מגדר ואי ספיקה של הלב הסוכרתי:
מה מייחד אישה מהגבר

ד"ר מיכל לאופר פרל

מנהלת מרפאות הלב

מנהלת שירות אי ספיקת לב

המרכז הרפואי תל אביב ע"ש סוראסקי

מזכירת החוג למחלות שריר הלב, האיגור הקרדיולוגי הישראלי

AstraZeneca ההרצאה בחסות

HF, and T2D are interrelated, leading to a vicious circle of cardiac, renal and metabolic risk

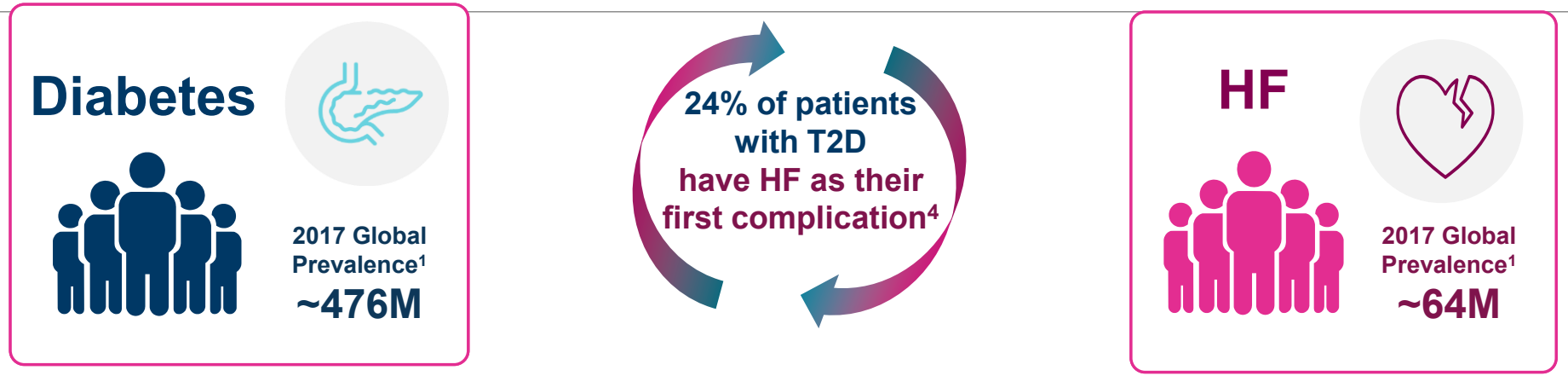
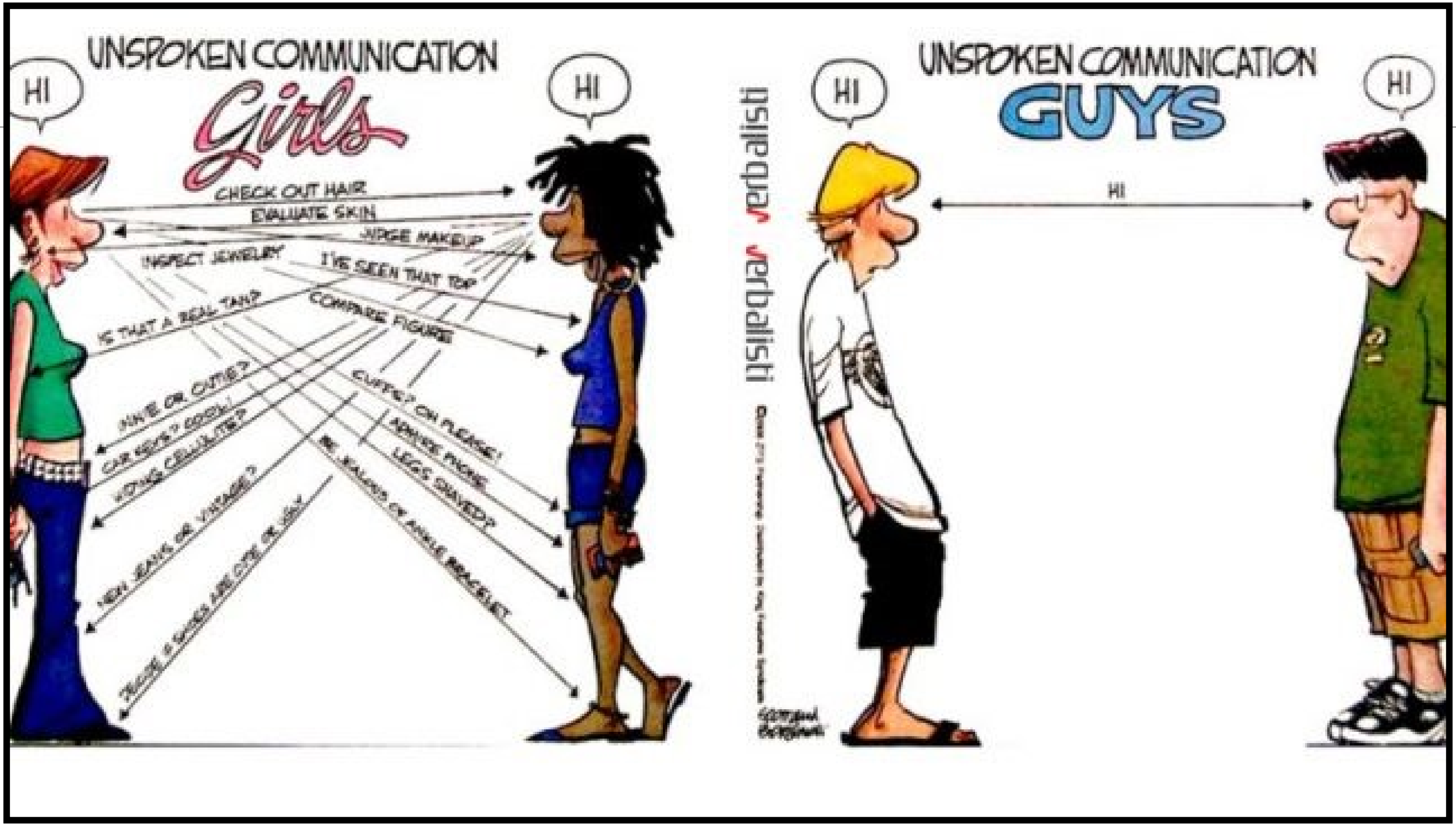


Table 2 Prevalence of type 2 diabetes mellitus in patients with heart failure in the general population

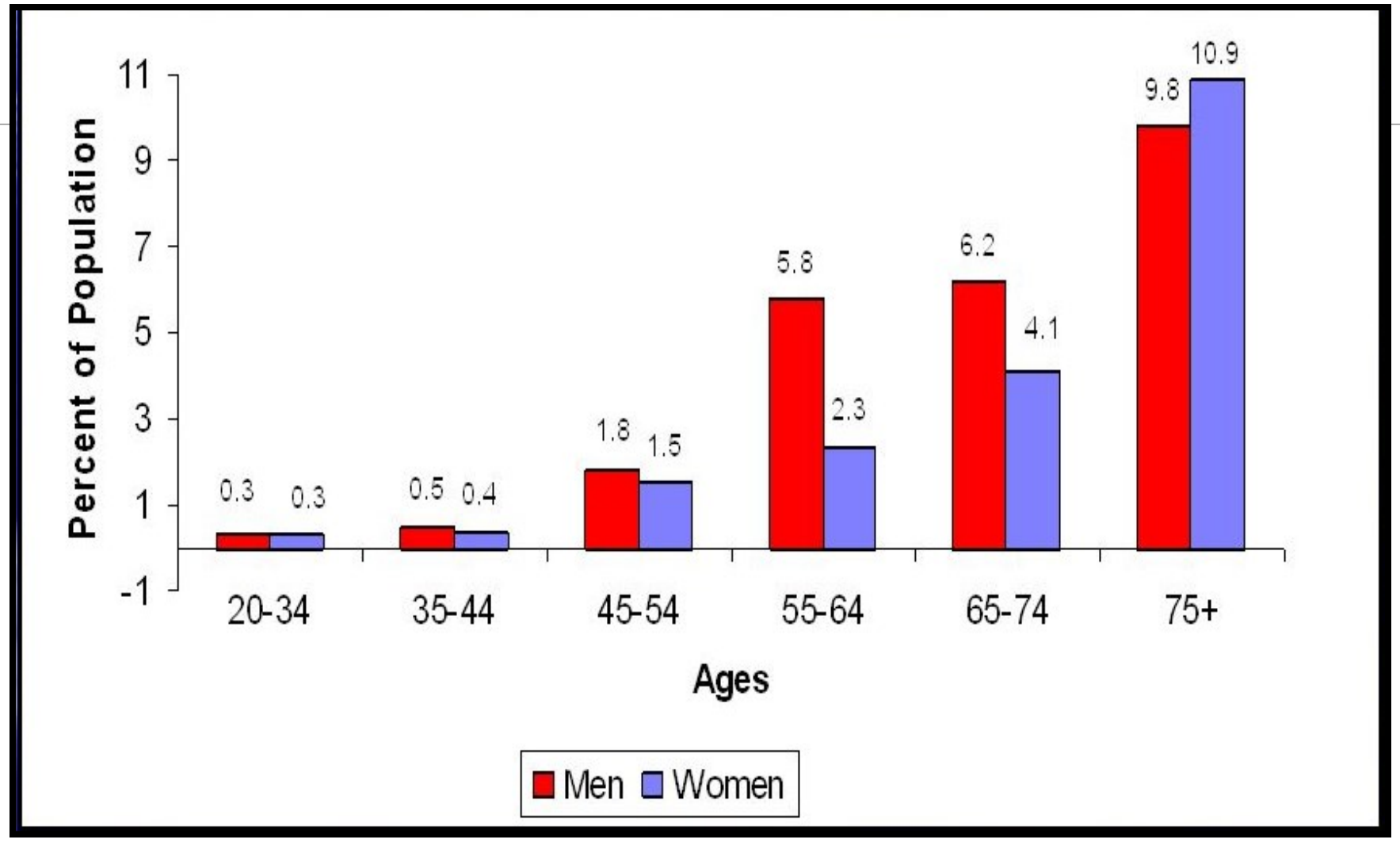
Study	Year of publication	Age (years)	Prevalence of T2DM in HF	Prevalence of T2DM without HF
England[25]	2001	>45	24%	3%
Rotterdam[26]	2001	55–94	18%	10%
Italy[27]	1997	>65	30%	13%
Reykjavik[9]	2005	33–84	12%	3%
Copenhagen[28]	2005	Mean 69	25%	NA
USA, Olmsted County[29]	2006	Mean 77	20%	NA

HF, heart failure; NA, not available (cohort of HF patients only); T2DM, type 2 diabetes mellitus.

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. *Lancet.* 2018;392:1789-1858; 2. Ronco C et al. *J Am Coll Cardiol.* 2008;52:1527-1539;
3. Parving HH et al. *Kidney Int.* 2006;69:2057-2063; 4. Birkeland KI et al. *Diabetes Obes Metab. 2020:*22:1607-1618., European journal of heart failure. Type 2 diabetes mellitus and heart failure. 2018.


UNSPOKEN COMMUNICATION
Girls
HI
HI
CHECK OUT HAIR
EVALUATE SKIN
JUDGE MAKEUP
INSPECT JEWELRY
I'VE SEEN THAT TOP
IS THAT A REAL TAN?
COMPARE FIGURES
CUPPIE? OH PLEASE!
ADMIRE PIONE
LEGS SHAVED?
CAR KEYS? GOOD!
NEW JEANS OR VINTAGE?
UNSPOKEN COMMUNICATION
GUYS
HI
HI
HI

Heart Failure and Gender differences by age

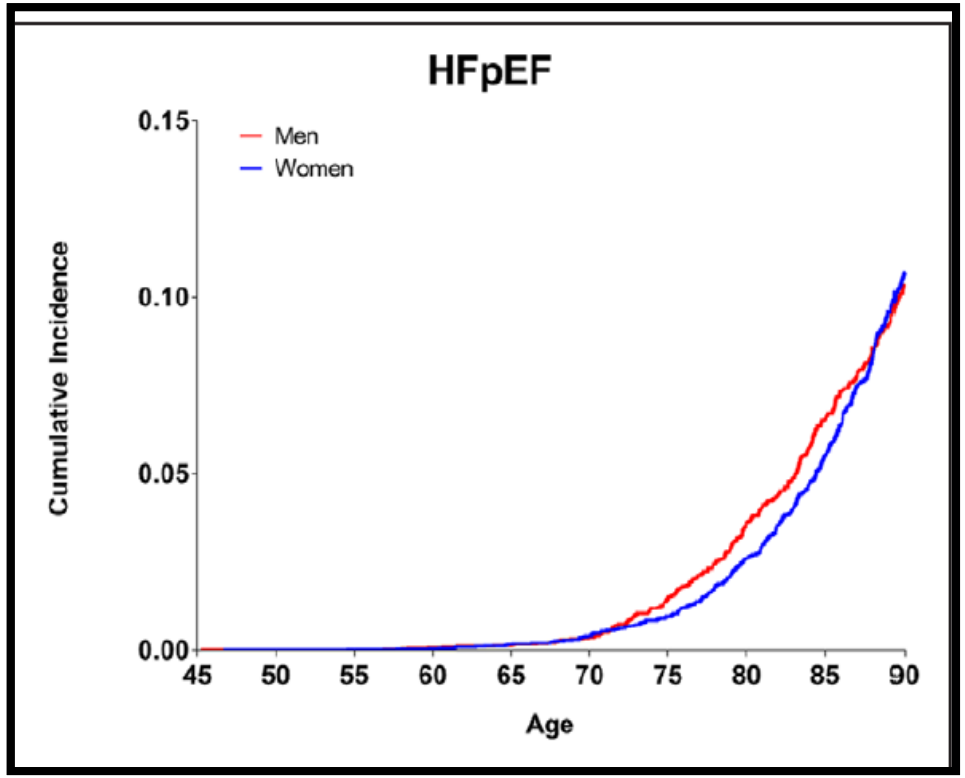


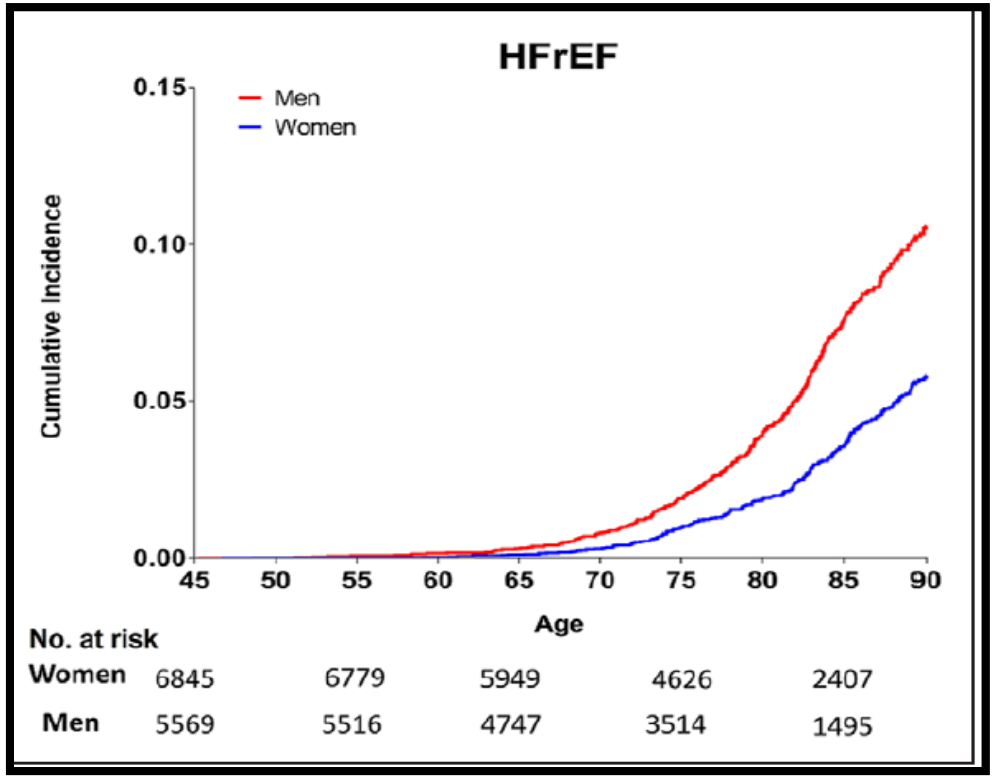
Braunwald, 11th edition.

Higher female prevalence in HFpEF

TABLE 1 Selected Baseline Characteristics According to Sex and HF Phenotype

	HFpEF (N = 9,957)		HFmrEF (N = 9,225)		HFrEF (N = 23,805)	
	Males (n = 4,515, 45%)	Females (n = 5,442, 55%)	Males (n = 5,596, 61%)	Females (n = 3,629, 39%)	Males (n = 16,949, 71%)	Females (n = 6,856, 29%)



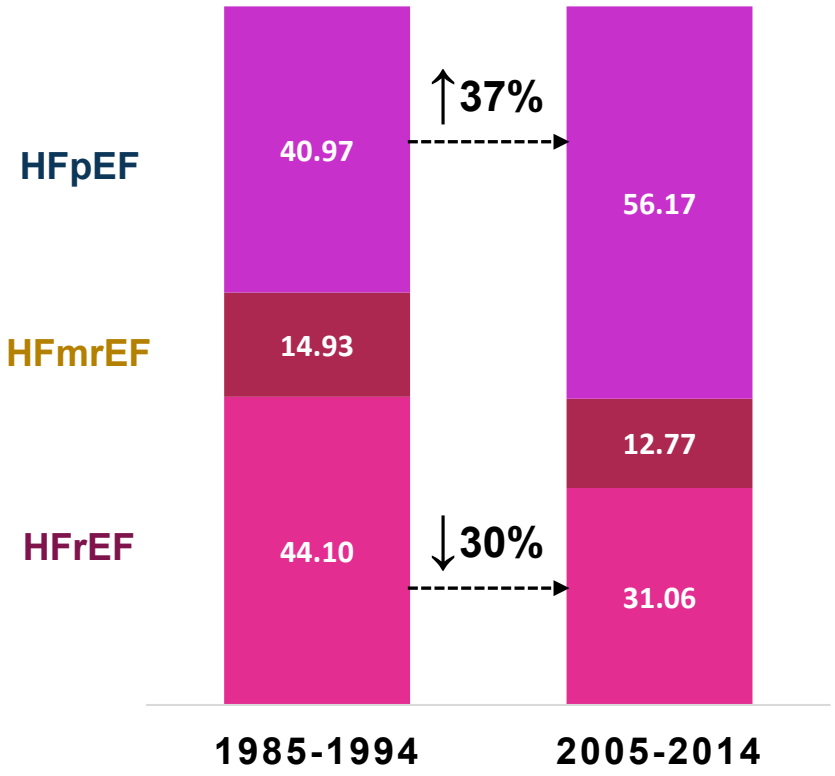


Stolfo et al. JACC Heart Failure 2019

HFpEF

HFpEF Prevalence Rising

Percentage of Patients Within Each LVEF Category[1,a]



Reasons for Increased HFpEF Prevalence[2]

Increasing Life Expectancy and Aging of the Population

- Global population is rapidly aging
- Rate of HFpEF among patients with HF increases with age
- Increase in comorbidities associated with aging

Epidemic of Cardiac and Non-cardiac Comorbidities

- Improved survival after onset of CAD
- Rate of AF increasing due to an aging general population and increased longevity
- Increasing incidence of **obesity, metabolic syndrome, and diabetes**

Increased Clinical Recognition

- Improved diagnostic techniques
- Development of diagnostic guidelines

[a]HF prevalence data for 894 outpatients with new onset HF from the community based, Framingham Study over 3 decades (1985-2014). LVEF categories were defined as HFrEF (EF <40%), HF with mid-range EF (EF 40-<50%), and HFpEF (EF ≥50%).

AF = atrial fibrillation; CAD = coronary artery disease; EF = ejection fraction; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction.

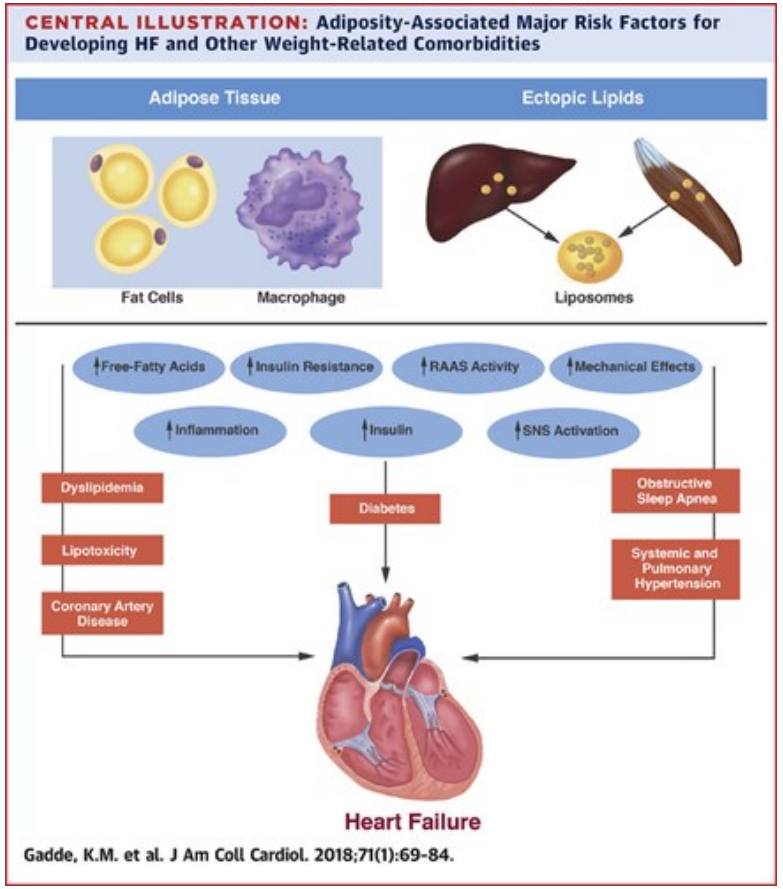
1. Vasan RS et al. *JACC Cardiovasc Imaging*. 2018;11:1-11; 2. Oktay AA et al. *Curr Heart Fail Rep*. 2013;10:401-410.

Table 2 **Principal clinical and pathophysiological characteristics of inflammatory-metabolic heart failure with a preserved ejection fraction**

- Exertional dyspnoea due to heart failure with a left ventricular ejection fraction that is generally >40%
- Primarily a disease of women
- Generally accompanied by a chronic systemic inflammatory or metabolic disorder that is characterized by a derangement of adipose tissue biology (e.g. obesity, diabetes, metabolic syndrome, non-alcoholic fatty liver disease, rheumatoid arthritis, psoriasis)
- Increased biomarkers reflecting systemic inflammation or insulin resistance (e.g. C-reactive protein)
- Mildly increased systolic blood pressure or taking medications for the treatment of hypertension
- Echocardiography reveals normal to modestly increased left ventricular volumes (indexed for gender and body surface area), generally with diastolic filling abnormalities, but without marked septal thickening
- Magnetic resonance imaging demonstrates increased epicardial adipose tissue volume, with variable degrees of fibrosis
- Coronary microvascular dysfunction, ideally measured by reduced coronary flow reserve during adenosine-induced hyperaemia, but approximated by provocative testing during non-invasive imaging
- Renal dysfunction (typically, an estimated glomerular filtration rate of 50–80 mL/min/1.73 m^2), with evidence of increased perirenal fat or renal microvascular disease related to systemic inflammation
- Potentially impaired systemic venous capacitance (often with plasma volume expansion) leading to an increase in central blood volume
- Potential reduction in adverse heart failure-related outcomes with mineralocorticoid receptor antagonists and neprilysin inhibitors

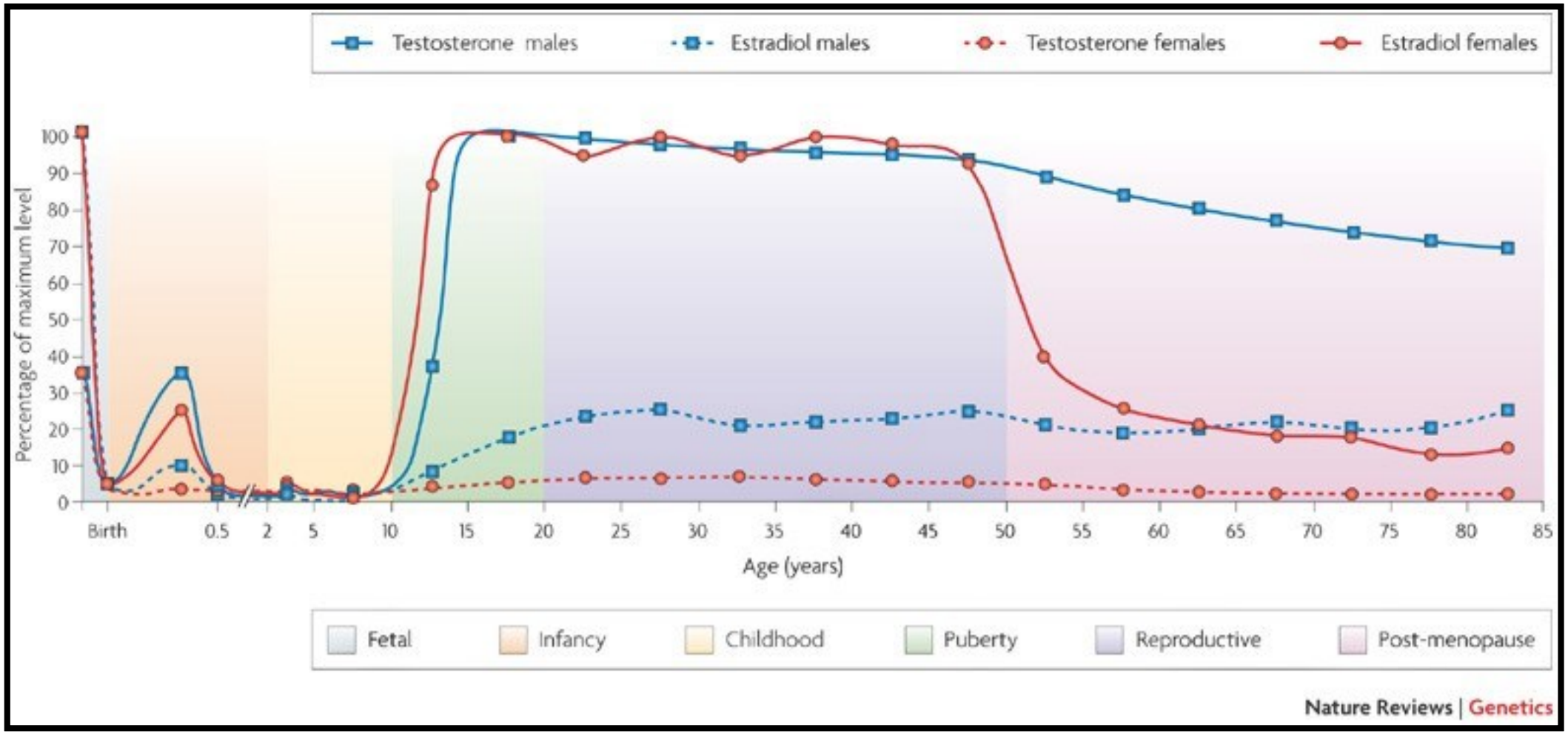
Pathophysiology

- The majority have a phenotype linked to systemic and adipose tissue inflammation, and is **primarily seen in women**.
- **Obesity** causes greater structural changes in the hearts of women.
- **Both adiposity and diabetes are important determinants of LV mass and wall thickness in women, but not in men**.
- Epicardial fat volume particularly increased in **women**, particularly as they age and become postmenopausal.
- Epicardial fat accompanied by inflammation, increases in systolic blood pressure, coronary microcirculatory abnormalities and abnormalities of diastolic filling in **women**, but not in men.
- Intramyocardial fat accumulation particularly characteristic of **women**



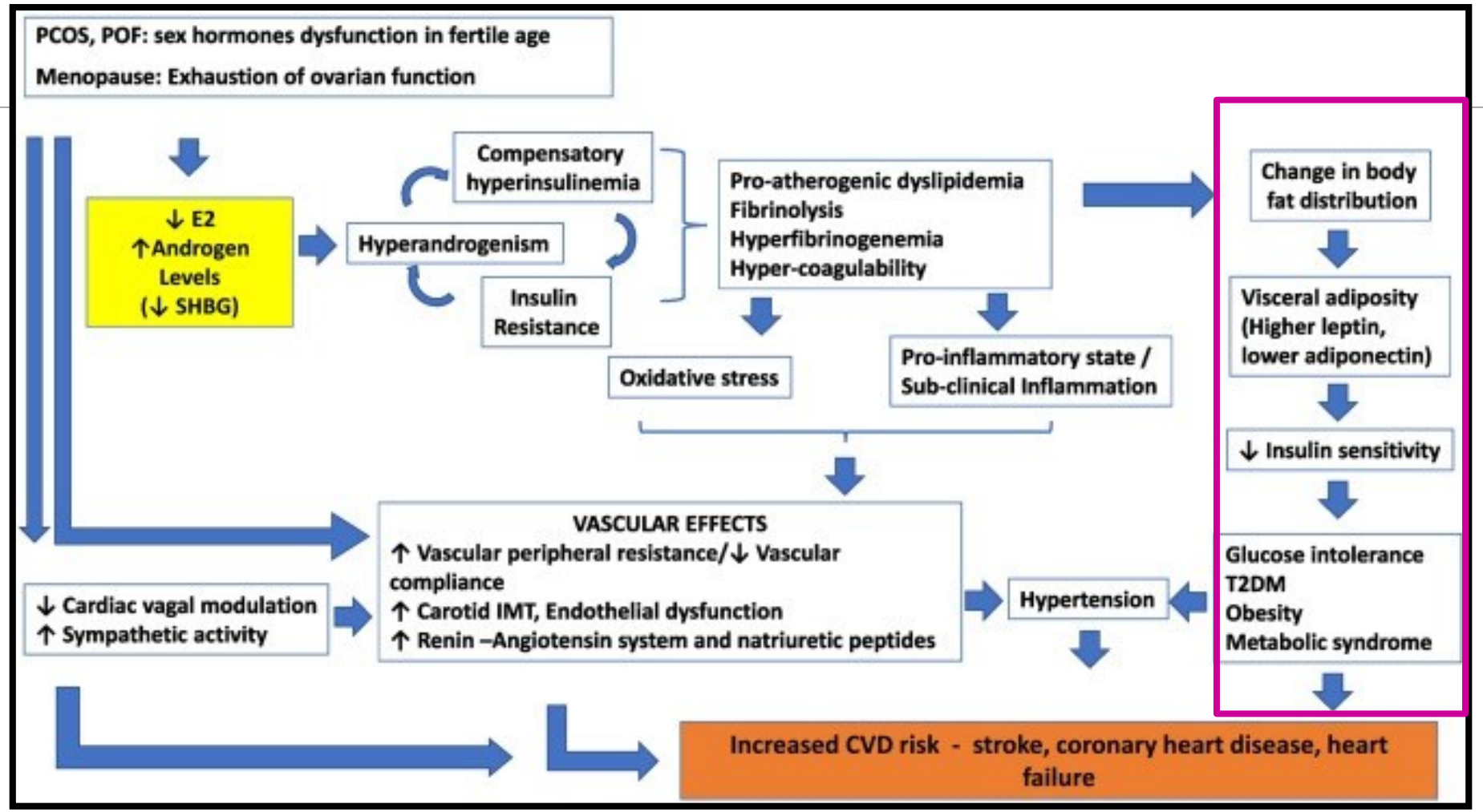
WHY?

Sex Hormones changes over life time



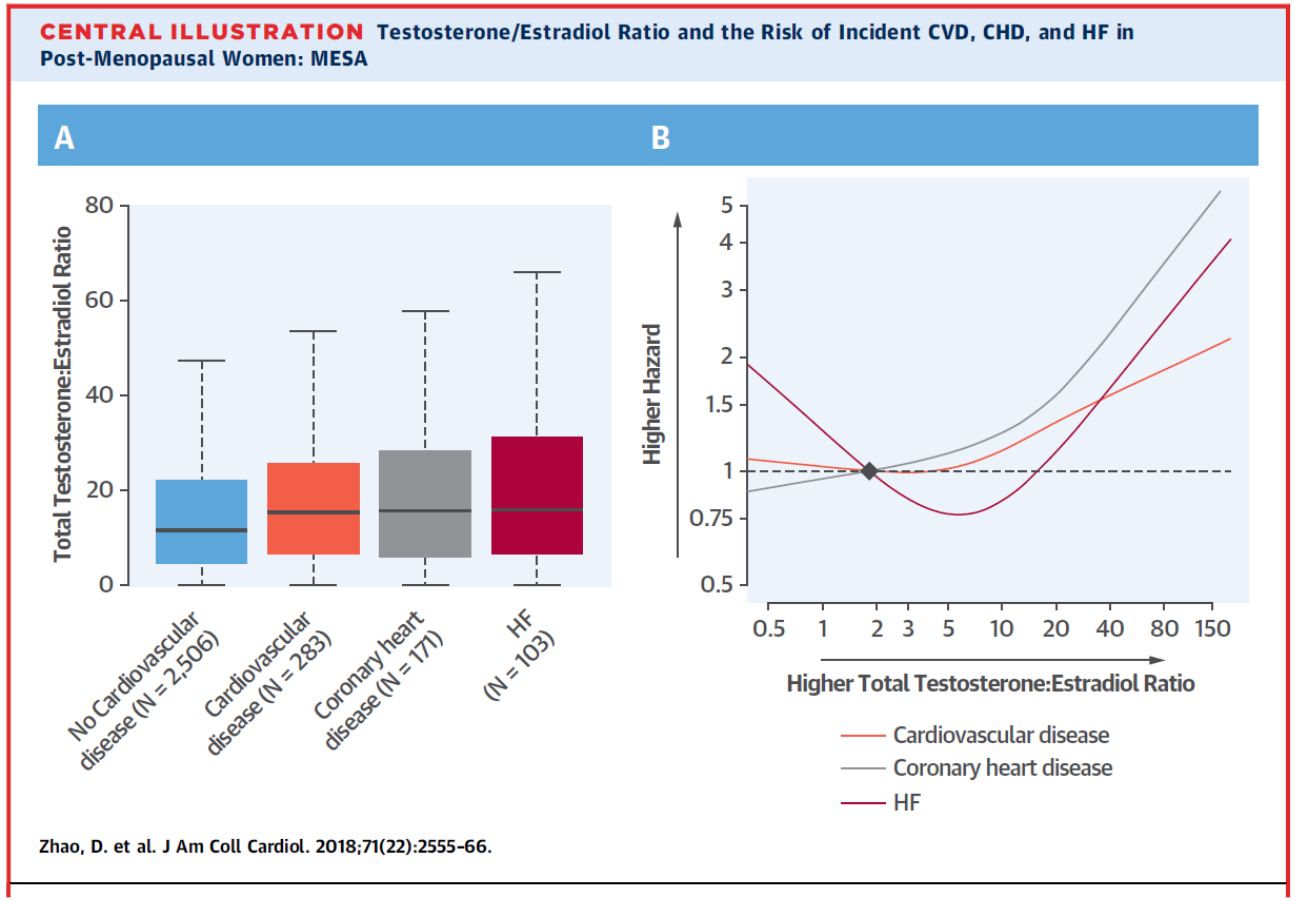
Ober C et al. Nat Rev Genetics 2008

Sex Hormones and Cardiovascular Risk



Maffei S et al. Int J Cardiol 2019

- A higher total testosterone/estradiol ratio independently associated with an increased risk of incident CVD, CHD, and HF.



Treatment

ESC HF 2020 – No specific therapy, all trials were negative

Recommendations for the treatment of patients with heart failure with preserved ejection fraction

Recommendations	Class[a]	Level[b]
Screening for, and treatment of, aetiologies, and cardiovascular and non-cardiovascular comorbidities is recommended in patients with HFpEF (see relevant sections of this document).	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.[137]	I	C

Treatment – Spironolactone

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 10, 2014 VOL. 370 NO. 15

Spironolactone for Heart Failure with Preserved Ejection Fraction

Bertram Pitt, M.D., Marc A. Pfeffer, M.D., Ph.D., Susan F. Assmann, Ph.D., Robin Boineau, M.D., Inder S. Anand, M.D., Brian Claggett, Ph.D., Nadine Clausell, M.D., Ph.D., Akshay S. Desai, M.D., M.P.H., Rafael Diaz, M.D., Jerome L. Fleg, M.D., Ivan Gordeev, M.D., Ph.D., Brian Harty, M.A., John F. Heitner, M.D., Christopher T. Kenwood, M.S., Eldrin F. Lewis, M.D., M.P.H., Eileen O'Meara, M.D., Jeffrey L. Probstfield, M.D., Tamaz Shaburishvili, M.D., Ph.D., Sanjiv J. Shah, M.D., Scott D. Solomon, M.D., Nancy K. Sweitzer, M.D., Ph.D., Song Yang, Ph.D., and Sonja M. McKinlay, Ph.D., for the TOPCAT Investigators*

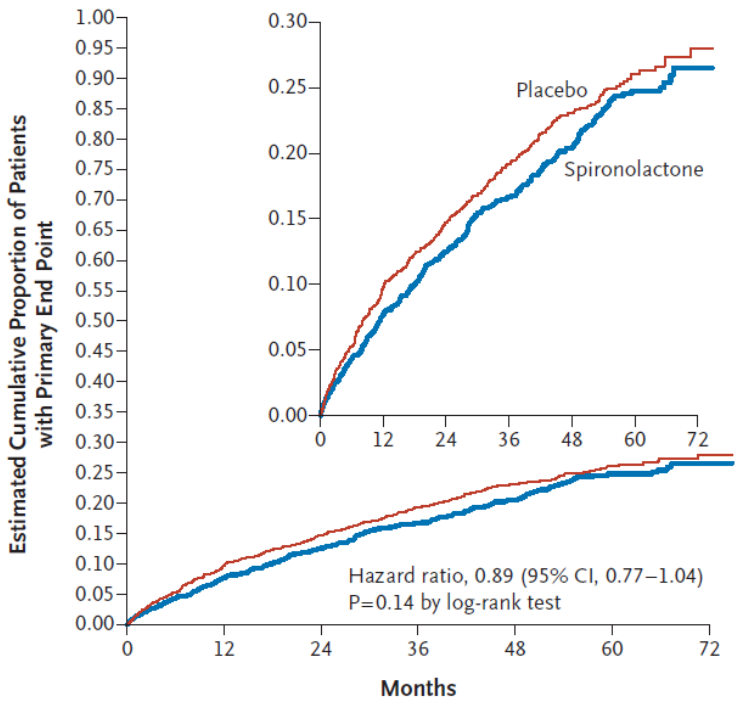


Figure 1. Kaplan–Meier Plot of Time to the First Confirmed Primary-Outcome Event.

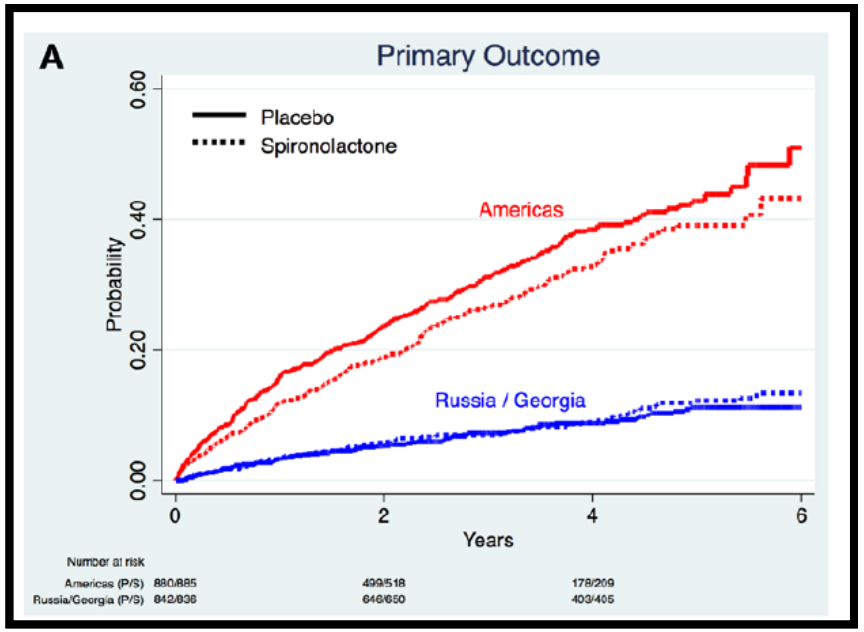
Table 2. Incidence Rates of the Primary Composite Outcome, Its Components, and Additional Secondary Outcomes.*

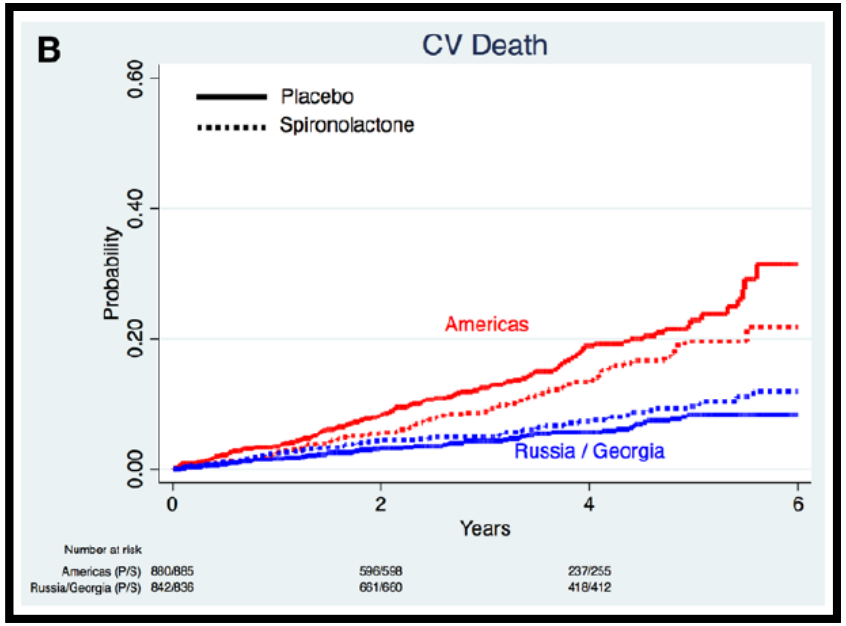
Outcome	Spironolactone (N=1722)		Placebo (N=1723)		Hazard Ratio with Spironolactone (95% CI)†	P Value
	Participants with Event	Incidence Rate	Participants with Event	Incidence Rate		
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary outcome	320 (18.6)	5.9	351 (20.4)	6.6	0.89 (0.77–1.04)	0.14
Components of the primary outcome						
Death from cardiovascular causes	160 (9.3)	2.8	176 (10.2)	3.1	0.90 (0.73–1.12)	0.35
Aborted cardiac arrest	3 (0.2)	0.05	5 (0.3)	0.09	0.60 (0.14–2.50)	0.48
Hospitalization for heart failure	206 (12.0)	3.8	245 (14.2)	4.6	0.83 (0.69–0.99)	0.04
Additional secondary outcomes						
Death from any cause	252 (14.6)	4.2	274 (15.9)	4.6	0.91 (0.77–1.08)	0.29
Hospitalization for any reason	766 (44.5)	18.8	792 (46.0)	20.0	0.94 (0.85–1.04)	0.25
Myocardial infarction	65 (3.8)	1.2	64 (3.7)	1.1	1.00 (0.71–1.42)	0.98
Stroke	57 (3.3)	1.0	60 (3.5)	1.1	0.94 (0.65–1.35)	0.73

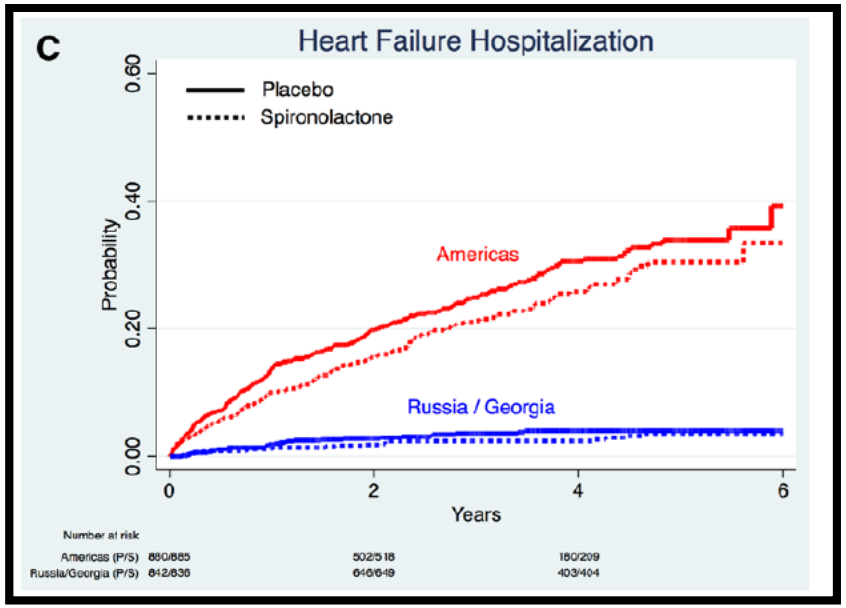
Heart Failure

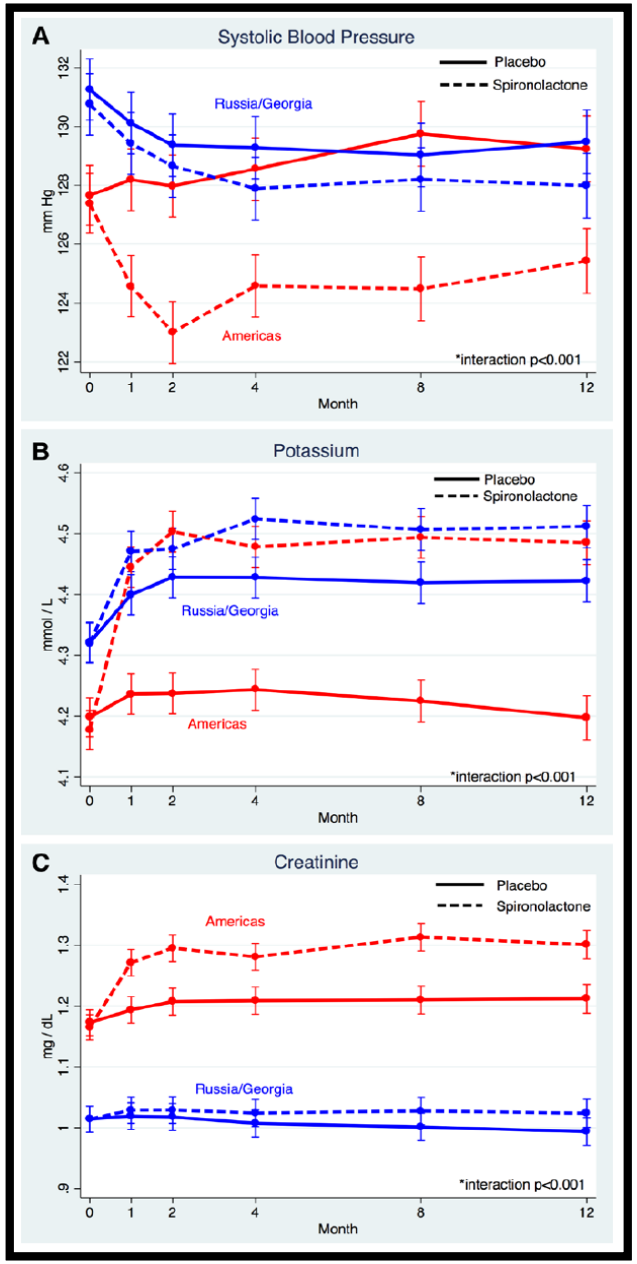
Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial

Marc A. Pfeffer, MD, PhD; Brian Claggett, PhD; Susan F. Assmann, PhD; Robin Boineau, MD; Inder S. Anand, MD; Nadine Clausell, MD, PhD; Akshay S. Desai, MD, MPH; Rafael Diaz, MD; Jerome L. Fleg, MD; Ivan Gordeev, MD; John F. Heitner, MD; Eldrin F. Lewis, MD, MPH; Eileen O'Meara, MD; Jean-Lucien Rouleau, MD; Jeffrey L. Probstfield, MD; Tamaz Shaburishvili, MD, PhD; Sanjiv J. Shah, MD; Scott D. Solomon, MD; Nancy K. Sweitzer, MD, PhD; Sonja M. McKinlay, PhD; Bertram Pitt, MD









Circulation. 2015;131:34-42.

JACC: HEART FAILURE
VOL. 7, NO. 3, 2019

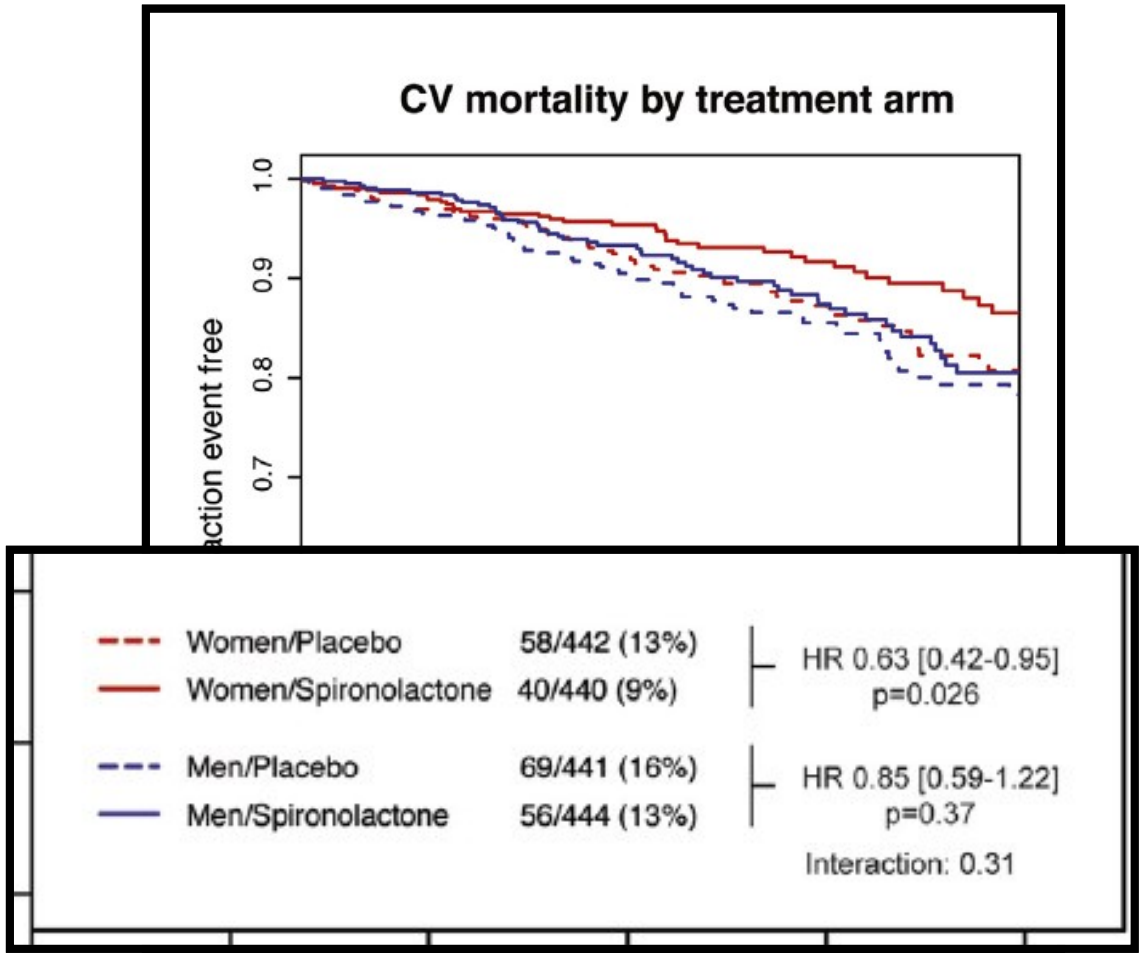
PUBLISHED BY ELSEVIER

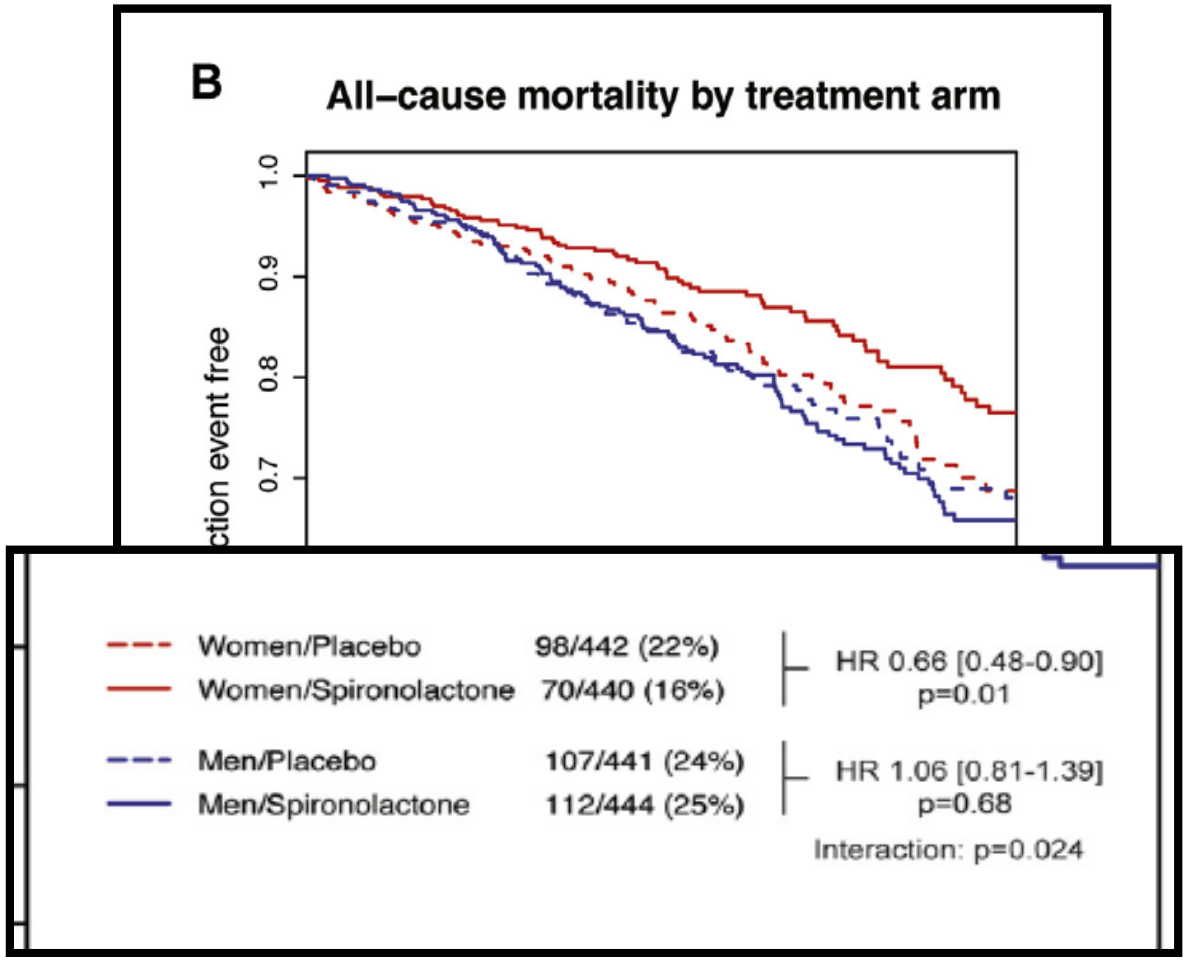
Sex Differences in Outcomes and Responses to Spironolactone in Heart Failure With Preserved Ejection Fraction

A Secondary Analysis of TOPCAT Trial

Miranda Merrill, MD,[a] Nancy K. Sweitzer, MD,[b] JoAnn Lindenfeld, MD,[c] David P. Kao, MD[d]

Reduced CV mortality and all-cause mortality among women





Merrill et al. A C C : H E A R T F A I LUR E. VOL. 7, NO. 3, 2019

Treatment – Sacubitril-Valsartan

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 24, 2019 VOL. 381 NO. 17

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, I.S. Anand, J. Ge, C.S.P. Lam, A.P. Maggioni, F. Martinez, M. Packer, M.A. Pfeffer, B. Pieske, M.M. Redfield, J.L. Rouleau, D.J. van Veldhuisen, F. Zannad, M.R. Zile, A.S. Desai, B. Claggett, P.S. Jhund, S.A. Boytsov, J. Comin-Colet, J. Cleland, H.-D. Düngen, E. Goncalvesova, T. Katova, J.F. Kerr Saraiva, M. Lelonek, B. Merkely, M. Senni, S.J. Shah, J. Zhou, A.R. Rizkala, J. Gong, V.C. Shi, and M.P. Lefkowitz, for the PARAGON-HF Investigators and Committees*

- Negative primary endpoint in total population
- However…

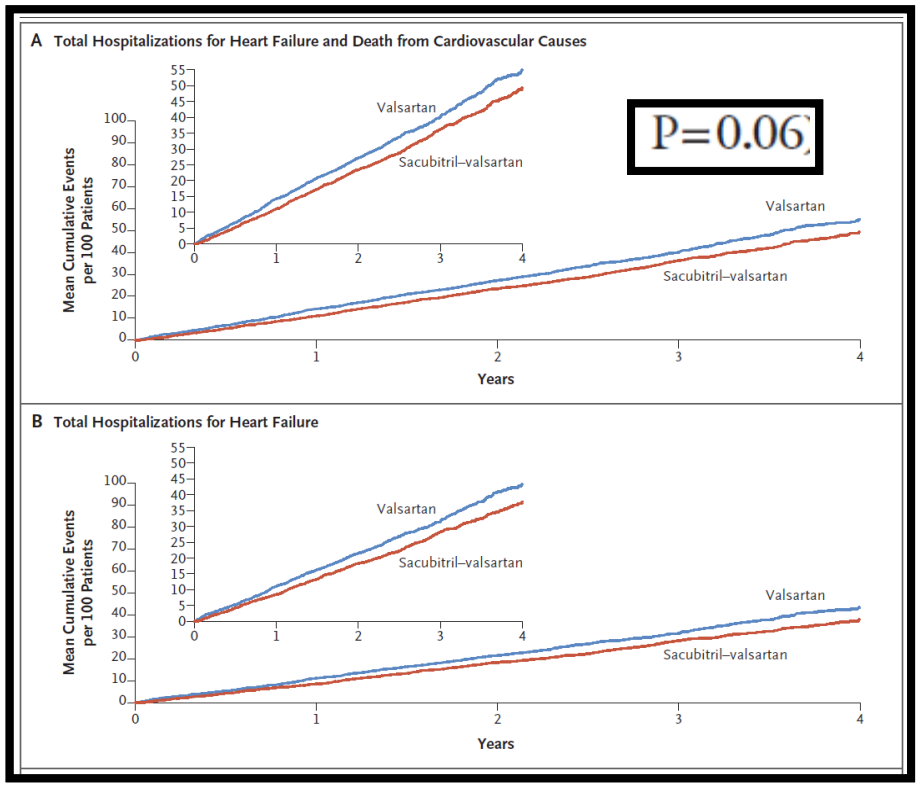
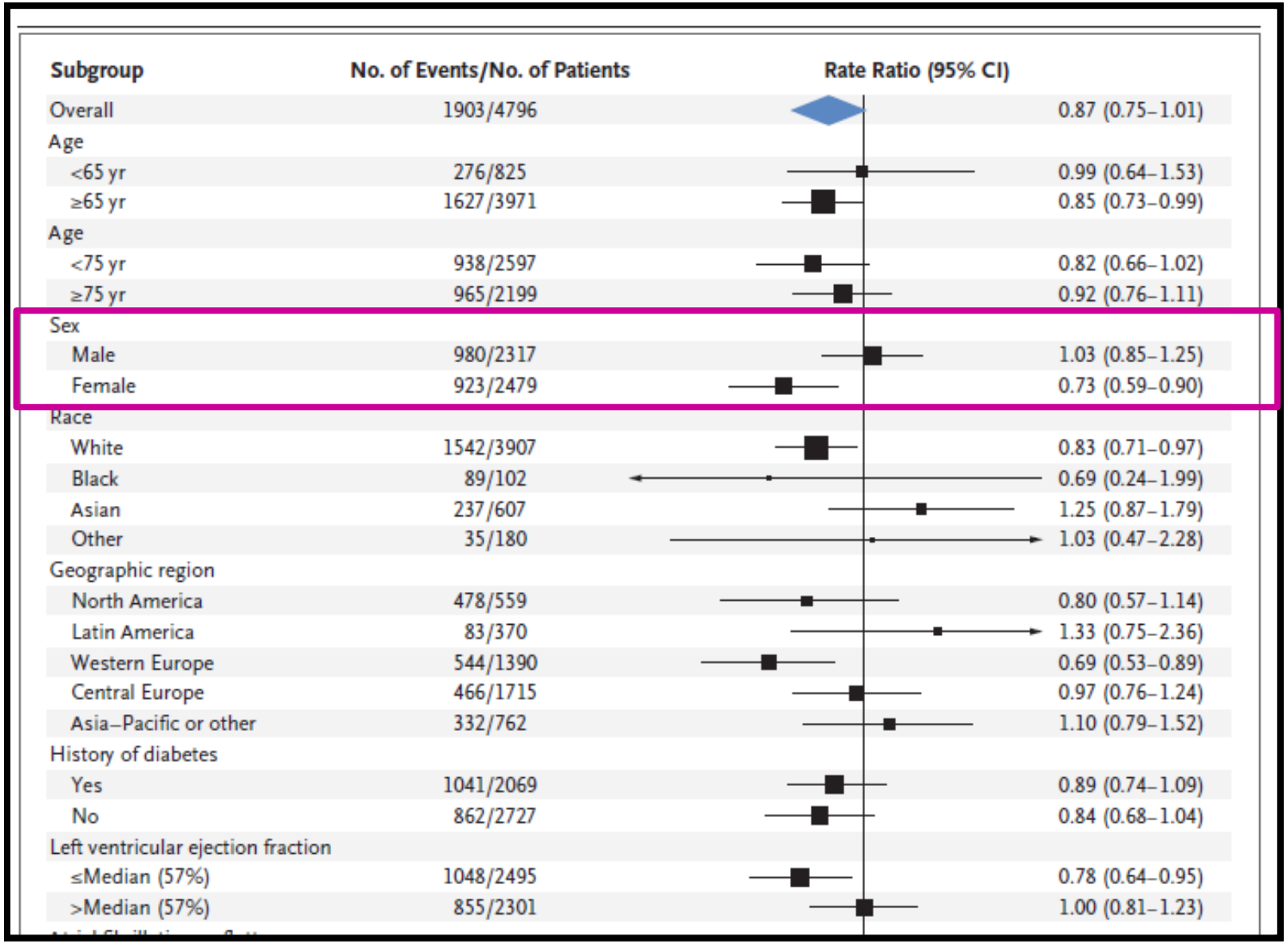


Table 2. Primary and Secondary Outcomes.*

Outcome	Sacubitril–Valsartan (N=2407)	Valsartan (N=2389)	Ratio or Difference (95% CI)
Primary composite outcome and components			
Total hospitalizations for heart failure and death from cardiovascular causes†			RR, 0.87 (0.75–1.01)
Total no. of events	894	1009	
Rate per 100 patient-yr	12.8	14.6	
Total no. of hospitalizations for heart failure	690	797	RR, 0.85 (0.72–1.00)
Death from cardiovascular causes — no. (%)	204 (8.5)	212 (8.9)	HR, 0.95 (0.79–1.16)
Secondary outcomes			
Change in NYHA class from baseline to 8 mo — no./total no. (%)			OR, 1.45 (1.13–1.86)
Improved	347/2316 (15.0)	289/2302 (12.6)	
Unchanged	1767/2316 (76.3)	1792/2302 (77.8)	
Worsened	202/2316 (8.7)	221/2302 (9.6)	
Change in KCCQ clinical summary score at 8 mo‡	−1.6±0.4	−2.6±0.4	Difference, 1.0 (0.0–2.1)
Renal composite outcome — no. (%)§	33 (1.4)	64 (2.7)	HR, 0.50 (0.33–0.77)
Death from any cause — no. (%)	342 (14.2)	349 (14.6)	HR, 0.97 (0.84–1.13)

Solomon et al. PARAGON-HF. NEJM 2019

Women benefit with significant reduction in HFH and CV mortality



Subgroup	No. of Events/No. of Patients	Rate Ratio (95% CI)
Overall	1903/4796	0.87 (0.75–1.01)
Age		
<65 yr	276/825	0.99 (0.64–1.53)
≥65 yr	1627/3971	0.85 (0.73–0.99)
Age		
<75 yr	938/2597	0.82 (0.66–1.02)
≥75 yr	965/2199	0.92 (0.76–1.11)
Sex		
Male	980/2317	1.03 (0.85–1.25)
Female	923/2479	0.73 (0.59–0.90)
Race		
White	1542/3907	0.83 (0.71–0.97)
Black	89/102	0.69 (0.24–1.99)
Asian	237/607	1.25 (0.87–1.79)
Other	35/180	1.03 (0.47–2.28)
Geographic region		
North America	478/559	0.80 (0.57–1.14)
Latin America	83/370	1.33 (0.75–2.36)
Western Europe	544/1390	0.69 (0.53–0.89)
Central Europe	466/1715	0.97 (0.76–1.24)
Asia–Pacific or other	332/762	1.10 (0.79–1.52)
History of diabetes		
Yes	1041/2069	0.89 (0.74–1.09)
No	862/2727	0.84 (0.68–1.04)
Left ventricular ejection fraction		
≤Median (57%)	1048/2495	0.78 (0.64–0.95)
>Median (57%)	855/2301	1.00 (0.81–1.23)

Solomon et al. NEJM 2019n engl j med 381;17

As compared with valsartan, sacubitril-valsartan seemed to reduce the risk of heart failure hospitalization more in women than in men

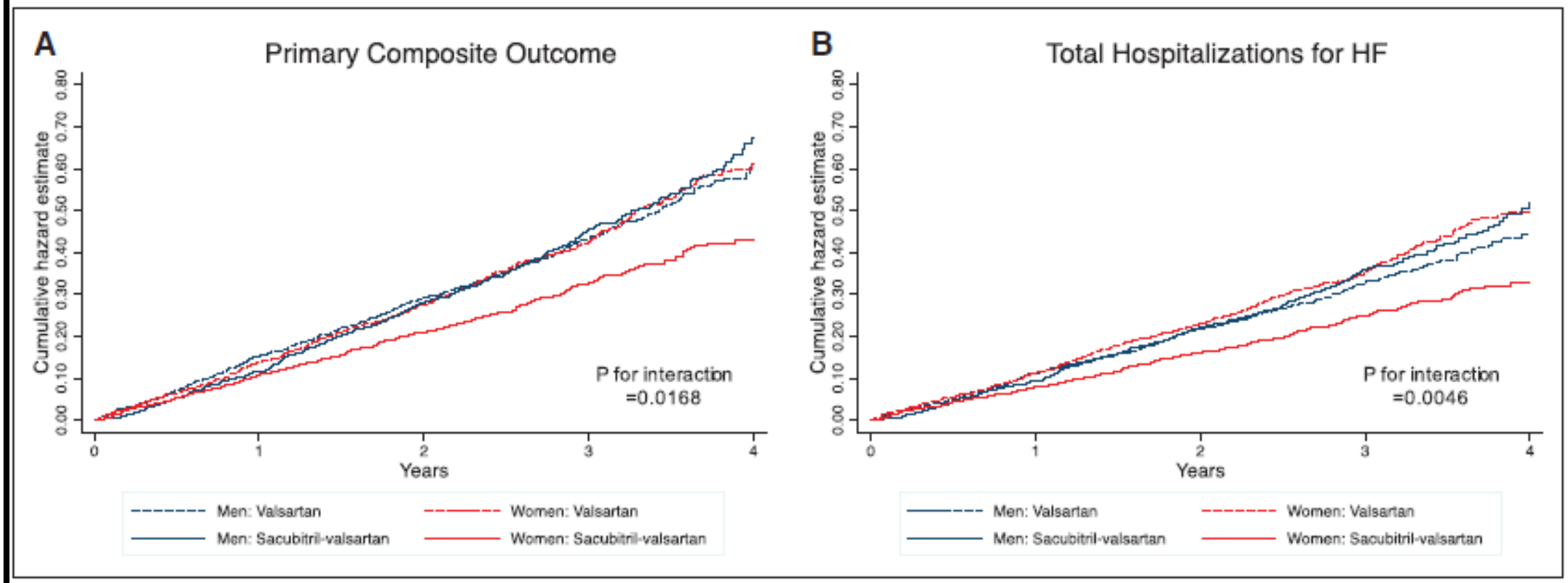


Figure 1. Cumulative hazard estimate for the primary composite outcome and total hospitalizations for heart failure (first and repeat) according to sex and treatment in the PARAGON-HF trial (Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction). **A**, Cumulative hazard estimate for the primary composite outcome. **B**, Cumulative hazard estimate for total hospitalizations for heart failure (HF).

McMurray et al. Circulation 2019

Why?

1. Age-related arterial stiffening is more pronounced in women than in men and has been postulated to be a key pathophysiologic factor in HFpEF.

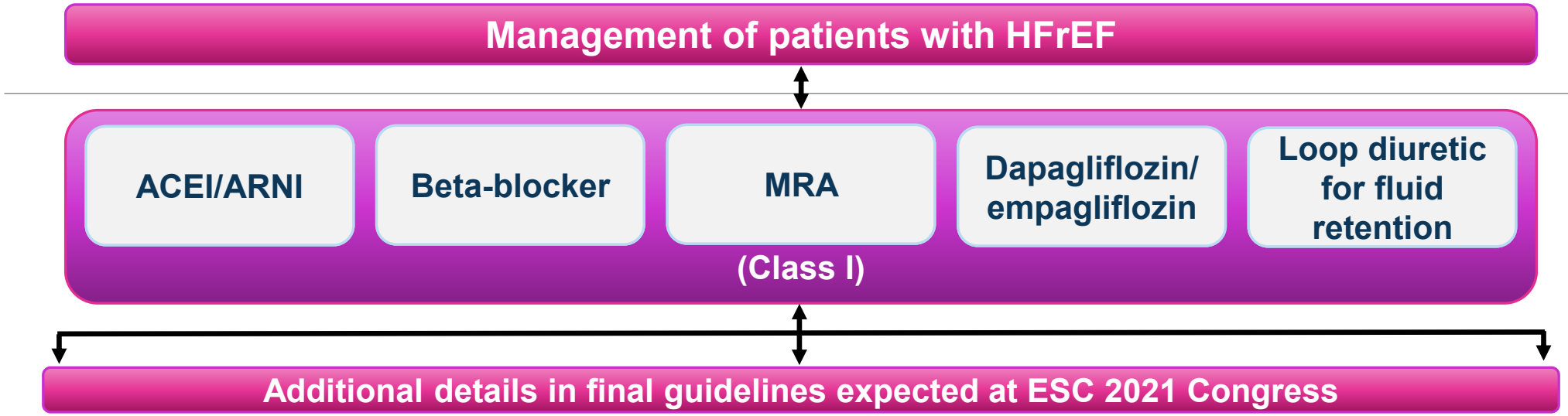
2. Pro-BNP levels are lower in women => more visceral obesity, decrease after menopause => by augmenting natriuretic peptides, sacubitril-valsartan may be of greater benefit in women.

3. A much smaller proportion of women were current or former smokers => smoking was the variable most strongly associated with plasma neprilysin level.

4. Man have been a larger subgroup of patients not responsive to sacubitril-valsartan - cardiac amyloidosis or genetic hypertrophic cardiomyopathy.

Treatment – SGLT2i

ESC 2021 Heart Failure Guidelines: SGLT2 Inhibitors Recommended as First-Line Therapy in All Patients With HFrEF



Drugs recommended in all patients with HFrEF	Class[a]	Level[b]
ACEI is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	I	A
MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACEI in patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B

[a]Class of recommendation; [b]Level of evidence.

ACEI = angiotensin-converting enzyme inhibitor; ARNI = angiotensin-receptor neprilysin inhibitor; ESC = European Society of Cardiology; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid-receptor antagonist; SGLT2 = sodium-glucose cotransporter 2.

Metra M. Presented at ESC-HF 2021 Online Congress; June 29-July 1, 2021.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner–La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S.J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S.P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators*

- 5988 patients with HF and LVEF>40% to receive empagliflozin or matching placebo, in addition to usual therapy.
- The primary outcome was a composite of CV death or hospitalization for HF.

Table 1. Characteristics of the Patients at Baseline.*

Female sex — no. (%)	1338 (44.6)	1338 (44.7)
Race — no. (%)†		
White	2286 (76.3)	2256 (75.4)
Black	133 (4.4)	125 (4.2)
Asian	413 (13.8)	411 (13.7)
Other or missing	165 (5.5)	199 (6.7)
Geographic region — no. (%)		
North America	360 (12.0)	359 (12.0)
Latin America	758 (25.3)	757 (25.3)
Europe	1346 (44.9)	1343 (44.9)
Asia	343 (11.4)	343 (11.5)
Other	190 (6.3)	189 (6.3)
NYHA functional classification — no. (%)		
Class I	3 (0.1)	1 (<0.1)
Class II	2432 (81.1)	2451 (81.9)
Class III	552 (18.4)	531 (17.8)
Class IV	10 (0.3)	8 (0.3)
Body-mass index‡	29.77±5.8	29.90±5.9
Heart rate — beats per minute	70.4±12.0	70.3±11.80
Systolic blood pressure — mm Hg	131.8±15.6	131.9±15.7
Left ventricular ejection fraction		
Mean left ventricular ejection fraction — %	54.3±8.8	54.3±8.8
Left ventricular ejection fraction >40% to <50% — no. (%)§	995 (33.2)	988 (33.0)
Left ventricular ejection fraction ≥50% to <60% — no. (%)	1028 (34.3)	1030 (34.4)
Left ventricular ejection fraction ≥60% — no. (%)	974 (32.5)	973 (32.5)
Median NT-proBNP (interquartile range) — pg/ml	994 (501–1740)	946 (498–1725)
Heart failure category — no. (%)		
Ischemic	1079 (36.0)	1038 (34.7)
Nonischemic	1917 (64.0)	1953 (65.3)
Cardiovascular history — no. (%)		
Diabetes mellitus	1466 (48.9)	1472 (49.2)
Hypertension	2721 (90.8)	2703 (90.4)

Positive Primary endpoint!

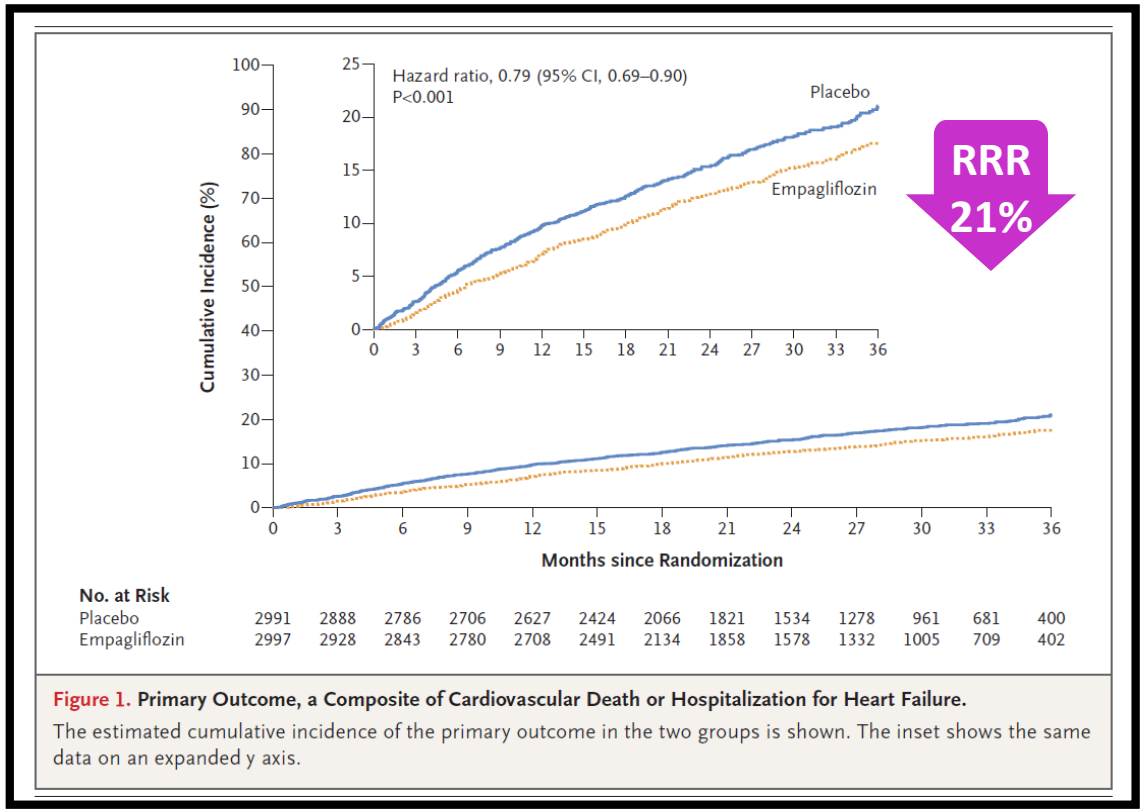


Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.
The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

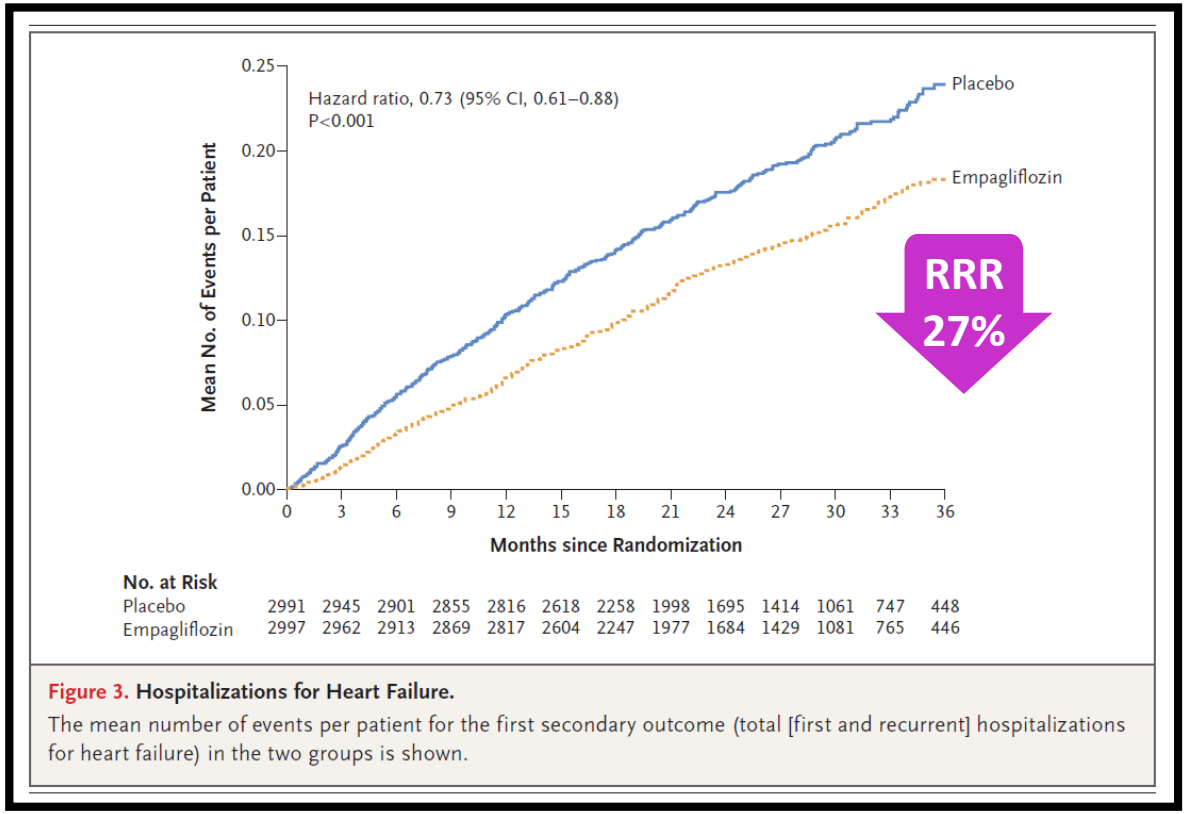


Figure 3. Hospitalizations for Heart Failure.
The mean number of events per patient for the first secondary outcome (total [first and recurrent] hospitalizations for heart failure) in the two groups is shown.

Anker et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. DOI: 10.1056/NEJMoa2107038

Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Overall	415/2997	511/2991	0.79 (0.69–0.90)
Diabetes at baseline			
Yes	239/1466	291/1472	0.79 (0.67–0.94)
No	176/1531	220/1519	0.78 (0.64–0.95)
LVEF at baseline			
<50%	145/995	193/988	0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64–0.99)
≥60%	132/974	145/973	0.87 (0.69–1.10)
Age			
<70 yr	134/1066	152/1084	0.88 (0.70–1.11)
≥70 yr	281/1931	359/1907	0.75 (0.64–0.87)
Sex			
Male	253/1659	297/1653	0.81 (0.69–0.96)
Female	162/1338	214/1338	0.75 (0.61–0.92)

No sex differences

Anker et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. DOI: 10.1056/NEJMoa2107038

No sex differences in all Endpoints

Table 2. Effect of Empagliflozin on Primary and Secondary Outcomes According to Sex

	Placebo		Empagliflozin			
	n/N	Events/100 patient-y	n/N	Events/100 patient-y	HR (95% CI)	$P_{interaction}$
Cardiovascular death or HF hospitalization						
Men	297/1653	9.15	253/1659	7.59	0.81 (0.69, 0.96)	0.536
Women	214/1338	8.09	162/1338	5.97	0.75 (0.61, 0.92)	
Total (first and recurrent) HF hospitalization						
Men	308		253		0.75 (0.59, 0.95)	0.780
Women	233		154		0.71 (0.53, 0.94)	
First HF hospitalization						
Men	198/1653	6.10	151/1659	4.53	0.72 (0.58, 0.89)	0.836
Women	154/1338	5.82	108/1338	3.98	0.70 (0.54, 0.89)	
Cardiovascular death						
Men	148/1653	4.17	138/1659	3.90	0.94 (0.74, 1.18)	0.673
Women	96/1338	3.37	81/1338	2.83	0.86 (0.64, 1.16)	
All-cause mortality						
Men	267/1653	7.53	269/1659	7.60	1.02 (0.86, 1.20)	0.778
Women	160/1338	5.61	153/1338	5.35	0.98 (0.78, 1.22)	

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, B. Claggett, R.A. de Boer, D. DeMets, A.F. Hernandez, S.E. Inzucchi, M.N. Kosiborod, C.S.P. Lam, F. Martinez, S.J. Shah, A.S. Desai, P.S. Jhund, J. Belohlavek, C.-E. Chiang, C.J.W. Borleffs, J. Comin-Colet, D. Dobreanu, J. Drozdz, J.C. Fang, M.A. Alcocer-Gamba, W. Al Habeeb, Y. Han, J.W. Cabrera Honorio, S.P. Janssens, T. Katova, M. Kitakaze, B. Merkely, E. O'Meara, J.F.K. Saraiva, S.N. Tereshchenko, J. Thierer, M. Vaduganathan, O. Vardeny, S. Verma, V.N. Pham, U. Wilderäng, N. Zaozerska, E. Bachus, D. Lindholm, M. Petersson, and A.M. Langkilde, for the DELIVER Trial Committees and Investigators*

- 6263 patients with HF and LVEF>40% to receive dapagliflozin or matching placebo, in addition to usual therapy.
- The primary outcome was a composite of worsening HF or CV death.

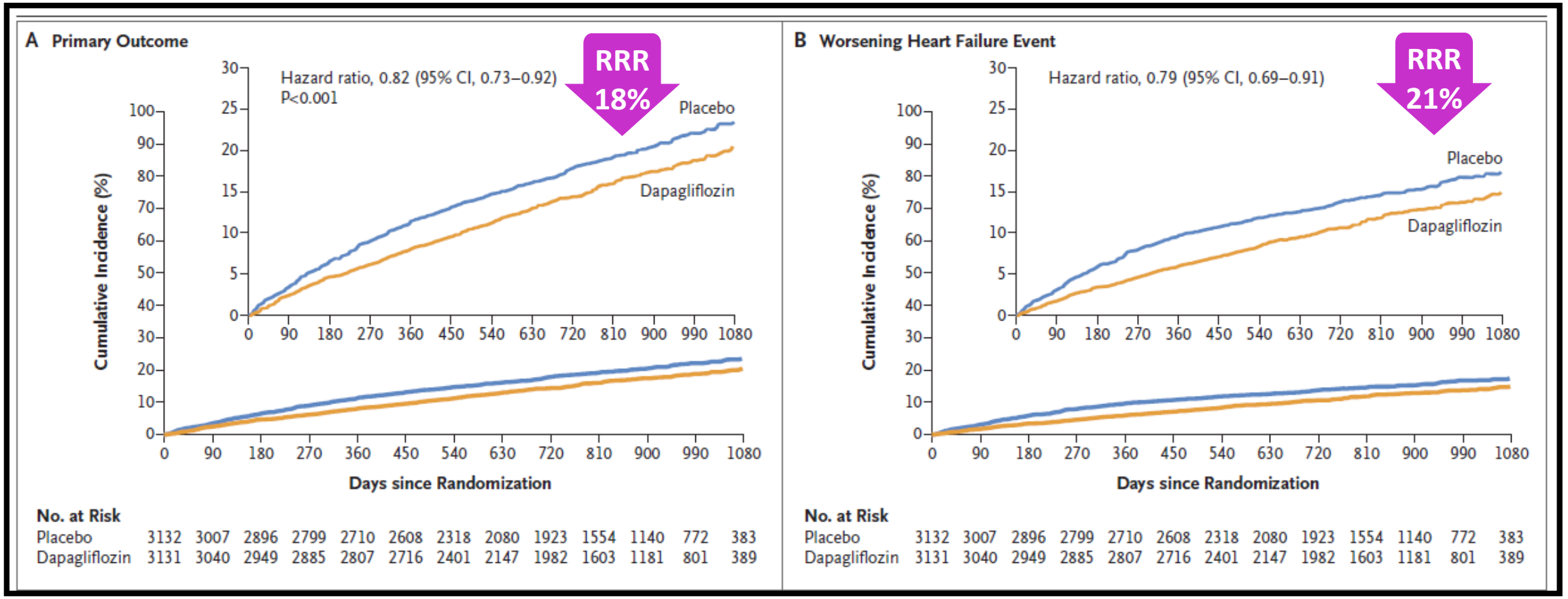
Table 1. Characteristics of the Patients at Baseline.*

Female sex — no. (%)	1364 (43.6)	1383 (44.2)
Race — no. (%)†		
Asian	630 (20.1)	644 (20.6)
Black	81 (2.6)	78 (2.5)
White	2214 (70.7)	2225 (71.0)
Other	206 (6.6)	185 (5.9)
Geographic region — no. (%)		
North America	428 (13.7)	423 (13.5)
Latin America	602 (19.2)	579 (18.5)
Europe or Saudi Arabia	1494 (47.7)	1511 (48.2)
Asia	607 (19.4)	619 (19.8)
NYHA class — no. (%)‡		
II	2314 (73.9)	2399 (76.6)
III	807 (25.8)	724 (23.1)
IV	10 (0.3)	8 (0.3)
Left ventricular ejection fraction		
Mean — %	54.0±8.6	54.3±8.9
Distribution — no. (%)		
≤49%	1067 (34.1)	1049 (33.5)
50–59%	1133 (36.2)	1123 (35.9)
≥60%	931 (29.7)	960 (30.7)
Medical history — no. (%)		
Type 2 diabetes mellitus	1401 (44.7)	1405 (44.9)

Female sex — no. (%) 1364 (43.6) 1383 (44.2)
Type 2 diabetes mellitus 1401 (44.7) 1405 (44.9)

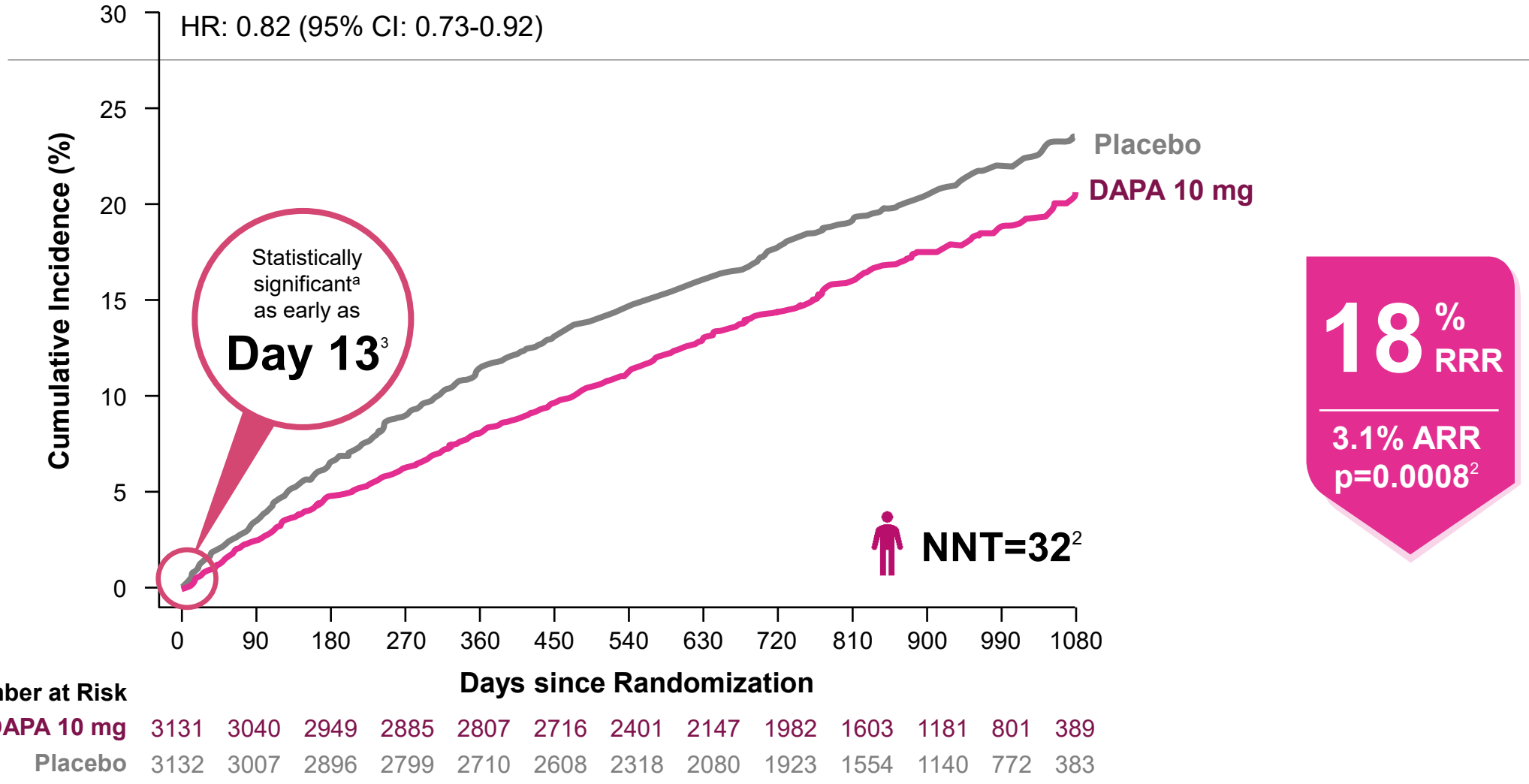
Solomon et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. DOI: 10.1056/NEJMoa2206286

Positive Primary endpoint!



Solomon et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. DOI: 10.1056/NEJMoa2206286

Primary Composite of CV Death, hHF or Urgent HF Visit[1]



[a]Nominal significance at Day 13 (HR, 0.45; 95% CI, 0.20-0.99; p=0.046), with sustained statistical significance starting at Day 15.

1. Solomon SD et al. *N Engl J Med*. 2022;387(12):1089-1098; 2. Solomon SD. Presented at: ESC Congress; August 26-29, 2022; Barcelona, Spain; 3. Vaduganathan M et al. Online ahead of print. *JAMA Cardiol*. 2022.

Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
All patients	512/3131	610/3132	0.82 (0.73–0.92)
Age			
≤72 yr	247/1545	306/1604	0.82 (0.69–0.97)
>72 yr	265/1586	304/1528	0.81 (0.69–0.96)
Sex			
Female	195/1364	243/1383	0.81 (0.67–0.97)
Male	317/1767	367/1749	0.82 (0.71–0.96)

No sex differences

Solomon et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. DOI: 10.1056/NEJMoa2206286

Dapagliflozin Significantly Reduced the Risk of Each Endpoint Across the Range of LVEF

Death

CV death

14% RRR

1.5% ARR
p=0.01

HR: 0.86
95% CI: 0.76-0.97

All-cause death

10% RRR

1.5% ARR
p=0.03

HR: 0.90
95% CI: 0.82-0.99

hHF

Total[a] hHF

29% reduction

6.0% ARR
p<0.001

RR: 0.71
95% CI: 0.65-0.78

First hHF

26% RRR

3.2% ARR
p<0.001

HR: 0.74
95% CI: 0.66-0.82

MACE

CV death, MI, or stroke

10% RRR

1.3% ARR
p=0.045

HR: 0.90
95% CI: 0.81-1.00

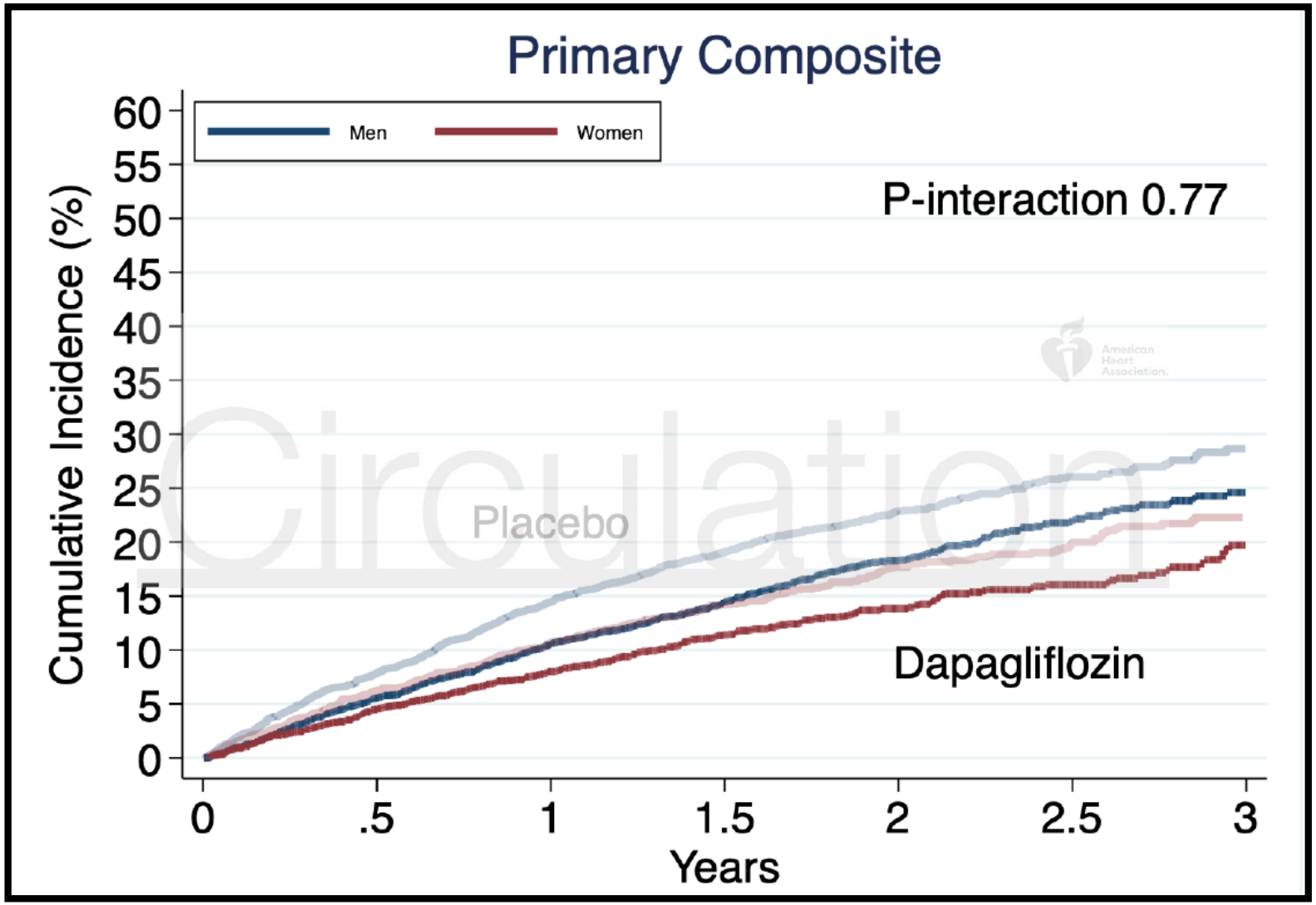
Effect was consistent across the full range of LVEF

[a]First and repeat.

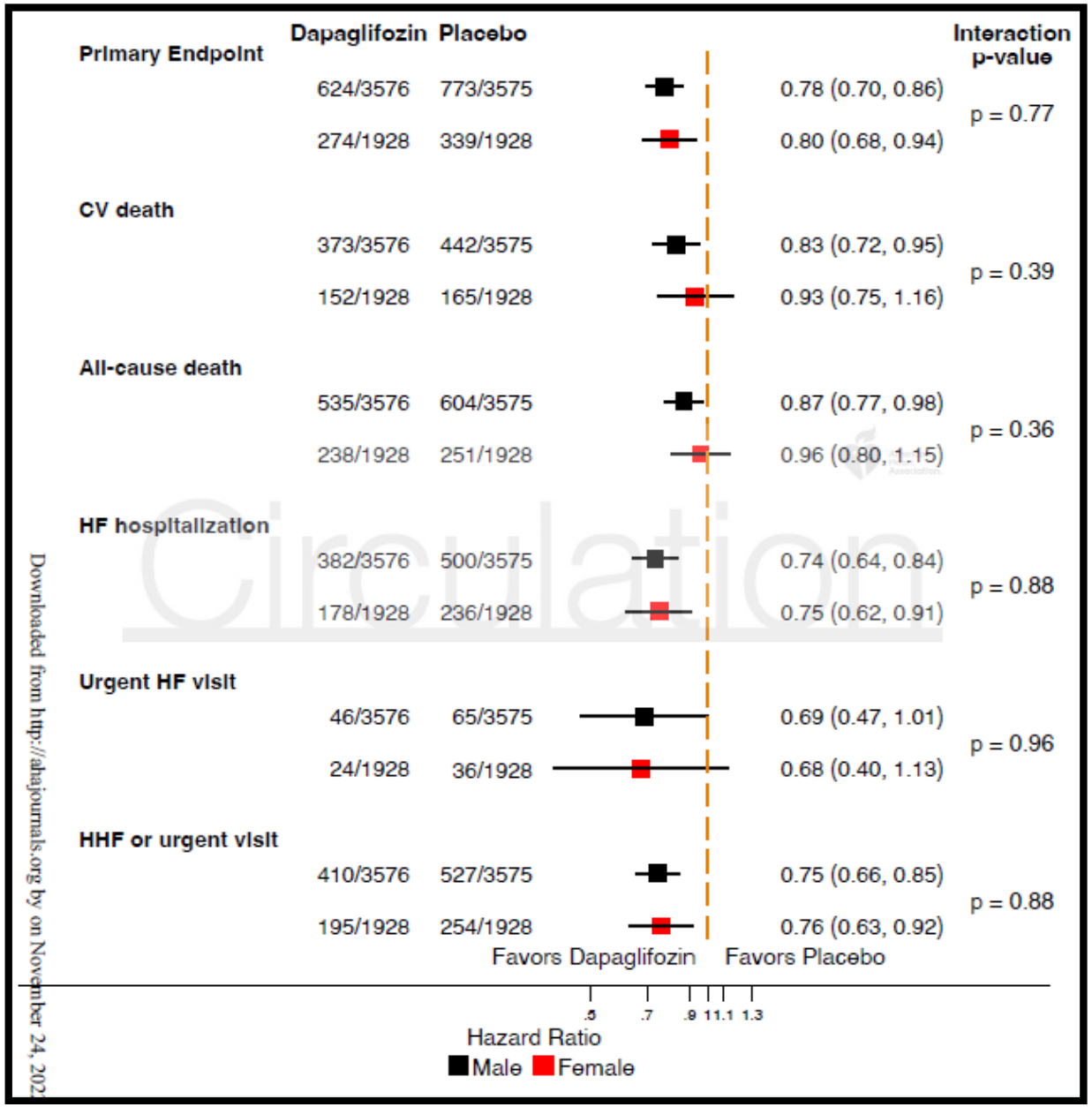
Jhund PS et al. Online ahead of print. *Nat Med*. 2022.

Sex Differences in Characteristics, Outcomes and Treatment Response with Dapagliflozin across the Range of Ejection Fraction in Patients with Heart Failure:
Insights from DAPA-HF and DELIVER

Running title: *Lam et al.; Sex differences in DAPA-HF and DELIVER*

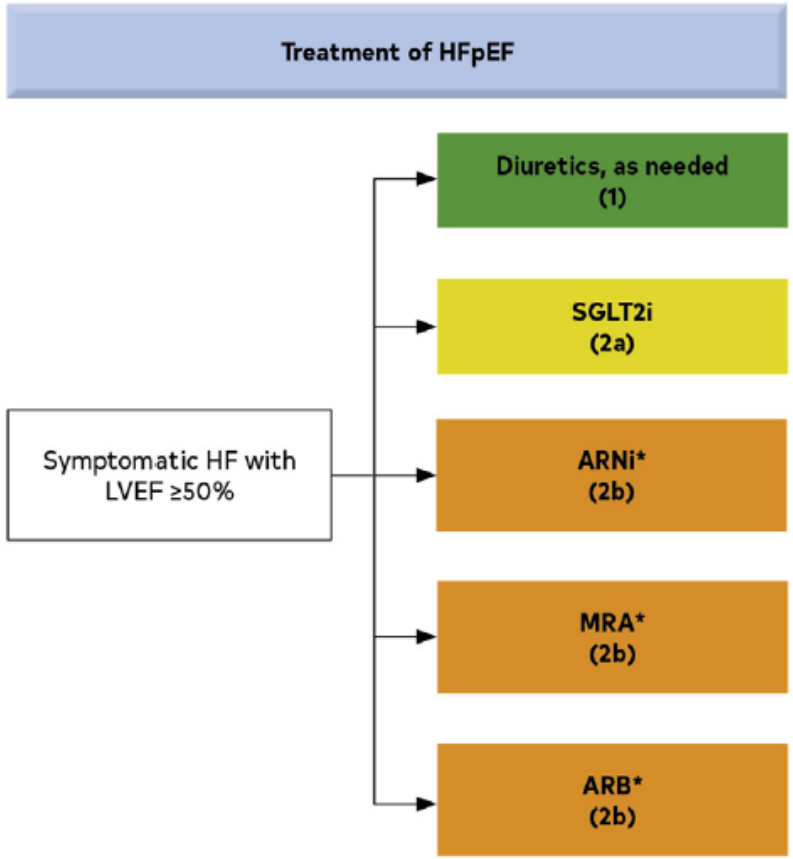


No sex differences



ACC 2022

FIGURE 3 Recommendations for Patients With Preserved LVEF (≥50%)



Summary

1. **Women ≠ Men**
2. **HFpEF is the predominant phenotype in women**
3. **SGLT2i are the first-class medication with positive endpoints in HFpEF.**
4. **No sex differences.**
5. **The full spectrum of LVEF**