

¿Hemos de tratar con betabloqueantes a los pacientes con IC y Fracción de Eyección Preservada (ICFEP)?

NO

**J. Montes Santiago**Complejo Hospitalario Universitario
VIGO

18/XI/200

#### DOES HEART FAILURE WITH PRESERVED EJECTION FRACTION IN ELDERLY PATIENTS PROGRESS TO SYSTOLIC DYSFUNCTION?

Nancy Sanchez-Gomez 1, Jose Ignacio Garcia-Sanchez 1, Miguel Yebra-Yebra<sup>1</sup>, Ismael Said-Criado<sup>1</sup>, Jose Luis Santiago-Ruiz<sup>1</sup>, Cristina Fernandez-Fernandez<sup>1</sup>, Miriam Moralejo-Martin<sup>1</sup> Javier Fresneda-Moreno<sup>1</sup>, Ana Royuela<sup>2</sup>, Luis Manzano<sup>1</sup>, <sup>1</sup>Heart Failure and Vascular Risk Unit. Internal Medicine Department. Hospital Universitario Ramon Y Cajal Hospital. Universidad De Alcalá. Madrid, Spain; <sup>2</sup>Biostatistic Unit. Hospital Universitario Ramon Y Cajal Hospital. Universidad De Alcalá. Madrid, Spain



VIIIth Congress of European Federation of Internal Medicine May 27-30, 2009 WOW Hotels & Convention Center **ISTANBUL - TÜRKİYE** 

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Introduction: Heart failure with preserved ejec count for around 50% of HF cases in population suggested that HF-PEF may be an earlier stage o tion. However, there are no consistent data abou

Objectives: We have studied the progression of E HF-PEF followed by echocardiography.

Materials & methods: Setting: all outpatients re nal medicine unit offering integrated care to elderl and standardized diagnostic assessment was per echocardiography. In addition to clinical evaluat PEF, patients had to have an EF >50% and eith BNP >100 pg/ml. We excluded patients with sev pericardial disease. Patients with a follow up dopp were included. Changes in EF were assessed by V Results: 54 consecutive patients with at least tw were evaluated. Their mean age was 79 (SD 6.2 more than 95% had hypertension, left ventricu diabetes, and 24% confirmed coronary heart di were in NYHA II or III functional class. The me up was 24 months. Mean basal and follow-up EF (SD 8.9), respectively (p=0.24). Only one patier levels below 50%

Discussion & conclusion: HF-PEF in elderly I progress to systolic dysfunction. Our results suj and systolic HF are different pathophysiologic r investigation of the HF-PEF pathogenesis are u design specific trials for this syndrome.

Keywords: Heart failure, preserved ejection frac

#### BLOOD PRESSURE IN YOUNG ADULTS

Helder Dores 1, Fernando Salvador 2, Pedro Santi Liliana Paixão2, Rui Pereira2, Nídia Gonçalves2 Cândida Fonseca<sup>3</sup>, Fátima Ceia<sup>3</sup>. <sup>1</sup>Departament Faculdade De Ciências Médicas Da Universidae Universitário De Medicina I Do Hospital De São Journal of Internal Medicine 20S (2009), S1-S283

#### P0855

#### PREVALENCE OF NONCARDIAC COMORBIDITIES IN PATIENTS HOSPITALIZED FOR HEART FAILURE IN SPAIN

Julio Montes-Santiago <sup>1</sup> Catalina Fernández <sup>1</sup>, Ricardo Guijarro-Merino <sup>2</sup>, Carlos San Roman-Teran<sup>3</sup>, Manuel Monreal<sup>4</sup>. <sup>1</sup>Complejo Hospitalario Univesitario, Vigo, Pontevedra, Spain; <sup>2</sup>Complejo Hospitalario Carlos Haya, Málaga, Spain; <sup>3</sup>Hospital Comarcal De La Axarquía, Vélez-málaga, Spain; <sup>4</sup>Hospital Universitario Germans Trias i Pujol, Badalona, Barcelona,

more relevant possibilities to develop CAD than diabet

DOES HEART FAILURE WITH PRESERVED EJECTION FRACTION I ELDERLY PATIENTS PROGRESS TO SYSTOLIC DYSFUNCTION?

Nancy Sanchez-Gomez 1, Jose Ignacio Garcia-Sanchez 1 Miguel Yebra-Yebra 1, Ismael Said-Criado 1, Jose Luis Santiago-Ruiz ristina Fernandez-Fernandez 1, Miriam Moralejo-Martin 1 wier Fresneda-Moreno 1, Ana Royuela 2, Luis Manzano 1, 1 Heart Failur nd Vascular Risk Unit. Internal Medicine Department. Hospital niversitario Ramon Y Cajal Hospital. Universidad De Alcalá. Madrid. pain; <sup>2</sup>Biostatistic Unit. Hospital Universitario Ramon Y Cajal Hospital niversidad De Alcalá. Madrid, Spain

Introduction: Heart failure with preserved ejection fraction (HF-PEF) ac ount for around 50% of HF cases in population-based studies. It has been aggested that HF-PEF may be an earlier stage of HF with systolic dysfuncon. However, there are no consistent data about the natural history of this

Objectives: We have studied the progression of EF in a cohort of patient with IF-PEF followed by echocardiography

Materials & methods: Setting: all outpatients referred to a specialized interal medicine unit offering integrated care to elderly patients with HF. Rigorous nd standardized diagnostic assessment was performed, including BNP and hocardiography. In addition to clinical evaluation, for a diagnosis of HF-EF, patients had to have an EF >50% and either left atrial enlargement or NP ≥100 pg/ml. We excluded patients with severe valvulopathy or relevant cardial disease. Patients with a follow up doppler-echocardiographic study ere included. Changes in EF were assessed by Wilcoxon test.

Results: 54 consecutive patients with at least two echocardiographic studies ere evaluated. Their mean age was 79 (SD 6.2) years, 82% were women. ore than 95% had hypertension, left ventricular hypertrophy 72%, 44% labetes, and 24% confirmed coronary heart disease. Most of them (74%) ere in NYHA II or III functional class. The mean echocardiographic follow was 24 months. Mean basal and follow-up EF were 67% (SD 7.5) and 68% SD 8.9), respectively (p=0.24). Only one patient exhibited decline in EF to

iscussion & conclusion: HF-PEF in elderly patients apparently does not ogress to systolic dysfunction. Our results support the view that HF-PEF d systolic HF are different pathophysiologic models. Further research and estigation of the HF-PEF pathogenesis are urgently required in order to ign specific trials for this syndrome.

ywords: Heart failure, preserved ejection fraction, echocardiography

hypertension and 27.4% high normal blood pressure. In males, 43.9% had hypertension, while in females only 10.5%. High hypertension prevalence in overweight (50.8%) and obese persons (50.0%) was detected. 27.2% of the individuals under stress had isolated systolic hypertension. A tendency towards hypertension was found in females under oral contraceptive therapy and in young people with 1st degree relatives with hypertension.

hypertension in the sample was 24.9%, 20.4% of these had isolated systolic

Discussion and conclusion: Hypertension and high normal blood pressure prevalence's in the population studied of university students were rise. A statistical significance relation was showed between blood pressure values and gender, BMI and between stress and isolated systolic hypertension.

Keywords: Hypertension, university students, gender, body mass index,

#### PREVALENCE OF NONCARDIAC COMORBIDITIES IN PATIENTS HOSPITALIZED FOR HEART FAILURE IN SPAIN

Julio Montes-Santiago<sup>1</sup>, Catalina Fernández<sup>1</sup>, Ricardo Guijarro-Merino<sup>2</sup>, Carlos San Román-Terán3, Manuel Monreal4. 1 Complejo Hospitalario Univesitario, Vigo, Pontevedra, Spain; <sup>2</sup>Complejo Hospitalario Carlos Haya, Málaga, Spain; <sup>3</sup>Hospital Comarcal De La Axarquía, Vélez-málaga, Spain; 4 Hospital Universitario Germans Trias i Pujol, Badalona, Barcelona,

Introduction: Patients hospitalized for heart failure are elderly and with extensive noncardiac comorbidities. However, there are few studies adressed the prevalence of these comorbid conditions affecting the care of these patients. Objectives: To determine the prevalence of important comorbidities in hospitalized patients with heart failure (HF) in Spain and the costs of hospitalizations

Materials & methods: Heart failure specifically Diagnosis-Related Groups (DRG) from the National Health System (NHS) Minimum Basic Data Set were analyzed: DRG 127 (Heart failure and shock) and DRG 544 (Congestive heart failure and cardiac arrythmia with major complications) in 2006. In these DRG secondary diagnoses for selected important comorbidities were analyzed. Costs of heart failures hospitalizations were calculated according the the standars by Spanish Ministy of Health.

Results: In 2006 there were 86148 discharges in patients 35 years older with a main diagnosis of HF in the Spanish NHS. Of these, 56% were women, mean age was 78(SD:11) years, mean hospital stay was 9,2 days and inhospital mortality was 10,4%. There was no differences in main hospital stay between discharged alive and death patients. However, death patiens were older (mean age: 81,SD±10) and 80% of deaths were in patients 75 years older). Table show the prevalence of various important noncardiac comorbidities in patients with HF. Costs of hospitalizatios for HF were calculated in 424,4 millions (1,7% of global hospitalary budget).

#### BLOOD PRESSURE IN YOU

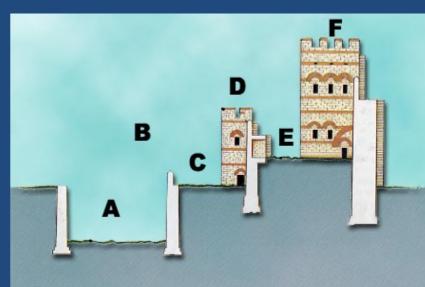
Helder Dores 1, Fernando Salv Liliana Paixão2, Rui Pereira Cândida Fonseca3, Fátima Cei Faculdade De Ciências Médic Universitário De Medicina I I.

De Lisboa, ancisco Xa rial hypert

<sup>2</sup>Departamento De Saúde Pública Da Faculdade Discussion & conclusion: HF-PEF in elderly patients apparently does not progress to systolic dysfunction. Our results support the view that HF-PEF and systolic HF are different pathophysiologic models. Further research and Chonic pulmonary disease 35,0% Cerebrovascular disease 5,5% Dementia 3,6% 7.7% Peripheral vascular disease Diabetes 38,0% 12.9% Renal disease Atrial fibrillation 47,5% Age-adjusted Charlson comorbidity index 5.9 10.4% Mortality





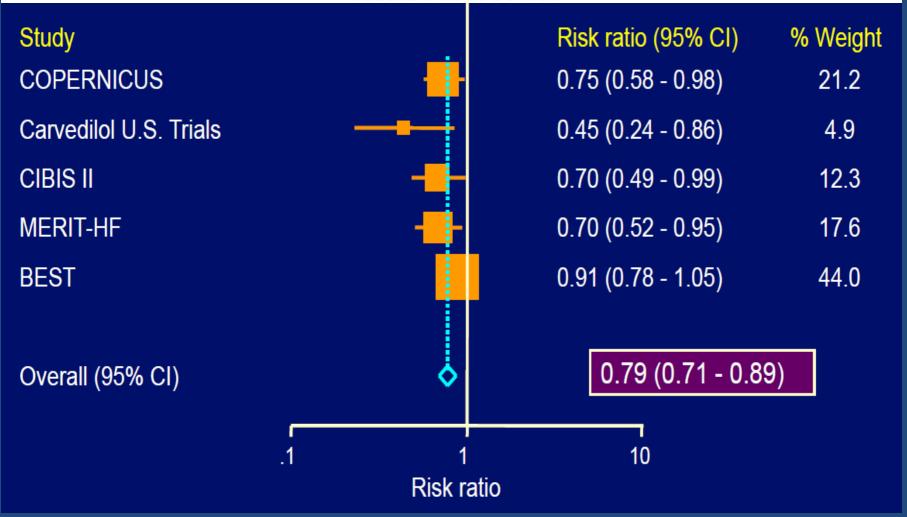






## opioqueantes: erectivos con independencia de edad

Do Elderly Systolic Heart Failure Patients Benefit from Beta Blockers to the Same Extent as the Non-Elderly? Meta-Analysis of > 1 2,000 Patients in Large-Scale Clinical Trials



## Betablocker prescriptions by age from 1995 to 2004



997

2000

2004

p<0.0001

65.9%

2001-2004 BRING-UP 1-2





## Mehmet II ante Constantinopla 1453



## Argumentos

- I) Guías de práctica clínica
- II) Estudios clínicos randomizados/Metanálisis
- III) Estudios observacionales
- IV) Experiencia
- V) Expertos

# Argumentos de grueso calibre



La Gran Bombarda (9 m)

## ecientes Guías y Betabloqueantes ESC (Europa, ACC/AHA (EEUU,



doi:10.1093/eurheartj/ehn/s09

European Journal of Heart Failure doi:10.1016/j.ejheart.2008.08.005 **ESC GUIDELINES** 

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

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM)

Authors/Task Force Members: Kenneth Dickstein (Chairperson) (Norway)\*, Alain Cohen-Solal (France), Gerasimos Filippatos (Greece), John J.V. McMurray (UK), Piotr Ponikowski (Poland), Philip Alexander Poole-Wilson (UK), Anna Strömberg (Sweden), Dirk J. van Veldhuisen (The Netherlands), Dan Atar (Norway), Arno W. Hoes (The Netherlands), Andre Keren (Israel), Alexandre Mebazaa (France), Markku Nieminen (Finland), Silvia Giuliana Priori (Italy), Karl Swedberg (Sweden)

ESC Committee for Practice Guidelines (CPG): Alec Vahanian (Chairperson) (France), John Camm (UK), Raffaele De Caterina (Italy), Veronica Dean (France), Kenneth Dickstein (Norway), Gerasimor Filippatos (Greece), Christian Funck-Brentano (France), Irene Hellemans (The Netherlands), Steen Dalby Kristensen (Denmark), Keith McGregor (France), Udo Sechtem (Germany), Sigmund Siber (Germany), Michal Tendera (Poland), Petr Widmisky (Czech Republic), Des Luis Zamorano (Spain)

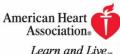
Document Reviewers: Michal Tendera (CPG Review Coordinator) (Poland), Angelo Auricchio (Świtzerland), Jeroen Bax (The Netherlands), Michael Bohm (Germany), Ugo Corrá (Italy), Paodo della Bella (Italy), Perry M. Ellior (UK), Ferner follah (Świtzerland), Mihai Gherghlade (USA), Yonathan Hasin (Israel), Anders Hemborg (Śweden), Tiny Jaarsma (The Netherlands), Michel Komajda (France), Ran Kornowski (Israel), Massimo Piepoli (Italy), Bernard Prendergast (UK), Luigi Tavazzi (Italy), Jean-Luc Yachiery (Belgium), Freek W. A. Verheugt (The Netherlands), Jose Luis Zamorano (Spain), Faiez Zannad (France)

#### 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</li>
- 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 cardio-vascular causes or admission with HF) but did show a significant reduction in the risk of investigator-reported admissions for HF.<sup>130</sup> 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.<sup>131</sup>

No mención





2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Sharon Ann Hunt, William T. Abraham, Marshall H. Chin, Arthur M. Feldman, Gary S. Francis, Theodore G. Ganiats, Mariell Jessup, Marvin A. Konstam, Donna M. Mancini, Keith Michl, John A. Oates, Peter S. Rahko, Marc A. Silver, Lynne Warner Stevenson and Clyde W. Yancy

Circulation published online Mar 26, 2009; DOI: 10.1161/CIRCULATIONAHA.109.192065 Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX

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#### Class IIb

- Restoration and maintenance of sinus rhythm in patients with atrial fibrillation and HF and normal LVEF might be useful to improve symptoms. (Level of Evidence: C)
- The use of <u>beta-adrenergic blocking agents</u>, ACEIs, ARBs, or calcium antagonists in patients with HF and normal LVEF and controlled hypertension might be effective to minimize symptoms of HF. (Level of Evidence: C)
- The usefulness of digitalis to minimize symptoms of HF in patients with HF and normal LVEF is not well established. (Level of Evidence: C)

Útiles para control síntomas (evid.

## Más Guías



Cardiol Clin 25 (2007) 497-506

CARDIOLOGY CLINICS

## Guidelines for the Management of Heart Failure: Differences in Guideline Perspectives

Mariell Jessup, MD\*, Susan C. Brozena, MD

Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Comparison of recommendations from international guidelines for treatment of chronic heart failure with preserved left ventricular ejection fraction

Topic discussed	Scottish Intercollegiate Guidelines Network 2007	Canadian Cardiovascular Society 2006	Heart Failure Society of America 2006	European Society of Cardiology 2005	American College of Cardiology/ American Heart Association 2005
ACE inhibitors	No good evidence	For most patients	All patients with other risk factors such as atherosclerotic disease or	May improve relaxation	Might be effective to control HF
Beta-blockers	No good evidence	For most patients	For symptomatic patients who have prior MI, hypertension, or atrial fibrillation	Use to lower heart rate and increase diastolic filling time	Might be effective to control HF
ARBs Digoxin	No good evidence	Consider to reduce HF hospitalization May be considered to minimize	All patients with LVDD	High dose may decrease hospitalizations	Might be effective to control HF Use is not well established
Diuretics	No good evidence	symptoms Use to control pulmonary congestion and edema	Necessary with fluid overload, but use cautiously to avoid lowering preload		Necessary with fluid overload, but use cautiously to avoid lowering preload
Calcium antagonists	No good evidence	May be considered to minimize symptoms	For control of rate in atrial fibrillation, angina, hypertension	Verapamil-type drugs may be used	Might be effective to minimize symptoms

Abbreviations: HF, heart failure; LVDD, left ventricular diastolic dysfunction; MI, myocardial infarction.

## Clases de recomendacion/Niveles de evidencia

#### Table I Classes of recommendations

Classes of Recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Table 2 Levels of evidence

Level of Evidence A	Date derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Date derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

## Guías ACC/AHA (2005 y 2009)

Recomendaciones	Clase	Niveles de evidencia
Control TAS y TAD	I	A
Control Fc en FA	I	C
Diuréticos para control volemia		C
Revascularización para	lla	C
isquemia Restaurar ritmo sinusal	IIb	C
Bbloqueantes, IECA, ARA II,	IIb	C
Digital para minimizar síntomas	IIb	C

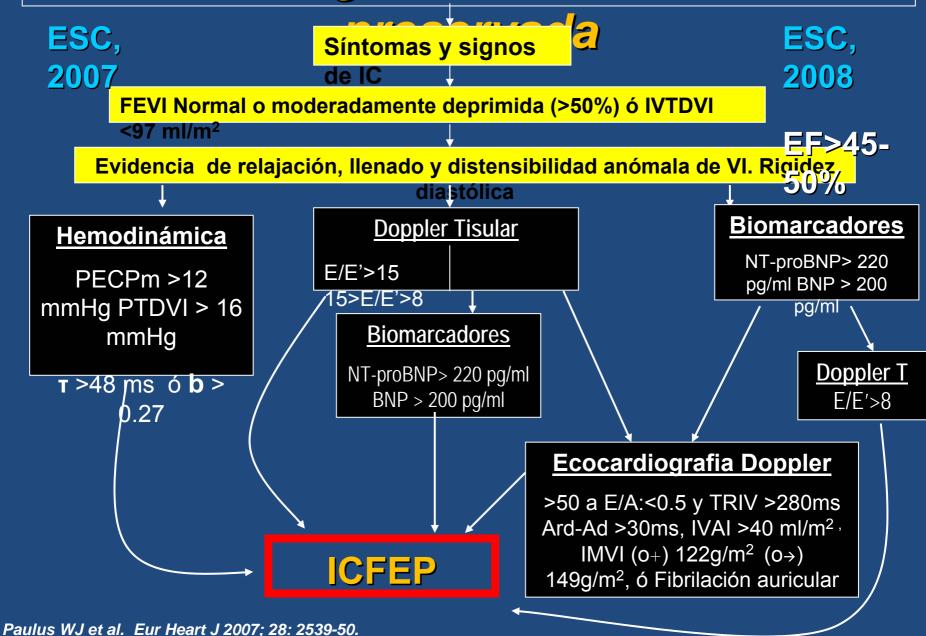
Jessup M, Abraham WT, Casey DE, et al. 2009 Focused Update: **ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults.** 2009 WRITING GROUP TO REVIEW NEW EVIDENCE AND UPDATE THE 2005 GUIDELINE FOR THE MANAGEMENT OF PATIENTS WITH CHRONIC HEART FAILURE WRITING ON BEHALF OF THE 2005 HEART FAILURE WRITING CONMITTEE. *Circulation* 2009:119:1977-2016:



Un poco de humo...



## Cómo diagnosticar IC con FEVI

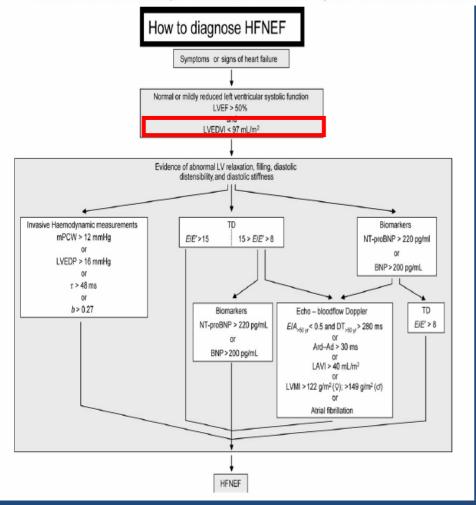


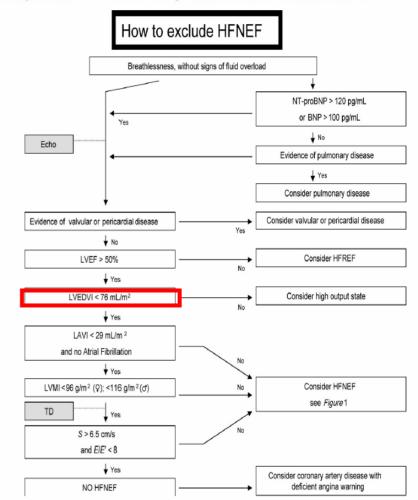




How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology

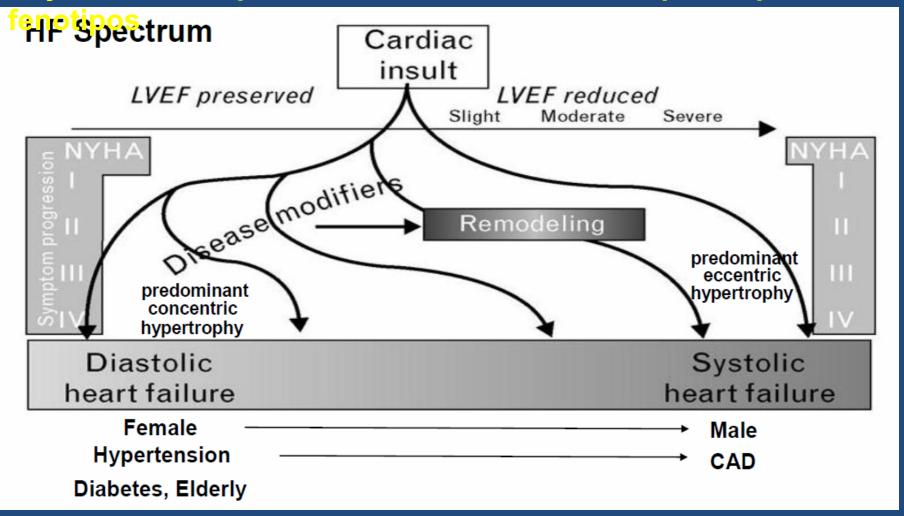
Walter J. Paulus<sup>1\*</sup>, Carsten Tschöpe<sup>2</sup>, John E. Sanderson<sup>3</sup>, Cesare Rusconi<sup>4</sup>, Frank A. Flachskampf<sup>5</sup>, Frank E. Rademakers<sup>6</sup>, Paolo Marino<sup>7</sup>, Otto A. Smiseth<sup>8</sup>, Gilles De Keulenaer<sup>9</sup>, Adelino F. Leite-Moreira<sup>10</sup>, Attila Borbély<sup>11</sup>, István Édes<sup>11</sup>, Martin Louis Handoko<sup>1</sup>, Stephane Heymans<sup>12</sup>, Natalia Pezzali<sup>4</sup>, Burkert Pieske<sup>13</sup>, Kenneth Dickstein<sup>14</sup>, Alan G. Fraser<sup>15</sup>, and Dirk L. Brutsaert<sup>9</sup>





## enfermedad?

La ICC es un solo proceso, pero con múltiples y divergentes trayectorias temporales, resultando en un amplio espectro de



## doble bnico ESC-2008

## IC: presentación/evolución como síndrome único, ICFED precede a ICFED

. Camping anne o

- Distribución unimodal de FE en ensayos clínicos de IC
- Continuo declinar del acortamiento de la velocidad del eje largo desde ICFEP hasta ICFED
- Progresión a remodelado VI en hipertensos, especialemente africanos y asiáticos.
- Progresión a remodelado VI excéntrico en estado final de la Paulmiocardiopatía hipertrófica.

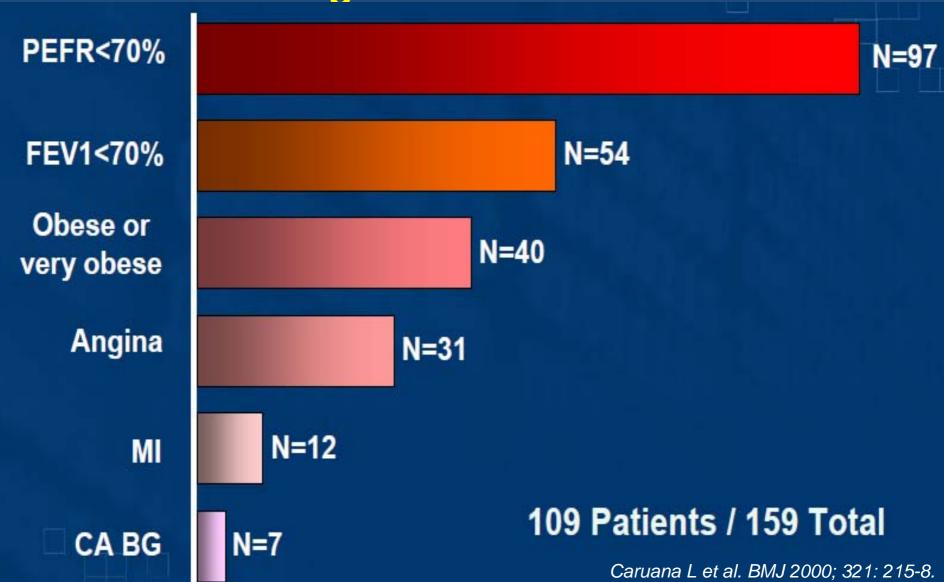
## **Doble**

### **ESC-2007**

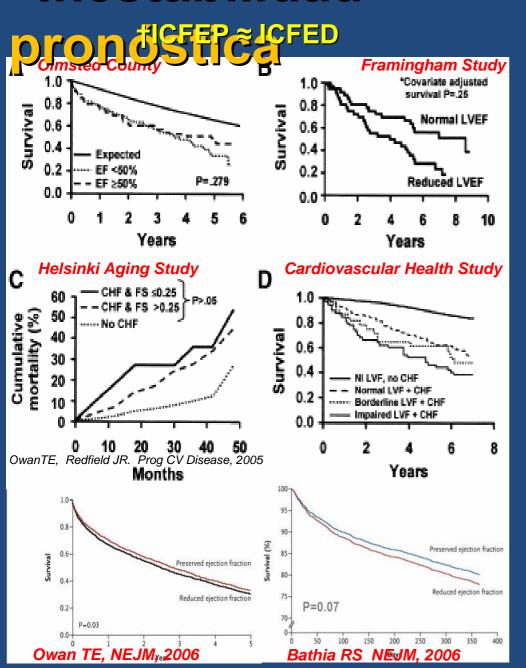
IC: presentación/evolución como 2 síndromes con remodelado concéntrico y principal disfunción diastólica VI (ICD) y otros con remodelado excéntrico y disfunción sistó-diastólica combinada (ICS)

- Remodelado concéntrico VI en ICD y excéntrico en ICS
- † tensión de reposo de miocitos en ICS in vitro
- Isoformas distintas de proteína titina
- Distintas formas de metaloproteinasas (MP)de matriz y de inhb. tisulares de MP
- No down -regulation de recep. de BB en ICD

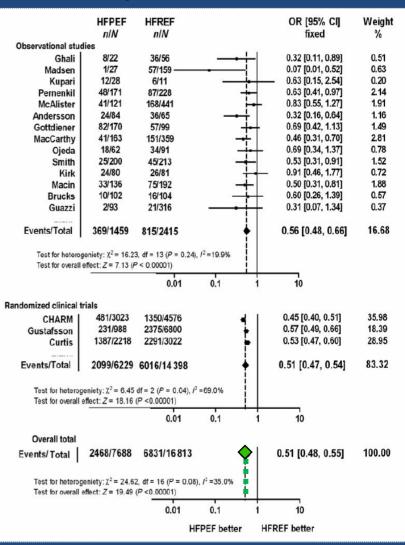
IC y FEP insuficiencia cardiaca diastólica o diagnóstico erróneo?



## "Inestabilidad"



#### †ICFEP ≈ ½ ICFED



Somaratne JB et al. Eur J Heart Fail 2009; 11: 855-62.

## FE: siguen las dudas



### Ejection fraction: a measure of desperation?

Charlotte H Manisty and Darrel P Francis

Heart 2008;94;400-401 doi:10.1136/hrt.2007.118976

Rev Clin Esp. 2009;209 Supl 2:3-10



### Revista Clínica Española

www.elsevier.es/rce



### Heart ONLINE

## Left ventricular ejection fraction: are the revised cut-off points for defining systolic dysfunction sufficiently evidence based?

G Mahadevan, R C Davis, M P Frenneaux, F D R Hobbs, G Y H Lip, J E Sanderson and M K Davies

Heart 2008;94;426-428 doi:10.1136/hrt.2007.123877

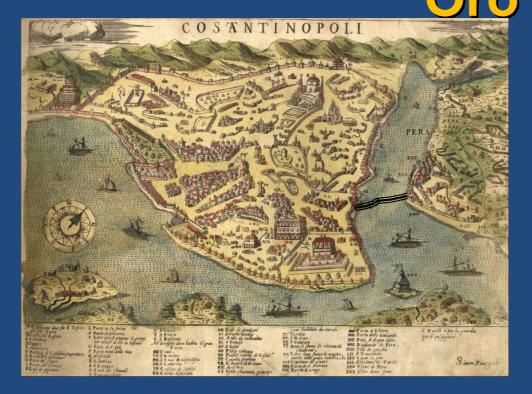
#### Insuficiencia cardíaca con función sistólica conservada. Definición y epidemiología

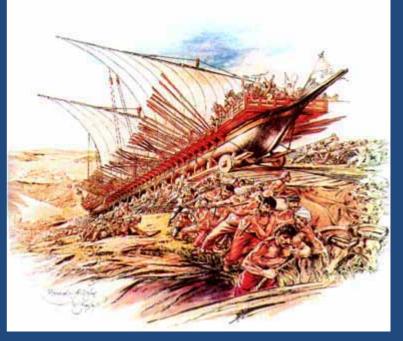
J. Montes-Santiago\*

Servicio de Medicina Interna. Complejo Hospitalario Universitario de Vigo. Vigo. Pontevedra. España.

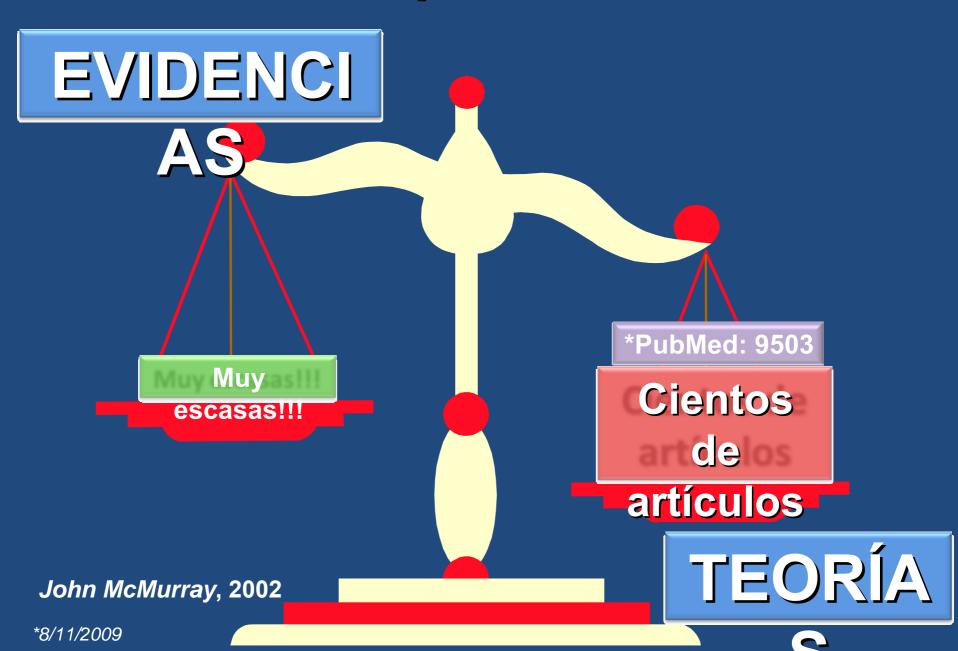
Insuficiencia cardíaca con fracción de eyección preservada: problemas históricos de una definición como contrapuesta a la IC con fracción de eyección deprimida [ICFED], etc.). Aquí se seguirá la nomenclatura de las Guías ESC-2008 sobre IC y se denominará preferentemente como ICFEP. Como fruto de tales controversias, se ha deri-

## El traslado de las naves al Cuerno de





## Tratamiento óptimo de la ICFEP



## Ensayos clínicos

ClinicalTrials.gov A service of the U.S. National Institutes of Health	Home Search	Study Topics Glossar Search
Basic Search		
Enter a word or phrase, such as the name of a medical condition or intervention.		
Example: Heart Attack AND Los Angeles		
Heart failure Search	0014	1/0000
Advanced Search Help	(18/1	1/2009
Search Tips:	<b>5 5</b> 7 1	.,
Search rips.		
Use AND (all upper case) to search for multiple terms. For example:		

Contact Help Desk

Lister Hill National Center for Biomedical Communications, U.S. National Library of Medicine, U.S. National Institutes of Health, U.S. Department of Health & Human Services, USA.gov. Copyright, Privacy. Accessibility, Freedom of Information Act



 HEART FAILURE: intervencionales
 1923 estudios

prostate cancer AND radiation heart disease AND stroke AND California

410 observacionales

1510

DIASTOLIC HEART FAILURE: 141
 intervencionales
 166 estudios
 25 observacionales

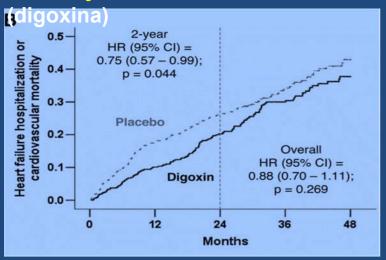
# ICFEP (Ensayos clínicos randomizados)

—Caracteri	<del>sticas</del> —	CHARM-Pr	ARM-Pr PEP-CHF I-Preser	
	(N=988)	(N=3025)	(N=850)	(N=4128)
Mean age (yrs)	67	67	75	72
Women (%)	41	40	56	60
Mean LVEF (%)	55	54	64	59
Hypertension	60	64	79	63
MI	50	44	27	23
A Fibrillation	Excluded	29	21	29
DM	29	28	21	27
Treatment (%)				
ACE inhibitor	86	19	Excluded	25
Digoxin	Excluded	28	12	14
ССВ	Santa <del>-</del> Colo	31	33	40
Beta blocker	-	56	55	59
Nitrates	39	33	51	
Diuretics	76	75	100	83
Loop	- 100 -	-	46	-
Thiazide		14	55	-
Sprironolactone	8	12	10	15

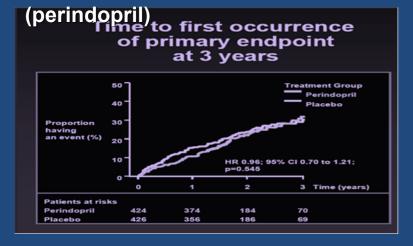
#### IOI LI (LIISAYOS CIIIIICOS

# randomizados) Resultados

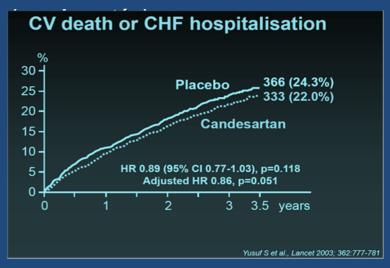
**Ancillary-DIG** 



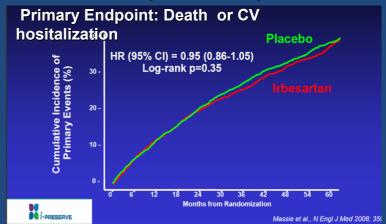
#### **PEP-CHF**



#### **CHARM-Preserved**



#### I-PRESERVE (irbesartán)



# Bbloqueantes en IC con disfunción diastólica

Pocos estudios pequeños

Latudioa i dilidolliladdoa de

- SWEDIC
- SENIORS (Subestudio de Eco)
- SENIORS

### Estudios Eco-goppier en

## **ICFEP**

## **SWEDIC** Eco-doppler (N=97)(6 meses)

7 95	Placebo	Placebo (N=50) Ca		ilol(N=47)	D Value
	Baseline	6Months	Baseline	6Months	— P-Value
E/A ratio	0.71	0.76	0.72	0.83	0.046
IVRT (ms)	106	99	101	100	0.53
DT (ms)	215	223	224	234	0.71
Pul V S/D ratio	1.55	1.62	1.56	1.52	0.87

Bergström A et al. Eur J Heart Fail 2004; 6: 435-61.

### **SENIORS** Eco-doppler subestudio (N=61)(12 meses)

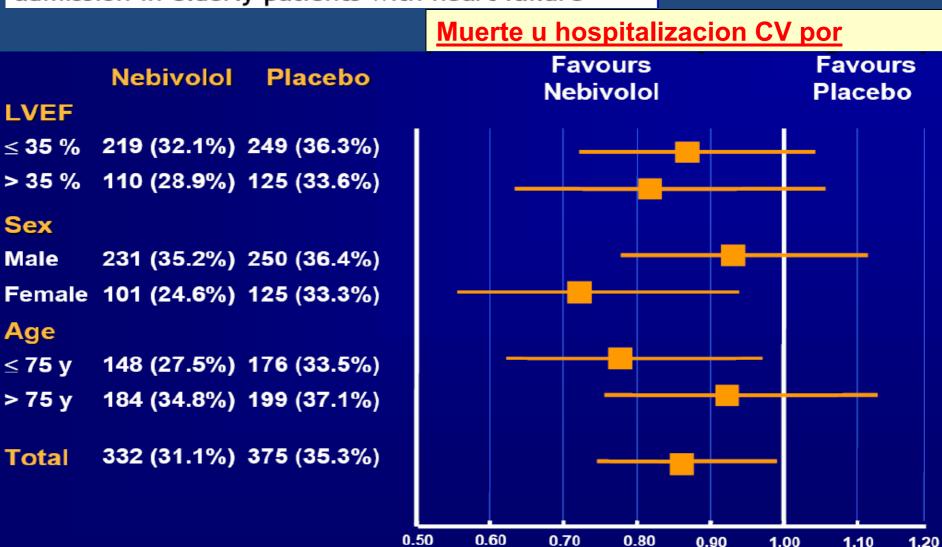
	Nebivolol (N	=27)	Placebo (N	l=34)	P-Value
1000	Baseline	1 YR	Baseline	1YR	
LVEF (%)	54.5	55.5	49.0	50.2	0.988
E/A	0.9	0.9	0.9	1.0	0.956
EDT (ms)	200	207	192	202	0.500
TAPSE (mm)	2.2	2.3	2.0	2.1	0.098
LVEDV (mL)	118	112	145	137	0.750
LVESV (mL)	56	54	77	71	0.768

## studio SENIORS

FASTTRACK Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure



Hazard ratio and 95% Cl



## FE ¿Qué límite? No diferencias



Beta-Blockade With Nebivolol in Elderly Heart Failure Patients With Impaired and Preserved Left Ventricular Ejection Fraction

LVEF ≤0.30, HR 0.81 (95%CI 0.64-1.03)

LVEF 0.31-0.35, HR 0.92 (95%CI 0.69-1.22)

LVEF 0.36-0.46, HR 0.84 (95%CI 0.59-1.20)

LVEF > 0.46, HR 0.76 (95%CI 0.52-1.11)

Objetivo primario

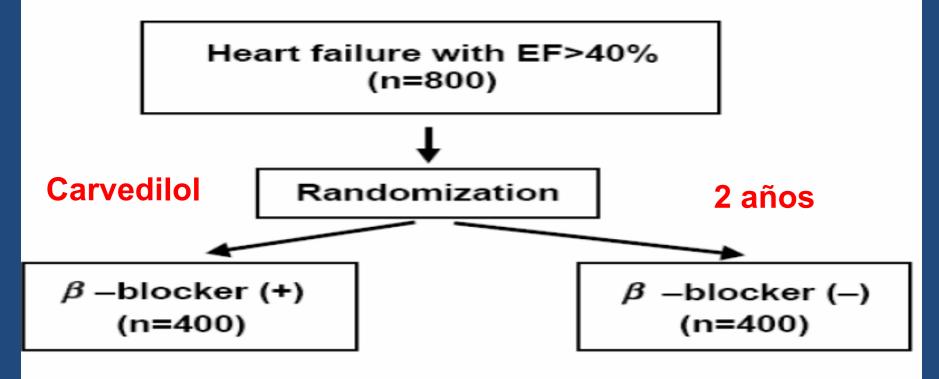
LVEF <0.40 HR 0,86 95%CI 0,73-1.03

LVEF >0.40 HR 0,83 95%CI 0,62-1,11

### 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)

Journal of Cardiac Failure Vol. 11 No. 7 2005



■ J-DHF (Japanese Diastolic Heart Failure Study) ■ 拡張期心不全の治療法確立のための大規模臨床試験 試験ポータルサイト

# IC FEP: Lo conocido y lo desconocido

REVIEW Circ J 2009; 73: 404-410

#### **Heart Failure With Preserved Ejection Fraction**

— What is Known and Unknown —

Kazuhiro Yamamoto, MD\*,\*\*; Yasushi Sakata, MD\*\*; Tomohito Ohtani, MD\*,\*\*; Yasunaru Takeda, MD\*,\*\*; Toshiaki Mano, MD\*\*

There is an emerging interest in heart failure with preserved ejection fraction (HFPEF) because of its high prevalence in the community and several specific characteristics compared with "classic" heart failure with reduced ejection fraction. HFPEF patients are older and more often female, and lack left ventricular dilatation. A likely principal cause of HFPEF is diastolic dysfunction, particularly ventricular stiffening; however, the clinical phenotype of HFPEF is also modulated by dysfunction of other organs such as kidney, vasculature, etc. Despite its social burden, the diagnostic criteria and therapeutic strategies remain to be established. In particular, the lack of established diagnostic criteria has resulted in conceptual confusions about HFPEF in clinical practice. In this review, what is known and unknown about HFPEF is discussed, and several challenging proposals about its diagnosis and therapy are raised. (Circ J 2009; 73: 404–410)

Key Words: Diastole; Heart failure; Ventricular function

eft ventricular (LV) ejection fraction (EF) is preserved or only minimally depressed in 40% of patients with heart failure (HF)! Diastolic dysfunction is one of the principal causes for this phenotype of HF? and is termed "diastolic heart failure" (DHF). In contrast to HF with reduced EF, that is, systolic heart failure (SHF), the prevalence of DHF has been increasing? DHF patients are older and more often female compared with cases of SHF, and its principal underlying disease is hypertension. Previous reports demonstrated that the survival rate of DHF and SHF patients did not different from each other and that the difference was small even if statistically significant? In the past 2 decades, the prognosis has improved for SHF, but not DHF? In this review, we will discuss what is known and unknown about DHF.

Despite the social burden of DHF, conceptual confusion still exists. LV diastolic dysfunction is not specific to DHF (Figure 1).6 LV systolic dysfunction occurs in some DHF

#### Pathophysiology of HFPEF

#### Cardiac Dysfunction

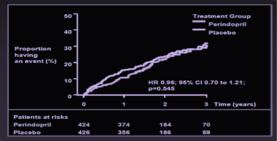
The abnormality of LV relaxation and stiffness is present in HFPEF patients<sup>2,10</sup> Kawaguchi et al showed that the abnormality of the index for LV stiffness is present in HFPEF patients! Our experimental study in an HFPEF rat model of hypertension showed that the LV relaxation abnormality occurs at the compensatory hypertrophic stage, but that myocardial stiffening leads to overt HF without further progression of the relaxation abnormality! That result indicated that LV relaxation abnormality is an early sign of diastolic dysfunction, and that LV stiffening plays a crucial role in the transition from asymptomatic diastolic dysfunction to HFPEF.

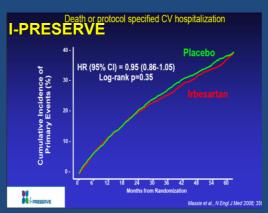
One of the causes of LV stiffening is interstitial fibrosis! Exaggerated accumulation of collage is associated with enhanced cross-linking and an increased ratio of col-

## Estudios observacionales en



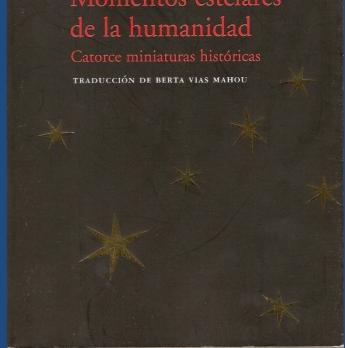
## PEP-CHime to first occurrence of primary endpoint at 3 years Treatment Group = Perindopril Placebo





# La Karkanarta

Stefan Zweig Momentos estelares de la humanidad



## Falta de Datos

Br J Pharmacol 2007; 64: 406-14.

## The contribution of observational studies to the knowledge of drug effectiveness in heart failure

Daniela Dobre, Dirk J. van Veldhuisen,¹ Mike J. L. deJongste,¹ Eric van Sonderen, Olaf H. Klungel,² Robbert Sanderman, Adelita V. Ranchor & Flora M. Haaijer-Ruskamp³

Northern Centre for Healthcare Research and <sup>1</sup>Department of Cardiology, Thoraxcentre, University Medical Centre Groningen, University of Groningen, Groningen, <sup>2</sup>Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute of Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht and <sup>3</sup>Department of Clinical Pharmacology, University Medical Centre Groningen, University of Groningen, the Netherlands

Aunque varios estudios evaluaron la efectividad de BB en ancianos con IC, ha de notarse que ningún estudio hasta ahora ha explorado la efectividad de BB en ICFEP.

## Registro

Clinical Presentation, Management, and In-Hospital Outcomes of Patients Admitted With Acute Decompensated Heart Failure With Preserved Systolic Function A Report From the Acute Decompensated Heart Failure National Registry (ADHERE) Database

#### Table 7. Multivariate\* Odds Ratios and 95% Confidence Intervals for Identified Mortality Risk Factors

	All Patient Episodes with Quantitative LVEF	Systolic 1	Function	No LVEF
Mortality Risk Factors	Assessment	Preserved	Reduced	Assessment
Systolic BP ≤125 mm Hg	2.58 (2.33-2.86)	2.66 (2.28-3.11)	2.33 (2.03-2.68)	2.23 (2.03–2.44)
BUN >37 mg/dl	2.53 (2.22-2.87)	2.57 (2.11-3.14)	2.51 (2.12-2.97)	2.03 (1.81-2.28)
Sodium ≤132 mmol/l	1.99 (1.76-2.26)	1.72 (1.40-2.12)	2.15 (1.83-2.52)	1.97 (1.76-2.21)
Age >73 yrs	1.76 (1.58-1.96)	2.08 (1.74-2.48)	1.62 (1.41-1.85)	2.13 (1.92-2.36)
Dyspnea at rest	1.55 (1.40-1.72)	1.56 (1.34-1.82)	1.55 (1.35-1.77)	1.56 (1.42-1.71)
Cr > 1.5 mg/dl	1.39 (1.22-1.58)	1.24 (1.02-1.52)†	1.50 (1.27-1.77)	1.37 (1.22-1.54)
No chronic beta-blocker	1.37 (1.23-1.51)	1.51 (1.29-1.77)	1.28 (1.17-1.46)	1.60 (1.46-1.76)
Heart rate >78 beats/min	1.34 (1.20-1.49)	1.55 (1.32-1.84)	1.14 (0.98-1.32)‡	1.40 (1.27-1.54)

p < 0.0001 unless noted otherwise. \*Adjusted for all variables shown in the table. †p = 0.03. ‡p = 0.08.

BP = blood pressure; BUN = blood urea nitrogen; Cr = creatinine; LVEF = left ventricular ejection fraction.

## Estudio de Cádiz

Mortality and morbidity of newly diagnosed heart failure with preserved systolic function treated with beta-blockers: A propensity-adjusted case-control populational study

1085 adultos con 1º dco. de ICFEP

5 años. 378 en BB

Mortalidad total. RR: 0.37 [0.21-0.50]

Mortalidad CV: RR: 0.31 [0.18-0.45]

Hospitalización: 13.6 vs. 19.2 (p<0,001)

#### **CONCLUSIONES**

El inicio de tto. con bisoprolol o carvedilol se asocia con menor morbimortalidad en pacientes con nuevo diagnóstico de ICFEP

## Estudio en pacientes MEDICARE

Shah et al. Am J Cardiol 2008: 101: 207-22.

13300 pacientes >65 años (Medicare) hospitalizados con IC + EF>45%

### ACE y B-bloqueantes *al alta*

Effect of angiotensin-converting enzyme (ACE) inhibitors and  $\beta$  blocker on 1- and 3-years mortality\*

Medications	1 Year 3 Ye		ear	
	Risk Ratio	95% CI	Risk Ratio	95% CI
ACE inhibitors	0.88	0.82-0.95	0.93	0.89-0.98
β Blocker	0.93	0.87-1.10	0.92	0.87–0.97

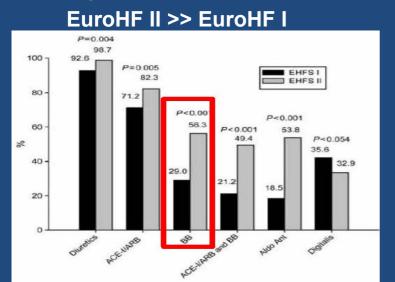
¿¿Los toman??

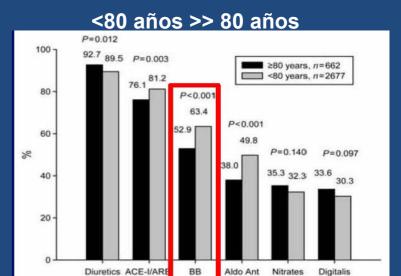
## Registro EFFECT

(Canacá) 9943 pacientes. 1026 p. con FE>50%: níngún beneficio en mortalidad

## **EURO Heart Failure Survey II**

Manejo contemporáneo de octogenarios hospitalizados por IC





#### Predictores de mortalidad en el seguimiento tras el alta en octogenarios

Variable	Crude hazard ratio (95% CI) <sup>a</sup>	Adjusted hazard ratio (95% CI) <sup>b</sup>
Age (per 5 year increase)	1.55 (1.29-1.87)	1.51 (1.24-1.84)
SBP (per 10 mmHg decrease)	1.05 (1.00-1.10)	1.04 (0.99-1.09)
Diabetes mellitus	1.36 (0.98-1.89)	1.56 (1.12-2.18)
Self-care problems	1.82 (1.21-2.75)	1.60 (1.03-2.49)
Creatinine (mg/dL)	1.51 (1.26-1.80)	1.48 (1.21-1.80)
ACE-inhibitors/ARB	0.48 (0.35-0.66)	0.56 (0.40-0.79)
Statins	0.59 (0.41-0.85)	0.67 (0.45-0.99)
Beta-blockers	0.72 (0.53-0.98)	0.87 (0.63-1.20)

## Registro OPTIMIZE-HF

#### Clinical Effectiveness of Beta-Blockers in Heart Failure

Findings From the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) Registry

1.0

0.9

0.8

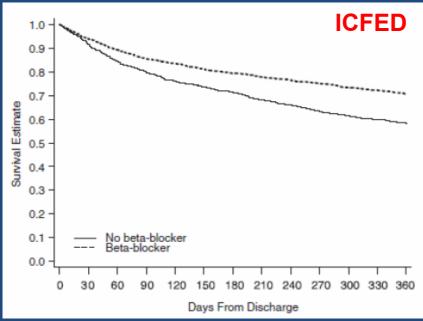
0.7

0.6

0.98 (0.90-1.06)

0.98 (0.91-1.06)

7154 p. >65 años elegibles para BB. Inicio en 3241 (49%) Mortalidad 1 año: 33%, Hospitalización por todas causas: 64%.

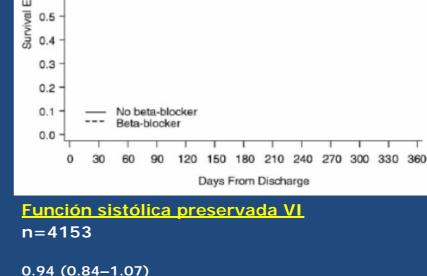




Mortalidad 0.77 (0.68–0.87)

Readmisión 0.89 (0.80–0.99)

Mortalitdad o readmisión 0.87 (0.79–0.96)



Hernández AF et al. JACC 2009; 53: 184-92

**ICFEP** 

## La experiencia Estudio ATICA



586 p.

77 años >50% IC FEP

6 meses:

282/544 (52%)

Mala adherencia:

38%

Ff 2º: 16%

IC-27

ADHERENCIA AL TRATAMIENTO FARMACOLÓGICO EN INSUFICIENCIA CARDIACA. ESTUDIO ATICA

J. Casado Cerrada<sup>1</sup>, E. Visus<sup>2</sup>, J. Recio Iglesias<sup>3</sup> M. Sánchez-Ledesma<sup>4</sup>, M. Chimeno Viñas<sup>5</sup>, B. Roca<sup>6</sup> P. Conthe Gutiérrez<sup>2</sup> y Grupo ATICA

<sup>1</sup>Medicina Interna, La Princesa, Madrid, <sup>2</sup>Medicina Interna, Gregorio Marañón. Madrid. 3Medicina Interna. Valle Hebrón. Barcelona. 4Medicina Interna. Cínico de Salamanca. Salamanca. Medicina Interna, Virgen de la Concha, Zamora, Medicina Interna. Hospital de Castellón. Castellón.

Objetivos. Evaluar el grado de cumplimiento del tto. en pacientes con ICC. También identificar los factores de riesgo de deficiente adherencia y valorar si los pacientes con deficiente adherencia presentan diferencias en reingresos.

Material y métodos. Seguimiento prospectivo iniciado con el ingreso en la planta de Medicina Interna con diagnóstico de ICC. Se realizarán visitas de seguimiento a los 3, 6, 9 y 12 meses, en las revisiones se realiza entrevista sobre el cumplimiento del tratamiento pautado. En el estudio se recogieron datos de un total de 586 pacientes, mostrando solo los de los que han completado la visita de los seis meses, al no estar completada la base de datos por el momento del total de las visitas.

Resultados. El 42% de los pacientes eran hombres v 58% mujeres La media de edad de los hombres fue 76 años y la de las mujeres 78. Más de la mitad de los pacientes tiene FE conservada. El número de pacientes que ha completado los seis meses de seguimiento es de 282. De ellos el 62% tenían buena adherencia al tratamiento frente al 38% que tenía mala. No existieron diferencias significativas entre buena y mala adherencia y apoyo familiar. En el grupo de mala adherencia había una mayor proporción de analfabetos con respecto al grupo de buena adherencia (12% vs 5%) y una menor proporción de universitarios (1% vs 4%), p = 0,147. Se objetivó una menor tasa de reingresos a los seis meses en el grupo de buena adherencia con respecto al de mala (10% vs 22%), p < 0.005. Entre las causas de mala adherencia la desmotivación apareció en un 22%, seguida de efectos secundarios: 16%.

Discusión. La mayoría de nuestros pacientes son mujeres con edad media avanzada y predomina la FE conservada, contrastando con la mayoría de los estudios que se han desarrollado clásicamente en pacientes con ICC. Una de las limitaciones fundamentales es la pérdida de pacientes, va que solo cerca de la mitad de ellos completaron la visita de los seis meses, poniendo de manifiesto la complejidad y dificultades sociales de los pacientes que ingresan en los servicios de Medicina Interna que dificulta seguimientos en consultas externas.

Conclusiones. La adherencia al tratamiento es una pieza fundamental para una evolución satisfactoria de la enfermedad como demuestra este estudio al objetivarse una menor tasa de reingresos en aguellos pacientes que demostraron tener buena adherencia.

	After Any HF Hospitalization	After the Initial HF Hospitalization	After the Second HF Hospitalization
% of patients hospitalized for any reason	30% in 2-3 months (13)	69% (4)	60% (4)
	27% in 3 months (8)		
	38% in 6 months (14)		
	67% (3)		
% of patients hospitalized for HF	22% in 2 yrs (15)	16% (EF <40%) (6)	36% (4)
		14% (EF >50%) (6)	
		22% (4)	
		30%* (5)	
% of patients hospitalized for cardiovascular reasons	<sup>43% (3)</sup> 67% no CV	44% (4)	57% (4)
	42% (10)	50%* (5)	
% of hospitalized patients with HF as the primary cause	<u></u>	32% (4)	60% (4)
% of hospitalized patients with cardiovascular diseases as the primary cause	64% (3)	49% (4)	95% (4)
ospitalizations in Patients	37% (3)	26% (EF <40%) (6)	44% (4)
ith Heart Failure: Who and Why*	31% (14)	22% (EF >50%) (6)	
ith Heart Failure: who and why"	42% (16)	34% (4)	

29% (EF ≥50%) (17)

32% (EF < 50%) (17)

con una FE mayor o igual de 50% (insuficiencia cardiaca con fracción de eyección preservada). Se recogieron las características clínicas así como las causas de muerte de cada paciente. Se definieron cuatro causas de muerte: 1) insuficiencia cardíaca; 2) Muerte súbita; 3) otras causas de muerte cardiovascular (ictus, infarto agudo de miocardio, o tromboembolismo pulmonar) y 4) otras causas no incluidas en las categorías anteriores.

paciente Soko Setoguchi, MD, DRPH, Lynne Warner Stevenson, MD‡

evecciól Boston, Massachusetts

Resultados. En el período de tiempo definido se siguieron a 289 pacientes con el diagnóstico de insuficiencia cardíaca. Se incluyeron en el grupo de insuficiencia cardíaca con FE conservada 199 pacientes y 88 en el de FE disminuida. Ocurrieron 30 muertes, de las cuales 18 correspondieron a pacientes con FE preservada (FE media 63,4%) y 12 con FE reducida (FE media de 36,5%). La edad media fue de 80 en ambos grupos. El tiempo medio del fallecimiento tras el diagnóstico fue de 26 y 28 meses. Los pacientes con FE conservada tuvieron una mayor prevalencia de hipertensión arterial (96,2% vs. 66,6%, p = 0,011) y menor de cardiopatía isquémica (18% vs. 50% p = 0,044). La mortalidad causada por insuficiencia cardíaca fue significativa-

## Grupo R y

33% (18)

Conclusiones Los pacientes ancianos con insuficiencia cardíaca con FE conservada fallecen principalmente por causas no cardiovasculares.

(Sitges, noviembre 2007)





## Los "expertos"

**Levy** D. (Director, Framingham Heart Study). We know **so little** about the optimal treatment of heart-failure patients with preserved ejection fractions... (09/2009).



Clin Geriatr Med 23 (2007) 83-106

CLINICS IN GERIATRIC MEDICINE

Para delinear el papel de BB en ICD se requieren ensayos grandes, bien diseñados...

Diastolic Heart Failure in the Elderly Dalane W. Kitzman, MD\*, Kurt R. Daniel, DO

Department of Internal Medicine, Wake Forest University Health Sciences Center, Medical Center Boulevard, Winston-Salem, NC 27157, USA

JAMA 2008; 300: 431-2.

#### Heart Failure With Preserved Ejection Fraction

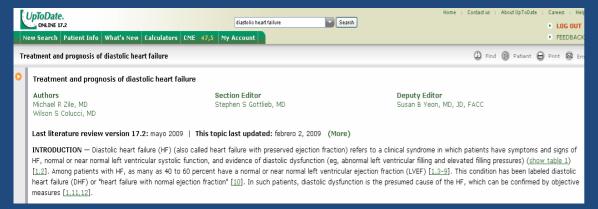
Treat Now by Treating Comorbidities

Sanjiv J. Shah, MD Mihai Gheorghiade, MD (36%-53%), atrial fibrillation (32%-41%), (32%-45%), chronic kidney disease (23% vascular disease (15%),² as well as obesity

Pitt B. ARCH INTERN MED/VOL 168 (NO. 22), DEC 8/22, 2008 2431

Los BB <u>no</u> han demostrado reducir ni mortalidad y hospitalizaciones en paciente con IC y EF normal.

Kaplan NM. Beta-blockers in hypertension. JACC 2008;52:1490-1. Taquiarritm, posIAM, ICFED



At present, there is no good demonstration that beta blockade is beneficial for the treatment of HF with preserved ejection fraction.

# Perspectivas futuras ¿¿Y los betabloqueantes??

STATE-OF-THE-ART PAPER

#### Heart Failure With Normal Left Ventricular Ejection Fraction

JACC 2009; 53:908-18.

Micha T. Maeder, MD, David M. Kaye, MD, PhD Melbourne, Australia

Table 3

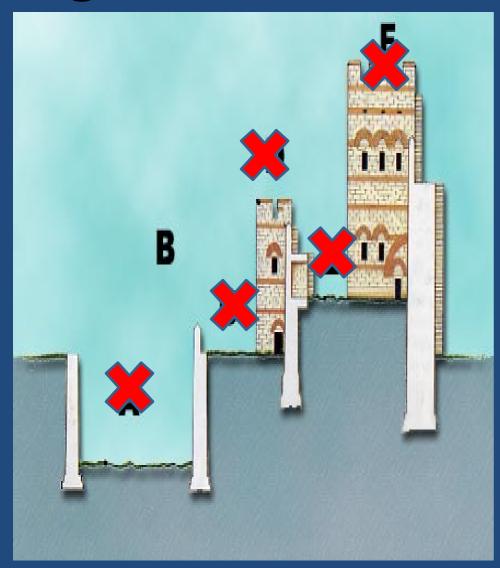
Substances Evaluated for the Treatment of Patients With HFNEF in Completed but Unpublished or Ongoing Clinical Studies (According to NIH Clinical Trials Registry\*)

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 <sub>f</sub> channel)	Heart rate, duration of diastole

<sup>\*</sup>National Institutes of Health (NIH) Clinical Trials Registry (78).

RAAS - renin-anglotensin-aidosterone system; other abbreviations as in Table 1.

# ¿Que queda de los argumentos?





Seniors
J-DHF???

Endios observacionales

Contradictorios
OPTIMIZE-HF: en contra

Exriencia
Bien tolerado pero efectivo???

Exertos Contradictorios

#### HataiiiiGiito ug iofer. Lo

esencia

• No tto. convincente ►↓morbimortalidad ICFEP (Ponikowski P, ESC(Barc-09).

- 1) Control de TA (↓activación neurohumoral→Prevenir/Tto.)
  - IECA/ARA II >> CA¹ IECA/ARA II >> BB (↓HVI)²
- 2) Control del ritmo (BB>>digoxina>>CA)
- 3) Diagnosticar y tratar la isquemia
- 4) Evitar desencadenantes
  - (AHA/2009: AINEs, *BB*, CA)(Alcohol, drogas ilegales)
  - Neumonía, enf. Víricas (Vacunación: 27-37% hospitalización por IC)<sup>3</sup>
- 5) Tratamiento de comorbilidades
  - EPOC ¡Ojo!
     → Bisoprolol → ↓FEV₁ en IC + EPOC⁴
  - Obesidad (SAOS), diabetes, anemia, TEP...



#### El Cid Campeador (Valencia, 1094) 1010 años de †

## **Betabloqueantes** IC con FED

La tarea es tu Valencia

Rev Clin Esp. 2005;205(4):147-8 EDITORIAL

¿Qué más evidencias se necesitan para extender el uso de bloqueadores beta en la insuficiencia cardíaca?

L. Manzano y R. Redondo

Unidad de Insuficiencia Cardíaca y Riesgo Vascular del Anciano. Servicio de Medicina Interna. Hospital Universitario Ramón y Cajal. Universidad de Alcalá. Madrid.

#### IC con FEP

¡Dejemos de cazar dragones!

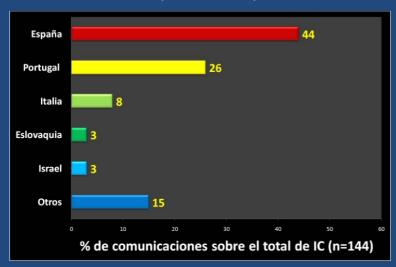


¡¡Dios, que buen cavallero si oviesse buen senyor!!



## De Estambul...

Comunicaciones sobre IC en Congresos Europeos (1997-2009)



## Muchas

## ...a Estocolmo

