SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

Roma, 30 novembre – 3 dicembre 2022
Università Cattolica Sacro Cuore

L'insufficienza cardiaca nell'anziano

Le nuove terapie dello scompenso nell'anziano: il ruolo del genere nel successo-insuccesso terapeutico

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Università di Napoli Federico II

THE LANCET

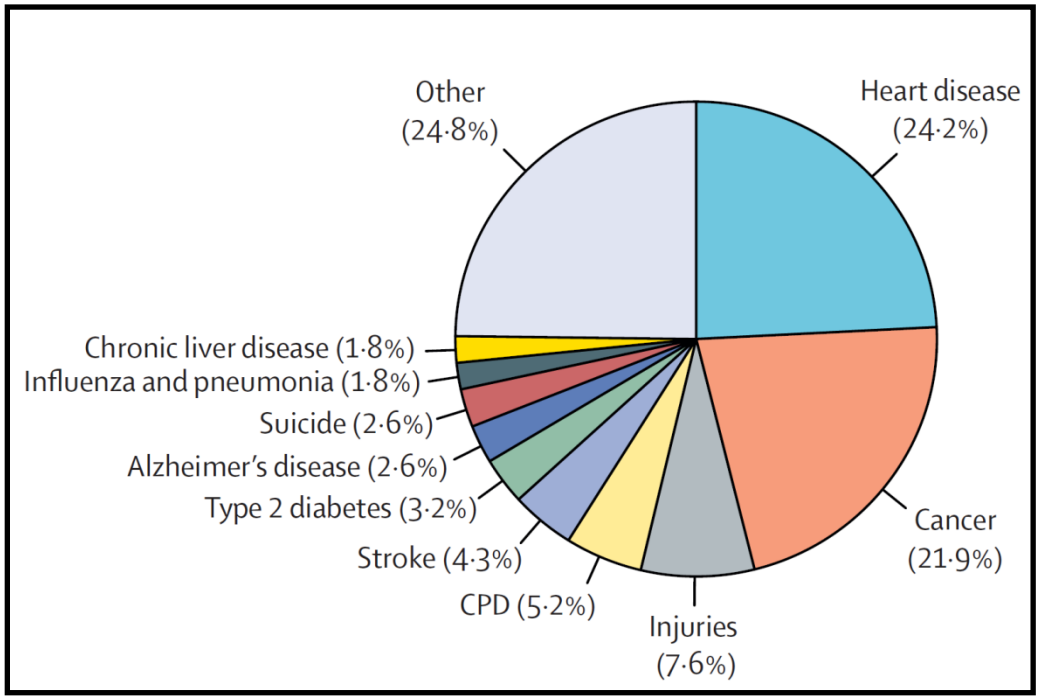
The Lancet Commissions

The *Lancet* women and cardiovascular disease Commission: reducing the global burden by 2030

Birgit Vogel, Monica Acevedo, Yolande Appelman, C Noel Bairey Merz, Alaide Chieffo, Gemma A Figtree, Mayra Guerrero, Vijay Kunadian, Carolyn S P Lam, Angela H E M Maas, Anastasia S Mihailidou, Agnieszka Olszanecka, Jeanne E Poole, Clara Saldarriaga, Jacqueline Saw, Liesl Zühlke, Roxana Mehran

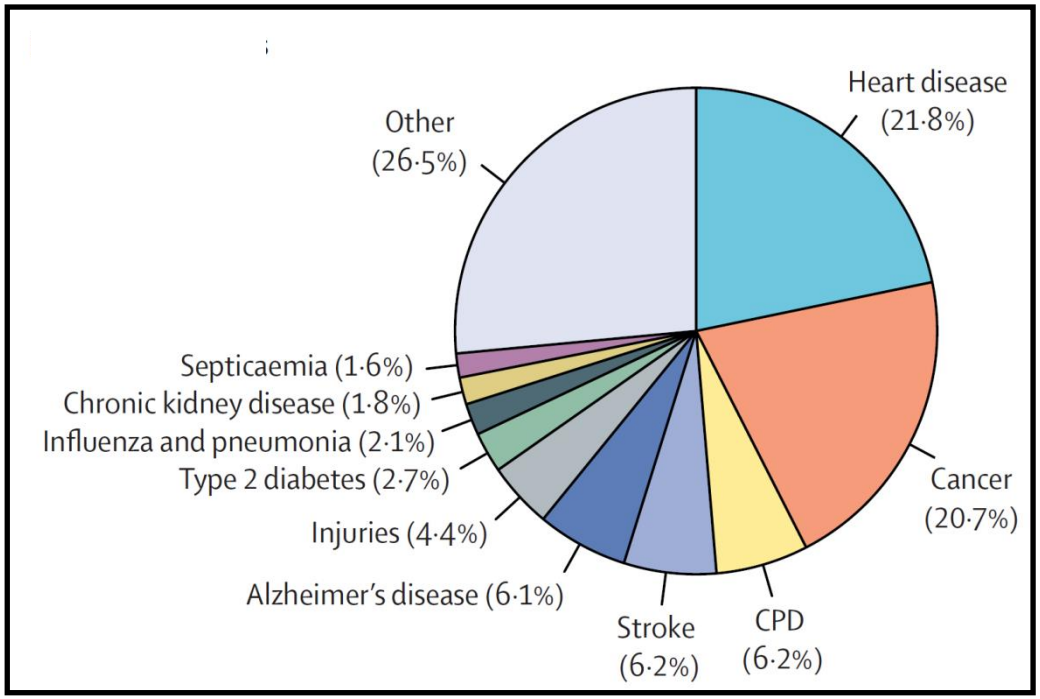
Percent distribution of the ten leading causes of death, by sex: USA, 2017

males



Heart disease 24.2%

females



Heart disease 21.8%

Mauvais-Jarvis M et al., Lancet 2020

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- **Gender and heart failure**
- **Gender and drugs used in Heart Failure (HF)**
- **Under-representation of females in HF trials**
- **Gender and HF with *reduced* Ejection Fraction(HFrEF)**
- **Gender and HF with *preserved* Ejection Fraction (HFpEF)**
- **Conclusions**

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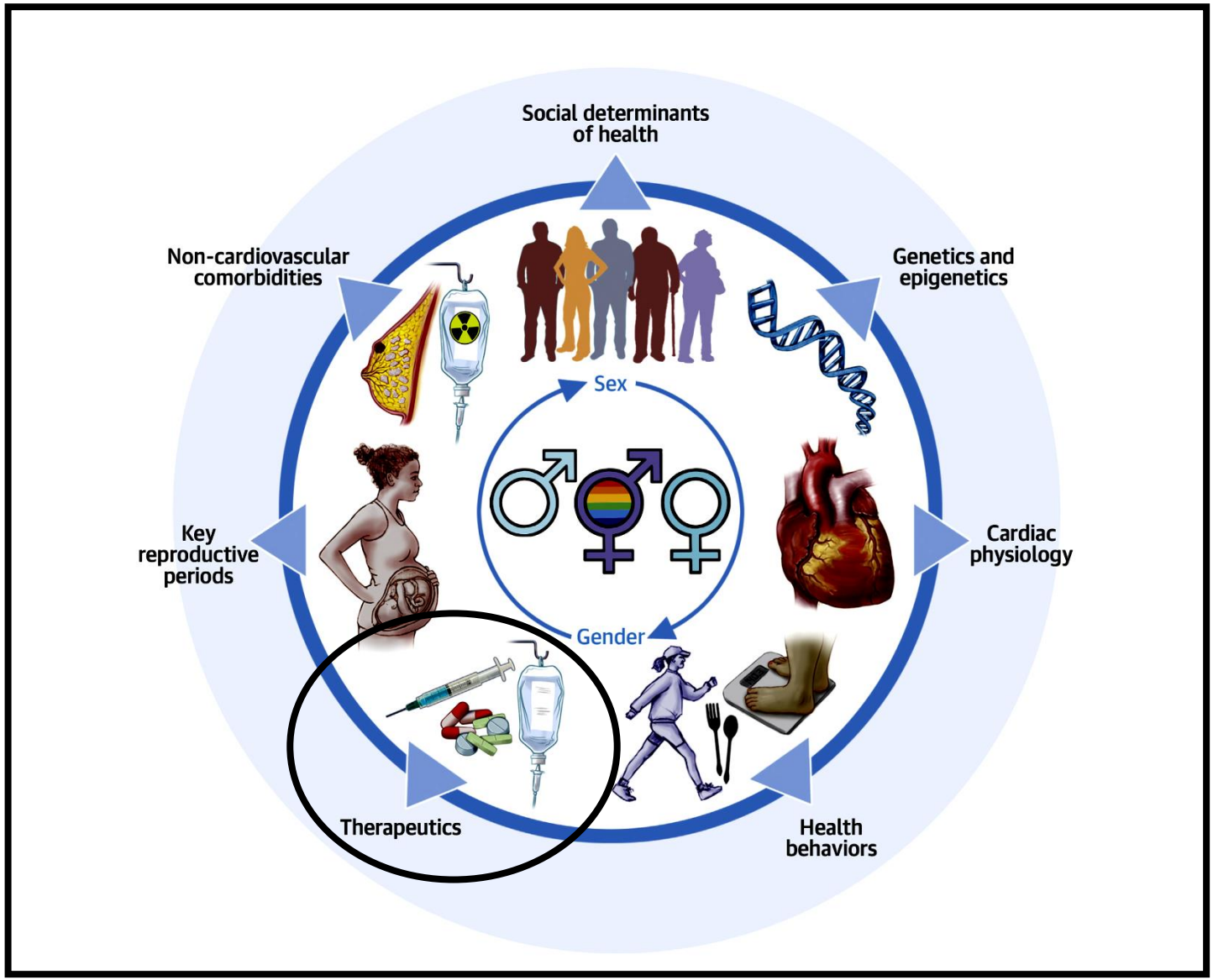
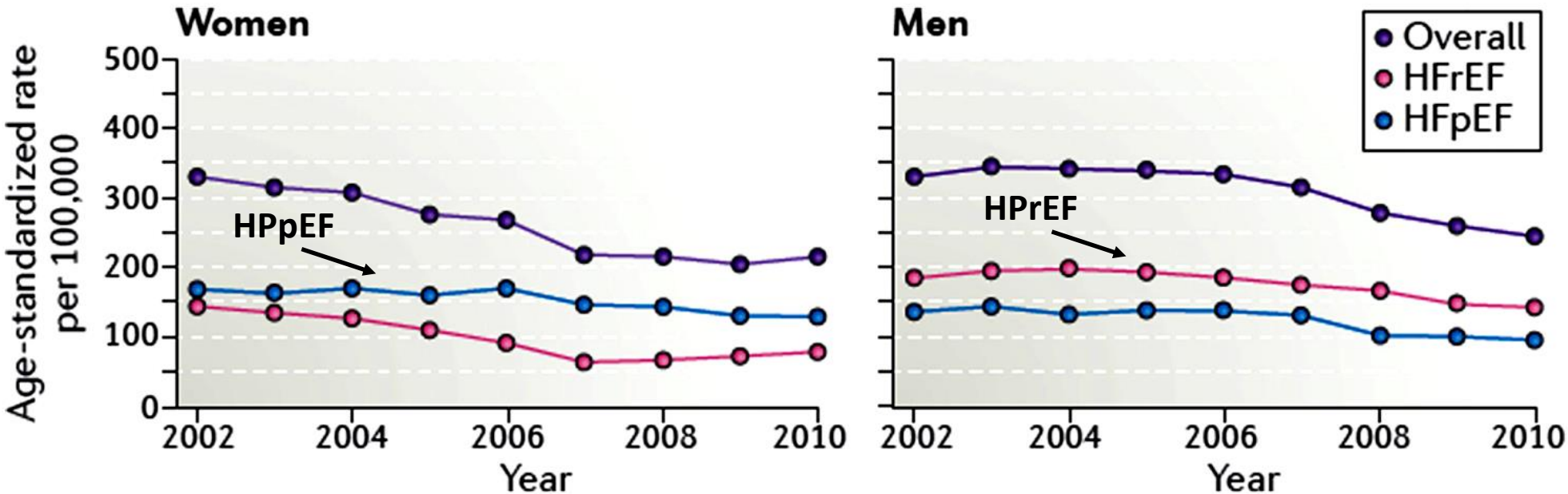
Intersection of Sex and Gender in Heart Failure



Khan SS et al, JACC 2022

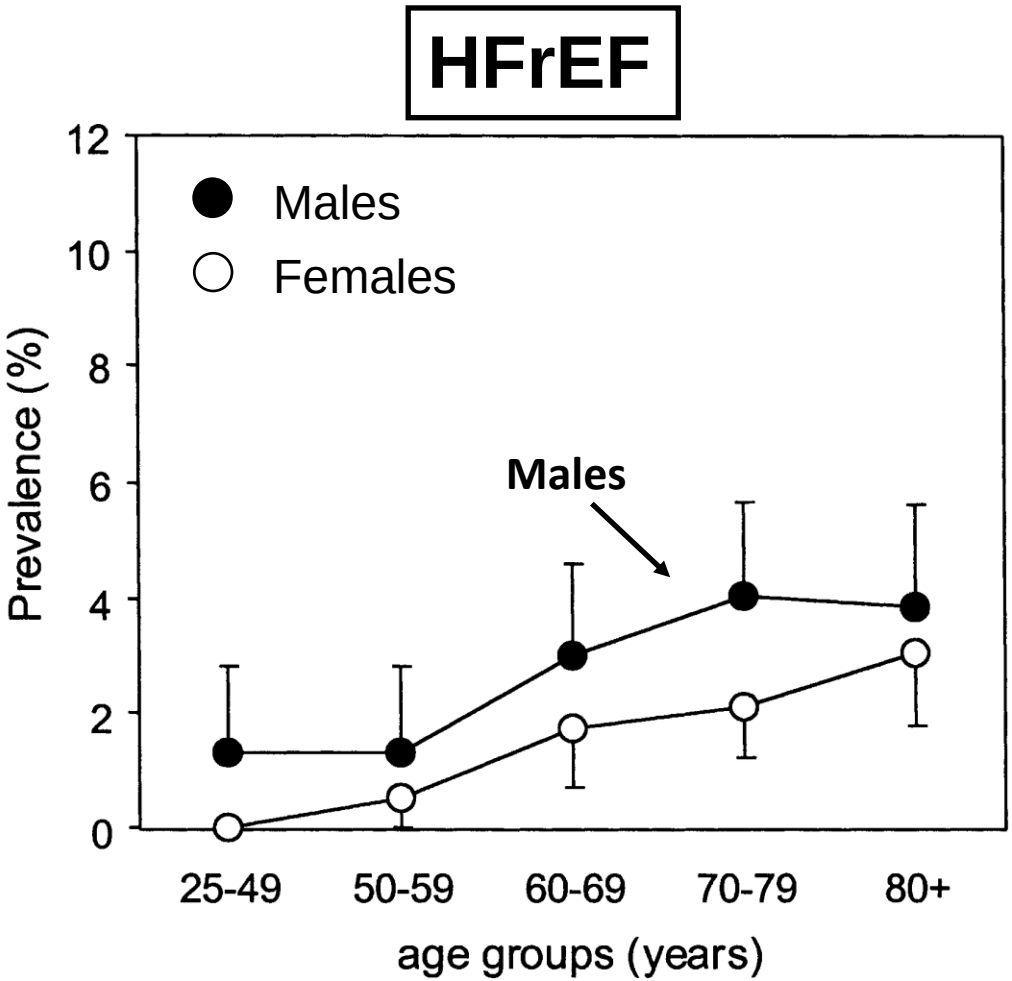
Incidence of Heart Failure with *reduced* (HFrEF) and *preserved* Ejection Fraction (HFpEF) "Olmsted County"

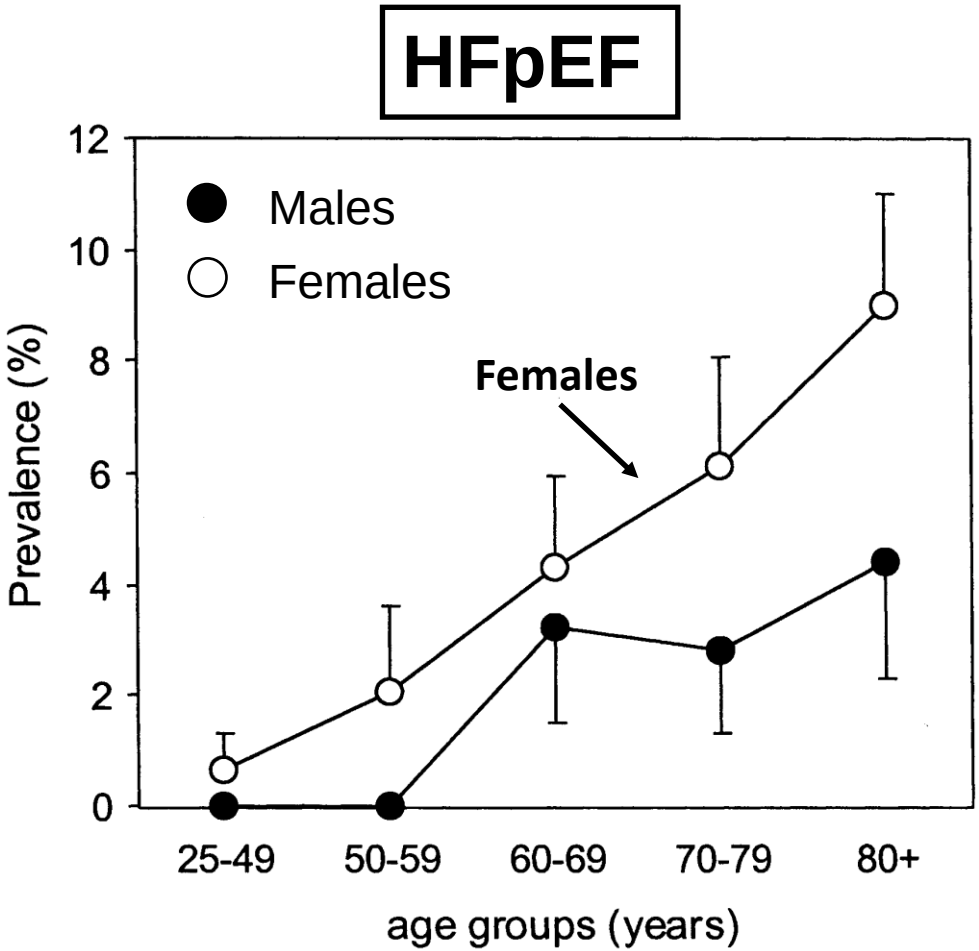


Gerber, Y. et al. , JAMA Intern. Med. 2015

Age- and gender prevalence rates of Heart Failure with *reduced* (HFrEF) and *preserved* Ejection Fraction (HFpEF)

The EPICA study

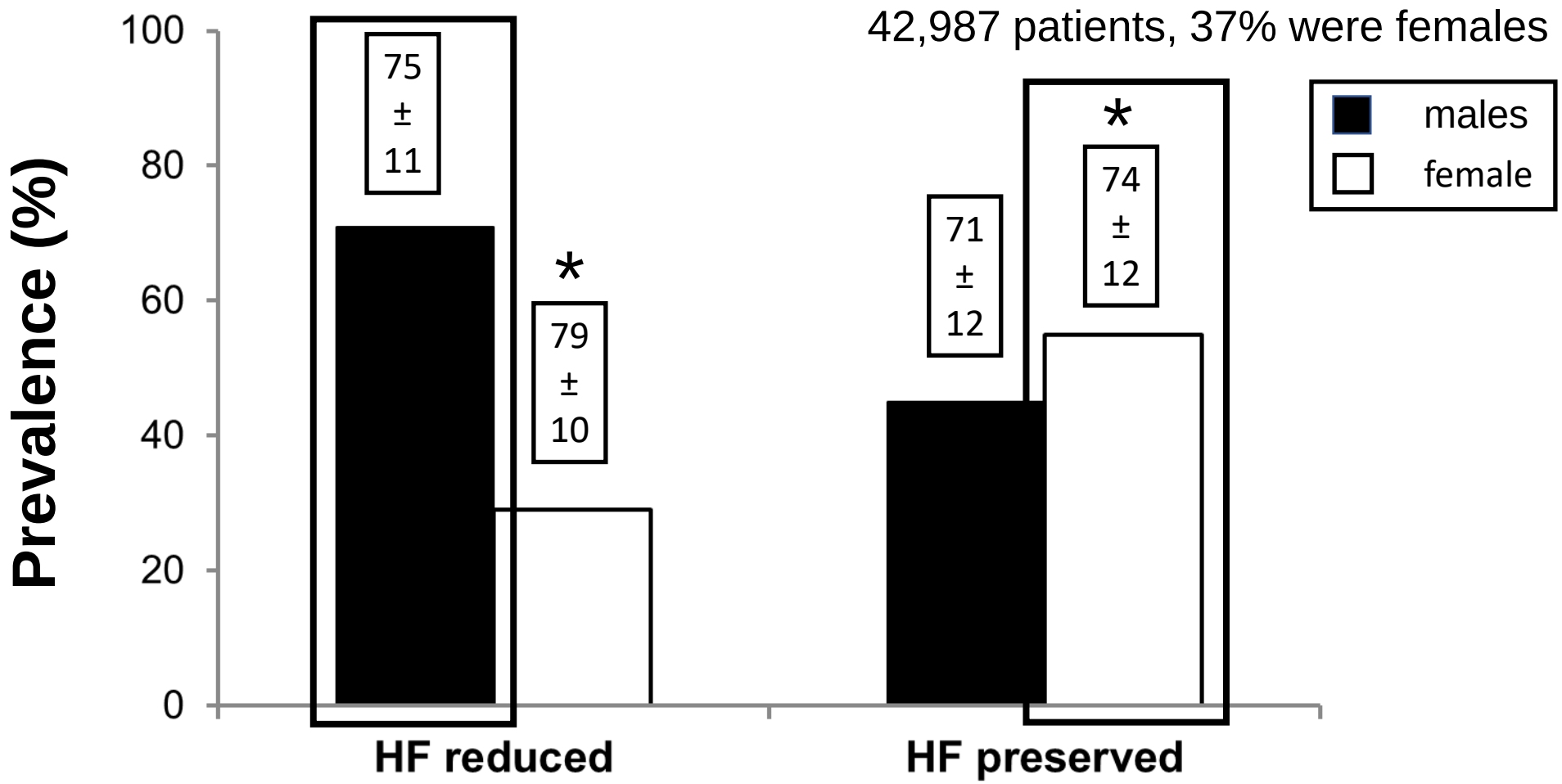




Ceia F et a., Eur J Heart Fail , 2002

Baseline Characteristics According to Age, Sex and Heart Failure Phenotype

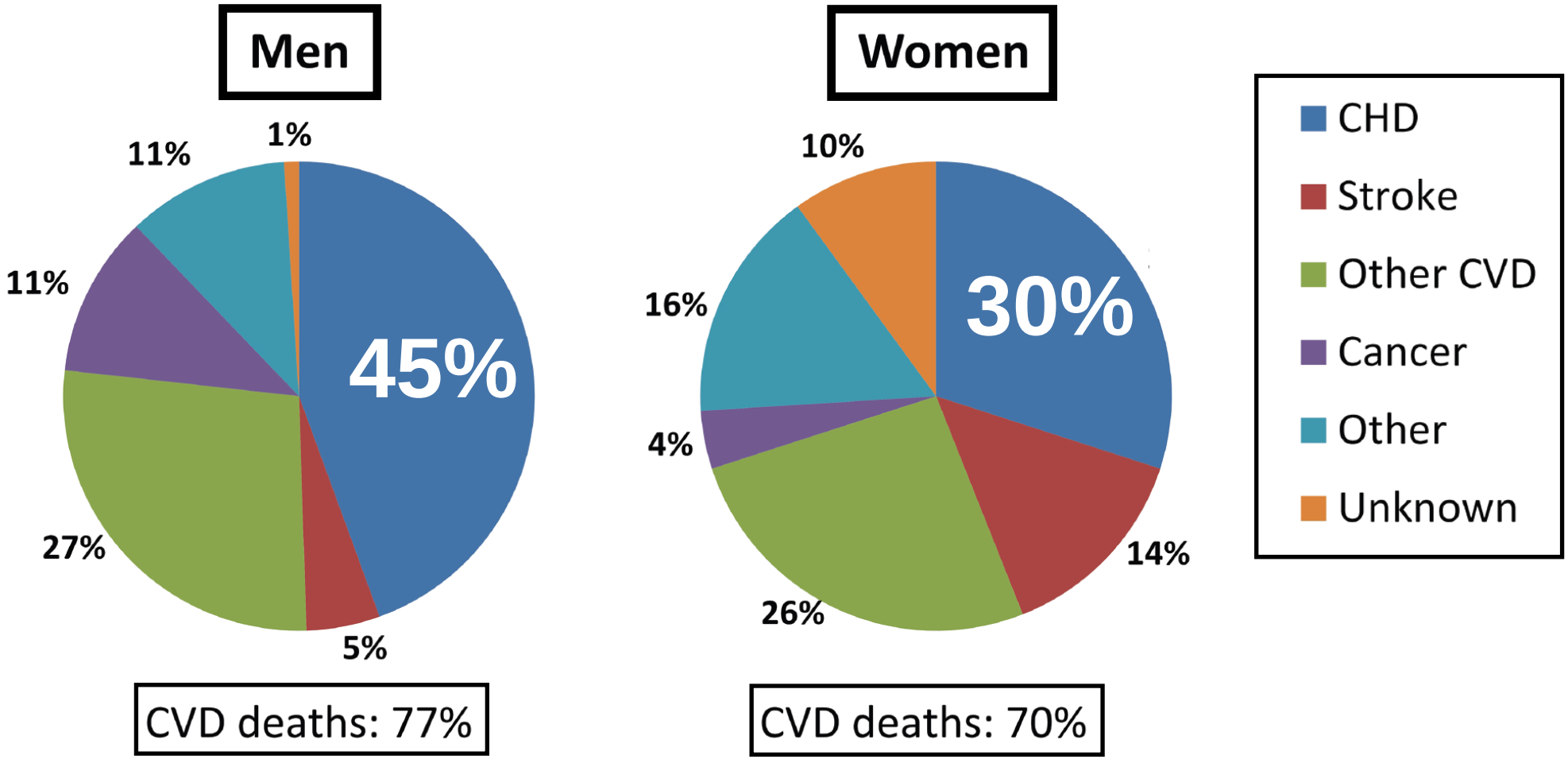
Swedish Heart Failure Registry



* p<0.001 vs male

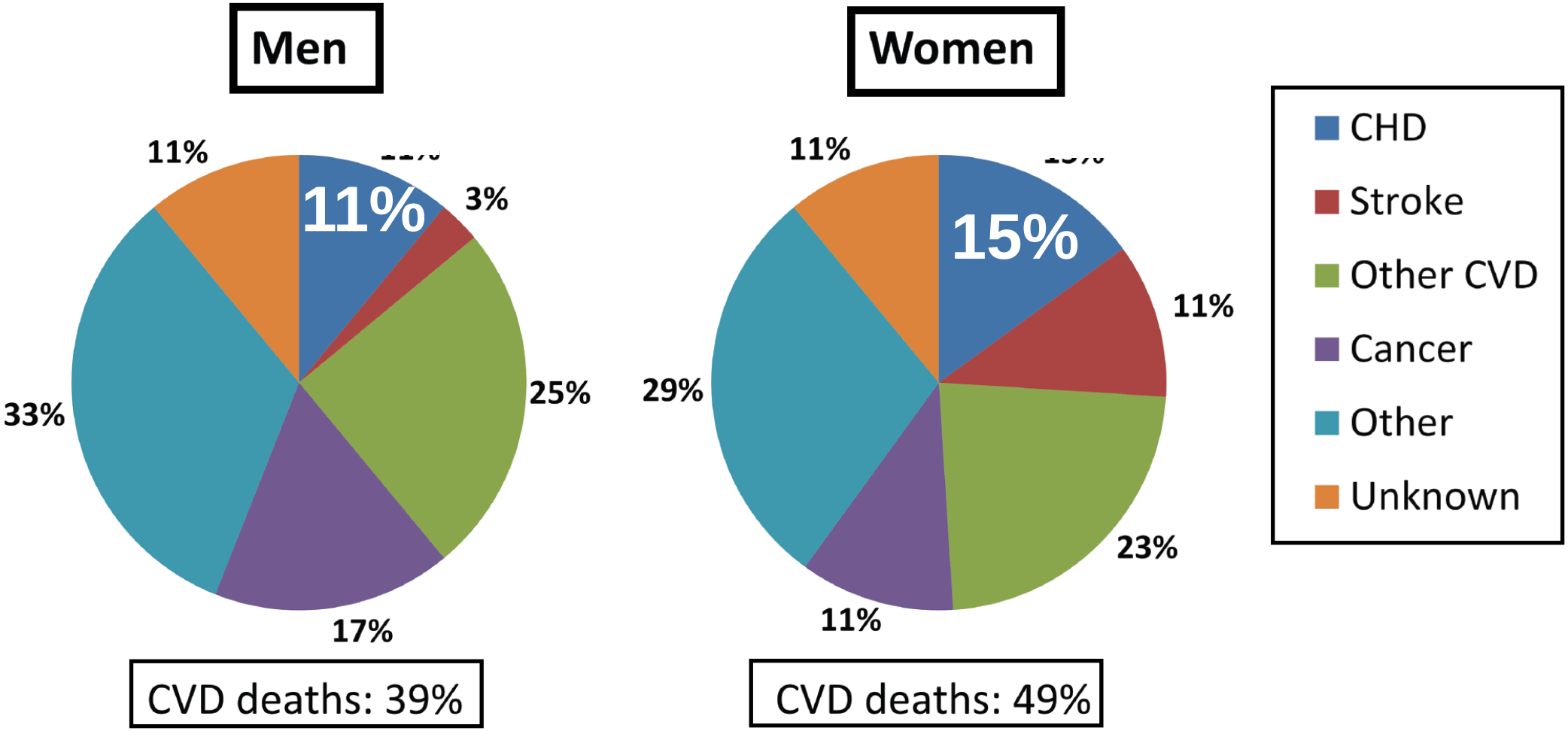
Stolfo D et al. JACC 2019

Underlying causes of death by gender and *reduced* left ventricular Ejection Fraction
Framingham Heart Study



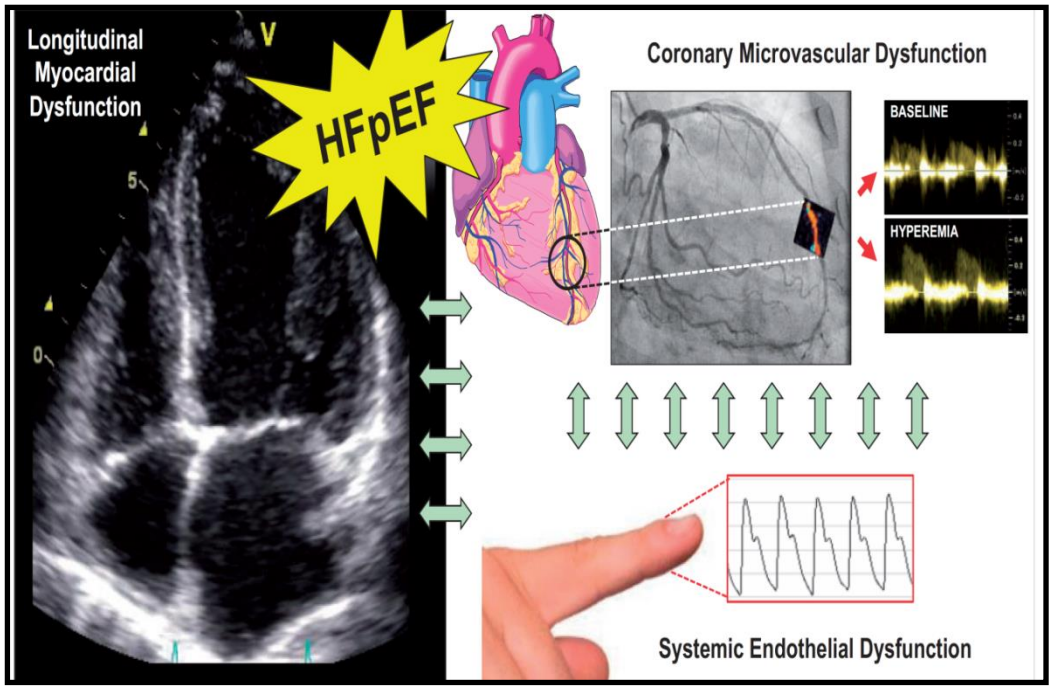
Groenewegen A et al, Eur J Heart Fail 2020

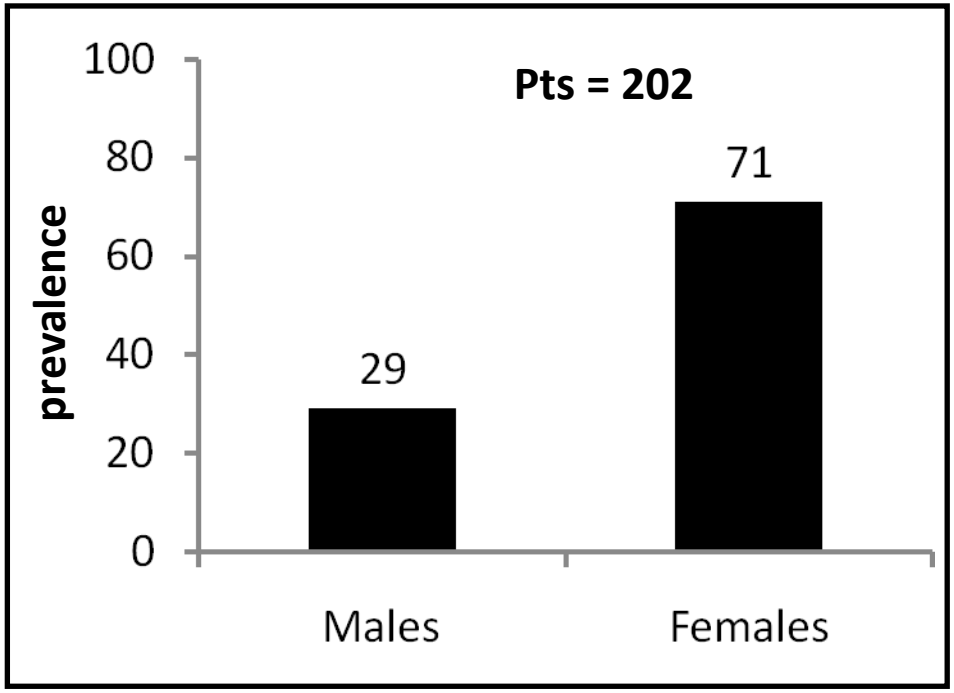
Underlying causes of death by gender and *preserved* left ventricular Ejection Fraction Framingham Heart Study



Groenewegen A et al, Eur J Heart Fail 2020

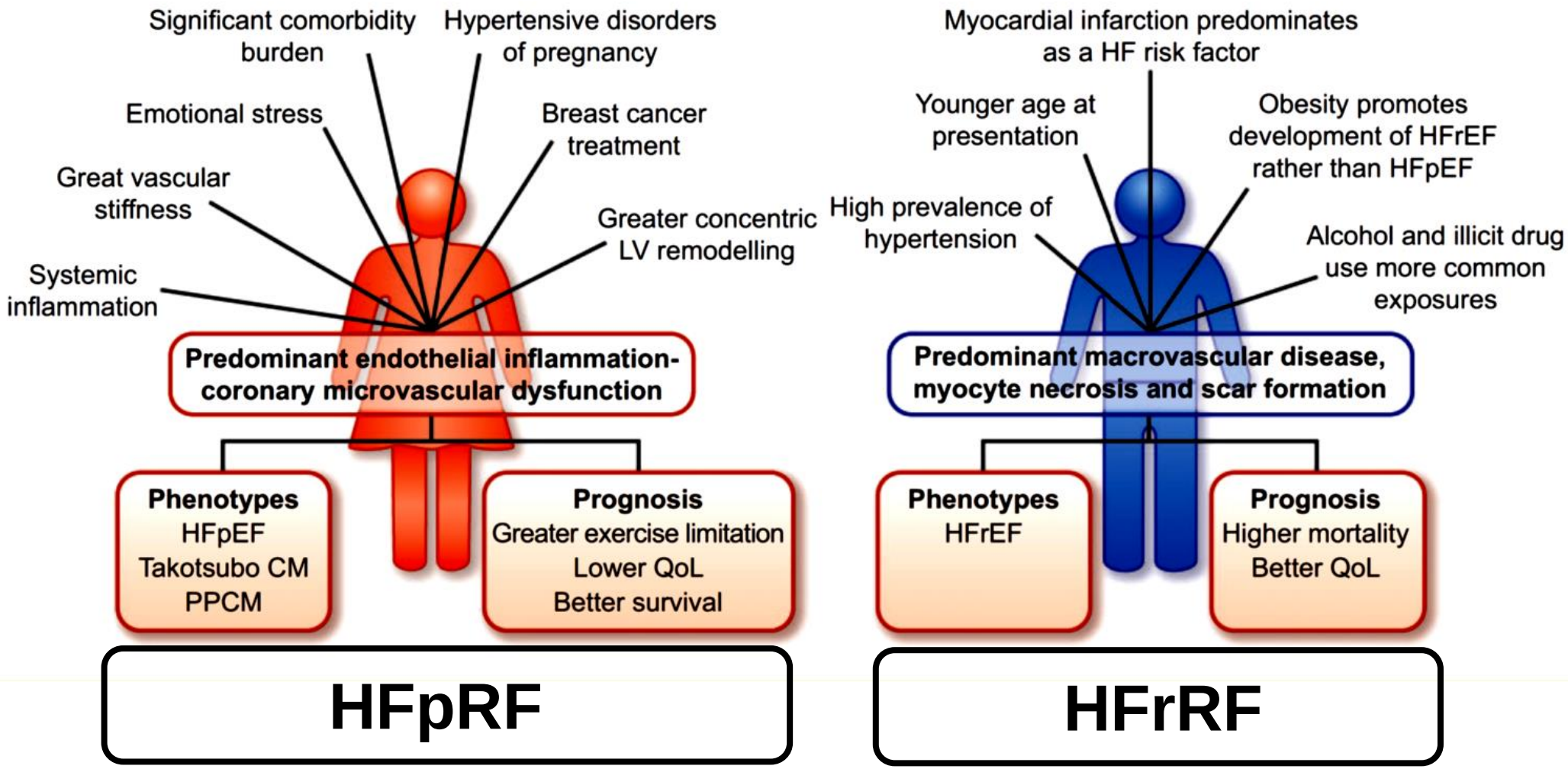
Coronary microvascular dysfunction in Heart Failure with *preserved* Ejection Fraction (HFpEF) PROMIS-HFpEF





Shah SJ et L., Eur Hear J 2018

Sex differences in heart failure



CM=cardiomipathy
PPCM=peripartum cardiomyopathy

Lam CSP et al., Eur Heart J 2019

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Differences in pharmacokinetic and pharmacodynamic in male and female are summarized.

Sex difference	Hormonal influence	
CYP1A2	Female > Male	Inhibited by oral contraceptives
CYP 2A6, CYP2B6	Female > Male	Induced by estrogens / oral contraceptives
CYP 3A4	Female > Male	Induced by testosterone / progesterone

- Estrogen dependent reduction of renin angiotensin system activity
- Adverse reaction to ACE-inhibitors in female (cough)
- Estrogen dependent expression of Beta-1 adrenergic receptors

Pharmacodynamic

- Estrogen dependent reduction of renin angiotensin system activity
- Adverse reaction to ACE-inhibitors in female (cough)
- Estrogen dependent expression of Beta-1 adrenergic receptors

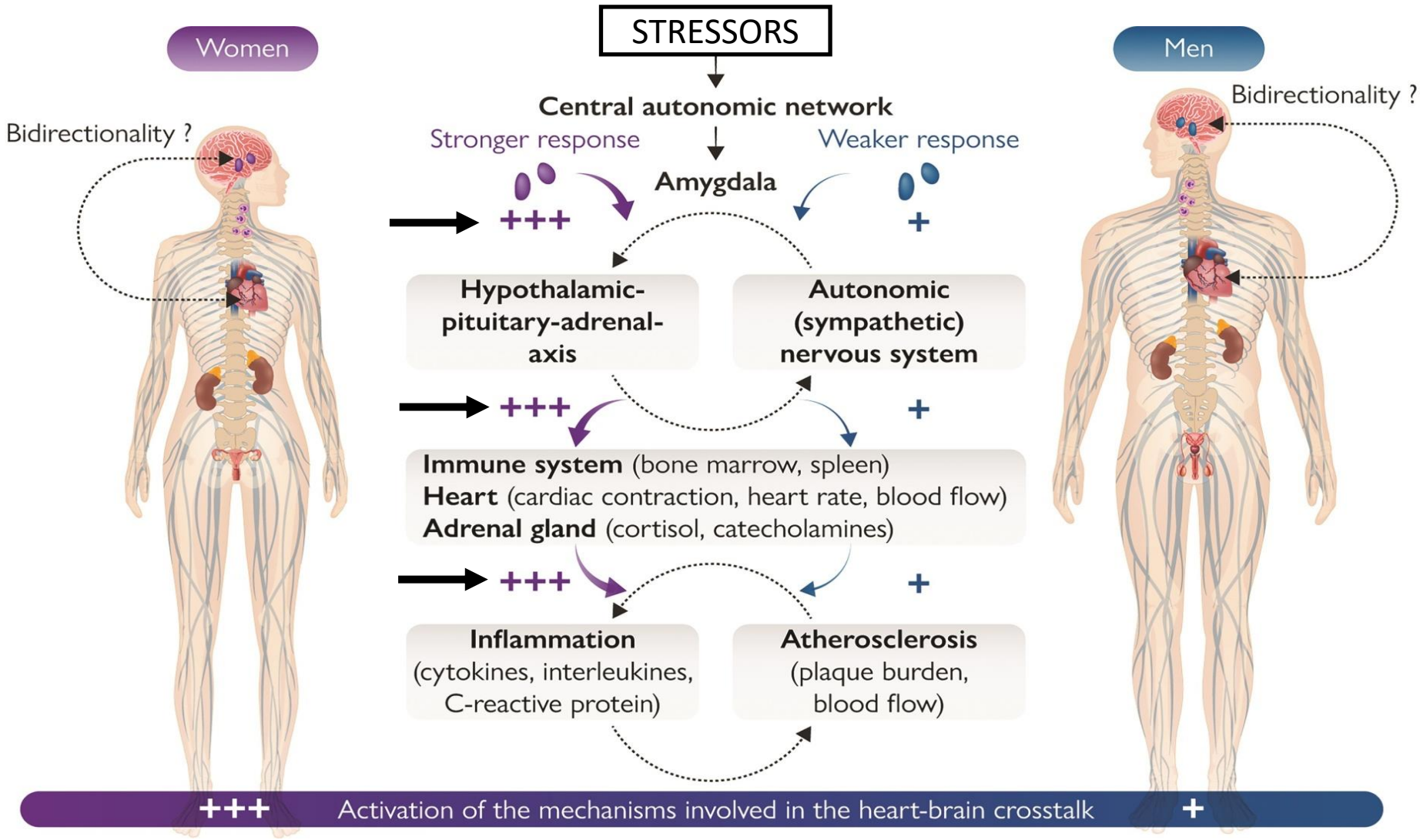
Iacoviello M et al., Current Heart Failure Reports 2022

Gender-Related Pharmacodynamic Differences in Heart Failure Therapy

	pharmacokinetic difference	pharmacodynamic difference
ACE-inhibitors	YES	- Estrogen mediated RAS inhibition; - Greater sensitivity to lower doses; - Increased incidence of cough.
Angiotensin II Receptor blockers (ARB)	NO	NO
Mineralocorticoid receptor antagonist (MRA)	NO	NO
Angiotensin II receptor neprilysin inhibitors (ARNI)	NO	NO
β-blockers	YES	- Different expression of beta-1 receptor; - Greater sensitivity to lower doses.
Inhibitors of type 2 renal sodium-glucose co-transporter (SLGT1)	NO	NO

Iacoviello M et al., Current Heart Failure Reports 2022

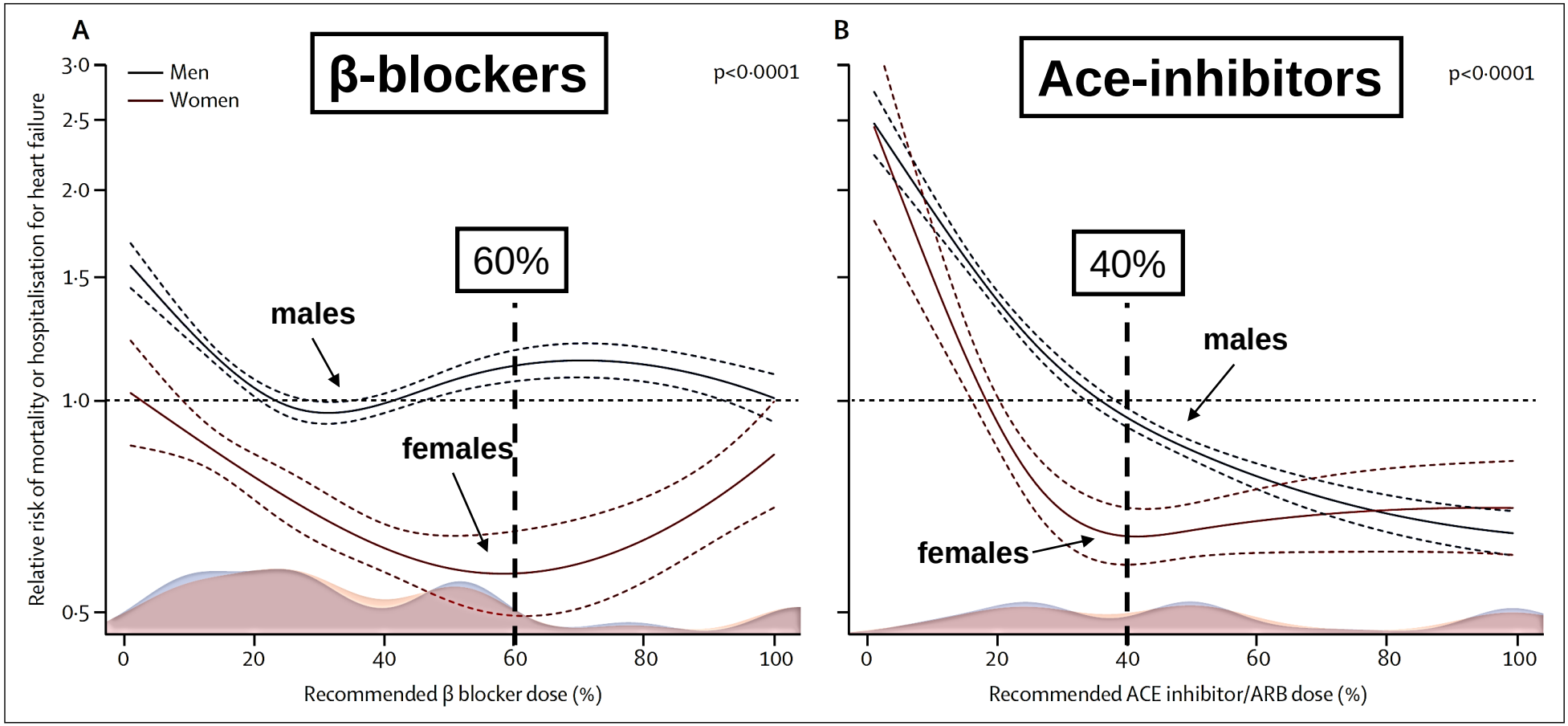
Sex-related mechanisms involved in the heart–brain crosstalk.



Rossi A et al., Eur Heart J 2022

Identifying optimal doses of heart failure medications in men compared with women

BIOSTAT-CHF study



Santema BT et al., Lancet 2019

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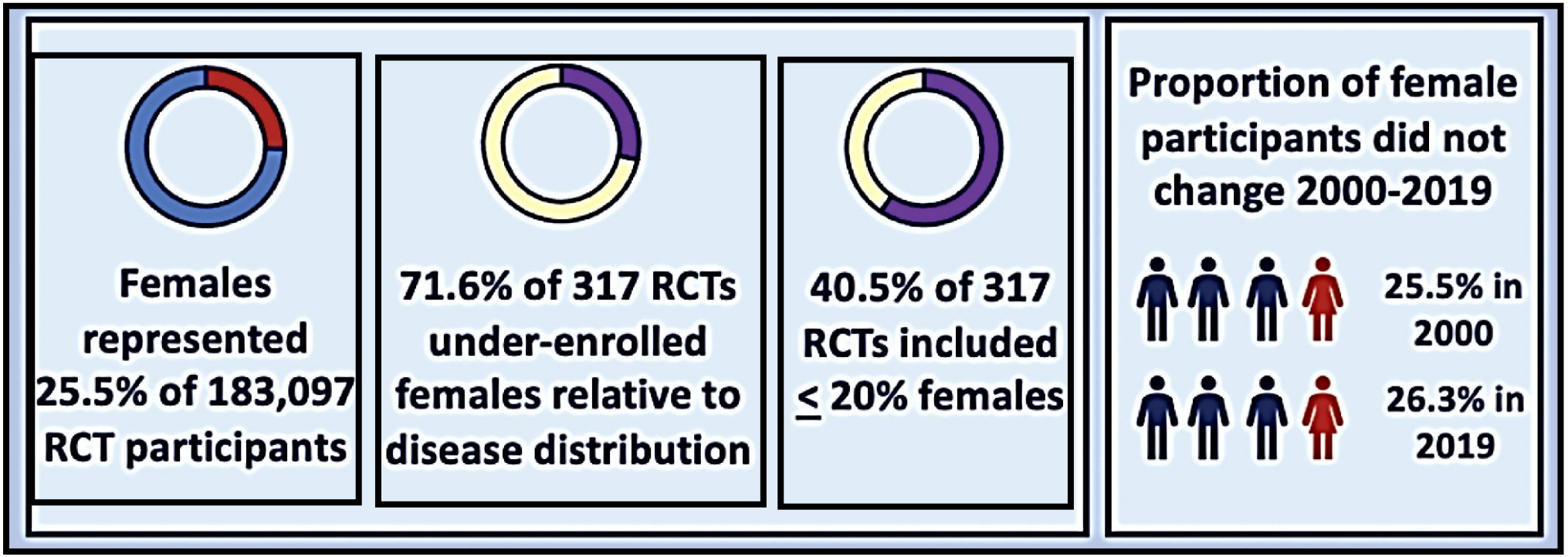
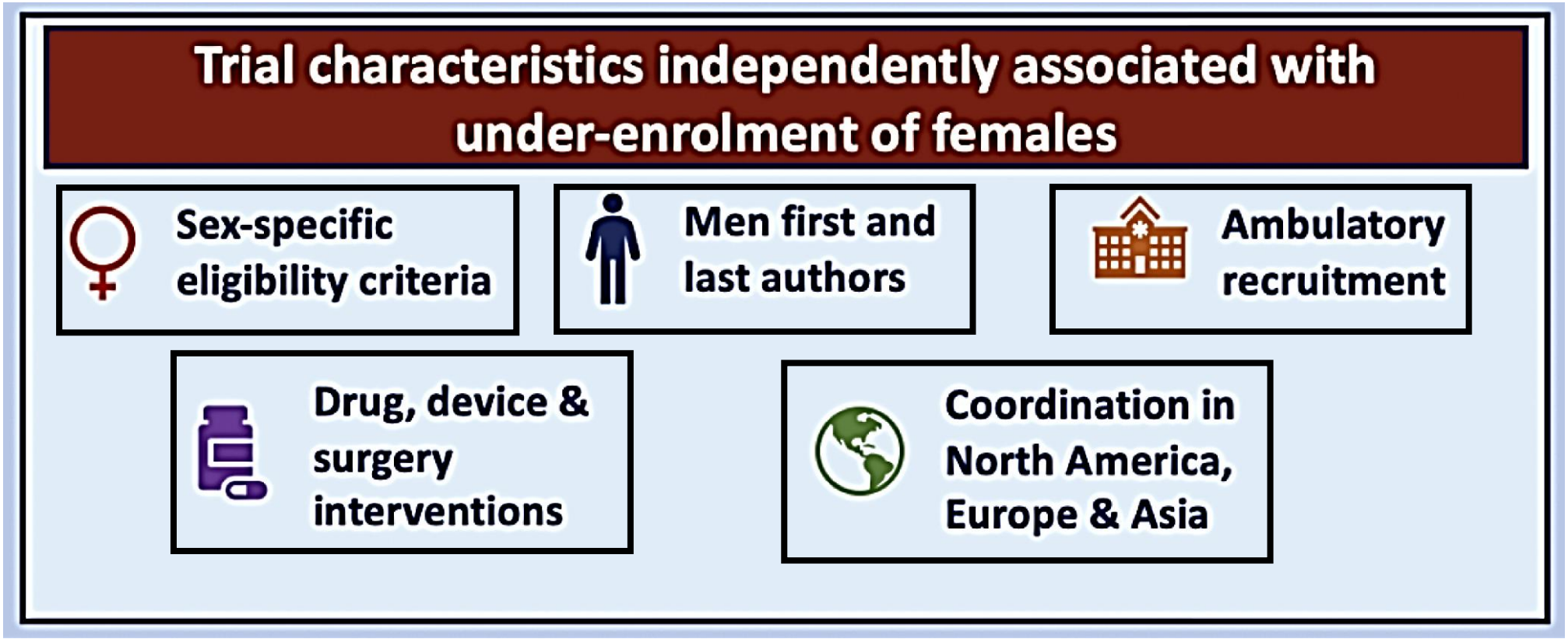
Under-representation of females as participants in heart failure randomised controlled trials: a limitation in sex-specific analysis



Whitelaw S et al., Eur Heart J 2020

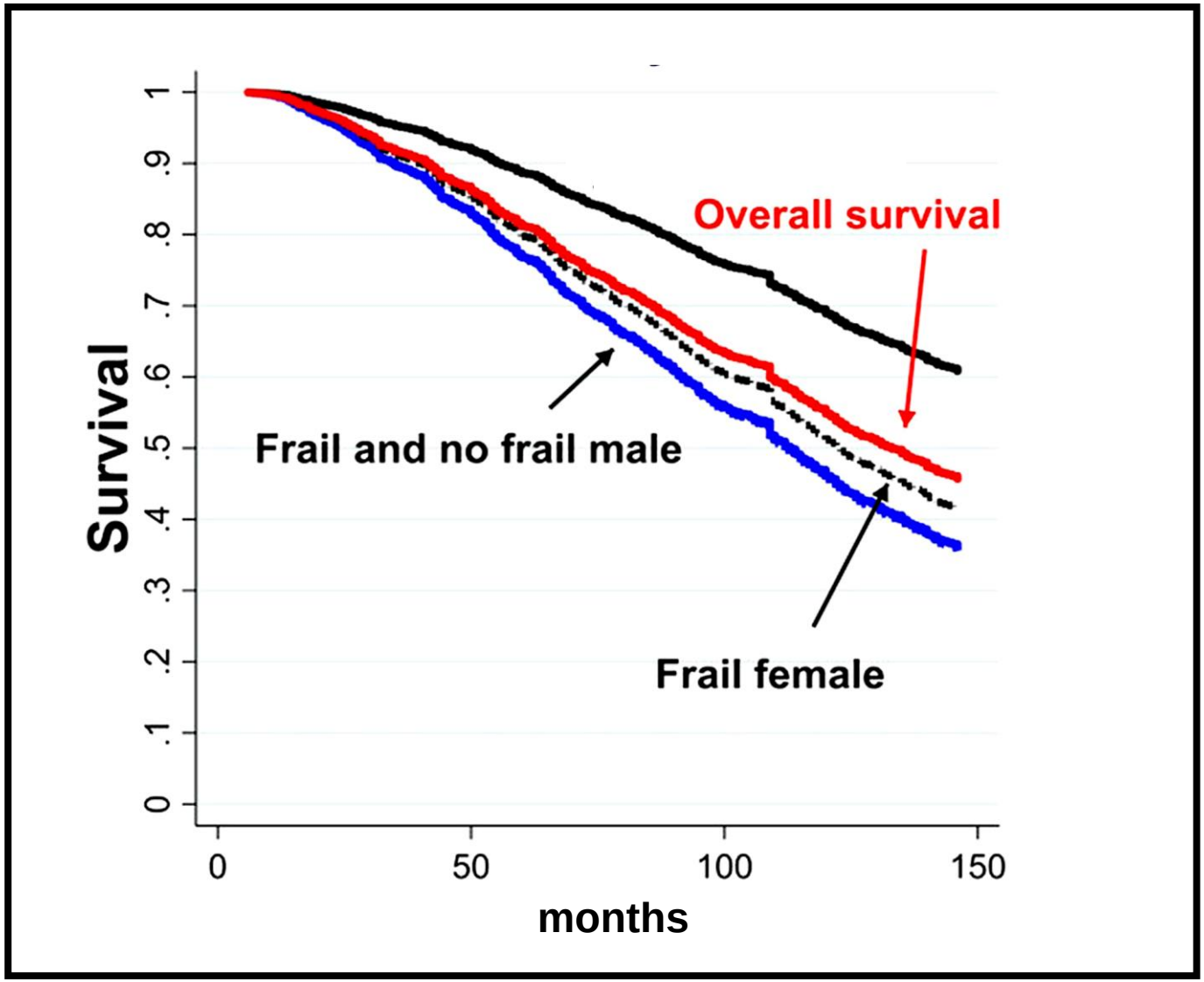
Under-representation of females as participants in heart failure randomised controlled trials: a limitation in sex-specific analysis



Whitelaw S et al., Eur Heart J 2020

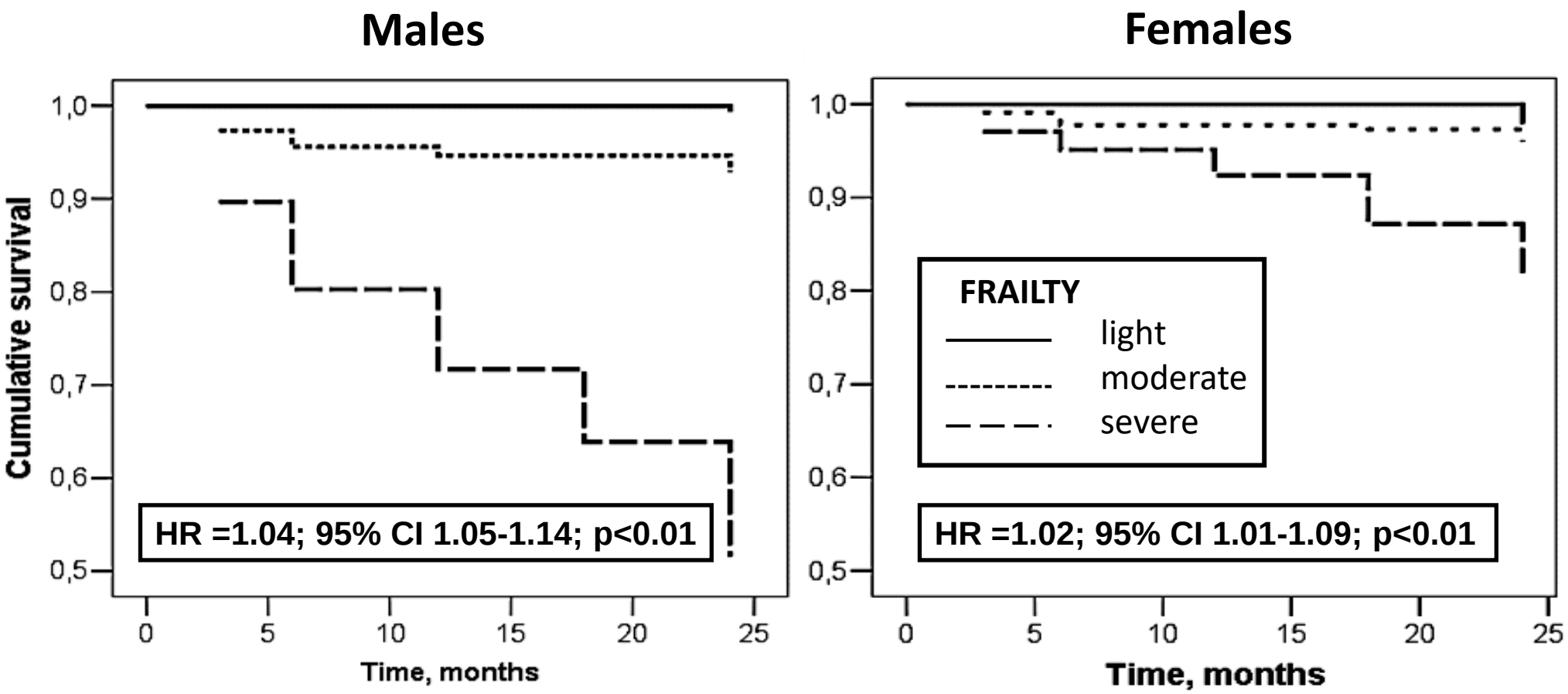
Gender and frailty interaction adjusted survival curves

"Osservatorio Geriatrico Campano"



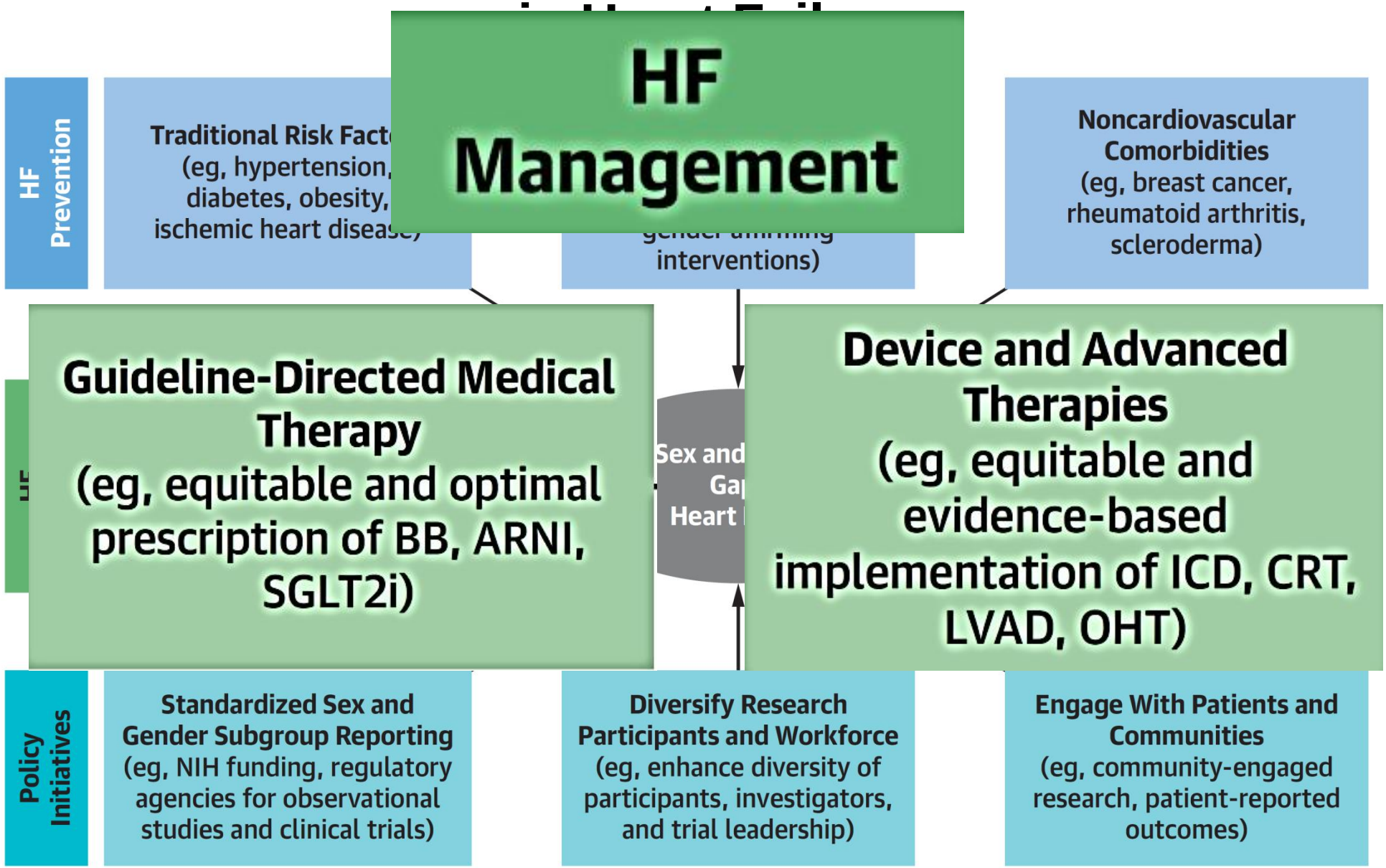
Corbi MG et al., Scientific Reports 2019

Frailty-related 24 months mortality according to sex
"Italian Frailty index"



Abete P et al ., ACER 2017

A Roadmap to Close the Sex and Gender Gap



Khan SS et al, JACC 2022

Heart Failure Reviews
https://doi.org/10.1007/s10741-022-10275-1

Sex-specific differences in the efficacy of heart failure therapies: a meta-analysis of 84,818 patients

Nelson Wang[1,2,4] · Jack Evans[3] · Sonia Sawant[2] · James Sindone[2] · Sean Lal[2,4]

Accepted: 20 September 2022

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Summary of sex differences in baseline characteristics

Women included in the studies = ≈ 35%

Characteristics	n. of trials	n. of patients, women/men	Mean for women/men	Hetero-geneity
Mean age (years)	8	9970/19821	69.2/64.9	86%
Mean body mass index (kg/m^2)	7	8967/15814	29.8/28.4	66%
Mean left ventricular EF (%)	8	9970/19821	46.8/34.6	93%
Mean systolic BP (mmHg)	8	9970/19821	130.3/125.7	71%
Heart rate (beats/minute)	7	8967/15814	74.0/75.5	28%

Wang N et al., Heart Failure Reviews 2022

Sex differences in baseline characteristics

Characteristics	Number of trial	Numer women	Number men	p
White race, *n* (%)	7	6005 (80.3%)	15404 (84.7%)	< 0.001
Black race, *n* (%)	3	319 (7.6%)	566 (7.0%)	0.214
Ischemic cardiomyopathy, *n* (%)	6	2392 (36.2%)	9672 (58.2%)	< 0.001
NYHA class III/IV, *n* (%)	6	5485 (55.0%)	10493 (52.9%)	< 0.001
Hypertension, *n* (%)	6	7109 (84.1%)	9597 (70.1%)	< 0.001
Diabetes, *n* (%)	8	3362 (33.7%)	6299 (31.8%)	< 0.001
Obesity, *n* (%)	3	2847 (46.8%)	2898 (38.2%)	< 0.001
Atrial fibrillation, *n* (%)	7	2888 (32.2%)	4878 (30.8%)	0.026
COPD, *n* (%)	4	717 (10.3%)	1241 (14.6%)	< 0.001
Beta-blocker use, *n* (%)	5	5509 (69.2%)	8444 (67.7%)	0.023
Ace inhibitor/Sartans use, *n* (%)	8	7125 (71.5%)	16,884 (85.2%)	< 0.001
Anti-aldosteron use, *n* (%)	3	1751 (28.8%)	3510 (46.3%)	< 0.001

Wang N et al., Heart Failure Reviews 2022

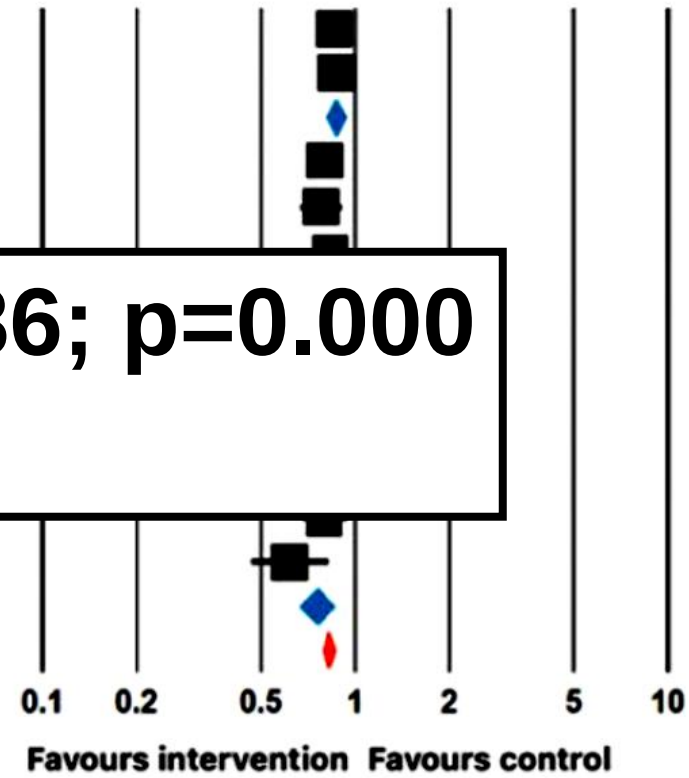
Relative risk for cardiovascular death and hospitalization Heart Failure with *reduced* Ejection Fraction (HFrEF)

MEN

Group by Drug Class	Study name	RR	LCL	UCL	p-Value	I²
ACEI/ARB	CHARM-REDUCED	0.86	0.80	0.94	0.001	
	VAL-HEFT	0.87	0.78	0.98	0.017	
	Overall	0.87	0.81	0.93	0.000	0%
ARNI	PARADIGM-HF	0.80	0.73	0.89	0.000	
Beta-blocker	COPERNICUS	0.76	0.64	0.90	0.001	
Ivabradine	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
MRA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
SGLT2I	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
	EMPEROR-REDUCED	[illegible]	[illegible]	[illegible]	[illegible]	
	SOLOIST-WHF	0.62	0.47	0.82	0.001	
	Overall	0.75	0.67	0.85	0.000	20%
Overall		0.82	0.79	0.86	0.000	10%

Statistics for each study

Risk ratio and 95% CI



RR=0.82; CI 95% 0.79-0.86; p=0.000

-18%

Wang N et al., Heart Failure Reviews 2022

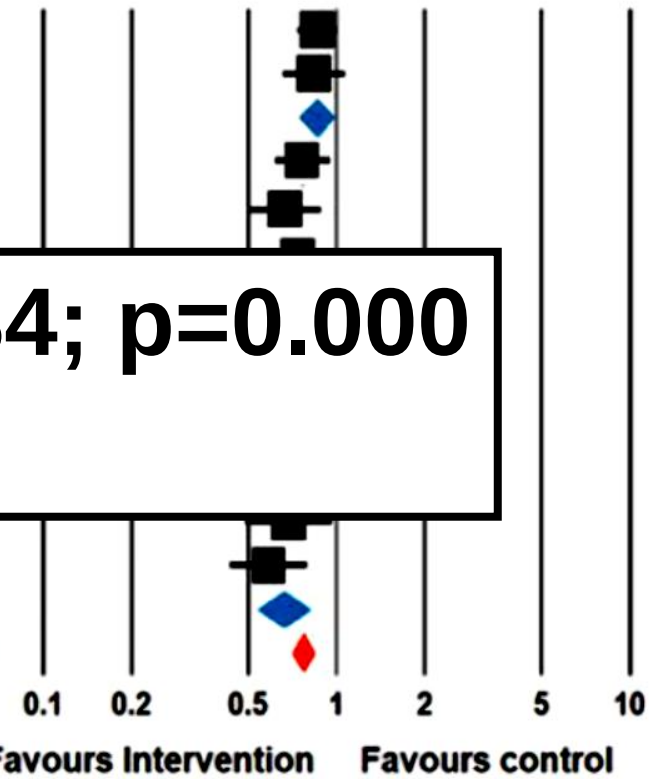
Relative risk for cardiovascular death and hospitalization
Heart failure with *reduced* Ejection Fraction (HFrEF)

WOMEN

Group by Drug Class	Study name	RR	LCL	UCL	p-Value	I²
ACEI/ARB	CHARM-REDUCED	0.86	0.74	1.00	0.058	
	VAL-HEFT	0.84	0.66	1.06	0.143	
	Overall	0.86	0.75	0.97	0.017	0%
ARNI	PARADIGM-HF	0.77	0.62	0.94	0.012	
Beta-blocker	COPERNICUS	0.67	0.51	0.89	0.005	
Ival						
MR						
SGL						
	DAPA-HF	0.69	0.49	0.97	0.031	
	EMPEROR REDUCED	0.59	0.44	0.80	0.001	
	Overall	0.66	0.54	0.81	0.000	0%
Overall		0.77	0.71	0.84	0.000	44%

Statistics for each study

Risk ratio and 95% CI



RR=0.77; CI 95% 0.71-0.84; p=0.000

-23%

Wang N et al., Heart Failure Reviews 2022

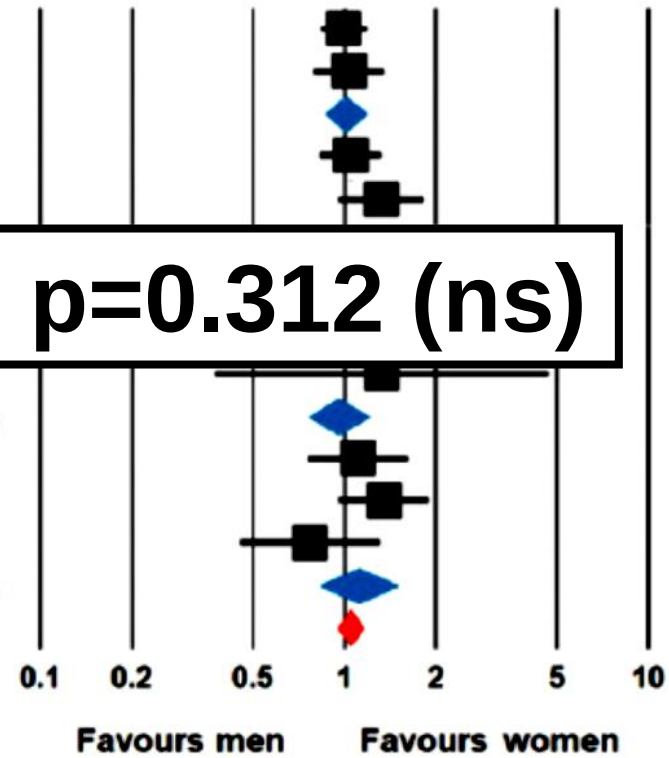
Relative risk for cardiovascular death and hospitalization
Heart failure with *reduced* Ejection Fraction (HFrEF)

MEN VS. WOMEN

Group by Drug Class	Study name	RRR	LCL	UCL	p-Value	I²
ACEI/ARB	CHARM-REDUCED	1.00	0.84	1.19	0.986	
	VAL-HEFT	1.04	0.80	1.35	0.772	0%
	Overall	1.01	0.88	1.17	0.861	
ARNI	PARADIGM-HF	1.05	0.83	1.32	0.680	
Beta-blocker	COPERNICUS	1.27	0.90	1.79	0.179	
	J-EMPHASIS	1.33	0.38	4.69	0.654	
	Overall	0.96	0.77	1.19	0.706	15%
SGLT2I	DAPA-HF	1.12	0.77	1.63	0.567	
	EMPEROR REDUCED	1.36	0.97	1.90	0.077	
	SOLOIST-WHF	0.78	0.46	1.31	0.344	
	Overall	1.11	0.83	1.49	0.467	35%
Overall		1.05	0.96	1.14	0.312	0%

Statistics for each study

Risk ratio and 95% CI



RR=1.05; CI 95% 0.96-1.14; p=0.312 (ns)

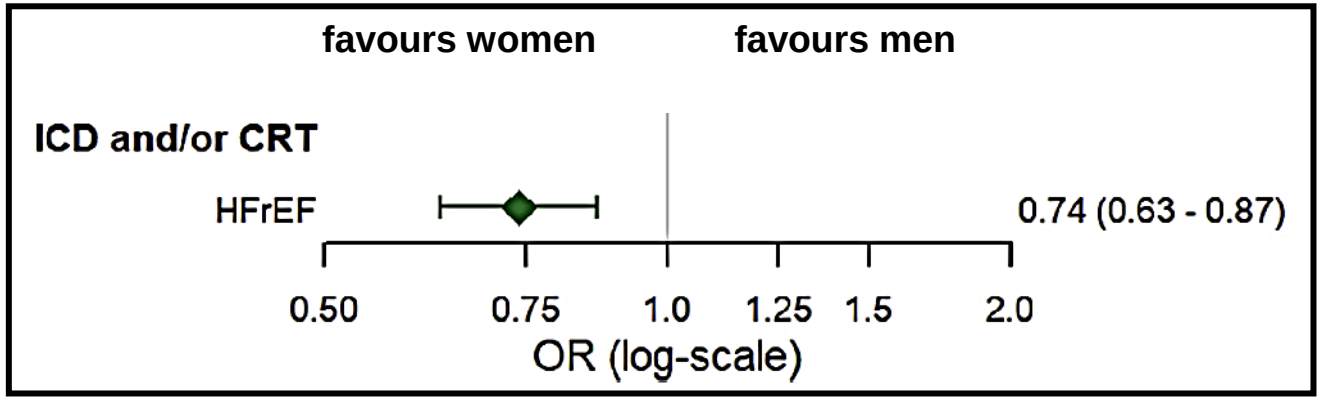
Wang N et al., Heart Failure Reviews 2022

Representation of female patients in trials of CRT or CRT-D therapy

Trial	Female (%)	Study arm	HR (95% CI) Female	HR (95% CI) Male
MADIT-CRT	25%	CRT-D vs ICD	0.37 (0.22-0.61)	0.76 (0.59-0.97)
RAFT	17%	CRT-D vs ICD	0.52 (0.35-0.85)	0.82 (0.70-0.95)
REVERSE	21%	CRT-ON vs CRT-OFF	0.75 (0.26-2.19);	0.69 (0.43-1.11)
CARE-HF		CRT vs pharmacologic		49-0.79)
COMPANI				40-0.90)

RR=0.74; CI 95%0.63-0.87; p=0.000

-26%

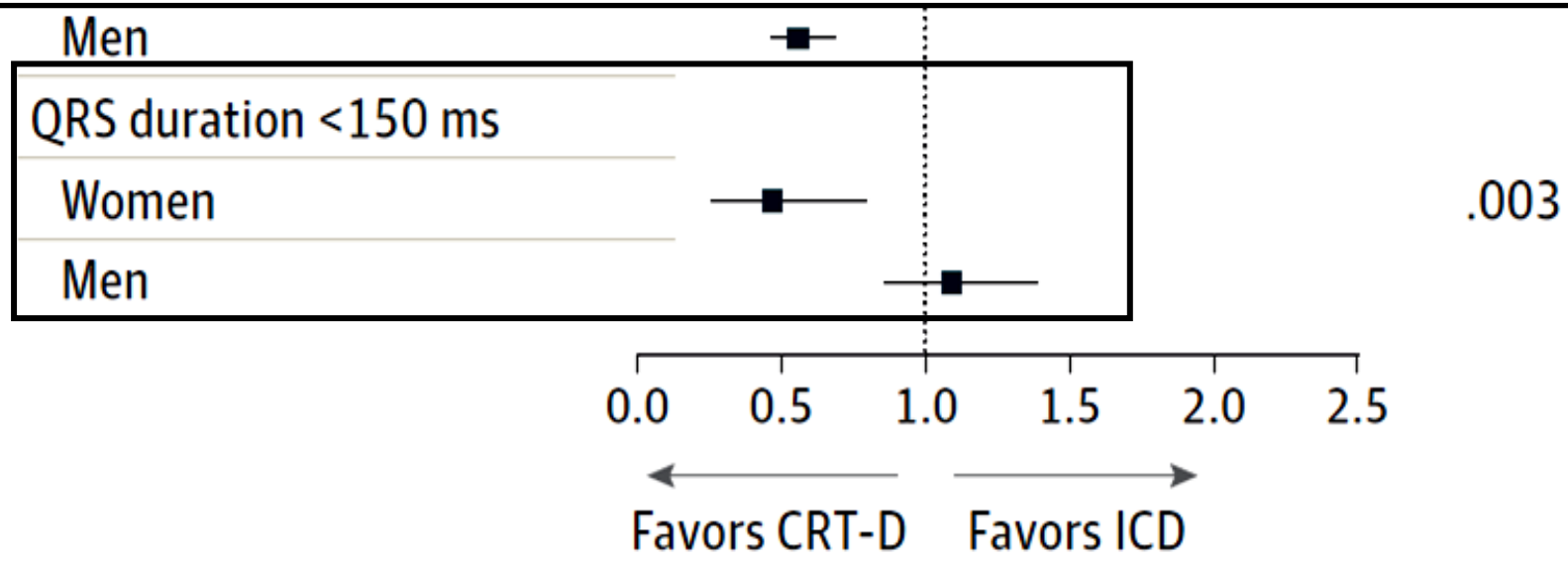


Sullivan K et al., Can J Cardiol 2021

Cardiac Resynchronization Therapy inWomen

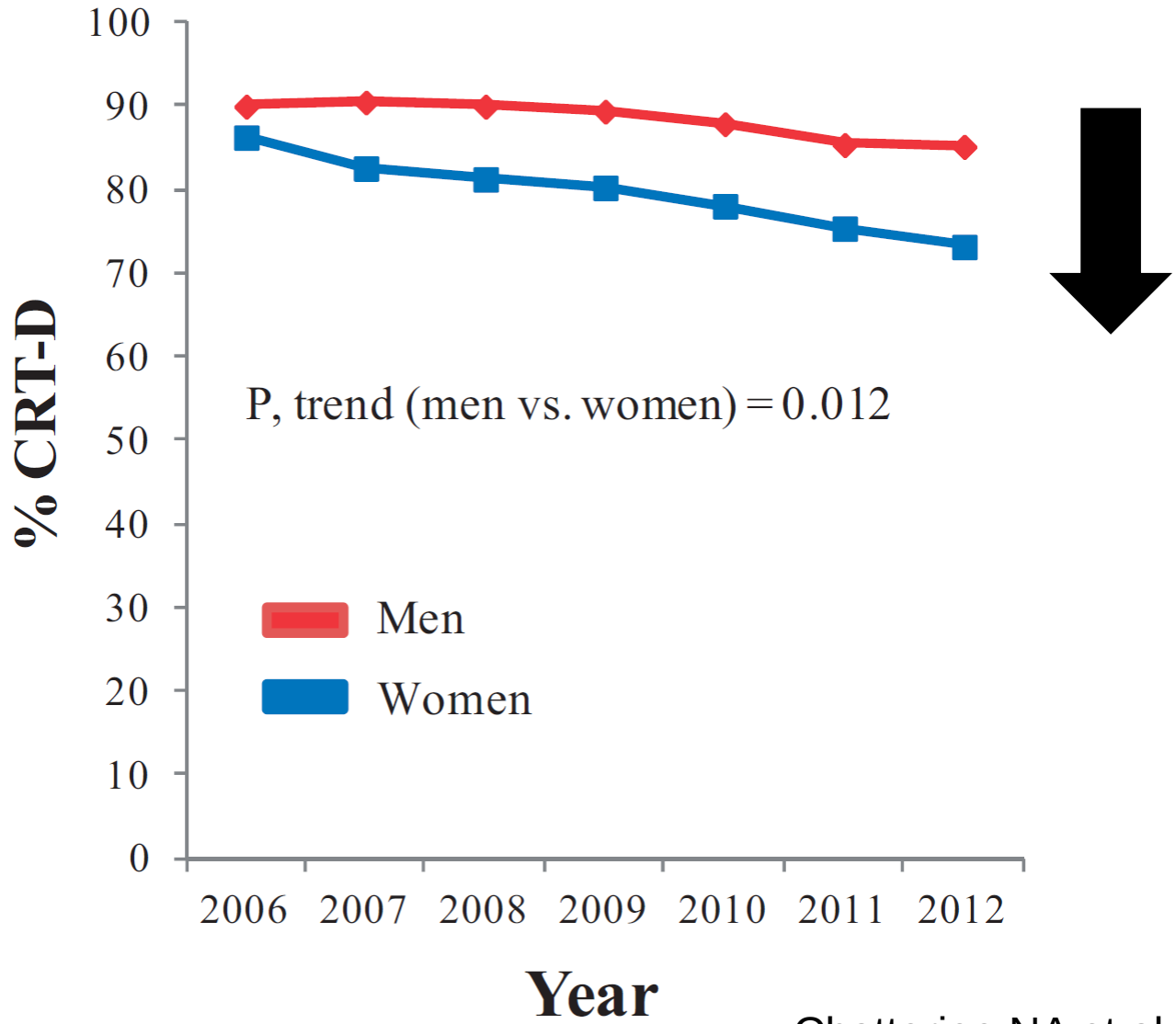
76% reduction in HF or death

(HR=0.24; 95% CI: 0.11-0.53) from CRT-D for women, with no significant benefit in men at a QRS duration between 130-149 milliseconds….



Zusterzeel R et al. Jama Internal Medicine 2014

Trend in the percentage of CRT devices implanted with an ICD in men vs. women between 2006 and 2012



Chatterjee NA et al Eur Heart J 2017

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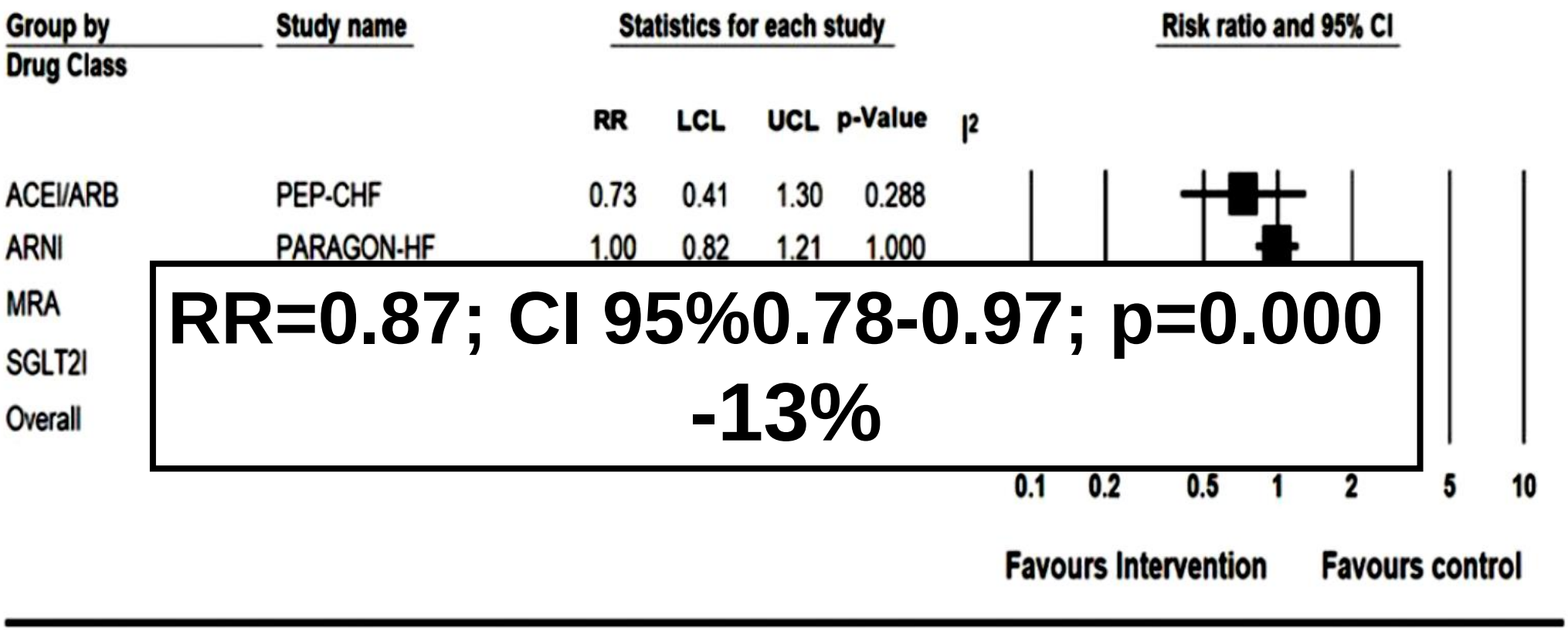
Relative risk for cardiovascular death and hospitalization Heart Failure with *preserved* Ejection Fraction (HFpEF)

MEN



RR=0.87; CI 95%0.78-0.97; p=0.000

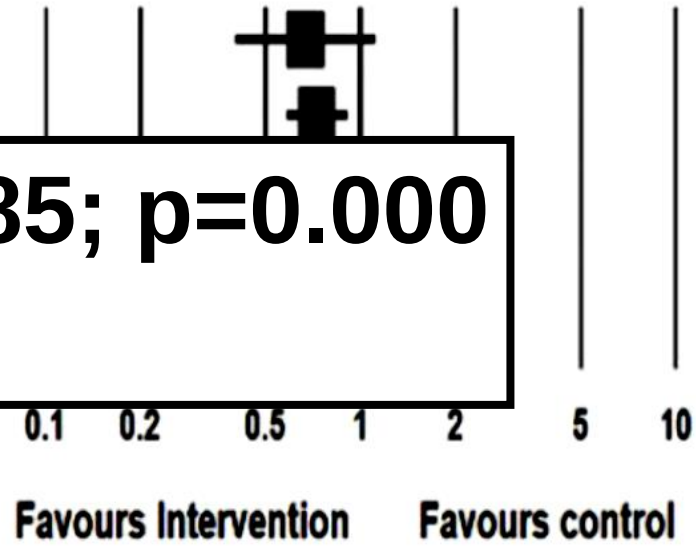
-13%

Wang N et al., Heart Failure Reviews 2022

Relative risk for cardiovascular death and hospitalization Heart Failure with *preserved* Ejection Fraction (HFpEF)

WOMEN

Group by Drug Class	Study name	RR	LCL	UCL	p-Value	I^2
ACEI/ARB	PEP-CHF	0.67	0.40	1.11	0.121	
ARNI	PARAGON-HF	0.73	0.59	0.91	0.004	
MRA						
SGLT2I						
Overall						



RR=0.75; CI 95% 0.66-0.85; p=0.000

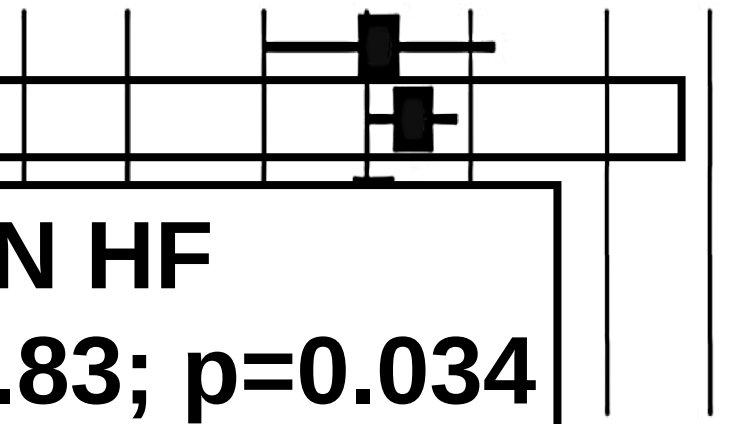
-25%

Wang N et al., Heart Failure Reviews 2022

Relative risk for cardiovascular death and hospitalization Heart Failure with *preserved* Ejection Fraction (HFpEF)

MEN vs.WOMEN

Group by Drug Class	Study name	RRR	LCL	UCL	p-Value	I^2
ACEI/ARB	PEP-CHF	1.09	0.50	2.35	0.827	
ARNI	PARAGON-HF	1.37	1.02	1.83	0.034	
MRA						
SGLT2I						
Overall						



ARNI / PARAGON HF

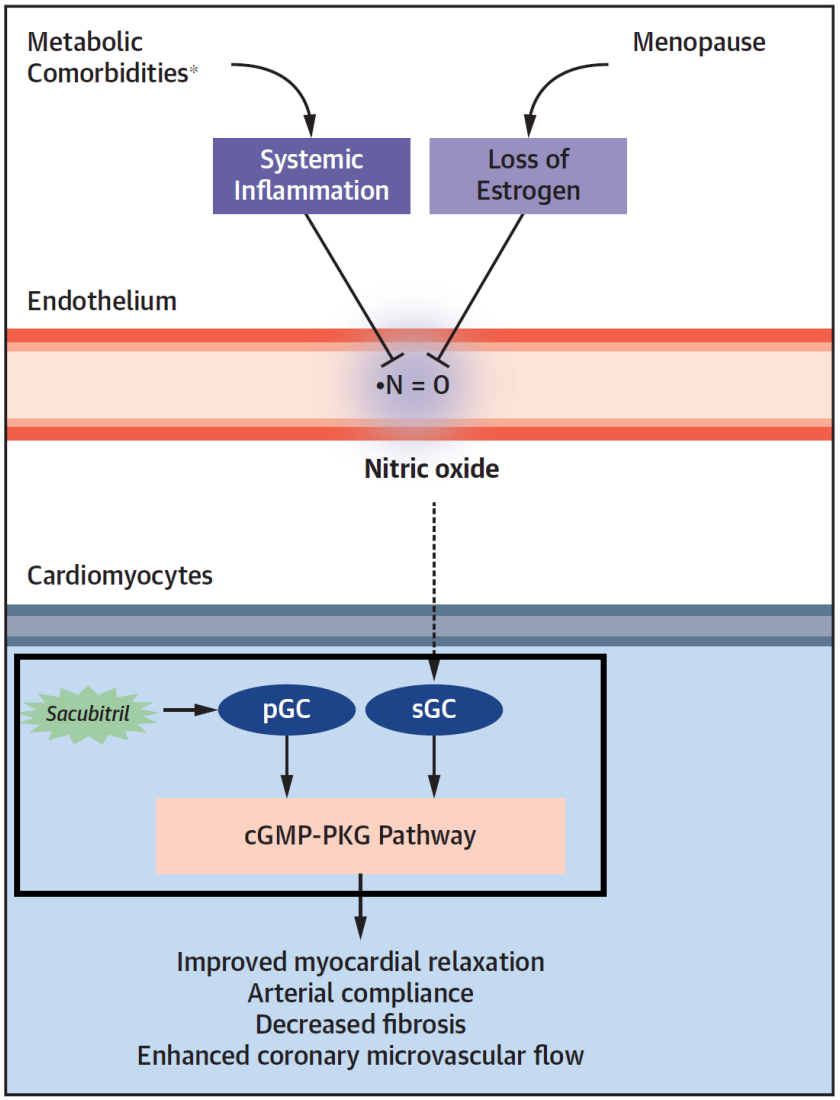
RR=1.37; CI 95% 1.02-1.83; p=0.034

+37%

Favours men Favours women

Wang N et al., Heart Failure Reviews 2022

Targeting cyclic guanosine monophosphate (cGMP) to treat Heart Failure



Loss of estrogen following menopause as well as systemic inflammation caused by comorbidities (eg, obesity) leads to reduced signaling of the cGMP-protein kinase.
As a result, **sacubitril/valsartan**, which increases cGMP-protein kinase G signaling, may uniquely benefit postmenopausal women, particularly those with metabolic comorbidities, such as obesity and diabetes.

Emdin M et al., JACC 2020

L'insufficienza cardiaca nell'anziano

Le nuove terapie dello scompenso nell'anziano: il ruolo del genere nel successo-insuccesso terapeutico

- **Gender and heart failure**
- **Gender and drugs used in Heart Failure (HF)**
- **Under-representation of females in HF trials**
- **Gender and HF with *reduced* Ejection Fraction(HFrEF)**
- **Gender and HF with *preserved* Ejection Fraction (HFpEF)**
- **Conclusions**

CONCLUSIONS (1)

- **Women have a higher incidence and prevalence of Heart Failure with preserved Ejection Fraction (HFpEF)** compared with men.

- Gender-related **pharmacodynamic differences** in HF therapy have been found for **beta-blockers and ACE-inhibitors.**

- **Under-representation of females** as participants in HF randomised controlled trials represents a great limitation in sex-specific analysis.

- Taken alone, **male and females show a risk reduction** by pharmacological therapy in HF both with preserved and reduced Ejection Fraction.

CONCLUSIONS (2)

- **In Heart Failure with "reduced" Ejection Fraction (HFrEF) no statistical difference** were found in sex-specific analysis. However, compared to males, **females may derive greater benefit from CRT but receive CRT/ICD less commonly**.

- The sex-based subgroup analysis in PARAGON-HF identified a more favorable treatment **effect with Angiotensin-receptor blocker/neprilysin inhibitor (ARNI) in women in Heart Failure with "preserved" Ejection Fraction (HFpEF)** compared with men.

- **Stricter adherence to sex- and race-specific inclusion criteria** in clinical trials with pre-specified sex-specific subgroup analyses will address many still pending questions.