Modern treatment of HFpEF

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HFpEF definition (ESC)

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–128
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ESC GUIDELINES

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

Table 3 Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

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; LV = left ventricle; LVEF = left ventricular ejection fraction.

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.

[b]For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.

[c]For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

What do the ESC guidelines say about treatment of HFmrEF & HFpEF

Recommendations for treatment of chronic HF – *HFmrEF*	**Class**
An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	**IIb**
An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	**IIb**
A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	**IIb**
An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	**IIb**
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	**IIb**
Recommendations for treatment of chronic HF – *HFpEF*	**Class**
Screening for, and treatment of, aetiologies, and CV and non-CV comorbidities are recommended in patients with HFpEF (see relevant sections of this document).	**I**

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

(before SGLT2i trials in HF)

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

Recommendations for the primary prevention of heart failure in patients with risk factors for its development

Recommendations	Class[a]	Level[b]
Treatment of hypertension is recommended to prevent or delay the onset of HF, and to prevent HF hospitalizations.[287–290]	I	A
Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations.[291,292]	I	A
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations.[293–297]	I	A
Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF.[298–302]	I	C

Multidisciplinary interventions recommended for the management of chronic heart failure

Recommendations	Class[a]	Level[b]
It is recommended that HF patients are enrolled in a multidisciplinary HF management programme to reduce the risk of HF hospitalization and mortality.[309,314,315,316]	I	A
Self-management strategies are recommended to reduce the risk of HF hospitalization and mortality.[309]	I	A
Either home-based and/or clinic-based programmes improve outcomes and are recommended to reduce the risk of HF hospitalization and mortality.[310,317]	I	A
Influenza and pneumococcal vaccinations should be considered in order to prevent HF hospitalizations.[315,316]	IIa	B

Etiological treatment

- Hypertension : all antihypertensive drugs
- CAD: revascularisation, BB ….
- AF : amiodarone, ablation
- Infections : vaccinations
- Renal failure: ACE-I
- Anemia
- Diabetes : ACE-I, MRA, SGLT2i

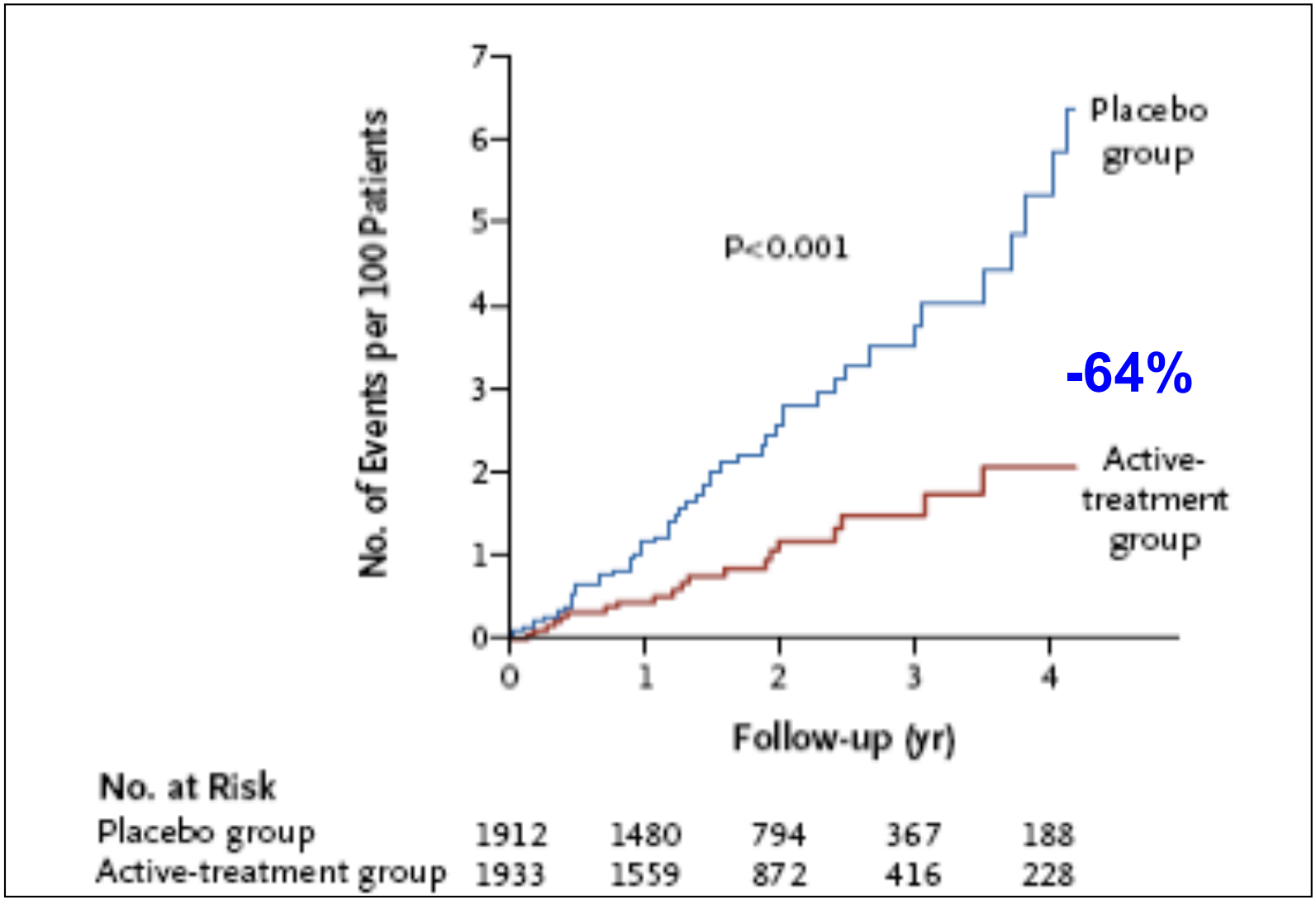
HFpEF patients often have the GMDT of HFpEF when the etiology is treated …

Diuretics

- Illogical (no major RAS stimulation, hypervolemia ..)
- Risk of hypovolemia
- Often at low doses

Perindopril/indapamide vs placebo in systolic aged HT

HYVET

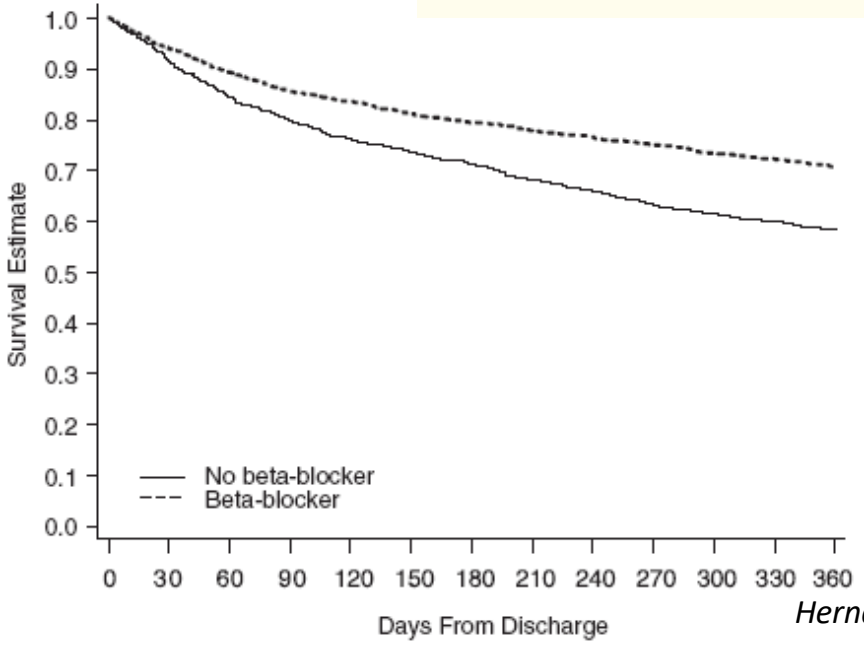


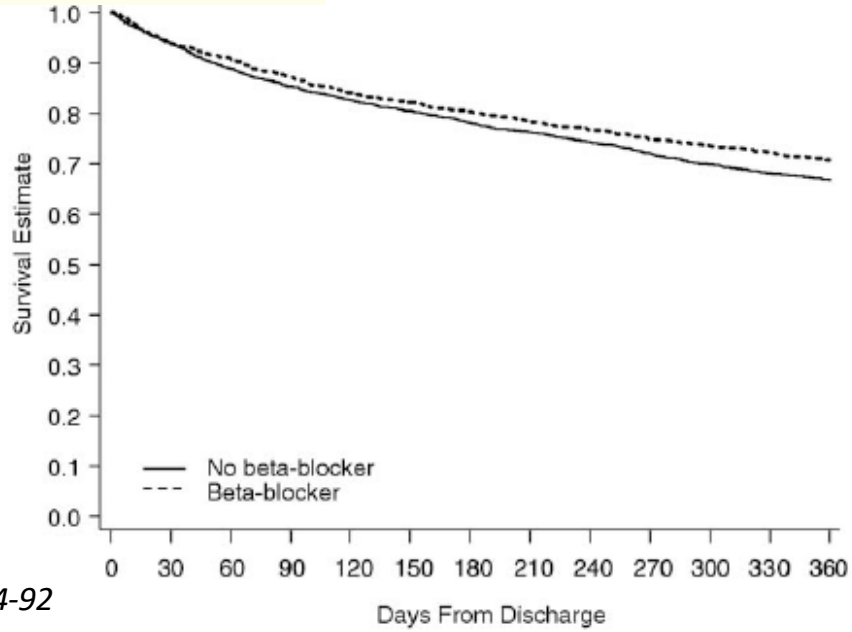
Betablockers

- No trials in HFpEF
- SENIORS
  - Positive effect of nebivolol when LVEF was > 35%
  - But effect entirely driven by patients with LVEF between 35 and 50%

Effects of betablockers in registries (OPTMIZE-HF)

Population and Outcome	Hazard Ratio (95% Confidence Interval) Unadjusted	Inverse-Weighted
Left ventricular systolic dysfunction (n = 3,001)		
Mortality	0.65 (0.57–0.73)	0.77 (0.68–0.87)
Readmission	0.82 (0.75–0.90)	0.89 (0.80–0.99)
Combined	0.79 (0.72–0.86)	0.87 (0.79–0.96)
Preserved systolic dysfunction (n = 4,153)		
Mortality	0.87 (0.77–0.97)	0.94 (0.84–1.07)
Readmission	0.96 (0.88–1.03)	0.98 (0.90–1.06)
Combined	0.95 (0.88–1.02)	0.98 (0.91–1.06)



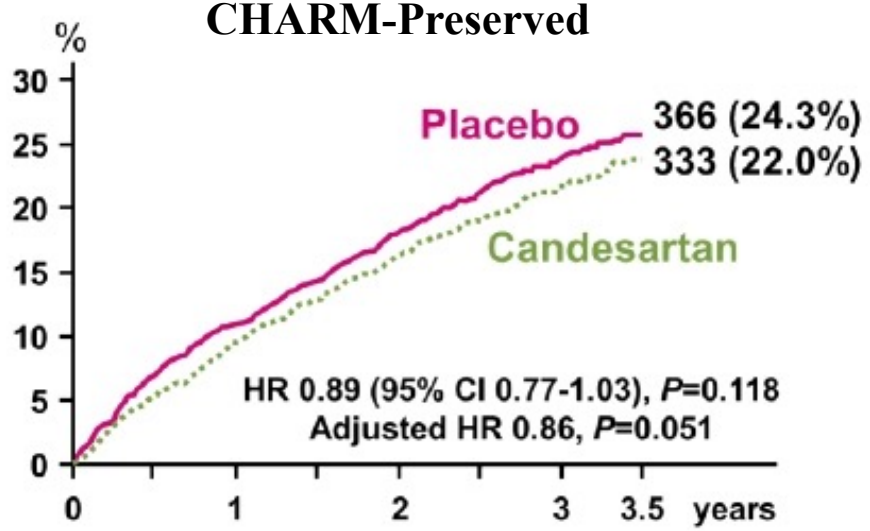


Hernandez JACC 09; 53: 184-92

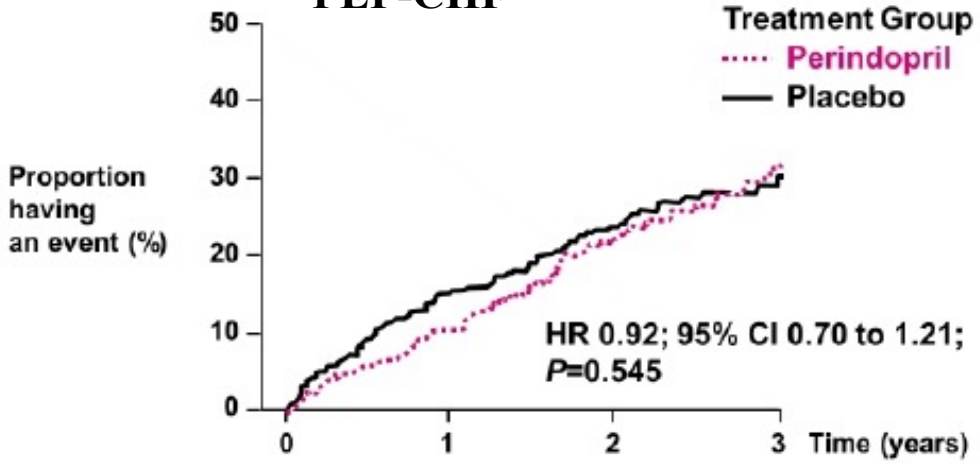
RAS inhibitors (ACE-I, ARB)

ACE-I/ARB: Outcome-studies in HFpEF

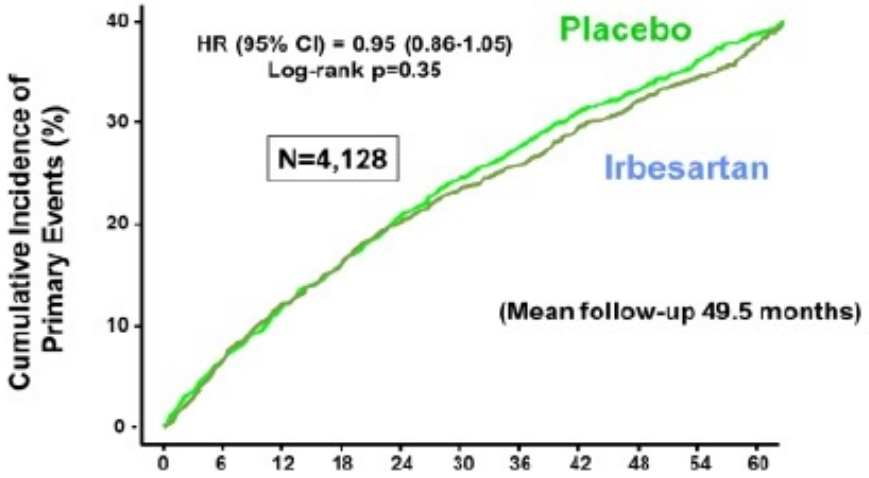
CHARM-Preserved



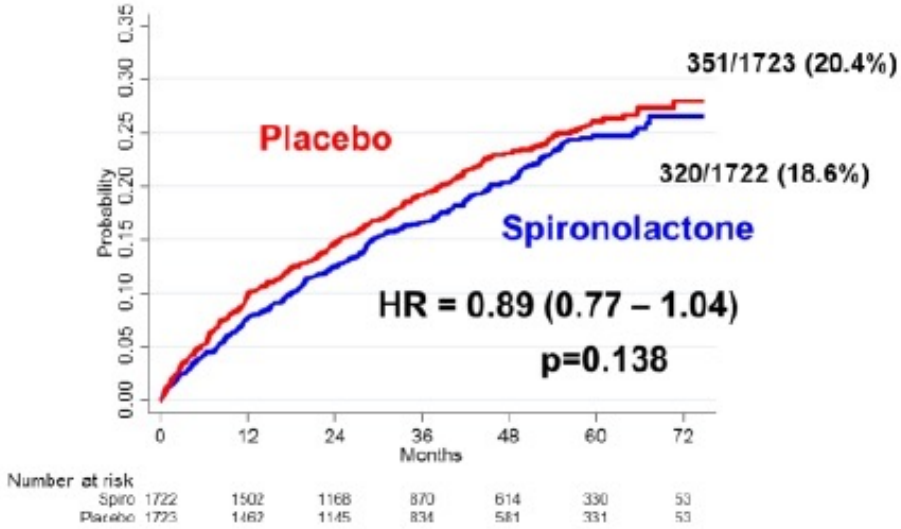
PEP-CHF



I-PRESERVE



TOPCAT

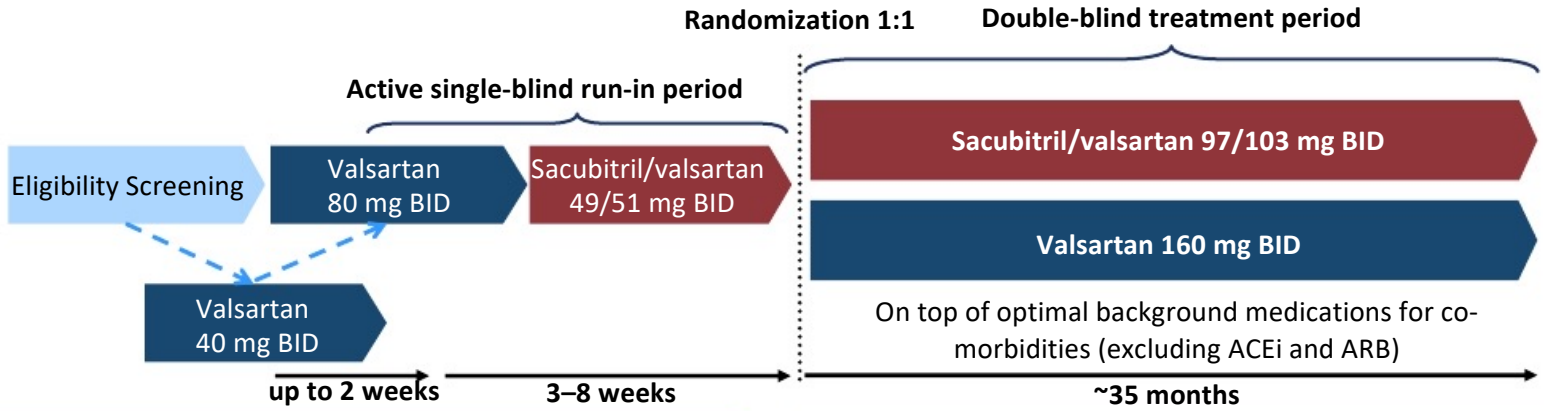


Sacubitril/valsartan

- Poorly effective when LVEF < 56% ..

PARAGON-HF study design

Randomized, double-blind, active comparator trial testing the hypothesis that sacubitril/valsartan, compared with valsartan, would reduce the composite outcome of total HF hospitalizations and CV death



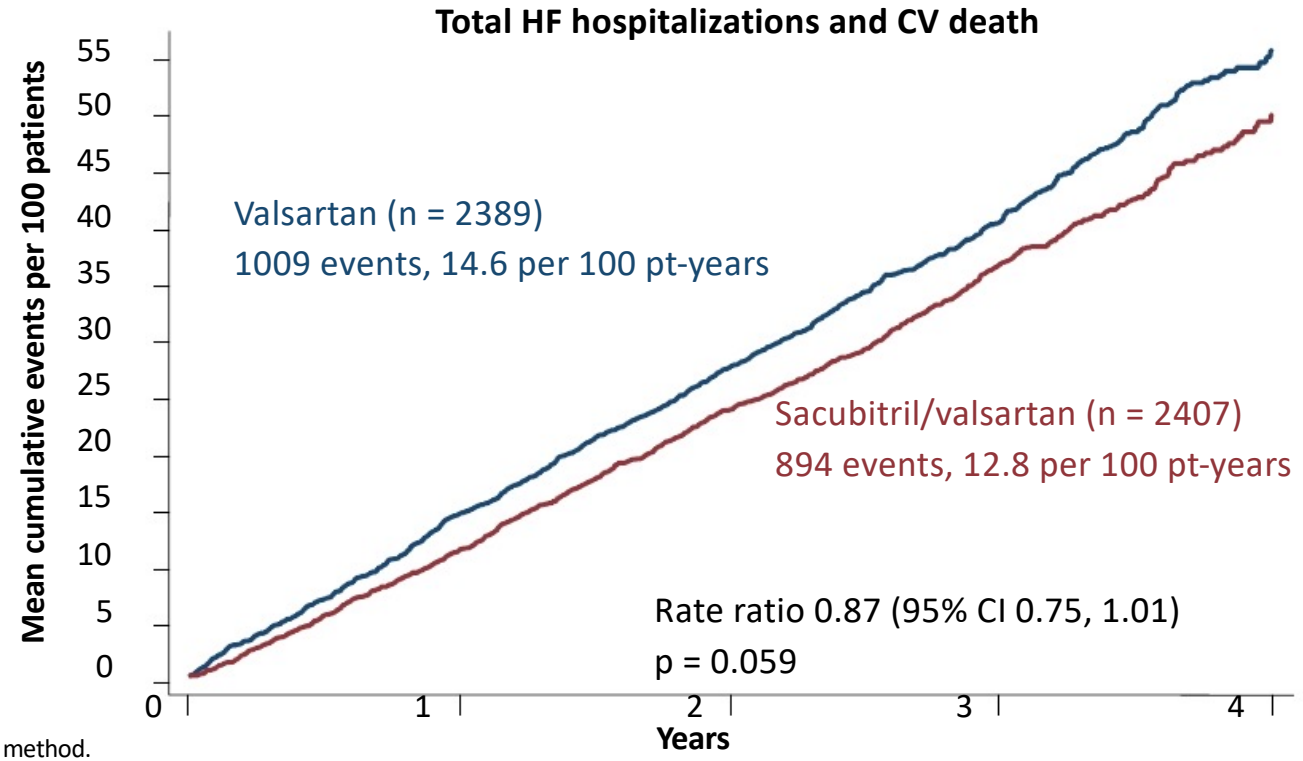
Primary Endpoint
Composite of total (first and recurrent) HF hospitalizations and CV death

Secondary Endpoints:
- Improvement in NYHA functional classification at 8 months
- Changes in KCCQ clinical summary score at 8 months
- Time to first occurrence of worsening renal function
- Time to all-cause mortality

Solomon SD, *et al. JACC-Heart Fail* 2017; 5(7):471-482.

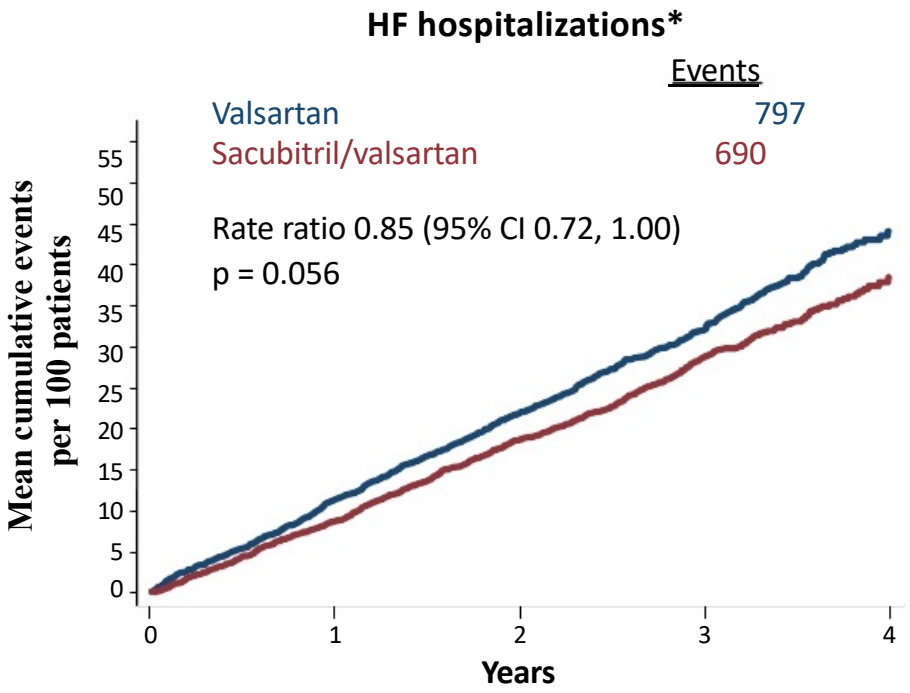
PARAGON-HF primary results

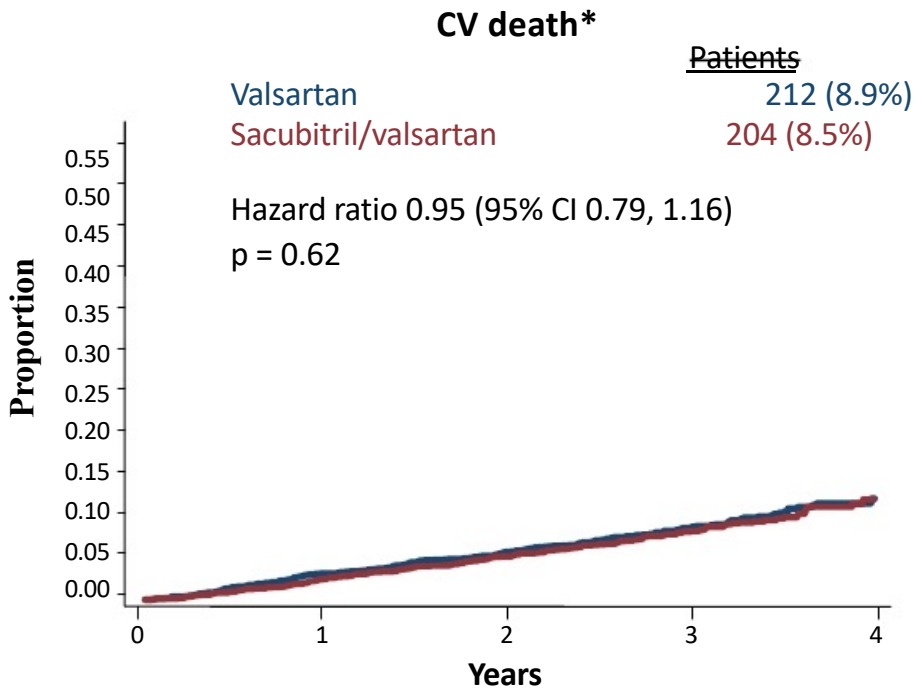
Recurrent event analysis of total HF hospitalizations and CV death*



*Semiparametric LWYY method.

HF hospitalizations and CV death



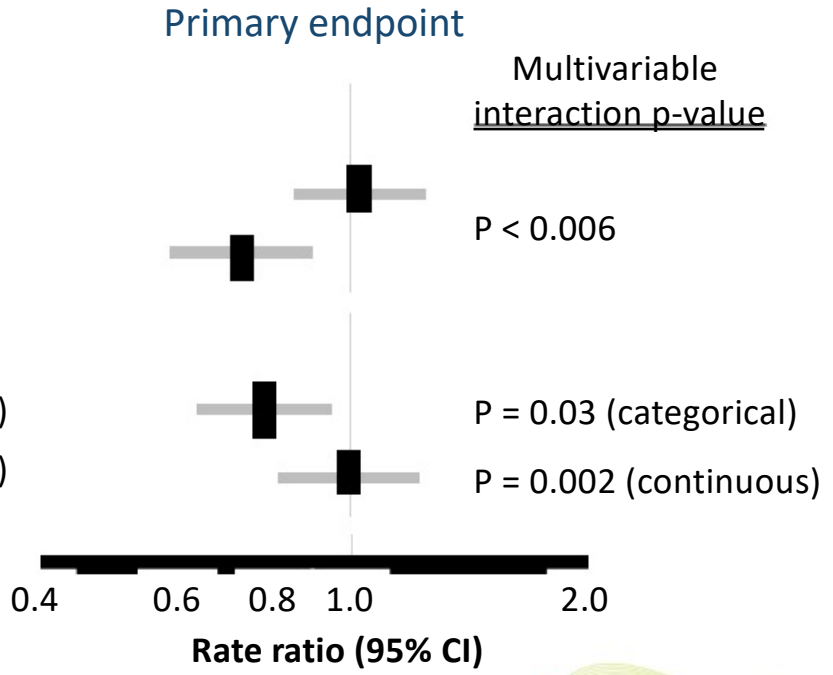


*Semiparametric LWYY method

Significant Heterogeneity in Multivariate Analysis by Ejection Fraction and Sex

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)



Circulation

ORIGINAL RESEARCH ARTICLE

Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure

Editorial, see p 362

BACKGROUND: While disease-modifying therapies exist for heart failure (HF) with reduced left ventricular ejection fraction (LVEF), few options are available for patients in the higher range of LVEF (>40%). Sacubitril/valsartan has been compared with a renin-angiotensin-aldosterone–system inhibitor alone in 2 similarly designed clinical trials of patients with reduced and preserved LVEF, permitting examination of its effects across the full spectrum of LVEF.

METHODS: We combined data from PARADIGM-HF (LVEF eligibility≤40%; n=8399) and PARAGON-HF (LVEF eligibility≥45%; n=4796) in a prespecified pooled analysis. We divided randomized patients into LVEF categories: ≤22.5% (n=1269), >22.5% to 32.5% (n=3987), >32.5% to 42.5% (n=3143), > 42.5% to 52.5% (n=1427), > 52.5% to 62.5% (n=2166), and >62.5% (n=1202). We assessed time to first cardiovascular death and HF hospitalization, its components, and total heart failure hospitilizations, all-cause mortality, and noncardiovascular mortality. Incidence rates and treatment effects were examined across categories of LVEF.

RESULTS: Among 13 195 randomized patients, we observed lower rates of cardiovascular death and HF hospitalization, but similar rates of noncardiovascular death, among patients in the highest versus the lowest groups. Overall sacubitril/valsartan was superior to renin-angiotensin-aldosterone–system inhibition for first cardiovascular death or heart failure hospitalization (Hazard Ratio [HR] 0.84 [95% CI, 0.78–0.90]), cardiovascular death (HR 0.84 [95% CI, 0.76–0.92]), heart failure hospitalization (HR 0.84 [95% CI, 0.77–0.91]), and all-cause mortality (HR 0.88 [95% CI, 0.81–0.96]). The effect of sacubitril/valsartan was modified by LVEF (treatment-by-continuous LVEF interaction P=0.02), and benefit appeared to be present for individuals with EF primarily below the normal range, although the treatment benefit for cardiovascular death diminished at a lower ejection fraction. We observed effect modification by LVEF on the efficacy of sacubitril/valsartan in both men and women with respect to composite total HF hospitalizations and cardiovascular death, although women derived benefit to higher ejection fractions.

CONCLUSIONS: The therapeutic effects of sacubitril/valsartan, compared with a renin-angiotensin-aldosterone–system inhibitor alone, vary by LVEF with treatment benefits, particularly for heart failure hospitalization, that appear to extend to patients with heart failure and mildly reduced ejection fraction. These therapeutic benefits appeared to extend to a higher LVEF range in women compared with men.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifiers: NCT01920711 (PARAGON-HF), NCT01035255 (PARADIGM-HF).

Scott D. Solomon, MD | Muthiah Vaduganathan, MD, MPH | Brian L. Claggett, PhD | Milton Packer, MD | Michael Zile, MD | Karl Swedberg, MD | Jean Rouleau, MD | Marc A. Pfeffer, MD, PhD | Akshay Desai, MD | Lars H. Lund, MD, PhD | Lars Kober, MD | Inder Anand, MD | Nancy Sweitzer, MD | Gerard Linssen, MD | Bela Merkely, MD | Juan Luis Arango, MD | Dragos Vinereanu, MD | Chen-Huan Chen, MD | Michele Senni, MD | Antonio Sibulo, MD | Sergey Boytsov, MD | Victor Shi, MD | Adel Rizkala, PharmD | Martin Lefkowitz, MD | John J.V. McMurray, MD

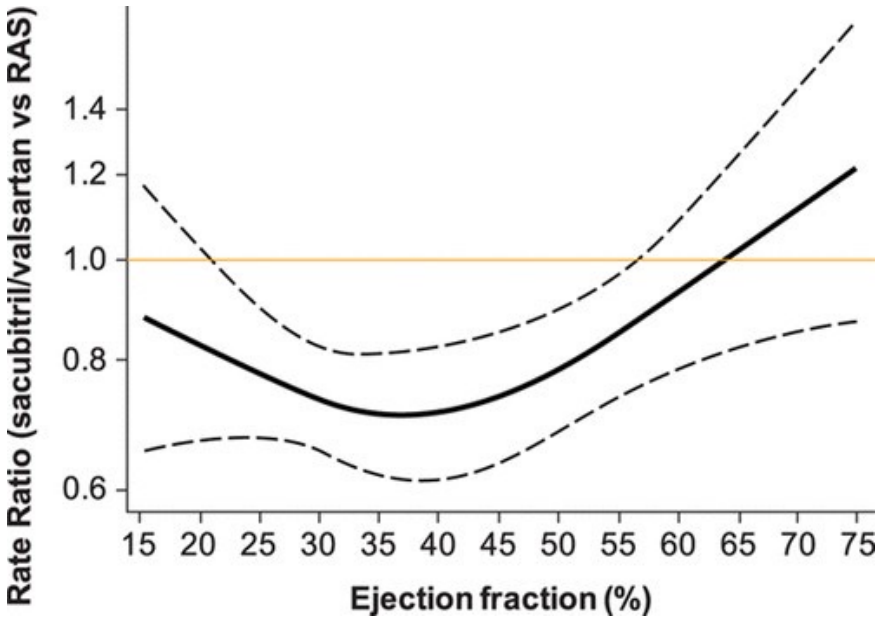
Key Words: clinical efficacy ■ heart failure ■ sacubitril/valsartan ■ ventricular ejection fraction

Sources of Funding, see page 360

https://www.ahajournals.org/journal/circ

Circulation. 2020;141:352–361. DOI: 10.1161/CIRCULATIONAHA.119.044586

Treatment effects of sacubitril/valsartan vs active comparator across a range of ejection fraction for the composite of total HF hospitalization and CV death



ScottD.Solomon.Circulation. 2020;352-361 ,

MRAs

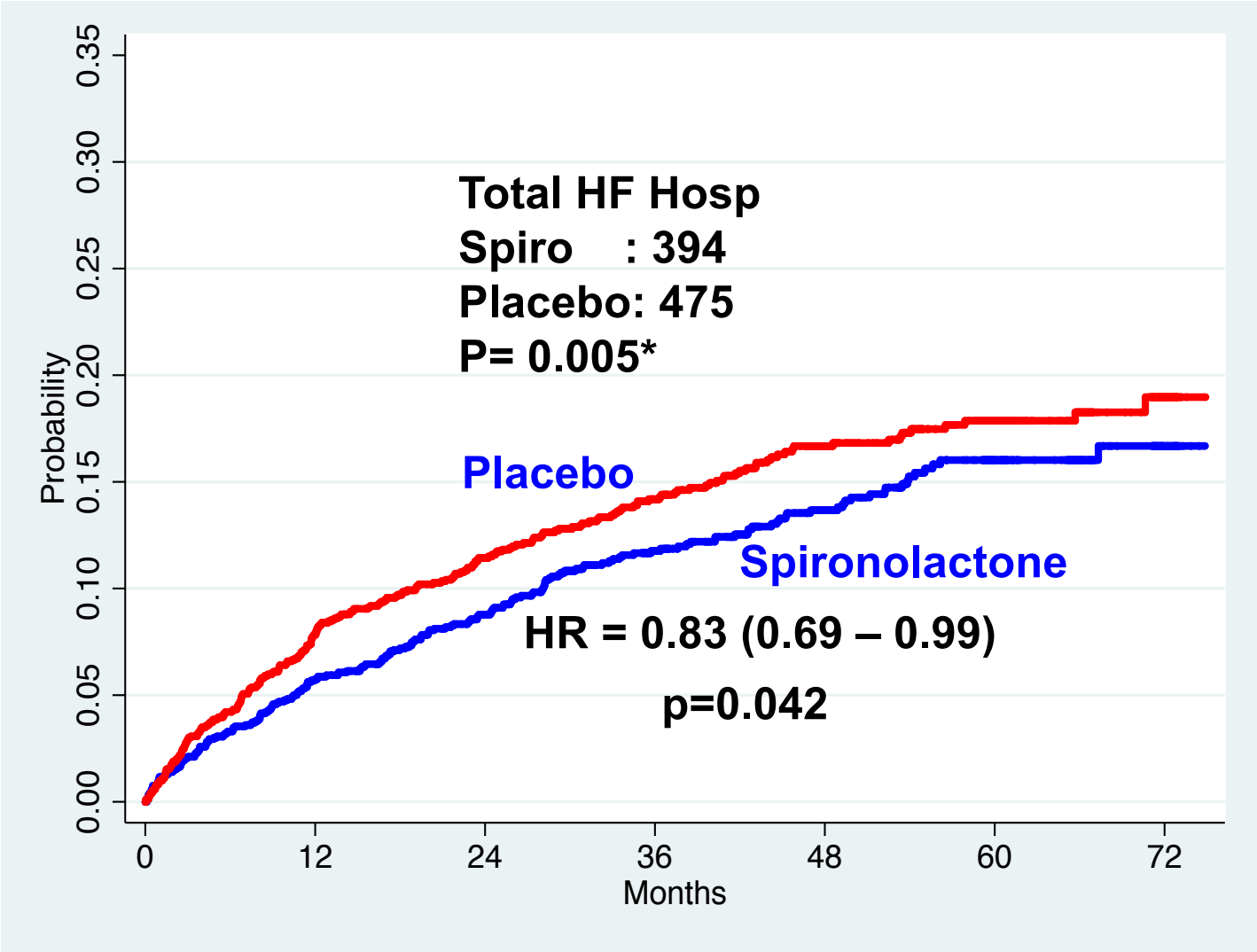
- NIH sponsored trial
- Spironolactone vs placebo in patients with LVEF > 35%

TOPCAT
Summary of the results

End points	Spironolactone (%) n=1722	Placebo (%) n=1723	HR (95% CI	P
Primary*	18.6	20.4	0.89 (0.77–1.04)	0.138
CV mortality	9.3	10.2	0.90 (0.73–1.12)	0.354
Aborted cardiac arrest	<1.0	<1.0	0.60 (0.14–2.50)	0.482
HF hospitalization	12.0	14.2	0.83 (0.69–0.99)	0.042

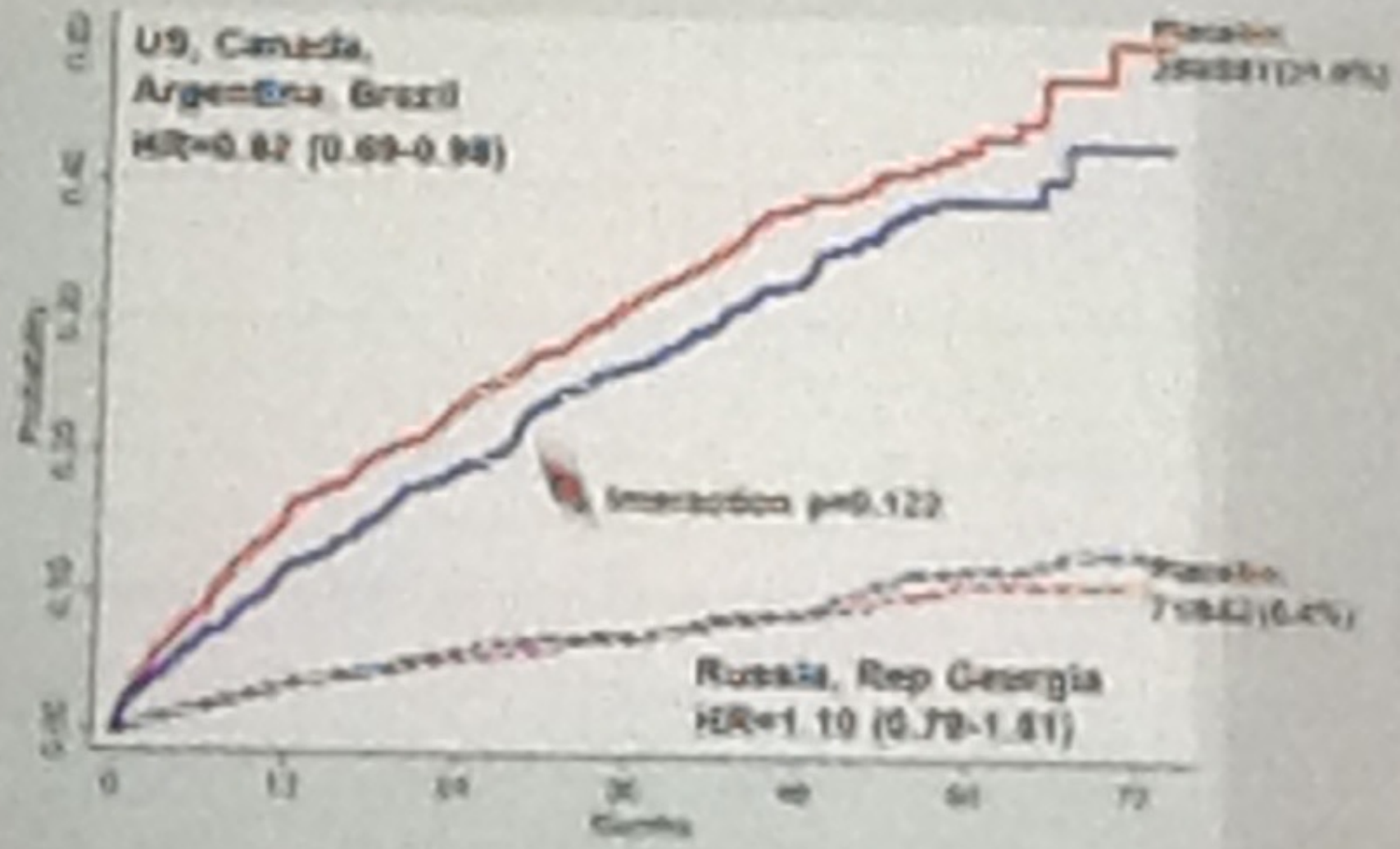
*CV mortality, aborted cardiac arrest, or HF hospitalization

TOPCAT
spiro vs placebo
Heart Failure Hospitalizations



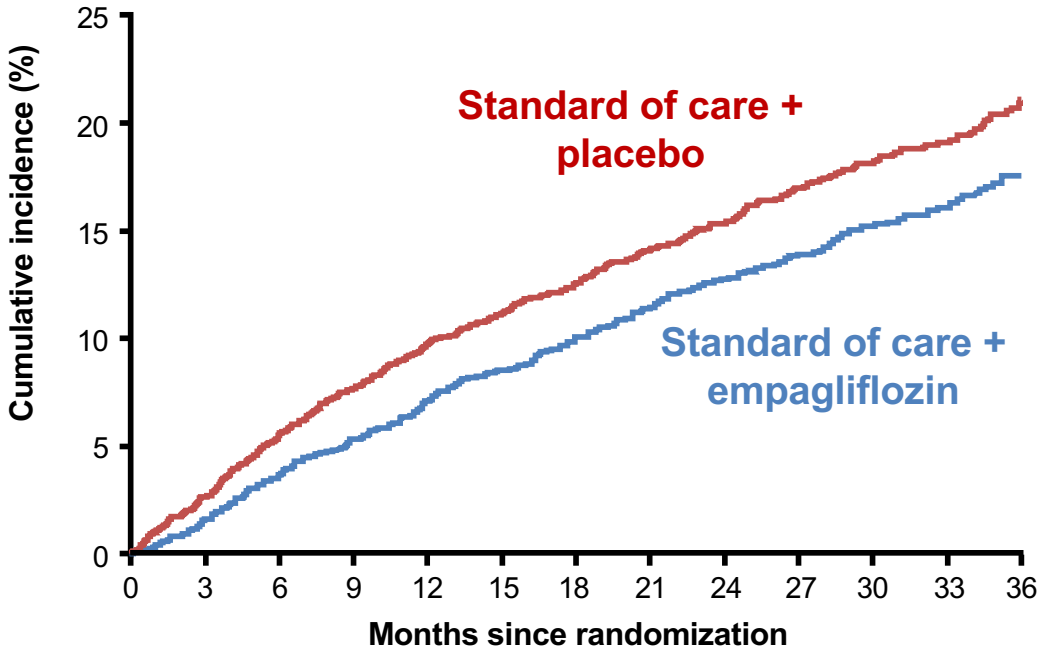
*poisson regression

Exploratory (post-hoc): Placebo vs. Spiro by region



SGLT2i

EMPEROR-Preserved: reduction in CV death or HHF in patients with HFpEF

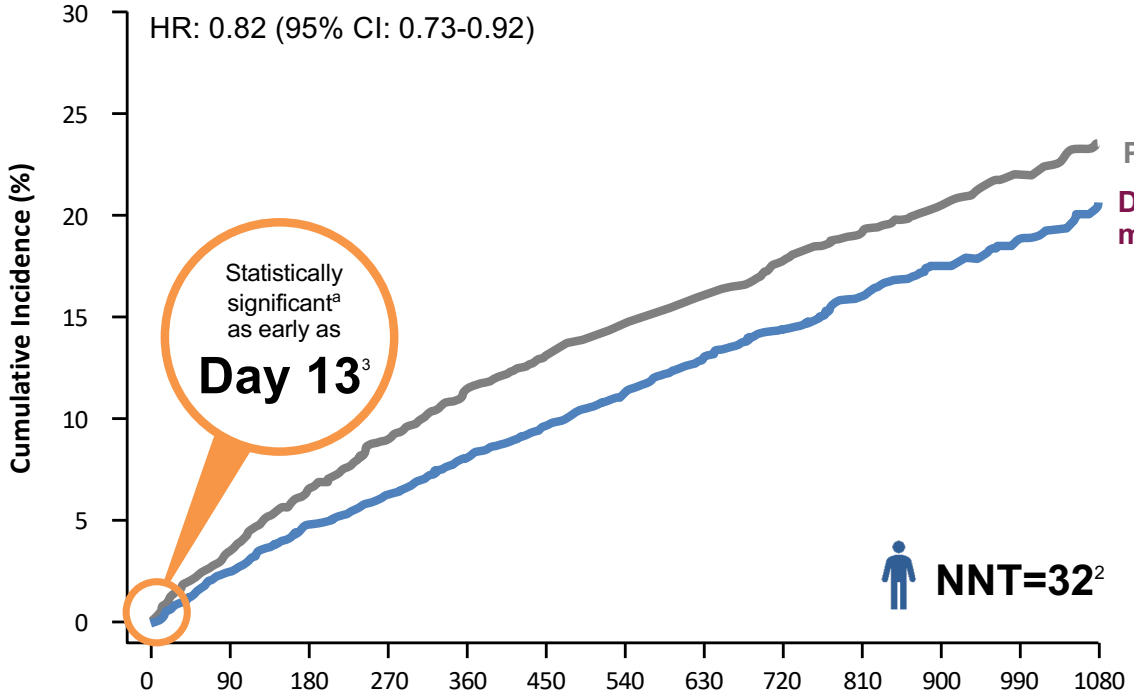


	RRR	ARR	NNT*
All pts	21%	3.3%	31

HR: 0.79
(95% CI: 0.69, 0.90)
p<0.001

*During a median trial period of 26 months.
Anker S *et al. N Engl J Med.* 2021;385:1451.

DELIVER- Primary Composite of CV Death, hHF or Urgent HF Visit



18 % RRR

3.1% ARR

p=0.0008[2]

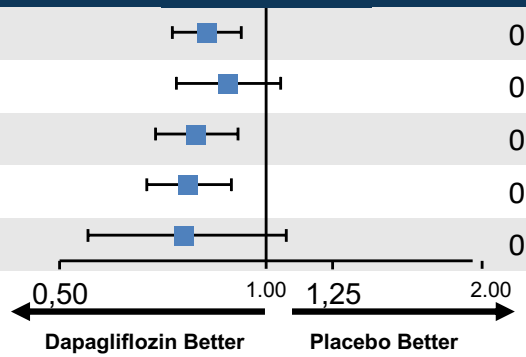
Number at Risk

DAPA 10 mg	3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389
Placebo	3132	3007	2896	2799	2710	2608	2318	2080	1923	1554	1140	772	383

- [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.

DELIVER

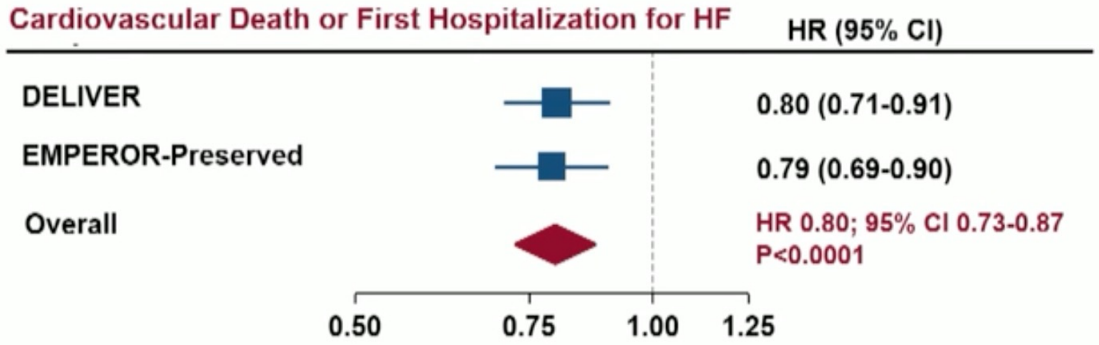
Outcome, n (%)	DAPA 10 mg n=3131	Placebo n=3132	HR (95% CI)	HR (95% CI)	p-value
CV death or worsening HF[a]	512 (16.4)	610 (19.5)		0.82 (0.73-0.92)	0.0008[2]
CV death[b]	231 (7.4)	261 (8.3)		0.88 (0.74-1.05)	
Worsening HF[a]	368 (11.8)	455 (14.5)		0.79 (0.69-0.91)	
hHF	329 (10.5)	418 (13.3)		0.77 (0.67-0.89)	
Urgent HF visit	60 (1.9)	78 (2.5)		0.76 (0.55-1.07)	

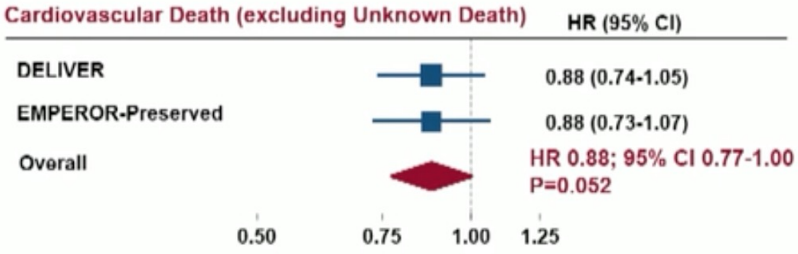


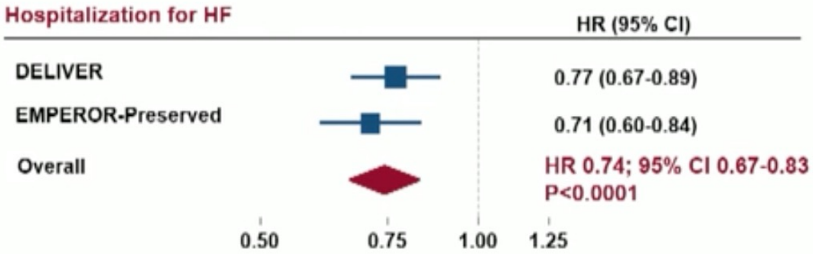
Consistent treatment benefit across all prespecified subgroups

- [a]hHF or an urgent HF visit; [b]Also a prespecified secondary endpoint.
- 1. Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022; 2. Solomon SD. Presented at: ESC Congress; August 26-29, 2022; Barcelona, Spain.

DELIVER and EMPEROR-Preserved Meta-Analysis:
↓ 20% (13-27%) Relative Risk Reduction of Primary Endpoint with Consistent Reductions in Both Components

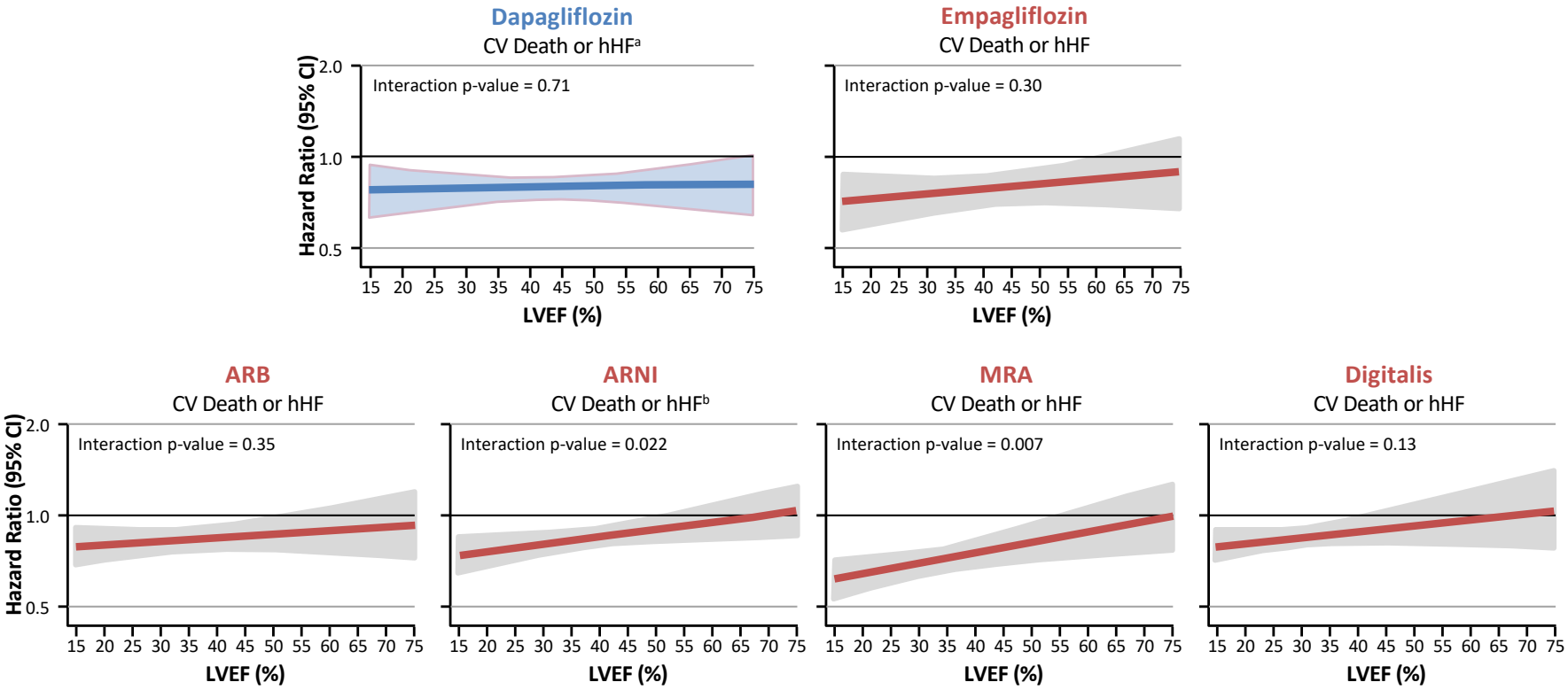






$P_{heterogeneity}$ >0.40 for all endpoints

Benefit of SGLT2i is Consistent, With no Attenuation, Across LVEF[1,2]



Differences among trial design, patient population, and treatment groups impact ability to directly compare results across different trials.

- 1. Kondo T et al. *Eur Heart J.* 2022;43(5):427-429; 2. In House Data, AstraZeneca. Data on file 161903.

ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–13
https://doi.org/10.1093/eurheartj/ehad195

ESC GUIDELINES

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With the special contribution of the Heart Failure Association (HFA) of the ESC

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

Exercise Training in Diastolic Heart Failure

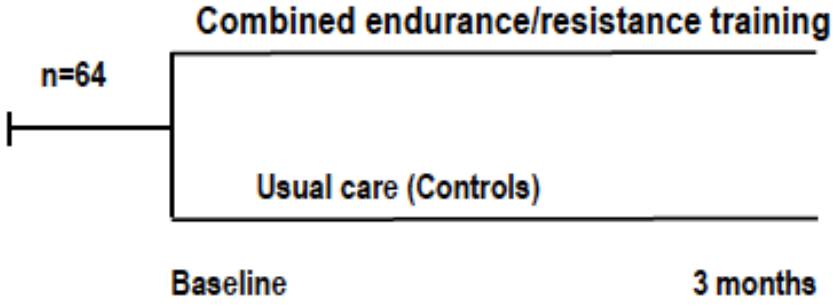
Kompetenznetz Herzinsuffizienz

A prospective, randomised, controlled study to determine the effects of exercise training on exercise capacity and quality of life

Primary Endpoint: Change in maximum exercise capacity (peak VO_2) at 3 months compared to baseline

Secondary Endpoints: Quality of life, echo determined diastolic function, submaximal exercise tolerance, neurohumoral activation; adhaerence and safety of exercise training

Flow Chart:

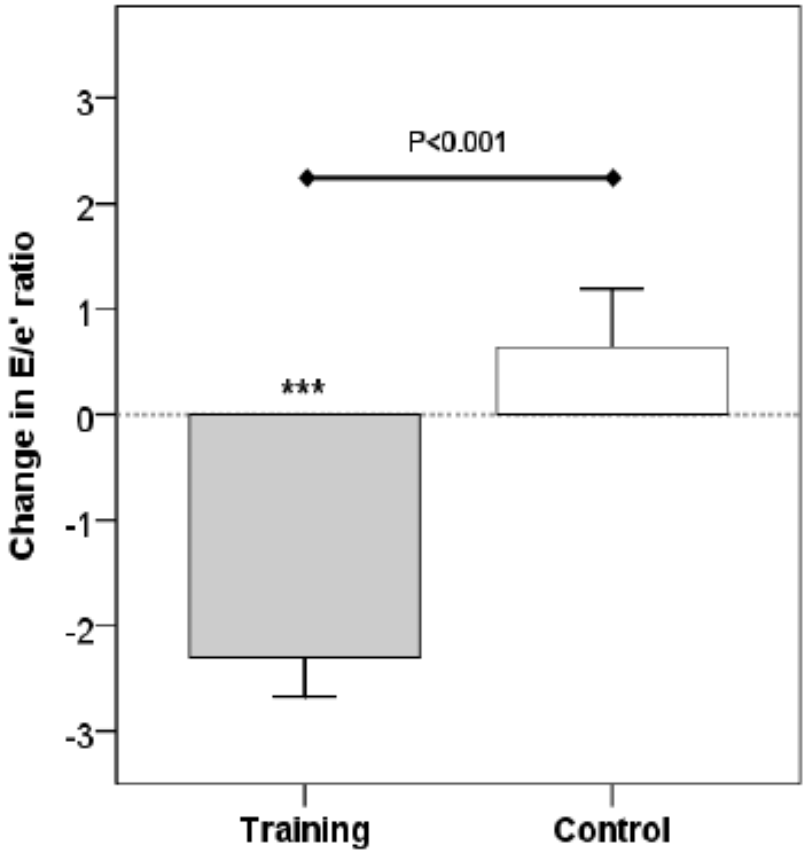


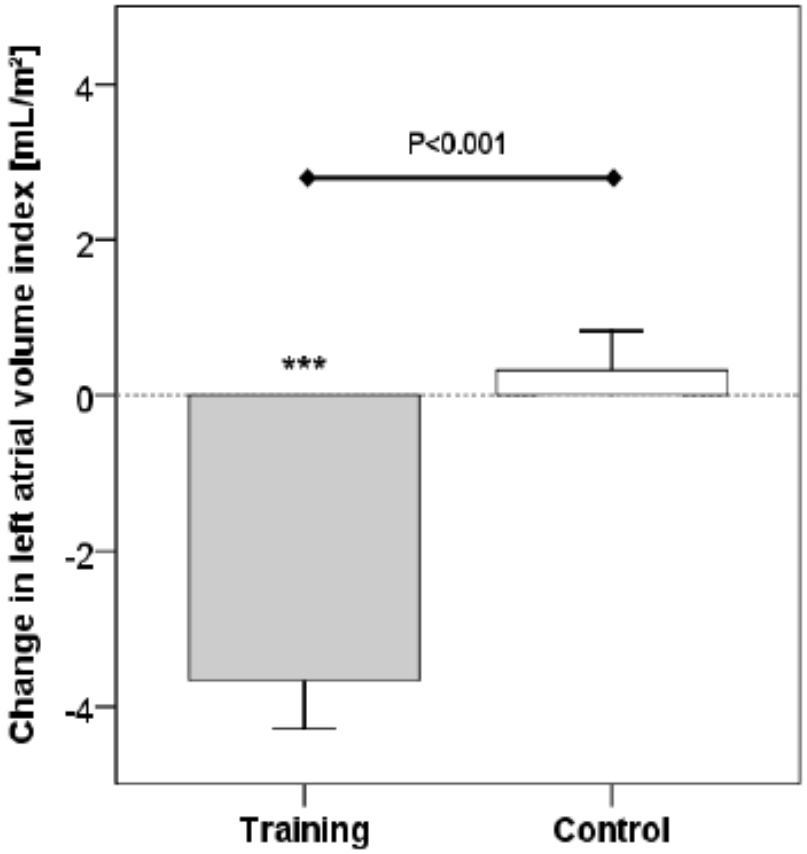
Baseline characteristics (n=64):

	Training (n=44)	Controls (n=20)	
Age (years)	64±8	65, ±6	n.s.
LVEF (%)	68±7	67±9	
NYHA II/III	35/ 9	20/ 1	
Grade diastolic dysfunction I/ II	33/ 11	13/ 7	
RR sys/dia (mmHg)	140/ 82	141/ 82	

Edelmann et al., J Am Coll Cardiol 2011

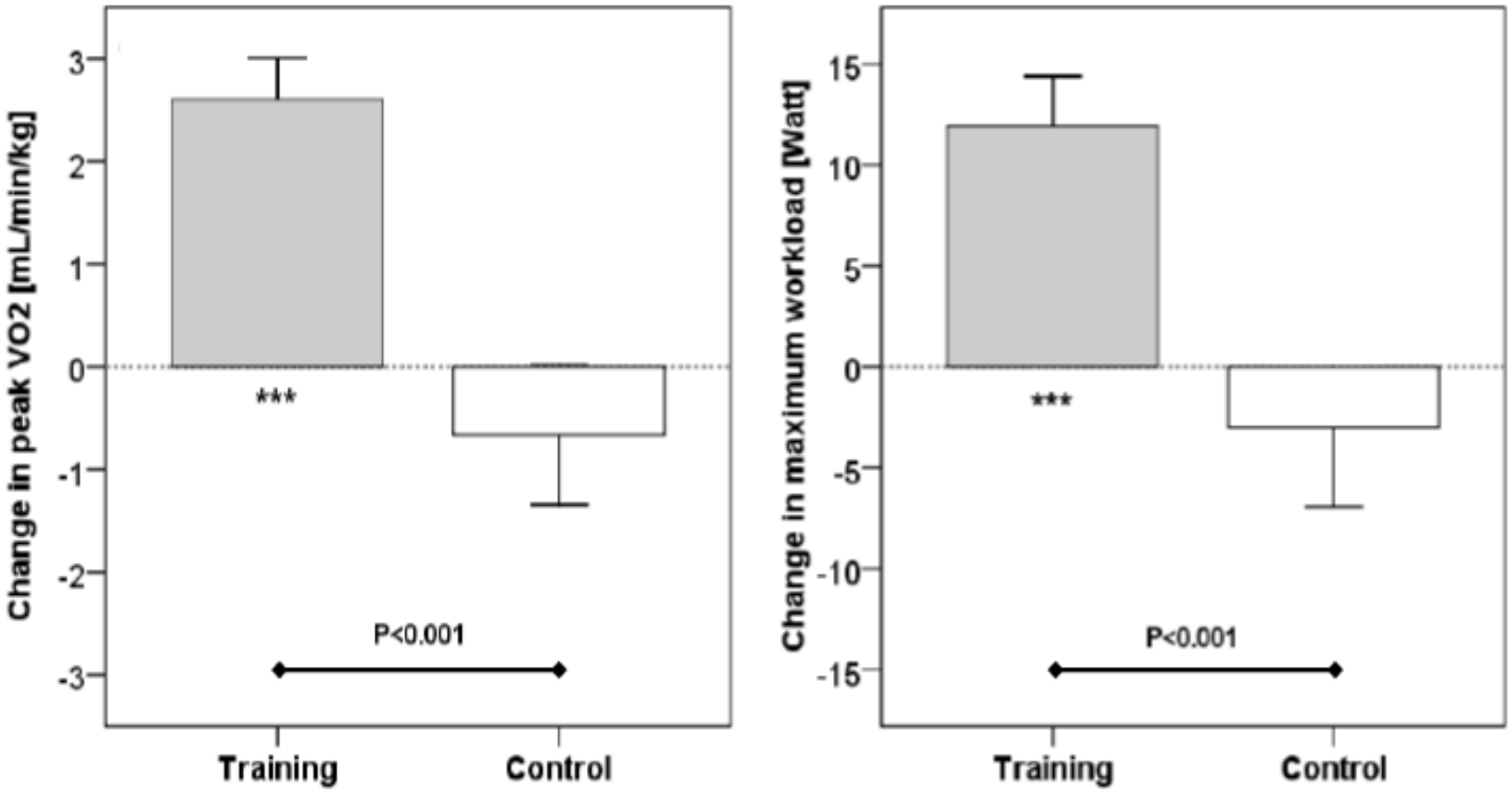
Echocardiography





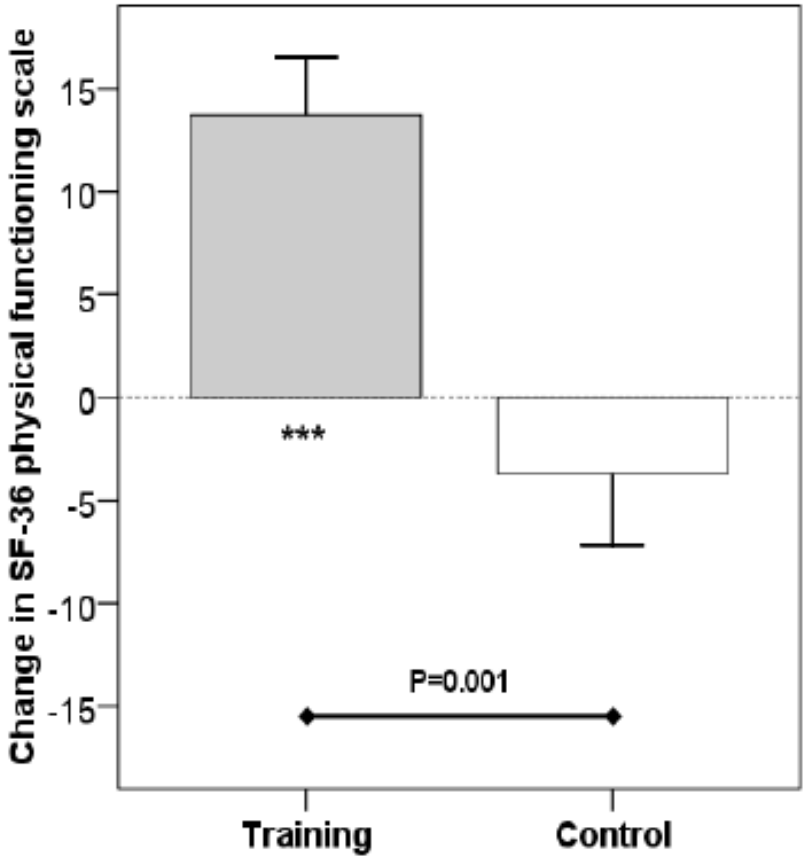
Edelmann et al., J Am Coll Cardiol 2011

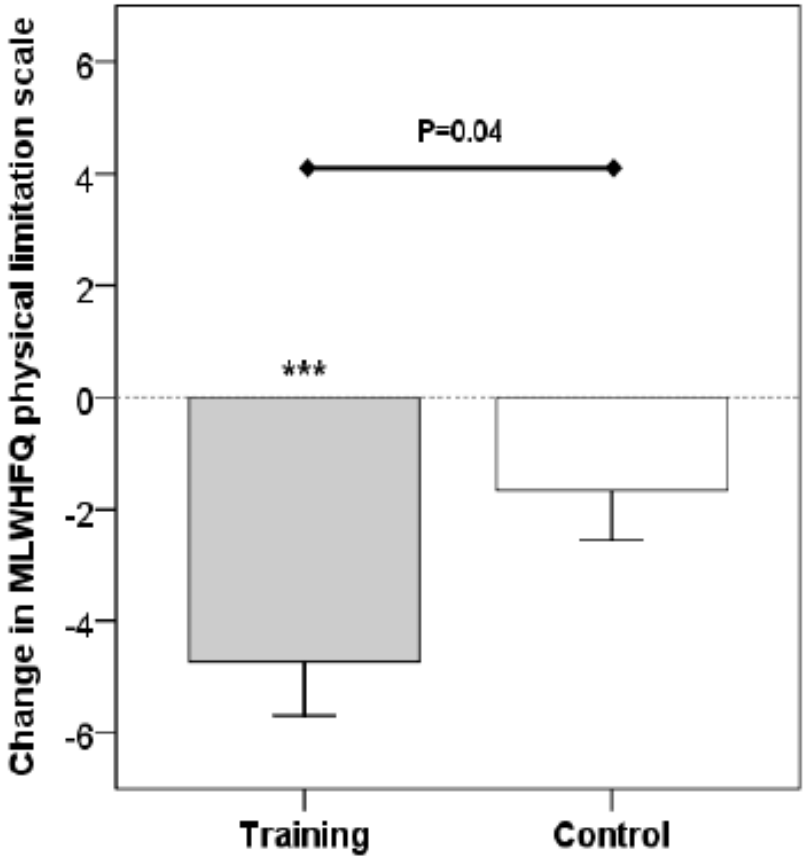
Spiroergometry



Edelmann et al., J Am Coll Cardiol 2011

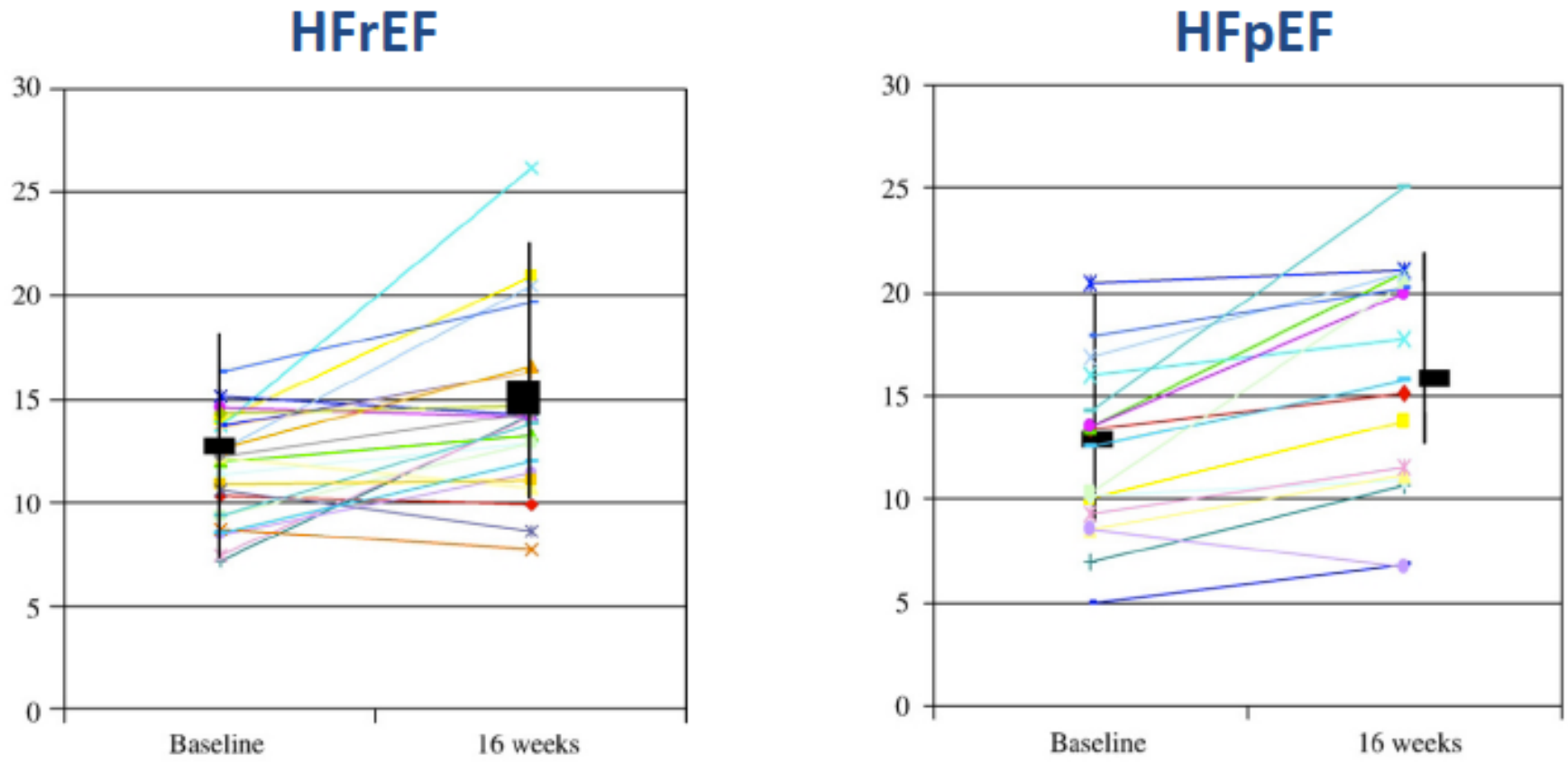
Quality of Life





Edelmann et al., J Am Coll Cardiol 2011

Peak VO_2 with Exercise Training



Quality of life also significantly improved in both groups with exercise

Smart N et al., Am Heart J 2007,153:530-536

A NOVEL PARADIGM FOR HEART FAILURE WITH PRESERVED EJECTION FRACTION: COMORBIDITIES DRIVE MYOCARDIAL DYSFUNCTION AND REMODELING THROUGH CORONARY MICROVASCULAR ENDOTHELIAL INFLAMMATION

by
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Word Count: 5962

Running Title: Myocardial Remodeling in HFPEF

Supported by a grant from the European Commission (FP7-Health-2010; MEDIA-261409)
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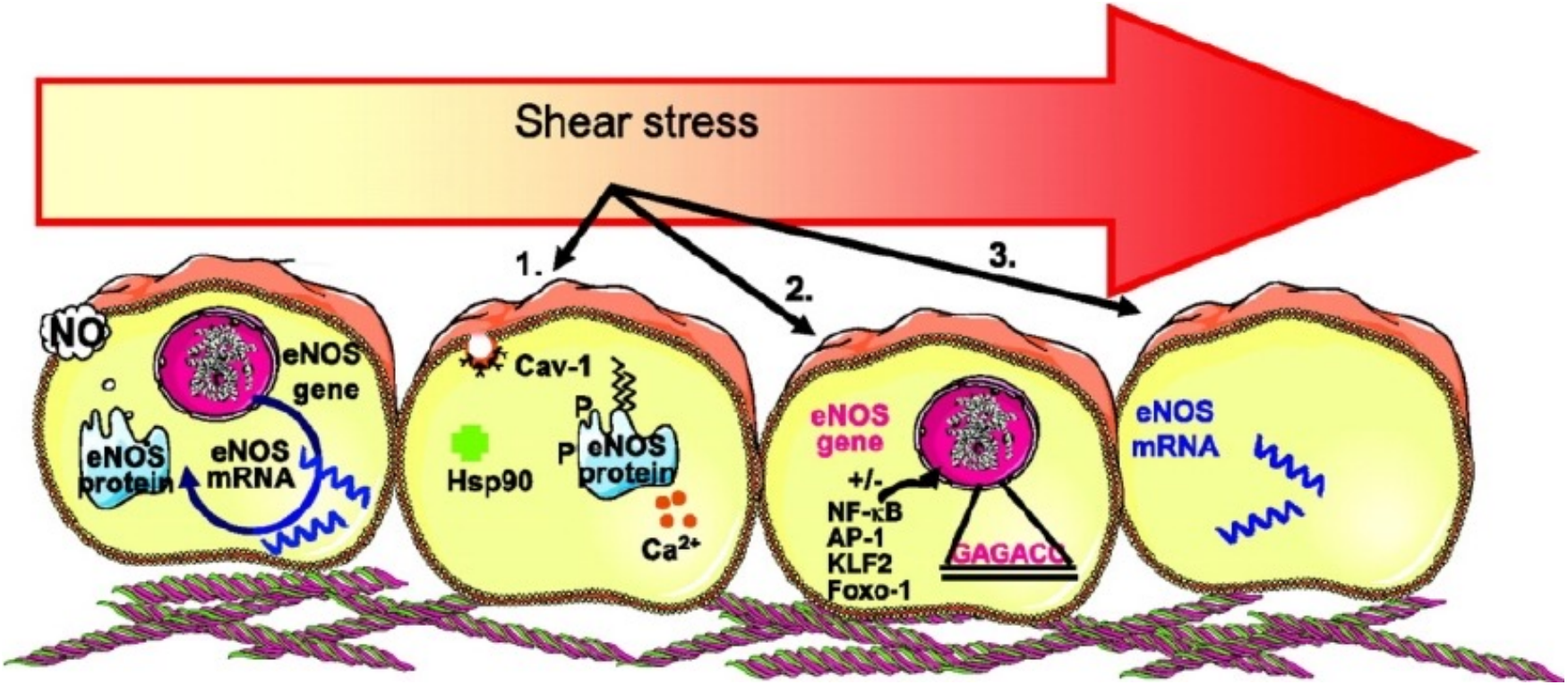
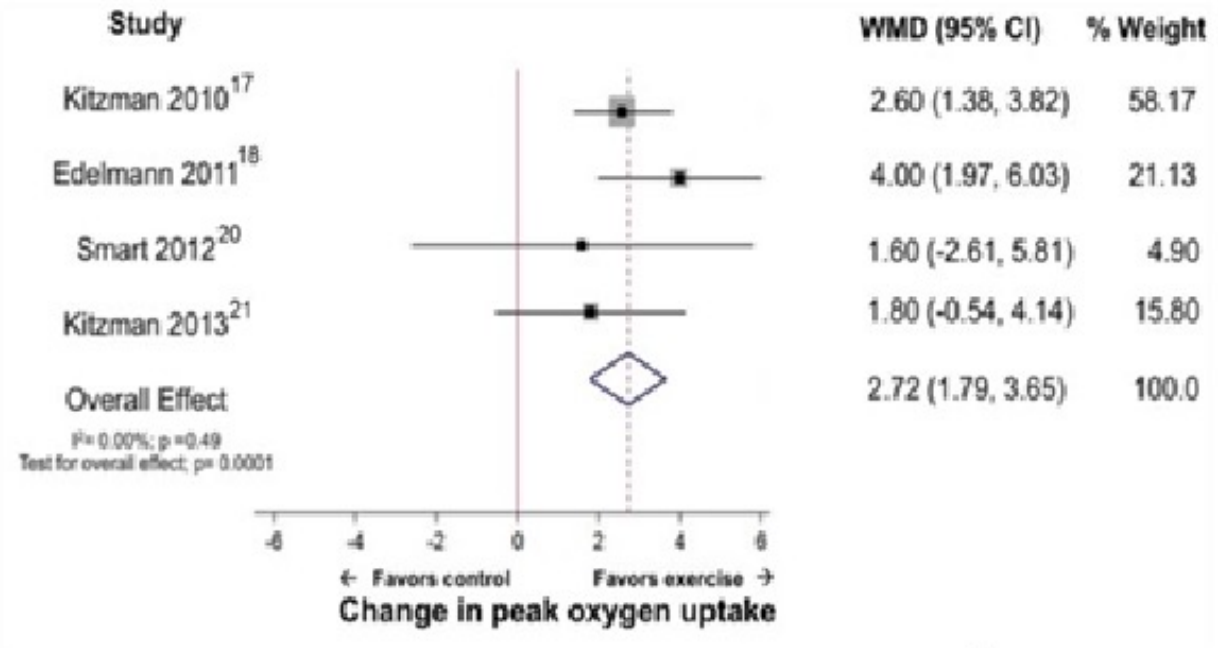
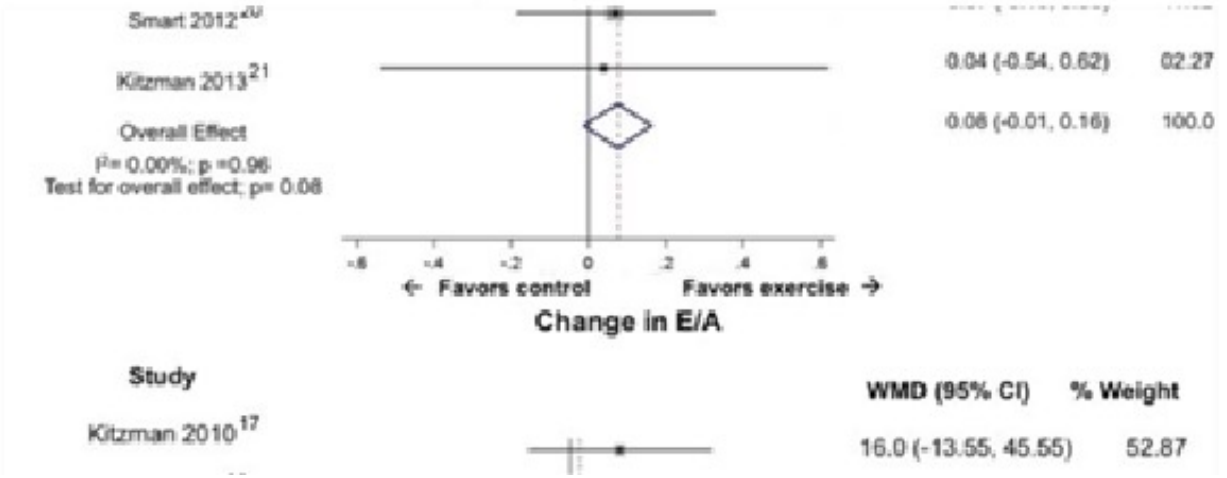
Shear stress and sport in HFpEF



J.-L. Balligand et al. Physiol Rev 2009;89:481-534

Effect of sport on cardiorespiratory fitness in HFpEF





Pandey A, et al. Circ HF 2015

Non-pharmacological management in HFpEF- Recommantations

Exercise prescription

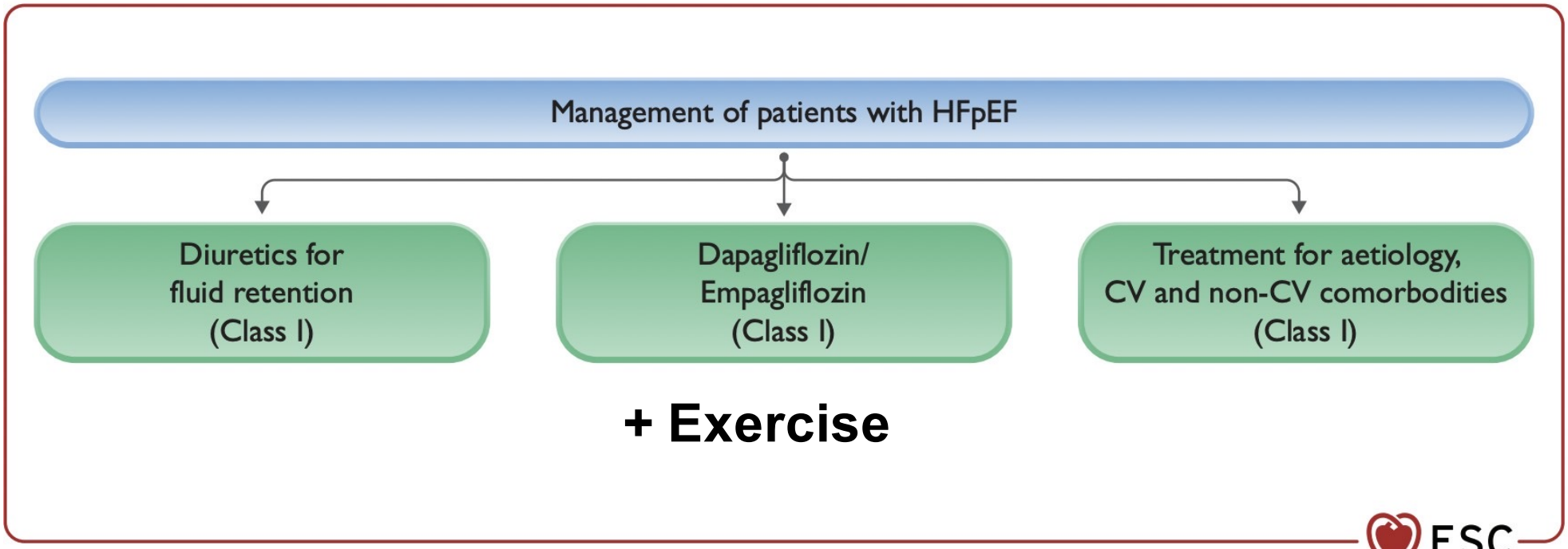
Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that regular aerobic exercise is encouraged in patients with heart failure to improve functional capacity and symptoms.	I	A	262, 263

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.

McMurray JJ et al., Eur Heart J 2012;33:1787-847

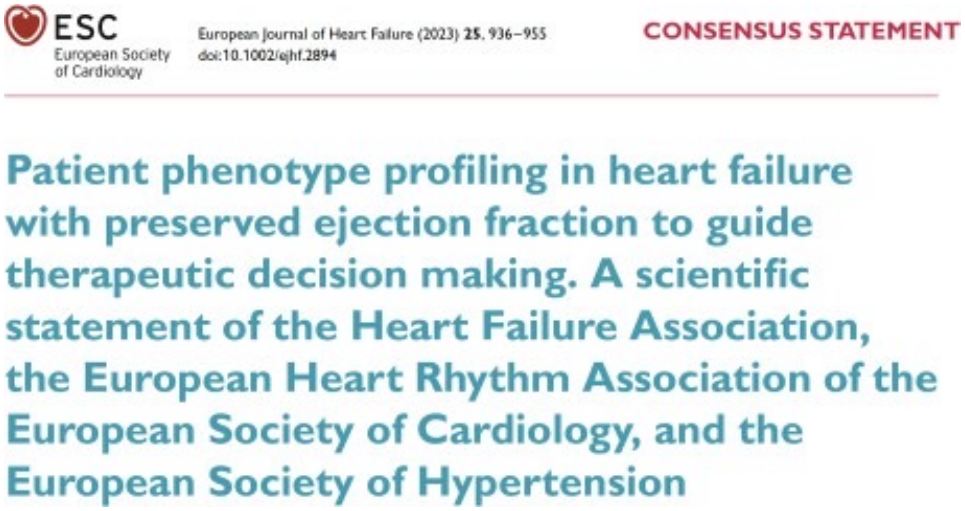
Management of patients with HFpEF



ESC Guidelines on HF. Eur Heart J 2023

Comorbidities

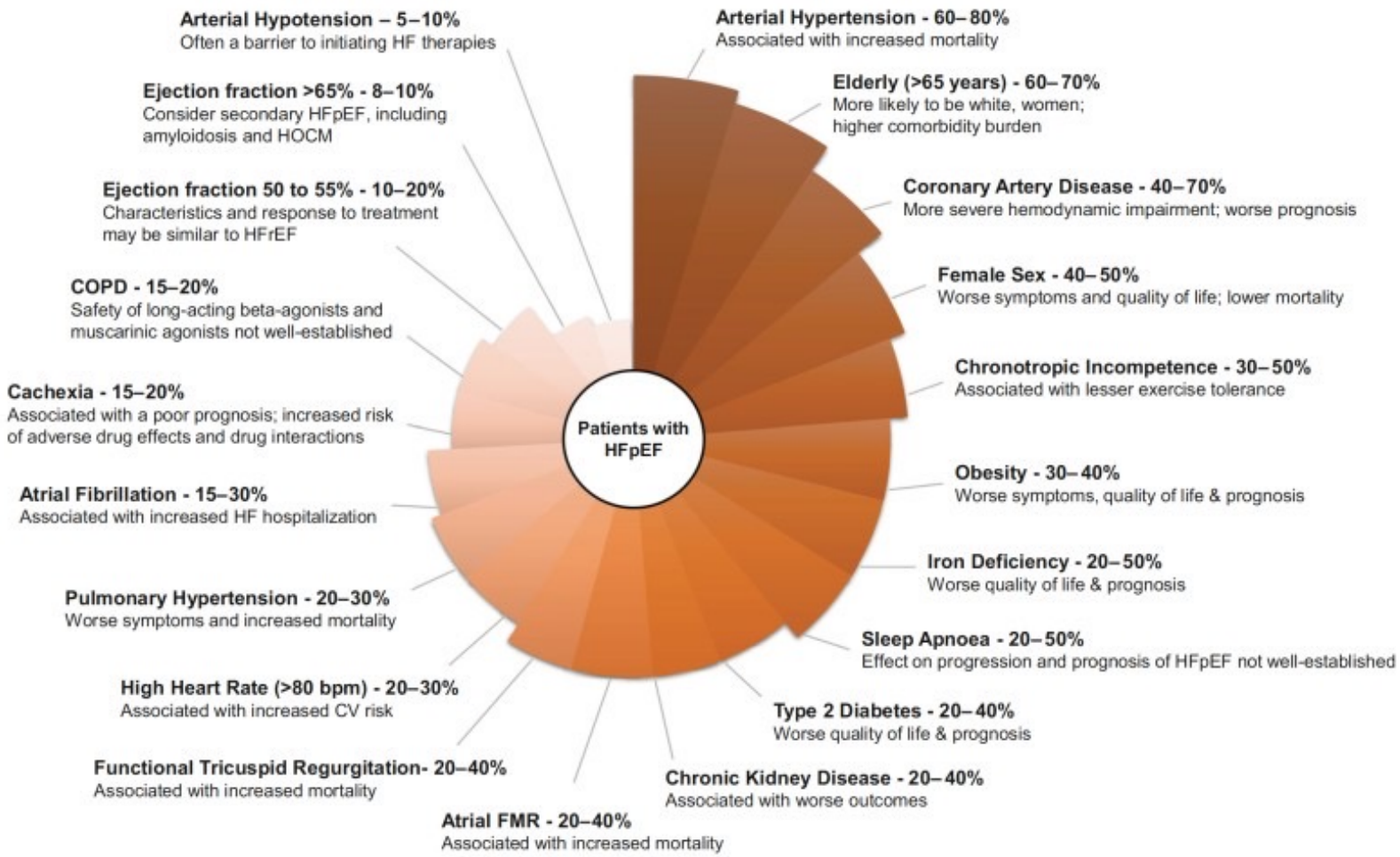
HFPEF statements in 2023



Anker SD, et al. Eur J Heart Fail 2023;25:936-55.

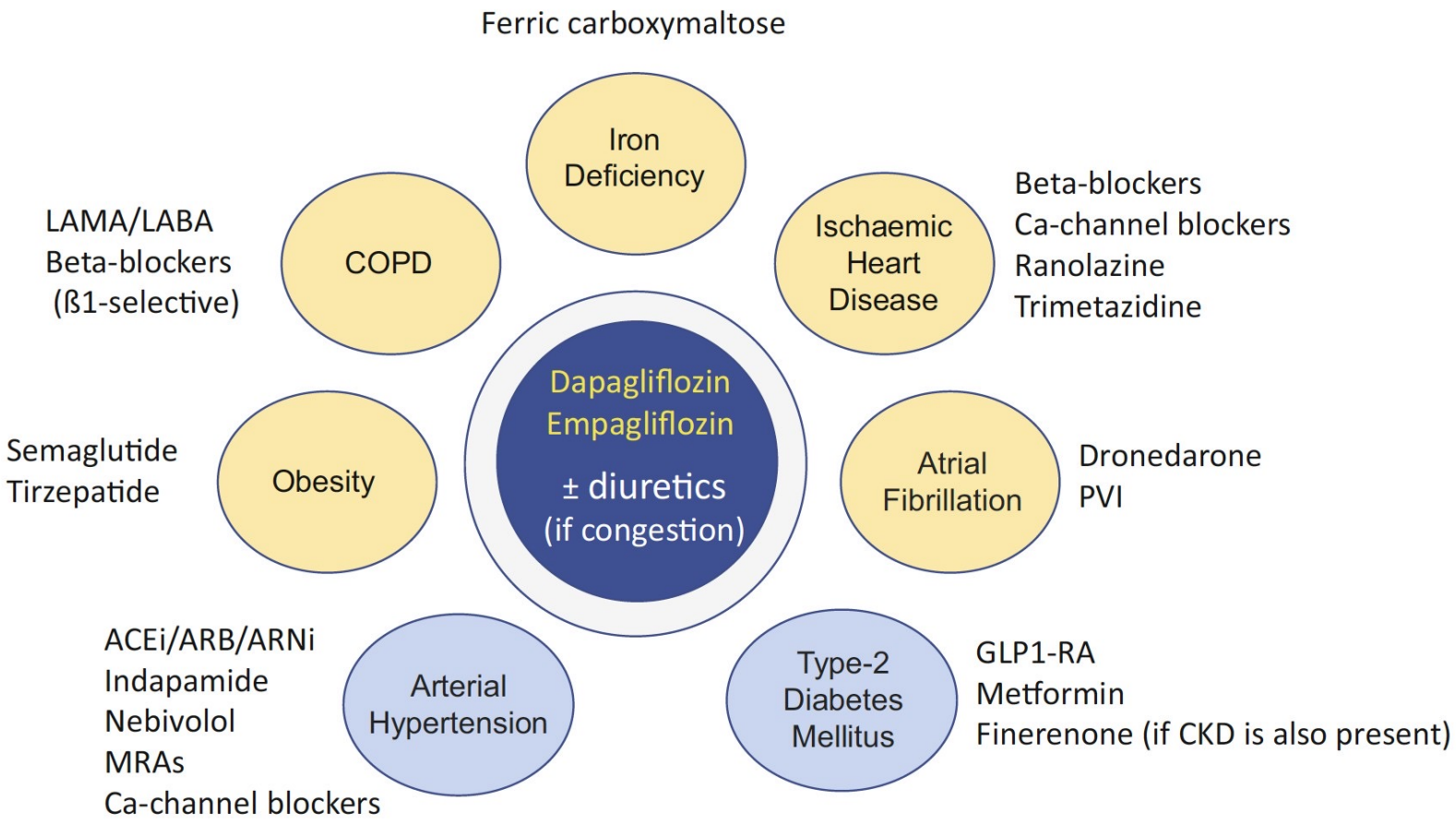
Borlaug BA, et al. JACC Scientific statement 2023

Estimated prevalence of primary HFPEF phenotypes



Anker SD, et al. Eur J Heart Fail 2023;25:936-55.

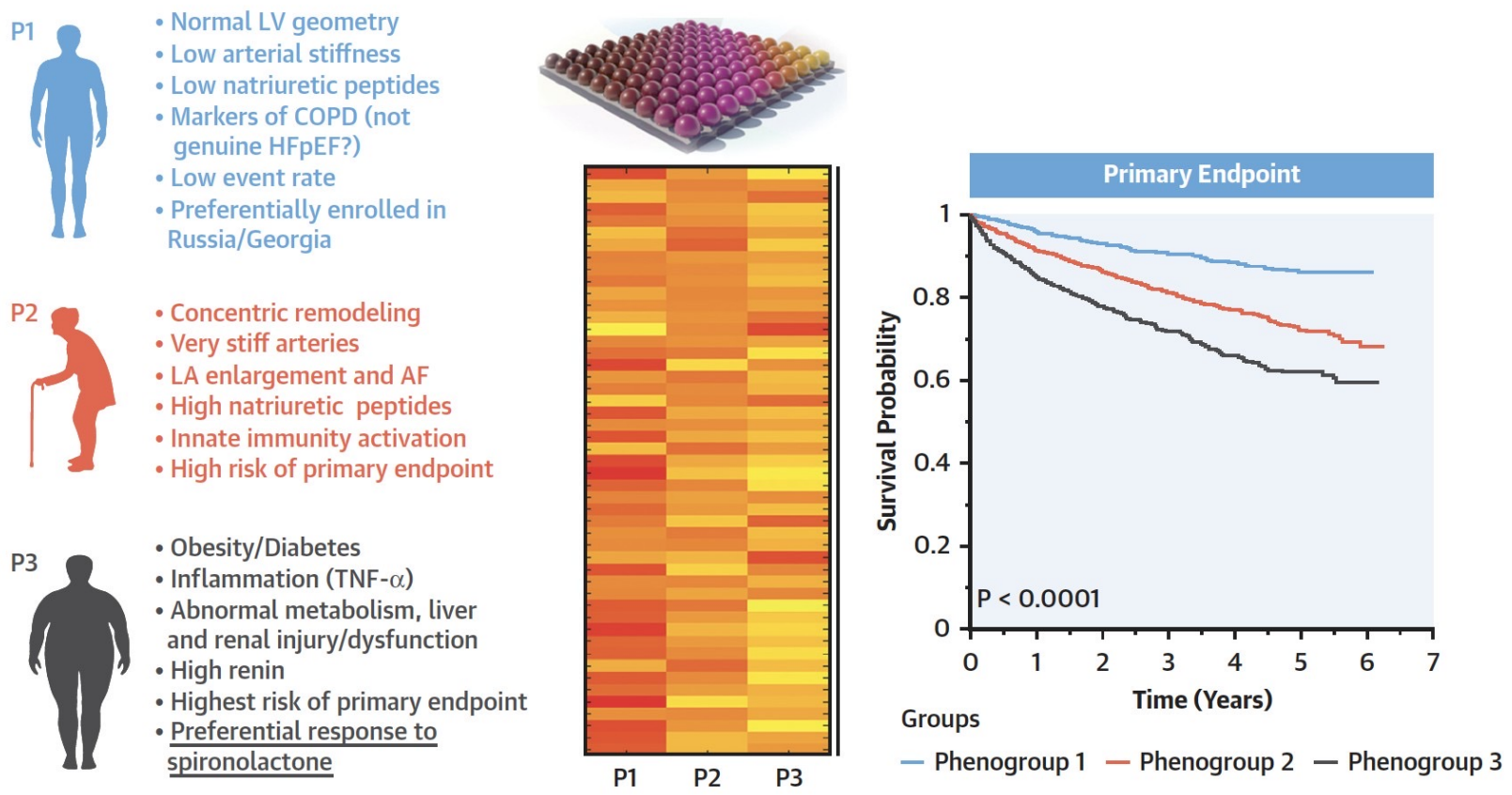
Patient profiling in HFpEF and consequent therapeutic considerations



Anker SD, et al. Eur J Heart Fail 2023;25:936-55.

Clinical phenogroups of HFpEF patients: TOPCAT trial

- **Biomarkers**
- **Echo**
- **Vascular**



Cohen, J.B. et al. J Am Coll Cardiol HF. 2020;8(3):172-84.

ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–13
https://doi.org/10.1093/eurheartj/ehad195

ESC GUIDELINES

2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

Recommendation	Class[a]	Level[b]
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ESC European Society of Cardiology
European Heart Journal - Cardiovascular Imaging (2024) **25**, 1517–1524
https://doi.org/10.1093/ehjci/jeae201

REVIEW

Contemporary treatment options in heart failure with preserved ejection fraction

Alexander Peikert [1] **and Scott D. Solomon** [2]*