Do We Need Sex Specific HF Diagnostic Criteria in 2020?

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Conflict of Interest Disclosures

- **Grants/research support**: HSFC grant for BioAIMI-HF (Biomarkers in Heart Failure of Ischemic Etiology)
- **Consultation and speaker fees paid to the MHI Research Center** from: Amgen, Merck and Novartis
- **Consultation and speaker fees** from: AstraZeneca, Bayer, Boehringer Ingelheim.
- **Steering committee and National leader for clinical studies** fees paid to my institution (MHI Research Center) from: American Regent, AstraZeneca, Cytokinetics, Merck and Novartis
- **Clinical trial participation**: Amgen, Abbott, American Regent, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Eidos, Novartis, Merck, Pfizer, Sanofi

Learning Objectives

- Describe between gender differences in HF risk profiles
- Describe the differences between male and female with regards to HF phenotypes and outcomes
- Understand that heart failure therapy response varies according to sex and LVEF

Characteristics of Women and Men with HFpEF

Table 1. Sex-specific differences in risk factors in HFpEF patients.

Reference	Sample Size	Women/Men (%)	Study Type	Main Findings
Goyal et al. [6]	1,889,608 pts hospitalized for HFpEF	1,208,763 (64)	Short follow-up	Arterial hypertension, obesity, and anemia were significantly more prevalent among women than men with HFpEF. Diabetes was more prevalent in women younger than 75 years and in men older than 75 years. Atrial fibrillation and coronary artery disease were more prevalent in men.
Harada et al. [7]	733 HFpEF pts	529 (72)	Cross-sectional	Obesity (BMI > 25 kg/m^2), diabetes, coronary artery disease and atrial fibrillatio were more frequent in men than in women with HfpEF.
Duca et al. [8]	260 HFpEF pts	181 (70)	30 month follow-up	No difference in cardiovascular risk factors between women and men with HFpEF, except smoking and chronic obstructive lung disease.
Pandey et al. [10]	12,417 subjects	6854 (55.2)	11.6 year follow-up	The lifetime risk of HFpEF did not differ between women and men.
Eaton et al. [29]	42,170 postmenopausal women	All	13.2 year follow-up	Hypertension, diabetes, and obesity were independent predictors only of HFpEF, but not HFrEF. The white race, and not African American and Hispanic, was associated with both, HFpEF and HFrEF.

BMI—body mass index, HFpEF—heart failure with preserved ejection fraction, HFrEF—heart failure with reduced ejection fraction.

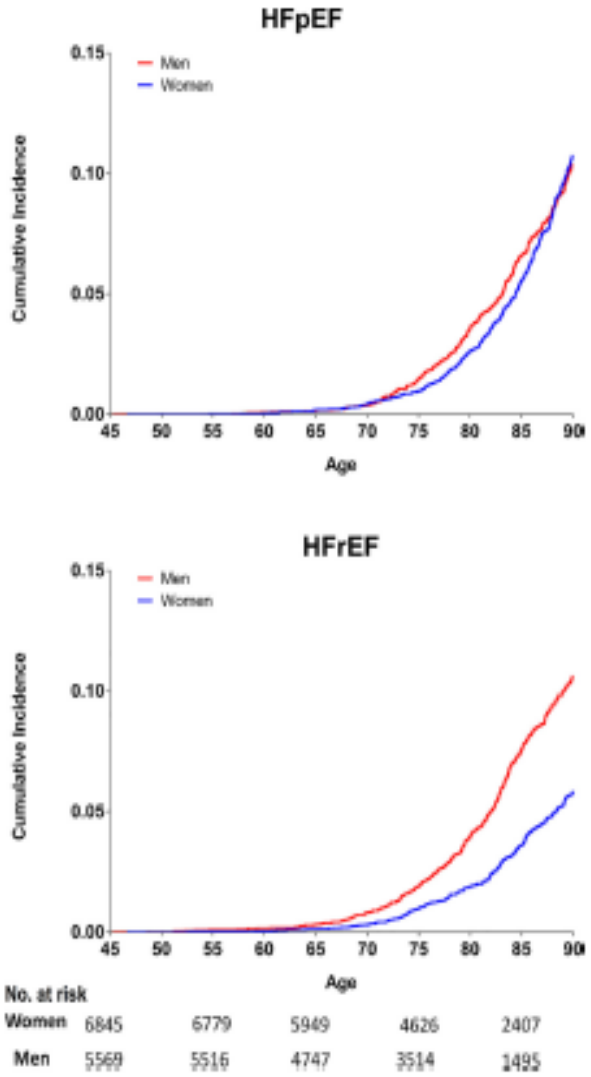


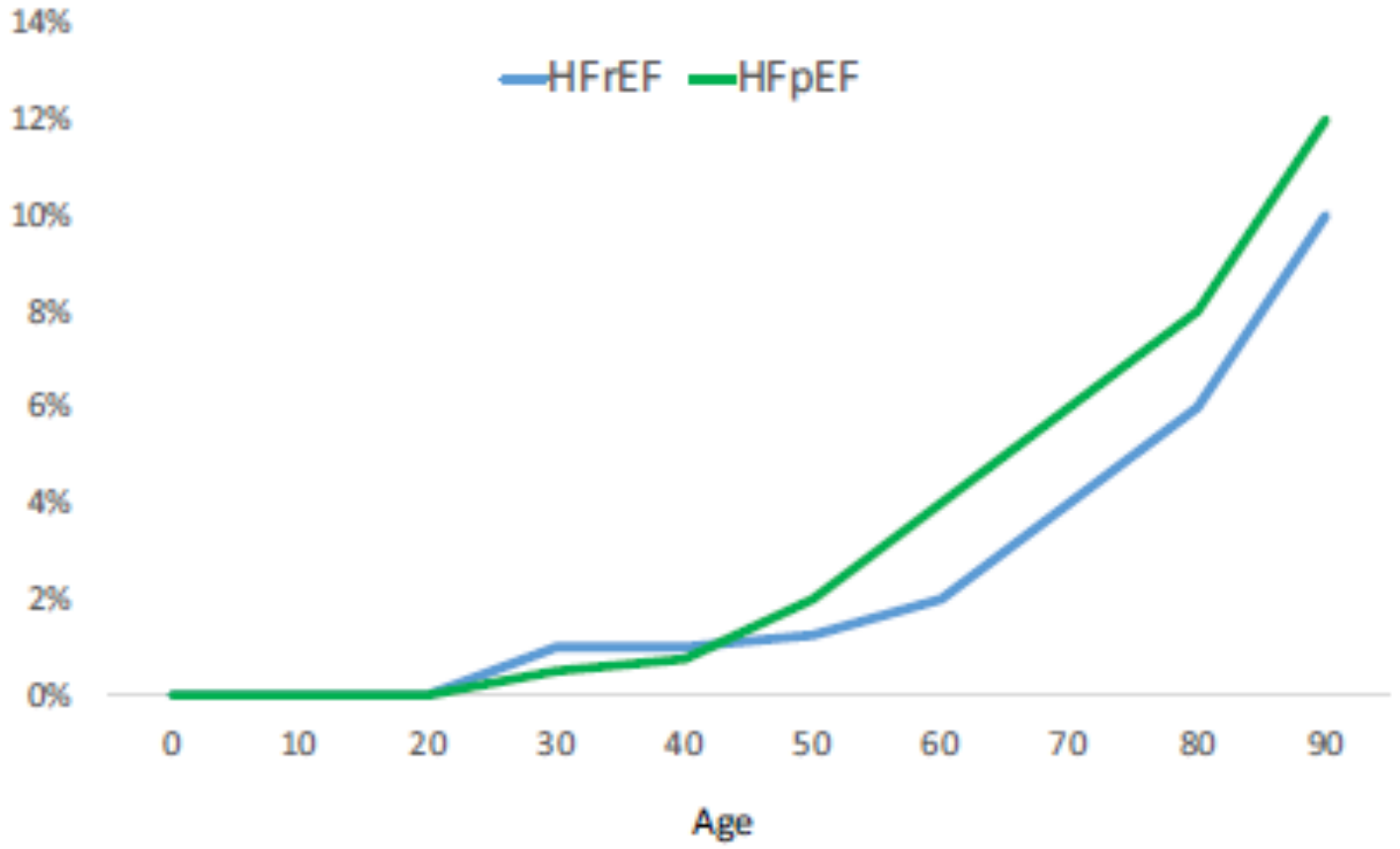
Figure 1:
Sex-stratified remaining lifetime risk of HFpEF and HFrEF in study participants at index age 45 through 90. Number of participants at risk for HFpEF & HFrEF in each subgroup at different index ages (45, 55, 65,75, 85) are shown below the x-axis.

Tadic M et al. J. Clin. Med. **2019**, 8, 792; doi:10.3390/jcm8060792

Circulation. 2018 April 24; 137(17): 1814–1823. doi:10.1161/CIRCULATIONAHA.117.031622

Risk of HF in Women

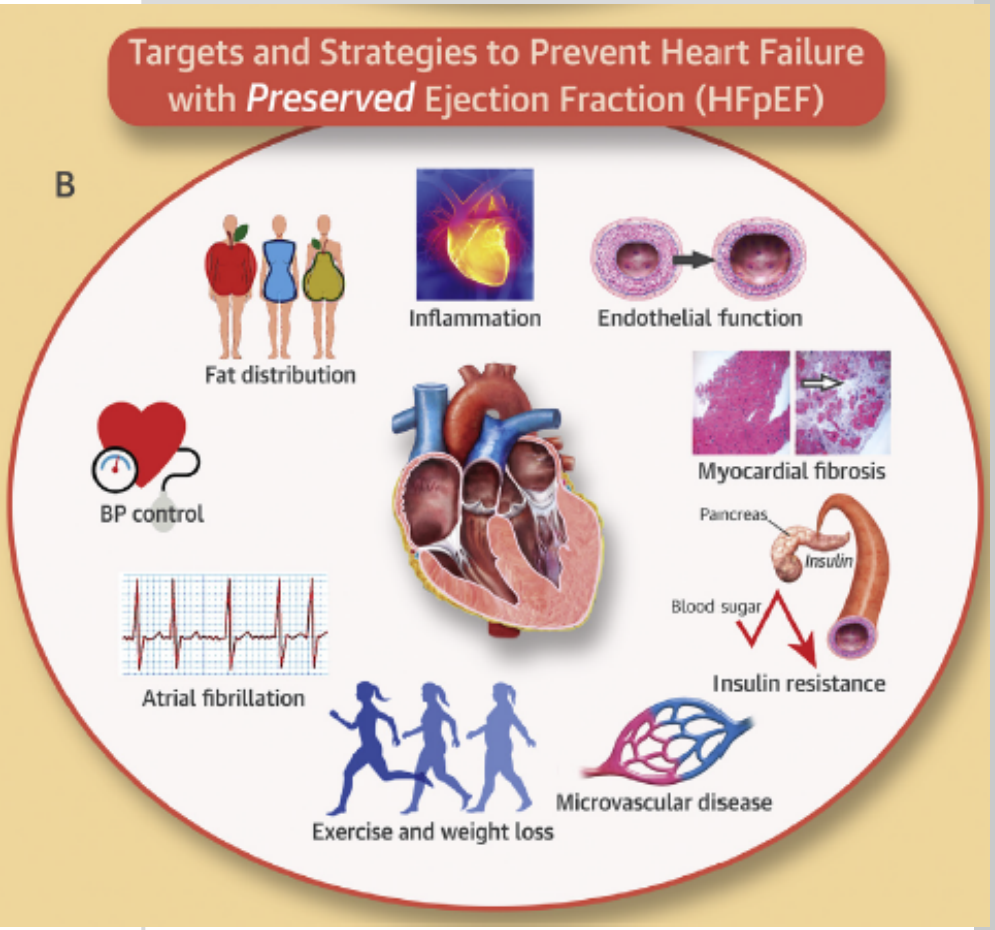
FIGURE 1 Prevalence of HF in Women Across the Lifespan

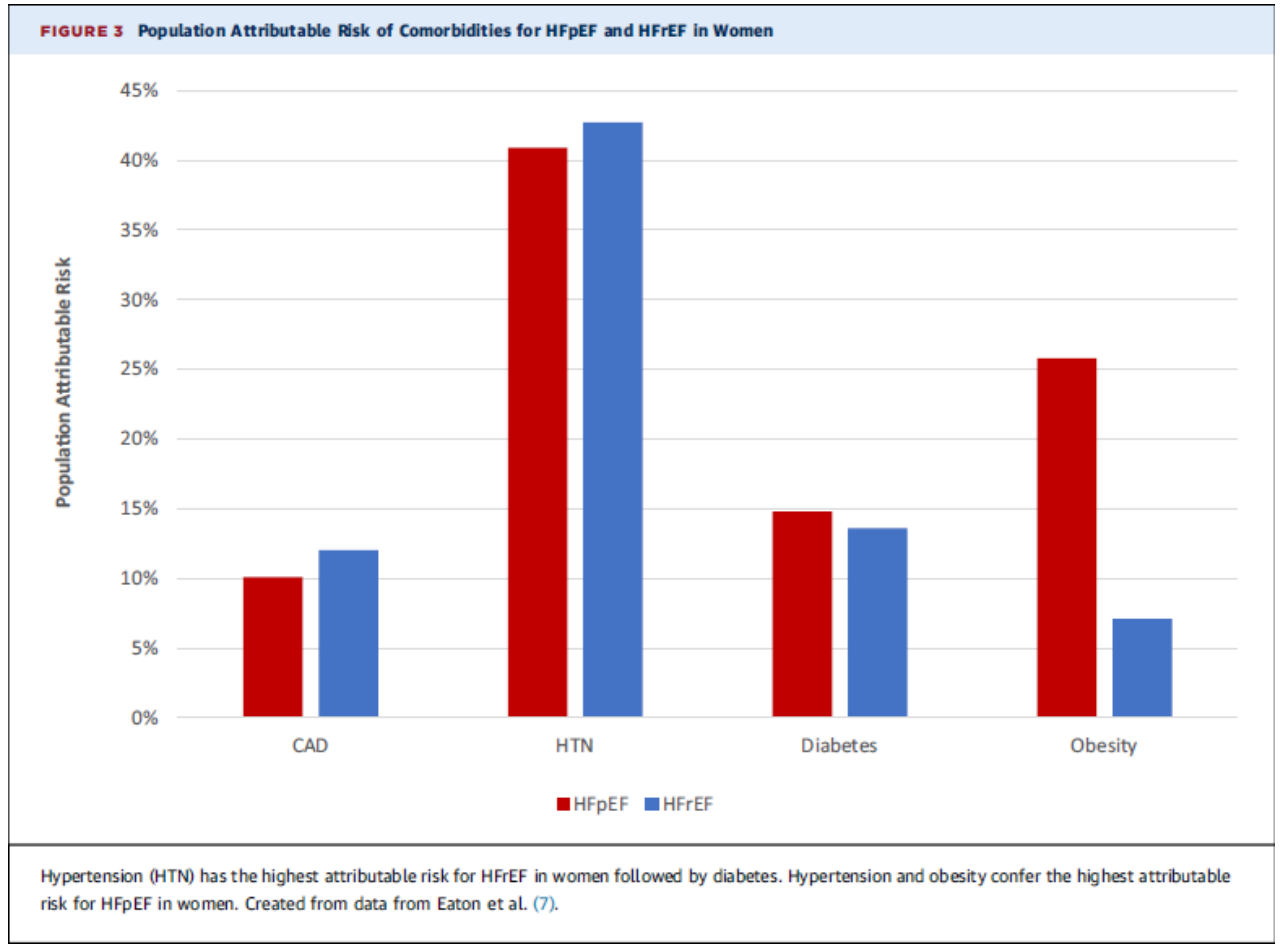


The proportion of women affected by heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) increases across the lifespan. Created from data from Benjamin et al. (1), Kao et al. (47), and Mehta and Cowie (71).

Daubert MA, Douglas PS, JACC: Heart Failure Vol 7, No 3, 20

Prevention of HF in Women





Daubert MA, Douglas PS, JACC: Heart Failure Vol 7, No 3, 2019.

ORIGINAL ARTICLE

Sex-Related Differences in Heart Failure With Preserved Ejection Fraction

Pooja Dewan, MBBS; Rasmus Rørth, MD; Valeria Raparelli, MD, PhD; Ross T. Campbell, MBChB, PhD; Li Shen, MBChB, PhD; Pardeep S. Jhund, MBChB, PhD; Mark C. Petrie, MBChB; Inder S. Anand, MD, DPhil; Peter E. Carson, MD; Akshay S. Desai, MD, MPH; Christopher B. Granger, MD; Lars Køber, MD, DMSc; Michel Komajda, MD; Robert S. McKelvie, MD, PhD; Eileen O'Meara, MD; Marc A. Pfeffer, MD, PhD; Bertram Pitt, MD; Scott D. Solomon, MD; Karl Swedberg, MD, PhD; Michael R. Zile, MD; John J.V. McMurray, MD

BACKGROUND: To describe characteristics and outcomes in women and men with heart failure

METHODS: Baseline characteristics (including biomarkers and quality of life) and outcome of first heart failure hospitalization or cardiovascular death) were compared in 4458 wor CHARM-Preserved (Candesartan in Heart failure: Assessment of Reduction in Mortality and (Irbesartan in heart failure with Preserved ejection fraction), and TOPCAT-Americas (Treatmer Heart Failure with an Aldosterone Antagonist trial).

RESULTS: Women were older and more often obese and hypertensive but less likely to have fibrillation. Women had more symptoms and signs of congestion and worse quality of life. De outcome was lower in women (hazard ratio, 0.80 [95% CI, 0.73–0.88]), as was the risk ratio, 0.70 [95% CI, 0.62–0.80]), but there was no difference in the rate for first hospitalizati 0.92 [95% CI, 0.82–1.02]). The lower risk of cardiovascular death in women, compared wit a substantially lower risk of sudden death (hazard ratio, 0.53 [0.43–0.65]; $P<0.001$). E/A versus 1.2).

CONCLUSIONS: There are significant differences between women and men with heart failure Despite worse symptoms, more congestion, and lower quality of life, women had similar ra survival than men. Their risk of sudden death was half that of men.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT0085

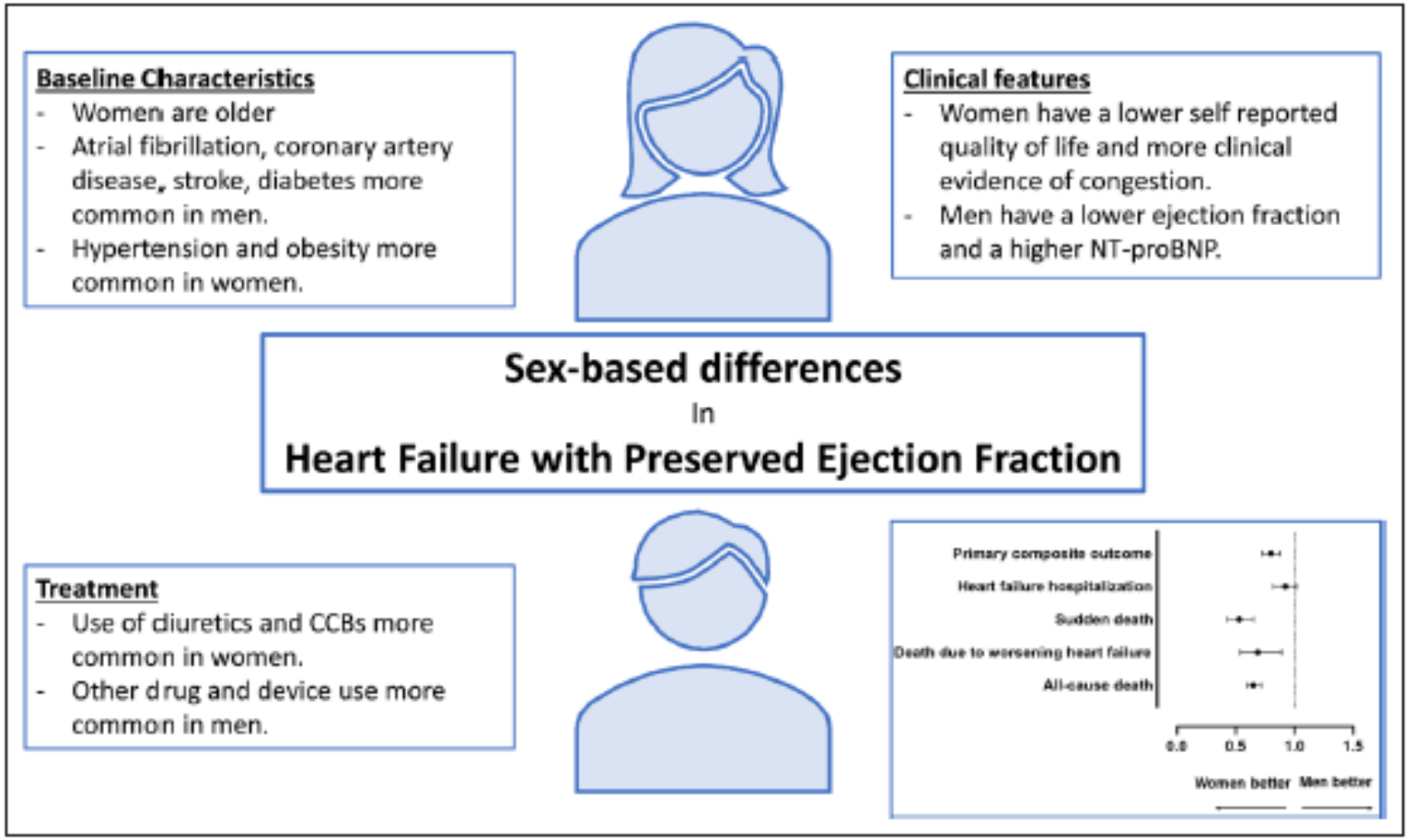


Figure 1. **Sex-based differences in heart failure with preserved ejection fraction.**
CCB indicates calcium channel blocker; and NT-proBNP, N-terminal pro B-type natriuretic peptide.

Circ Heart Fail. 2019;12:e006539.
DOI: 10.1161/CIRCHEARTFAILURE.

WHY?
Cardiac structure, metabolism and function HFpEF in Women

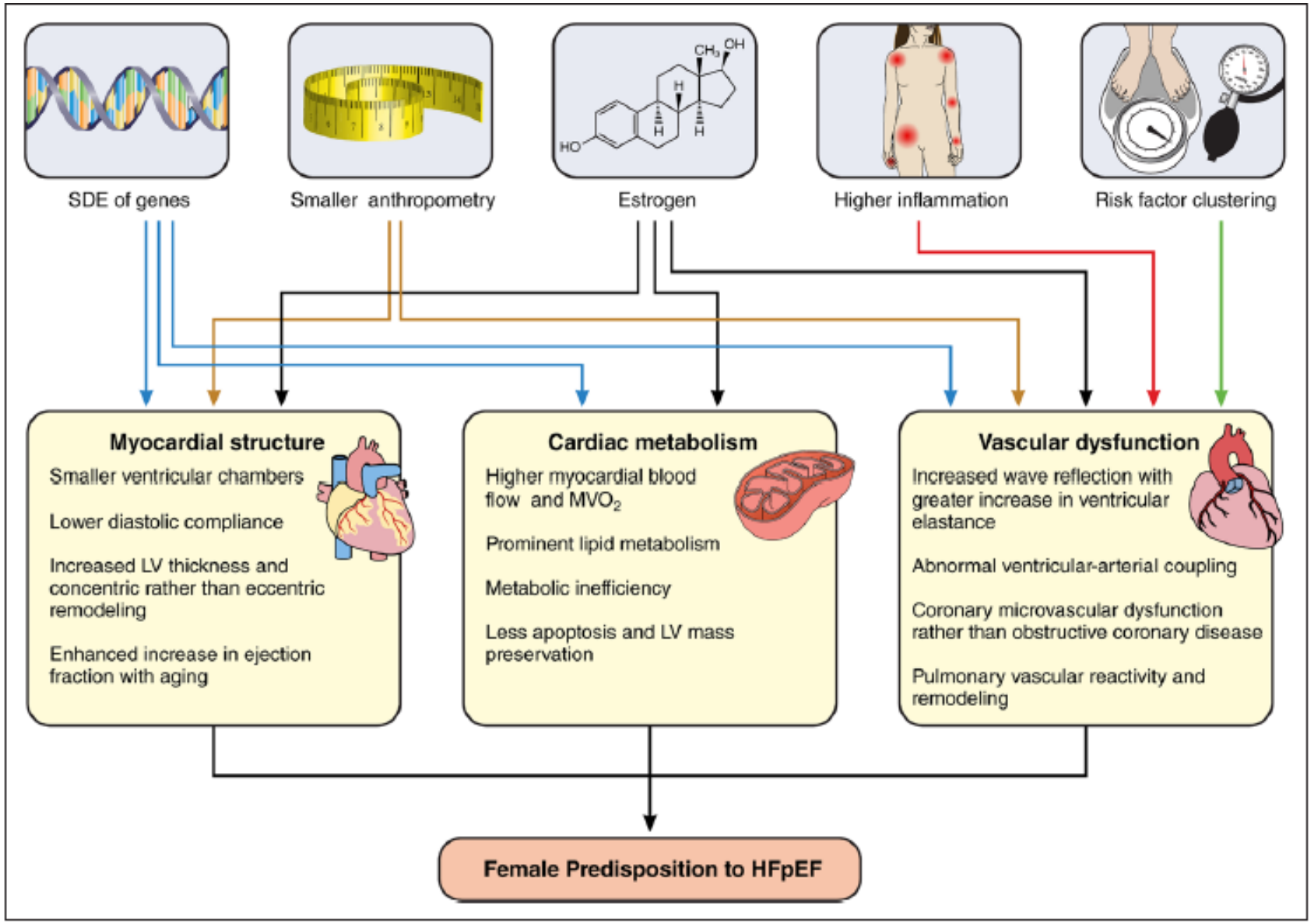


Figure 1. Fundamental sex differences that predispose women to the development of HFpEF.
Interactions between estrogen, gene expression, inflammation, anthropometry, and comorbidities drive the higher relative prevalence of HFpEF in women. HFpEF indicates heart failure with preserved ejection fraction; LV, left ventricle; MVO_2, myocardial oxygen consumption; and SDE, sex differential expression.

Beale AL, et al. *Circulation.* 2018;138:198–205.

Women predisposed to HFpEF: Comorbid Conditions

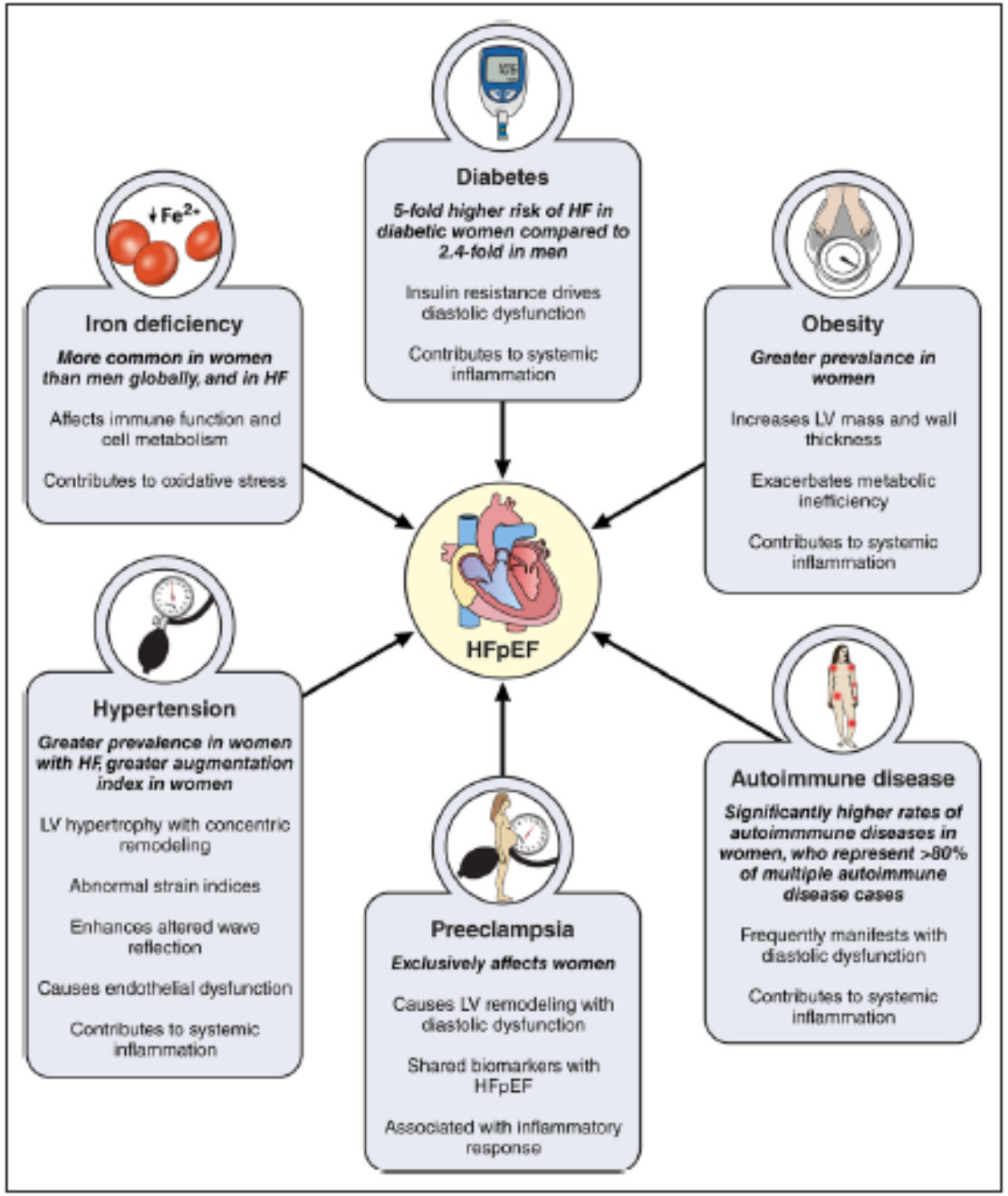


Figure 2. The influence of comorbidities on the development of HFpEF in women.
Comorbidities including iron deficiency, diabetes mellitus, obesity, preeclampsia, hypertension, and autoimmune diseases contribute to HFpEF risk through cardiac structural and functional changes, and systemic inflammation. HF indicates heart failure; HFpEF, heart failure with preserved ejection fraction; and LV, left ventricle.

Beale AL, et al. *Circulation.* 2018;138:198–205.

Current Characteristics of Patients Hospitalized for HF

All Phenotypes

Sebastian Göbel, Lukas Hobohm, Mir A. Ostad, Carl J. Lavie, Tommaso Gori, Thomas Münzel, Philip Wenzel, Karsten Keller

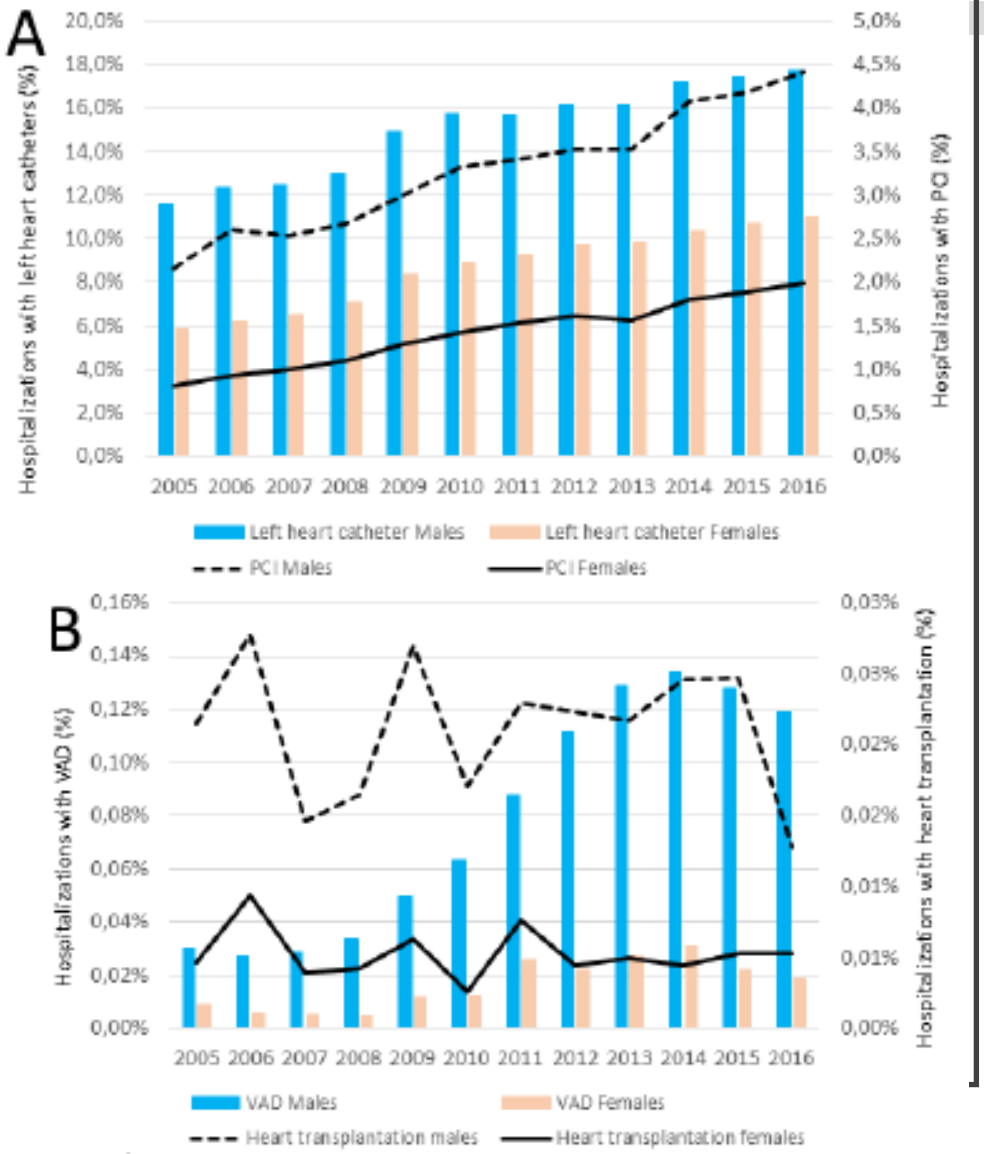
German Nationwide Inpatient Sample

Table 1: Baseline characteristics, medical history, presentation and outcomes of the 4,538,977 heart failure patients stratified according sex

Parameters	Males (n= 2,176,481; 48.0%)	Females (n= 2,362,496; 52.0%)	P-value
Age (years)	76.0 (69.0-82.0)	82.0 (75.0-87.0) ★	<0.001
Age ≥70 years	1,590,541 (73.1%)	2,083,876 (88.2%)	<0.001
In-hospital stay (days)	5 (9-14)	6 (9-14)	<0.001
Obesity	235,957 (10.8%)	260,753 (11.0%)	<0.001
NYHA functional class			
NYHA ≤II	136,329 (6.3%)	146,726 (6.2%)	<0.001
NYHA III	638,184 (29.3%)	642,881 (27.2%)	
NYHA IV	1,019,382 (46.8%)	1,110,340 (47.0%) ★	
Not classified according NYHA classification	382,586 (17.6%)	462,549 (19.6%) ★	
Comorbidities			
Cancer	98,411 (4.5%)	71,138 (3.0%)	<0.001
Coronary artery disease ★	1,094,184 (50.3%)	724,710 (30.7%)	<0.001
Atrial fibrillation/flutter	1,056,922 (48.6%)	1,201,684 (50.9%)	<0.001
Chronic obstructive pulmonary disease ★	446,140 (20.4%)	335,197 (14.2%)	<0.001
Essential arterial hypertension	968,600 (44.5%)	1,073,947 (45.5%)	<0.001
Hyperlipidemia ★	552,780 (25.4%)	433,154 (18.3%)	<0.001
Diabetes mellitus ★	862,695 (39.6%)	913,164 (38.7%)	<0.001
Chronic Renal insufficiency (GFR <60 ml/min/1.73 m²) ★	674,678 (31.0%)	700,548 (29.7%)	<0.001
Depression	62,389 (2.9%)	143,247 (6.1%) ★	<0.001

Progress in Cardiovascular Diseases, March 2020
https://doi.org/10.1016/j.pcad.2020.03.013

Temporal Trends



Current Characteristics of Patients Hospitalized for HF

	♂	♀	
Adverse events during hospitalization			
In-hospital mortality	193,537 (8.9%)	239,799 (10.2%)	<0.001
MACCE	238,131 (10.9%)	282,704 (12.0%)	<0.001
Pneumonia	290,964 (13.4%)	277,577 (11.7%)	<0.001
Acute renal failure	125,703 (5.8%)	115,079 (4.9%)	<0.001
Shock	32,270 (1.5%)	23,985 (1.0%)	<0.001
Myocardial infarction	47,548 (2.2%)	44,873 (1.9%)	<0.001
Stroke (ischemic or hemorrhagic)	14,203 (0.65%)	16,751 (0.71%)	<0.001
Intracerebral bleeding	1,053 (0.05%)	960 (0.04%)	<0.001
Subarachnoid bleeding	214 (0.01%)	228 (0.01%)	0.845
Gastro-intestinal bleeding	16,484 (0.8%)	17,464 (0.7%)	**0.025**
Transfusion of blood constituents	116,611 (5.4%)	129,917 (5.5%)	<0.001
Treatment			
Pacemaker	14,551 (0.7%)	14,400 (0.6%)	<0.001
Cardiac resynchronization therapy (CRT)	2,048 (0.09%)	1,530 (0.06%)	<0.001
Implantable cardioverter-defibrillator	46,926 (2.2%)	12,966 (0.5%)	<0.001
Catheter ablation for the treatment of cardiac arrhythmias	5,274 (0.2%)	2,353 (0.1%)	<0.001
Left heart catheterization	333,503 (15.3%)	208,437 (8.8%)	<0.001
Percutaneous transluminal vascular intervention on heart and coronary vessels (PCI)	73,614 (3.4%)	34,226 (1.4%)	<0.001
Heart valve surgery	2,142 (0.10%)	1,355 (0.06%)	<0.001
Transcatheter aortic valve replacement (TAVR)	854 (0.04%)	828 (0.035%)	**0.020**
Percutaneous edge-to-edge mitral regurgitation valve repairs with the MitraClip® implantation	1,205 (0.06%)	676 (0.03%)	<0.001
Ventricular assist device (VAD)	1,823 (0.08%)	399 (0.02%)	<0.001
Heart transplantation	458 (0.021%)	124 (0.005%)	<0.001

Abbreviations: NYHA, New York Heart Association; MACCE, major adverse cardio-cerebral-vascular events

Progress in Cardiovascular Diseases, March 2020
https://doi.org/10.1016/j.pcad.2020.03.013

- "… Our data indicate an underuse of interventional treatments in women, although the beneficial impact of these treatments on survival are comparable between both sexes...

- In accordance with our results, sex differences with regard to CRT utilization in patients hospitalized due to HF have been reported recently, demonstrating that women were less likely to receive CRT despite greater mortality risk reduction… "

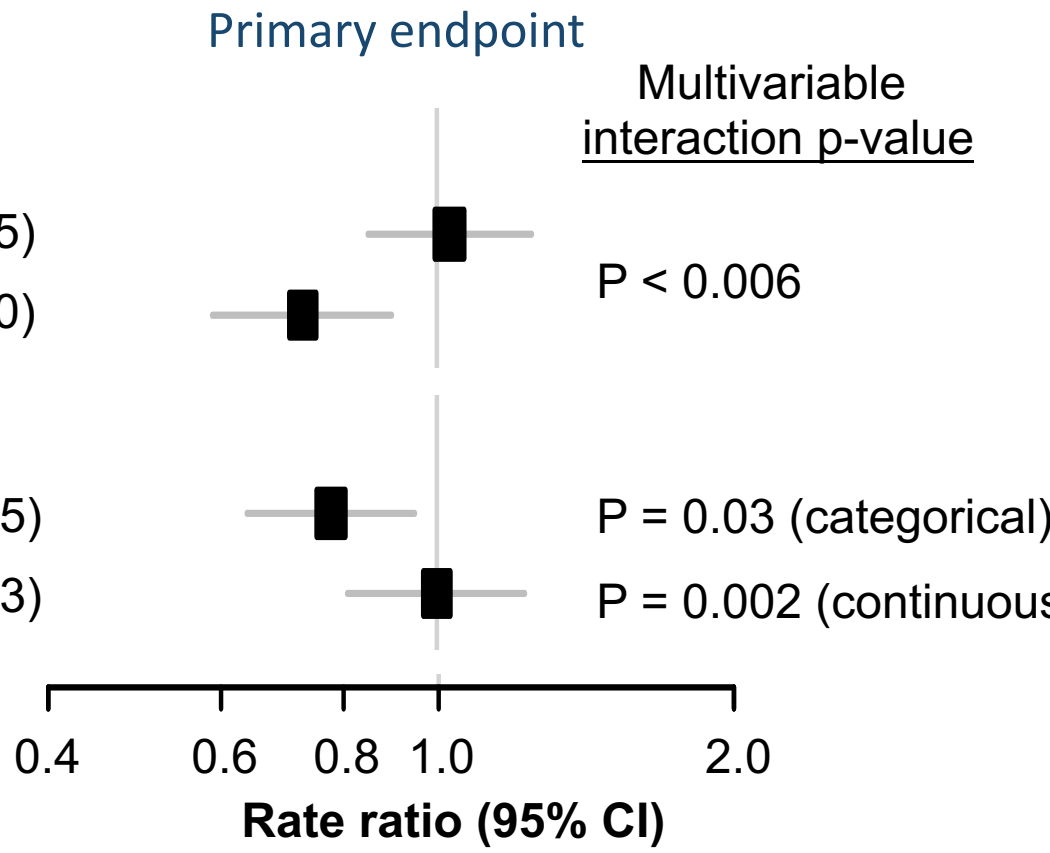
Progress in Cardiovascular Diseases, March 2020
https://doi.org/10.1016/j.pcad.2020.03.013

Heterogeneity in Multivariate Analysis

Gender and Ejection Fraction in the PARAGON-HF trial

Only interactions for sex and ejection fraction remained nominally significant

Subgroup	No. of events/ patients	Rate ratio (95% CI)
Sex		
Male	980/2317	1.03 (0.85–1.25)
Female	923/2479	0.73 (0.59–0.90)
LVEF		
at or below median (57%)	1048/2495	0.78 (0.64–0.95)
above median (57%)	855/2301	1.00 (0.81–1.23)



Solomon SD, *et al. NEJM* 2019

Interactions between left ventricular ejection fraction, sex and effect of neurohumoral modulators in heart failure

Pooja Dewan[1], Alice Jackson[1], Carolyn S.P. Lam[2,3,4], Marc A. Pfeffer[5], Faiez Zannad[6], Bertram Pitt[7], Scott D. Solomon[5], and John J.V. McMurray[1*]

European Journal of Heart Failure, April 2020

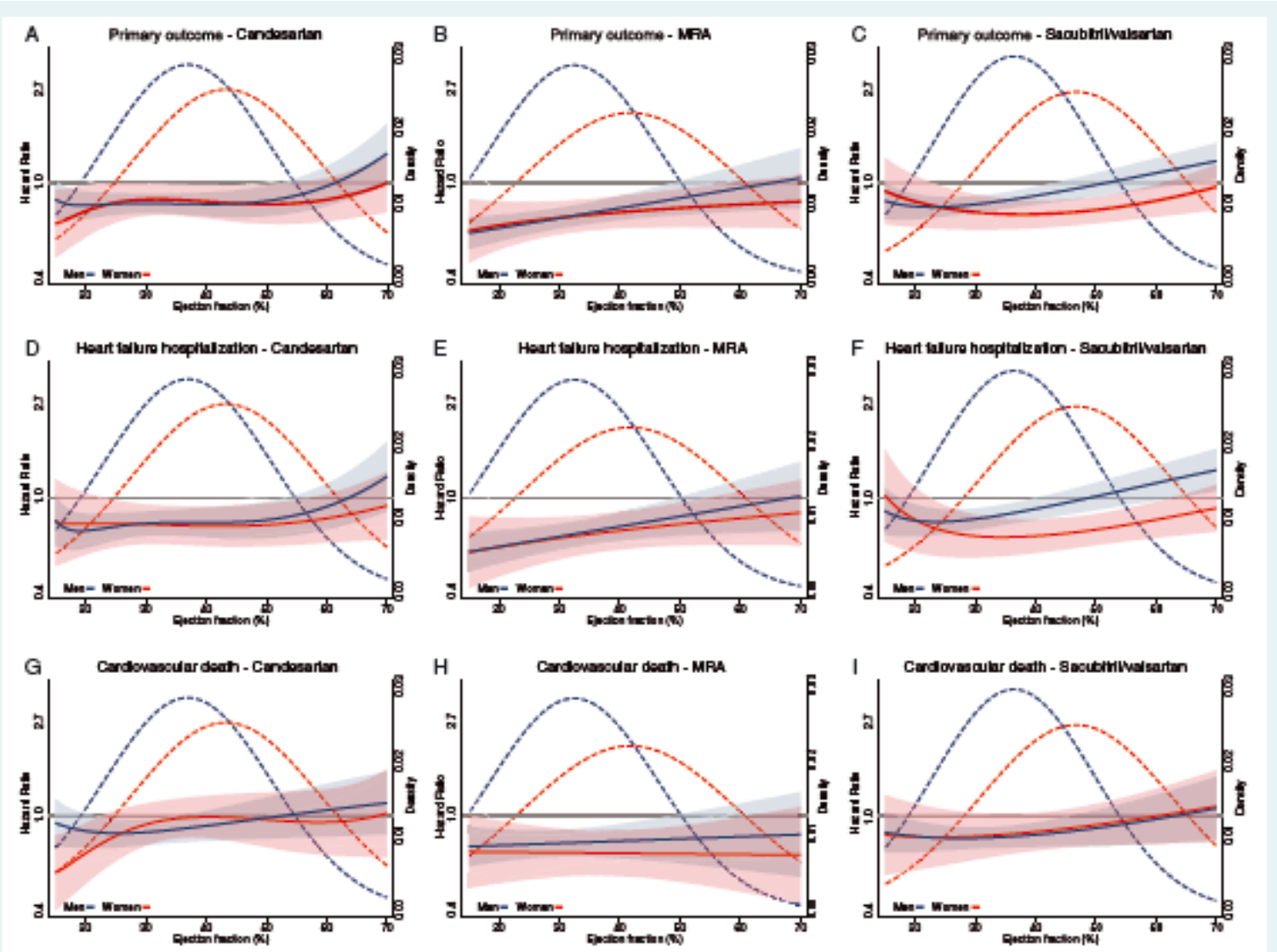


Figure 1 Variation of treatment effect with left ventricular ejection fraction in heart failure. Dotted curves show normalized distribution of left ventricular ejection fraction (LVEF) in men and women. Solid lines show a continuous hazard ratio for the primary composite and its components, according to treatment group in the range of LVEF included. The shaded areas represent the 95% confidence intervals. Primary outcome (heart failure hospitalization/cardiovascular death): (*A*) candesartan vs. placebo; (*B*) mineralocorticoid receptor antagonist (MRA) vs. placebo; (*C*) sacubitril/valsartan vs. renin–angiotensin–aldosterone system inhibitor. Heart failure hospitalization: (*D*) candesartan vs. placebo; (*E*) MRA vs. placebo; (*F*) sacubitril/valsartan vs. renin–angiotensin–aldosterone system inhibitor. Cardiovascular death; (*G*) candesartan vs. placebo; (*H*) MRA vs. placebo; (*I*) sacubitril/valsartan vs. renin–angiotensin–aldosterone system inhibitor.

ESC European Society of Cardiology
European Journal of Heart Failure (2020)
doi:10.1002/ejhf.1805

EDITORIAL COMMENT

Evolving towards a more realistic app
the importance of left ventricular eje
fraction and sex in heart failure and i

Nadia Bouabdallaoui and Jean Rouleau*

Department of Medicine, The Montreal Heart Institute and Université de Montréal, Montreal, Canada

(iv) For researchers in the field of HF, whether clinical trialists or others, inclusion of more detailed pre-specified subgroups that go beyond strict LVEFs, and better assessment of sex-related differences would be important.

B

Sexual Dimorphism in HF

Clinical presentation	**More** frequently HFpEF, **More** signs/symptoms of HF and **poorer** QoL despite **similar** LVEF and **lower** NT-proBNP
Comorbidities	Older, **more** hypertension, obesity, and kidney disease, **less** CAD, and diabetes
Cardiac function and geometry	**Higher** LVEFs, **smaller** LV chambers, **higher** filling pressures, **more** dependence on heart rate to maintain cardiac output, **more** concentric LVH in response to stress, **more** systolic dysfunction in HFpEF despite similar LVEF
Vascular	**More** arterial stiffening with age, **steeper** pulmonary artery PV slope, **more** frequent microvascular dysfunction, **more** predisposition to Pulmonary Hypertension
Neurohumoral and Metabolic activity	**Increased** cardiac sympathetic activation, **differences** in pre- and post-menopausal hormonal and enzymatic activity
GDMT utilization	**Underuse** of GDMT, **smaller** body size, **differences** in drug distribution, metabolism and excretion all leading to **differences** in drug levels and greater risk of related adverse effects, **differences** in susceptibility to adverse effects (long QT syndrome)
Outcomes	**Higher** crude morbidity/mortality at higher LVEFs and **lower** crude morbidity/mortality at lower LVEFs, but **lower adjusted** morbidity/mortality regardless of LVEF

So… Do We Need Sex Specific HF Diagnostic Criteria in 2020?

- In my opinion, the DIAGNOSIS of HF should NOT differ based on GENDER
- However, we DO need to better recognize that SEX-RELATED differences EXIST between women and men with HF:
  - Pathophysiology of HF, phenotypes and etiology
  - Comorbid conditions and CV risk factors differ between women and men
  - Access to CV/HF therapy and response to HF therapy differ between women and men
  - Clinical outcomes differ between women and men (differences may vary depending on context – long-term/outpatients vs. acute/inpatients)
- Studies on HF - population registries and clinical trials – should include enough women to allow for analyses that relate to sex-related differences
- Our understanding of these gender differences is incomplete and should be improved