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¿Se pueden extrapolar los ensayos a los pacientes con insuficiencia cardiaca atendidos en Medicina Interna?

¿Se pueden extrapolar los ensayos a los pacientes con insuficiencia cardiaca atendidos en Medicina Interna?

Instauración de un tratamiento

Eficaz

Ensayos clínicos aleatorizados

MEDICINA BASADA EN LA EVIDENCIA

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Ensayos clínicos

BMJ

Internal and external validity of cluster randomised trials: systematic review of recent trials

BMJ 2008;336:876–80

Sandra Eldridge, Deborah Ashby, Catherine Bennett, Melanie Wakelin and Gene Feder

Validez Interna

Validez Externa

Rothwell, Lancet 2005; 365:82-93

Bonell et al. BMJ 2006;333:346–49

Ensayos clínicos

CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials

David Moher,[1] Sally Hopewell,[2] Kenneth F Schulz,[3] Victor Montori,[4] Peter C Gøtzsche,[5] P J Devereaux,[6] Diana Elbourne,[7] Matthias Egger,[8] Douglas G Altman[2]

CONSORT 2010 lista de comprobación de la información que hay que incluir al comunicar un ensayo clínico aleatorizado *

http://www.consort-statement.org/

Sección/tema	Ítem nº	Ítem de la lista de comprobación
Título y resumen		
	1a	Identificado como un ensayo aleatorizado en el título
	1b	Resumen estructurado del diseño, métodos, resultados y conclusiones del ensayo (para una orientación específica, véase "CONSORT for abstracts")
Introducción		
Antecedentes y objetivos	2a	Antecedentes científicos y justificación
	2b	Objetivos específicos o hipótesis
Métodos		
Diseño del ensayo	3a	Descripción del diseño del ensayo (p. ej., paralelo, factorial), incluida la razón de asignación
	3b	Cambios importantes en los métodos después de iniciar el ensayo (p. ej., criterios de selección) y su justificación

. . . . . .

Discusión
Item 21. Posibilidad de generalización (Validez externa, aplicabilidad) de los resultados

BMJ* 2010;340:c869** ***Lancet online 24 March 2010 ***Ann Int Med 2010; 152***

Evaluación de la validez externa

Población de estudio

¿Es un reflejo de la población de la práctica clínica diaria?

Posible generalización

¿Se pueden extrapolar los resultados más allá de los criterios de selección?

How to assess the external validity of therapeutic trials: a conceptual approach. OM Dekkers et al. *Int J Epidemiol 2010;39:89–94*

Checklist for the qualitative evaluation of clinical studies with particular focus on external validity and model validity. G Bornhöft et al. *BMC Medical Research Methodology 2006, 6:56*

Evaluación de la validez externa

Características de los pacientes con insuficiencia cardiaca en Medicina Interna

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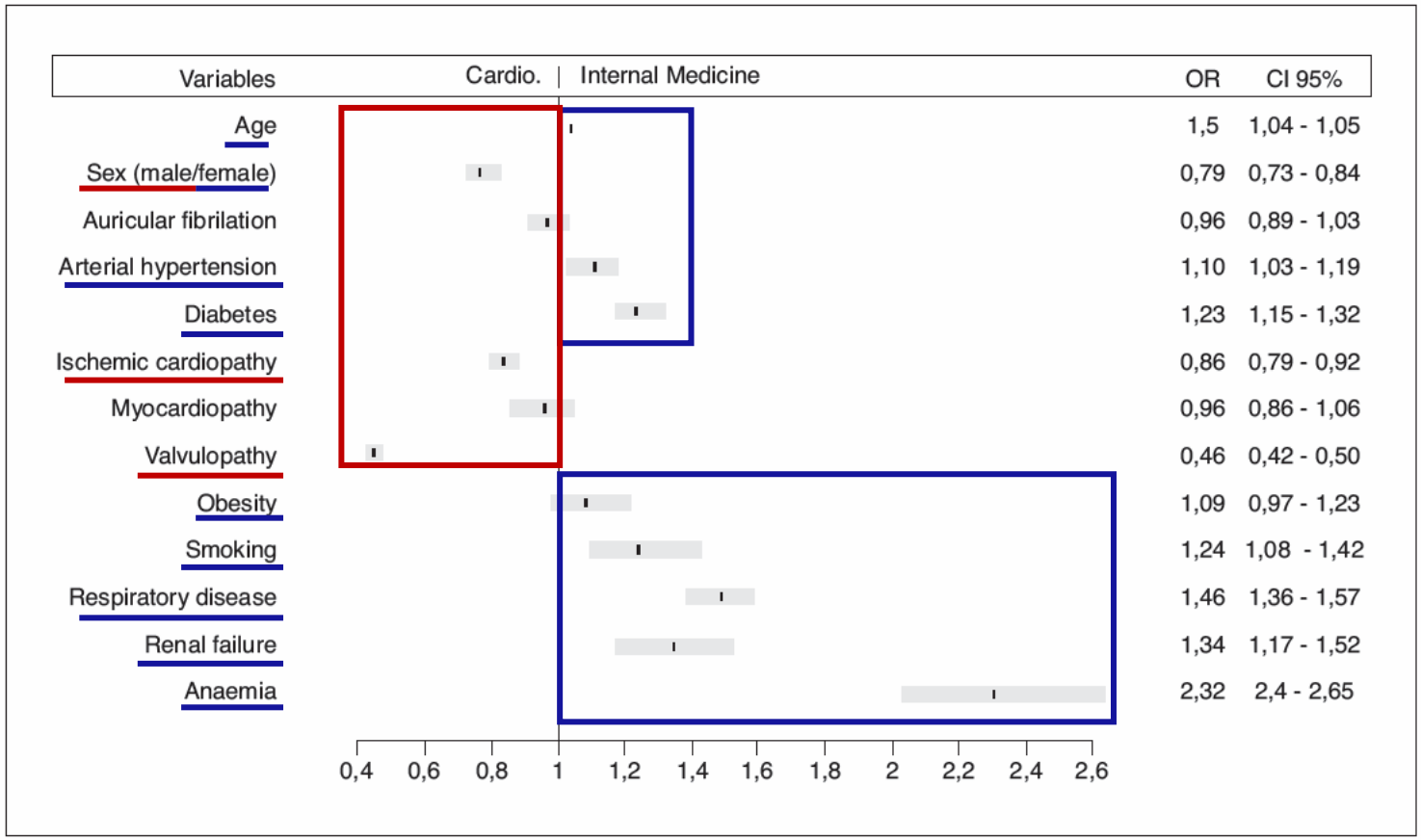
Insuficiencia cardiaca en los servicios de Medicina Interna en España

SEMI –IC Med Clin 2002; 118: 605-10

51 hospitales; 2145 pacientes

- Edad: 77 años
- Mujeres: 57%
- Comorbilidad: > 60%
- FE preservada: 54%
- Etiología hipertensiva: 45%
- Deterioro funcional y/o mental: 67%

Análisis de 27.248 altas hospitalarias por I. cardiaca



Paciente de > edad, mujer, con HTA, diabetes, obesidad, tabaquismo, Enf. Respiratoria, I. renal o anemia es más probable que ingrese en M. Interna

Paciente de < edad, varón, con cardiopatía isquémica, o valvulopatía es más probable que sea hospitalizado en Cardiología

San Roman Teran et al. Rev Clin Esp. 2008;208:281-7

Población de estudio en los ensayos clínicos

¿Es un reflejo de la población de la práctica clínica diaria?

- Edad
- Género
- Comorbilidad
- FE preservada

Int J Epidemiol 2010;39:89–94

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Representación de pacientes de edad avanzada en ensayos clínicos en Insuficiencia Cardiaca

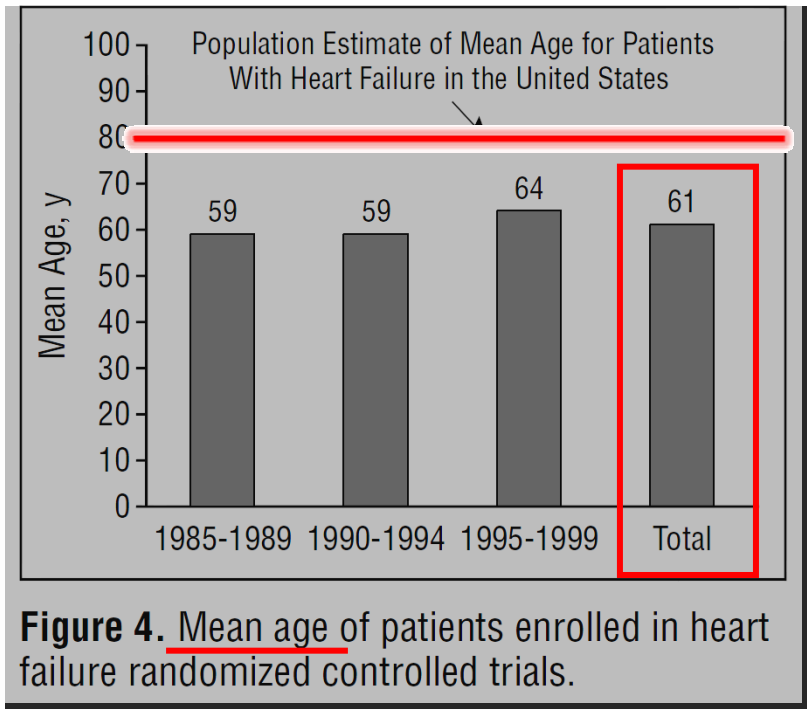


Figure 4. Mean age of patients enrolled in heart failure randomized controlled trials.

Exclusión explícita por edad: 29% de ECA (17/59)

Solo 15% incluyen > 80 años

Arch Int Med 2002; 162:1682-8

Vol. 171 No. 6, March 28, 2011 TABLE OF CONTENTS >
Original Investigation

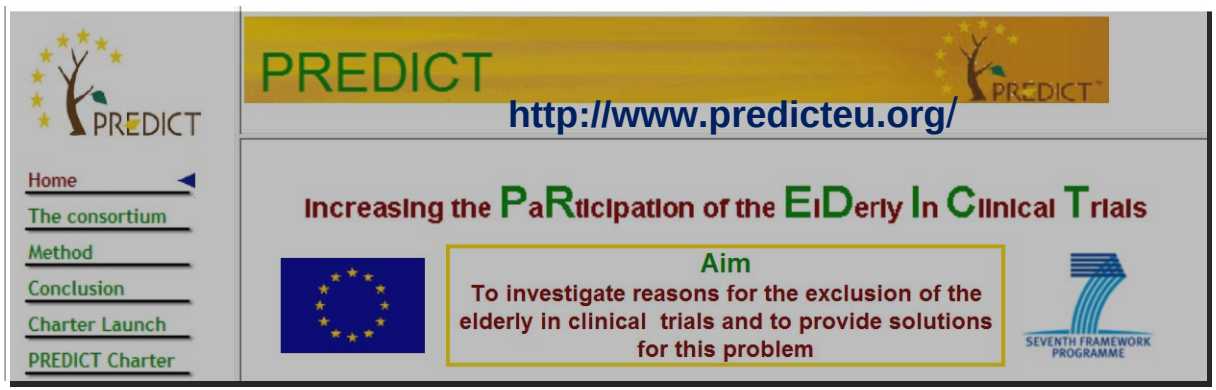
The Persistent Exclusion of Older Patients From Ongoing Clinical Trials Regarding Heart Failure

Arch Int Med 2011; 171:550-56

Antonio Cherubini, MD, PhD; Joaquim Oristrell, MD, PhD; Xavier Pla, MD; Carmelinda Ruggiero, MD, PhD; Roberta Ferretti, MD; Germán Diestre, MD; A. Mark Clarfield, MD, FRCPC; Peter Crome, MD, DSc;

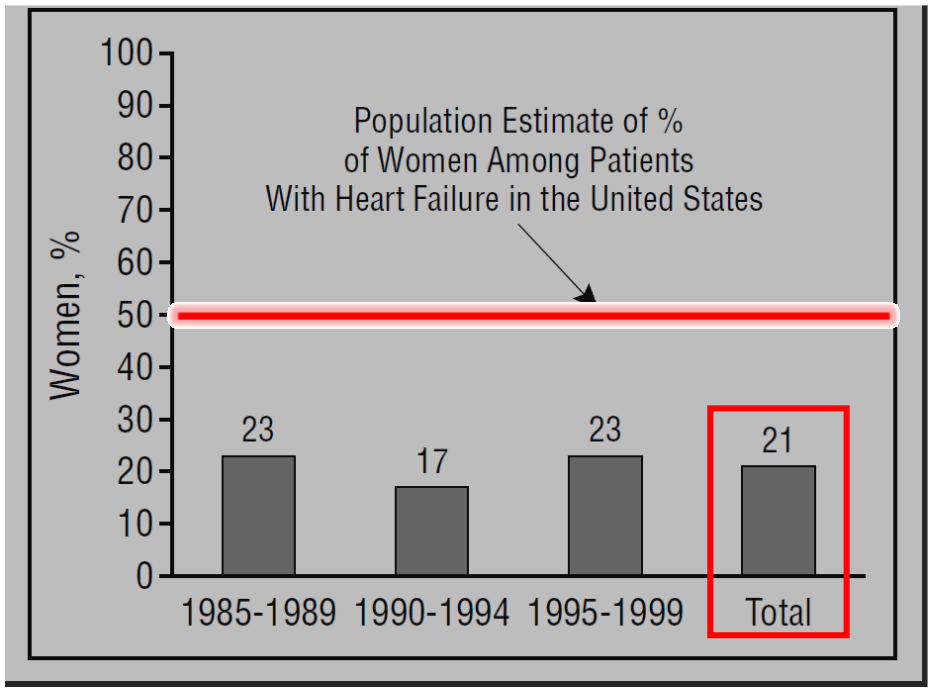
➢ **Exclusión arbitraria por límite superior de edad 25,5% (64/251 ensayos)**

Iniciativas para aumentar la inclusión de ancianos en Ensayos Clínicos



US FDA. ***Guideline for the Study of Drugs Likely to Be Used in the Elderly***.
Rockville, MD: Food and Drug Administration/Center for Drug Evaluation and Research; 1989.

Representación de mujeres en ensayos clínicos en Insuficiencia Cardiaca



% de Mujeres en Ensayos clínicos randomizados

¡ Exclusión explícita de mujeres !

V-HeFT-II N Engl J Med 1992; 325:303-10;
V-HeFT-III Circulation 1997;96:856-863

Arch Int Med 2002; 162:1682-8

Inclusión de mujeres en ensayos clínicos cardiovasculares (1997-2006)

Table. Comparison of the Mean Proportion of Women in NHLBI Sponsored Phase 3–4 Cardiovascular Randomized Controlled Trials Published Between 1997 and 2006 to Proportion of Women Among the General Population With Cardiovascular Disease

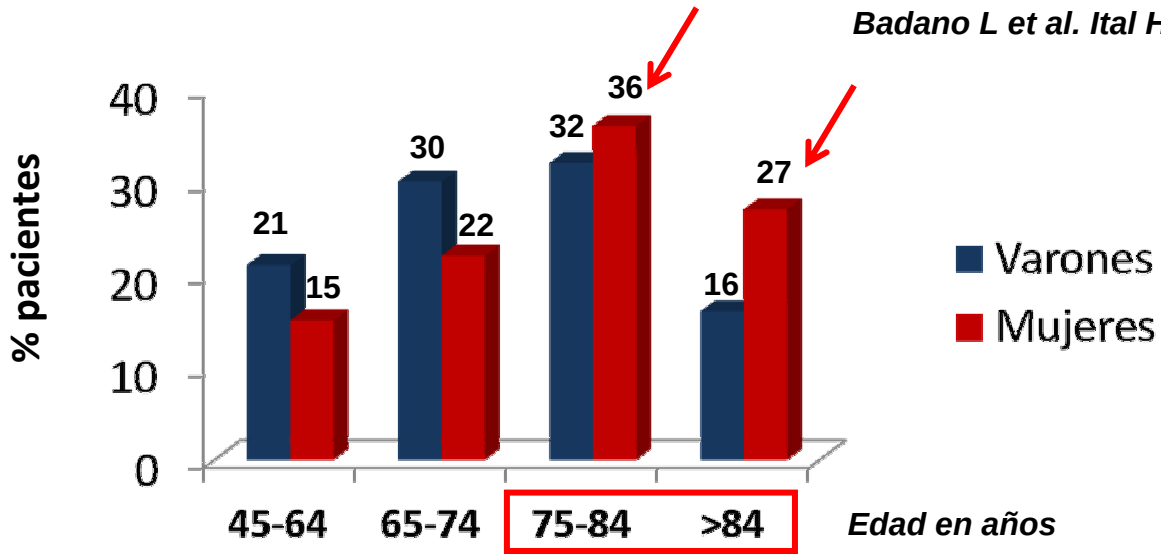
Disease Type	% Women (mean)	% Women Among Those With Disease	Source
Coronary Artery Disease[32,37,38,39,40,41,42,43]	29%	46%	AHA
Congestive Heart Failure[44,45,46]	23%	52%	ADHERE
		60%	NHFP
		50%	AHA
Sudden Cardiac Death[47,48,49,50,51,52]	17%	23%	AVID registry
		16%	MUSTT registry
		32%	Seattle/King EMS
Atrial Fibrillation[53]	39%	55%	AHA
Hypertension[54]	47%	53%	AHA
Cardiovascular Disease[15]	27%	53%	AHA

Arterioscler Thromb Vasc Biol 2009, 29:279-283

Al disminuir la inclusión de personas mayores disminuye la inclusión de mujeres

Distribución por sexo y edad de pacientes con IC en el "mundo real"

Badano L et al. Ital Heart J. 2003; 4:84-91.



Iniciativas para aumentar la inclusión de mujeres en E. Clínicos

USA: Ley Pública 103-48 (Jun 10, 1998)
NIH Guideline on The Inclusion of Women and Minorities as Subjects in Clinical Research - Updated August 1, 2000

NIH: http://grants.nih.gov/grants/funding/women _min/guidelines_uptdate.htm

Representación de pacientes con pluripatología

Exclusión por comorbilidades: 80% de ECA sobre IC

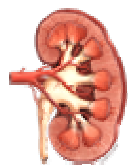
- **I. Renal, hepática. Enf. Neurológicas, pulmonares**

Arch Int Med 2011; 171:550-56

E. Renal Crónica

JAMA

Underrepresentation of Renal Disease in Randomized Controlled Trials of Cardiovascular Disease



Coca et al. JAMA 2006;296:1377-84

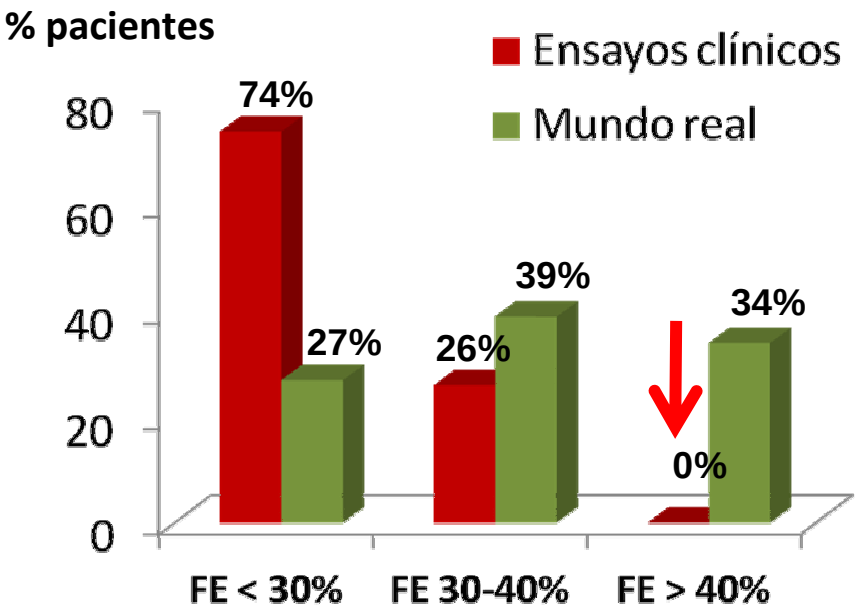
Exclusión por E. renal 56% de EC (83/153)

Exclusión por E. renal 39,8 % de EC; (100/251)

Cherubini et al. Arch Int Med 2011; 171:550-56

Representación de pacientes con F.E. preservada

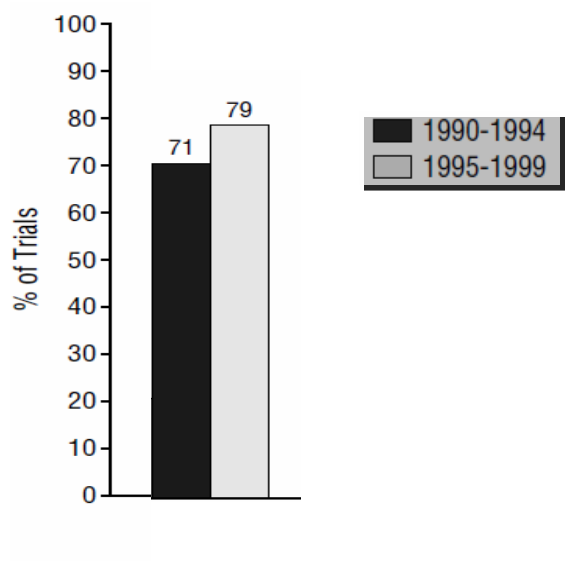
Distribución de pacientes con IC según la FE en Ensayos y en el mundo real



27 ECA (1987-2001)

Badano L et al. Ital Heart J. 2003; 4:84-91.

% ECA con exclusión FEP



Arch Int Med 2002;162:1682-1688.

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Ensayos clínicos en pacientes con F.E. preservada

Edad y % Mujeres en IC con FEP

	Edad	% Mujeres	FE
CHARM- preserved (Candesartan)	67	40%	FE > 40%
I-PRESERVE (Irbesartan)	72	60%	FE > 45%
PEP-CHF (Perindopril)	75	55%	FE > 40%
Dig-Ancillary (Digoxina)	67	41%	FE > 45%
Hong-Kong DHF (Ramipril / Irbesartan)	74	61%	FE > 45%

CHARM-preserved Lancet 2003; 362:777–81

I-Preserve. N Engl J Med 2008; 359:2456-67

PEP- CHF. Eur Heart J 2006; 27:2338–45

Dig-Ancillary Circulation. 2006;114:397-403

Hong- Kong DHF. Heart 2008;94:573–580

Diferencias entre ensayos clínicos y el mundo real

	N	Mortalidad 1º año	Seguimiento (meses)
Ensayos clínicos*	24.049	5-25%	21 ± 15
Scottish-wide Retrospective Cohort-study *Circulation. 2000;102:1126*	66.547	45%	---
Goldberg et al *Arch Int Med 2007;167:490*	2.445	37%	---

** CONSENSUS; SOLVD-T, V-HeFT-II; SOLVD-P, Carvedilol US, DIG, CIBIS II, MERIT, RALES*

Soler, Rev Esp Cardiol Supl. 2006;6:25C-8C

Diferencias en Cumplimiento terapéutico

Icumplimiento en el mundo real: 10 - 94%

Mayo Clin Proc 2011; 86:273 *Circulation 2009;120:1141*

Población de estudio de los ensayos clínicos

¿Es un reflejo de la población de la práctica clínica diaria?

¿Podría mi paciente ser incluido en un ensayo clínico?

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Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure

Frederick A. Masoudi, MD, MSPH,[a,b,c] Edward P. Havranek, MD,[a,b,c] Pam Wolfe, MA, MS,[c] Cary P. Gross, MD,[d] Saif S. Rathore, MPH,[d] John F. Steiner, MD, MPH,[b] Diana L. Ordin, MD, MPH,[c] and Harlan M. Krumholz, MD[d]
Denver and Aurora, Colo, New Haven, Conn, and Boston, Mass

Am Heart J 2003;146:250–7

20.388 pacientes ≥ 65 años, diagnóstico principal I. cardiaca

Exclusión

SOLVD	**FE> 35%, Edad > 80 a, Creatinina > 2mg/dl, Angina inestable…**
MERIT-HF	**FE > 40%, Edad > 80 a, EPOC, Demencia, Angina inestable…**

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Denver and Aurora, Colo, New Haven, Conn, and Boston, Mass

Am Heart J 2003;146:250–7

20.388 pacientes ≥ 65 a.

Exclusión → **FE > 35%**
54%; (n= 10.943)

9.445 pacientes

Exclusión → **Contraindicaciones**
17%; (n= 3.556)

5.879 pacientes

Exclusión → **Otra Comorbilidad**
3%; (n= 523)

5.356 pacientes

Exclusión → **Edad > 80 años**
9%; (n= 1.777)

3.579 (18 %) SOLVD

20.388 pacientes ≥ 65 a.

Exclusión → **FE > 40%**
46% (n= 9.362)

11.026 pacientes

Exclusión → **Contraindicaciones**
29%; (n= 5.937)

5.089 pacientes

Exclusión → **Otra Comorbilidad**
2%; (n= 503)

4.586 pacientes

Exclusión → **Edad > 80 años**
9%; (n= 1.860)

2.726 (13 %) MERIT

Contraindicaciones: Creat > 2, Intolerancia, IAM, Angina inestable

Población de estudio de los ensayos clínicos

Menos de un 20% de pacientes del mundo real podría haberse incluido en EC

No es un reflejo de la población de la práctica clínica diaria

- Más jóvenes
- Predominio de varones
- Escasa comorbilidad
- Disfunción sistólica
- Menor mortalidad

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Generalización más allá de los criterios de selección

Aunque los pacientes de los ensayos clínicos sean diferentes a los del mundo real

¿Se pueden extrapolar los resultados de los EC a los pacientes de la práctica diaria?

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¿Se pueden extrapolar los resultados de los EC a los ancianos ?

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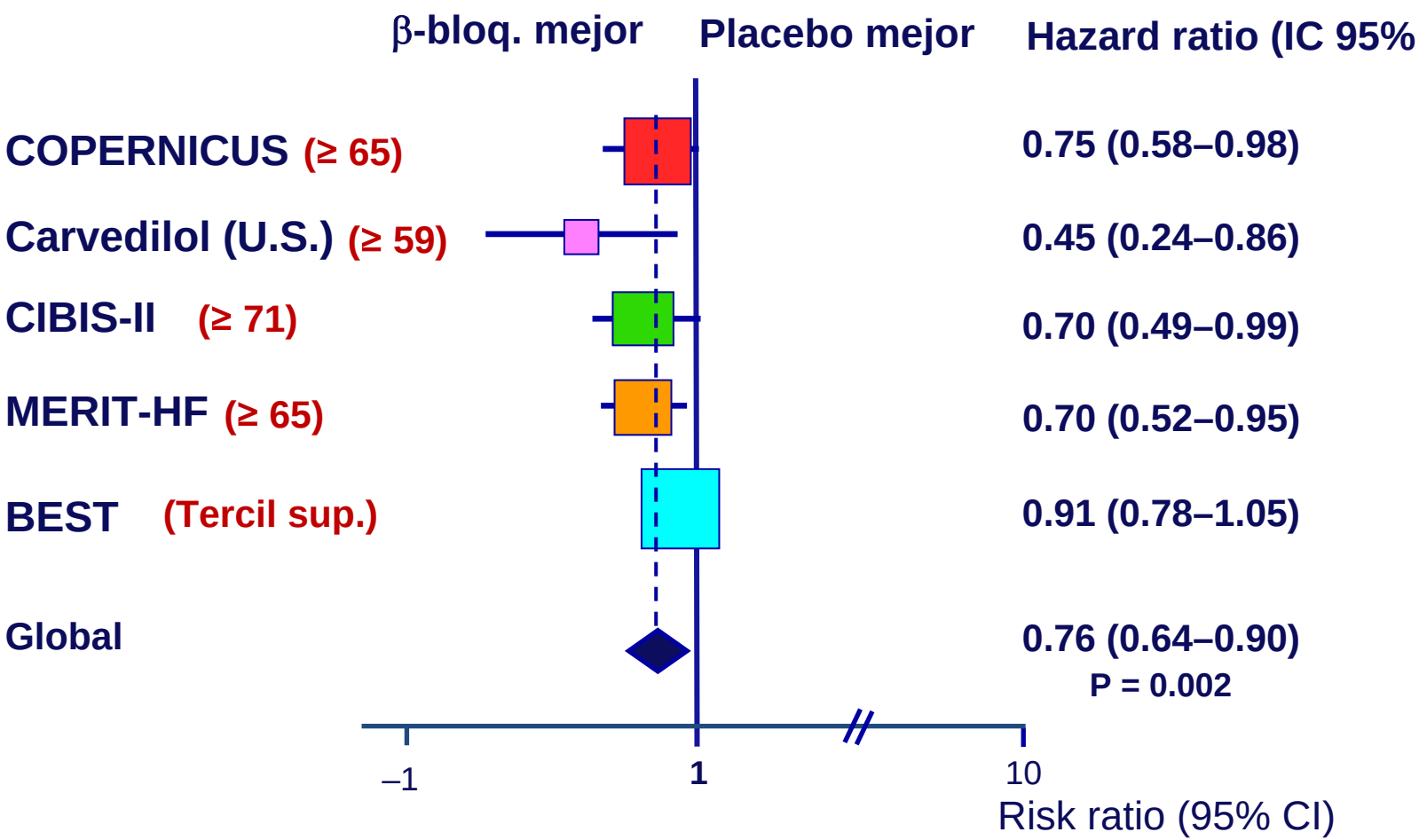
β-Bloqueantes en ancianos con IC y disfunción sistólica



Dulin BR et al. *Am J Cardiol* 2005;95:896-8.

¿Se pueden extrapolar los ensayos a los pacientes con insuficiencia cardiaca atendidos en Medicina Interna?

β-Bloqueantes

SENIORS

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

Edad ≥ 70 años

Flather et al. Eur Heart J 2005; 26: 215-25.

IECA

Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients

Subgroup	Number of patients	Deaths	Odds ratio (95% CI)	p*
Sex				
Men	10 367	2506	0·79 (0·72–0·87)	0·54
Women	2396	671	0·85 (0·71–1·02)	
Age (years)				
<55	3165	495	0·76 (0·62–0·93)	0·47
> 75			**0,95 (0,74 - 1,22)**	
Diuretics at baseline				
Yes	6020	2109	0·80 (0·72–0·89)	0·72
No	6737	1065	0·83 (0·73–0·94)	
Aspirin at baseline				
Yes	7597	1699	0·85 (0·76–0·95)	0·23
No	5158	1475	0·75 (0·67–0·85)	
β-blockers at baseline				
Yes	2722	422	0·68 (0·55–0·84)	0·08
No	10 034	2752	0·83 (0·76–0·91)	

CHF=congestive heart failure; MI=myocardial infarction. *For heterogeneity.

Table 5: **Effects of ACE inhibitors on outcomes in selected subgroups from all five t**

Flahter et al. Lancet 2000; 355:1575-81

Fármacos en ancianos con IC

En ancianos :

- Menor efecto
- Menor tolerancia
- Más efectos adversos
- No se suele alcanzar dosis diana

Br J Clin Pharmacol 2006; 63: 356-64
J Gen Intern Med 2004; 19:676-83

JAMA 2003;289:1107-16
Ann Pharmacother 2000; 34:427-32
Fu. Int J Cardiol 2008; 125: 149-53

Fármacos en ancianos con IC

Menor uso el mundo real

Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II

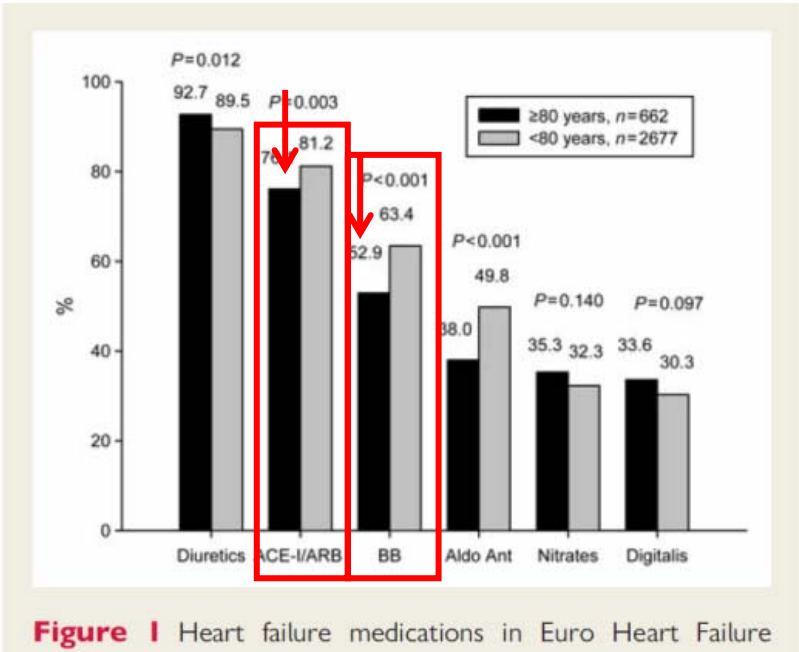


Figure 1 Heart failure medications in Euro Heart Failure

Eur Heart J 2009; 30: 478-86.

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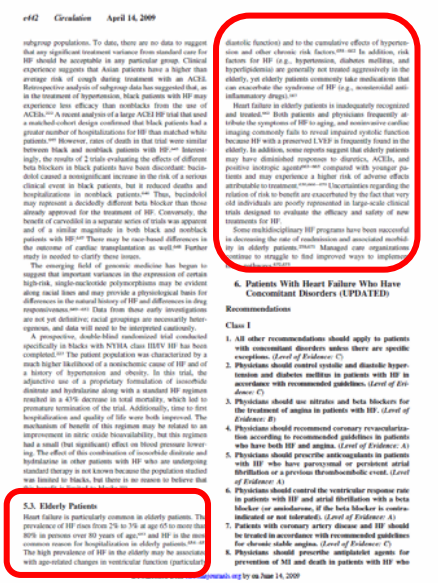
¿ Qué dicen las Guías de Práctica Clínica ?

Guías de Práctica Clínica Sociedad Americana del Corazón (2009)

En ancianos usar el tto basado en la evidencia considerando de forma individualizada la alteración de la capacidad de metabolizar o tolerar la medicación



e442 Circulation April 14, 2009

subgroup populations. To date, there are no data to suggest that any significant treatment variance from standard care for HF should be acceptable in any particular group. Clinical experience suggests that Asian patients have a higher than average risk of cough during treatment with an ACEI. Retrospective analysis of subgroup data has suggested that, in the treatment of hypertension, black patients with HF may experience less efficacy than nonblacks from the use of ACEIs.[...] A recent analysis of a large ACEI HF trial that used a matched-cohort design confirmed that black patients had a greater number of hospitalizations for HF than matched white patients.[...] However, rates of death in that trial were similar between black and nonblack patients with HF.[...] Interestingly, the results of 2 trials evaluating the effects of different beta blockers in black patients have been discordant: bucindolol caused a nonsignificant increase in the risk of a serious clinical event in black patients, but it reduced deaths and hospitalizations in nonblack patients.[...] Thus, bucindolol may represent a decidedly different beta blocker than those already approved for the treatment of HF. Conversely, the benefit of carvedilol in a separate series of trials was apparent and of a similar magnitude in both black and nonblack patients with HF.[...] There may be race-based differences in the outcome of cardiac transplantation as well.[...] Further study is needed to clarify these issues.

The emerging field of genomic medicine has begun to suggest that important variances in the expression of certain high-risk, single-nucleotide polymorphisms may be evident along racial lines and may provide a physiological basis for differences in the natural history of HF and differences in drug responsiveness.[...] Data from these early investigations are not yet definitive; racial groupings are necessarily heterogeneous, and data will need to be interpreted cautiously.

A prospective, double-blind randomized trial conducted specifically in blacks with NYHA class III/IV HF has been completed.[...] The patient population was characterized by a much higher likelihood of a nonischemic cause of HF and of a history of hypertension and obesity. In this trial, the adjunctive use of a proprietary formulation of isosorbide dinitrate and hydralazine along with a standard HF regimen resulted in a 43% decrease in total mortality, which led to premature termination of the trial. Additionally, time to first hospitalization and quality of life were both improved. The mechanism of benefit of this regimen may be related to an improvement in nitric oxide bioavailability, but this regimen had a small (but significant) effect on blood pressure lowering. The effect of this combination of isosorbide dinitrate and hydralazine in other patients with HF who are undergoing standard therapy is not known because the population studied was limited to blacks, but there is no reason to believe that

5.3. Elderly Patients

Heart failure is particularly common in elderly patients. The prevalence of HF rises from 2% to 3% at age 65 to more than 80% in persons over 80 years of age,[...] and HF is the most common reason for hospitalization in elderly patients.[...] The high prevalence of HF in the elderly may be associated with age-related changes in ventricular function (particular

diastolic function) and to the cumulative effects of hypertension and other chronic risk factors.[...] In addition, risk factors for HF (e.g., hypertension, diabetes mellitus, and hyperlipidemia) are generally not treated aggressively in the elderly, yet elderly patients commonly take medications that can exacerbate the syndrome of HF (e.g., nonsteroidal anti-inflammatory drugs).[...]

Heart failure in elderly patients is inadequately recognized and treated.[...] Both patients and physicians frequently attribute the symptoms of HF to aging, and noninvasive cardiac imaging commonly fails to reveal impaired systolic function because HF with a preserved LVEF is frequently found in the elderly. In addition, some reports suggest that elderly patients may have diminished responses to diuretics, ACEIs, and positive inotropic agents[...] compared with younger patients and may experience a higher risk of adverse effects attributable to treatment.[...] Uncertainties regarding the relation of risk to benefit are exacerbated by the fact that very old individuals are poorly represented in large-scale clinical trials designed to evaluate the efficacy and safety of new treatments for HF.

Some multidisciplinary HF programs have been successful in decreasing the rate of readmission and associated morbidity in elderly patients.[...] Managed care organizations continue to struggle to find improved ways to implement

6. Patients With Heart Failure Who Have Concomitant Disorders (UPDATED)

Recommendations

Class I

1. **All other recommendations should apply to patients with concomitant disorders unless there are specific exceptions. (*Level of Evidence: C*)**
2. **Physicians should control systolic and diastolic hypertension and diabetes mellitus in patients with HF in accordance with recommended guidelines. (*Level of Evidence: C*)**
3. **Physicians should use nitrates and beta blockers for the treatment of angina in patients with HF. (*Level of Evidence: B*)**
4. **Physicians should recommend coronary revascularization according to recommended guidelines in patients who have both HF and angina. (*Level of Evidence: A*)**
5. **Physicians should prescribe anticoagulants in patients with HF who have paroxysmal or persistent atrial fibrillation or a previous thromboembolic event. (*Level of Evidence: A*)**
6. **Physicians should control the ventricular response rate in patients with HF and atrial fibrillation with a beta blocker (or amiodarone, if the beta blocker is contraindicated or not tolerated). (*Level of Evidence: A*)**
7. **Patients with coronary artery disease and HF should be treated in accordance with recommended guidelines for chronic stable angina. (*Level of Evidence: C*)**
8. **Physicians should prescribe antiplatelet agents for prevention of MI and death in patients with HF who**

Poblaciones especiales - Ancianos -

- **Posible menor respuesta a IECA, diuréticos e inotrópicos positivos**
- **Mayor riesgo de efectos adversos**
- **Escasa representación de muy mayores en ECA**

***Circulation 2009;* 119; e391-e479;**

¿Qué dicen las Guías de Práctica Clínica ?

Se recomiendan ttos que han mostrado eficacia en pacientes de < edad

Valorar efectos 2º, interacciones, comorbilidad y tolerancia

Guías Sociedad Europea Cardiología (ESC) (2008)

Guías de Práctica Clínica Canadienses (2006)

Guías de Práctica Clínica Británicas (NICE) (2010)

Guías Práctica Clínica Soc. Americana de I. Cardiaca (2010)

Dickstein et al. Eur Heart J 2008; 29:2388-2442

Can J Cardiol 2006; 22: 23-45

NICE Clinical Guideline No 108

Journal of Cardiac Failure 2010; 16: e169-75

¿Se pueden extrapolar los resultados de los EC a las mujeres ?

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¿Se pueden generalizar los resultados de los ensayos clínicos a las mujeres?

Gender Differences in Advanced Heart Failure: Insights From the BEST Study
JACC 2003; 42:2128
Jalal K. Ghali, MD,* Heidi J. Krause-Steinrauf, MS,† Kirkwood F. Adams, JR, MD,‡

Evaluating and Managing Cardiovascular Disease in Women
Understanding a Woman's Heart
Alice K. Jacobs, MD; Robert H. Eckel, MD *Circulation 2005,111: 383*

Insuficiencia cardiaca. ¿Son diferentes las mujeres?
María G. Crespo Leiro y María J. Paniagua Martín *Rev Esp Cardiol 2006;59:725*

Insuficiencia cardiaca en la mujer. Diferencias de sexo en España
Rev Esp Cardiol Supl. 2008;8:23D-29D
Manuel F. Jiménez-Navarro[a] y Manuel Anguita-Sánchez[b]

What We Know and Do Not Know about Sex and Cardiac Disease
Konhilas JP, J Biomed Biotech 2010;

¿Qué tienen las mujeres en el corazón?
Manuel Martínez-Sellés *Rev Esp Cardiol. 2007;60:1118-21*

¿Se pueden generalizar los resultados de los ensayos clínicos a las mujeres?

Insuficiencia cardiaca en la mujer

- Epidemiología: mayor edad
- Etiología: > hipertensiva
- Fisiopatología: > FE preservada
- Clínica: > comorbilidad, sintomatología
- Manejo: menor uso IECA, B-bloqueantes
- Evolución: menor mortalidad

Ghali et al. JACC 2003; 42:2128–34
Crespo Leiro et al. Rev Esp Cardiol 2006;59:725-35.
Jiménez Navarro et al. Rev Esp Cardiol Supl. 2008;8:23D
Konhilas JP, J Biomed Biotech 2010; ID 562051
Martinez Selles, Rev Esp Cardiol. 2007;60:1118-21
Hsich. J Am Coll Cardiol 2009;54:491–8

¿Existen diferencias en fármacos en función del género?

JAMA
The Journal of the American Medical Association

REVIEW

Aspirin for the Primary Prevention of Cardiovascular Events in Women and Men

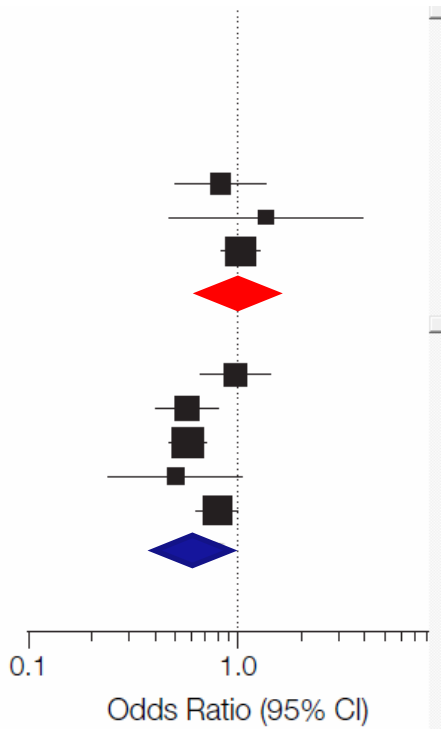
A Sex-Specific Meta-analysis of Randomized Controlled Trials

Jeffrey S. Berger, MD, MS
Maria C. Roncaglioni, MD

Context Aspirin therapy reduces the risk of cardiovascular disease in adults who are at increased risk. However, it is unclear if women derive the same benefit as men.

Myocardial Infarction

Study, y	Events, No./Total: Aspirin	Events, No./Total: Control/ Placebo	Odds Ratio (95% CI)
Women			
HOT,[12] 1998	29/4437	35/4446	0.83 (0.51-1.36)
PPP,[17] 2001	8/1277	6/1306	1.37 (0.47-3.95)
WHS,[9] 2005	198/19934	193/19942	1.03 (0.84-1.25)
Total	235/25648	234/25694	1.01 (0.84-1.21)
Men			
BDT,[15] 1988	80/3429	41/1710	0.97 (0.66-1.42)
HOT,[12] 1998	54/4962	93/4945	0.57 (0.41-0.81)
PHS,[14] 1989	139/11037	239/11034	0.58 (0.47-0.71)
PPP,[17] 2001	11/949	22/963	0.50 (0.24-1.04)
TPT,[16] 1998	154/2545	190/2540	0.80 (0.64-0.99)
Total	438/22922	585/21192	0.68 (0.54-0.86)



JAMA 2006;295:306-31

¿Existen diferencias en fármacos en función del género?

INTERACTION BETWEEN SEX AND DIGOXIN THERAPY

SEX-BASED DIFFERENCES IN THE EFFECT OF DIGOXIN FOR THE TREATMENT OF HEART FAILURE

SAIF S. RATHORE, M.P.H., YONGFEI WANG, M.S., AND HARLAN M. KRUMHOLZ, M.D.

Conclusions The effect of digoxin therapy differs between men and women. Digoxin therapy is associated with an increased risk of death from any cause among women, but not men, with heart failure and depressed left ventricular systolic function. (N Engl J Med 2002;347:1403-11.)

N Engl J Med 2002; 347:1403-11

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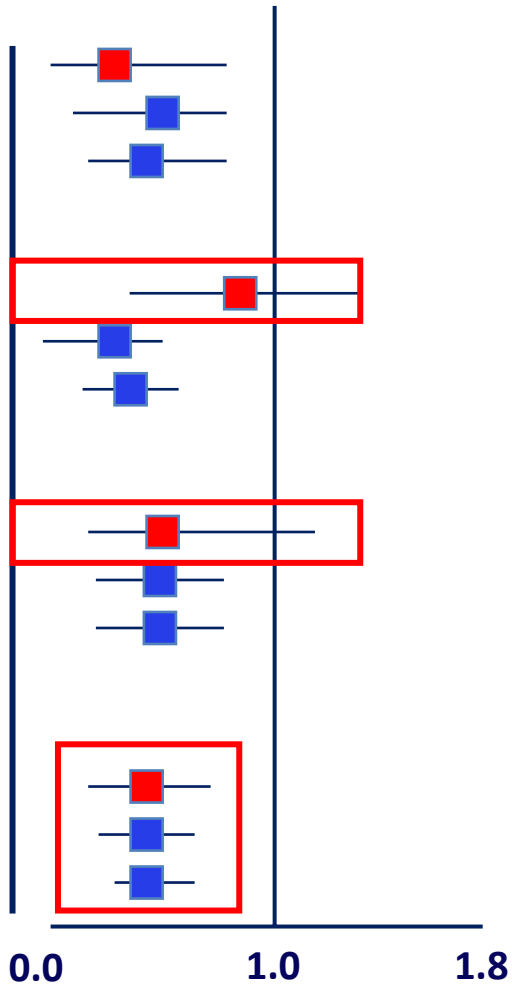
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

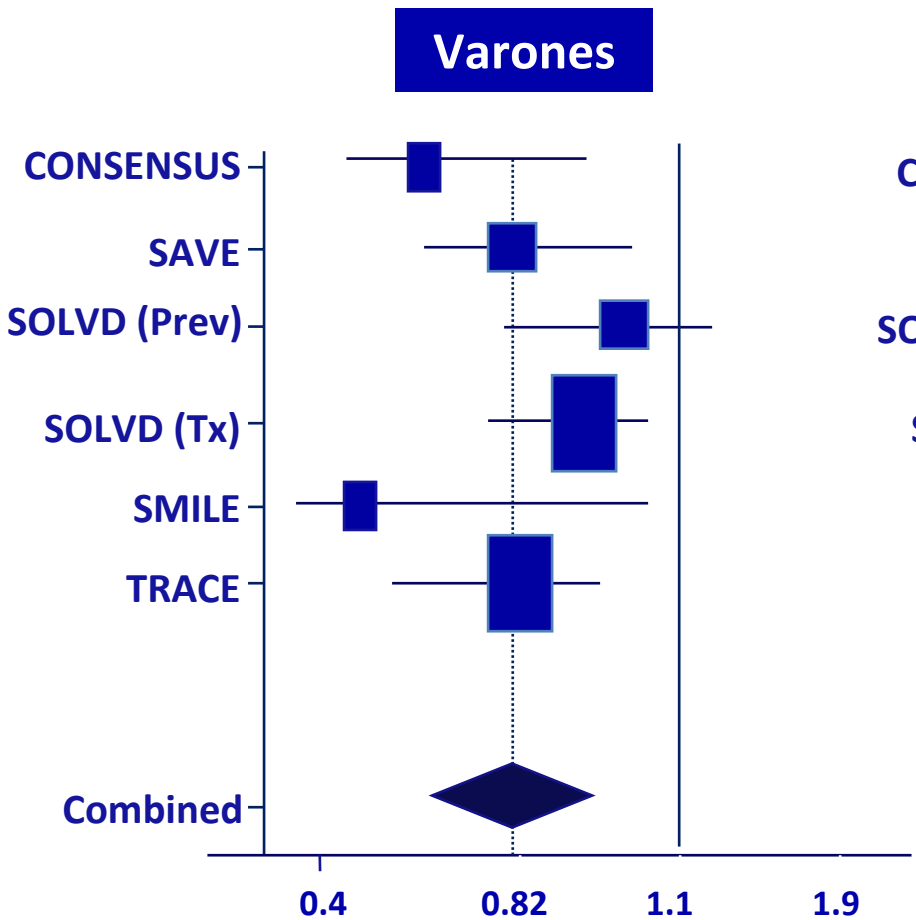
β-Bloqueantes en IC mujeres

	Nº Randomizados Placebo/β-bloq	Nº Muertes Placebo/β-bloq
CIBIS II		
Mujeres	258/257	35/18
Varones	1062/1070	193/138
Todos	1320/1327	228/156
MERIT-HF		
Mujeres	447/451	33/31
Varones	1554/1539	184/114
Todos	2001/1990	217/145
COPERNICUS		
Mujeres	NP	NP
Varones	NP	NP
Todos	1133/1156	190/130
Global		
Mujeres		
Varones		
Todos		

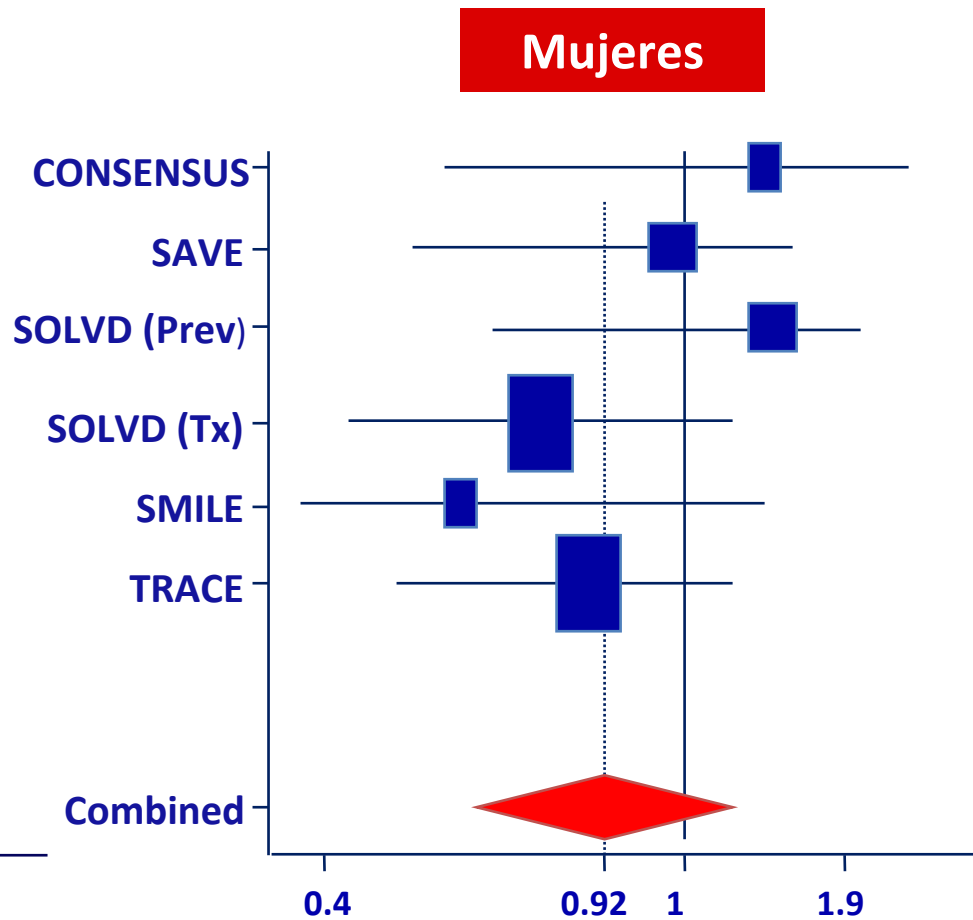


Shekelle PG et al, ***Circulation 2002, 105:1585-1591***

IECA en disfunción sistólica en mujeres



RR: 0,82 (IC 95% 0,74-0,90)



RR: 0,92 (IC 95% 0,81-1,04)

Shekelle PG et al, JACC 2003;41:1529 –38

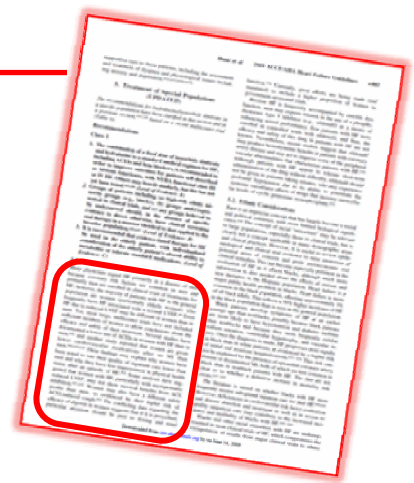
¿ Qué dicen las Guías de Práctica Clínica de IC ?

Poblaciones especiales – Mujeres -

Guías de Práctica Clínica Sociedad Americana del Corazón (2009)

- La mayoría de pacientes con IC en la población general son mujeres, predominantemente mayores, que con frecuencia tienen FE normal.
- Posible menor efecto de IECA en disfunción sistólica asintomática
- Diferente perfil de seguridad:
  - Mayor riesgo de tos por IECA
  - Posible ausencia de beneficio del tto con digoxina.

  Si se utiliza, vigilar la dosis y función renal



Circulation 2009; 119; e391-e479;

¿Qué dicen las Guías de Práctica Clínica de IC?

No mencionan diferencias de tratamiento en función del sexo

Guías Sociedad Europea Cardiología (ESC) (2008)

Guías de Práctica Clínica Canadienses (2006)

Guías de Práctica Clínica Británicas (NICE) (2010)

Guías Práctica Clínica Soc. Americana de I. Cardiaca (2010)

- menor nivel de evidencia -

Dickstein et al. Eur Heart J 2008; 29:2388-2442

Can J Cardiol 2006; 22: 23-45

NICE Clinical Guideline No 108

Journal of Cardiac Failure 2010; 16: e169-75

¿Se pueden generalizar los resultados de los EC clínicos a los pacientes con múltiples comorbilidades?

Co-Morbidity and Potential Treatment Conflicts in Elderly Heart Failure Patients

A Retrospective, Cross-Sectional Study of Administrative Claims Data

Caughey et al. Drugs Aging 2011; 28:575-81

6730 pacientes con IC ≥ 65 años.

Media de 6 comorbilidades

97,8% ≥ 1 comorbilidad con potencial interferencia con tto.

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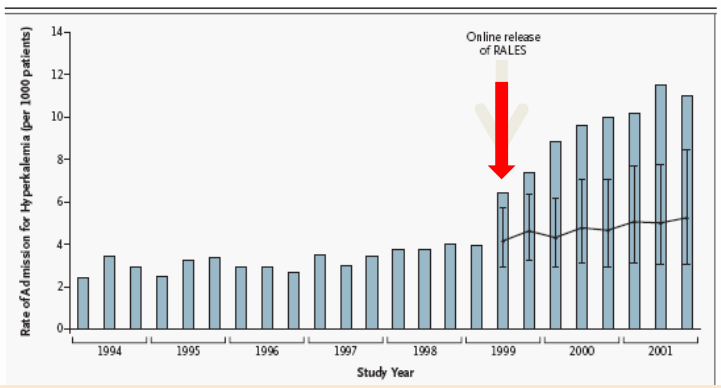
Uso de Espironolactona en el mundo real

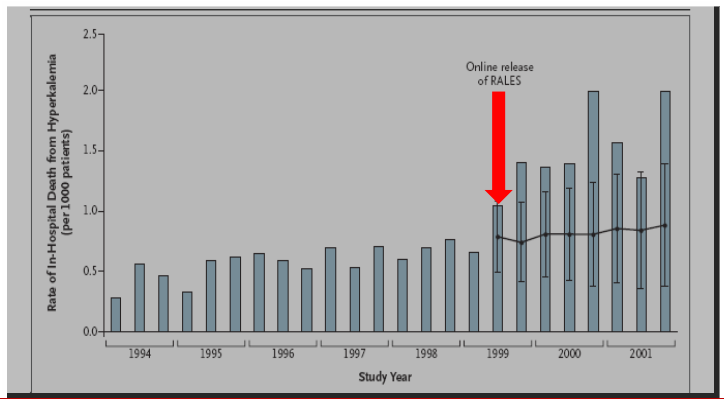
Rates of Hyperkalemia after Publication of the Randomized Aldactone Evaluation Study

David N. Juurlink, M.D., Ph.D., Muhammad M. Mamdani, Pharm.D., M.P.H., Douglas S. Lee, M.D., Alexander Kopp, B.A., Peter

NEJM 2004; 351:543



Tasa de **ingresos** por Hiperpotasemia en pacientes hospitalizados por IC en tto con IECA



Muertes asociadas a hiperK⁺ en pacientes hospitalizados por IC en tto con IECA

Complications of Inappropriate Use of Spironolactone in Heart Failure: When an Old Medicine Spirals Out of New Guidelines

Bozkurt et al. J Am Coll Cardiol 2003; 41:211-4

¿Se pueden generalizar los resultados de los EC en pacientes con función VI preservada ?

Muy pocos ECA, con pacientes más representativos de la población general, pero sin resultados concluyentes en cuanto a disminución de mortalidad

Shah et al. JAMA 2008; 300:431–433.

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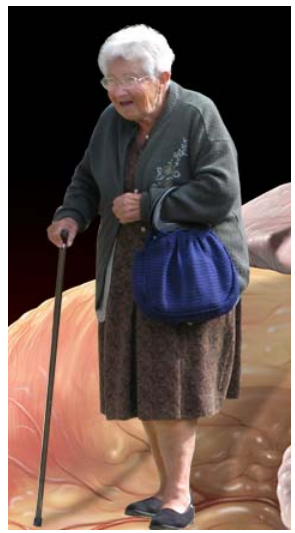
¿Se pueden generalizar los resultados de los EC en pacientes con función VI preservada ?

JAMA
The Journal of the American Medical Association

Heart Failure With Preserved Ejection Fraction
Treat Now by Treating Comorbidities



"Este es el perfil más frecuente del paciente atendido en M. Interna"

Shah et al. JAMA 2008; 300:431–433.

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Table 9. Differential Diagnosis in a Patient With Heart Failure and Normal Left Ventricular Ejection Fraction

Incorrect diagnosis of HF
Inaccurate measurement of LVEF
Primary valvular disease
Restrictive (infiltrative) cardiomyopathies
Amyloidosis, sarcoidosis, hemochromatosis
Pericardial constriction
Episodic or reversible LV systolic dysfunction
Severe hypertension, myocardial ischemia
HF associated with high metabolic demand (high output states)
Anemia, thyrotoxicosis, arteriovenous fistulae
Chronic pulmonary disease with right HF
Pulmonary hypertension associated with pulmonary vascular disorders
Atrial myxoma
Diastolic dysfunction of uncertain origin
Obesity

HF indicates heart failure; LV, left ventricular; and LVEF, left ventricular ejection fraction.

adversely affect the diastolic properties of the heart or decrease the time available for ventricular filling. There may also be sex-specific responses to hypertension and diabetes mellitus that make women more susceptible than men to the cumulative effects of aging on diastolic function.[506]

A number of recent investigations have focused on the differences between HF with preserved EF and that with low LVEF.[48,49,498] Myocardial infarction or other evidence of atherosclerotic disease appears to be less common in HF with normal LVEF, but hypertension is at least as common in this subgroup. The morbidity and mortality associated with HF and a relatively preserved LVEF may be nearly as profound as that with low LVEF; frequent and repeated hospitalizations characterize the patient with HF and a normal LVEF.[507,508] Most, but not all, series of patients with HF and relatively preserved LVEF have shown better survival than is seen in patients with HF and reduced LVEF; however, these comparisons are difficult to interpret, because it is difficult to be certain that such series do not contain at least some patients in whom the diagnosis of HF is erroneous.

4.3.2.2. Diagnosis

There have been several proposed criteria by which clinicians and investigators may define HF with a relatively preserved LVEF.[509–512] In general, a definitive diagnosis can be made when the rate of ventricular relaxation is slowed; this physiological abnormality is characteristically associated with the finding of an elevated LV filling pressure in a patient with normal LV volumes and contractility. In practice, the diagnosis is generally based on the finding of typical symptoms and signs of HF in a patient who is shown to have a normal LVEF and no valvular abnormalities (aortic stenosis or mitral regurgitation, for example) on echocardiography. Every effort should be made to exclude other possible explanations or disorders that may present in a similar manner[503,513] (Table 9).

Noninvasive methods (especially those that rely on Doppler echocardiography) have been developed to assist in the diagnosis of HF with normal LVEF, but these tests have significant limitations, because cardiac filling patterns are readily altered by nonspecific and transient changes in loading conditions in the heart and by aging, changes in heart rate, or the presence of mitral regurgitation.[514–520] The analysis of BNP levels in association with echocardiographic filling patterns can improve diagnostic accuracy. For example, a normal BNP level along with completely normal diastolic end-filling parameters makes HF much less likely; however, HF does remain a strictly clinical diagnosis.[521]

4.3.2.3. Principles of Treatment

In contrast to the treatment of HF due to reduced LVEF, few clinical trials are available to guide the management of patients with HF and relatively preserved LVEF. Although controlled studies have been performed with digitalis, ACEIs, ARBs, beta blockers, and calcium channel blockers in patients with HF who had a relatively preserved LVEF, for the most part, these trials have been small or have produced inconclusive results.[134,241,522–524] Nevertheless, many patients with HF and normal LVEF are treated with these drugs because of the presence of comorbid conditions (i.e., atrial fibrillation, hypertension, diabetes mellitus, and coronary artery disease). A large, randomized trial recently completed included patients with HF and normal LVEF, which demonstrates that studies in such patients can be accomplished.[327] In that trial, the addition of candesartan to the treatment regimen for patients with symptomatic HF and relatively preserved LVEF significantly reduced morbidity but did not reach the primary endpoint.

In the absence of other controlled clinical trials, the management of these patients is based on the control of physiological factors (blood pressure, heart rate, blood volume, and myocardial ischemia) that are known to exert important effects on ventricular relaxation.[503] Likewise, diseases that are known to cause HF with normal LVEF should be treated, such as coronary artery disease, hypertension, or aortic stenosis. Clinically, it seems reasonable to target symptom reduction, principally by reducing cardiac filling pressures at rest and during exertion.[497] Recommendations regarding the use of anticoagulation and antiarrhythmic agents apply to all patients with HF, irrespective of LVEF.

POTENTIAL TREATMENT STRATEGIES. Hypertension exerts a deleterious effect on ventricular function by causing both structural and functional changes in the heart. Increases in systolic blood pressure have been shown to slow myocardial relaxation,[525] and the resulting hypertrophy may adversely affect passive chamber stiffness. Physicians should make every effort to control both systolic and diastolic hypertension with effective antihypertensive therapy in accordance with published guidelines.[78] Consideration should at least be given to achieving target levels of blood pressure lower than those recommended for patients with uncomplicated hypertension (e.g., less than 130 mm Hg systolic and less than 80 mm Hg diastolic).[78,524,526] Because myocardial ischemia can impair ventricular relaxation, coronary revascularization should be considered in patients with coronary artery disease in whom

symptomatic or demonstrable myocardial ischemia is believed to be exerting a deleterious effect on cardiac function (for more information, see the ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery).[16]

Because tachycardia can shorten the time available for ventricular filling and coronary perfusion, drugs that slow the heart rate or the ventricular response to atrial arrhythmias (e.g., beta blockers, digoxin, and some calcium channel blockers) can provide symptomatic relief in patients with HF and normal LVEF. Similarly, patients with HF and preserved LVEF may be particularly sensitive to loss of atrial kick, which supports a potential benefit for restoration of sinus rhythm in patients with atrial fibrillation. The benefits of restoring sinus rhythm in these individuals are less clear, and the large trials of rhythm versus rate control in atrial fibrillation published recently have excluded patients with HF. Moreover, the presence of systolic or diastolic dysfunction may diminish the efficacy and enhance the toxicity of drugs used to achieve and maintain sinus rhythm.

Circulating blood volume is a major determinant of ventricular filling pressure, and the use of diuretics may improve breathlessness in patients with HF and normal LVEF as well as those with reduced LVEF. Other possible agents used to reduce diastolic filling pressures are nitrates or agents that block neurohumoral activation. Hypotension may be a significant problem in this population, especially in the very elderly, because they can be quite sensitive to preload reduction.

4.4. Patients With Refractory End-Stage Heart Failure (Stage D) (UPDATED)

The role of intermittent infusions as effective treatment for advanced HF has been further clarified by an additional multicenter trial (Table 4).

Recommendations

Class I

1. **Meticulous identification and control of fluid retention is recommended in patients with refractory end-stage HF.[279,282,527–532] (*Level of Evidence: B*)**
2. **Referral for cardiac transplantation in potentially eligible patients is recommended for patients with refractory end-stage HF.[533] (*Level of Evidence: B*)**
3. **Referral of patients with refractory end-stage HF to a HF program with expertise in the management of refractory HF is useful.[534–537] (*Level of Evidence: A*)**
4. **Options for end-of-life care should be discussed with the patient and family when severe symptoms in patients with refractory end-stage HF persist despite application of all recommended therapies. (*Level of Evidence: C*)**
5. **Patients with refractory end-stage HF and implantable defibrillators should receive information about the option to inactivate the defibrillator. (*Level of Evidence: C*)**

Class IIa

1. **Consideration of an LV assist device as permanent or "destination" therapy is reasonable in highly selected patients with refractory end-stage HF and an estimated 1-year mortality over 50% with medical therapy.[538,539] (*Level of Evidence: B*)**

Class IIb

1. **Pulmonary artery catheter placement may be reasonable to guide therapy in patients with refractory end-stage HF and persistently severe symptoms.[533,540] (*Level of Evidence: C*)**
2. **The effectiveness of mitral valve repair or replacement is not well established for severe secondary mitral regurgitation in refractory end-stage HF.[141,541,542] (*Level of Evidence: C*)**
3. **Continuous intravenous infusion of a positive inotropic agent may be considered for palliation of symptoms in patients with refractory end-stage HF.[543,544] (*Level of Evidence: C*)**

Class III

1. **Partial left ventriculectomy is not recommended in patients with nonischemic cardiomyopathy and refractory end-stage HF. (*Level of Evidence: C*)**
2. **Routine intermittent infusions of vasoactive and positive inotropic agents are not recommended for patients with refractory end-stage HF[545,546] (*Level of Evidence: A*)**

Most patients with HF due to reduced LVEF respond favorably to pharmacological and nonpharmacological treatments and enjoy a good quality of life and enhanced survival; however, some patients do not improve or experience rapid recurrence of symptoms despite optimal medical therapy. Such patients characteristically have symptoms at rest or on minimal exertion, including profound fatigue; cannot perform most activities of daily living; frequently have evidence of cardiac cachexia; and typically require repeated and/or prolonged hospitalizations for intensive management. These individuals represent the most advanced stage of HF and should be considered for specialized treatment strategies, such as mechanical circulatory support, continuous intravenous positive inotropic therapy, referral for cardiac transplantation, or hospice care.

Before a patient is considered to have refractory HF, physicians should confirm the accuracy of the diagnosis, identify any contributing conditions, and ensure that all conventional medical strategies have been optimally employed. Measures listed as Class I recommendations for patients in stages A, B, and C are also appropriate for patients in end-stage HF (see also Section 5). When no further therapies are appropriate, careful discussion of the prognosis and options for end-of-life care should be initiated (see Section 7).

4.4.1. Management of Fluid Status

Many patients with advanced HF have symptoms that are related to the retention of salt and water and thus will respond

Class of recommendation IIb, level of evidence B

Key evidence

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

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

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

method of revascularization should be based on ation of co-morbidities, procedural risk, coronary dence of the extent of viable myocardium in revascularized, LV function, and the presence of h significant valvular disease.

Key evidence

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

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

Routine coronary angiography is not recommended.

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

Coronary angiography

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

Class of recommendation I, level of evidence C

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

Class of recommendation I, level of evidence C

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

Class of recommendation IIa, level of evidence C

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

coronary intervention (PCI) should be considered in selected HF patients with CAD. Decisions regarding the choice of the

- The ESC Guidelines on the management of valvular disease apply to most patients with HF.[136] Although impaired LVEF is

Dickstein et al. Eur Heart J 2008; 29:2388-2442 / Dickstein et al. Rev Esp Cardiol. 2008;61:1329.e1-1329.e70

Conclusiones

El perfil más frecuente del paciente ingresado en M. Interna es una mujer, mayor, con comorbilidad y FE preservada, el prototipo de paciente que ha sido excluído de la mayoría de los EC

Para este paciente con FE preservada ningún tratamiento ha mostrado una disminución de mortalidad. Se recomienda tratar las comorbilidades (HTA, FA…)

En pacientes con disfunción sistólica, debemos aplicar, en la medida de lo posible, la evidencia obtenida en los ensayos clínicos

Acercar los pacientes incluidos en los ensayos clínicos a los pacientes del mundo real

Muchas gracias