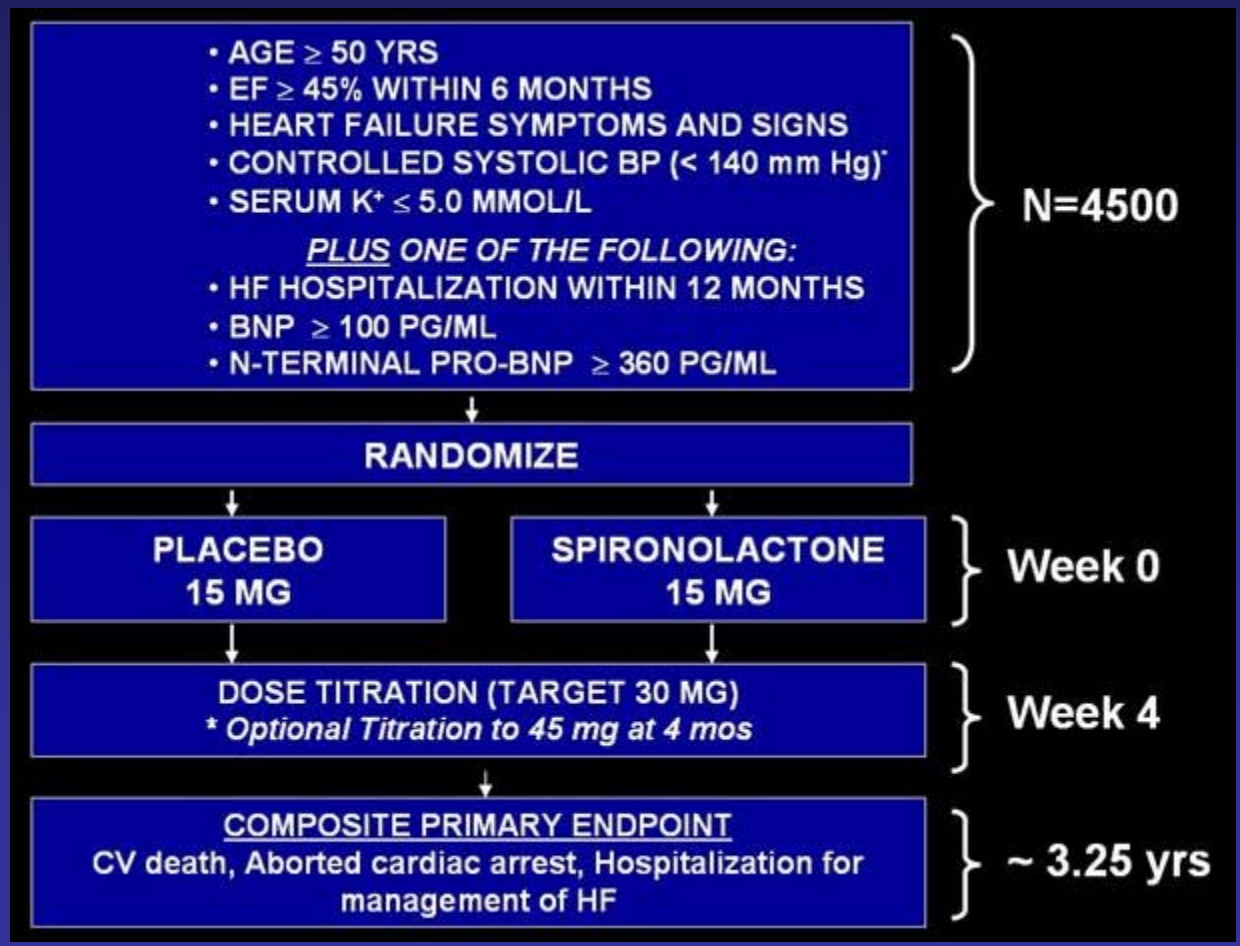
OBJETIVO PRIMARIO
Muerte CV + Ingreso por IC

Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist

TOPCAT

Funded by the NHLBI

A TRIAL FOR HEART FAILURE PATIENTS WITH PRESERVED SYSTOLIC FUNCTION



2006

↓

2010-11

¿ Qué debemos hacer ?

TRATAR LAS CONDICIONES ASOCIADAS Y LAS COMORBILIDADES

- Hipertensión arterial
- Cardiopatía isquémica
- Diabetes mellitus
- Anemia
- Fibrilación auricular
- EPOC – SAOS
- Insuficiencia renal
- Obesidad / Desnutrición

¿CUALES SON LOS OBJETIVOS IDONEOS EN IC?

¿CUAL ES EL MEJOR TRATAMIENTO PARA LOGRALOS?

CMAJ

Office management of patients with diastolic heart failure

Issue	American College of Cardiology/ American Heart Association[9]	Canadian Cardiovascular Society[1]
Hypertension	Physicians should control systolic and diastolic hypertension, in accordance with published guidelines (class I, level A evidence)	Systolic and diastolic hypertension should be controlled in accordance with the published hypertension guidelines (class I, level A evidence)
Atrial fibrillation: ventricular rate	Physicians should control ventricular rate in patients with atrial fibrillation (class I, level C evidence)	The ventricular rate should be controlled in patients with atrial fibrillation at rest and during exercise (class I, level C evidence)
Atrial fibrillation: restoration to sinus rhythm	Restoration and maintenance of sinus rhythm in patients with atrial fibrillation might be useful to improve symptoms (class IIb, level C evidence)	Restoration and maintenance of sinus rhythm in patients with atrial fibrillation may be considered to improve symptoms (class IIb, level C evidence)
Diuretics	Physicians should use diuretics to control pulmonary congestion and peripheral edema (class I, level C evidence)	Diuretics should be used to control pulmonary congestion and peripheral edema (class I, level C evidence)
Coronary revascularization	Coronary revascularization is reasonable in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to be having an adverse effect on cardiac function (class IIa, level C evidence)	Coronary artery bypass graft surgery may be considered for patients in whom symptomatic or demonstrable ischemia is judged to have an adverse affect on cardiac function (class IIa, level C evidence)
Drug therapy	The use of β-adrenergic blocking agents, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers or calcium-channel blockers in patients with controlled hypertension might be effective to minimize symptoms of heart failure (class IIb, level C evidence) The use of digitalis to minimize symptoms of heart failure is not well established (class IIb, level C evidence)	ACE inhibitors and β-blockers should be considered for most patients (class IIa, level B recommendation) Angiotensin-receptor blockers may be considered to reduce hospital admissions because of heart failure (class IIa, level B recommendation) β-Blockers, ACE inhibitors, calcium-channel blockers and digoxin may be considered to minimize symptoms of heart failure (class IIb, level C evidence)

CMAJ 2009; 180: 520-527

Explorar nuevas vías fisiopatológicas en la IC-FEP y su tratamiento

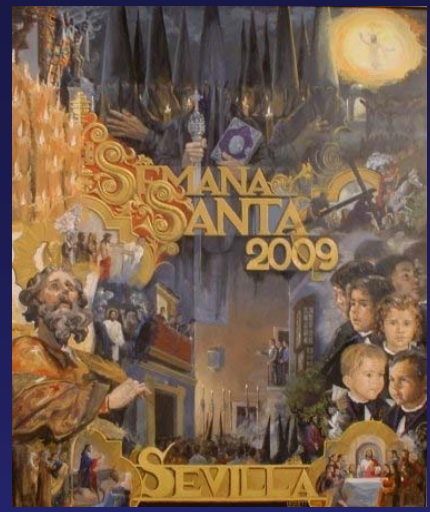
Substances Evaluated for the Treatment of Patients With HFNEF in Completed but Unpublished or Ongoing Clinical Studies (According to NIH Clinical Trials Registry*)

Substance	Drug Class	Postulated Targets
Valsartan	Angiotensin-receptor blocker	RAAS, blood pressure, LVH, LV relaxation
Aliskiren	Selective renin inhibitor	RAAS, blood pressure, LVH, LV relaxation
Spironolactone	Aldosterone antagonist	Collagen turnover, LV relaxation and stiffness
Eplerenone	Aldosterone antagonist	Collagen turnover, LV relaxation and stiffness, endothelial dysfunction
Sitaxsentan	Endothelin receptor A antagonist	Blood pressure, LVH
Alagebrium	Advanced glycation end products cross-links breaker	Advanced glycation end products, LV relaxation and stiffness
Atorvastatin	Statin	Collagen turnover, LV relaxation and stiffness, vascular function
Sildenafil	Phosphodiesterase-5 inhibitor	LVH, LV stiffness, vascular stiffness
Exenatide	Glucagon-like peptide-1 receptor antagonist	Aortic stiffness, LV stiffness
Ranolazine	Inhibitor of the slowly inactivating component of the cardiac Sodium current (late I_{Na} channel)	Intracellular calcium, LV relaxation
Ivabradine	Inhibitor of the "funny" channel (I_f channel)	Heart rate, duration of diastole

JACC 2009; 53: 905-918

CONCLUSIONES

- IC con FED y FEP son poblaciones con patrones etiológicos y clínicos diferentes pero con prevalencia y morbimortalidad similares.
- A pesar de que la IC con FEP representa la mitad de los pacientes con IC y tiene igual mortalidad que la IC FED, hay escasas evidencias científicas sobre el tratamiento adecuado de esta entidad.
- Hay pocos ensayos clínicos en IC-FEP, han utilizado criterios de inclusión heterogéneos, y sus resultados han sido poco alentadores en cuanto a mortalidad se refiere.
- Desconocemos los objetivos óptimos a alcanzar en estos pacientes en cuanto a cifras de TA, FC y ritmo cardiaco, peso, control de DM y de otras comorbilidades.
- Un grupo no despreciable de pacientes es difícilmente clasificable al tener FEVI entre el 40 y 50%.
- Esperamos los estudios en marcha que aportarán nuevas evidencias.



Gracias por su atención