



Mesa Redonda 25

IC - ¿Actuamos correctamente en nuestro día a día?

# Tratamiento de la IC crónica y sus comorbilidades

David Chivite Guillen

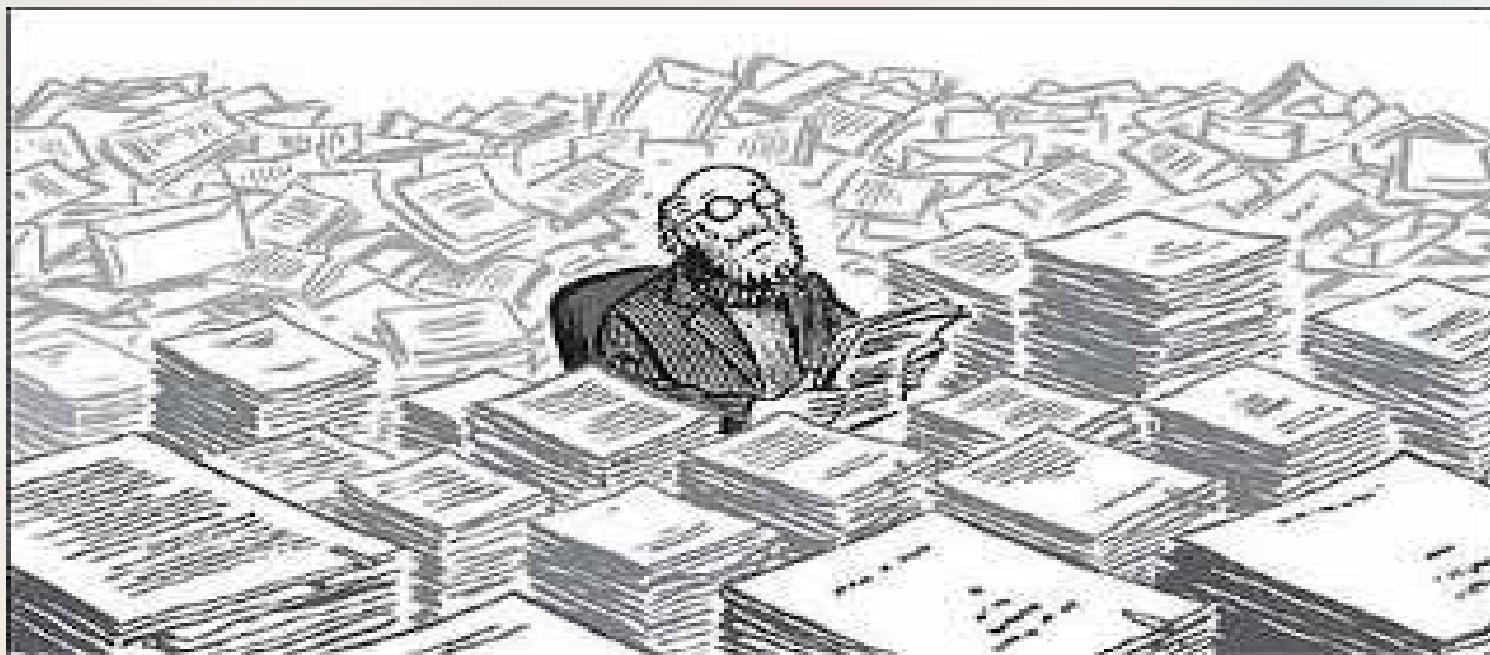
Servicio de Medicina Interna – Unidad de  
Geriatría

Hospital Universitari de Bellvitge – IDIBELL  
Universitat de Barcelona

L'Hospitalet de Llobregat



## Un encargo “sencillo”



**20'!**



## Tratamiento de la IC crónica y sus comorbilidades

### ¿Qué elegir?



## Guion

### ■ Perspectiva epidemiológica

### ■ Tratamiento de la IC crónica

- Situación actual ICFER/ICFEP
- Novedades

### ■ Tratamiento de la comorbilidad

- Comorbilidad y asociación con IC
- Comorbilidad clásica
- Comorbilidad emergente

*European Heart Journal* (1997) **18**, 736-753

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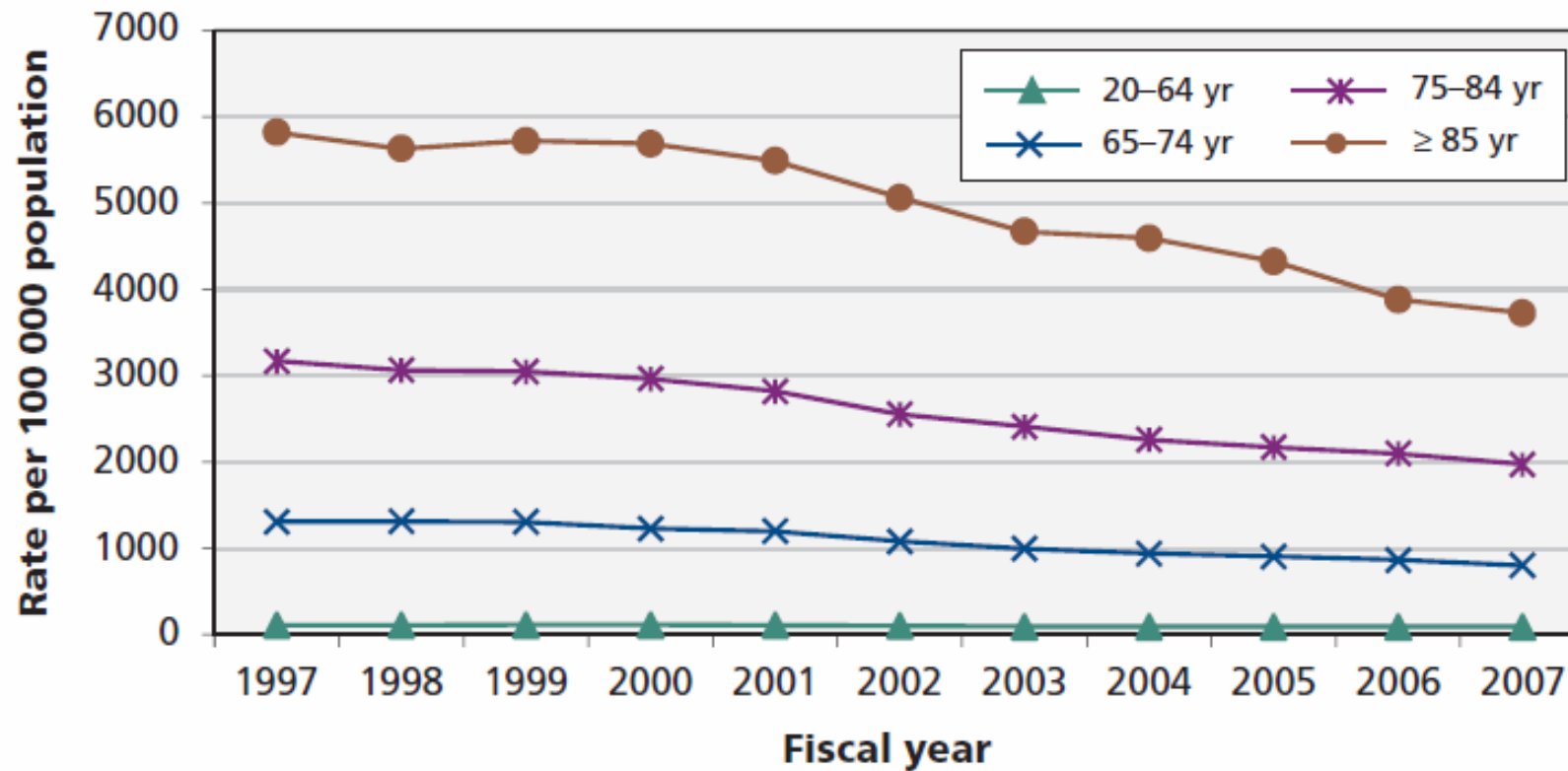
## ***Guidelines***

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### **The treatment of heart failure**

**The Task Force of the Working Group on Heart Failure of the  
European Society of Cardiology**

## **Incidencia en descenso...finalmente**

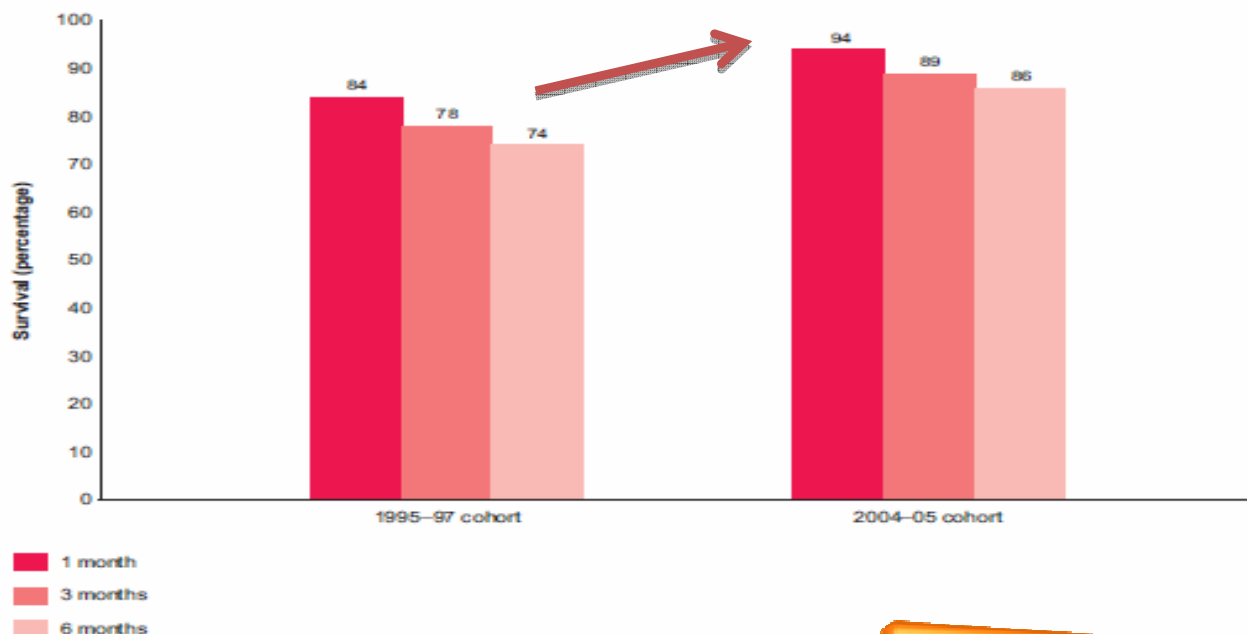


Yeung CMAJ 2012

## Mayor supervivencia

The Heart Foundation UK  
2010

Survival rates at one month, three months and six months post diagnosis, SE England, 1995–97 and 2004–05



Nakano BMC Health Serv Res 2013

Table 4 One-year mortality among patients diagnosed with incident heart failure in Denmark in 2010 vs. 2003

|           | Mortality 2003<br>N/total (%) | Mortality 2010<br>N/total (%) | Unadjusted HR<br>(95% CI) | Adjusted HR *<br>(95% CI) | Adjusted HR †<br>(95% CI) |
|-----------|-------------------------------|-------------------------------|---------------------------|---------------------------|---------------------------|
| Total     | 333/1624 (20.5)               | 488/3809 (12.8)               | 0.59 (0.51-0.67)          | 0.65 (0.56-0.75)          | 0.79 (0.65-0.96)          |
| LVEF ≤40% | 277/1379 (20.1)               | 408/3141 (13.0)               | 0.61 (0.52-0.71)          | 0.67 (0.57-0.78)          | 0.85 (0.69-1.05)          |
| LVEF >40% | 56/245 (22.9)                 | 79/668 (11.8)                 | 0.47 (0.31-0.74)          | 0.58 (0.40-0.84)          | 0.51 (0.30-0.89)          |

## Menos hospitalizaciones

Georghiade JACC 2013

**Table 2**

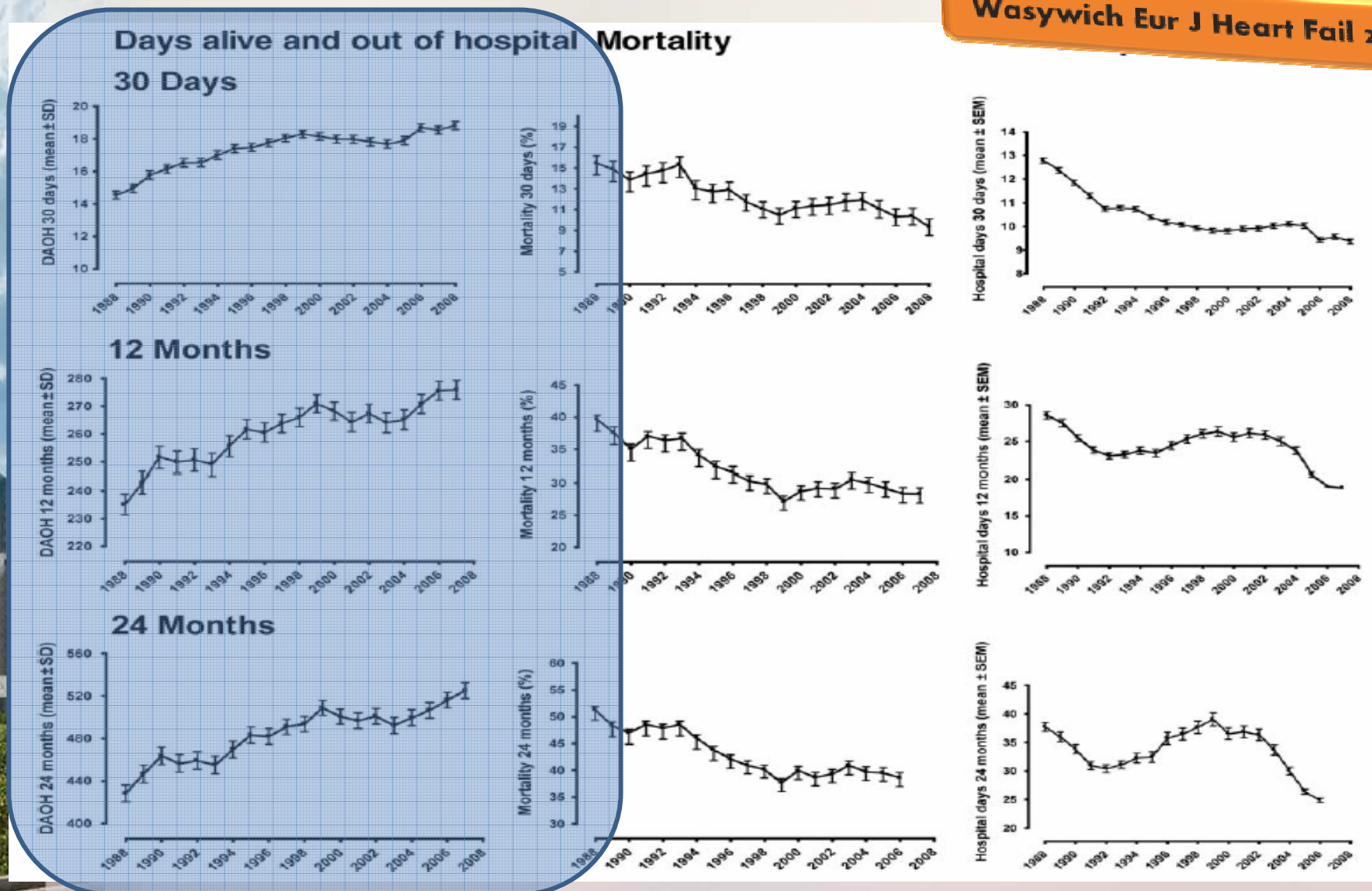
**Trends in Primary and Secondary Heart Failure Hospitalizations by Age and Sex Category**

| Characteristics  | Primary      |              |              | Secondary    |              |              |
|------------------|--------------|--------------|--------------|--------------|--------------|--------------|
|                  | 2001 to 2003 | 2004 to 2006 | 2007 to 2009 | 2001 to 2003 | 2004 to 2006 | 2007 to 2009 |
| <b>Age (yrs)</b> |              |              |              |              |              |              |
| 18-49            | 59           | 65           | 61           | 108          | 131          | 134          |
| 50-64            | 456          | 431          | 384          | 983          | 1,071        | 1,045        |
| 65-74            | 1,415        | 1,293        | 1,095        | 3,462        | 3,641        | 3,376        |
| 75-84            | 2,899        | 2,681        | 2,373        | 7,601        | 7,906        | 7,303        |
| ≥85              | 5,235        | 5,002        | 4,521        | 14,784       | 14,991       | 13,499       |
| <b>Sex</b>       |              |              |              |              |              |              |
| Female           | 565          | 520          | 462          | 1,448        | 1,532        | 1,438        |
| Male             | 503          | 509          | 472          | 1,205        | 1,312        | 1,285        |

Estimates per 100,000 population; p trends < 0.0001 for all categories.

## Un “outcome” con sentido para el paciente

Wasywich Eur J Heart Fail 2010



## 2 décadas de éxito - los nuevos paradigmas

Savino Cardiol Rev 2013

TABLE 1. The Heart Failure Model Paradigm

| Model        | Main Tenets                                                                                                                                           | Associated Pharmacologies                     |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Cardiorenal  | Elevated venous pressure causes peripheral and pulmonary edema by preventing venous return from kidney                                                | Diuretics                                     |
| Hemodynamic  | Myocardial stress impairs contractile force leading to peripheral compensation via vasoconstriction                                                   | Vasodilators                                  |
| Neurohumoral | Neurohumoral mediators activated after myocardial insult augment hemodynamics via sympathetic nervous system and renin-angiotensin-aldosterone system | $\beta$ -Blockers, ACE-I/ARBs, MR antagonists |
| Mechanical   | Systolic and diastolic dysfunctions are secondary to increased ventricular volume. LV remodeling contributes to progressive deterioration.            | Cardiac Resynchronization Therapy             |

## Efecto del tratamiento médico acumulativo

TABLE 1: Reductions in mortality observed in randomized, controlled trials evaluating drug or device therapies in patients with chronic heart failure that were powered for all-cause mortality and resulted in Level of Evidence A recommendations in clinical guidelines.

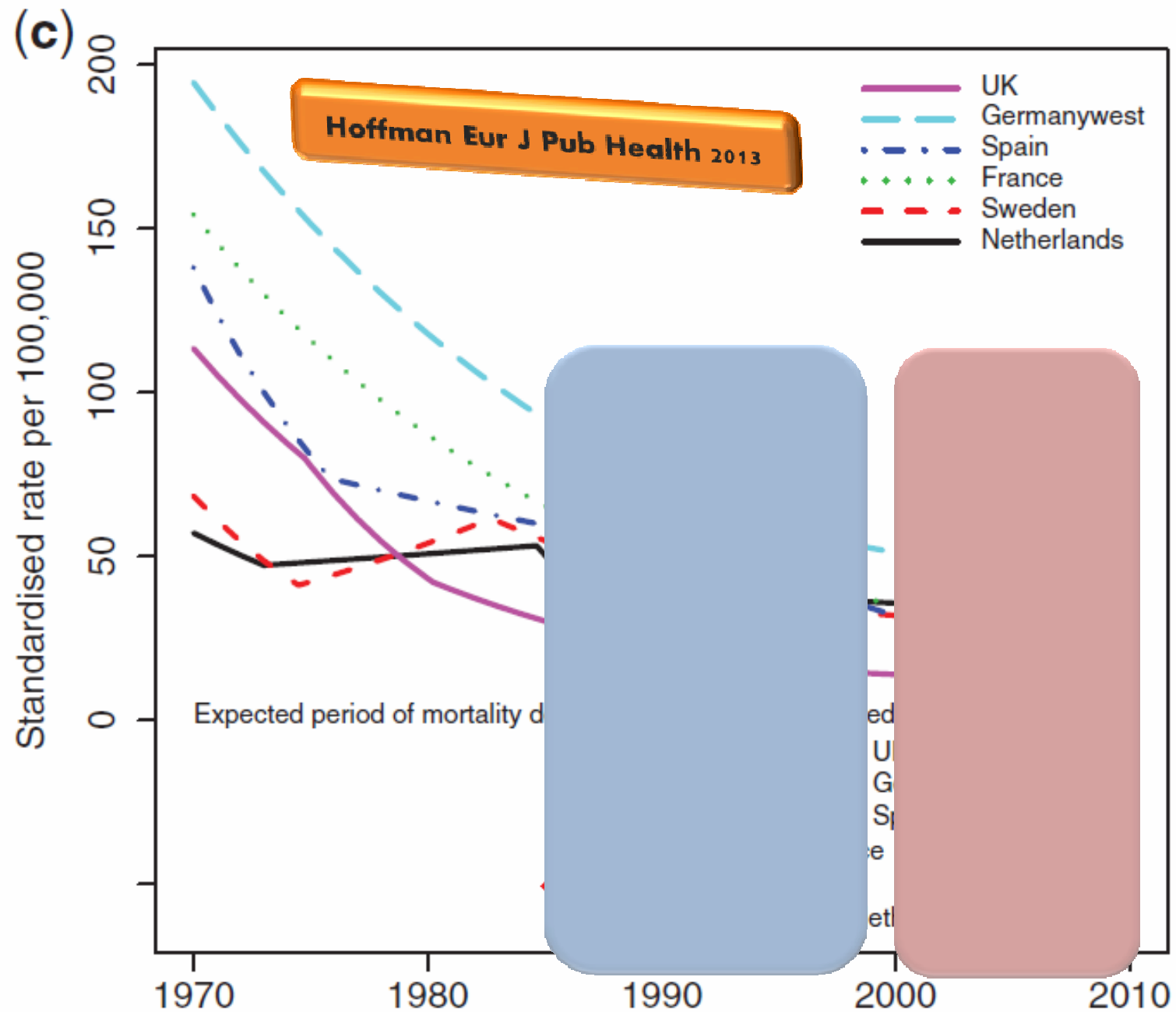
| Treatment                                                                      | Target population                                                                                                         | Mortality relative risk reduction | Trials                                        |
|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------------------|
| ACE inhibitor*                                                                 | HF with LVEF $\leq 40\%$                                                                                                  | 16–27%                            | CONSENSUS [65], SOLVD-T [52]                  |
| Beta blocker                                                                   | HF with LVEF $\leq 40\%$                                                                                                  | 34–35%                            | CIBIS II [61], MERIT-HF [60], COPERNICUS [59] |
| Mineralocorticoid receptor antagonist                                          | HF with LVEF $\leq 35\%$                                                                                                  | 24–30%                            | RALES [64], EMPHASIS HF [62]                  |
| Implantable cardioverter defibrillator                                         | HF with LVEF $\leq 30$ –35% despite optimal drug therapy                                                                  | 23–31%                            | MADIT-II [79], SCD-HeFT [78]                  |
| Cardiac resynchronization therapy $\pm$ implantable cardioverter defibrillator | HF with LVEF $\leq 30$ –35% with prolonged QRS duration $\geq 120$ –130 ms (especially LBBB) despite optimal drug therapy | 24–36%                            | COMPANION [94], CARE-HF [95], RAFT [92]       |

Atherton Scientifica (Hindawi) 279731

Table 18. Medical Therapy for Stage C HF/EF: Magnitude of Benefit Demonstrated in RCTs

| GDMT                   | RR Reduction in Mortality (%) | NNT for Mortality Reduction (Standardized to 36 mo) | RR Reduction in HF Hospitalizations (%) |
|------------------------|-------------------------------|-----------------------------------------------------|-----------------------------------------|
| ACE inhibitor or ARB   | 17                            | 26                                                  | 31                                      |
| Beta blocker           | 34                            | 9                                                   | 41                                      |
| Aldosterone antagonist | 30                            | 6                                                   | 35                                      |
| Hydralazine/nitrate    | 43                            | 7                                                   | 33                                      |

## ¿Es así? – influencia de IECA en mortalidad



# IC crónica, ¿cómo tratar?



European Heart Journal (2012) 33, 1787–1847  
doi:10.1093/eurheartj/ehs104

ESC GUIDELINES



## ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC

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Associations: European Association for Cardiovascular Prevention & Rehabilitation (EACPR), European Association of Echocardiography (EAE), European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI).

Working Groups: Acute Cardio Care, Cardiovascular Pharmacology and Drug Therapy, Cardiovascular Surgery, Genetic and Congenital Heart Disease, Hypertension and the Heart, Myocardial and Pericardial Diseases, Pulmonary Circulation and Right Ventricular Function, Thrombosis, Vascular Heart Disease, Councils: Cardiovascular Imaging, Cardiovascular Nursing and Allied Professions, Cardiology Practice, Cardiovascular Primary Care.

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## ACC/AHA Practice Guideline

### 2013 ACC/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American College of Chest Physicians, Heart Rhythm Society and International Society for Heart and Lung Transplantation

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation

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The online-only Comprehensive Relationships Table is available with this article at <http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0b013e31829e8776/-/DC2>.

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(*Circulation*. 2013;128:e240–e327.)

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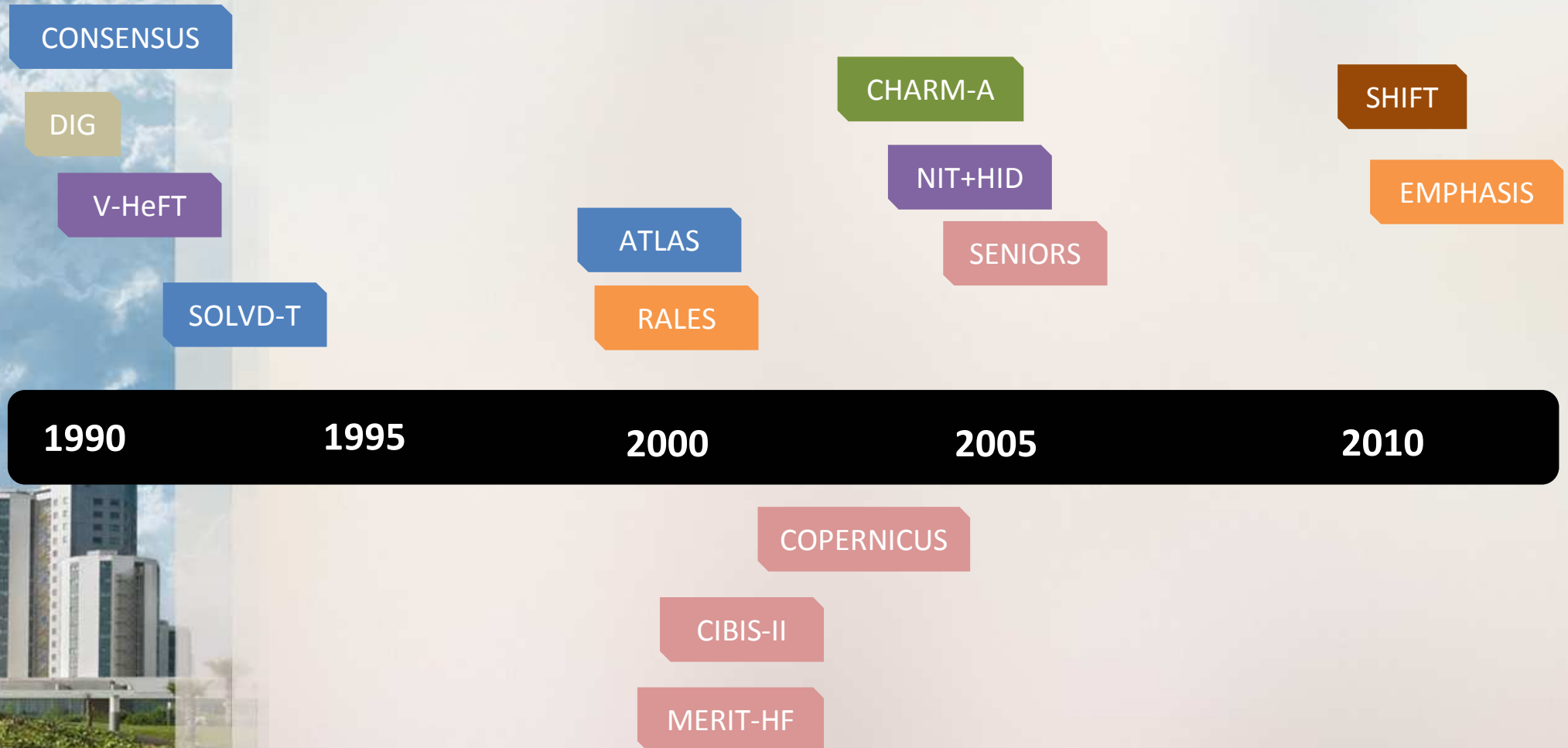
Tratamiento de la IC crónica y sus comorbilidades

## IC con recomendaciones claras

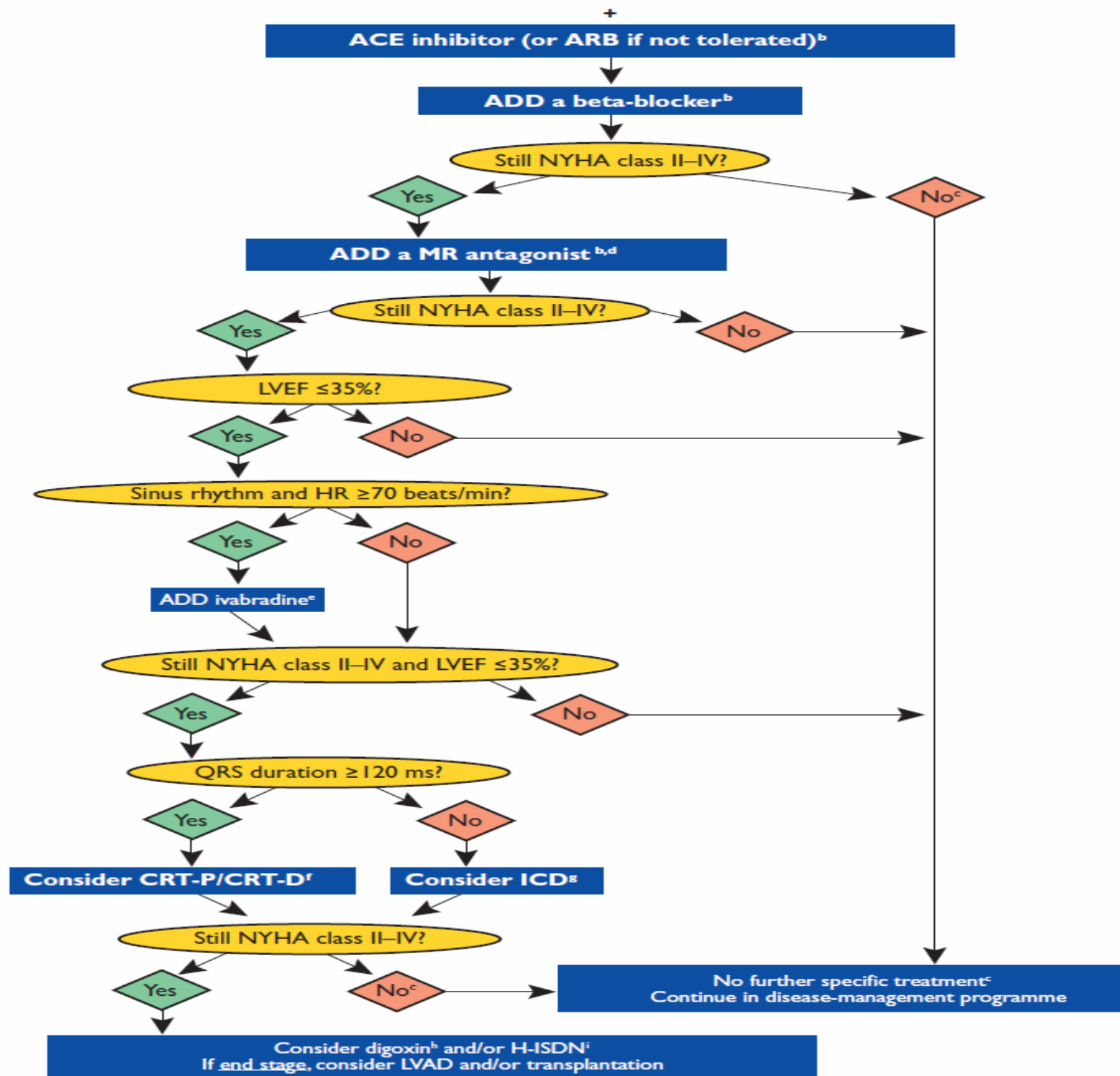


IC  
FER

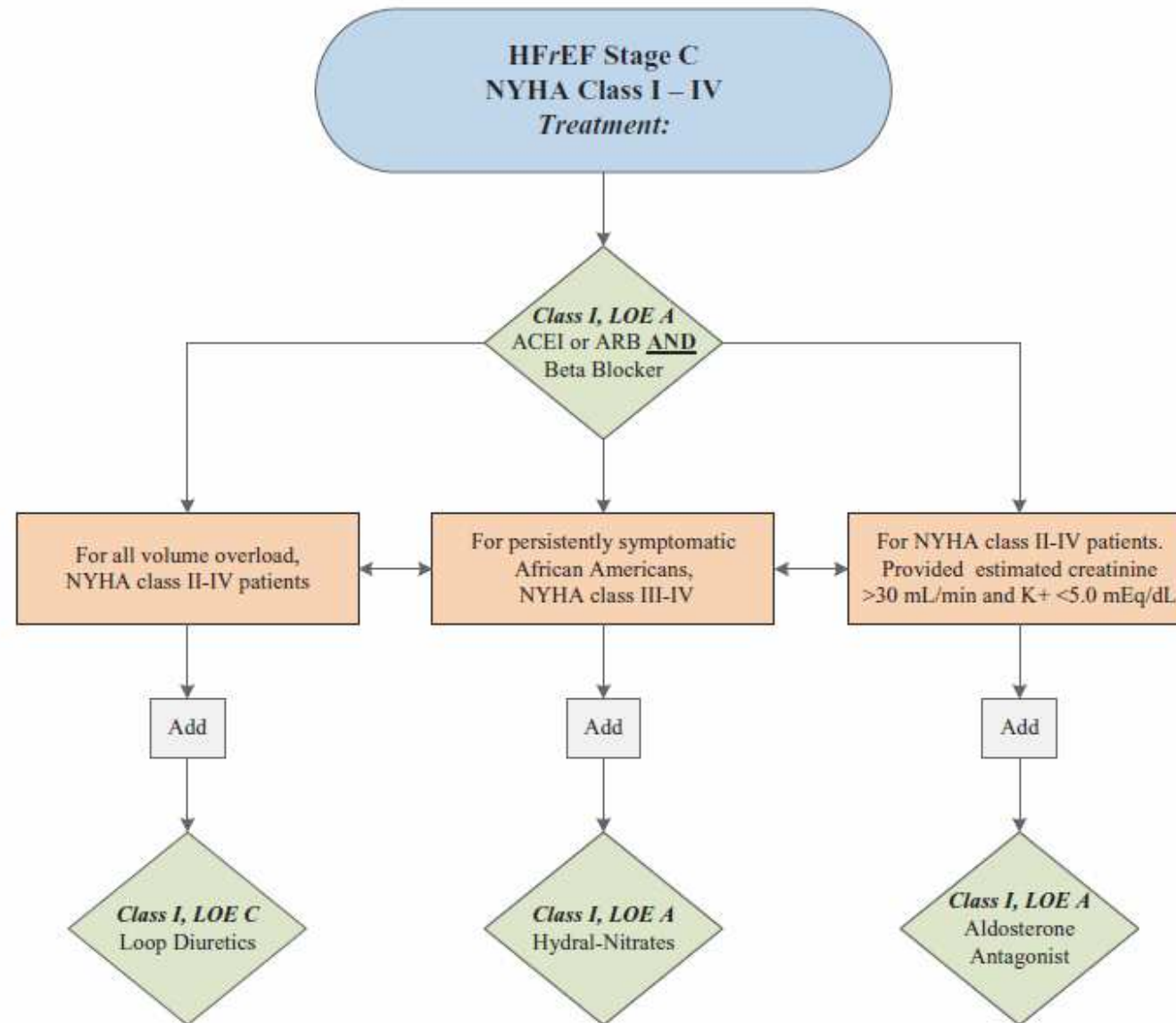
## ECA en IC FER 1986 – 2013 (sólo éxitos)



## Diuretics to relieve symptoms/signs of congestion<sup>a</sup>



## IC Crónica – guías AHA/ACC



**Table 19. Recommendations for Pharmacological Therapy for Management of Stage C HF/EF**

| Recommendations                                                                                                                                                                    | COR             | LOE | References         |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----|--------------------|
| <b>Diuretics</b>                                                                                                                                                                   |                 |     |                    |
| Diuretics are recommended in patients with HF/EF with fluid retention                                                                                                              | I               | C   | N/A                |
| <b>ACE inhibitors</b>                                                                                                                                                              |                 |     |                    |
| ACE inhibitors are recommended for all patients with HF/EF                                                                                                                         | I               | A   | 343, 412–414       |
| <b>ARBs</b>                                                                                                                                                                        |                 |     |                    |
| ARBs are recommended in patients with HF/EF who are ACE inhibitor intolerant                                                                                                       | I               | A   | 108, 345, 415, 450 |
| ARBs are reasonable as alternatives to ACE inhibitors as first-line therapy in HF/EF                                                                                               | IIa             | A   | 451–456            |
| Addition of an ARB may be considered in persistently symptomatic patients with HF/EF on GDMT                                                                                       | IIb             | A   | 420, 457           |
| Routine <i>combined</i> use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful                                                                            | III: Harm       | C   | N/A                |
| <b>Beta blockers</b>                                                                                                                                                               |                 |     |                    |
| Use of 1 of the 3 beta blockers proven to reduce mortality is recommended for all stable patients                                                                                  | I               | A   | 346, 416–419, 448  |
| <b>Aldosterone receptor antagonists</b>                                                                                                                                            |                 |     |                    |
| Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV who have LVEF $\leq 35\%$                                                                       | I               | A   | 425, 426, 478      |
| Aldosterone receptor antagonists are recommended in patients following an acute MI who have LVEF $\leq 40\%$ with symptoms of HF or DM                                             | I               | B   | 446                |
| Inappropriate use of aldosterone receptor antagonists may be harmful                                                                                                               | III: Harm       | B   | 479, 480           |
| <b>Hydralazine and Isosorbide dinitrate</b>                                                                                                                                        |                 |     |                    |
| The combination of hydralazine and isosorbide dinitrate is recommended for African Americans with NYHA class III–IV HF/EF on GDMT                                                  | I               | A   | 423, 424           |
| A combination of hydralazine and isosorbide dinitrate can be useful in patients with HF/EF who cannot be given ACE inhibitors or ARBs                                              | IIa             | B   | 449                |
| <b>Digoxin</b>                                                                                                                                                                     |                 |     |                    |
| Digoxin can be beneficial in patients with HF/EF                                                                                                                                   | IIa             | B   | 484–491            |
| <b>Anticoagulation</b>                                                                                                                                                             |                 |     |                    |
| Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke should receive chronic anticoagulant therapy*              | I               | A   | 508–514            |
| The selection of an anticoagulant agent should be individualized                                                                                                                   | I               | C   | N/A                |
| Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but are without an additional risk factor for cardioembolic stroke* | IIa             | B   | 509–511, 515–517   |
| Anticoagulation is not recommended in patients with chronic HF/EF without AF, a prior thromboembolic event, or a cardioembolic source                                              | III: No Benefit | B   | 518–520            |
| <b>Statins</b>                                                                                                                                                                     |                 |     |                    |
| Statins are not beneficial as adjunctive therapy when prescribed solely for HF                                                                                                     | III: No Benefit | A   | 533–538            |
| <b>Omega-3 fatty acids</b>                                                                                                                                                         |                 |     |                    |
| Omega-3 PUFA supplementation is reasonable to use as adjunctive therapy in HF/EF or HFpEF patients                                                                                 | IIa             | B   | 539, 540           |
| <b>Other drugs</b>                                                                                                                                                                 |                 |     |                    |
| Nutritional supplements as treatment for HF are not recommended in HF/EF                                                                                                           | III: No Benefit | B   | 544, 545           |
| Hormonal therapies other than to correct deficiencies are not recommended in HF/EF                                                                                                 | III: No Benefit | C   | N/A                |
| Drugs known to adversely affect the clinical status of patients with HF/EF are potentially harmful and should be avoided or withdrawn                                              | III: Harm       | B   | 546–557            |
| Long-term use of an infusion of a positive inotropic drug is not recommended and may be harmful except as palliation                                                               | III: Harm       | C   | N/A                |
| <b>Calcium channel blockers</b>                                                                                                                                                    |                 |     |                    |
| Calcium channel–blocking drugs are not recommended as routine treatment in HF/EF                                                                                                   | III: No Benefit | A   | 551, 574, 575      |

Tratamiento de la IC crónica y sus comorbilidades

## IC sin recomendaciones claras (por decir algo suave)



IC  
FEP

## Recomendaciones ESC ICFEP –seguimos igual

### Management of heart failure due to diastolic dysfunction

#### THERAPEUTIC APPROACH IN THE HEART FAILURE PATIENTS WITH PREDOMINANT DIASTOLIC DYSFUNCTION

There is very little evidence from clinical trials or observational studies as to how to treat diastolic dysfunction.

Causes of diastolic heart failure include: myocardial ischaemia, hypertension, myocardial hypertrophy and myocardial/pericardial constriction. These should be identified and treated appropriately.

1. Tachyarrhythmias should be corrected and sinus rhythm restored whenever possible.
2. Treatment can be tried with a  $\beta$ -blocker to lower heart rate and increase the diastolic period. Verapamil may be used for the same reason. Nitrates can be used when ischaemia is suspected. However, as with diuretics, care should be taken not to lower preload excessively.
3. Diuretics should be used cautiously so as not to lower preload excessively and thereby reduce stroke volume and cardiac output.
4. ACE inhibitors may improve ventricular relaxation directly and have a long-term effect through regression of hypertrophy.
5. Cardiac glycosides are probably contraindicated, as they may further decrease cardiac compliance.

### 8. Pharmacological treatment of heart failure with 'preserved' ejection fraction (diastolic heart failure)

No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF. Diuretics are used to control sodium and water retention and relieve breathlessness and oedema as in HF-REF. Adequate treatment of hypertension and myocardial ischaemia is also considered to be important, as is control of the ventricular rate in patients with AF (see Section 11). Two very small studies (<30 patients each) have shown that the heart rate-limiting calcium-channel blocker (CCB) verapamil may improve exercise capacity and symptoms in these patients.<sup>137,138</sup> Rate-limiting CCBs may also be useful for ventricular rate control in patients with AF and in the treatment of hypertension and myocardial ischaemia (which is not the case in patients with HF-REF where their negative inotropic action can be dangerous). Beta-blockers may also be used to control the ventricular rate in patients with HF-PEF and AF.

## IC FEP – recomendaciones AHA/ACC

**Table 21. Recommendations for Treatment of HFpEF**

| Recommendations                                                                                                             | COR             | LOE                |
|-----------------------------------------------------------------------------------------------------------------------------|-----------------|--------------------|
| Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines              | I               | B <sup>27,91</sup> |
| Diuretics should be used for relief of symptoms due to volume overload.                                                     | I               | C                  |
| Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT | IIa             | C                  |
| Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF                    | IIa             | C                  |
| Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF                                             | IIa             | C                  |
| ARBs might be considered to decrease hospitalizations in HFpEF                                                              | IIb             | B <sup>589</sup>   |
| Nutritional supplementation is not recommended in HFpEF                                                                     | III: No Benefit | C                  |

## ECA en IC FER – historia de una decepción

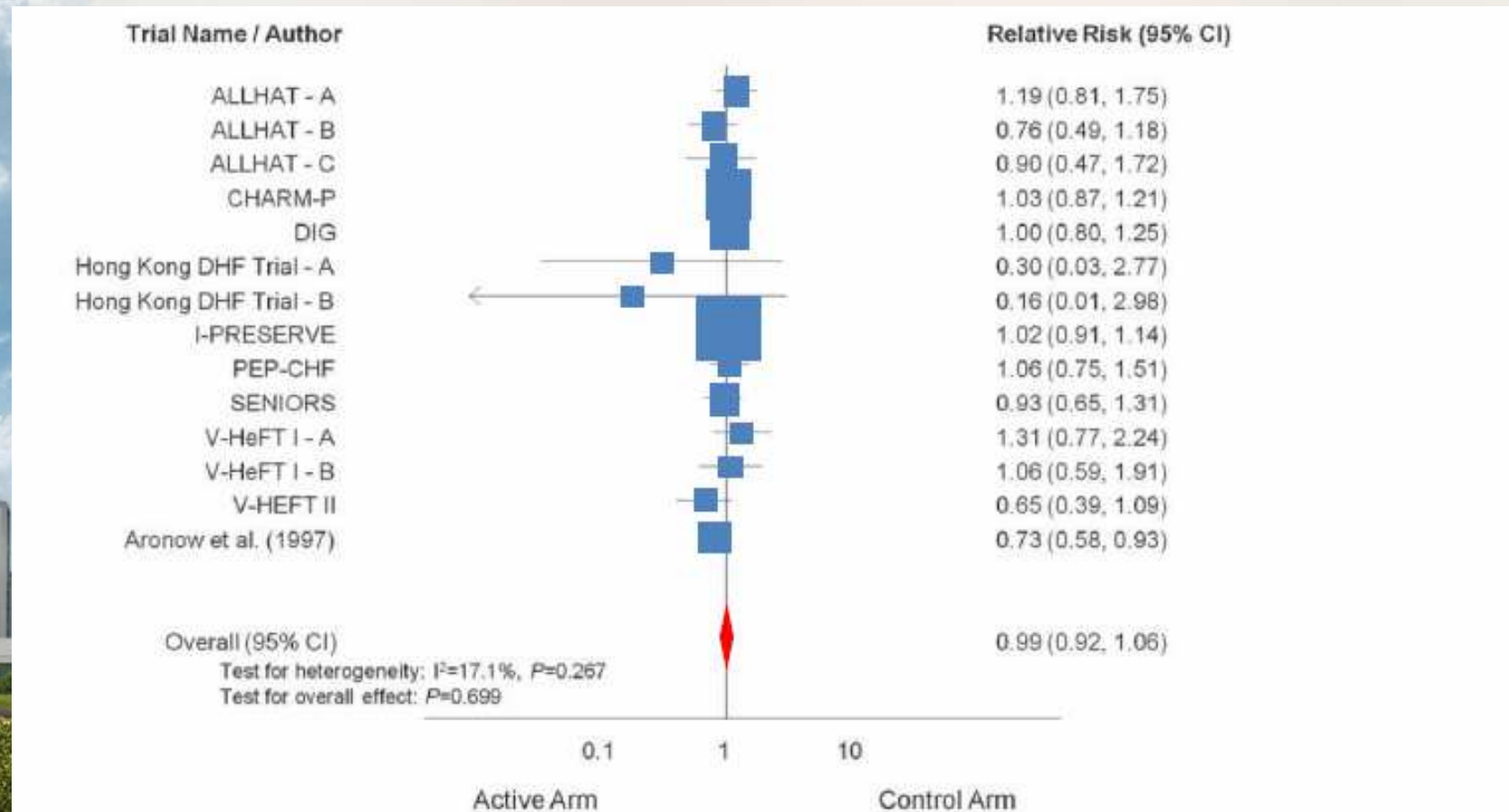
CHARM –P  
2003

PEP – CHF  
2006

I-PRESERVE  
2008

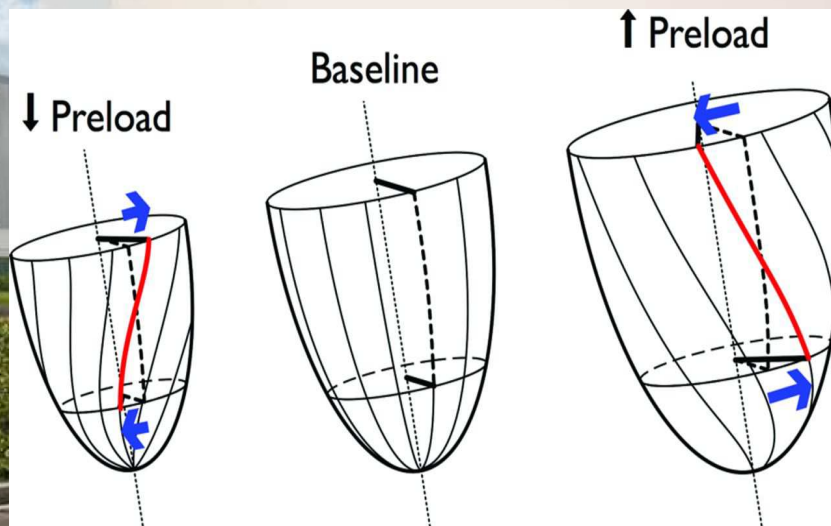
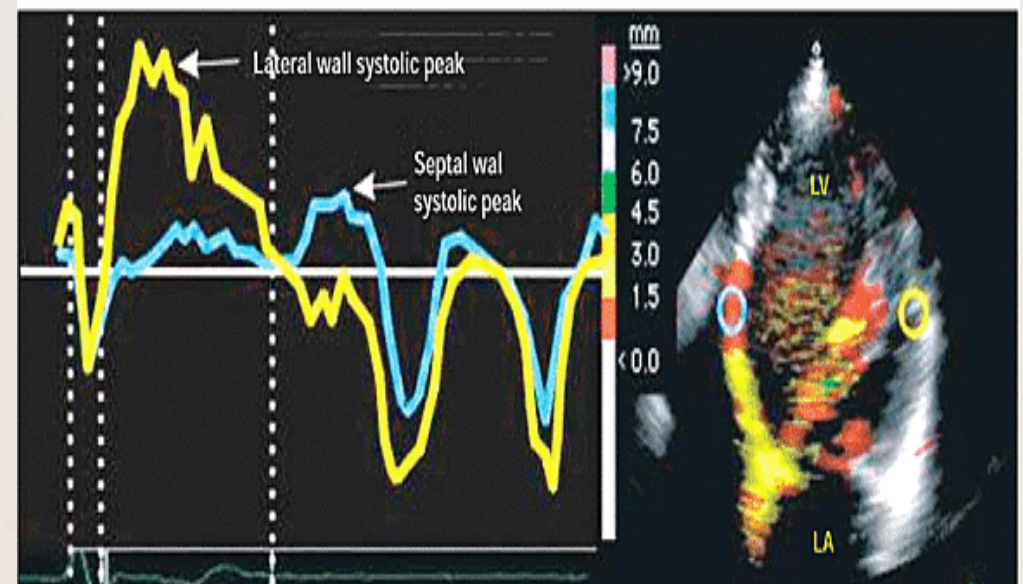
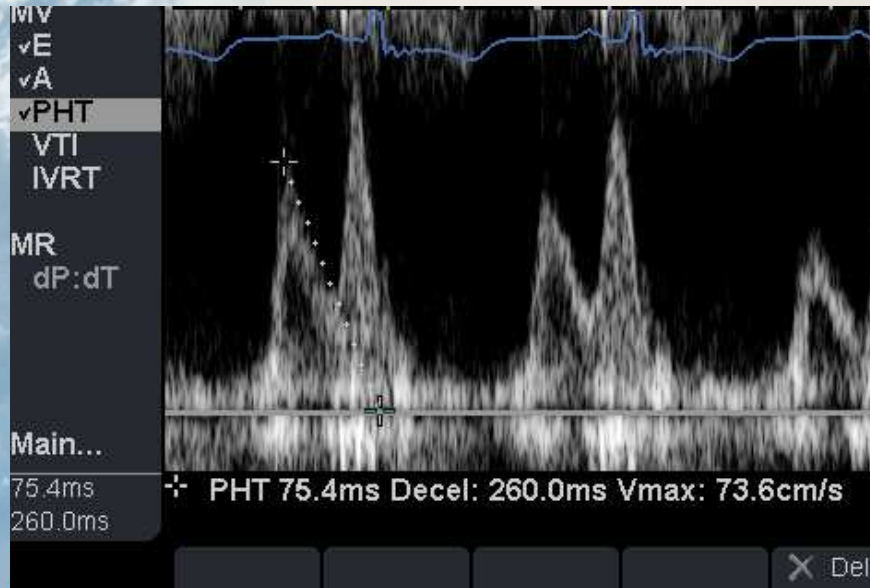
J-DHF  
2012

TOPCAT  
2013

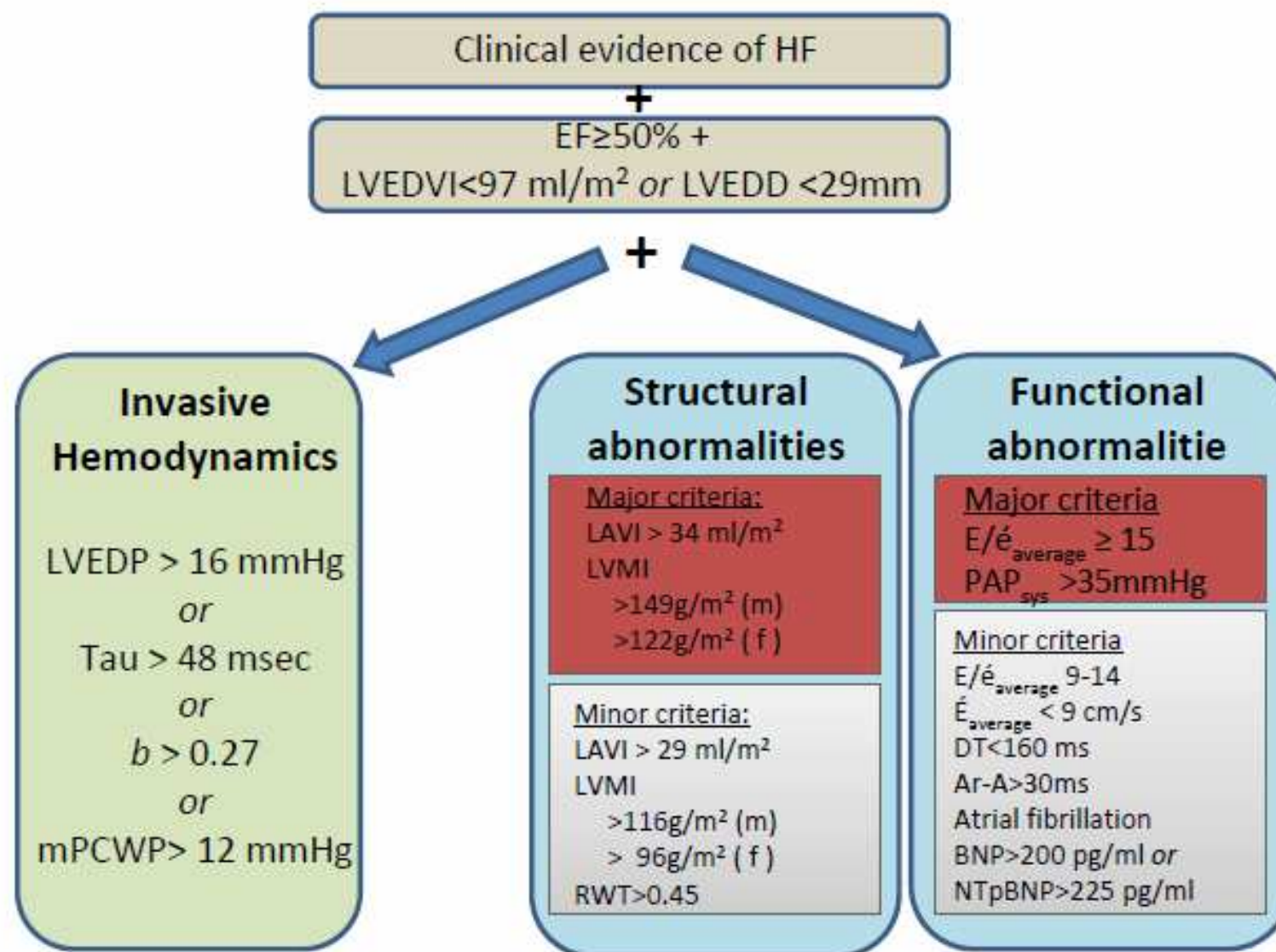


Holland DJ et al., J Am Coll Cardiol 2011;57:1676-1686

## ICFEP – a quien estamos tratando



## ICFEP – ¿un nuevo criterio diagnóstico en breve?



## Más categorías de IC huérfanas

IC  
FERe  
C

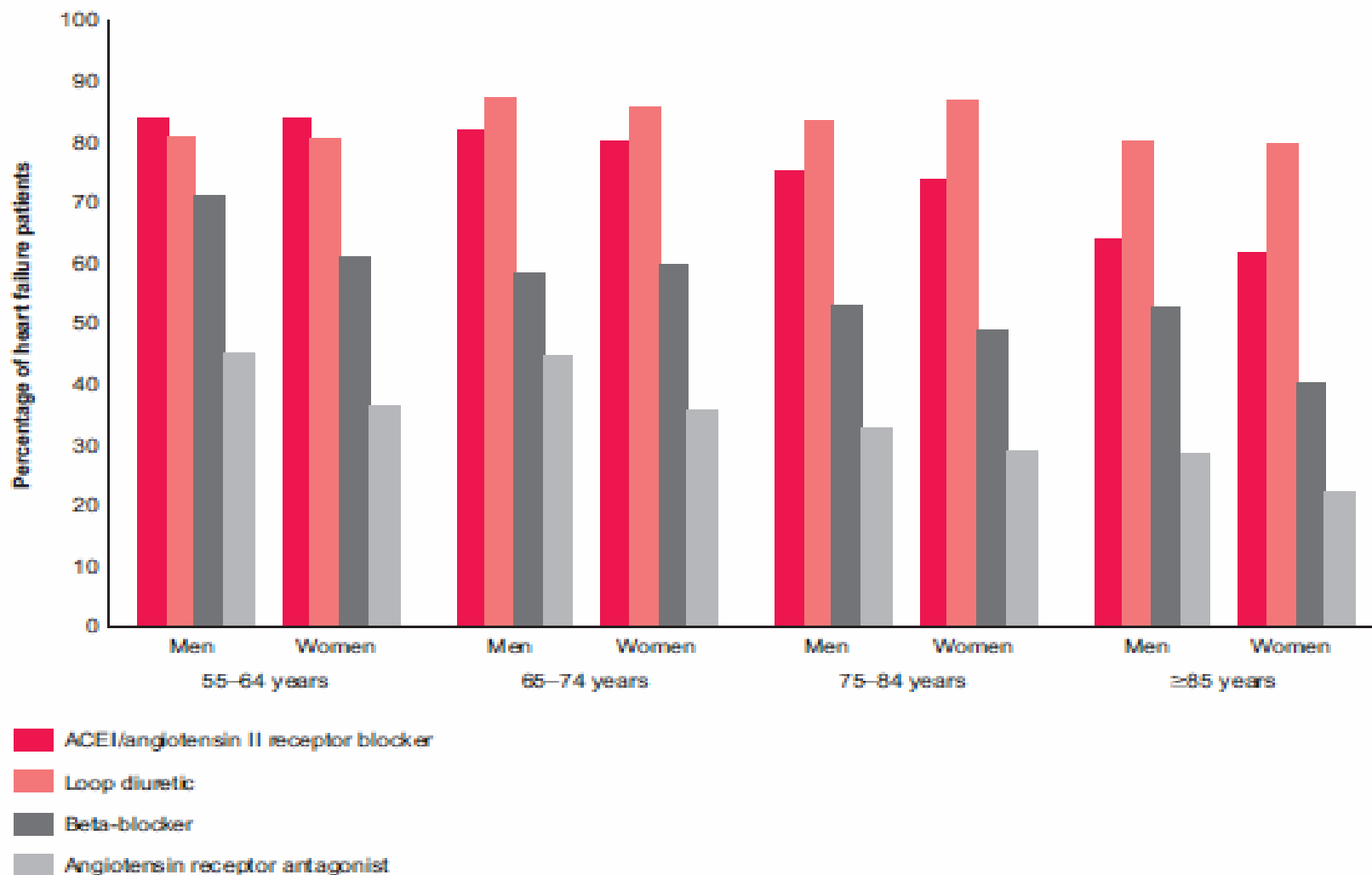
- FE “normalizada” tras tratamiento ICFER
- ¿Tratamiento mantenido ICFER o tratamiento específico?

IC  
feb

- FE 40 – 50%, “borderline”
- ¿Tratamiento ICFEP o ICFER?
  - ICFEP: ECA usualmente FEVI < 35%

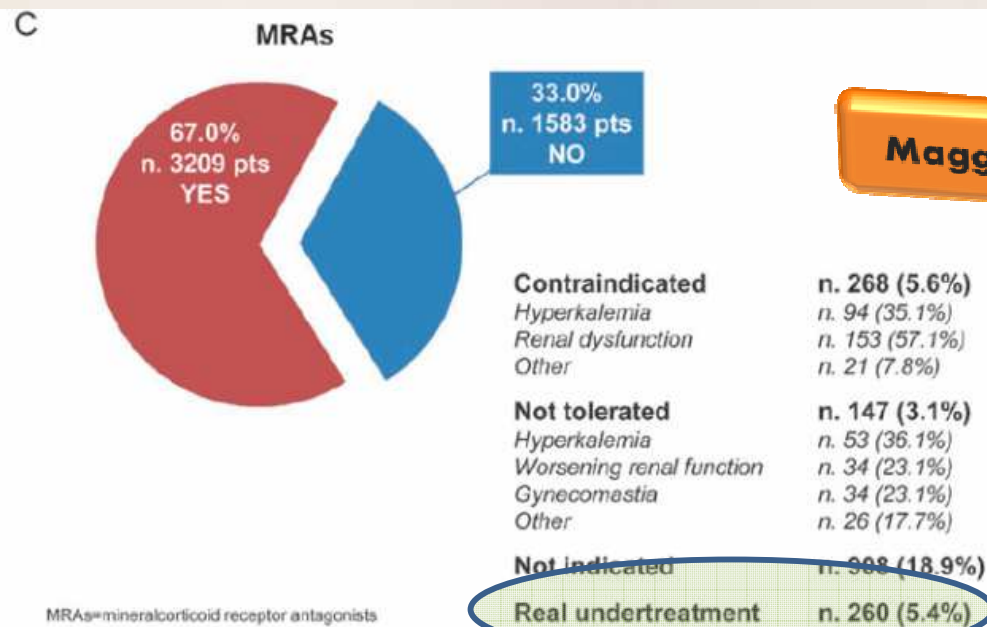
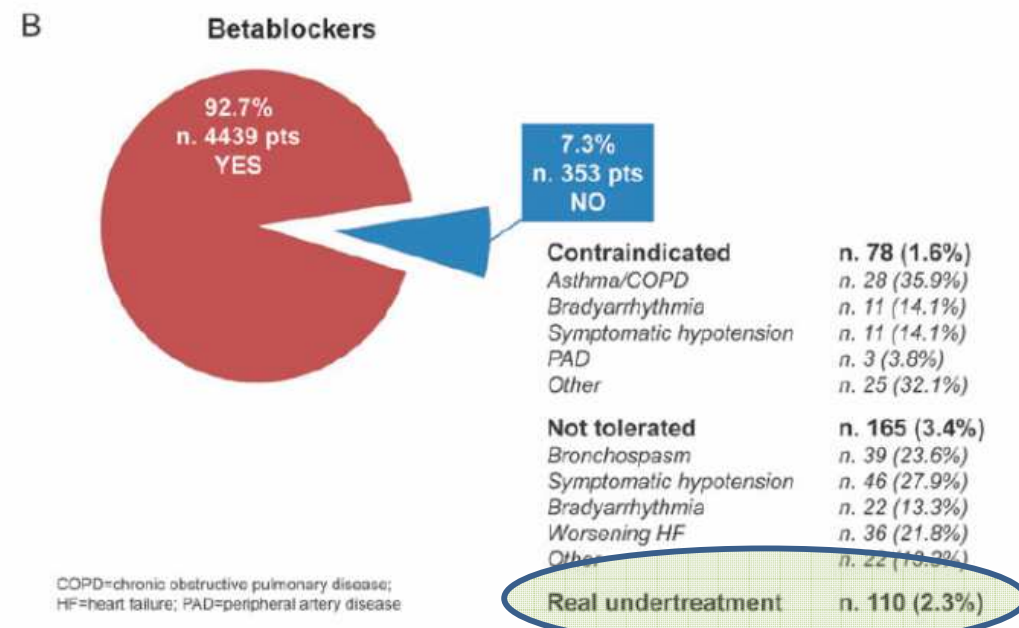
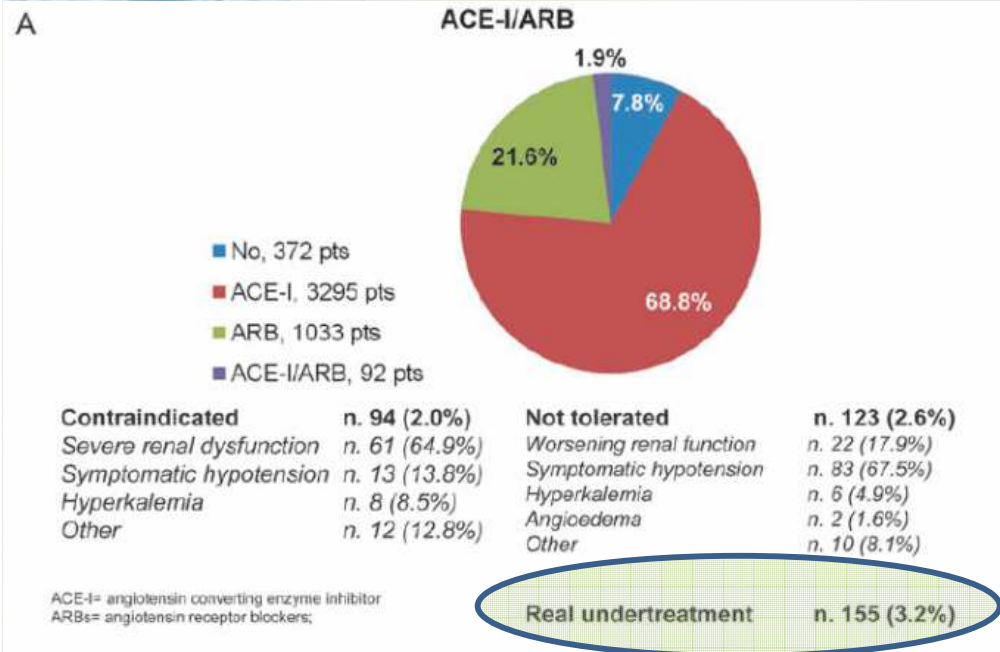
## ¿Se aplican las guías?

**Core treatments by age (55 and older) and sex in patients with left ventricular ejection fraction less than 40%**



Source: NHS Information Centre for Health and Social Care (2009b)

# Infratratamiento real



Maggioni Eur J Heart Fail 2013

# Más allá de la medicación

## Recommendations for exercise prescription and multidisciplinary management

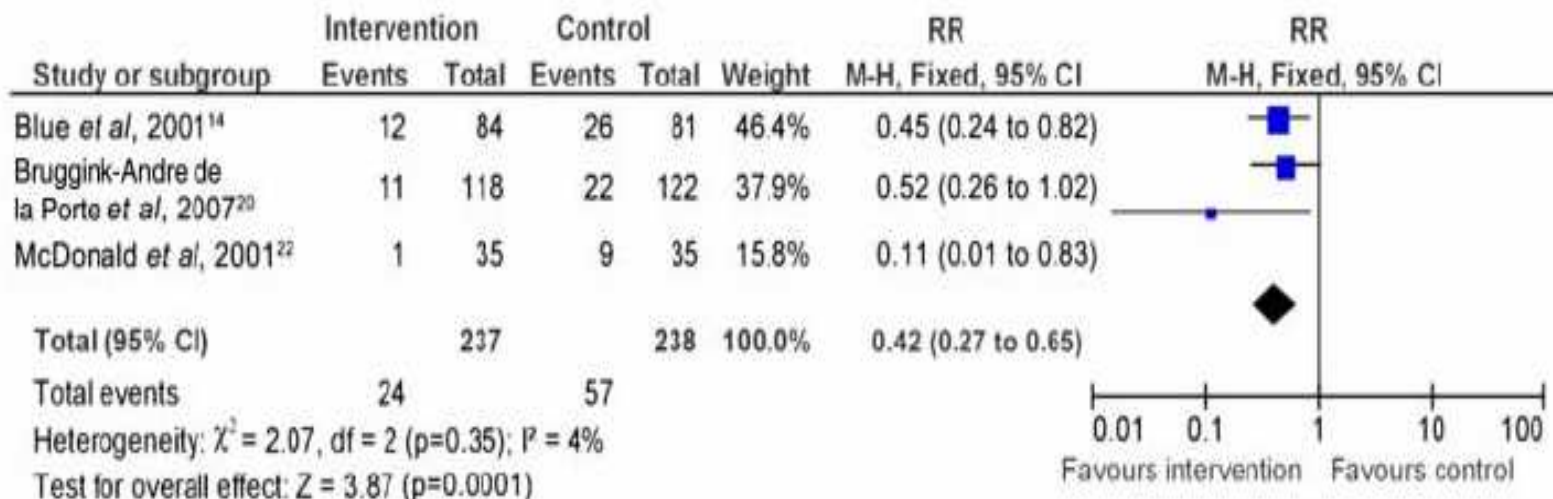
| Recommendations                                                                                                                                                       | Class <sup>a</sup> | Level <sup>b</sup> | Ref <sup>c</sup> |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|------------------|
| It is recommended that regular aerobic exercise is encouraged in patients with heart failure to improve functional capacity and symptoms.                             | I                  | A                  | 262, 263         |
| It is recommended that patients with heart failure are enrolled in a multidisciplinary-care management programme to reduce the risk of heart failure hospitalization. | I                  | A                  | 236, 259, 264    |

| Educational topic                | Patient skills and self-care behaviours                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Definition and aetiology         | <ul style="list-style-type: none"> <li>Understand the cause of heart failure and why symptoms occur</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Prognosis                        | <ul style="list-style-type: none"> <li>Understand important prognostic factors and make realistic decisions</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Symptom monitoring and self-care | <ul style="list-style-type: none"> <li>Monitor and recognize signs and symptoms</li> <li>Record daily weight and recognize rapid weight gain</li> <li>Know how and when to notify healthcare provider</li> <li>In the case of increasing dyspnoea or oedema or a sudden unexpected weight gain of &gt;2 kg in 3 days, patients may increase their diuretic dose and/or alert their healthcare team</li> <li>Use flexible diuretic therapy if appropriate and recommended after appropriate education and provision of detailed instructions</li> </ul>                                                  |
| Pharmacological treatment        | <ul style="list-style-type: none"> <li>Understand indications, dosing, and effects of drugs</li> <li>Recognize the common side effects of each drug prescribed</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Adherence                        | <ul style="list-style-type: none"> <li>Understand the importance of following treatment recommendations and maintaining motivation to follow treatment plan</li> <li>Sodium restriction may help control the symptoms and signs of congestion in patients with symptomatic heart failure classes III and IV</li> </ul>                                                                                                                                                                                                                                                                                  |
| Diet                             | <ul style="list-style-type: none"> <li>Avoid excessive fluid intake: fluid restriction of 1.5–2 L/day may be considered in patients with severe heart failure to relieve symptoms and congestion. Restriction of hypotonic fluids may improve hyponatraemia. Routine fluid restriction in all patients with mild to moderate symptoms is probably not of benefit. Weight-based fluid restriction (30 mL/kg body weight, 35 mL/kg if body weight &gt;85 kg) may cause less thirst</li> <li>Monitor and prevent malnutrition</li> <li>Eat healthily and keep a healthy weight (see Section 11)</li> </ul> |
| Alcohol                          | <ul style="list-style-type: none"> <li>Modest intake of alcohol: abstinence is recommended in patients with alcohol-induced cardiomyopathy. Otherwise, normal alcohol guidelines apply (2 units per day in men or 1 unit per day in women). 1 unit is 10 mL of pure alcohol (e.g. 1 glass of wine, 1/2 pint of beer, 1 measure of spirit)</li> </ul>                                                                                                                                                                                                                                                    |
| Smoking and drugs                | <ul style="list-style-type: none"> <li>Stop smoking and/or taking illicit drugs</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Exercise                         | <ul style="list-style-type: none"> <li>Understand the benefits of exercise</li> <li>Perform exercise training regularly</li> <li>Be reassured and comfortable about physical activity</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                        |
| Travel and leisure               | <ul style="list-style-type: none"> <li>Prepare travel and leisure activities according to physical capacity</li> <li>When travelling, carry a written report of medical history and current medication regimen and carry extra medication. Monitor and adapt fluid intake particularly during flights and in hot climates. Beware adverse reactions to sun exposure with certain medications (e.g. amiodarone)</li> </ul>                                                                                                                                                                               |
| Sexual activity                  | <ul style="list-style-type: none"> <li>Be reassured about engaging in sex and discuss problems with healthcare professionals. Stable patients can undertake normal sexual activity that does not provoke undue symptoms. For treatment of erectile dysfunction, see Section 11.10</li> </ul>                                                                                                                                                                                                                                                                                                            |
| Immunization                     | <ul style="list-style-type: none"> <li>Receive immunization against influenza and pneumococcal disease according to local guidelines and practice</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Sleep and breathing disorders    | <ul style="list-style-type: none"> <li>Recognize preventive behaviour such as reducing weight in obese patients, smoking cessation, and abstinence from alcohol</li> <li>Learn about treatment options if appropriate</li> </ul>                                                                                                                                                                                                                                                                                                                                                                        |
| Psychosocial aspects             | <ul style="list-style-type: none"> <li>Understand that depressive symptoms and cognitive dysfunction are common in patients with heart failure and the importance of social support</li> <li>Learn about treatment options if appropriate</li> </ul>                                                                                                                                                                                                                                                                                                                                                    |

## ¿Qué intervenciones funcionan mejor para evitar ingresos?

Thomas Heart 2013

Decreasing intensity



Metaanálisis 15 intervenciones multidisciplinarias

Reducción global del riesgo de reingreso RR 0.51 (95% CI 0.33 - 0.76)

Mejor resultado para las intervenciones con alta intensidad inicial

## Siglo XXI – nuevos paradigmas

**TABLE 1.** The Heart Failure Model Paradigm

| Model        | Main Tenets                                                                                                                                           | Associated Pharmacologies                                  |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| Cardiorenal  | Elevated venous pressure causes peripheral and pulmonary edema by preventing venous return from kidney                                                | Diuretics                                                  |
| Hemodynamic  | Myocardial stress impairs contractile force leading to peripheral compensation via vasoconstriction                                                   | Vasodilators                                               |
| Neurohumoral | Neurohumoral mediators activated after myocardial insult augment hemodynamics via sympathetic nervous system and renin-angiotensin-aldosterone system | $\beta$ -Blockers, ACE-I/ARBs, MR antagonists              |
| Mechanical   | Systolic and diastolic dysfunctions are secondary to increased ventricular volume. LV remodeling contributes to progressive deterioration.            | Cardiac Resynchronization Therapy                          |
| Genetic      | Changes at the genetic level, both inherited and acquired, contribute to the heart failure phenotype and the way it responds to therapy               | Gene therapy, Stem Cell therapy                            |
| Metabolic    | Changes in myocardial cellular metabolism contribute to maladaptive mechanisms that perpetuate CHF phenotype.                                         | Adenosine analogues, Allopurinol, Thyroxine, Trimetazidine |

ACE-I indicates angiotensin converting enzyme-inhibitor; ARB, angiotensin receptor blocker; CHF, congestive heart failure; LV, left ventricular; MR, mineralocorticoid.

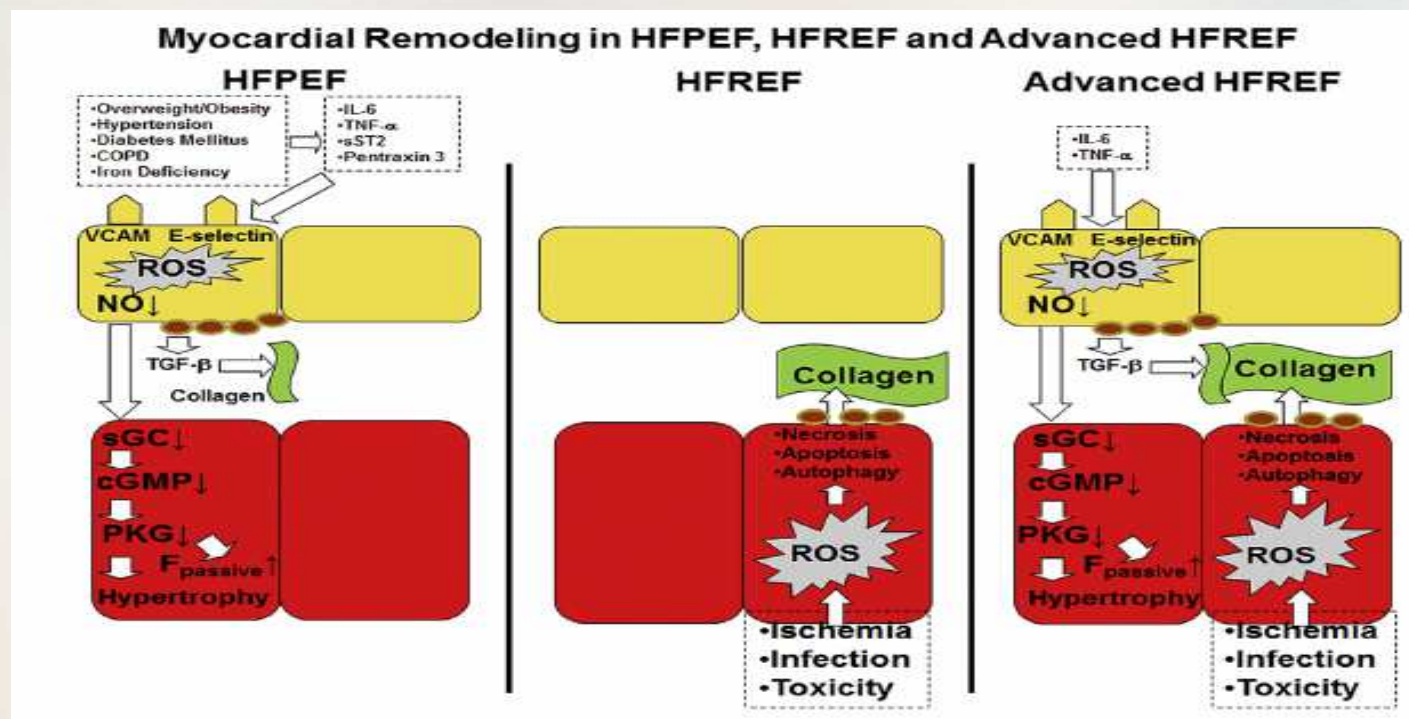
## A Novel Paradigm for Heart Failure With Preserved Ejection Fraction

Comorbidities Drive Myocardial Dysfunction and Remodeling Through Coronary Microvascular Endothelial Inflammation

Walter J. Paulus, MD, PhD,\* Carsten Tschöpe, MD, PhD†

**JACC** 2013

## Inflamación, inmunidad...

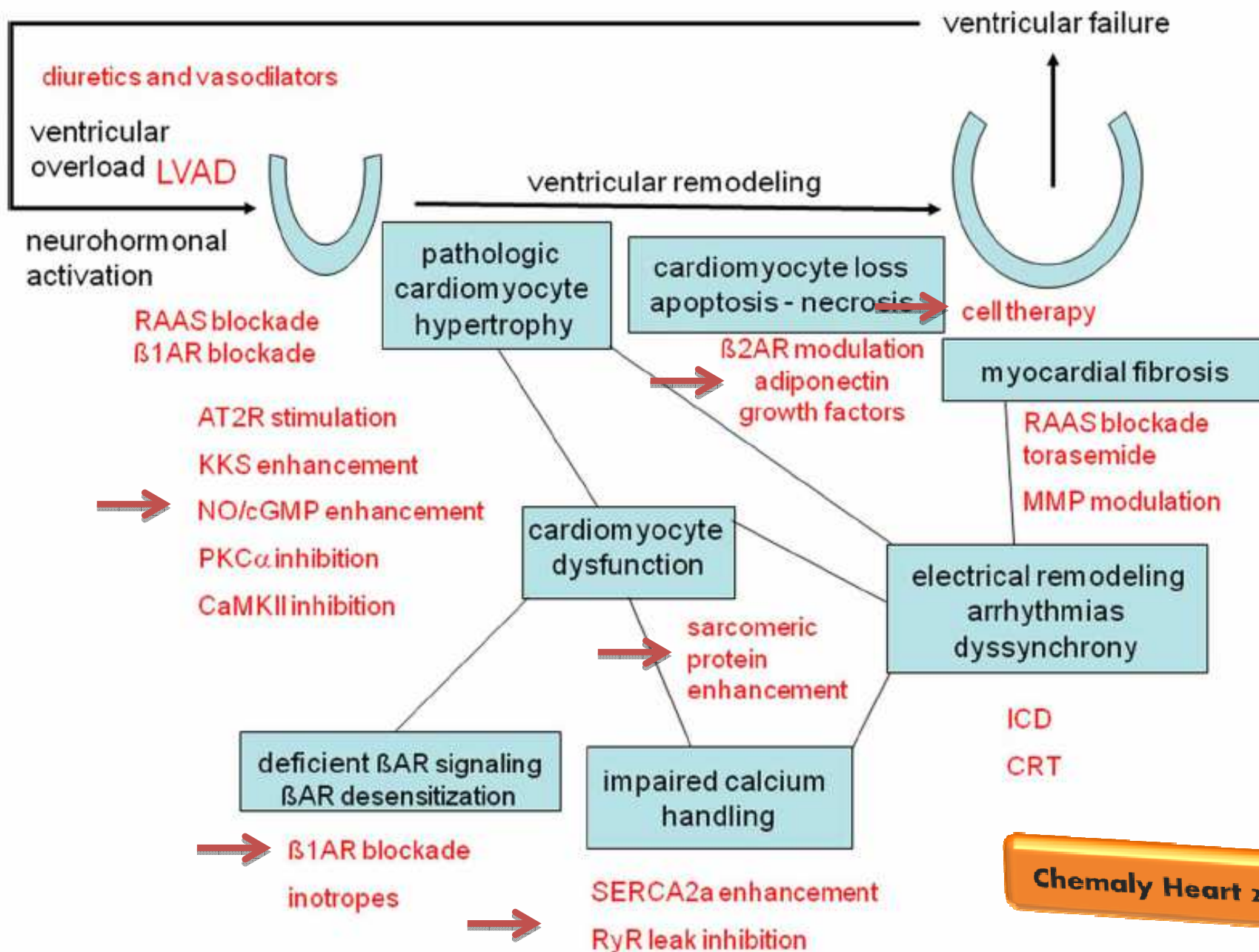


## Immunity strikes: heart failure as a systemic disease

Ulrich Hofmann<sup>1,2</sup> and Stefan Frantz<sup>1,2\*</sup>

Eur Heart J 2013

## ¿Algo nuevo?



**Chemaly Heart 2013**

## ICFER –nuevos tratamientos

### INOTROPISMO

- Activadores bomba ATPasa-Ca<sup>++</sup> reticulocitaria (SERCA-2)
  - Inotropismo via recaptación Ca en retículo citoplasmático
  - Terapia génica fase II (estudio CUPID)
- Estabilizadores rianodina (calcio)
- Neuregulina (endotelio)

Aronson Pharm Ther 2012

### Nuevos inhibidores eje RAA

- Inhibición directa renina: aliskiren
  - ASTRONAUT (post-ingreso) negativo
  - ATMOSPHERE (estable) en progreso AK vs IECA vs AK + IECA
- Inhibición combinada neprilisina/angiotensina: LCZ 696
  - PARADIGM-HF (LCZ 696 vs enalapril)
- Nuevos inhibidores/bloqueadores síntesis aldosterona

## IC FEP – Nuevos tratamientos

### ■ Inhibición PDE-5

- Sildenafil: RELAX, sin efecto en consumo =2 ni situación clínica

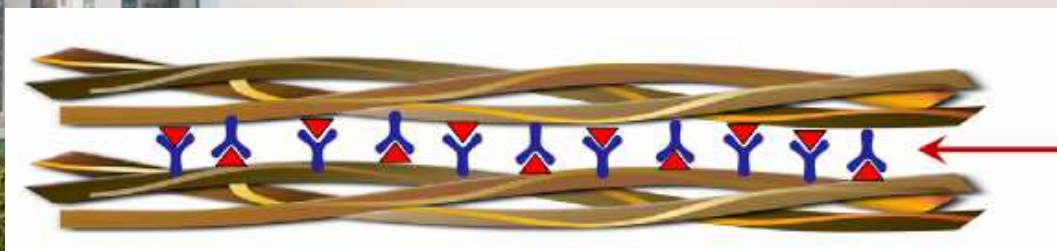
### ■ Nuevos inhibidores eje RAA

- LCZ696: PARAMOUNT, mejora parámetros ECO y PN

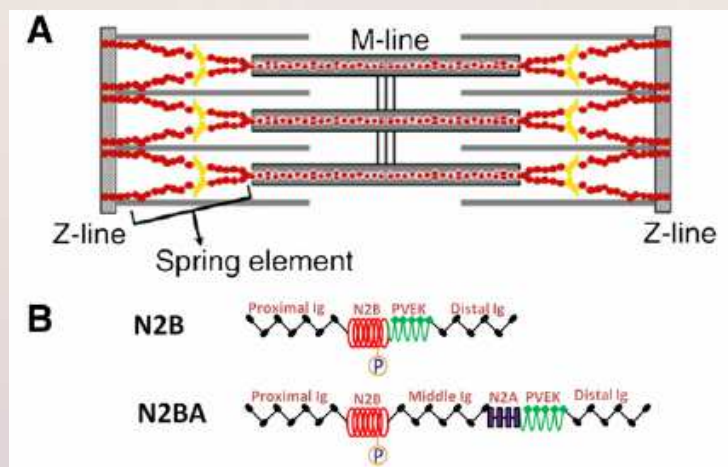
### ■ Anti-advanced glycation products (AGE)

- Alagebrium: ineficaz en ICFER, potencial en ICFEP...

### ■ Modulación titina (sarcómero) mediante fosforilación



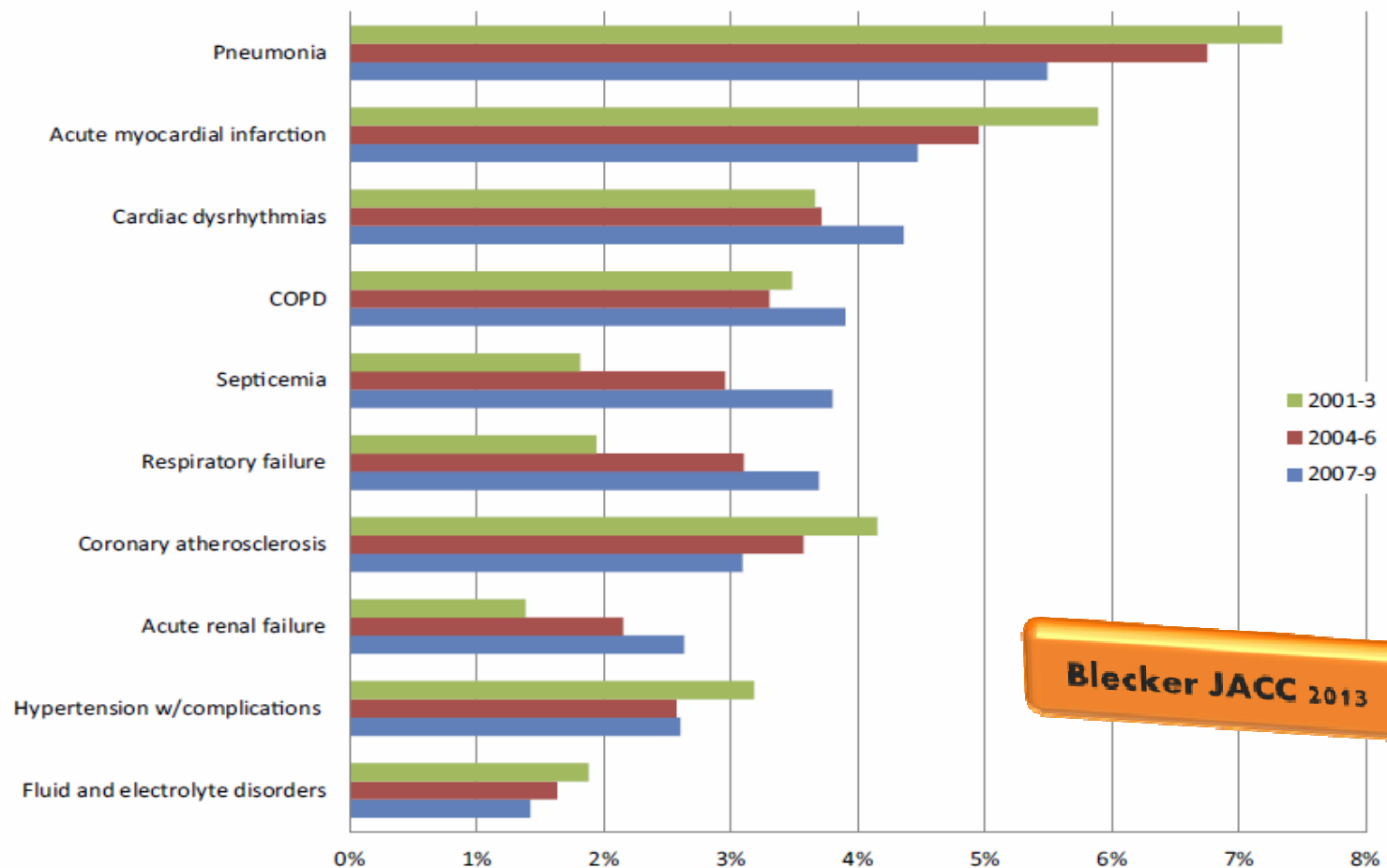
Aronson Pharm Ther 2012



## COMORBILIDAD



## Comorbilidad asociada a ingreso

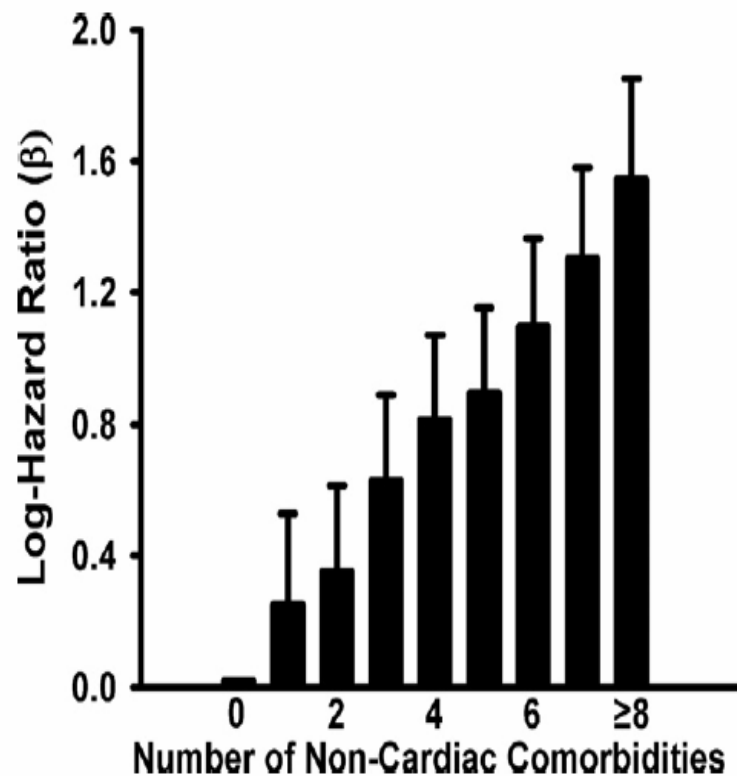


Blecker JACC 2013

**Figure 2** Trends in Prevalence of the 10 Most Common Primary Diagnoses for Heart Failure–Related Hospitalizations, Other Than Heart Failure Itself

Bars represent the percent of all heart failure–related hospitalizations that were related to a given diagnosis for a 3-year period. Values of  $p < 0.001$  for each diagnosis across all years. COPD = chronic obstructive pulmonary disease.

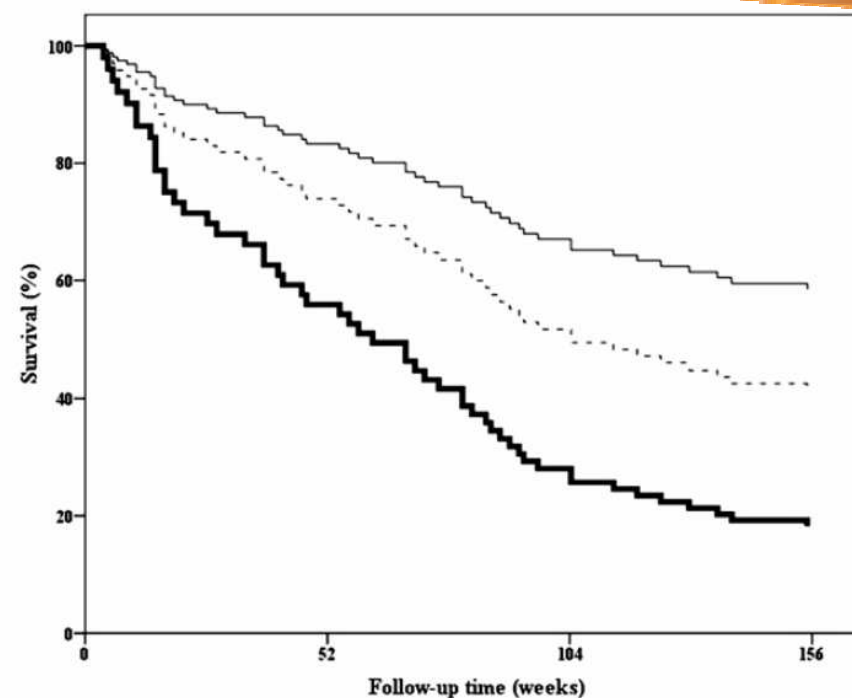
## Comorbilidad = mayor riesgo ingreso y mortalidad



**Figure 4** Risk for All-Cause Hospitalization Versus Number of Noncardiac Comorbidities

Log hazard ratios are based on Cox proportional hazards model ( $p < 0.001$ ). Number of noncardiac comorbidities was used as a categorical variable. **Error bars** represent the upper limit of the 95% confidence interval.

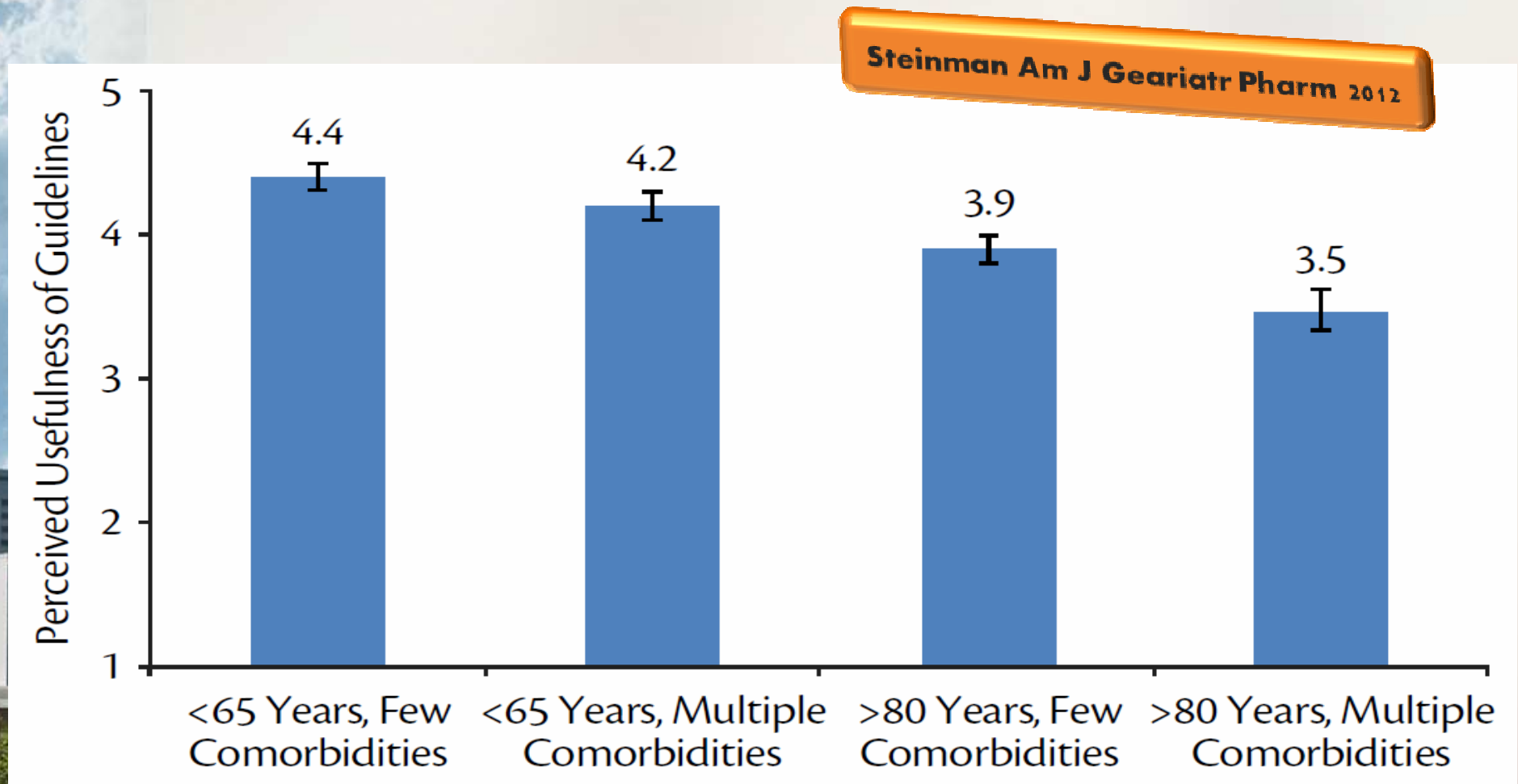
Oudejans J Heart Fail 2012



**Fig. 2.** Cox survival curves for geriatric patients with heart failure according to Charlson Comorbidity Index (CCI), adjusted for age and gender. Thin solid line: CCI 1–2 points; thin dashed line: CCI 3–4 points; thick solid line: CCI >4 points.

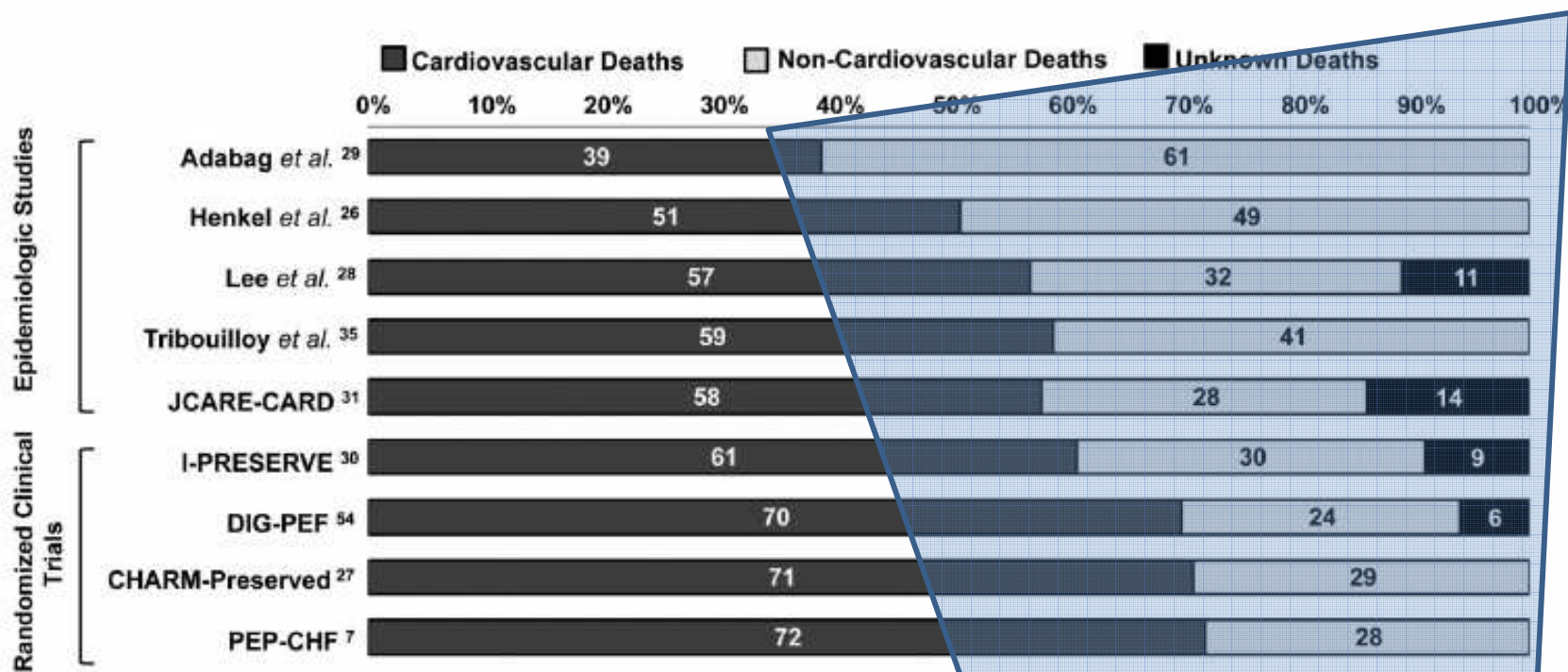
Ather J Am Colleg Cardiol 2011

## Comorbilidad = dificultades terapéuticas



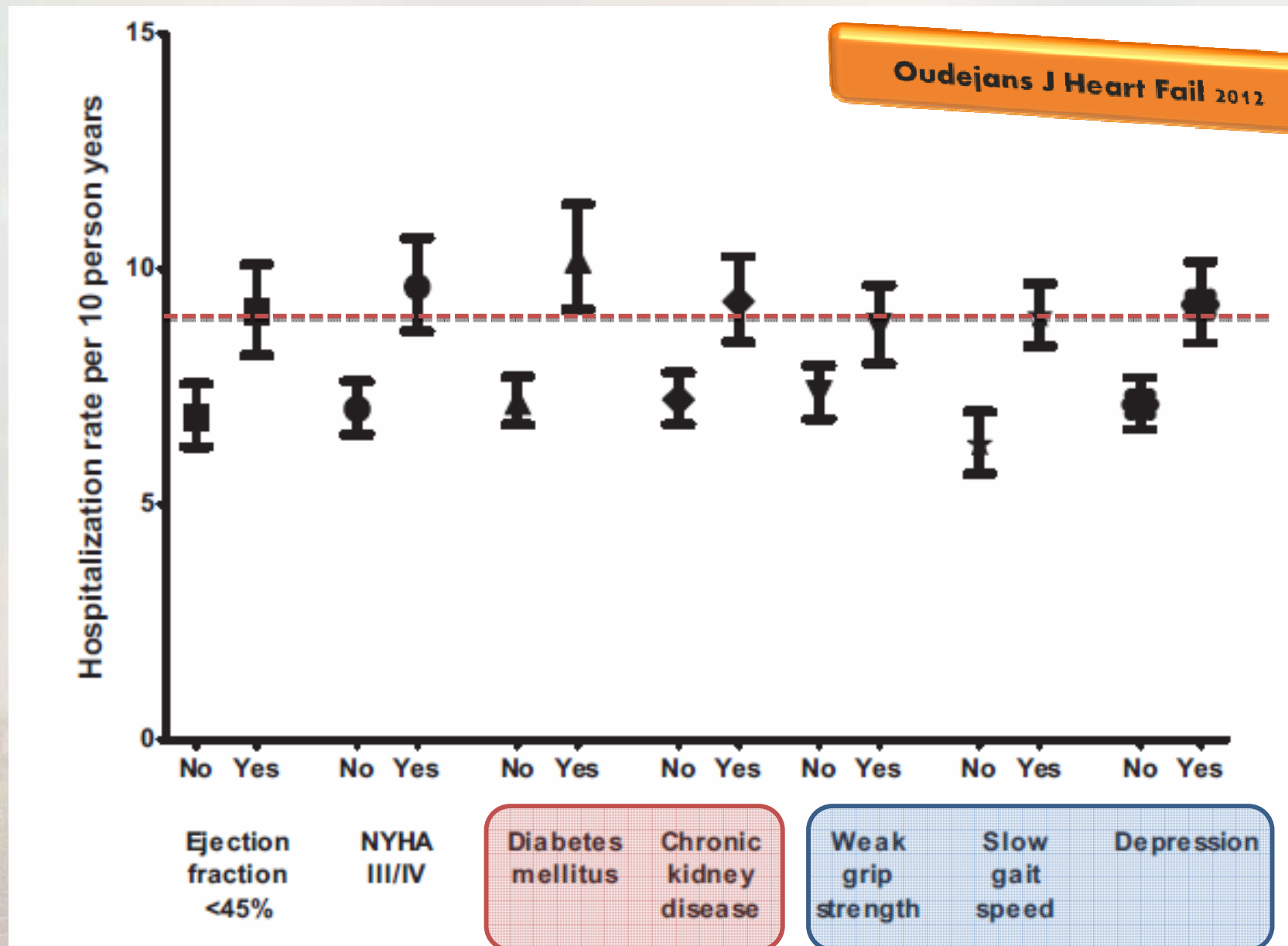
## Contribución de la comorbilidad a la mortalidad en IC

### Co-morbidities and modes of death in HFpEF



Char MM *et al.*, Eur J Heart Fail 2013;15:604-613

## ¡Todo tipo de comorbilidad!



# IRC, IC crónica y deterioro de la función renal

Damman Eur Heart J 2013

## Chronic Heart Failure

|                          |       |       |       |        |       |                    |      |
|--------------------------|-------|-------|-------|--------|-------|--------------------|------|
| Dries (SOLVD Prevention) | 167   | 757   | 397   | 2916   | 2.5%  | 1.80 [1.47, 2.20]  | 2000 |
| Hillege (PRIME II)       | 286   | 933   | 146   | 933    | 2.4%  | 2.38 [1.90, 2.98]  | 2000 |
| Dries (SOLVD Treatment)  | 363   | 772   | 397   | 1389   | 2.7%  | 2.22 [1.85, 2.66]  | 2000 |
| Marenzi                  | 34    | 56    | 33    | 92     | 0.7%  | 2.76 [1.39, 5.48]  | 2001 |
| McLellan                 | 113   | 252   | 130   | 413    | 1.8%  | 1.77 [1.28, 2.45]  | 2002 |
| Muntwyler                | 34    | 118   | 34    | 293    | 1.0%  | 3.08 [1.81, 5.27]  | 2002 |
| Pulignano (IN-CHF)       | 16    | 47    | 292   | 1638   | 0.8%  | 2.38 [1.28, 4.41]  | 2002 |
| Herzog                   | 7083  | 16633 | 38104 | 133367 | 3.4%  | 1.85 [1.79, 1.92]  | 2004 |
| Shlipak (DIG)            | 1309  | 3157  | 1066  | 3643   | 3.2%  | 1.71 [1.55, 1.89]  | 2004 |
| McAllister               | 207   | 419   | 103   | 335    | 1.9%  | 2.20 [1.63, 2.97]  | 2004 |
| Bibbins-Domingo (HERS)   | 159   | 425   | 69    | 297    | 1.7%  | 1.98 [1.42, 2.76]  | 2004 |
| Ezekowitz (APPROACH)     | 438   | 2513  | 196   | 3914   | 2.7%  | 4.00 [3.36, 4.78]  | 2004 |
| Shlipak (CHS)            | 107   | 140   | 75    | 139    | 1.0%  | 2.77 [1.66, 4.62]  | 2005 |
| Roik                     | 67    | 148   | 70    | 350    | 1.4%  | 3.31 [2.18, 5.02]  | 2006 |
| Go (ANCHOR)              | 11700 | 24473 | 10676 | 31694  | 3.4%  | 1.80 [1.74, 1.87]  | 2006 |
| Hillege (CHARM)          | 330   | 966   | 195   | 1714   | 2.5%  | 4.04 [3.31, 4.94]  | 2006 |
| Bruch                    | 66    | 135   | 17    | 134    | 0.8%  | 6.58 [3.58, 12.12] | 2007 |
| Shalaby                  | 49    | 209   | 17    | 121    | 0.8%  | 1.87 [1.02, 3.43]  | 2008 |
| Scrutinio                | 48    | 138   | 20    | 128    | 0.8%  | 2.88 [1.59, 5.21]  | 2009 |
| Anand (VALHEFT)          | 703   | 2916  | 273   | 2094   | 2.8%  | 2.12 [1.82, 2.47]  | 2009 |
| Cohen-Solal (SENIORS)    | 163   | 704   | 194   | 1408   | 2.3%  | 1.89 [1.50, 2.38]  | 2009 |
| Alehagen                 | 76    | 235   | 62    | 229    | 1.4%  | 1.29 [0.86, 1.92]  | 2009 |
| Wali                     | 414   | 2566  | 166   | 1651   | 2.6%  | 1.72 [1.42, 2.08]  | 2010 |
| Hebert                   | 34    | 338   | 72    | 963    | 1.3%  | 1.38 [0.90, 2.12]  | 2010 |
| Damman (COACH)           | 229   | 619   | 69    | 430    | 1.9%  | 3.07 [2.26, 4.17]  | 2010 |
| Waldum                   | 547   | 1080  | 305   | 1155   | 2.7%  | 2.86 [2.40, 3.41]  | 2010 |
| Damman (CIBIS II)        | 162   | 833   | 220   | 1797   | 2.4%  | 1.73 [1.39, 2.16]  | 2010 |
| Filippatos (BEST)        | 160   | 397   | 228   | 863    | 2.2%  | 1.88 [1.46, 2.42]  | 2011 |
| Scrutinio (2011)         | 237   | 422   | 157   | 529    | 2.1%  | 3.04 [2.32, 3.97]  | 2011 |
| Masson (GISSI-HF)        | 1035  | 2566  | 918   | 4369   | 3.1%  | 2.54 [2.28, 2.83]  | 2011 |
| Subtotal (95% CI)        |       | 64967 |       | 198998 | 60.5% | 2.26 [2.08, 2.47]  |      |

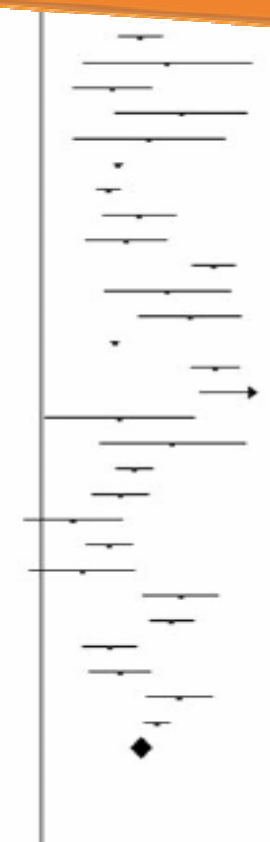
Total events

26336

54701

Heterogeneity:  $\tau^2 = 0.04$ ;  $\chi^2 = 255.62$ ,  $df = 29$  ( $P < 0.00001$ );  $I^2 = 89\%$

Test for overall effect:  $Z = 18.68$  ( $P < 0.00001$ )

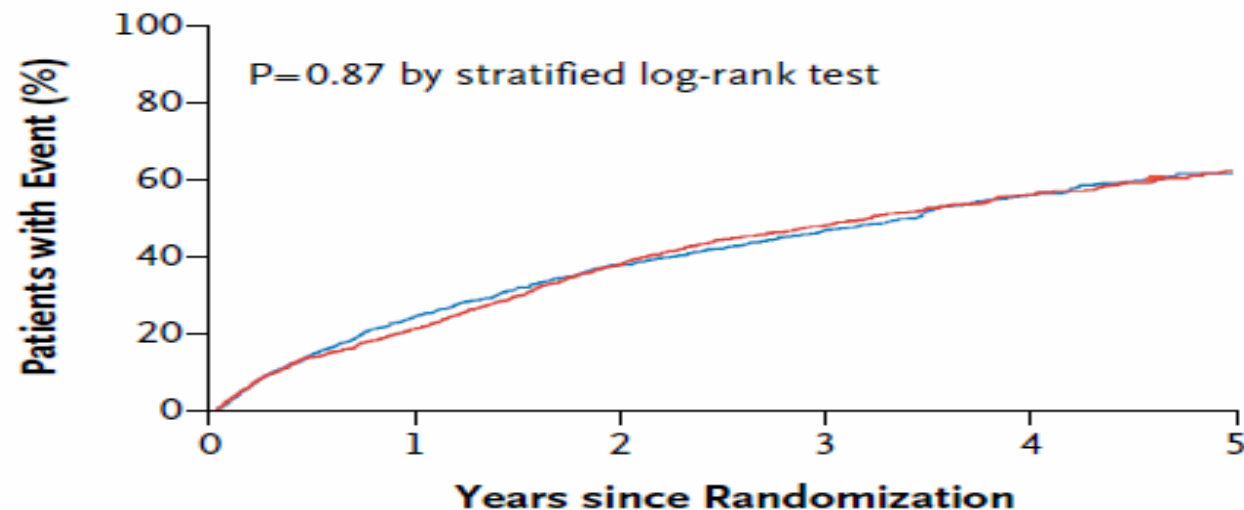


- Meta análisis > 30 artículos
- Tanto la presencia de IR como el deterioro significativo de la función renal se asocian a peor pronóstico vital ( $HR > 2$ ) en pacientes con IC crónica
- IRC basal, uso de diuréticos y edad creciente son los principales factores asociados a deterioro de función renal en IC

## ¿Mejor tratar hierro que Hb?

Swedberg NEJM 2013

### A Primary Composite Outcome

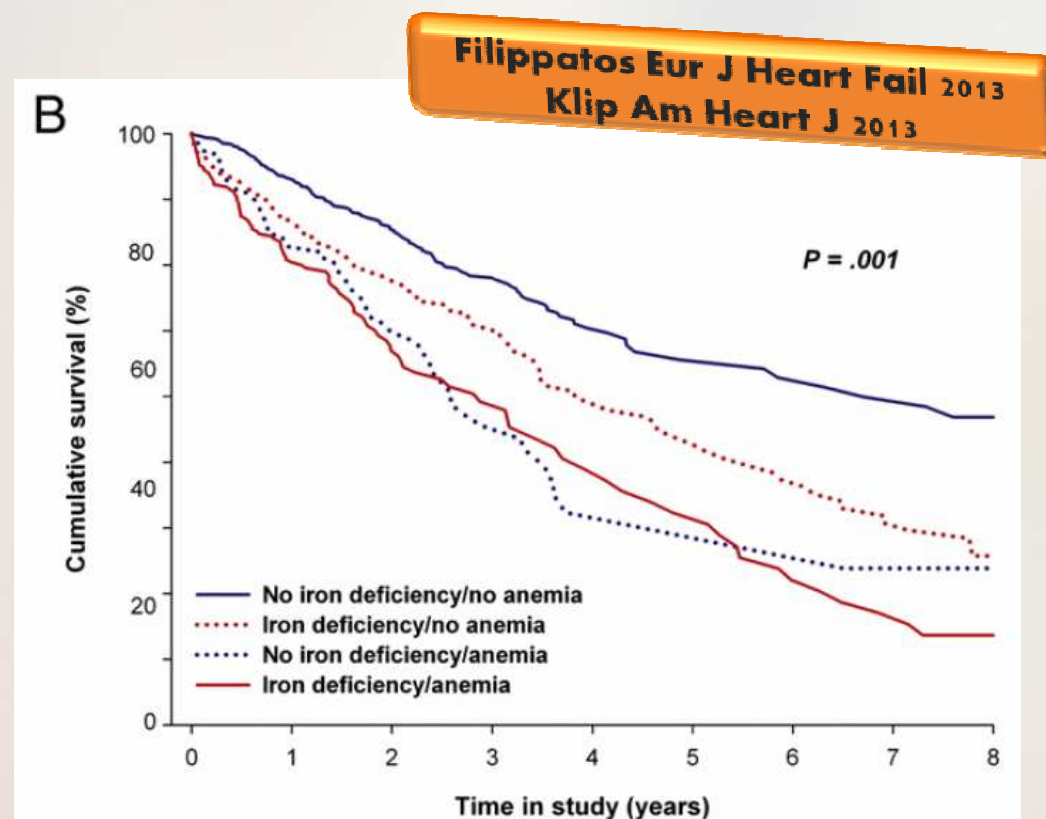
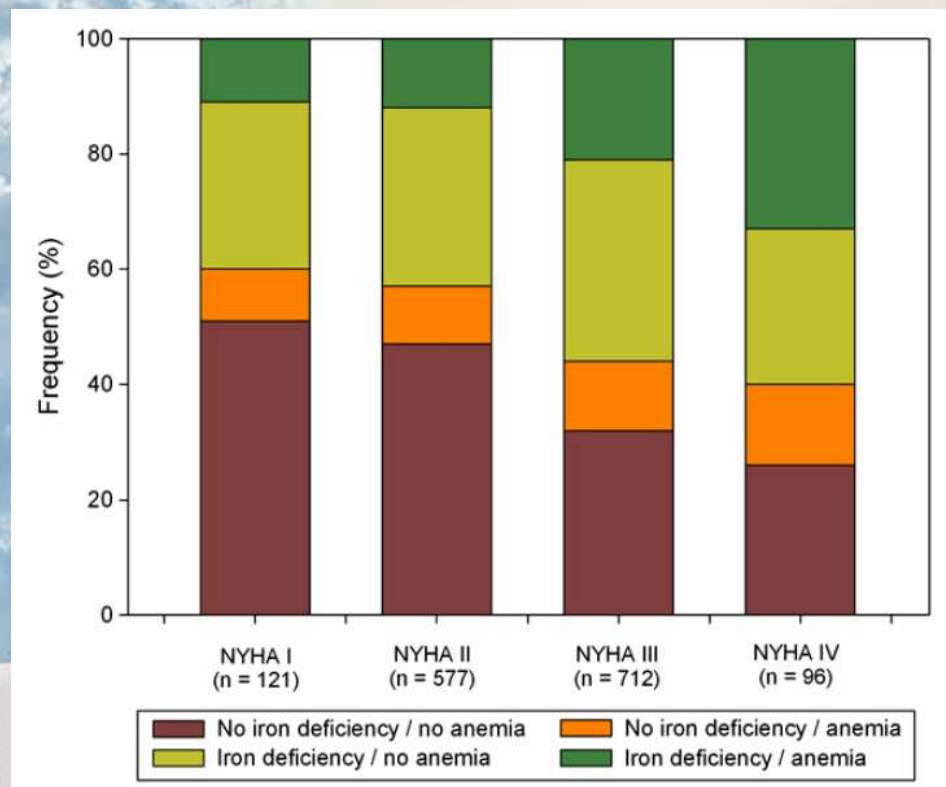


#### No. at Risk

|                  |      |     |     |     |     |     |     |     |     |     |     |
|------------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Placebo          | 1142 | 956 | 818 | 695 | 591 | 497 | 395 | 290 | 211 | 154 | 92  |
| Darbepoetin alfa | 1136 | 975 | 855 | 712 | 581 | 473 | 385 | 281 | 212 | 161 | 101 |

- ICFER, 70 años, depósitos de hierro correctos (IST > 20%)
- Hb basal cercana a 110 g/L
- Corrección Hb a > 130 g/L
- Sin efecto en muerte + reingreso por IC
- Mayor tasas de trombosis

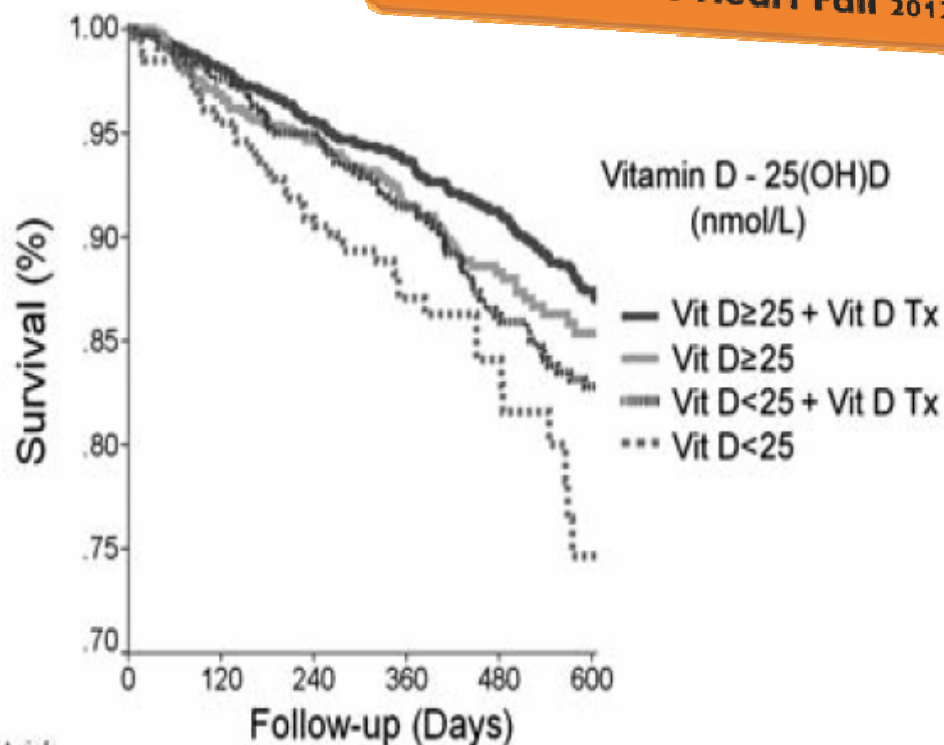
## El creciente papel de la ferropenia como diana



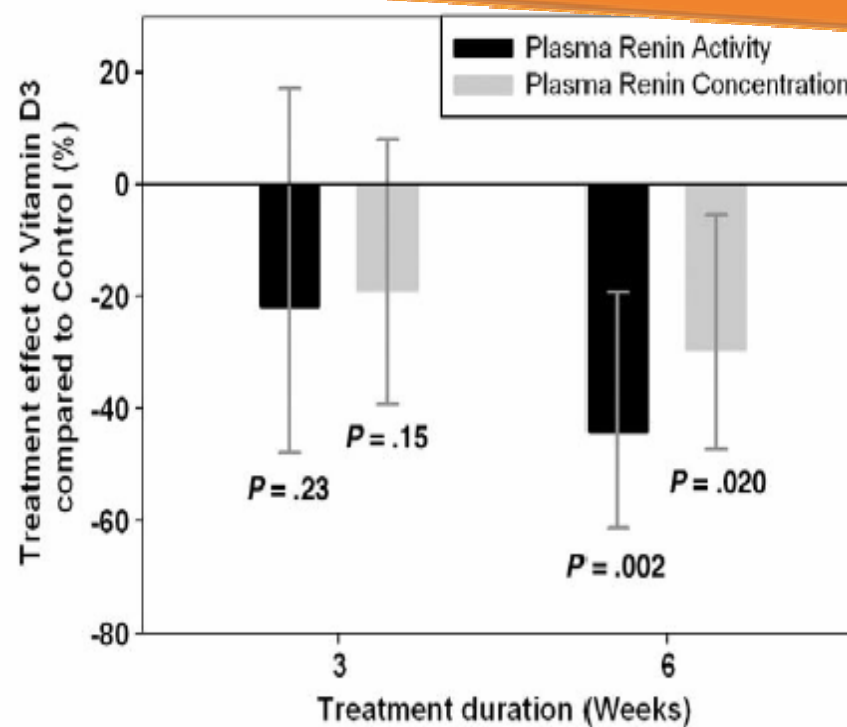
- La ferropenia aumenta en prevalencia a medida que se agrava la IC
- Su presencia es indicadora de mal pronóstico, con o sin anemia
- El tratamiento con Fe e.v. (FAIR-HF) mejora la situación clínica de los pacientes con ICFER, independientemente de la presencia de anemia

## ¿Sirve la vitamina D?

Gotsman Eur J Heart Fail 2012



Schroten Am Heart J 2013



- Resultados contradictorios en espera de ensayos clínicos
- Datos solo en ICFER
- Mecanismo más atractivo: disminución de la ARP mediada por vitamina D?
- Otros mecanismos: mejora sarcopenia, estímulo eritropoyesis, reducción inflamación vascular
- Seguridad???

## Conclusiones

- 20 años de “evidence based medicine” en IC parecen estar **ofreciendo resultados...**pero el progreso puede estar ralentizándose
- La **ICFER** en fase crónica dispone de **un tratamiento explícito**, ya bien **conocido** y generalmente aplicado de forma correcta, que resulta moderadamente efectivo.
- La **ICFEP**, por el contrario, aun está **en construcción**
- El próximo lustro puede traer **alguna novedad en ICFER**. En ICFEP, tras una década de decepciones, pronosticar parece aventurado
- Tanto la **comorbilidad clásica** como la **emergente** deben ser objeto de estudio y atención, especialmente si se trata de ICFEP
- En ningún caso deben olvidarse todos los **aspectos del manejo no farmacológico**, que posiblemente sean responsables en buena parte de la mejora clínica y pronóstica observada en los pacientes con IC en la última década

Gracias por vuestra atención

