7th Advances in Heart Failure 2024
10 e 11 de Outubro
FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

Fatores de risco não modificáveis para a IC:

Que caminho para uma abordagem personalizada e precoce?

- Género -

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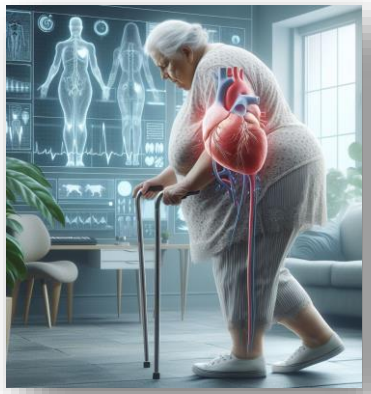
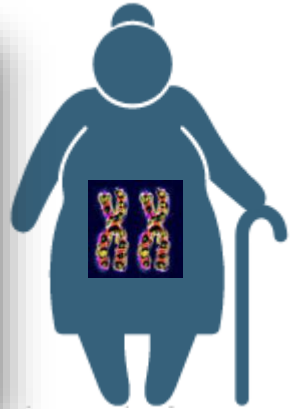
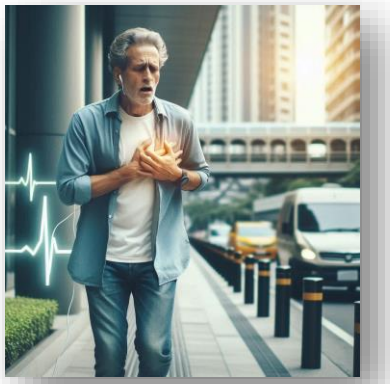
Sex & Gender differences in Heart Failure







Epidemiology

- Penetrance of genetic cardiomyopathies
- sex-specific conditions, eg peripartum cardiomyopathy

Pathophysiology

Clinical presentation

- HFrEF
- HFpEF

Response to treatments

Prognosis

Scientific knowledge

Sex & Gender differences in Heart Failure

Epidemiology

Comparable overall **lifetime risk** of HF

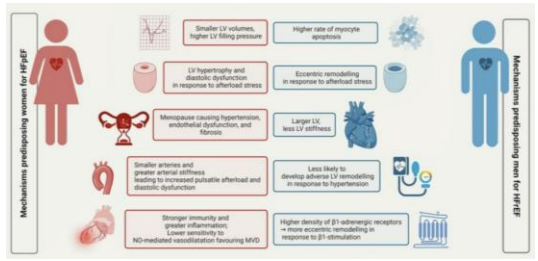
FHS: 20% vs 21% at age 40 years

Rotterdam Study: 29% vs 33% at age 55 years

Comparable **incidence** of HF

Pathophysiology

- Endothelial inflammation and coronary microvascular dysfunction
- Coronary microvascular dysfunction is present in 75% of patients with HFpEF



Clinical presentation

Considerable differences when considering

HF phenotype

Worse Symptoms in

- **HFpEF 2:1**
- HFpEF:

.obese, DM and abnormal diastology

.higher filling pressures → more prone to PH

.higher myocardial and arterial stiffness

.old and hypertensive

- **HFrEF 2 x higher risk than women**
- HFrEF - First and recurrent hospitalizations for acute HF

.HFpEF: old age + CKD + worse prognosis

NT-proBNP levels are higher in women than men across the LVEF spectrum

Sofia Cabral$_{2024}$

PROMIS-HFpEF. Eur Heart J 2018;39:3439–3450.

Sex & Gender differences in traditional risk factors for heart failure

Hypertension

- HF risk 3x in ♀ vs 2x in ♂
- more concentric remodeling in ♀

Tobacco Smoking

NHANES I

- independent association with an 88% higher risk of HF in ♀ vs 45% higher risk in ♂

Socio-economic status

Socioeconomic status is a powerful independent predictor of HF development and adverse outcomes: in the highest Gini index countries more prone to HF and worse prognosis

- Low income
- Low education level
- Lack of social support/social isolation

Genetics

- more severely affected in genetic cardiomyopathies ♂
- sex-specific phenotypes in X-linked mutations

Obesity

- ♀ more likely to develop HFpEF compared to HFrEF if obese or insulin resistant

Excess adipose tissue:

- Inflammation;
- enhanced pericardial constraint;
- epicardial fat-induced accelerated coronary atherosclerosis;
- Perirenal fat-associated accelerated renal dysfunction;
- adipose-derived vasoconstrictors -> capillary rarefaction and impaired tissue perfusion (myocardium, skeletal muscles)

Diabetes

- HF risk 5x in ♀ vs 2 x in ♂
- ♀ Worse and earlier adverse LV remodeling

Sistemic inflammation

Gender

Gender determines
. help-seeking behavior
. access to healthcare
. individual use of the healthcare system
. Referral to GMDT, devices, advanced HF therapies and end of life care

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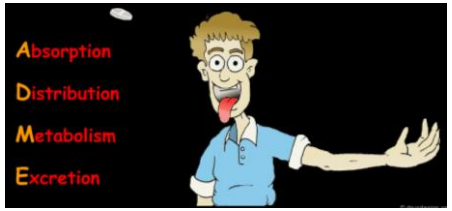
Sex & Gender differences in Heart Failure

Response to Pharmacological treatments

Different responses

Pharmacokinetics:

- Similar doses of **ACEIs**, **ARBs** and **BB** lead to the maximum dose plasma concentrations **2,5 higher** in



- ***lower weight and height***
- ***higher proportion of body fat***
- ***lower peripheral distribution volume***
- ***lower glomerular and hepatic filtration rate decrease drug clearance***
- **Different drug metabolism (Cytochrome P450 isoenzymes)**

Pharmacodynamic

- Similar doses of **BB** cause slower HR and lower blood pressure

Side effects:

- Experience up to twice the rate of adverse events from HF medications
- DIG trial - significantly higher risk of death (Adjusted HR 1,23)

N Engl J Med 2002;347:1403-1411

- Low-ceiling diuretics (thiazides) RR of adverse effects 4,02

*J. Clin. Pharmacol. **2012**, 74, 1045–1052*

Dose effect of GDMT:

Need for different sex-based dose targets in HFrEF

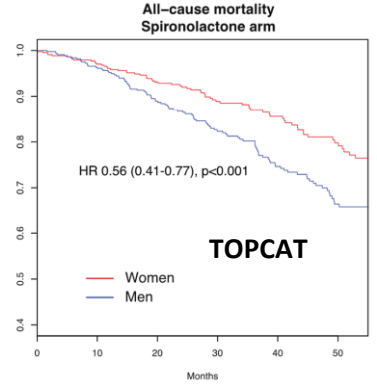
HFrEF

- highest risk reduction with 50-60% of **BB** traditional target dose
- highest risk reduction with 40-60% of **ACEI/ARB** traditional target dose

ATLAS (lisinopril high vs low dose)
HEAAL (losartan high vs low dose)
BIOSTAT-CHF

- progressive risk reduction with up-titration to target dose

sex-specific benefit of MRAs?

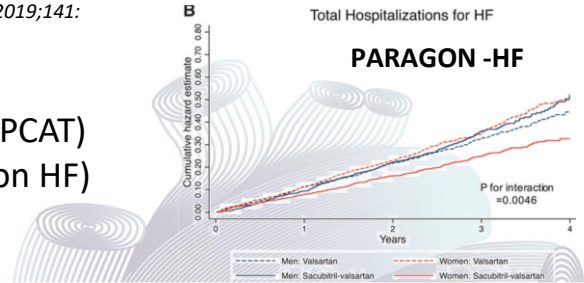


HFpEF

- benefit of RAS across ejection fraction spectrum ($TOPCAT_{American\ cohort}$) post-hoc, exploratory subgroup analysis
- greater benefit of ARNi in women (27% risk reduction CV death and HFH) (Paragon HF)

(pre-specified subgroup analysis)

Circulation 2019;141:



- benefit of RAS only at lower EF (TOPCAT)
- no risk reduction with ARNi (Paragon HF)

Sex & Gender differences in Heart Failure

Response to Cardiac Devices

ICD

Effectiveness of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death in women with advanced heart failure: a meta-analysis of randomized controlled trials

Hamid Ghanbari [1], Ghassan Dalloul, Reema Hasan, Marcos Daccarett, Souheil Saba, Shukri David, Christian Machado

DEFINITE
DINAMIT
MUSTT
MADIT-II
SCD-HeFT

Arch Inter Med; 2009;169(16):1500-6

Implantable cardioverter-defibrillator therapy for the **primary prevention** of sudden cardiac death in women **does not** reduce all-cause mortality.

22% reduction in mortality among men

Sex Differences in Outcomes of Patients with an Implantable Cardioverter-Defibrillator for the Secondary Prevention of Sudden Cardiac Death

Alwin B P Noordman [1], Michiel Rienstra [1], Yuri Blaauw [1], Bart A Mulder [1], Alexander H Maass [1]

J Cardiovasc Dev Dis 2024; 11(4): 116

Women with **secondary prevention** ICDs were **less likely** than men to receive appropriate ICD therapy (anti-tachycardia pacing therapy and ICD shocks).

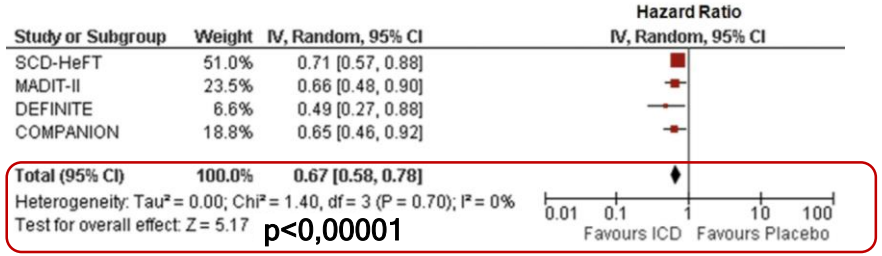
less myocardial scar tissue and a lower rate of ventricular arrhythmias resulting in sudden cardiac death

Gender differences in clinical outcome and primary prevention defibrillator benefit in patients with severe left ventricular dysfunction: a systematic review and meta-analysis

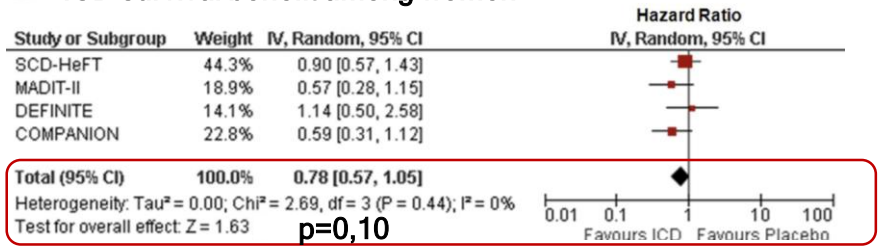
Pasquale Santangeli [1], Gemma Pelargonio, Antonio Dello Russo, Michela Casella, Caterina Bisceglia, Stefano Bartoletti, Pietro Santarelli, Luigi Di Biase, Andrea Natale

Heart Rhythm 2010; 7: 876-82

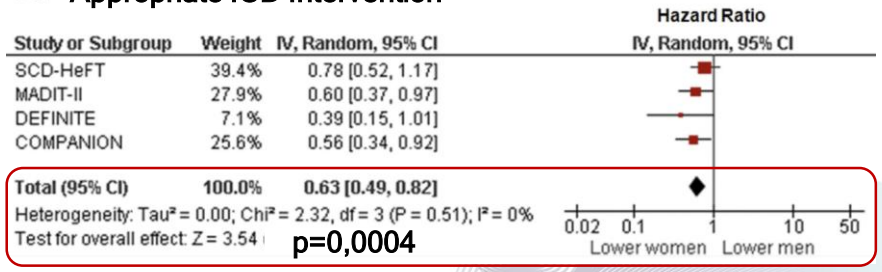
A. ICD survival benefit among men



B. ICD survival benefit among women



B. Appropriate ICD Intervention



Sex & Gender differences in Heart Failure

Response to Cardiac Devices

CRT

Under use of devices in CRT and ICD

Adjusted to age and comorbidities

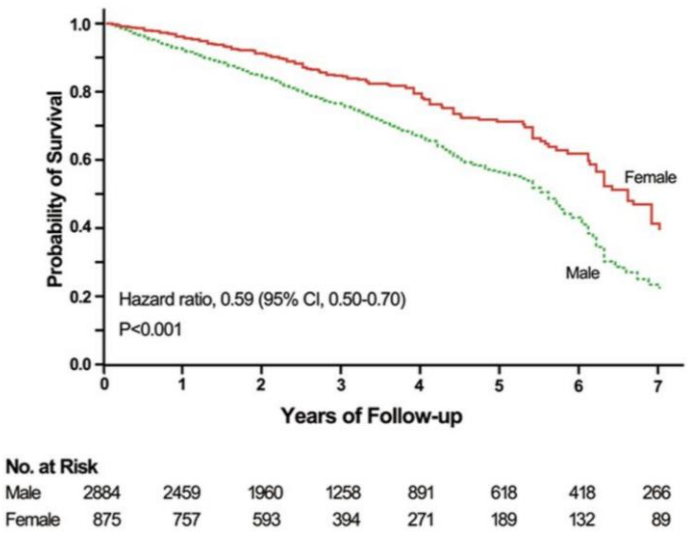
Swedish HF Registry: 26% less likely to receive defibrillator or cardiac resynchronization therapy

More Favorable Response to Cardiac Resynchronization Therapy in Women Than in Men

Meta analysis of 33 434 patients from 72 studies

Yun-Jiu Cheng, MD, Jing Zhang, MD, Wei-Jie Li, MD, Xiao-Xiong Lin, MD, Wu-Tao Zeng, MD, PhD, Kai Tang, MD, PhD, An-li Tang, MD

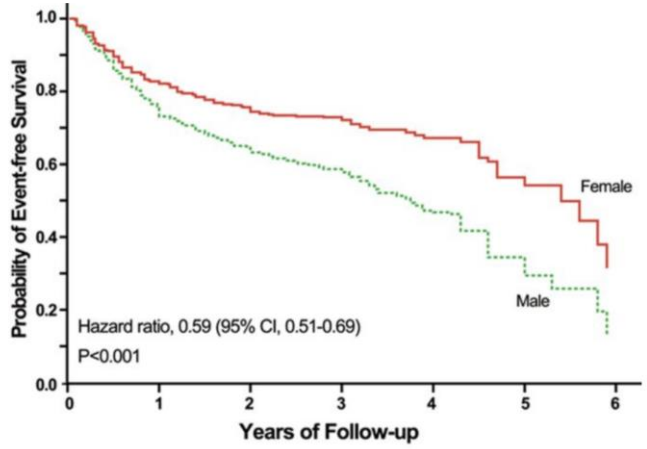
Death from any cause



No. at Risk

Male	2884	2459	1960	1258	891	618	418	266
Female	875	757	593	394	271	189	132	89

Death or Hospitalization for Heart Failure



No. at Risk

Male	2138	1498	952	649	334	223	169
Female	660	495	336	213	107	75	53

Changes in Echocardiographic and Clinical Parameters Between Baseline and Long-Term Follow-up for Cardiac Resynchronization -Treated Patients by Sex from 6 studies

	Women (n=1063)	Men (n=2452)	*P* Value
Echocardiographic parameters			
ΔLVEDV	−22.68±12.70	−10.88±7.24	<0.001
ΔLVESV	−24.79±9.73	−13.47±6.69	<0.001
ΔLVEF	9.42±8.60	7.64±8.32	<0.001
Clinical parameters			
ΔNYHA	−0.96±0.59	−0.95±0.65	0.51
ΔQoL	−16.65±15.23	−15.25±13.43	0.12
ΔWCT	87.35±62.47	78.69±56.60	0.37

Women had better outcomes from CRT compared with men - compared with men, women had about a 33% reduction in the risk of death from any cause and 20% reduction in the risk of death or HF

Women achieved greater reduction in LV volumes and improvement in LVEF compared with men after CRT therapy

Benefit at lower QRS duration

Circulation Arrhythmia and Eletrophysiology 2014
https://doi.org/10.1161/CIRCEP.113.00178

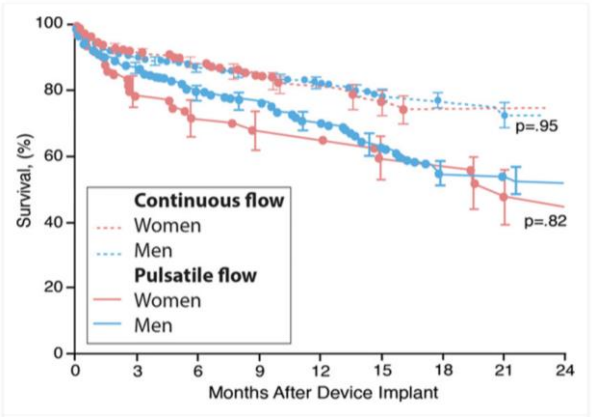
Sex Differences in Advanced Heart Failure Therapies

Non-pharmacological therapies

~80 % of VADs implants in ♂

- No sex differences in efficacy or mortality
- No sex differences in time to first device malfunction, bleeding, or infection
- Higher stroke rates in women

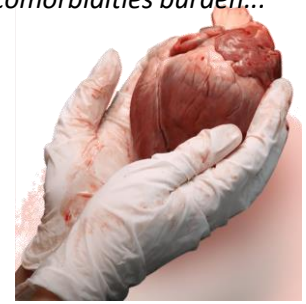
HeartMate 3 have no sex-related difference in stroke risk



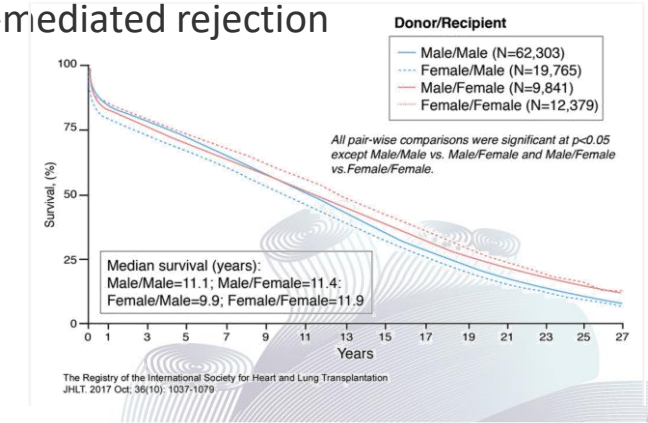
Circulation 2019;39(8):1080-1093

Possible explanations: older age, comorbidities burden...

~21 % of Heart Transplants occur in ♀



- worse prognosis in transplant waiting list (lower rates of mechanical circulatory support despite similar INTERMACS status)
- better long-term survival
- lower risk of coronary allograft vasculopathy
- lower risk of malignancy
- higher risk of antibody-mediated rejection



Sex differences in Heart Failure

PROMs:

Prognosis

much lower quality of life (QoL)*
more than 10-point median difference in KCCQ score
The additional years of life are of poorer quality

Am J Crit Care. (2002) 11:211-9 **Circ Heart Fail 2019;12:e006539*

much higher rates of anxiety and depression

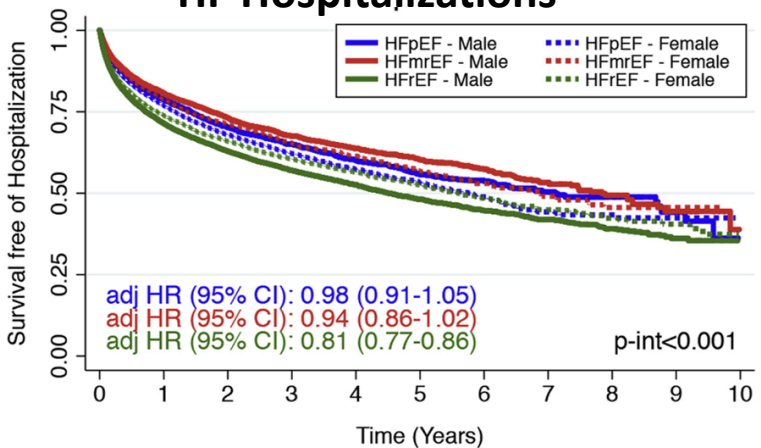
Am Coll Cardiol. (2004) 43:1542-9

Hospitalizations:

HFpEF and HFmEF: similar adjusted rates of hospital admissions

HFrEF: Lower risk of CV and HFH

HF Hospitalizations



Sex-Based Differences in HeartFailure Across the Ejection Fraction Spectrum: Phenotyping, and Prognostic and Therapeutic Implications

42,987 patients Swede HF Registry

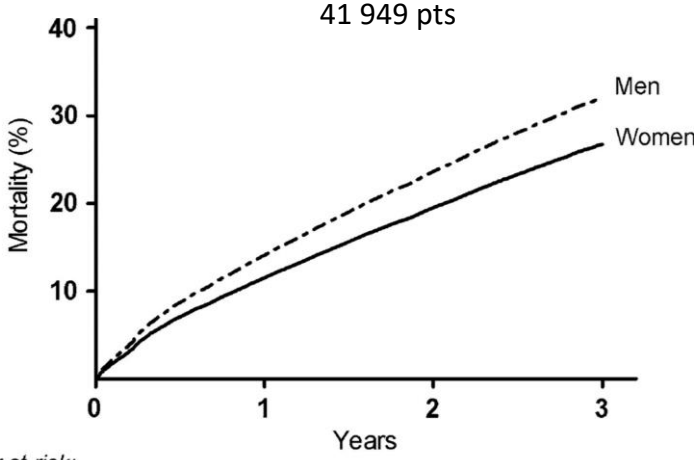
JACC Heart Failure 2019;7:505-515

Survival is better for women with heart failure compared with men, irrespective of EF

Adjusted lower risk of all-cause death and CV mortality

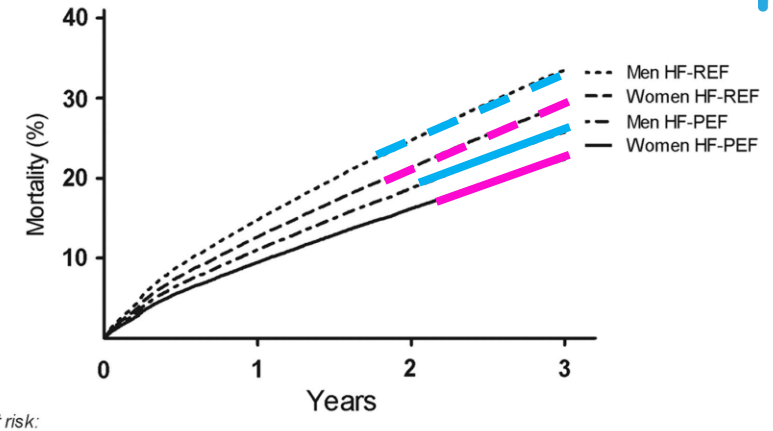
MAGGIC individual patient **meta-analysis**

41 949 pts



Number at risk:

Men	26881	19662	15515	11538
Women	13309	9429	7778	5800



Number at risk:

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

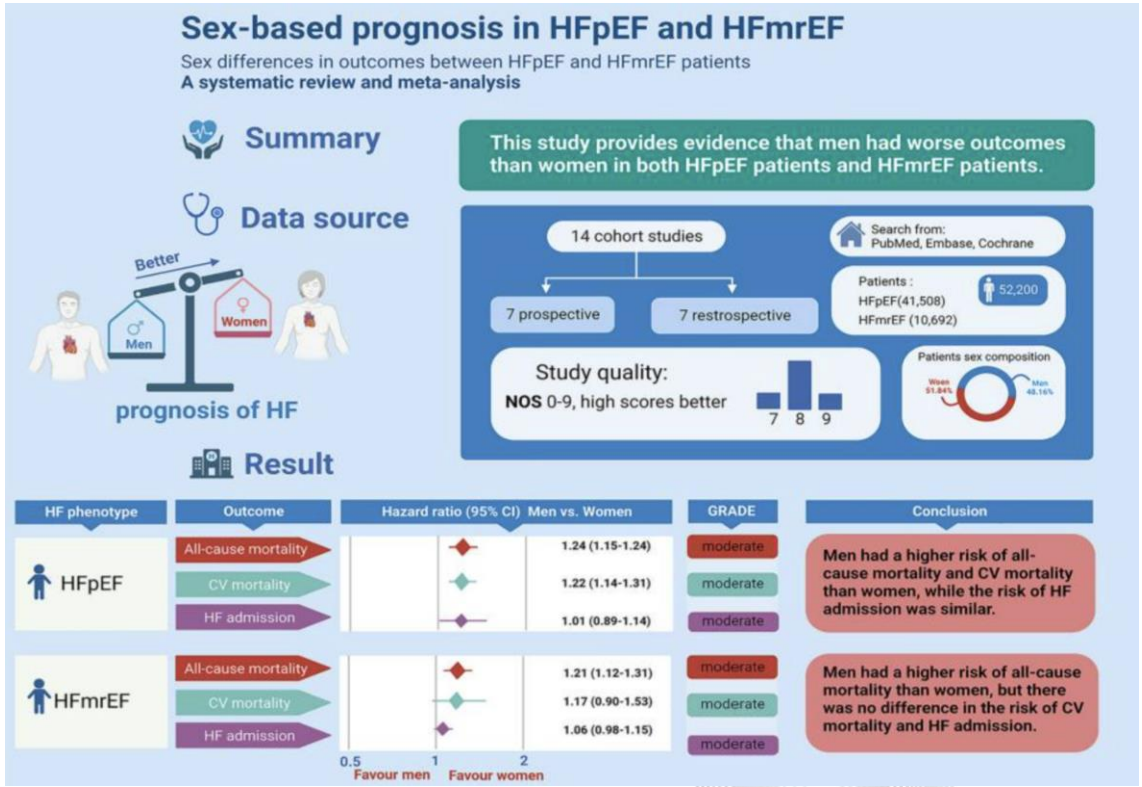
Eur J Heart Fail 2012;14:473-9

Sudden death*

Advanced HF

Sex differences in mortality and hospitalization in heart failure with preserved and mid-range ejection fraction: a systematic review and **meta-analysis** of cohort studies

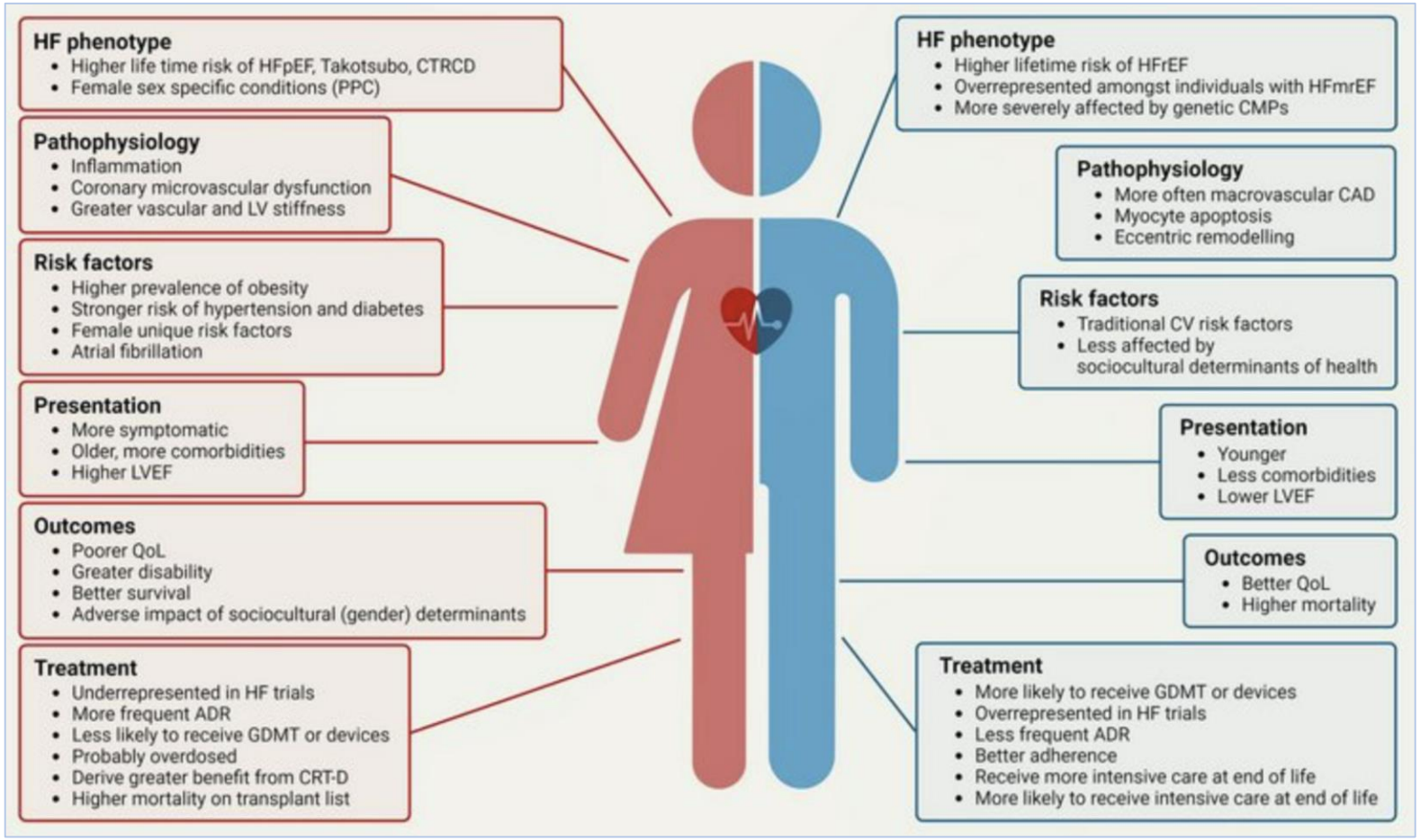
41,508 HFpEF patients (44.65% males)
10,692 HFmrEF patients (61.79% males)



Front Cardiovasc Med 2023;10:1257335

**Circ Heart Fail 2019;12:*e006539

Take Home Messages



- Distinctive epidemiological features
- Sex-related pathophysiology
- Different responses to treatments (doses, effects, adverse reactions, benefit)
- Referral inequities
- Biological determinism but also gender dependency
- Similar **Hospitalizations** but different **Survival** (men worse)
- Underrepresentation of women in clinical trials→ weaker evidence

Obrigada!

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Sofia Cabral 2024