

INSUFICIENCIA CARDIACA

UNA CUESTIÓN DE
GÉNERO

GENDER or SEX

are we talking about the same thing?

Sex

biological factors

Gender

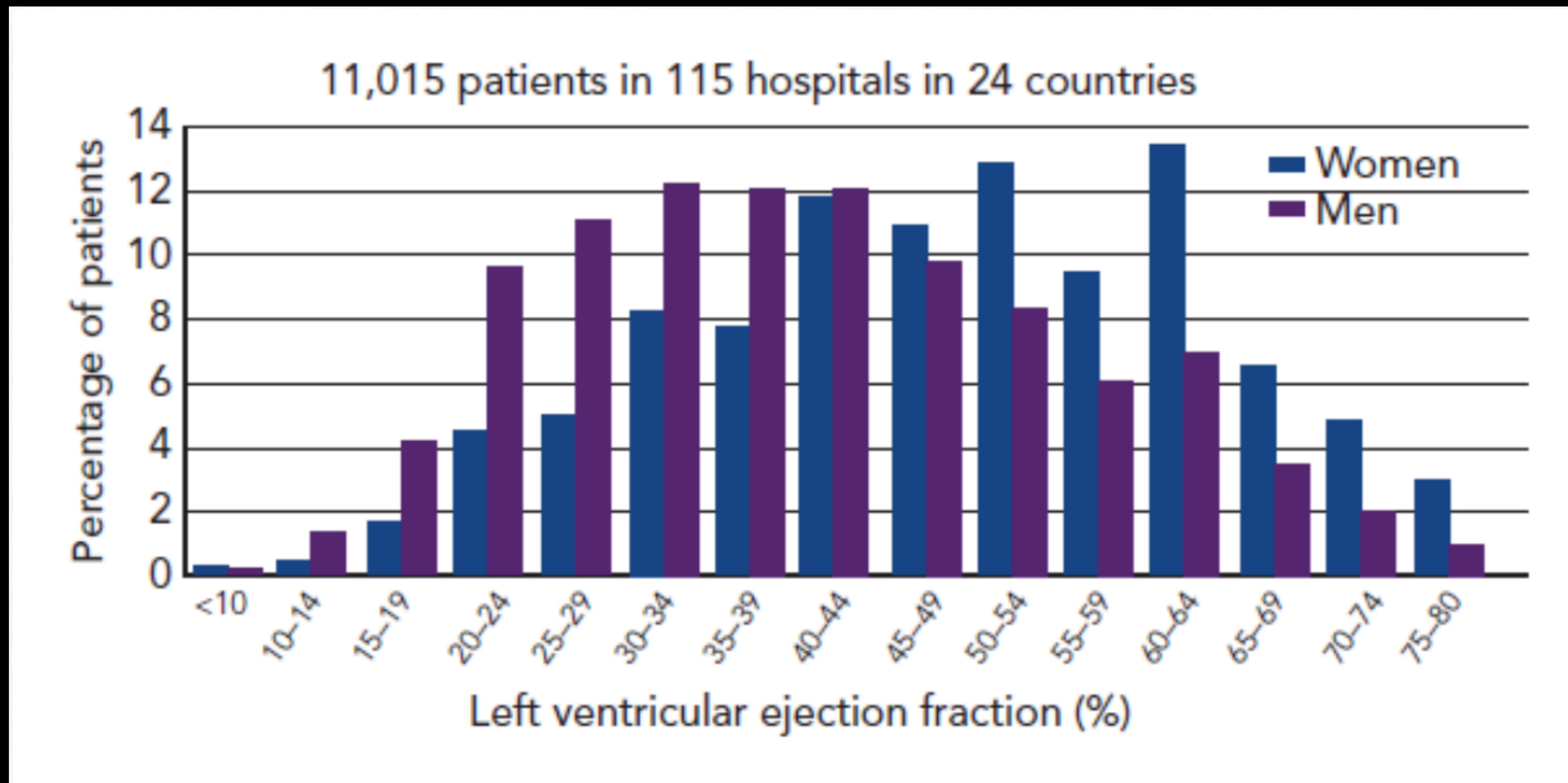
psychosocial and cultural factors

INSUFICIENCIA CARDIACA

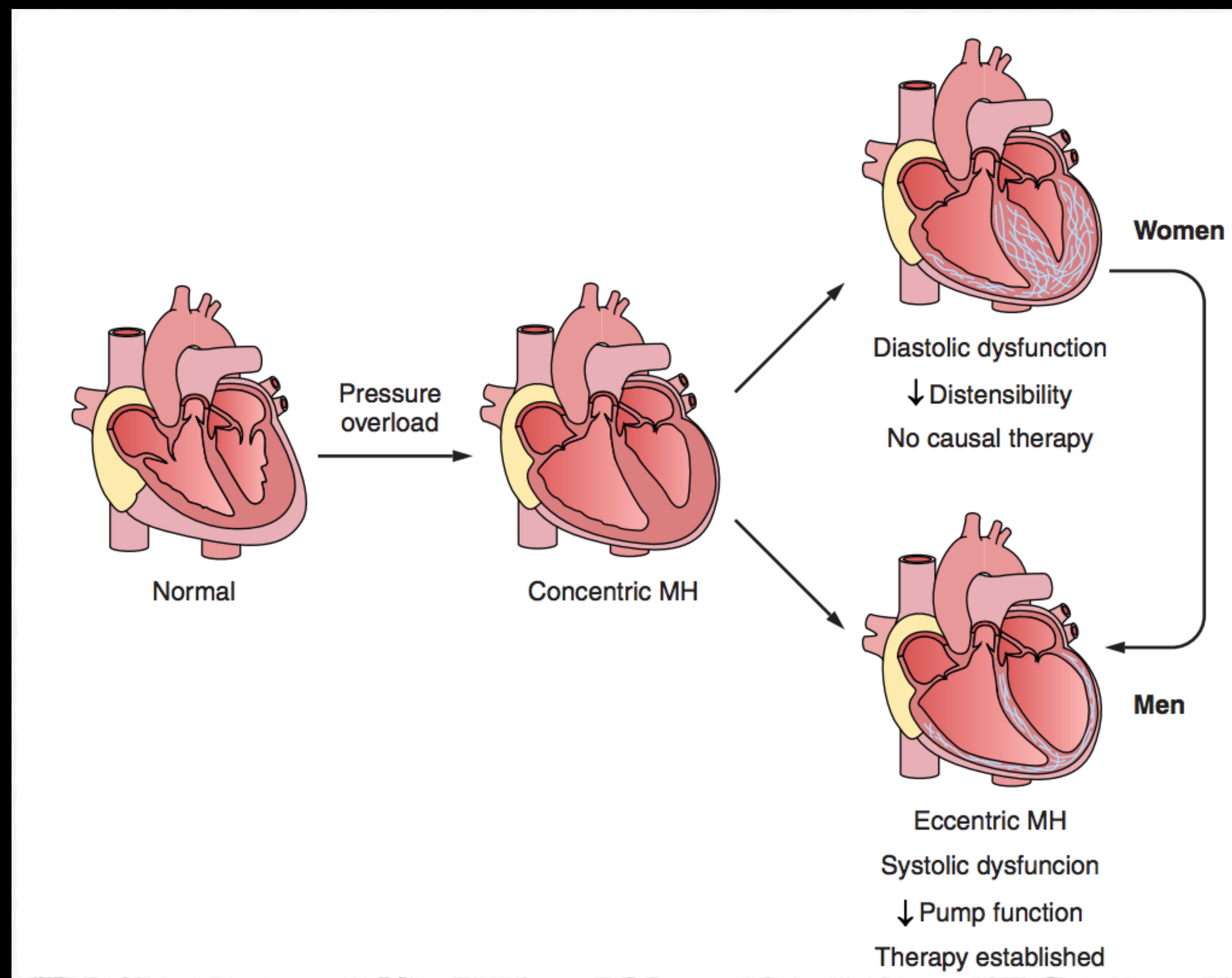
UNA CUESTIÓN DE
GÉNERO

Distribución de la FEVI según el sexo

EuroHeart Failure Survey 2000-2001



Diferencias sexuales en el remodelado cardiaco



Women are not small men

higher **BODY FAT**

smaller **KIDNEYS**



higher **HEART** arrhythmia susceptibility

different **LIVER** metabolism

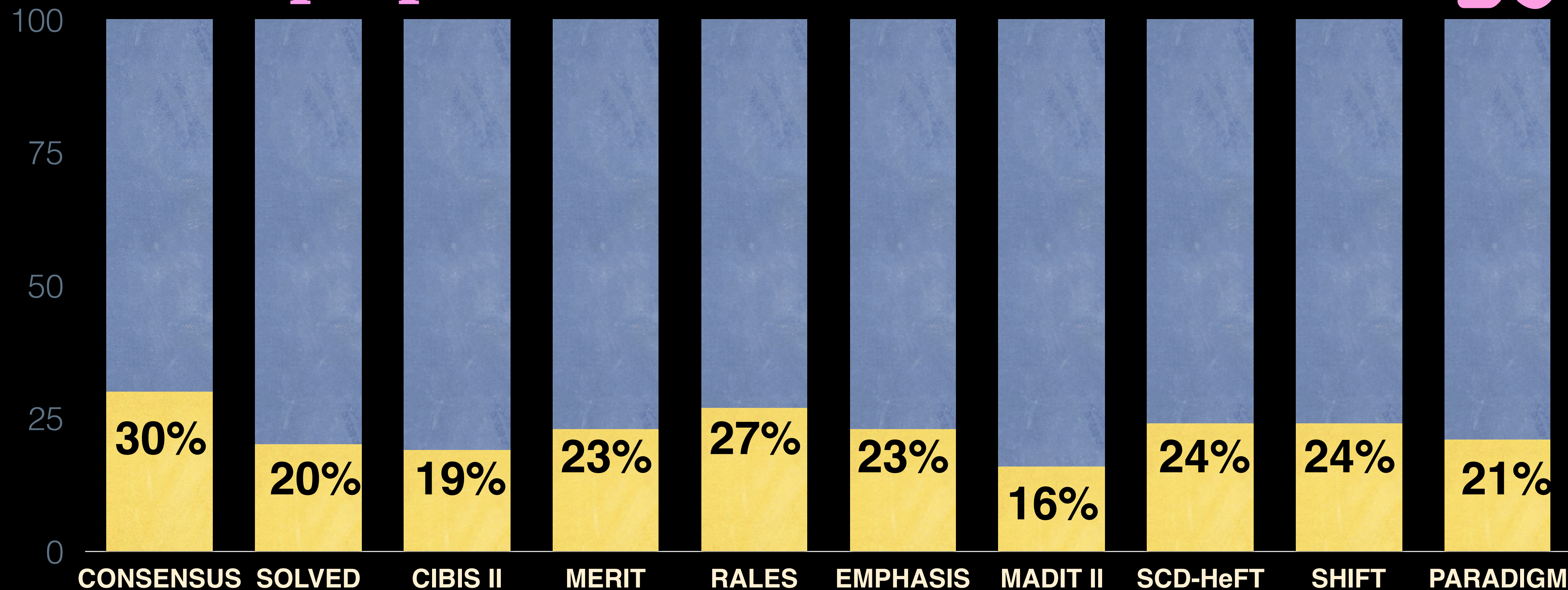
smaller **WEIGHT**

Gender differences in adverse drug reactions

- ▶ more frequent adverse drug reactions from diuretics (e.g. hyponatremia, hypokalemia, and severe arrhythmias)
- ▶ higher risk of drug-induced torsades de pointes (TdP, 2–2.3-fold greater risk in females)
- ▶ higher risk of cough with ACE-I (2-fold)
- ▶ higher risk of haemorrhagic complications with anticoagulants, platelet antiaggregants and thrombolytics
- ▶ higher risk of and myopathy with statins

Limitations in reaching conclusions about gender differences in drugs efficacy

proportion of women in HF trials **23%**



Reducción de mortalidad total o cv en el análisis de subgrupos

CONSENSUS	RR 1.14	(0.68-1.90)
SOLVED-T	RR 0.86	(0.67-1.09)
CIBIS II	RR 0.52	(0.30-0.89)
COMET	HR 0.97	(0.73-1.27)
EMPHASIS-HF	HR 0.65	(0.4-0.9)
MADIT II	HR 0.57	(0.28-1.16)
SCDHeFT	HR 0.96	(0.58-1.61)
PARADIGM-HF	HR 0.92	(0.6-1.1)



EUROPEAN
SOCIETY OF
CARDIOLOGY®

European Heart Journal (2015) **36**, 2677–2680

doi:10.1093/eurheartj/ehv161

CURRENT OPINION

Gender differences in the effect of cardiovascular drugs: a position document of the Working Group on Pharmacology and Drug Therapy of the ESC

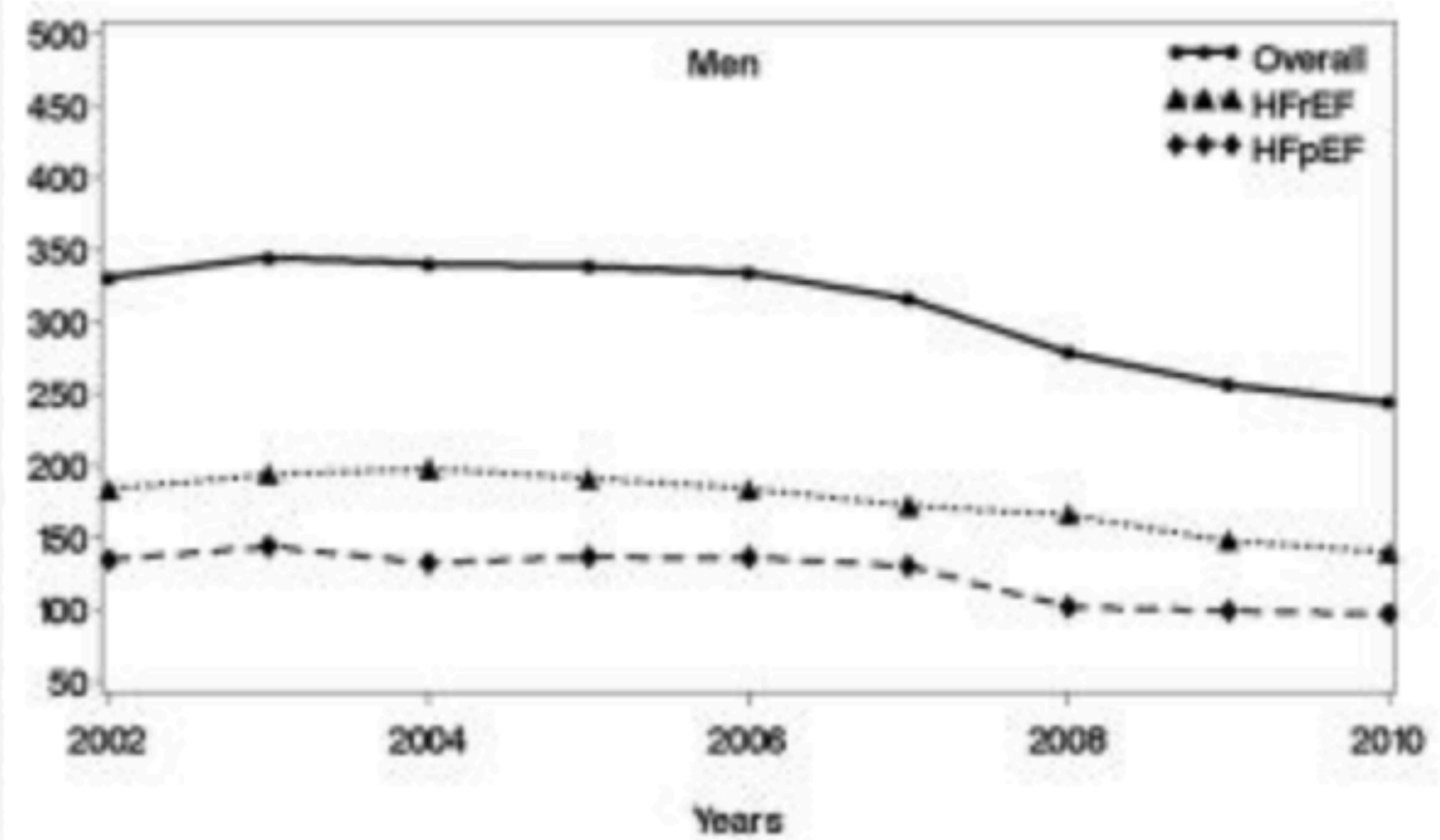
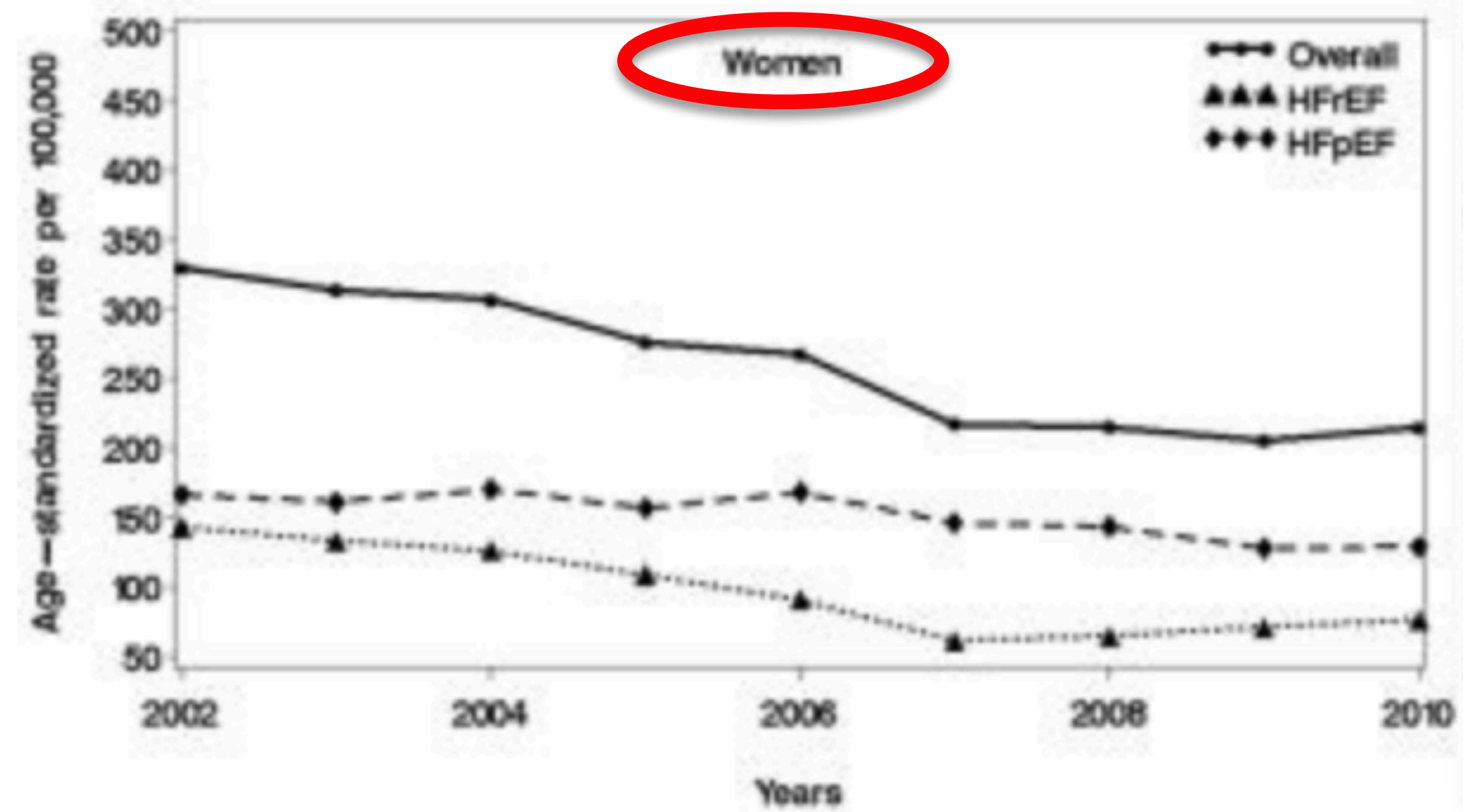
**Giuseppe M.C. Rosano^{1,2*}, Basil Lewis³, Stefan Agewall⁴, Sven Wassmann⁵,
Cristiana Vitale¹, Harald Schmidt⁶, Heinz Drexel⁷, Atul Patak⁸,
Christian Torp-Pedersen⁹, Keld Per Kjeldsen¹⁰, and Juan Tamargo¹¹**

INSUFICIENCIA CARDIACA EN LA MUJER

Epidemiología

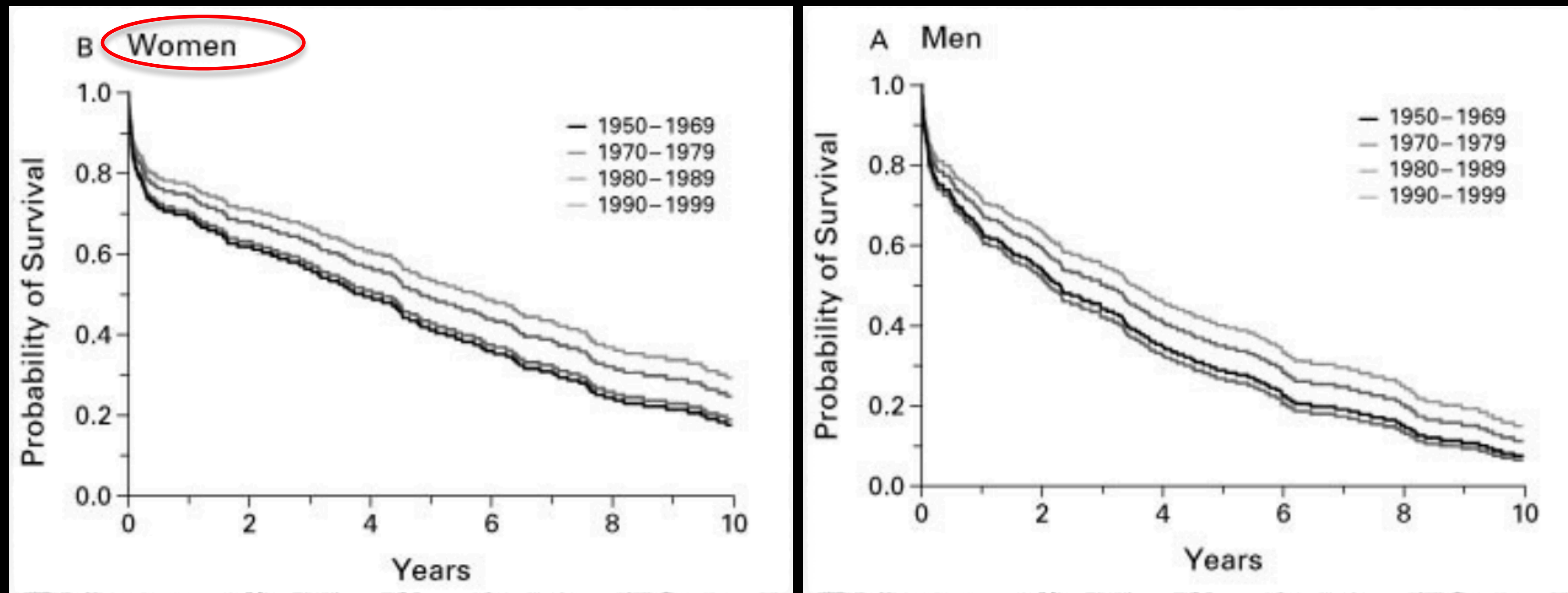
Temporal trends in heart failure **incidence rates** in Olmsted County (2000-2010)

age- and sex-adjusted incidence of HF

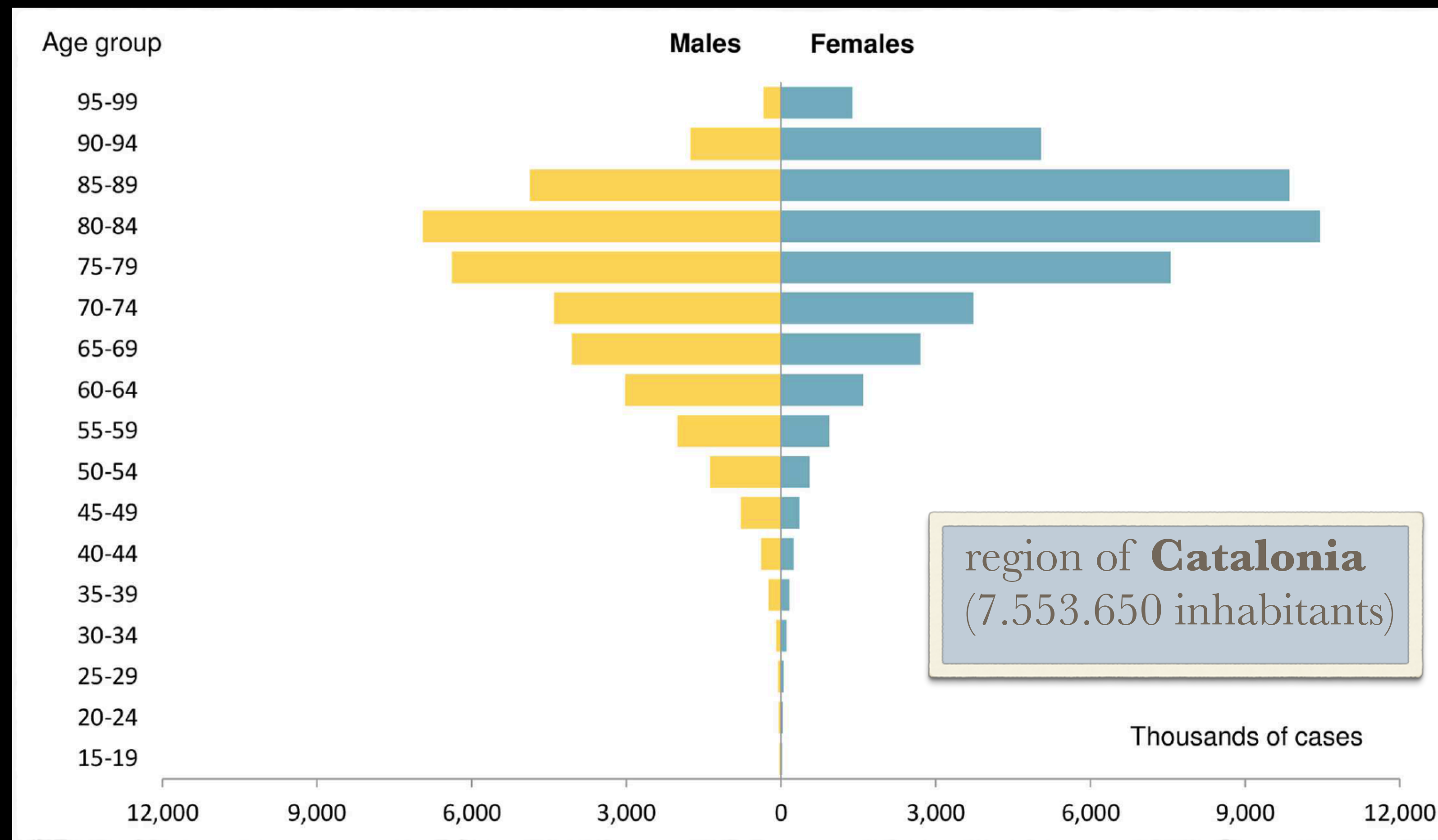


Temporal trends in the **age-adjusted mortality** after the onset of HF

Framingham Heart Study (1950-1999)



Prevalence of HF according to age and sex

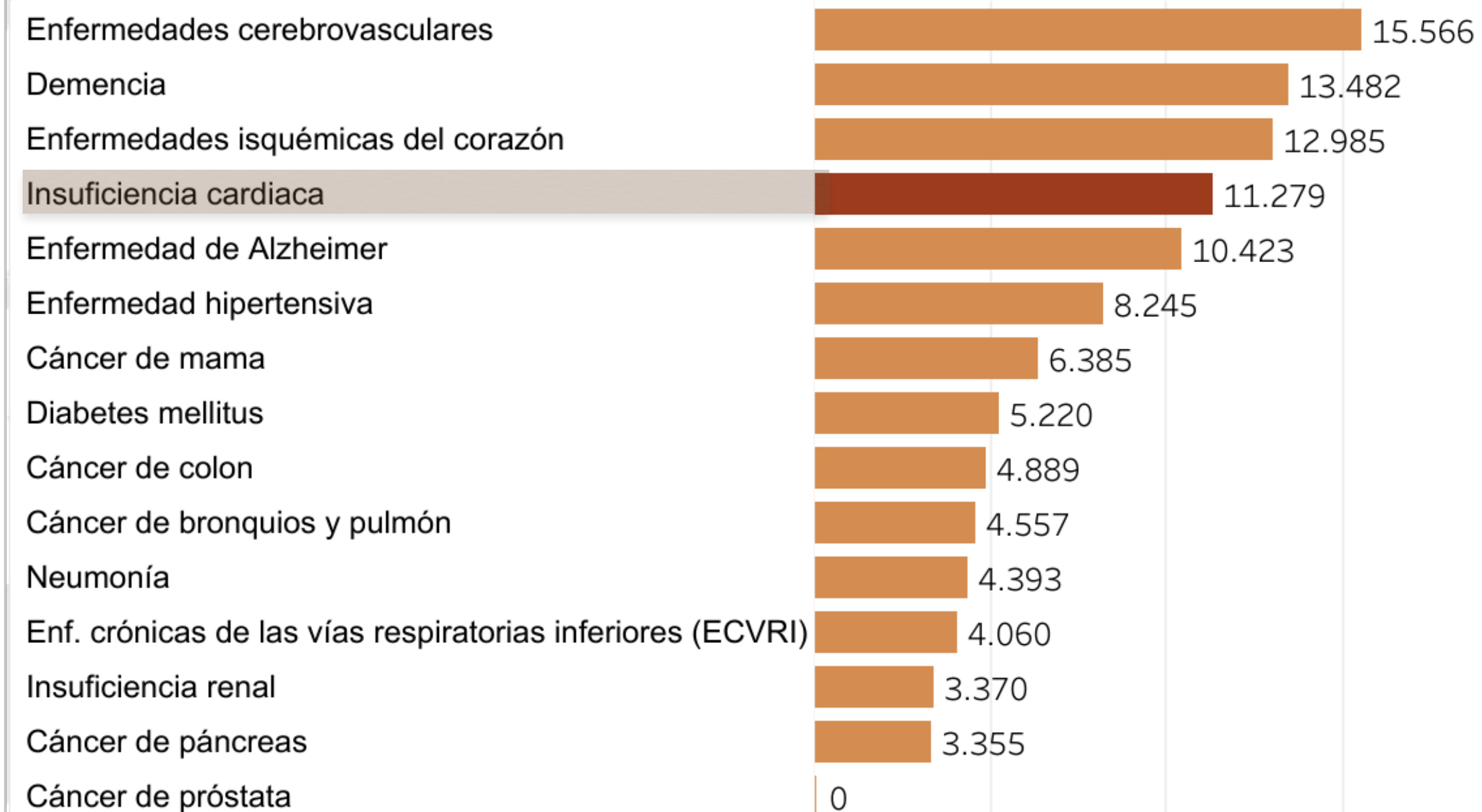


ESPAÑA EN CIFRAS: MORTALIDAD

mujeres

Número de defunciones

Nacional



Defunciones Totales, Mujeres

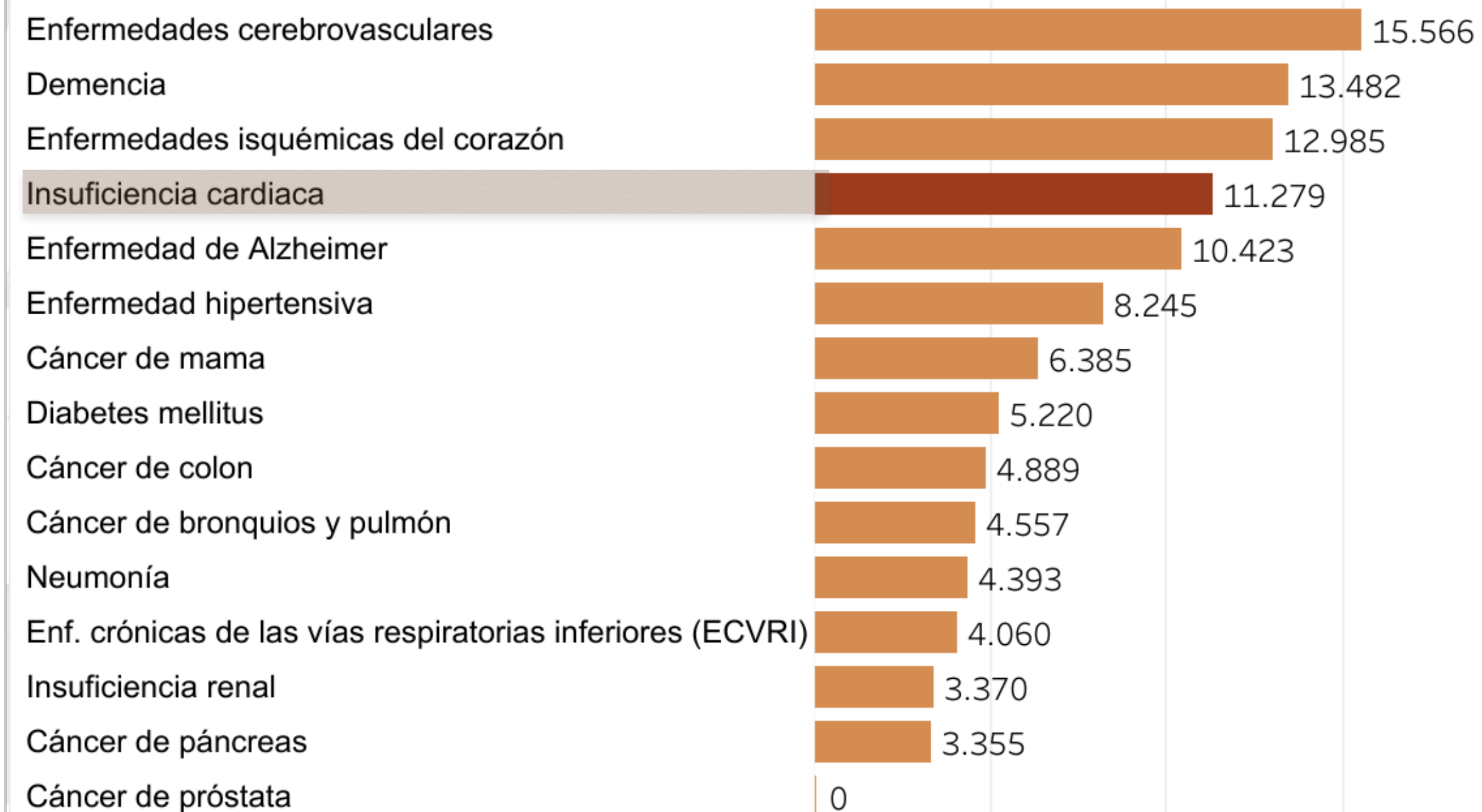
201.618

ESPAÑA EN CIFRAS: MORTALIDAD

mujeres

Número de defunciones

Nacional



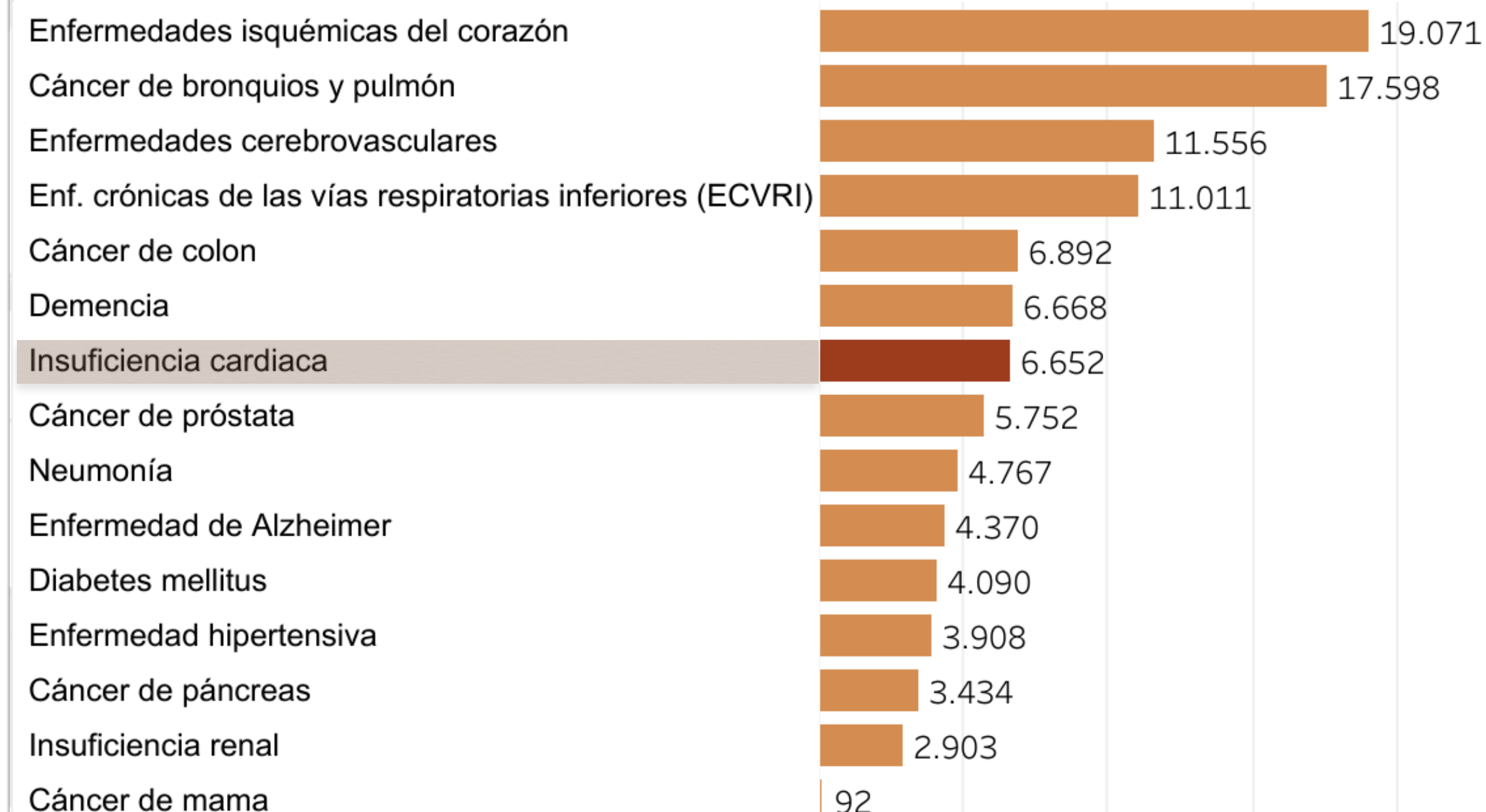
Defunciones Totales, Mujeres

201.618

hombres

Número de defunciones

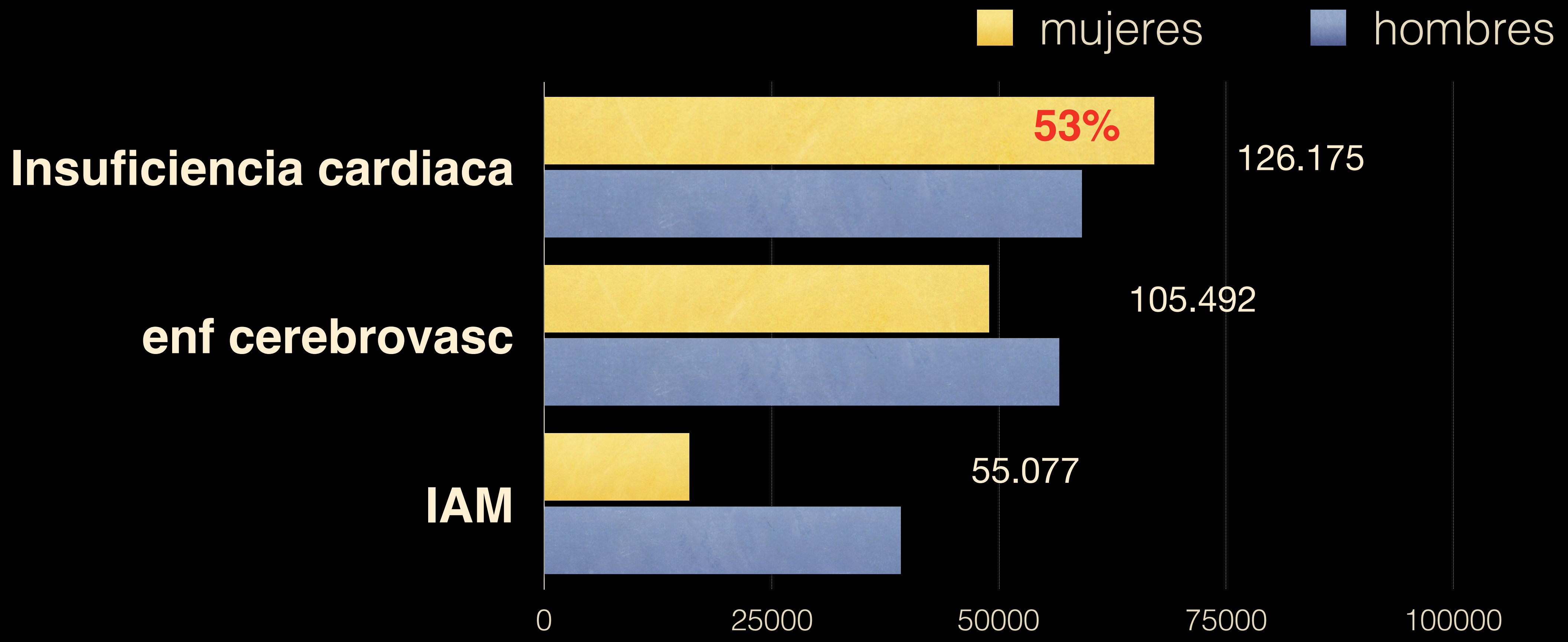
Nacional



Defunciones Totales, Hombres

208.993

Ingresos por enf. de apto circulatorio España 2016



INSUFICIENCIA CARDIACA EN LA MUJER

Características basales

Baseline characteristics of 41 949 patients included in 31 studies **by gender**. MAGGIC meta-analysis

	Men	Women 33%	P-value
n (31 studies)	28 052	13 897	
Age, years (SD)	65.6 (11.6)	70.5 (12.1)	<0.001
Medical history			
Hypertension	40.0	49.9	<0.001
Myocardial infarction	51.0	33.3	<0.001
Atrial fibrillation	19.7	21.6	<0.001
Diabetes	22.8	25.4	<0.001
Ischaemic aetiology	58.7	46.3	<0.001
Medication			
ACE inhibitor or ARB	80.3	71.1	<0.001
Beta-blocker	38.5	34.7	<0.001
Diuretic	80.2	83.6	<0.001
Spironolactone	22.5	20.9	0.004
Digoxin	44.2	41.2	<0.001
Clinical status			
Functional class (I/II/III/IV)	11.1/47.4/34.7/6.8	9.1/45.2/36.7/9.0	<0.001
Heart rate, b.p.m.	78.0 (17.5)	81.4 (19.6)	<0.001
SBP, mmHg	128.6 (21.7)	135.0 (24.5)	<0.001
DBP, mmHg	76.9 (12.2)	77.0 (13.2)	0.3245
Left ventricular EF, %	33.0 (24.5–44.0)	42.0 (30.0–57.0)	<0.001
Preserved EF, %	18.4	37.4	<0.001

SEX DIFFERENCES IN CHARACTERISTICS OF **HFrEF**. Post-hoc analysis of **main DIG-trial**

FEMALES (n= 1519; 22%)

- ▶ older (66 vs 64)
- ▶ higher EF (30 vs 28%)
- ▶ higher frequency of HF-related symptoms and signs
- ▶ worse NYHA functional status
- ▶ more comorbidities (diabetes, hypertension,...)
- ▶ more non-ischemic primary cause (38 vs 27%)

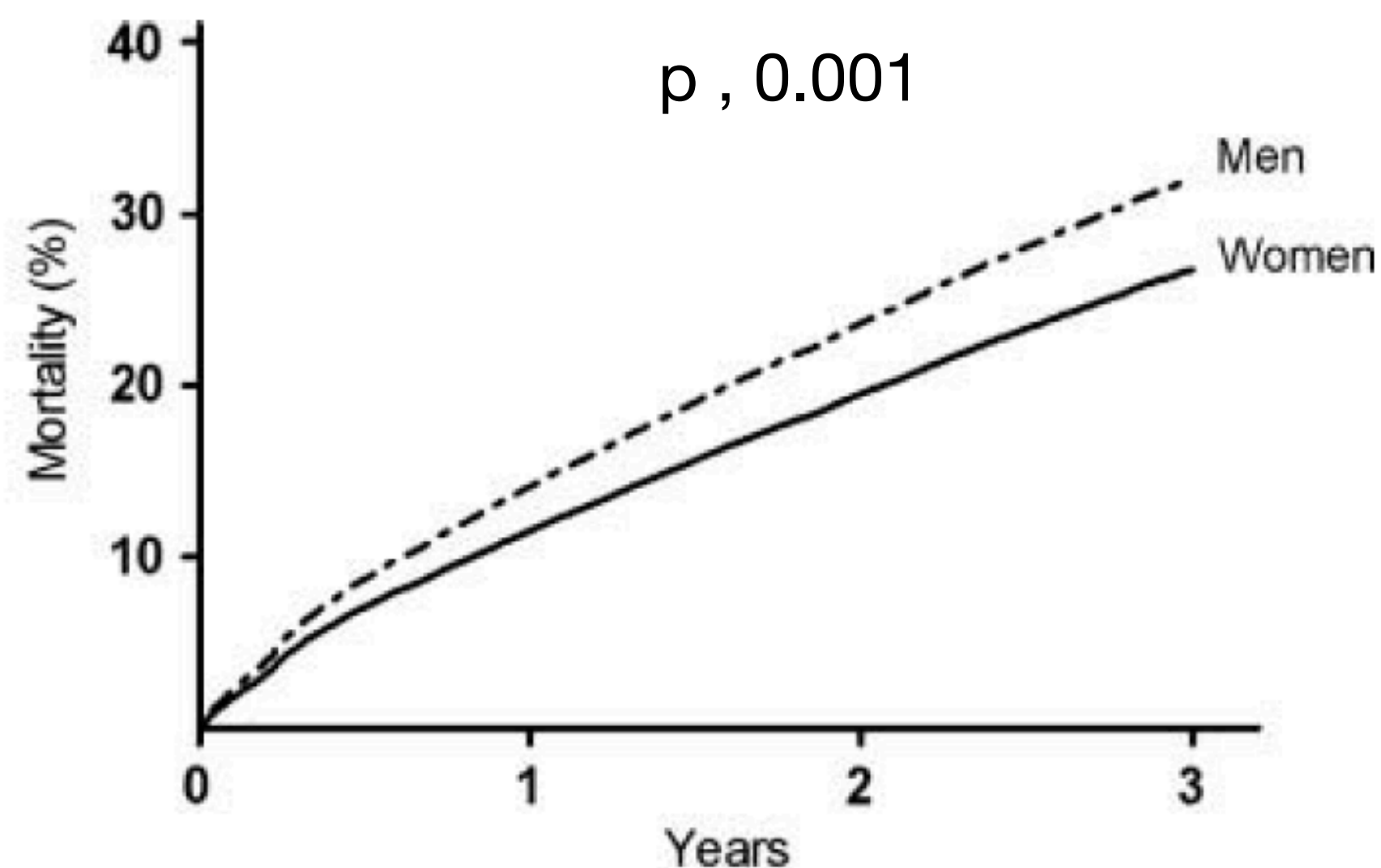
SEX DIFFERENCES IN CHARACTERISTICS OF **HFpEF**. Post-hoc analysis of **ancillary DIG-trial**

FEMALES (n= 341; 47%)

- older (70 vs 67)
- higher EF (59 vs 55%)
- higher frequency of HF-related symptoms and signs
- worse NYHA functional status
- more comorbidities (AF, diabetes, hypertension, anemia, iron deficiency, renal disease, arthritis, frailty, depression,...)
- less ischemic etiology (46% vs 56%)

Gender and survival in patients with HF: MAGGIC meta-analysis

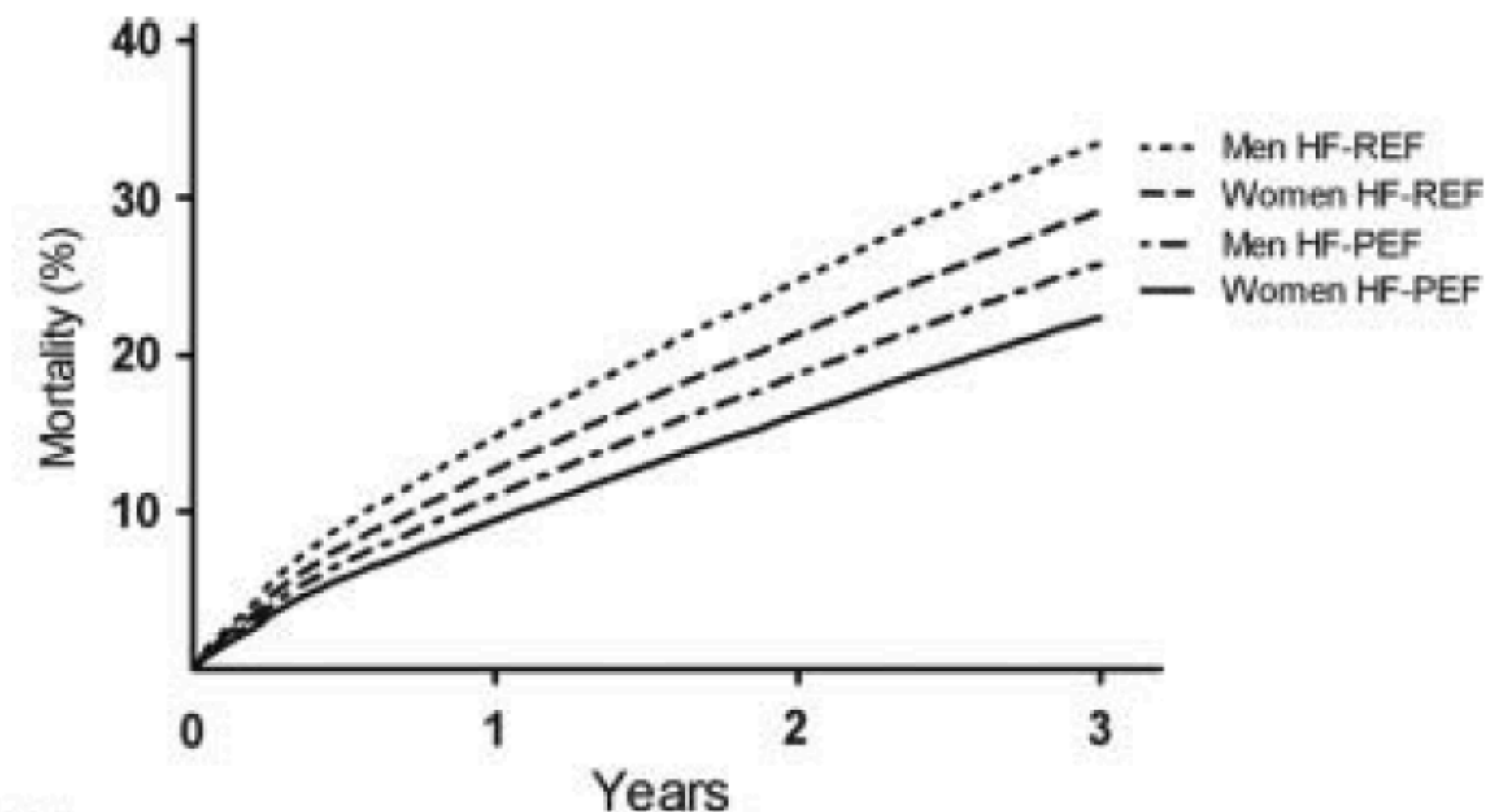
All-cause mortality for men and women adjusted for age



Number at risk:

	0	1	2	3
Men	26881	19662	15515	11538
Women	13309	9429	7778	5800

All-cause mortality for men and women with HFrEF en HFpEF adjusted for age



Number at risk:

	0	1	2	3
Men HF-REF	21914	16077	12461	9224
Women HF-REF	8284	5939	4813	3553
Men HF-PEF	4967	3584	3053	2313
Women HF-PEF	5025	3489	2964	2246

SEX DIFFERENCES IN PROGNOSIS OF HFpEF. Post-hoc analysis of DIG-TRIAL

Hazard ratios by gender for mortality and hospitalization			
Variable	Unadjusted Hazard Ratio (95% CI)	Age-Adjusted Hazard Ratio (95% CI)	Covariate-Adjusted Hazard Ratio (95% CI)
Mortality	0.97 (0.72–1.30)	0.84 (0.62–1.41)	0.59 (0.43–0.82)
HF hospitalization	1.76 (1.27–2.43)	1.61 (1.15–2.24)	1.06 (0.75–1.51)
CV hospitalization	1.21 (0.98–1.49)	1.19 (0.97–1.47)	1.04 (0.84–1.30)

BETTER PROGNOSIS (less mortality and similar hospitalization risk)
after adjustment for baseline clinical differences

INSUFICIENCIA CARDIACA EN LA MUJER

Causas

Factors independently associated with development of heart failure in women

Diabetes

FA

IAM previo

IRC

HTA (>140)

Tabaquismo

IMC >35

BRI

HVI

TABLE 2. Risk Factors for Developing Heart Failure in 2391 Postmenopausal Women With Coronary Disease

Characteristics	n (%) With Risk Factors	Adjusted Hazard Ratio (95% CI)	P
Diabetes	391 (16)	3.1 (2.3–4.2)	<0.001
Atrial fibrillation	23 (1)	2.9 (1.4–6.2)	0.005
No. of myocardial infarctions (compared with none)			
1	1061 (44)	1.4 (1.1–1.9)	0.02
>1	115 (5)	2.5 (1.7–3.7)	<0.001
Creatinine clearance			
40–60 mL/min	991 (41)	1.2 (0.9–1.7)	0.22
<40 mL/min	244 (10)	2.3 (1.4–3.6)	<0.001
Systolic blood pressure (compared with 80–120 mm Hg)			
120–139 mm Hg	994 (42)	1.6 (1.0–2.6)	0.04
140–159 mm Hg	656 (27)	2.1 (1.3–3.3)	0.002
>159 mm Hg	244 (10)	2.1 (1.2–3.6)	0.008
Smoking			
Former	1173 (49)	1.2 (0.9–1.6)	0.25
Current	310 (13)	1.9 (1.2–2.8)	0.005
Body mass index			
25–30 kg/m ²	927 (39)	1.2 (0.8–2.7)	0.34
30–35 kg/m ²	492 (21)	1.2 (0.8–2.0)	0.34
>35 kg/m ²	307 (13)	1.9 (1.1–3.0)	0.01
Left bundle-branch block	160 (7)	1.6 (1.0–2.4)	0.03
Left ventricular hypertrophy	225 (9)	1.5 (1.1–2.2)	0.02
Prior coronary artery bypass grafting	971 (41)	1.3 (1.0–1.7)	0.06

Data from backward selection multivariable Cox proportional-hazards models adjusted for all variables in Table 1. Age and medications included in all models.

INSUFICIENCIA CARDIACA EN LA MUJER

Diagnóstico

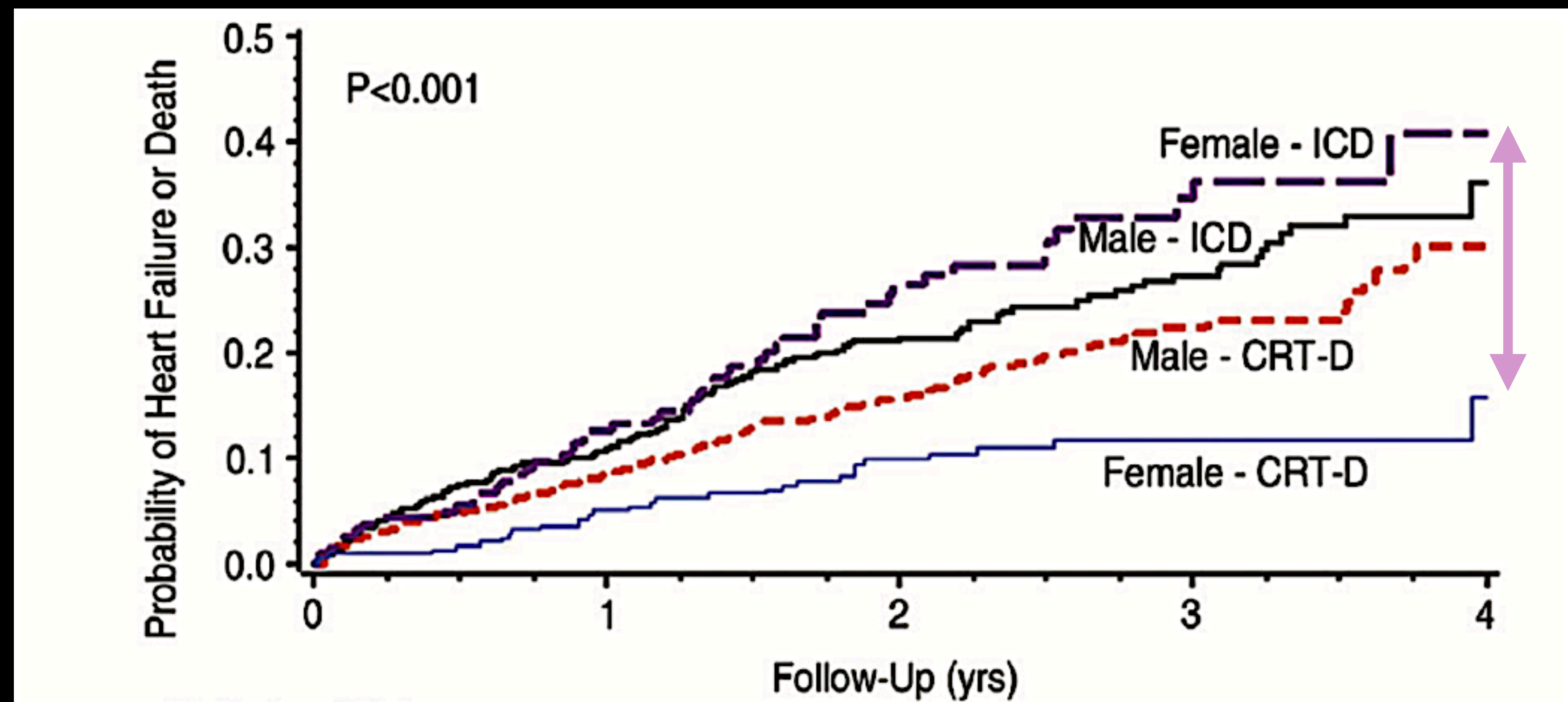
INSUFICIENCIA CARDIACA EN MUJERES

- ▶ Size and function differences according to sex
- ▶ BNP levels according to sex and age

INSUFICIENCIA CARDIACA EN LA MUJER

Tratamiento

Cardiac resynchronization therapy is **more effective** **in women** than in men: the **MADIT-CRT**



Women
RR 69%

Men
RR 28%

Sex differences in the use of cardiac resynchronization therapy

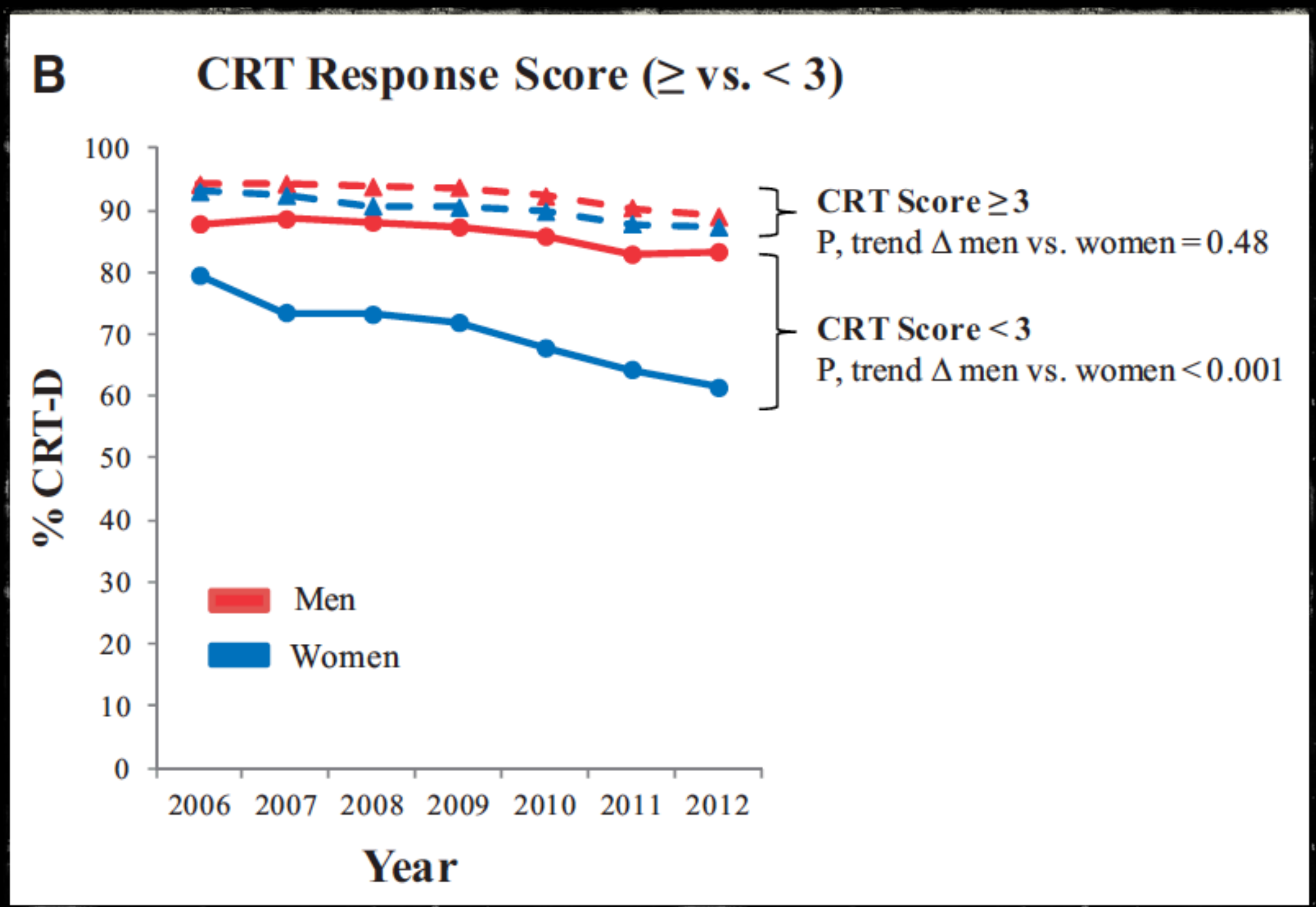
Table 1 Characteristics of patients undergoing CRT implantation, stratified by sex

	All (n = 311 009)	Female (n = 92 126)	Male (n = 218 883)	P-value
CRT response score $\geq 3^d$	116 223 (37.4)	43 560 (47.3)	72 663 (33.2)	<0.001

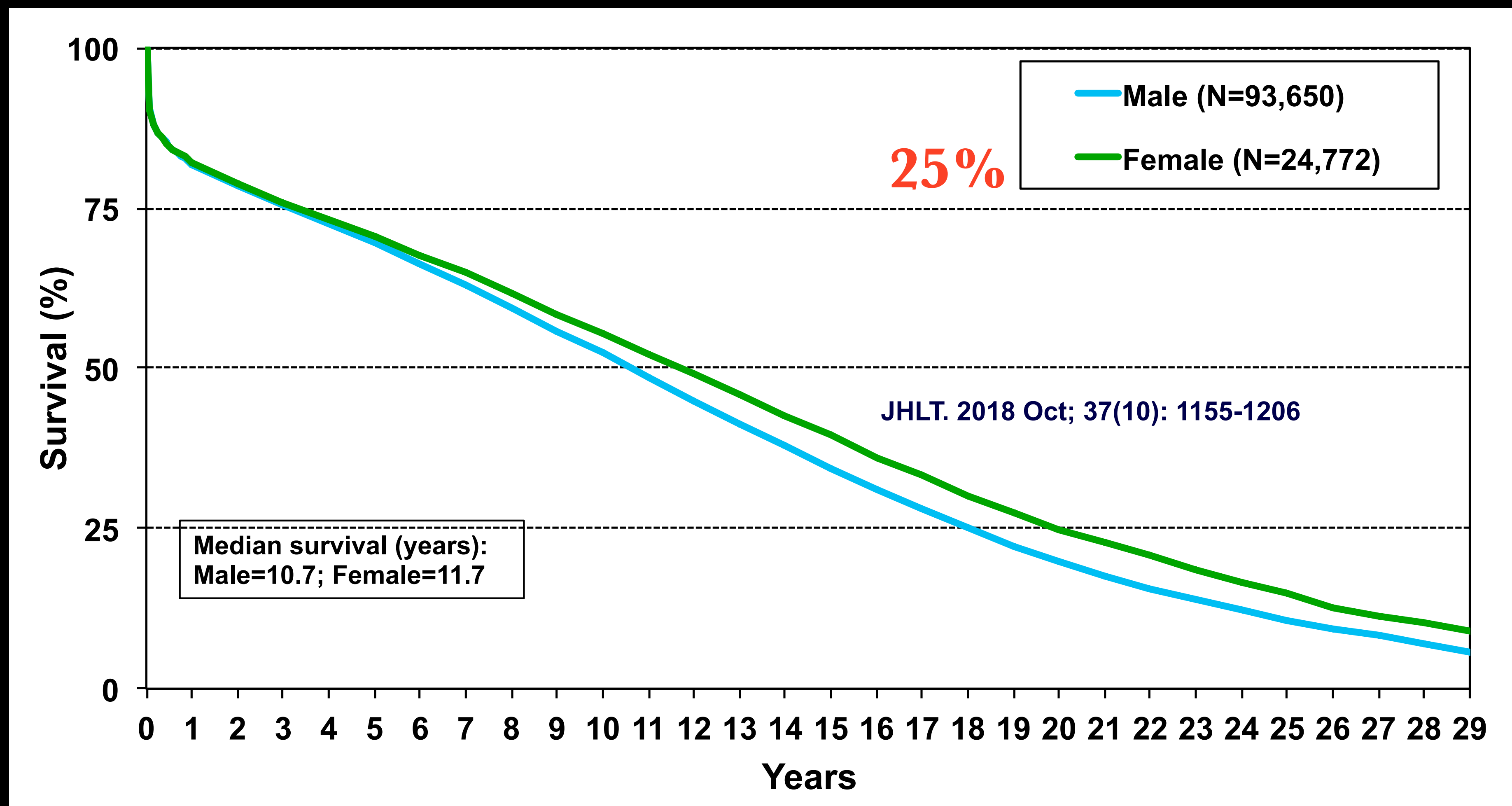
Table 2 Percentage of CRT implants with ICD (CRT-D), stratified by sex

	% CRT-D		Difference, % (95% CI) ^a
	Female (n = 73 822)	Male (n = 194 016)	
Overall	80.1	88.6	8.5 (7.6–9.4)
Reduced ICD Efficacy ^b			
0	85.5	87.8	2.4 (0.6–4.1)
1–2	79.2	88.7	9.5 (8.3–10.7)
≥ 3	79.1	88.7	9.6 (8.3–10.7)

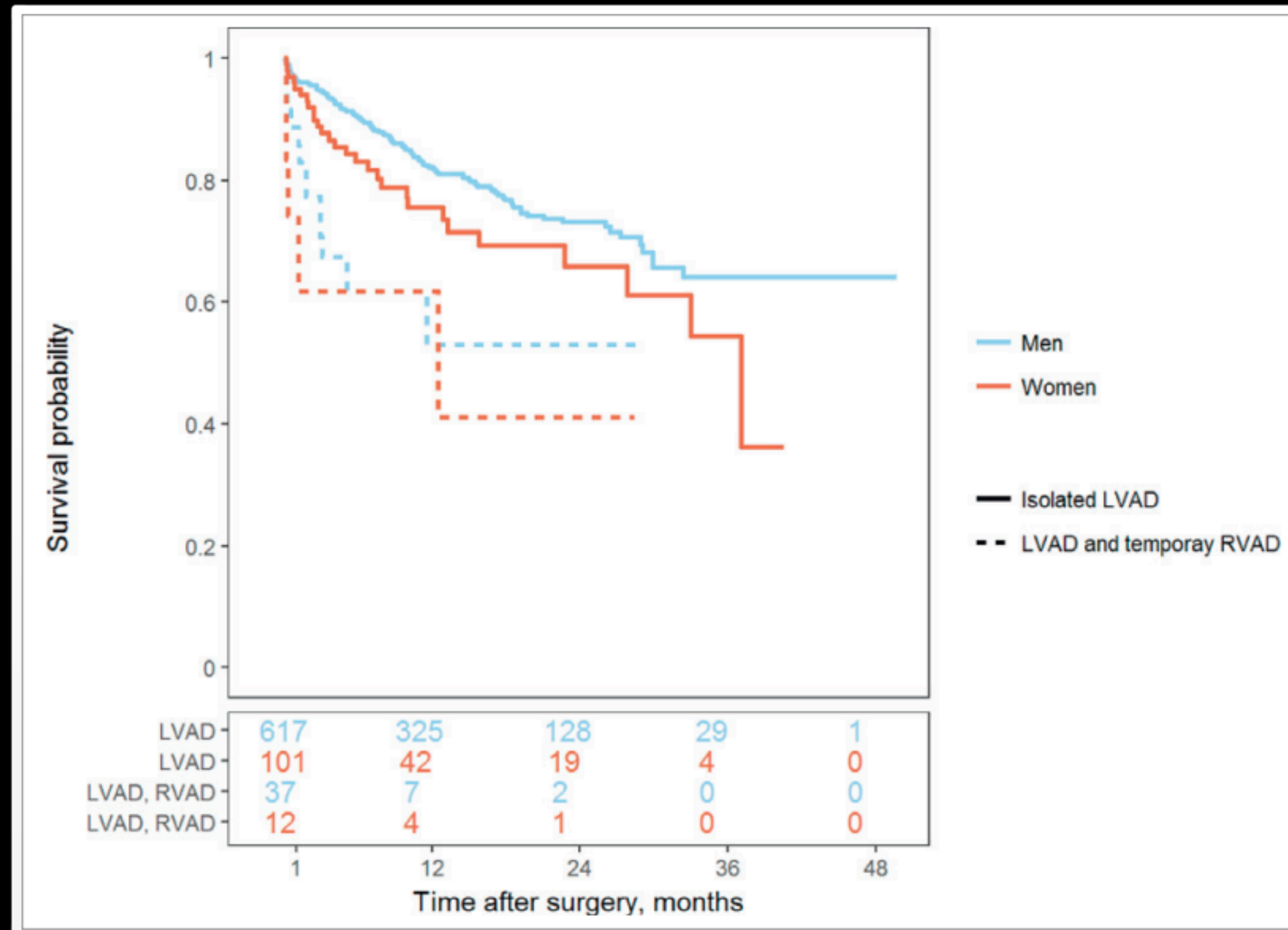
Increasing sex differences in the use of cardiac resynchronization therapy



Adult Heart Transplants. Kaplan-Meier Survival by recipient gender (January 1982-June 2016)



Gender differences and outcomes in **LEFT VENTRICULAR ASSIST DEVICES** support. **EUROMACS 2011-2014**



Gender differences and outcomes in **left ventricular assist device** support. **EUROMACS** 2011-2014

Basal characteristics

	men (n=815)	women (n=151)	p value
Age (years)	56	53	0,088
INTERMACS 1-2	41,6 %	51,7 %	0,025
TR moderate-severe	38,2 %	56,7 %	<0,001

Gender differences and outcomes in **left ventricular assist device** support. **EUROMACS** 2011-2014

Adverse events in the first 30 days

	men (n=815)	women (n=151)	p value
renal dysfunction	1,4 %	3,73 %	0,024
right ventricular failure	1,93 %	8,33 %	<0,001
arrhythmias	1,13 %	3,82 %	0,016
major bleeding	6,7 %	13,86 %	0,007

*“Knowing is not enough; we must apply.
Willing is not enough; we must do”*

— Goethe

Inclusion of women in clinical trials.

A historical perspective



1985... Report of the Public Health Service Task Force on Women's Health Issues

1987... National Institutes of Health (NIH) adopted a policy for the inclusion of women in clinical research

1990... **ORWH** was established in NIH to ensure that women are included in NIH-funded clinical studies.

1992... General Accounting Office (GAO) Report on Women's Health,⁷ drug trials under the guidance of the FDA were found to have inadequate inclusion of women.

1993... new FDA guideline, "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs"

1993... **Congress approved the NIH Revitalization Act: NIH policies on the inclusion of women and minorities in clinical research became law**

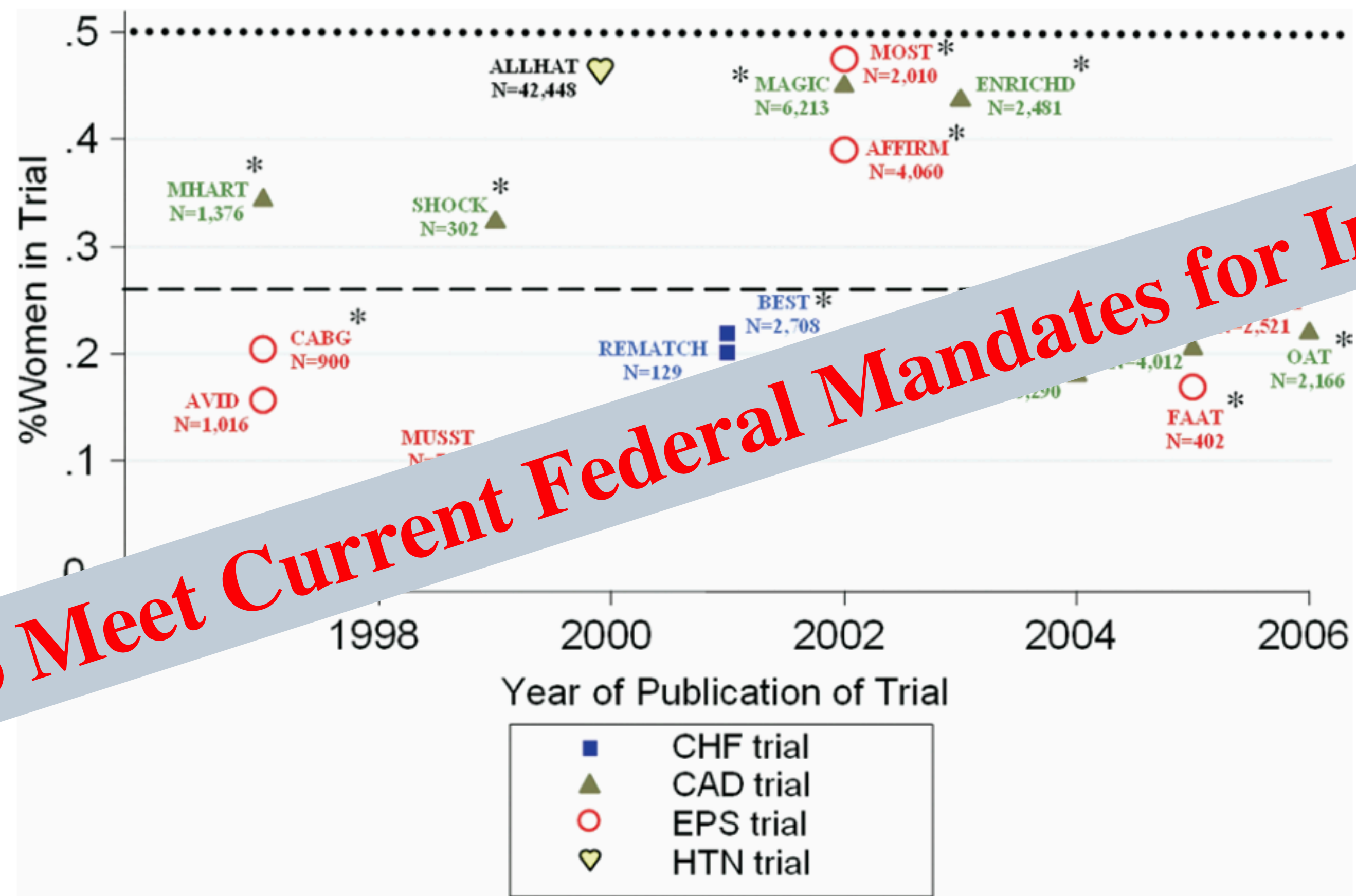
1998... new FDA regulation, "Demographic Rule"

Inclusion of women in clinical trials

The National Institute of Health
(NIH) **Revitalization Act**. 1993

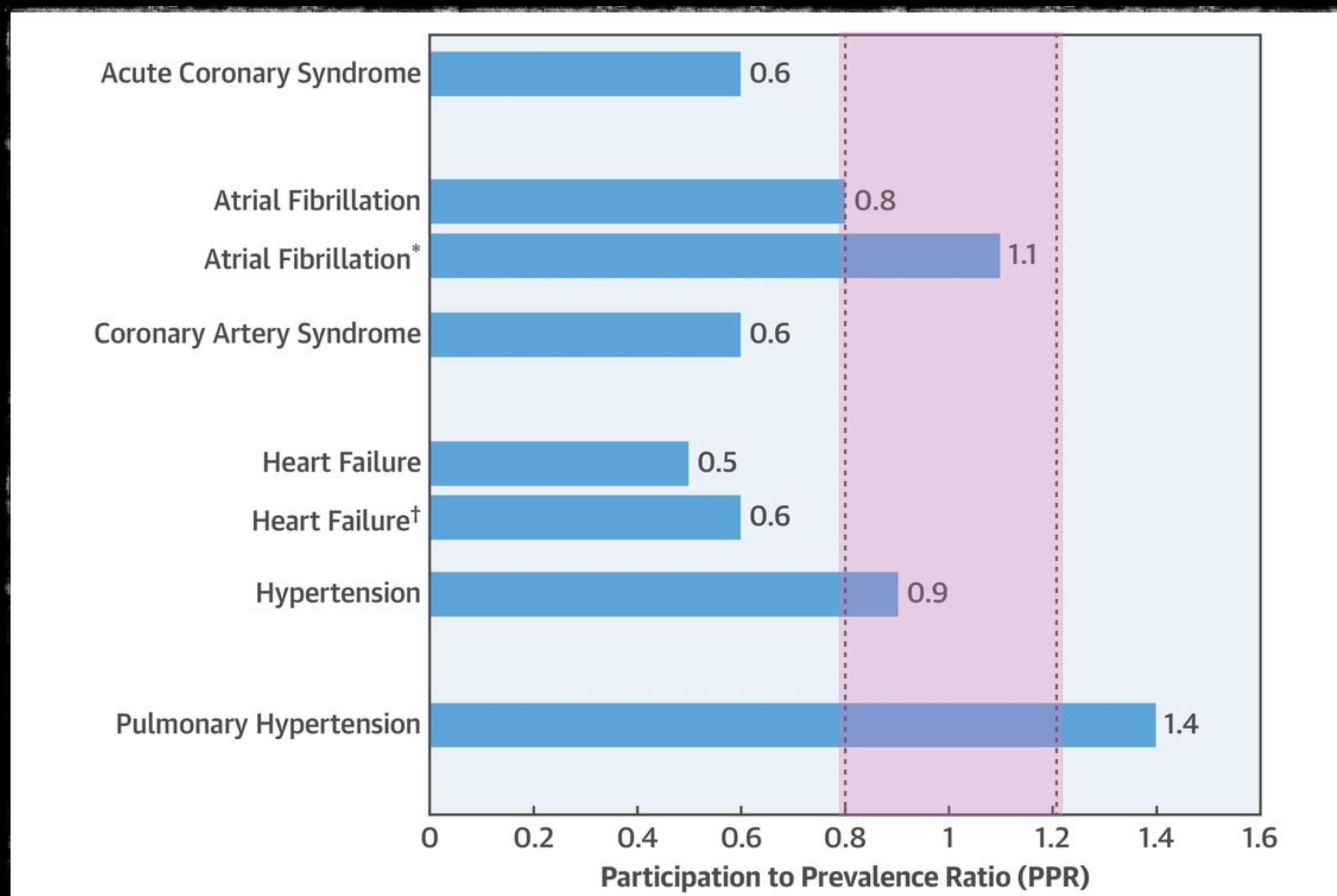
NIH policies (enroll women closer to 50%,
perform sex-based analyses) **became law!**

Enrollment of Women in NHLBI-Sponsored Phase 3 to 4 Cardiovascular Randomized Cardiovascular Trials From 1997 to 2006



Fails to Meet Current Federal Mandates for Inclusion

Participación de las mujeres en los EC farmacológicos cardiovasculares: relación participación/prevalencia (PPR)



Trials supporting 36 drug approvals from 2005 to 2015.

Public Education efforts to include women in research

“Red Dress” project
(2003, sponsored by NIH, NHLBI)

“Go red for women”
(2004, sponsored by AHA)

Sex-Specific Reporting of Scientific Research

- ✦ Identifying the sex of populations in journal populations
- ✦ Sharing of sex-identified raw data
- ✦ Giving “extra credit” in review to manuscripts that include sex-specific information
- ✦ Requiring sex-stratified analyses where applicable

*“Sex-specific medicine is just a form
of precision medicine, after all”*

– Dra. V Taqueti

Muchas gracias !!

