

Therapy of Heart Failure with Preserved Ejection Fraction

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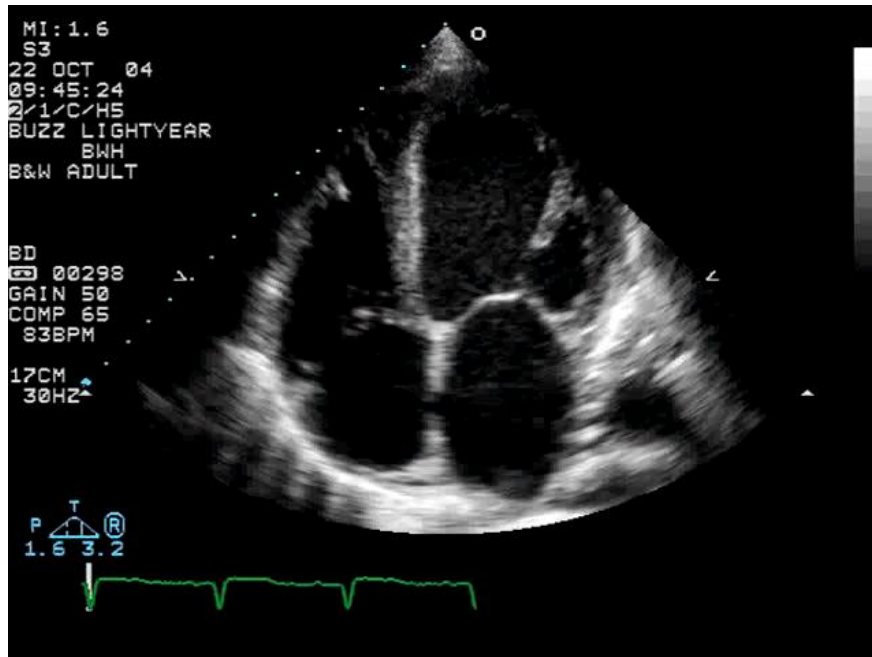
Boston, MA, USA



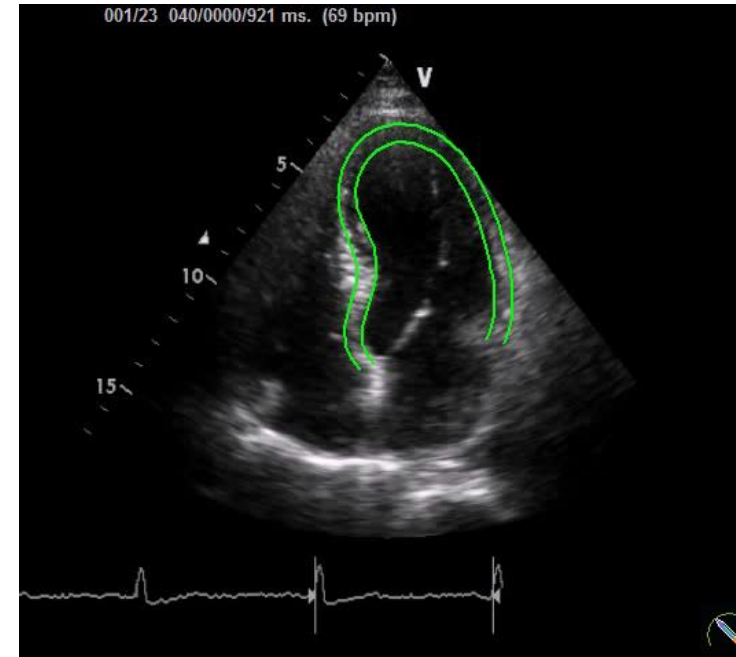
Disclosures

- Dr. Solomon has received research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Novartis, Sanofi Pasteur, Theracos, and has consulted for Akros, Alnylam, Amgen, AstraZeneca, Bayer, BMS, Cardior, Corvia, Cytokinetics, Gilead, GSK, Ironwood, Merck, Novartis, Roche, Takeda, Theracos, Quantum Genetics, Cardurion, AoBiome, Janssen, Cardiac Dimensions

The Two Faces of Heart Failure

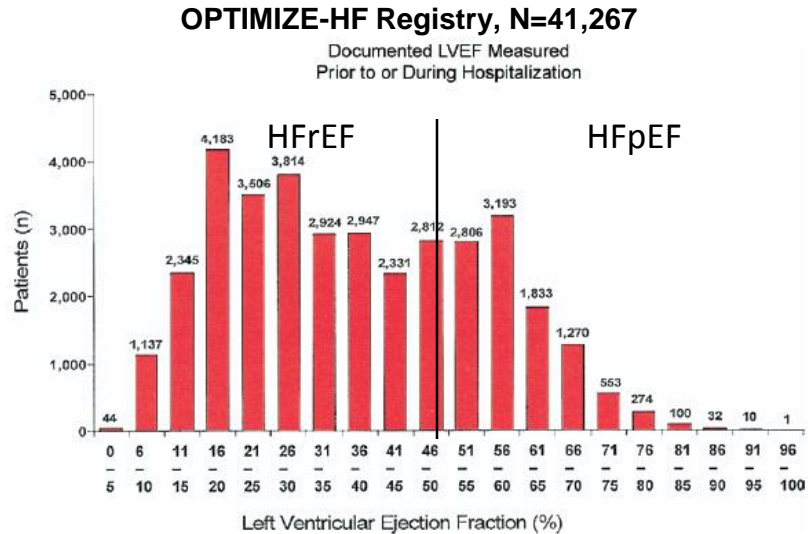


HFrEF

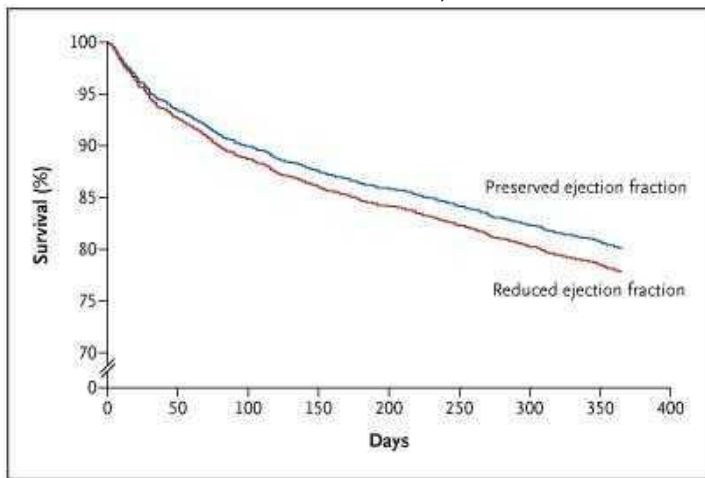


HFpEF

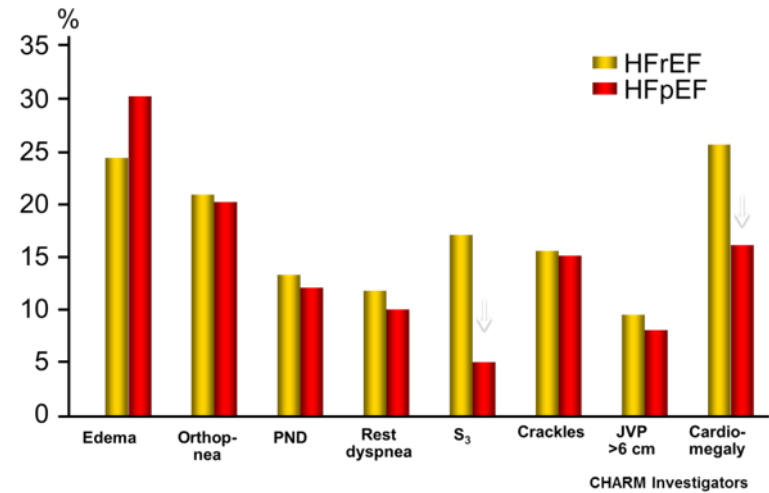
HFpEF Accounts for Nearly 50% of HF Admissions, Signs and Symptoms are Nearly Identical to HFrEF, Morbidity and Mortality are high, and the Incidence is Rising



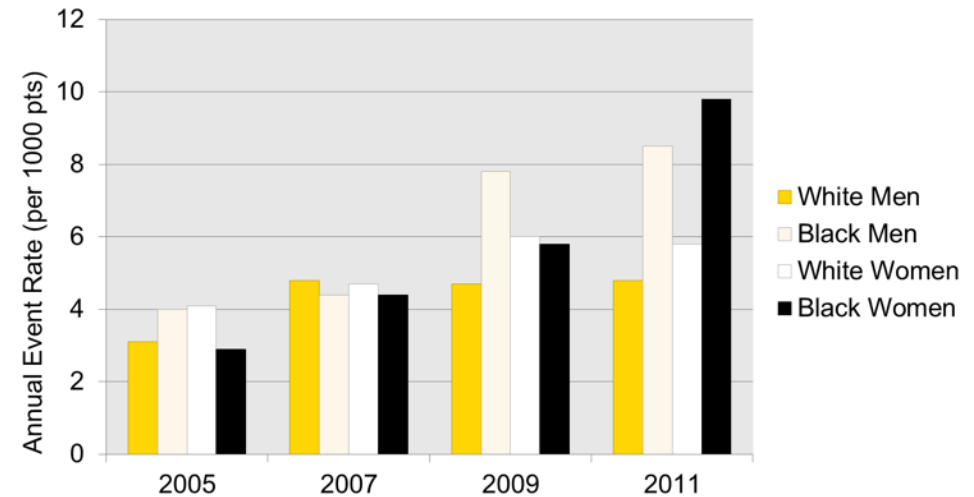
Left Ventricular Ejection Fraction (%)
 Fonarow G et al. JACC. 2007; 50:768-777.



Owan TE, et al. NEJM 2006; 355:251-9



CHARM Investigators



Rosemond. ARIC 2013 Unpublished



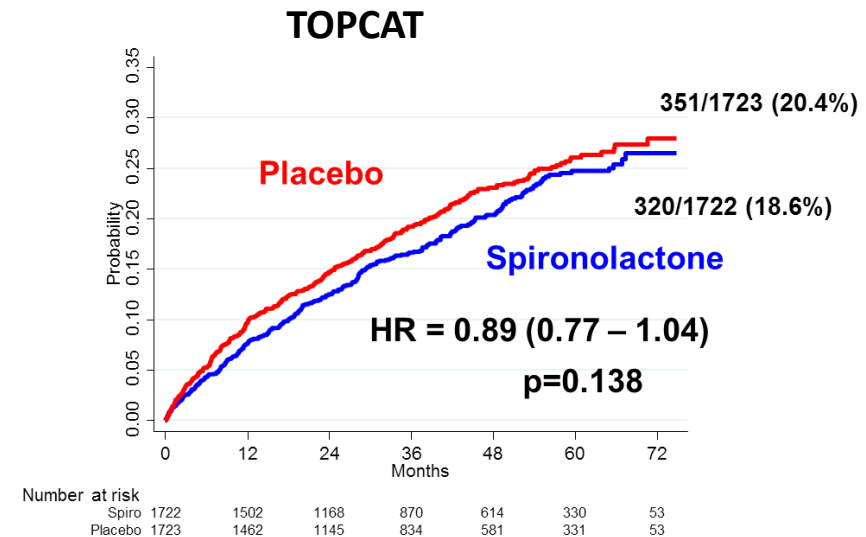
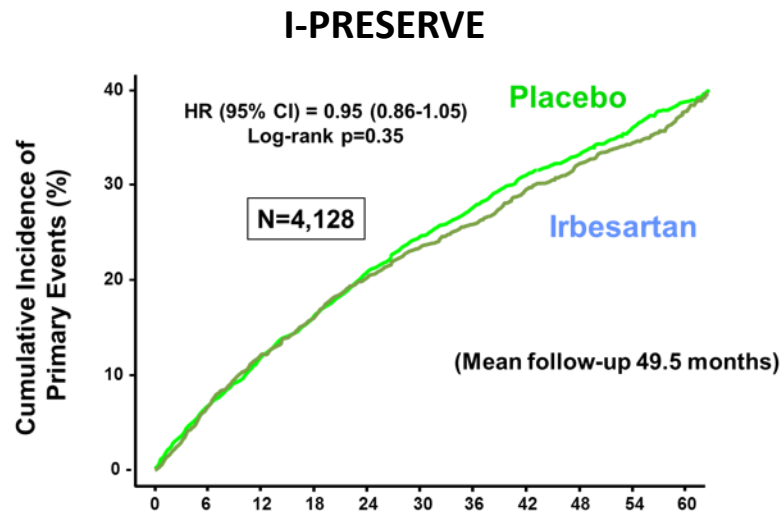
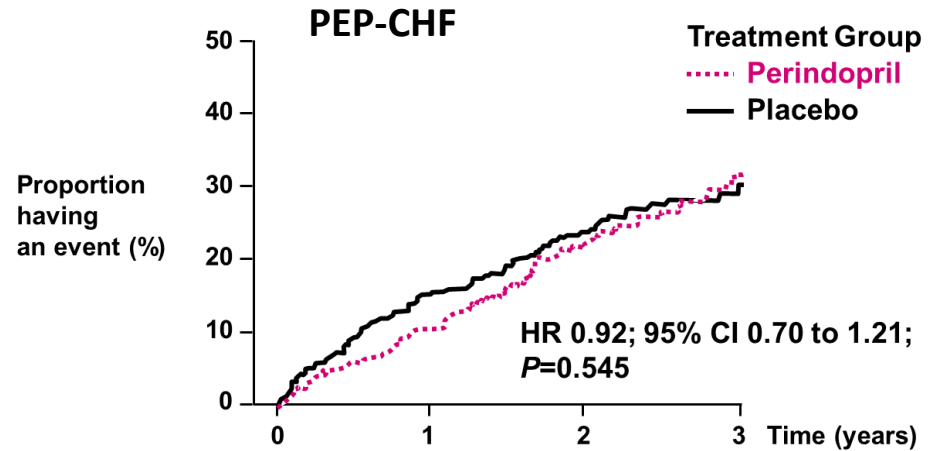
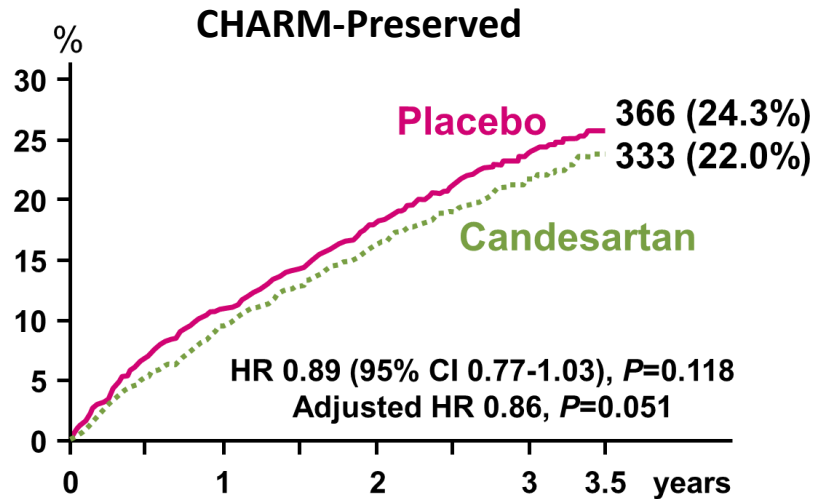
2012 ESC-Guidelines

- No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF.

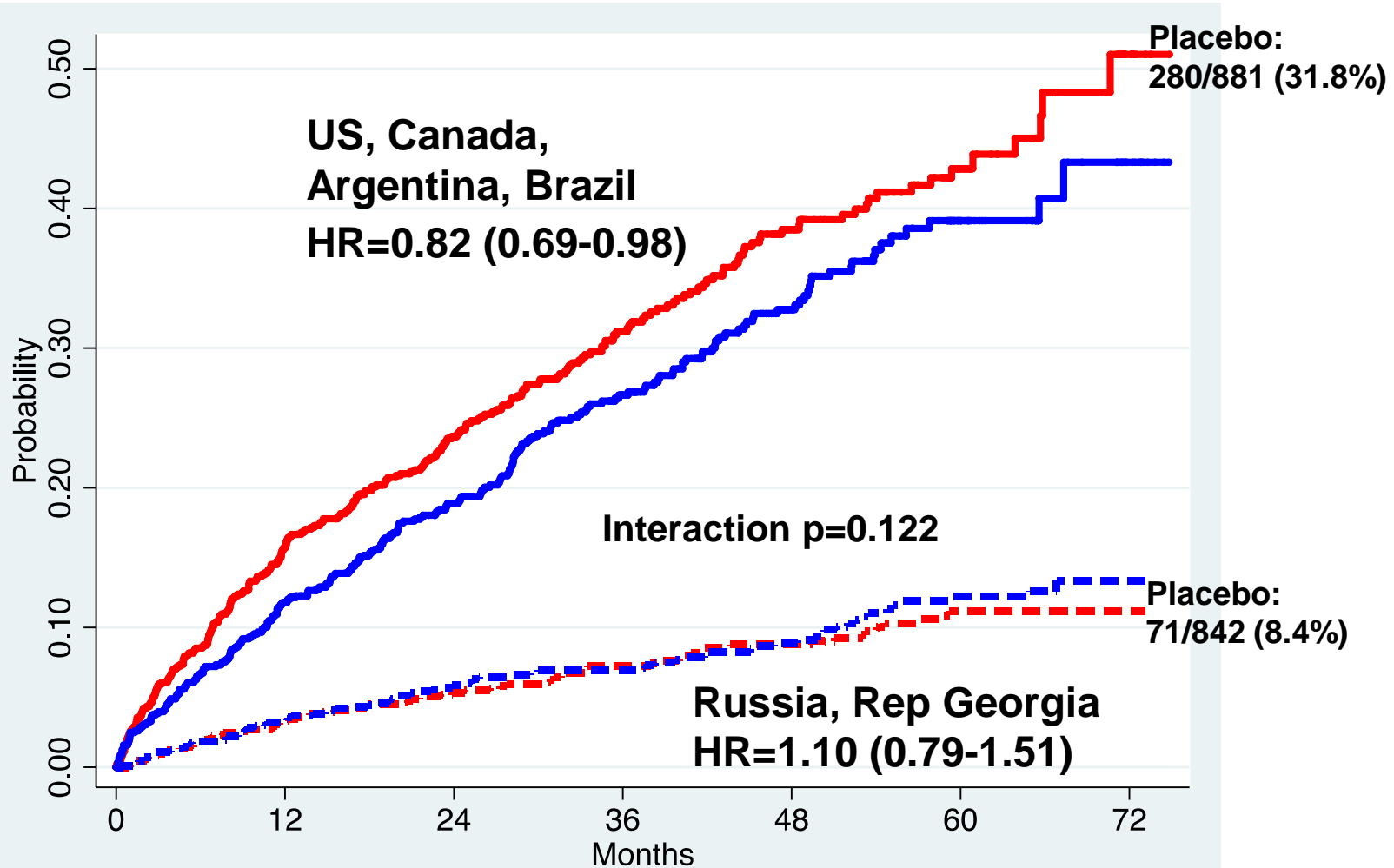
2016 ESC-Guidelines

- No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF.

Outcomes Trials in HFpEF



TOPCAT: Exploratory Analysis by Region





The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Heart Failure with Preserved Ejection Fraction

Margaret M. Redfield, M.D.



Current Treatment of HFpEF

- Consider Alternative Diagnoses
- Symptomatic Treatment with Diuretics
- Treatment of Hypertension
- Rate control in Atrial Fibrillation (? Maintain SR)
- Treat Ischemia
- ? Spironolactone

Alternative Diagnoses

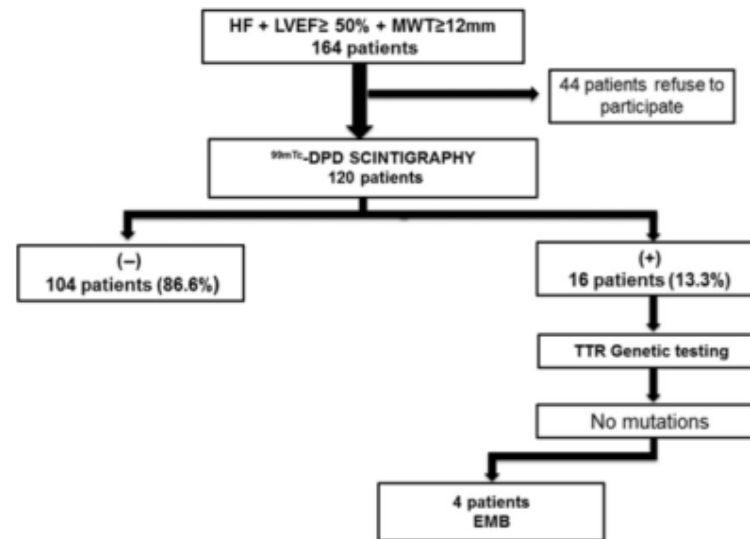
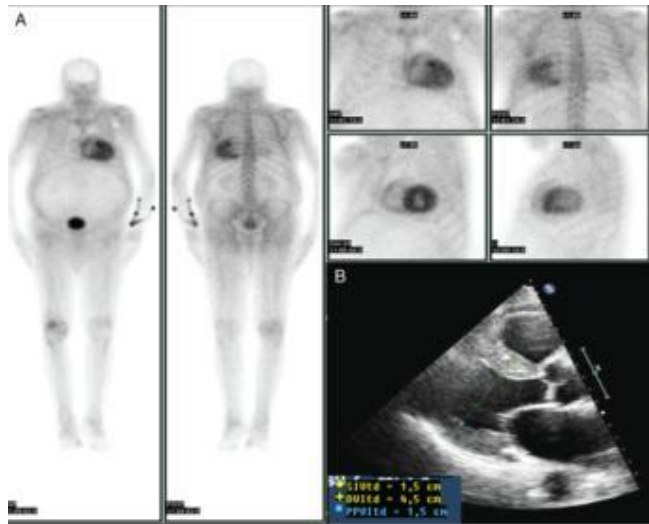
Potential Alternative Diagnoses in HFpEF

- Ischemic heart disease
- Lung disease masquerading as heart failure
- Anemia resulting in severe DOE
- Hypertensive Crisis
- Pheochromocytoma

Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction

Esther González-López¹, Maria Gallego-Delgado¹, Gonzalo Guzzo-Merello¹, F. Javier de Haro-del Moral², Marta Cobo-Marcos¹, Carolina Robles¹, Belén Bornstein^{3,4,5}, Clara Salas⁶, Enrique Lara-Pezzi⁷, Luis Alonso-Pulpon¹, and Pablo Garcia-Pavia^{1,7*}

- HFpEF is heterogeneous with multiple causes
- Prospectively screened consecutive patients ≥ 60 years old admitted due to HFpEF with LV hypertrophy (≥ 12 mm).
- 120 HFpEF patients (59% women, 82 + 8 years). TTR gene, and no mutations were found.
- diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy
-

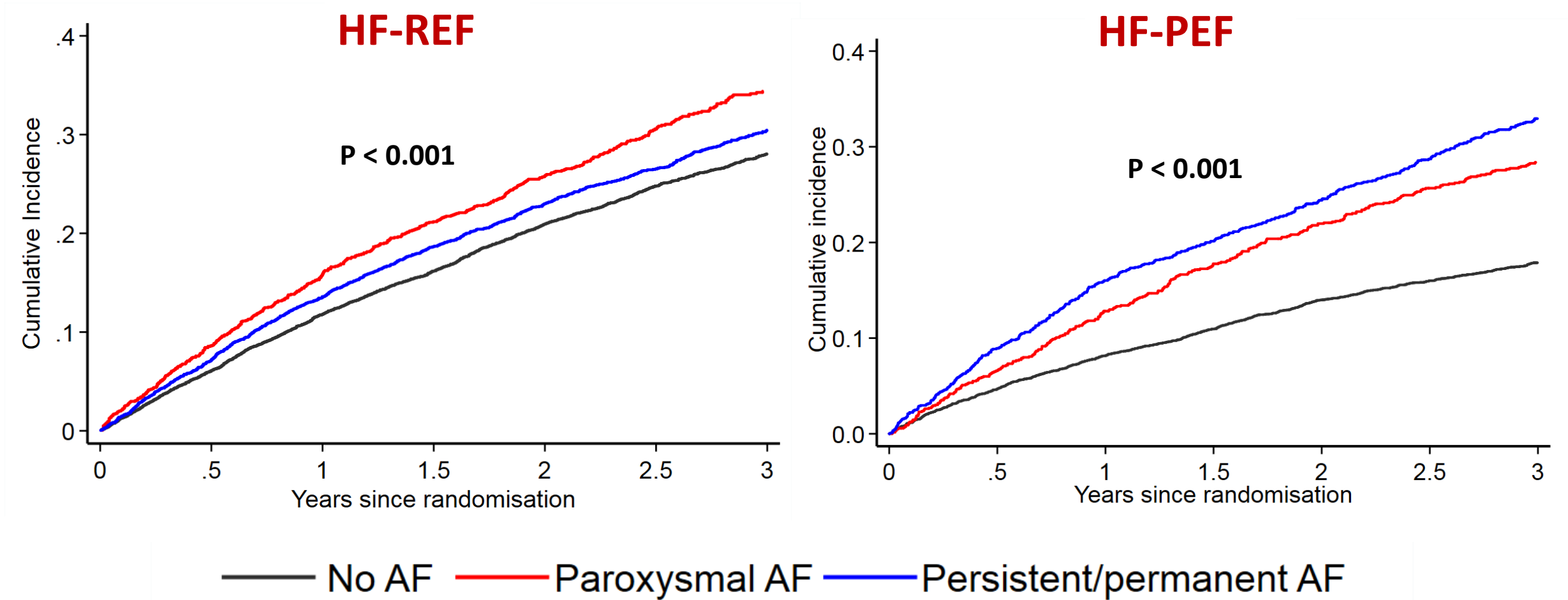


Diuretic Use in HFpEF

- If there is no need for diuretics, this is probably not heart failure!
- Diuretic use in HFpEF is empiric – but appears to work to reduce congestion.
- Loop and thiazide diuretics are reasonable
- Diuretic resistance should prompt assessment of renal arteries

Atrial Fibrillation in HFpEF: Common and Morbid!

Heart failure hospitalisation or cardiovascular death



HFpEF is Extremely Comorbid

Table 1. Characteristics of Patients.*

Characteristic	Reduced Ejection Fraction (<40%) (N=1570)	Preserved Ejection Fraction (>50%) (N=880)	P Value
Mean LVEF — %	25.9	62.4	<0.001
Age — yr	71.8 ± 12	75.4 ± 11.51	<0.001
Male sex — no. (%)	983 (62.6)	302 (34.3)	<0.001

	HFrEF	HFpEF	P-value
Age	71.8 ± 12	75.4 ± 11.5	< 0.001
Hypertension	49.2%	55.1%	0.005
Atrial Fibrillation	23.6%	31.8%	< 0.001
COPD	13.2%	17.7%	0.002
Anemia	9.9%	21.1%	< 0.001

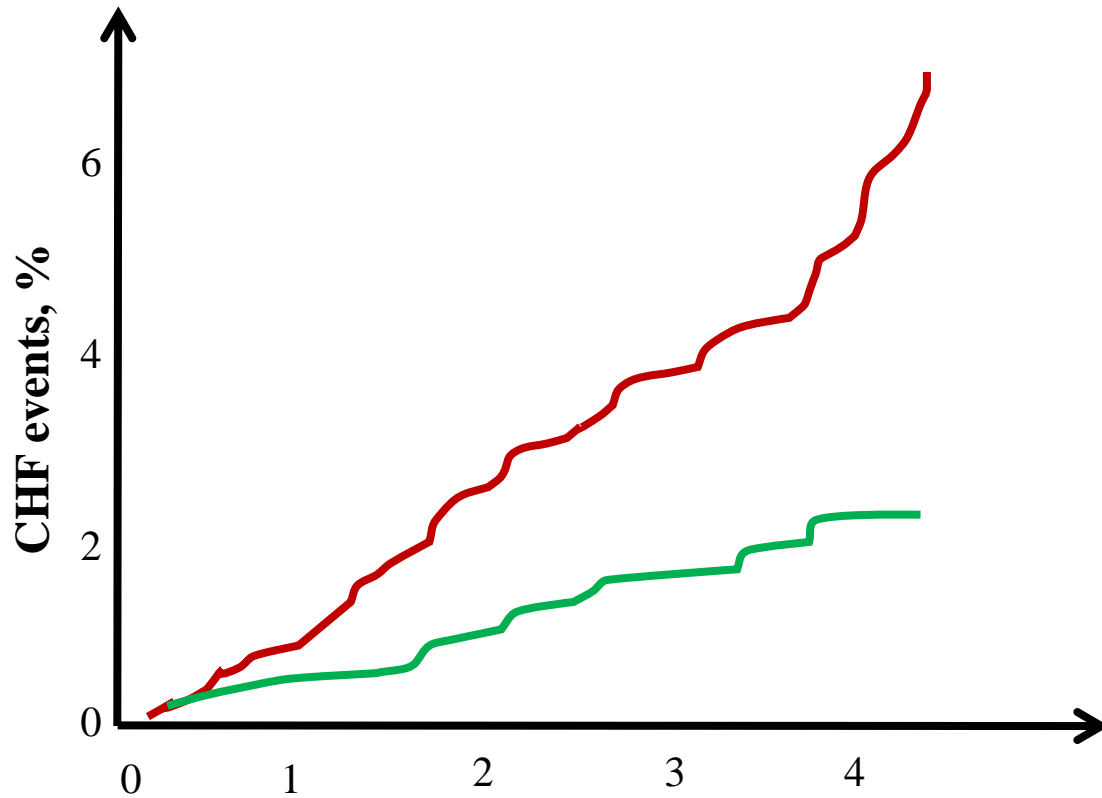
Prior PCI — no. (%)	48 (3.1)	16 (1.8)	0.07
Peptic ulcer disease — no. (%)	94 (6.0)	74 (8.4)	0.02
Hepatitis or cirrhosis — no. (%)	20 (1.3)	16 (1.8)	0.28
Dementia — no. (%)	76 (4.8)	49 (5.6)	0.43
Hemoglobin <10 g/dl — no. (%)	155 (9.9)	186 (21.1)	<0.001
Mean systolic blood pressure — mm Hg	146	156	<0.001
Mean respiratory rate — breaths/min	26	26	0.17
Serum sodium <136 mmol/liter — no. (%)	362 (23.1)	209 (23.8)	0.70
Serum creatinine >150 mmol/liter — no. (%)	296 (18.9)	195 (22.2)	0.95
Dialysis — no. (%)	18 (1.1)	9 (1.0)	0.78

Comorbidities in HFpEF: Treat according to guidelines

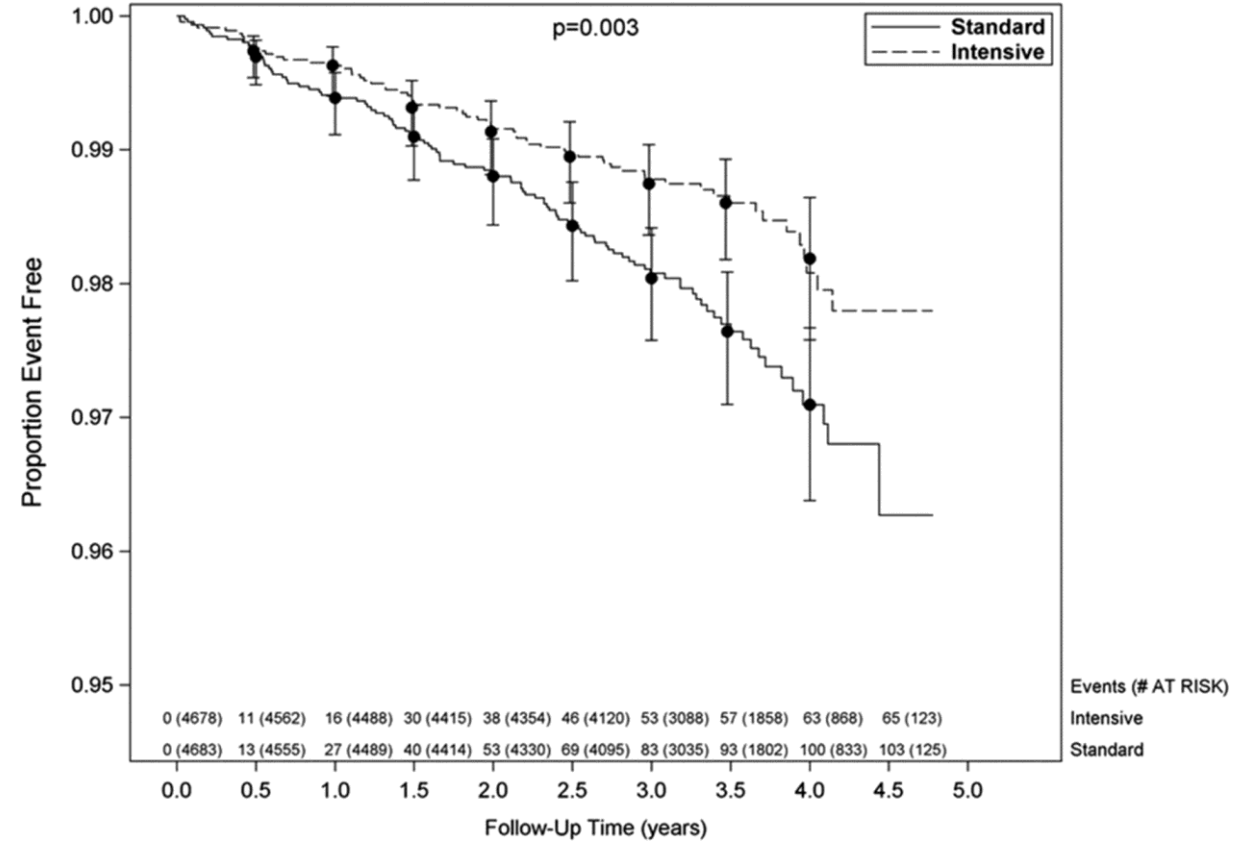
- Hypertension
- Diabetes mellitus
- Renal dysfunction
- Sleep apnea
- Anemia

Elevated Blood Pressure – Not a “symptom” but still bad!

HYVET Trial



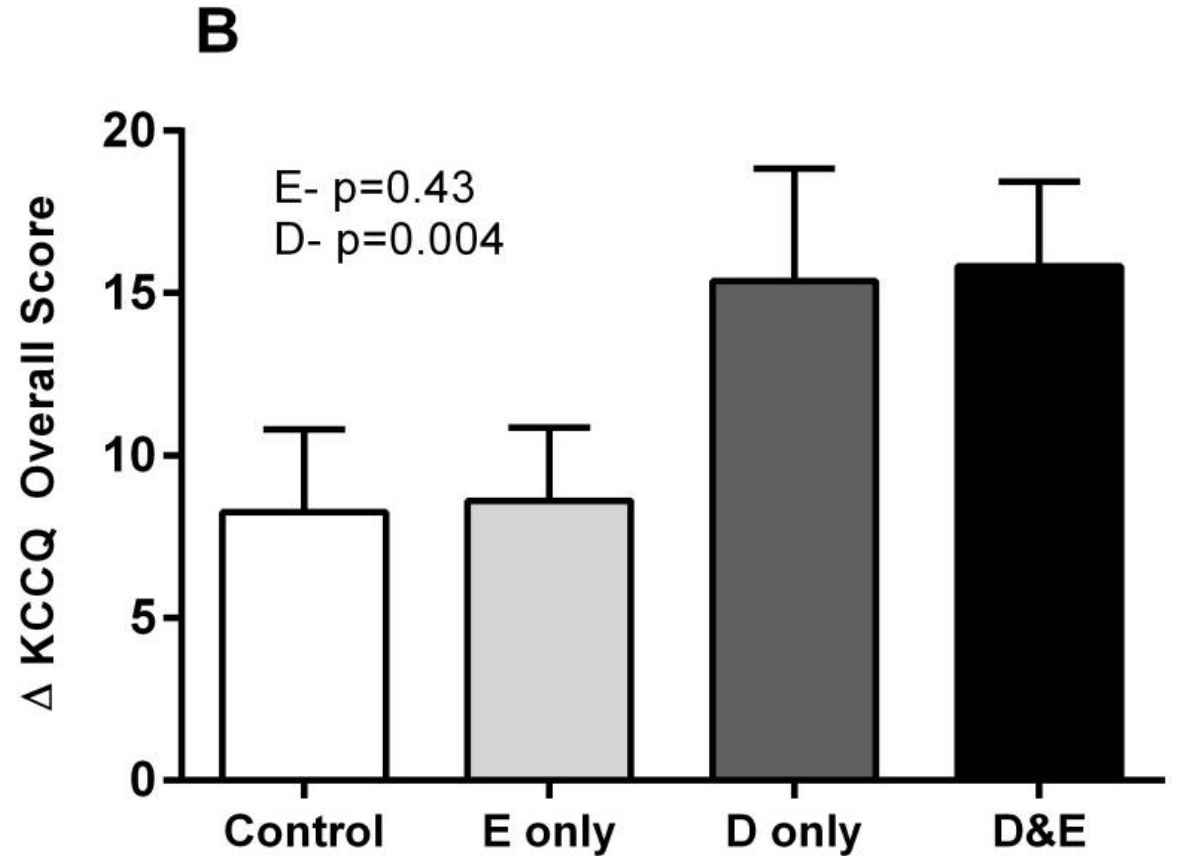
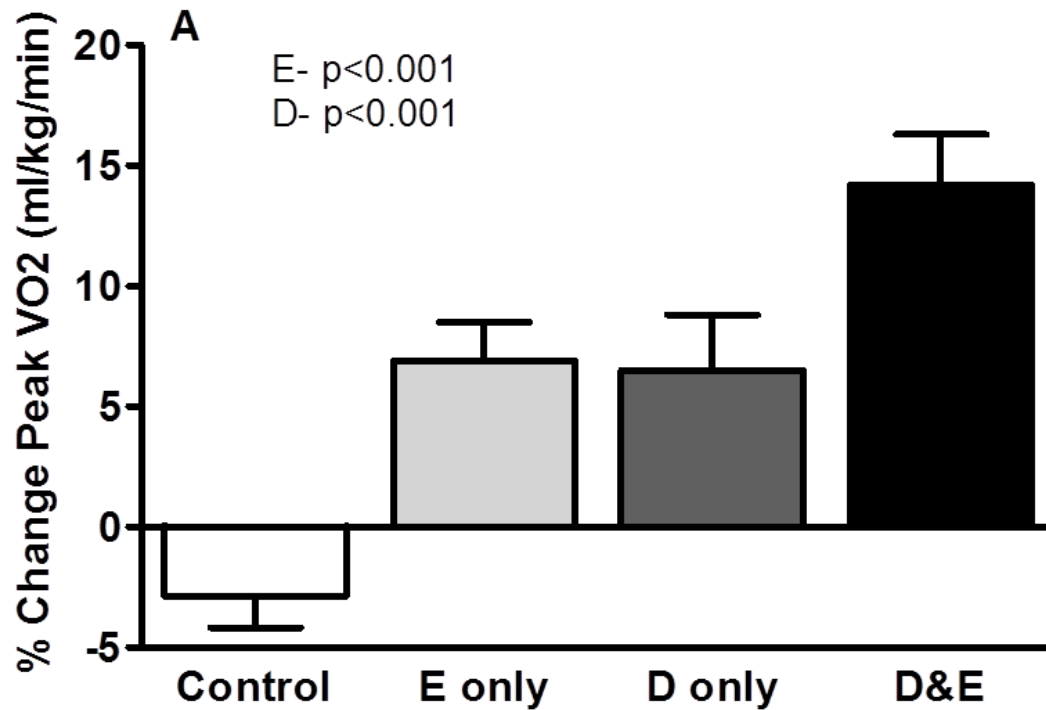
SPRINT Trial



Beckett N et al. N Engl J Med 2008;358:1887-1898



Exercise and Diet Improve Peak VO₂ and KCCQ in HFpEF





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www.glasbergen.com

“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”

The cover of 'Running Report' magazine, Issue 4, Vol. 3, Spring 2011. The title 'RUNNING REPORT' is in large, bold, red letters at the top. Below it, the issue information is listed. The cover features a photograph of two men in athletic wear. The man on the left is wearing a dark t-shirt with the text 'Improve Diastolic Function with Exercise' and '...and if that doesn't work try Viagra!'. The man on the right is wearing a dark t-shirt with the text 'A FASTER PACE FOR ANY RACE'. The cover also lists several articles with their page numbers: '2 DAY TRAINING DIASTOLIC TRAINING', '4 SPEEDY WORKOUTS', '6 BEST CROSS-TRAINING TIPS', 'Goteburg MARATHON PAGE 76', 'A FASTER PACE FOR ANY RACE PAGE 40', and 'BEGINNERS MOTIVATION 101 WEIGHT LOSS MADE EASY Stay Fit FOREVER page 45'. A barcode and the website 'magcover.com' are at the bottom right.

RUNNING REPORT

ISSUE 4 VOL. 3
spring 2011

- 2** DAY TRAINING DIASTOLIC TRAINING
- 4** SPEEDY WORKOUTS
- 6** BEST CROSS-TRAINING TIPS

Goteburg
MARATHON
PAGE 76

**Improve Diastolic Function
with Exercise**

...and if that doesn't work try Viagra!

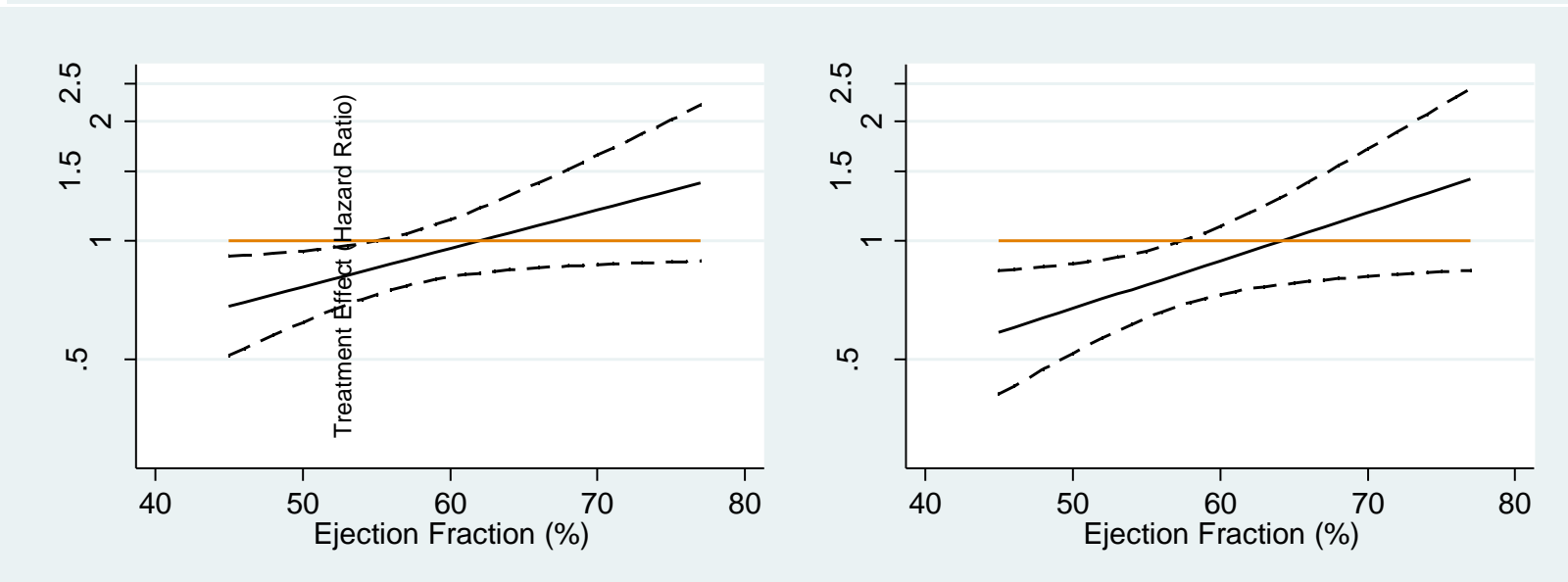
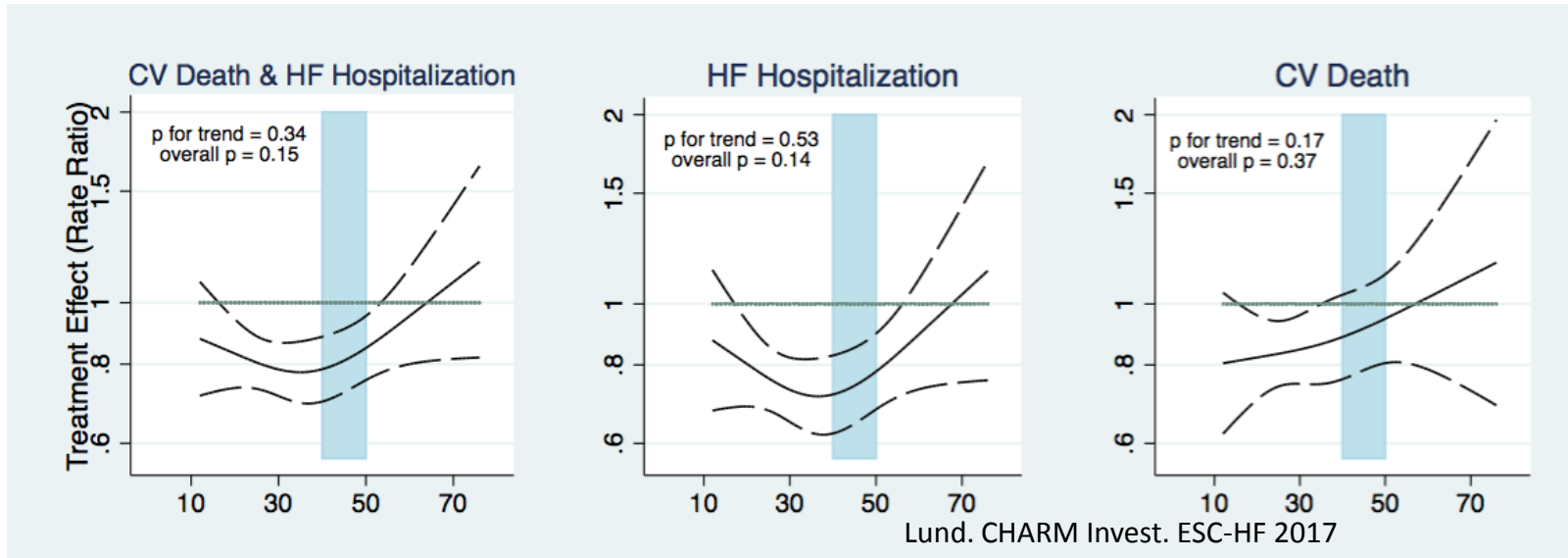
**A FASTER PACE
FOR ANY RACE**
PAGE 40

BEGINNERS
MOTIVATION 101
WEIGHT LOSS
MADE EASY

Stay Fit
FOREVER
page 45



RAAS inhibition may be beneficial in the “Mid-Range” of Heart Failure



No Support for Sildenafil in HFpEF

ONLINE FIRST

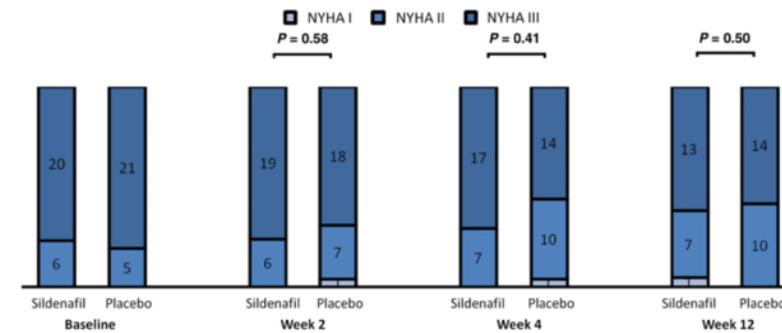
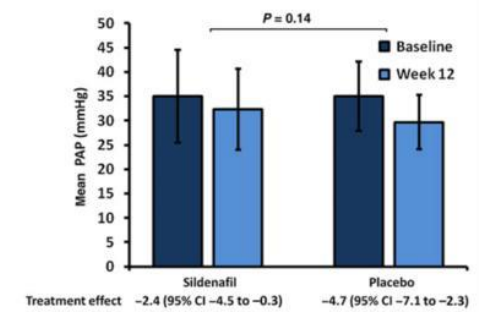
Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial

Table 3. Primary, Secondary, and Safety End Points

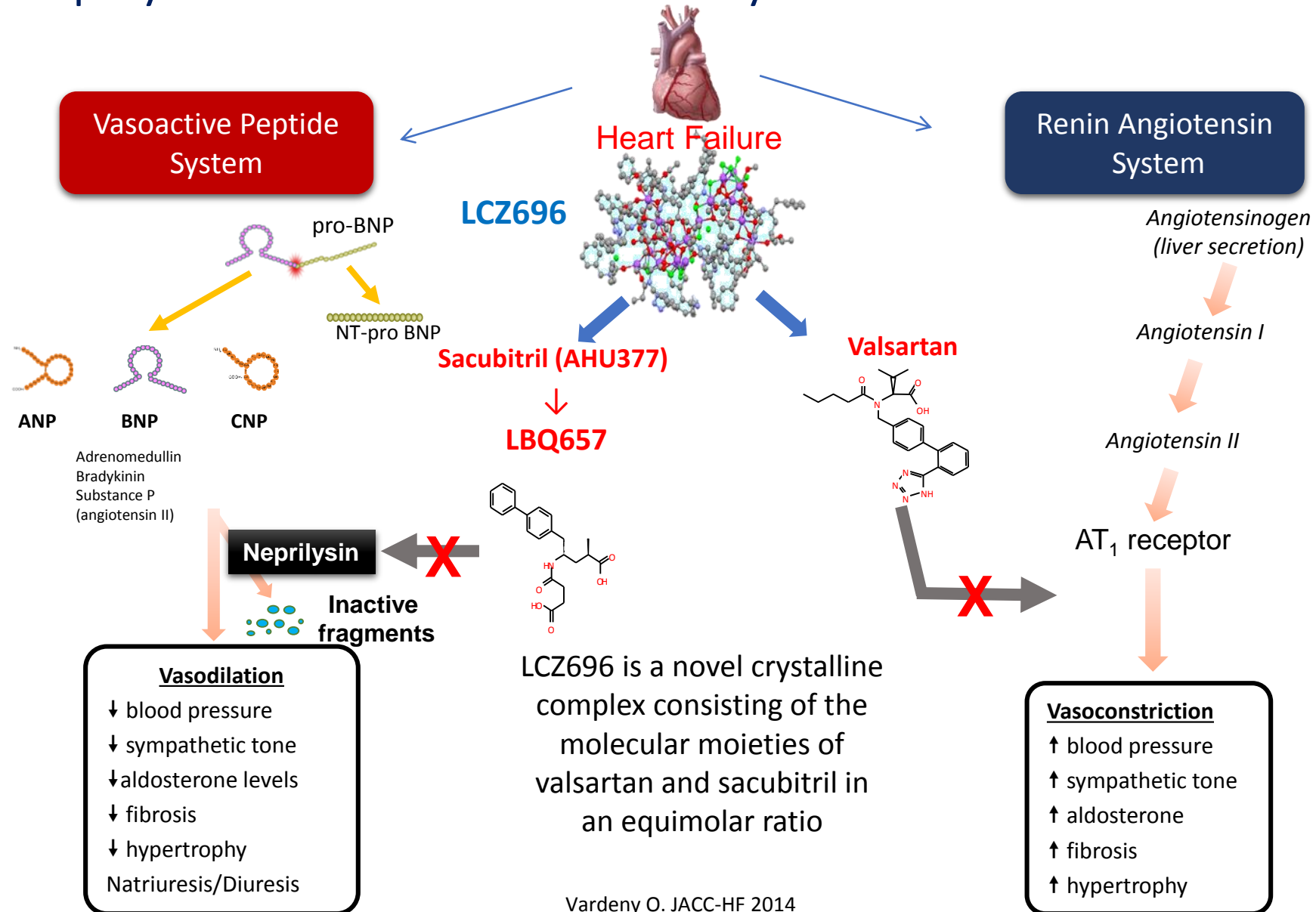
	Placebo		Sildenafil		P Value
	No. of Patients	Variable	No. of Patients	Variable	
Primary end point					
Change in peak oxygen consumption at 24 wk, median (IQR), mL/kg/min	94	-0.20 (-0.70 to 1.00)	91	-0.2 (-1.70 to 1.11)	.90
Secondary end points					
Clinical rank score, mean ^a	94	95.8	95	94.2	.85
Change in 6-minute walk distance at 24 wk, median (IQR), m	95	15.0 (-26.0 to 45.0)	90	5.0 (-37.0 to 55.0)	.92
Change in peak oxygen consumption at 12 wk, median (IQR), mL/kg/min	96	0.03 (-1.10 to 0.67)	97	0.01 (-1.35 to 1.25)	.98
Change in 6-minute walk distance at 12 wk, median (IQR), m	96	18.0 (-14.5 to 48.0)	99	10.0 (-25.0 to 36.0)	.13
Components of clinical rank score at 24 wk					
Death, No. (%) ^b	103	0	113	3 (3)	.25
Hospitalization for cardiovascular or renal cause, No. (%)	103	13 (13)	113	15 (13)	.69
Change in MLHFQ, median (IQR)	91	-8 (-21 to 5)	91	-8 (-19 to 0)	.44
Safety end points, No. (%)					
Adverse events	103	78 (76)	113	90 (80)	.49
Serious adverse events	103	16 (16)	113	25 (22)	.22
Change in left ventricular structure by CMRI at 24 wk					
Left ventricular mass by CMRI, g	47	0.6 (-5.7 to 7.9)	49	-1.5 (-5.9 to 7.1)	.93
Left ventricular end-diastolic volume by CMRI, mL	47	-4.3 (-15.5 to 8.1)	49	3.7 (-4.9 to 14.5)	.13
Change in diastolic function parameters at 24 wk					
Medial e', m/s	83	0.00 (-0.01 to 0.01)	77	0.00 (-0.01 to 0.01)	.88
E/e'	80	-1.6 (-4.7 to 2.2)	75	0.2 (-2.4 to 3.1)	.16
PA systolic pressure, mm Hg	58	-2 (-8 to 8)	45	2 (-5 to 7)	.94
Change in core laboratory biomarkers at 24 wk					
Creatinine, mg/dL	94	0.01 (-0.10 to 0.09)	94	0.05 (-0.04 to 0.15)	.047
Cystatin C, mg/L	95	0.01 (-0.08 to 0.11)	95	0.05 (-0.04 to 0.16)	.01
NT-proBNP, pg/mL	94	-23 (-198 to 139)	95	15 (-90 to 372)	.03
Endothelin-1, pg/mL	95	-0.01 (-0.48 to 0.47)	95	0.38 (-0.10 to 0.97)	.046
Aldosterone, ng/dL	95	0 (-7.0 to 4.8)	95	-1.1 (-7.7 to 3.0)	.85
NT-procollagen III, μ g/L	93	-0.03 (-1.49 to 1.54)	95	0.07 (-1.17 to 1.42)	.77

Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial

Elke S. Hoendermis^{1*}, Licette C.Y. Liu¹, Yoran M. Hummel¹, Peter van der Meer¹, Rudolf A. de Boer¹, Rolf M.F. Berger², Dirk J. van Veldhuisen¹, and Adriaan A. Voors¹

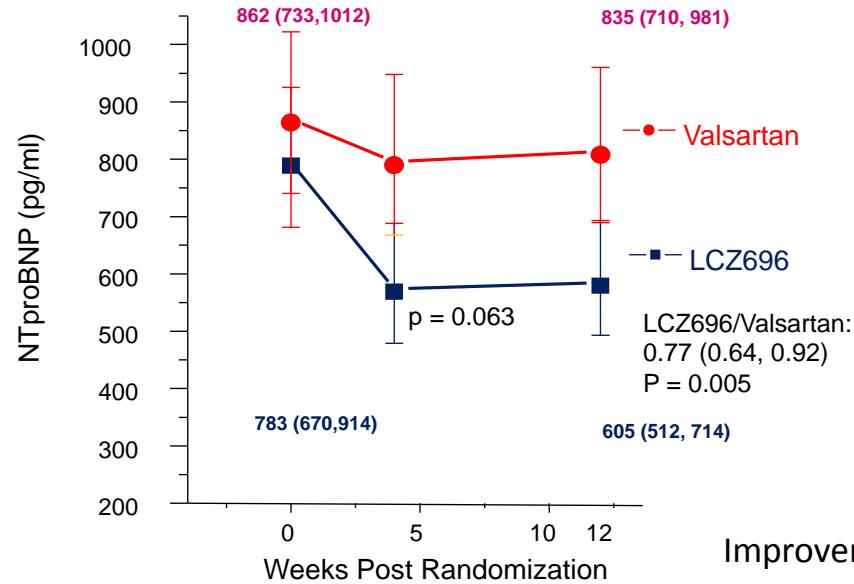


Sacubitril/valsartan – A first-in-class Angiotensin Receptor Neprilysin Inhibitor – Simultaneously Inhibits NEP and the RAS

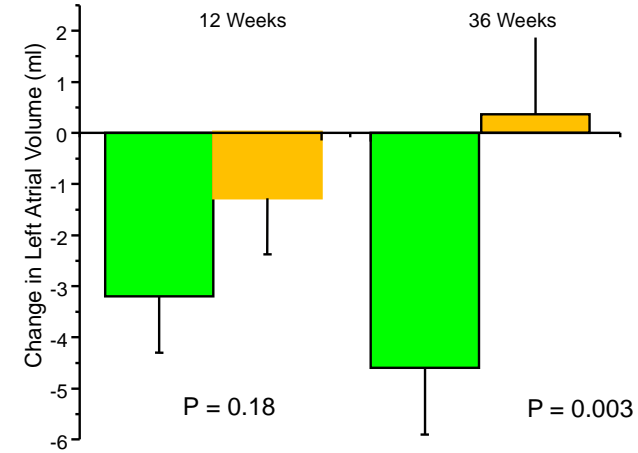


PARAMOUNT: Significant Improvement in Several Domains with Sacubitril/Valsartan

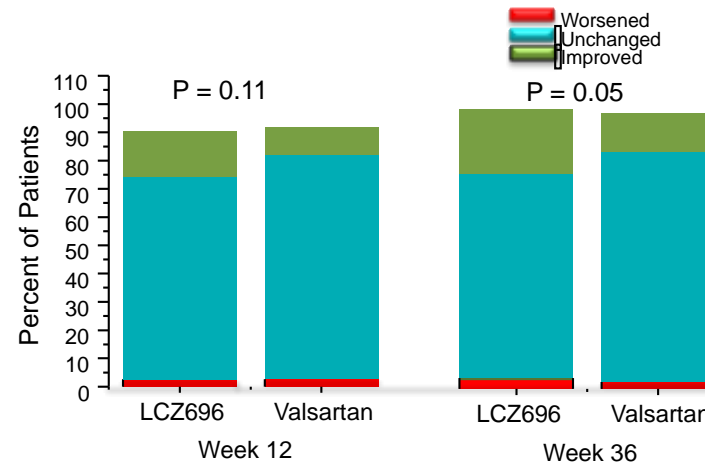
Improvement in NT-proBNP



Improvement in Left Atrial Size

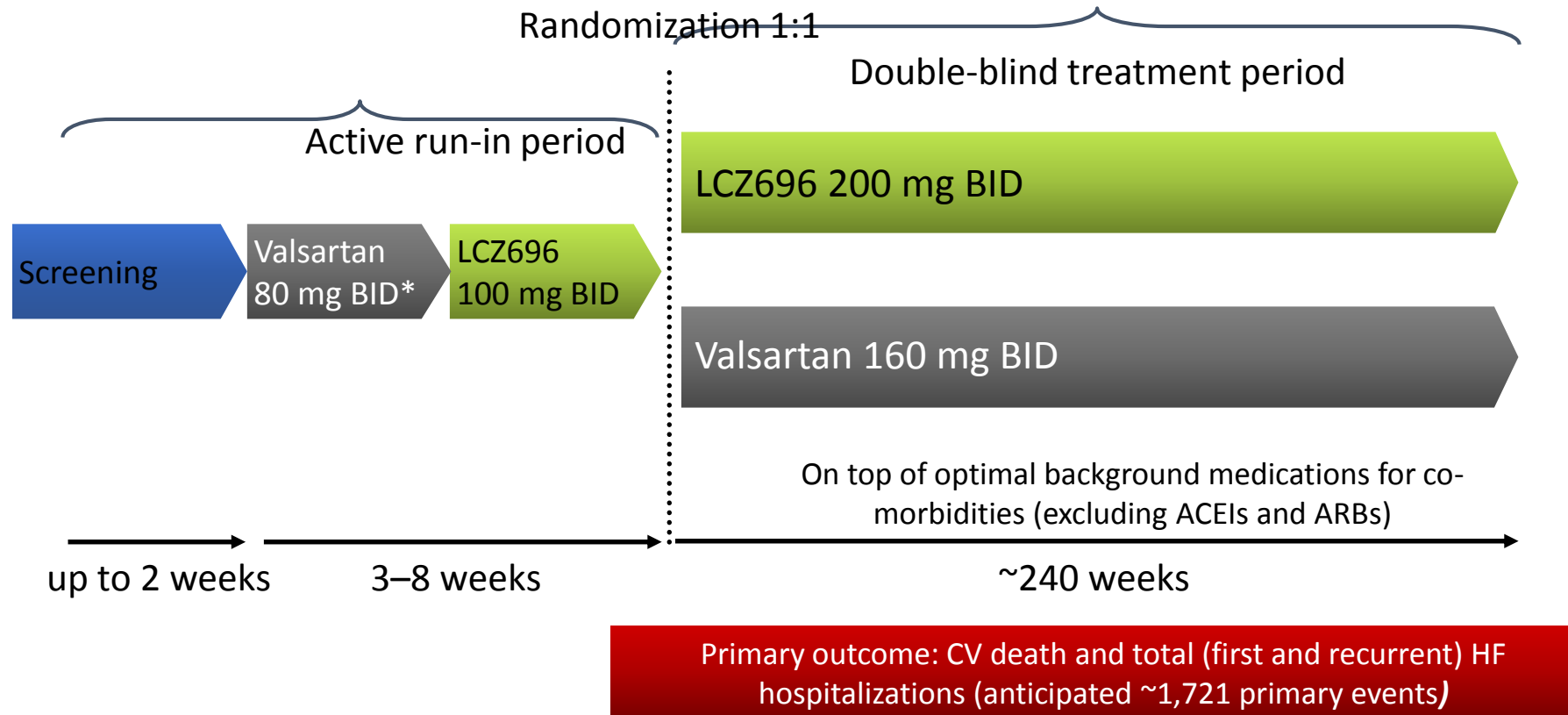


Improvement in NYHA Class





Target patient population: ~4,800 patients with symptomatic HF (NYHA Class II–IV) and LVEF \geq 45%

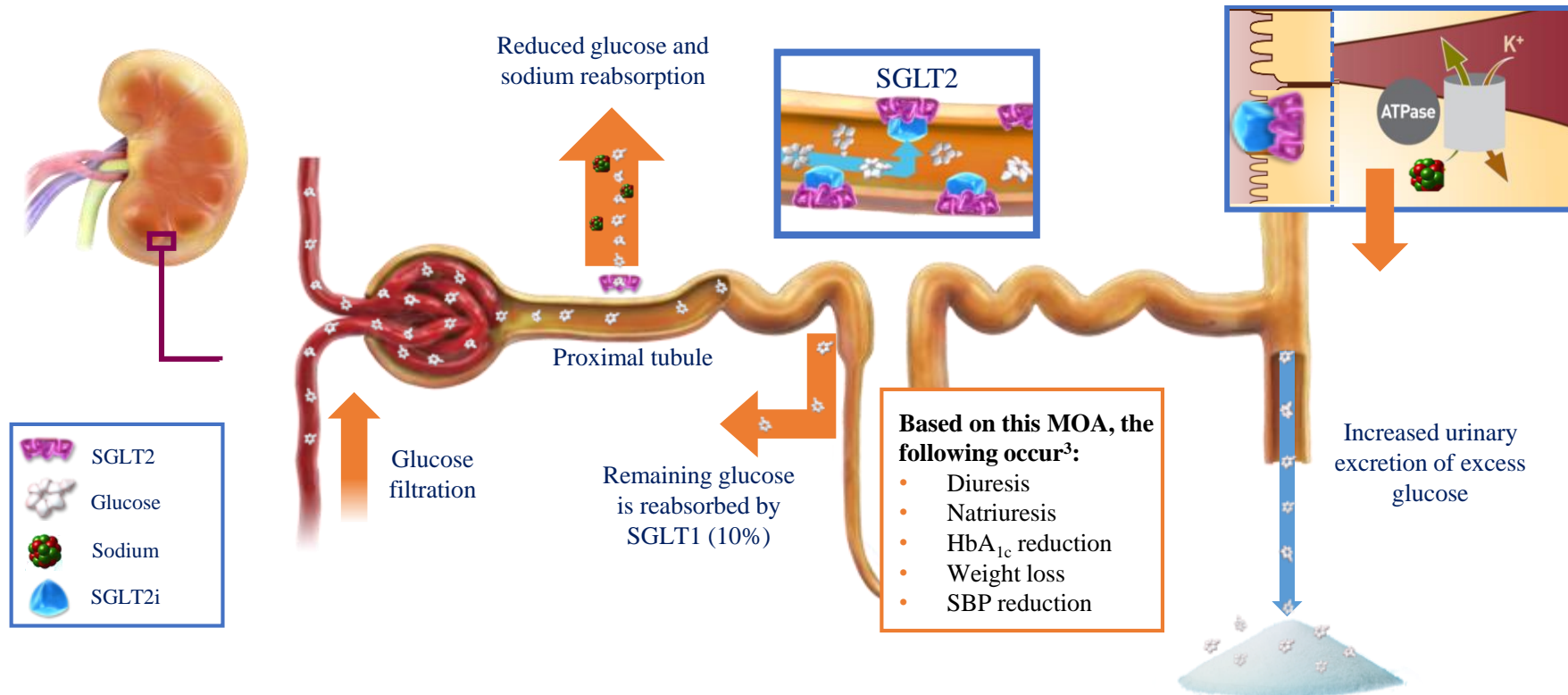


Steering Cmt: S. Solomon, co-Chair, J. McMurray, Co-Chair, I. Anand, F. Zannad, A. Maggioni, M. Packer, M. Zile, B. Pieske, J. Rouleau, M. Redfield, C. Lam, D. Van Veldhuisen, F. Martinez, J. Ge, H. Krum, M. Pfeffer

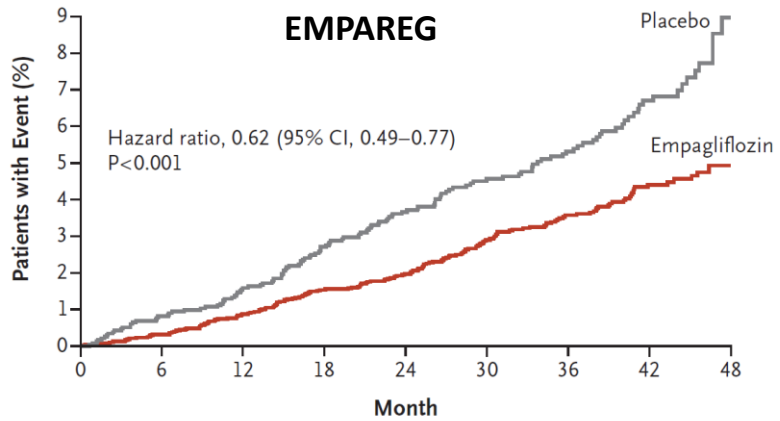
Solomon et al. JACC-HF 2017



SGLT2 Inhibitors Block SGLT2 and Reduce Glucose and Na⁺ Reabsorption

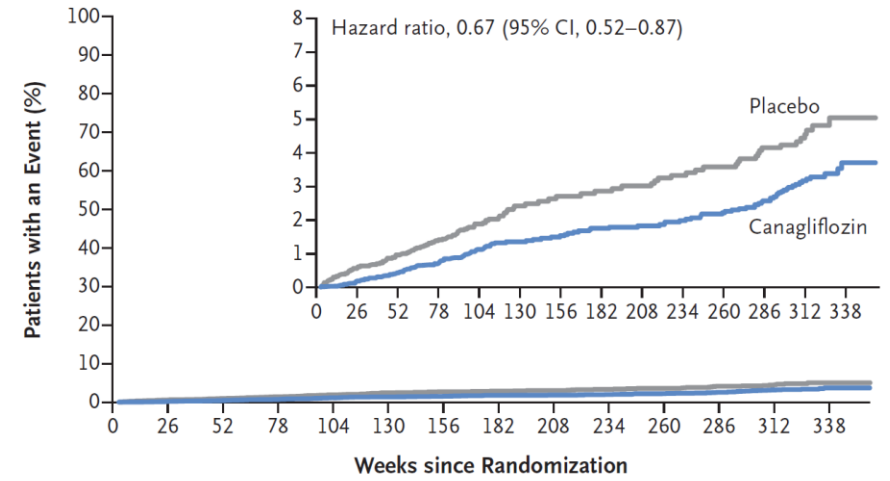


Outcomes in SGLT-2 Trials



No. at Risk	0	6	12	18	24	30	36	42	48
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

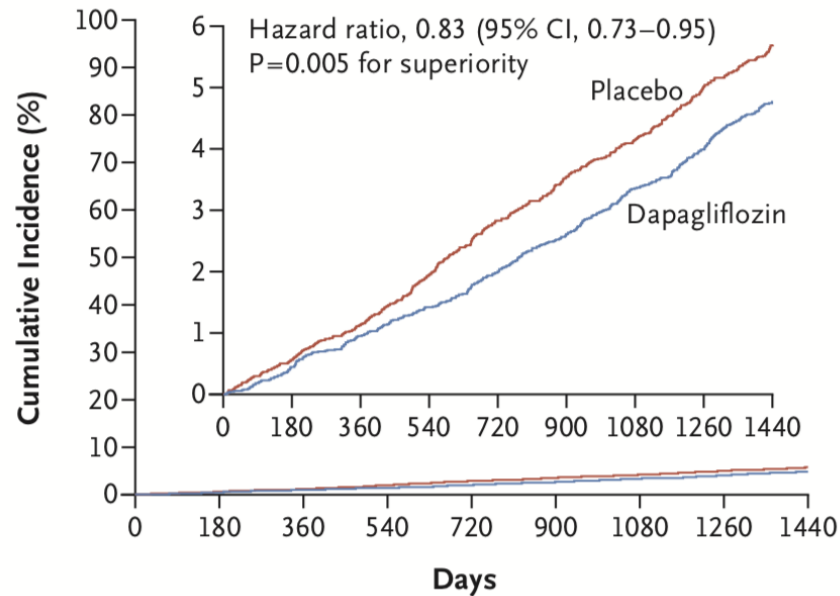
CANVAS HF Hospitalizations



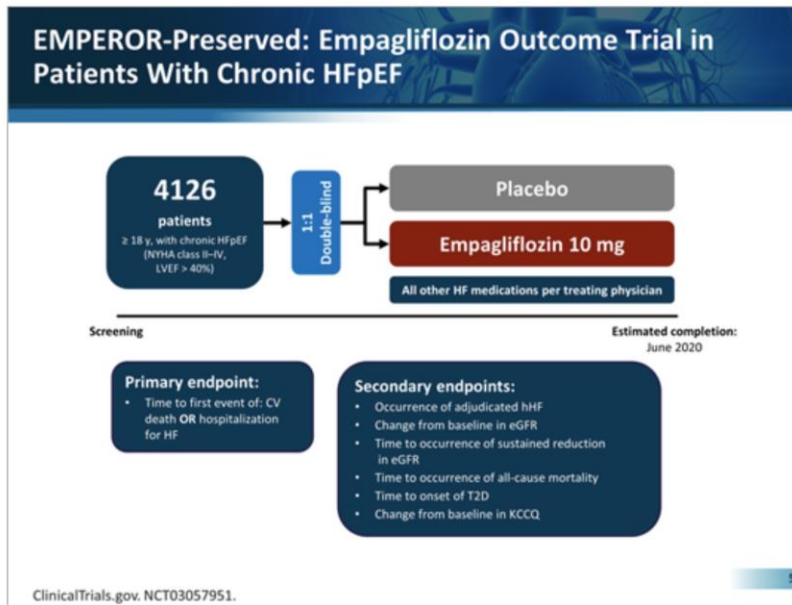
No. at Risk	0	26	52	78	104	130	156	182	208	234	260	286	312	338
Placebo	4347	4267	4198	4123	3011	1667	1274	1256	1236	1210	1180	1158	829	233
Canagliflozin	5795	5732	5653	5564	4437	3059	2643	2610	2572	2540	2498	2451	1782	490

A Cardiovascular Death or Hospitalization for Heart Failure

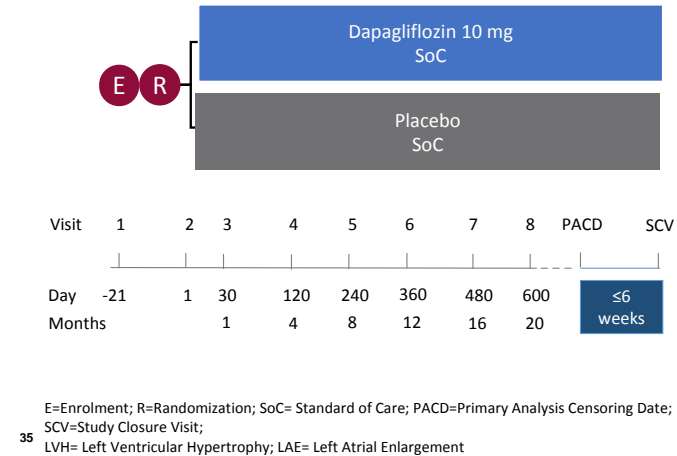
DECLARE



Two HFpEF Outcomes Trials with SGLT-2 Inhibitors



DELIVER Study Design Overview



Primary endpoint
Time to first adjudicated event of either:

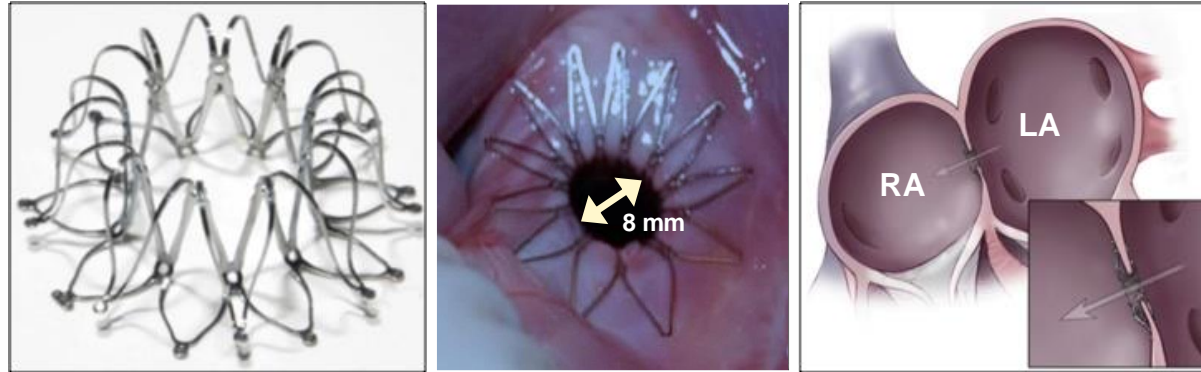
- CV death
- Hospitalization for HF
- urgent HF visit

4700 randomized patients

- ✓ Heart failure (NYHA class II-IV)
- ✓ Typical symptoms/signs for HF for ≥6 weeks
- ✓ Requiring treatment with diuretic(s) for HF
- ✓ LVEF >40% AND evidence of structural heart disease (LVH or LAE)
- ✓ Elevated NT-pro BNP
- ✓ Ambulatory OR Hospitalized (off intravenous heart failure therapy)
- ✓ No iv diuretics within 24 hours prior to randomization

ClinicalTrials.gov NCT03619213

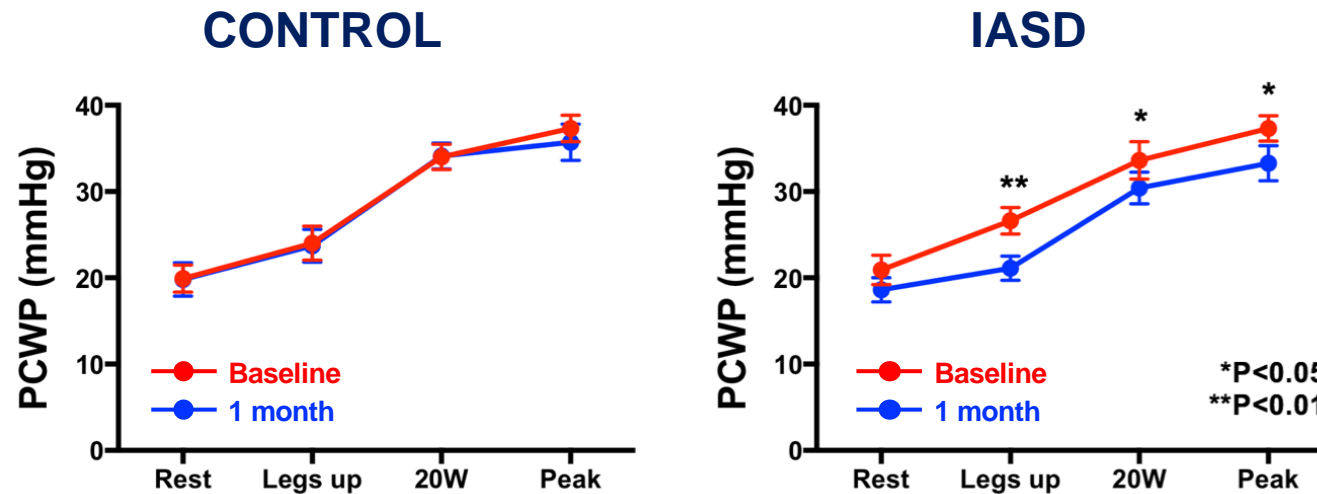
InterAtrial Shunt Device



IASD proposed mode of action: dynamic decompression of overloaded LA chamber by shunting blood from LA → RA

Feldman T...Shah SJ. *Circ Heart Fail* 2016

Change in PCWP: Baseline to 1 month



Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell



Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials