ACC Latin America Conference 2017

MEXICO CITY

JUNE 22 – 24, 2017

GLOBAL EXPERTS, LOCAL LEARNING

ACC Latin America Conference 2017

HFpEF, Mito or Realidad?

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Systolic HF versus HF with Preserved LVEF
ADHERE Registry

	EF <40%	EF >40%
Number (%)	42,113 (56%)	32,750 (44%)
Age	69.9	74.2 *
Female	39%	62% *
Diabetes	42%	46% *
CAD	61%	47% *
Atrial fibrillation	17%	21% *
Mean LOS (days)	6.2	6.0
In-hospital mortality	3.9%	2.8% *

* $p<0.0001$

from Fonarow et al. *Rev Cardiovasc Med* 2003;4 (suppl 7):21

Heart Failure with Preserved Ejection Fraction (HFPEF)

- HFPEF is defined by a normal or near-normal LVEF (>0.45 or 0.50). These cut points do not exclude systolic dysfunction nor do they necessarily indicate diastolic dysfunction.
- HFPEF is not a specific diagnosis or syndrome. It is a constellation of findings caused by diverse etiologies for which specific cardiac (valve abnormalities, dysrhythmias, or non-cardiac etiologies (anemia, renal dysfunction, shunts) are excluded.
- HFPEF is often equated with diastolic heart failure.

Are we dealing with one syndrome, or several syndromes with some common features?

Prevalence diastolic dysfunction
HF-PEF (DHF) EF ≥ 50% ~ 100 %

Kitzman
JAMA 288:2144-2150, 2002

Zile
NEJM 350:1953-1959, 2004

Kass
JACC 49:198-207, 2007

Redfield
Circ 115:1982-90, 2007

Westerman
Circ 117:2051-2060, 2008

Paulus
Circ 117:43-51, 2008

Relaxation

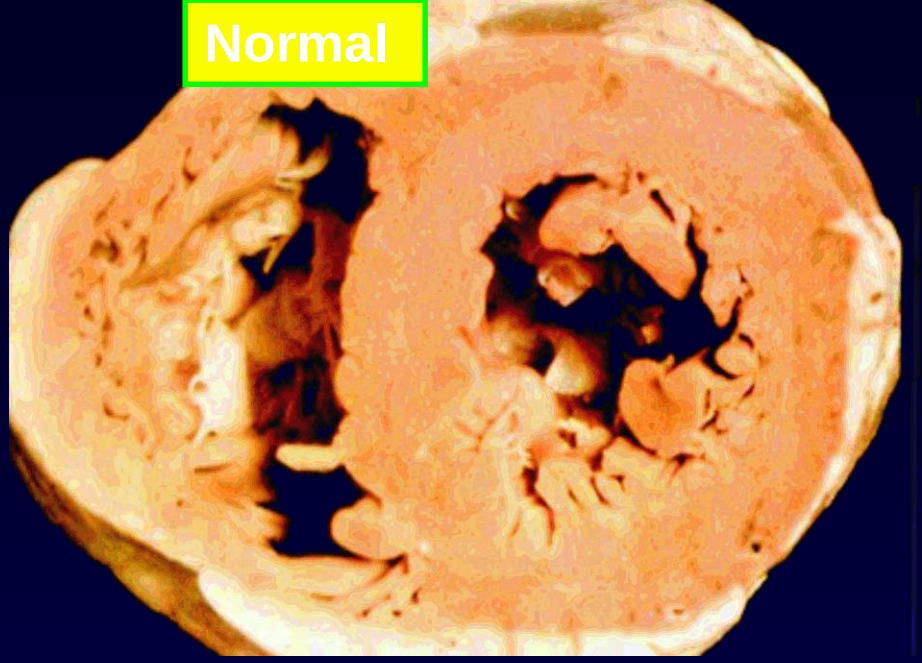
Pressure Decline	Slow
Diastolic Suction/recoil	↓↓
Filling Dynamics	↓↓

Distensibility

LV Chamber	↓↓
Myocardial	↓↓

Diastolic Pressures ↑↑

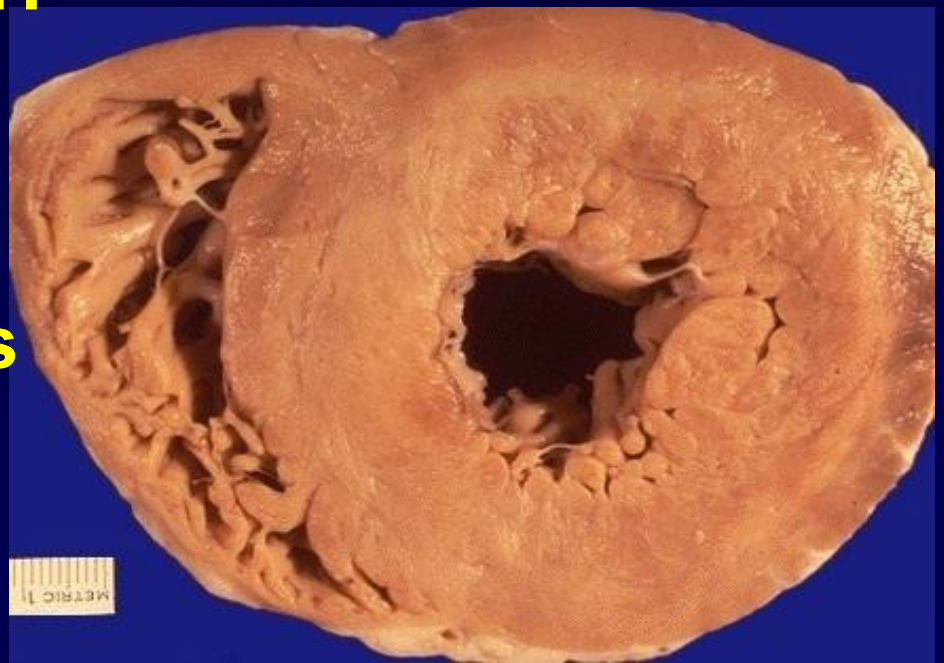
Normal



Circulation 2006
113: 296-304

HF NEF - DHF

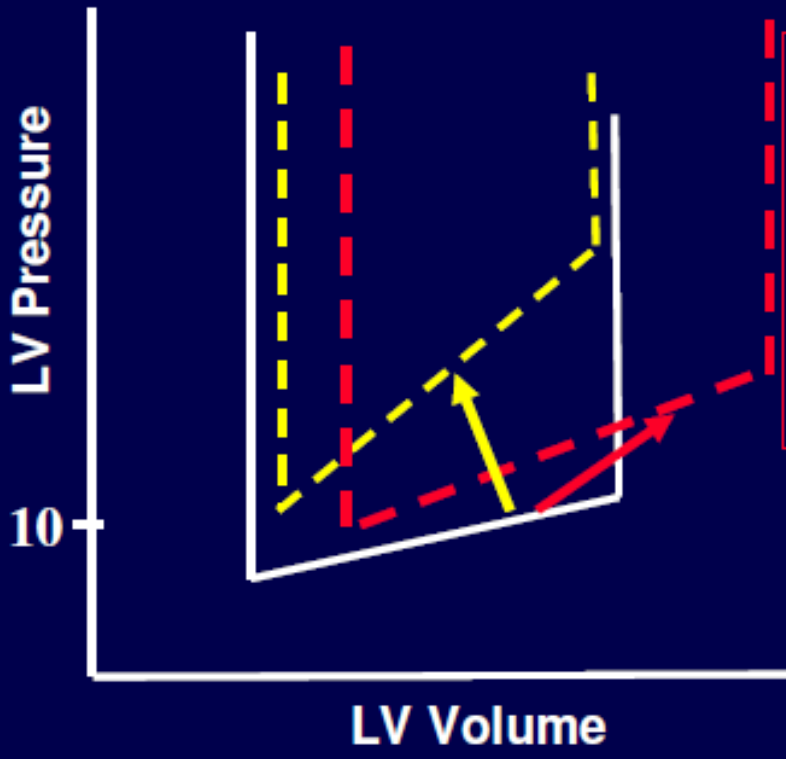
Concentric LVH
↑ LV Mass
↑RWT
↔ Volume
↓Volume/Mass



LV Dysfunction: Mechanisms

Diastolic dysfunction

- Hypertension
- Aging
- LVH
- Ischemia
- Concentric remodeling

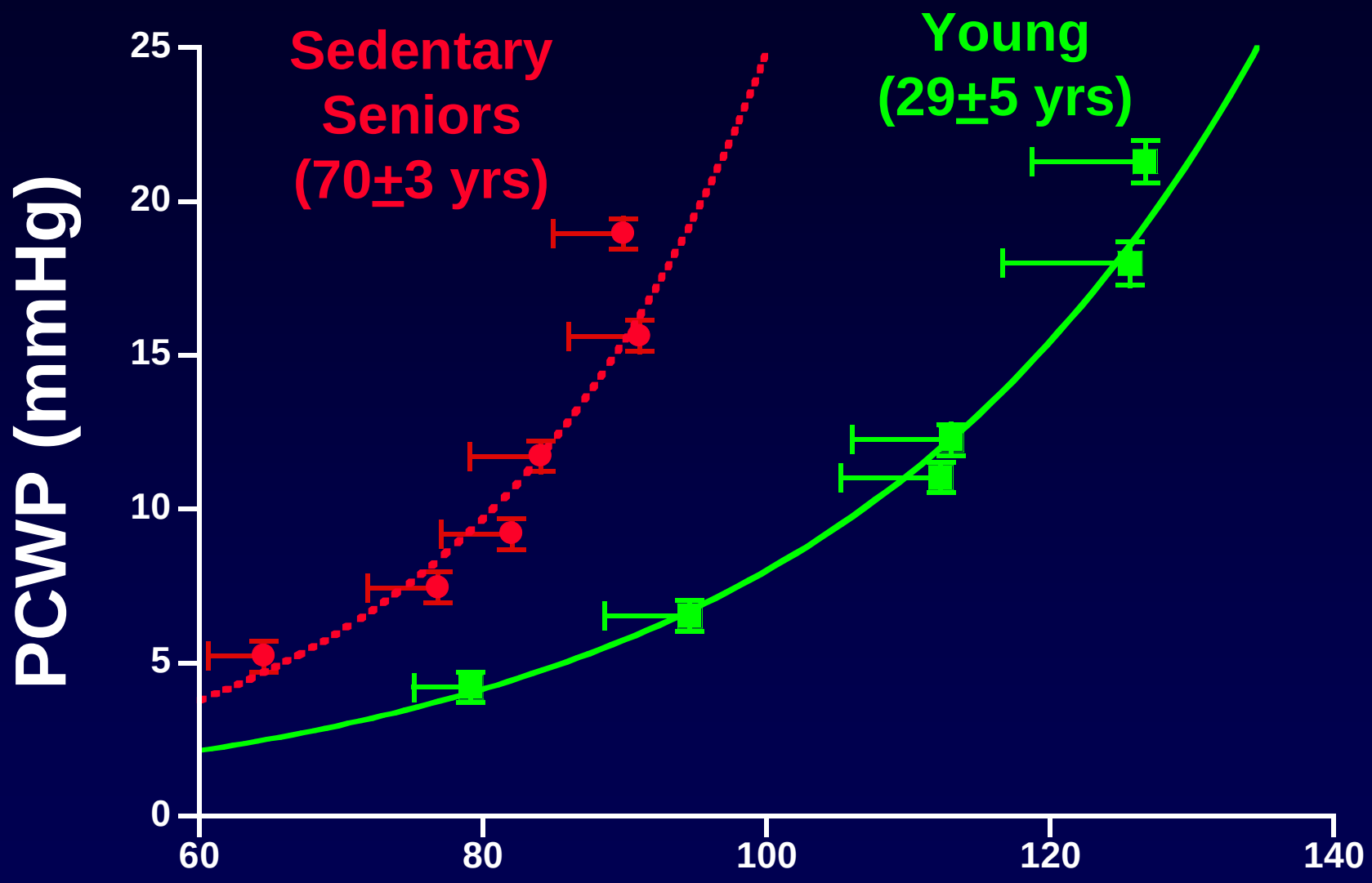


Systolic dysfunction

- MI, CM, volume overload
- Hypertension
- Eccentric remodeling

Mediators: angiotensin II, aldosterone, catecholamines

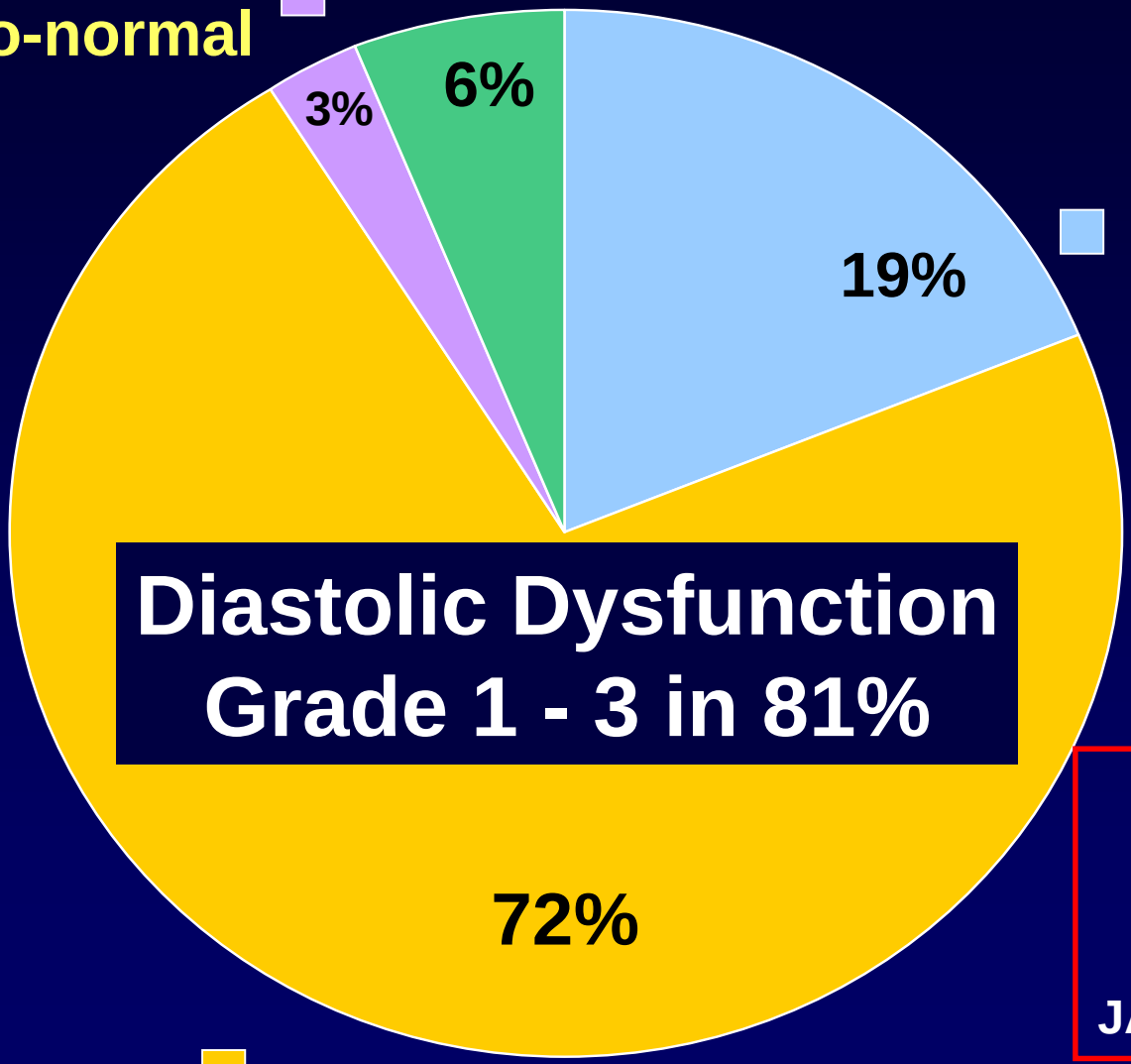
Example # 2 Pathophysiology: ↑ Diastolic Stiffness
Disease expression: ↓ exercise tolerance



Levine BD, Circulation
110:1799-1805, 2004

I-PRESERVE

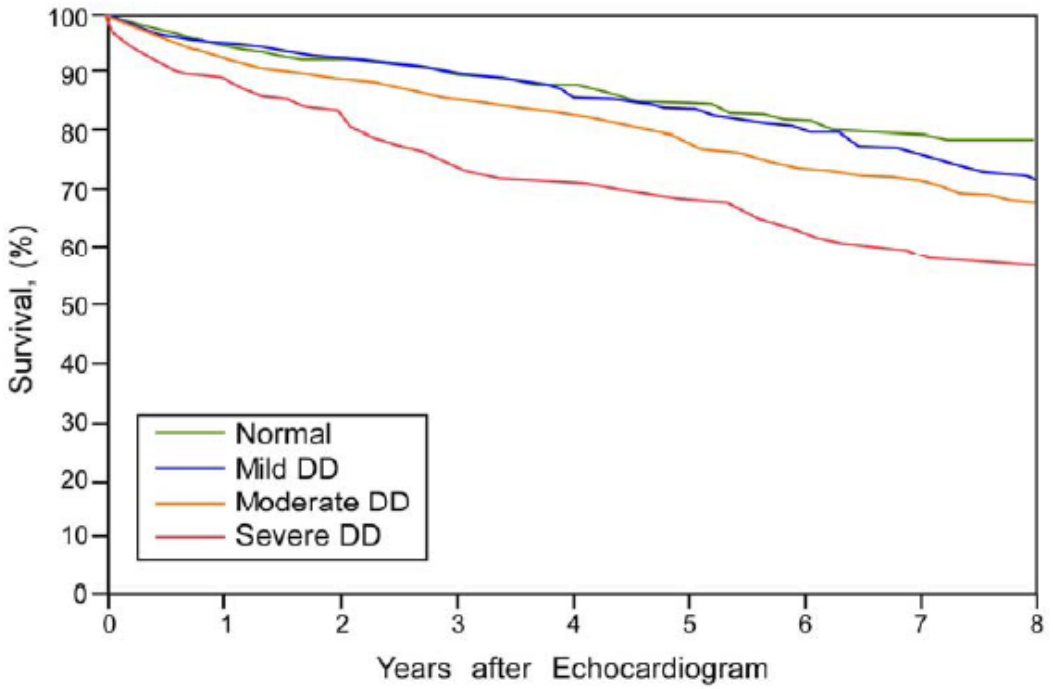
Diastolic Function



CHARM-Preserved 67%

JACC49:687-94,2007

Figure 2. Survival by diastolic stage for the matched patients (n=1,249)



Numbers at Risk:					
Normal	365	330	309	204	105
Mild	381	345	310	209	124
Moderate	375	331	294	189	112
Severe	127	104	88	56	31

Mortality Associated with Diastolic Dysfunction

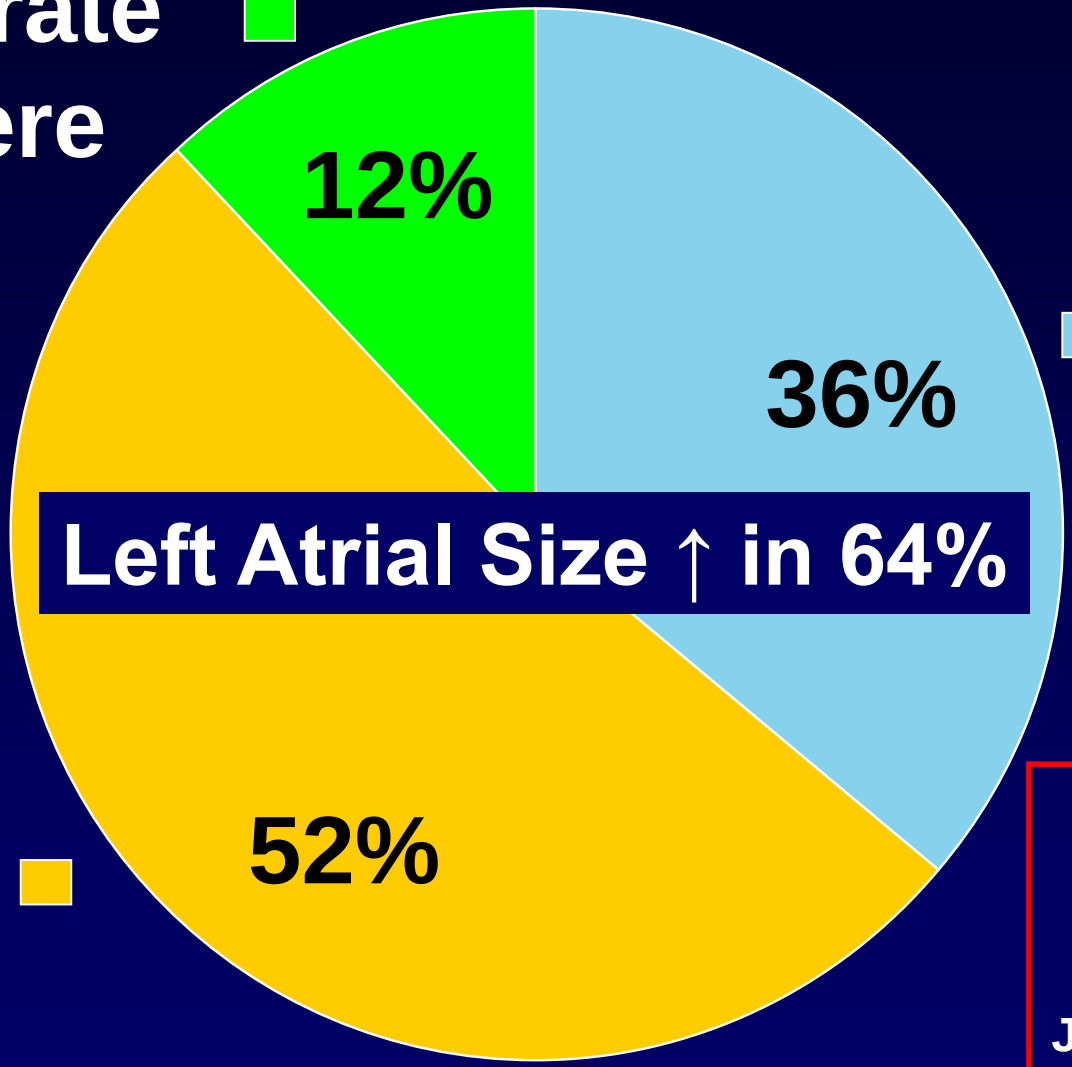
Risk Factor*	Hazard ratio (95%CI)	P-value
Mild diastolic dysfunction	1.11 (0.85, 1.47)	0.45
Moderate diastolic dysfunction	1.58 (1.20, 2.08)	0.0007
Severe diastolic dysfunction	1.84 (1.29, 2.62)	0.0009

* compared to normal diastolic function group

Halley et al. Arch Int Med June 201

I-PRESERVE

Left Atrial Size



CHARM-Preserved
71%
JACC49:687-94,2007

Left Atrial Size ≈ Hgb A1C for Diastolic pressure

Why Do HFPEF Patients Decompensate?

- Excess salt
- Inadequate diuretic Rx
- Worsening hypertension
- Medications: NSAIDs, thiazolidinediones, ?CCBs, ?alpha-blockers
- Atrial fibrillation
- Worsening renal function
- Myocardial ischemia
- Anemia
- Iatrogenic volume overload

CHARM Program: Outcomes overview

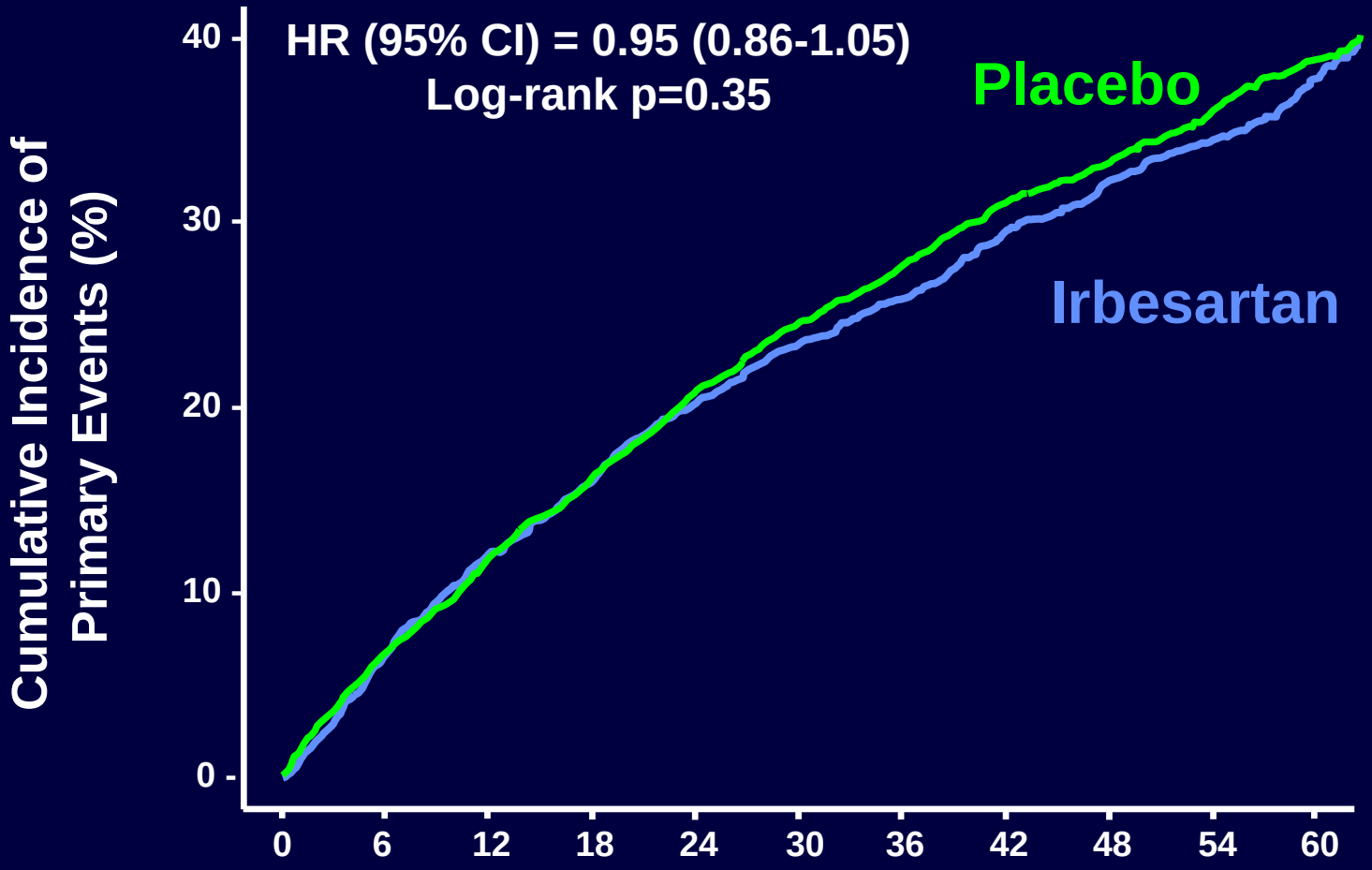
Parameter	Candesartan vs placebo			
	CHARM Added	CHARM Alternative	CHARM Preserved	CHARM Overall
Follow-up (months)	41	34	37	38
CV deaths (%)	23.7 vs 27.3*	21.6 vs 24.8	11.2 vs 11.3	18.2 vs 20.3*
HF hospitalization (%)	24.2 vs 28*	20.4 vs 28.2*	15.9* vs 18.3	19.9 vs 24.2*
Combined endpoint (%)	37.9 vs 42.3*	33 vs 40*	22 vs 24.3	30.2 vs 34.5*
NNT/year to prevent 1 CV death/HF hospitalization	85	40	132	73

*statistically significant

Gleiter CH et al. *Cardiovasc Drug Rev.* 2004;22:263-84.

I-PRESERVE: Primary Endpoint

Death or protocol specified CV hospitalization



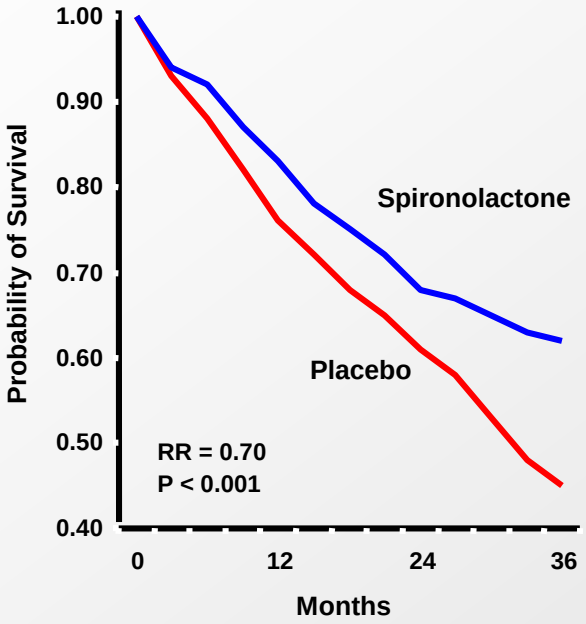
No. at Risk											
Irbesartan	2067	1929	1812	1730	1640	1569	1513	1291	1088	816	497
Placebo	2061	1921	1808	1715	1618	1539	1466	1246	1051	776	446

MRAs Beneficial in HFrEF and Post-MI LVD

TOPCAT
Funded by the NHLBI

RALES
(Severe HFrEF)

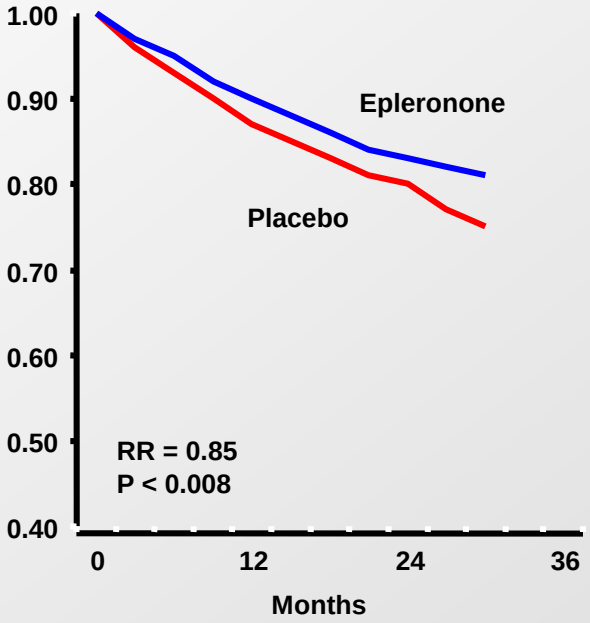
30% Risk Reduction



Pitt NEJM 1999

EPHESUS
(Post-MI)

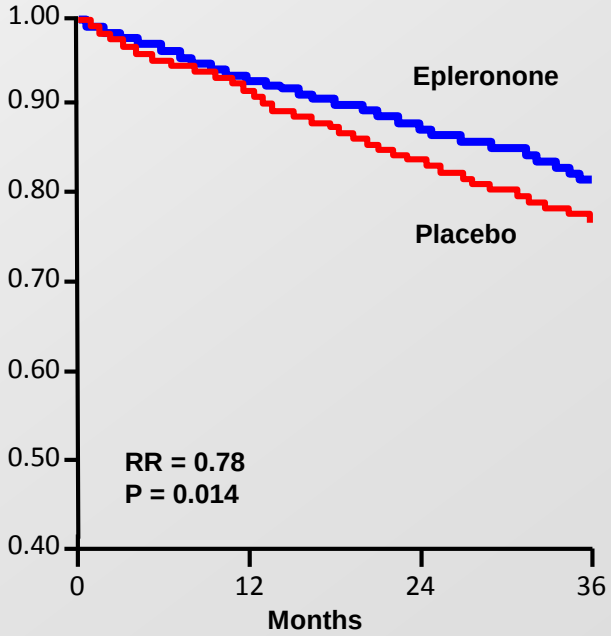
15% Risk Reduction



Pitt NEJM 2003

EMPHASIS
(Mild HFrEF)

22% Risk Reduction



Zannad NEJM 2011

Reviews of Mechanisms : Pitt Heart Fail Rev 2012; Kamalov,…,Weber JCV Pharm 2013

TOPCAT
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Baseline

*Variable**	Spironolactone N = 1722	Placebo N = 1723
NYHA Class		
II	63.3%	64.3%
III	33.0%	32.2%
LVEF %	56 (51, 61)	56 (51, 62)
Stratum		
Hosp. for HF	71.5%	71.5%
Natriuretic Peptide**	28.5%	28.5%
Age	69 (61, 76)	69 (61, 76)
Female	52%	51%
Hypertension	91%	92%
Coronary Artery Disease	57%	60%
Myocardial Infarction	26%	26%
Stroke	7%	8%
Atrial Fibrillation	35%	35%
Diabetes Mellitus	33%	32%
Smoking (current)	10%	11%

*Reported as % or median (Q1, Q3)

**(BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL)

S. Shah Circ HF 2012

Funded by the NHLBI

Baseline (2)

*Variable**	Spironolactone N = 1722	Placebo N = 1723
Systolic Blood Pressure	130 (120, 139)	130 (120, 140)
Diastolic Blood Pressure	80 (70, 80)	80 (70, 80)
Heart Rate	68 (62, 76)	68 (62, 76)
BMI (kg/m^2)	31 (27, 36)	31 (27, 36)
eGFR ($ml/min/1.73m^2$) < 60 ($ml/min/1.73m^2$)	65 (54, 79) 39%	66 (54, 79) 38%
Serum Potassium (mEq/L)	4.3 (4.0, 4.6)	4.3 (4.0, 4.6)
Hemoglobin (g/dl)	13.2 (12.1, 14.4)	13.3 (12.2, 14.5)
Medications		
ACE-I or ARB	84%	84%
Beta-blocker	78%	77%
Diuretic	81%	82%
Statin	53%	52%
Anticoagulant	23%	22%

*Reported as % or median (Q1, Q3)

A. Shah Circ HF 2013 (echo)
S. Shah Circ HF 2012 (baseline)

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Patient Participation

Randomized: N=3445; **Mean follow-up:** 3.3 years

US (1,151); **Russia** (1,066); **Rep. of Georgia** (612);
Canada (326); **Brazil** (167); **Argentina** (123)

Mean Dose at 8 months: spironolactone 25 mg; placebo 28 mg

Spironolactone N=1,722

% discontinued study medication:
1 year: 17.0%
2 year: 25.1%
End: 34.3%

Vital status unknown: 67 (3.9%)

Placebo N=1,723

% discontinued study medication:
1 year: 13.5%
2 year: 20.1%
End: 31.4%

Vital status unknown: 65 (3.8%)

1° Outcome
(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)

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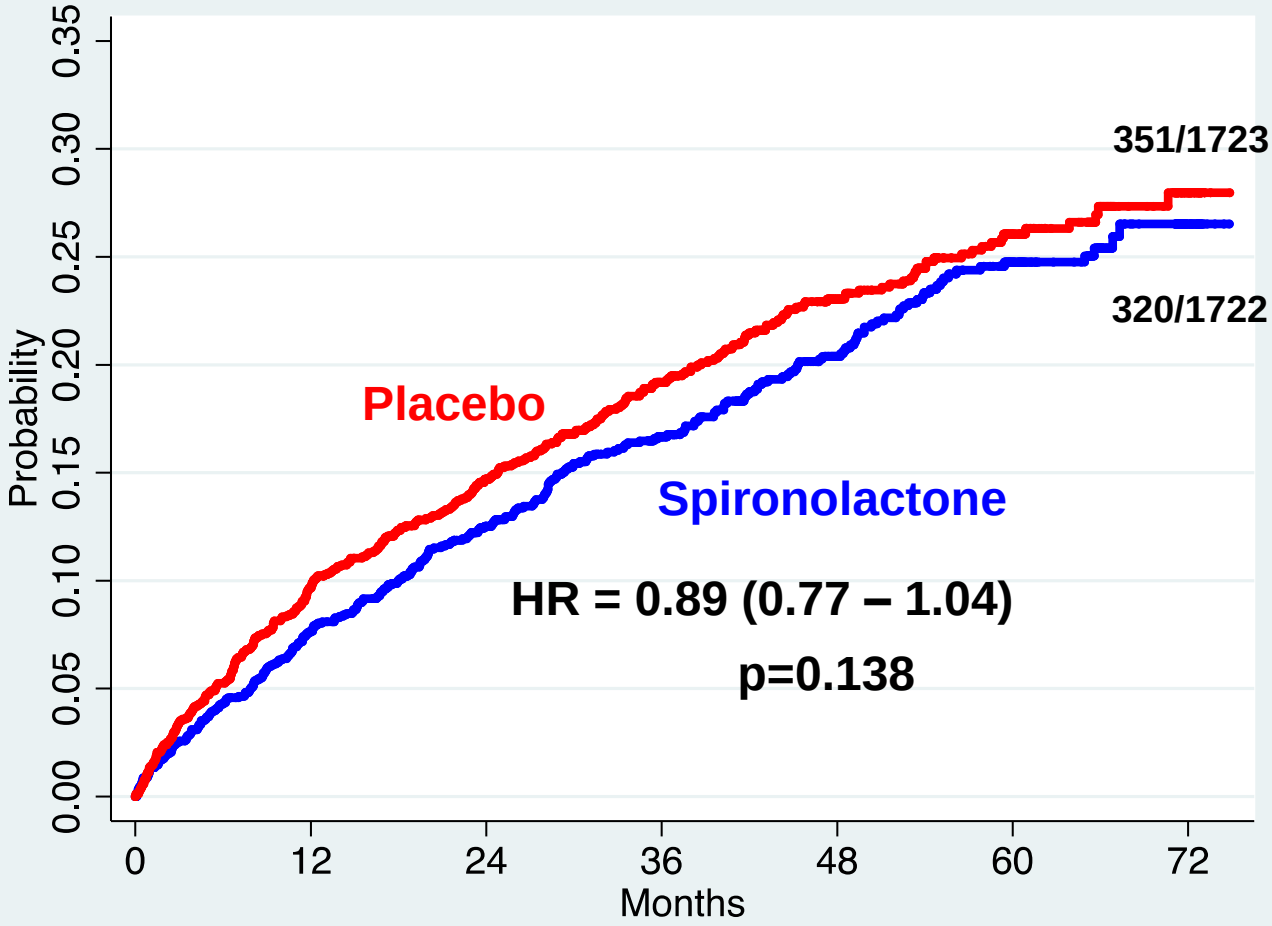


Number at risk

Spiro	1722	1502	1168	870	614	330	53
Placebo	1723	1462	1145	834	581	331	53

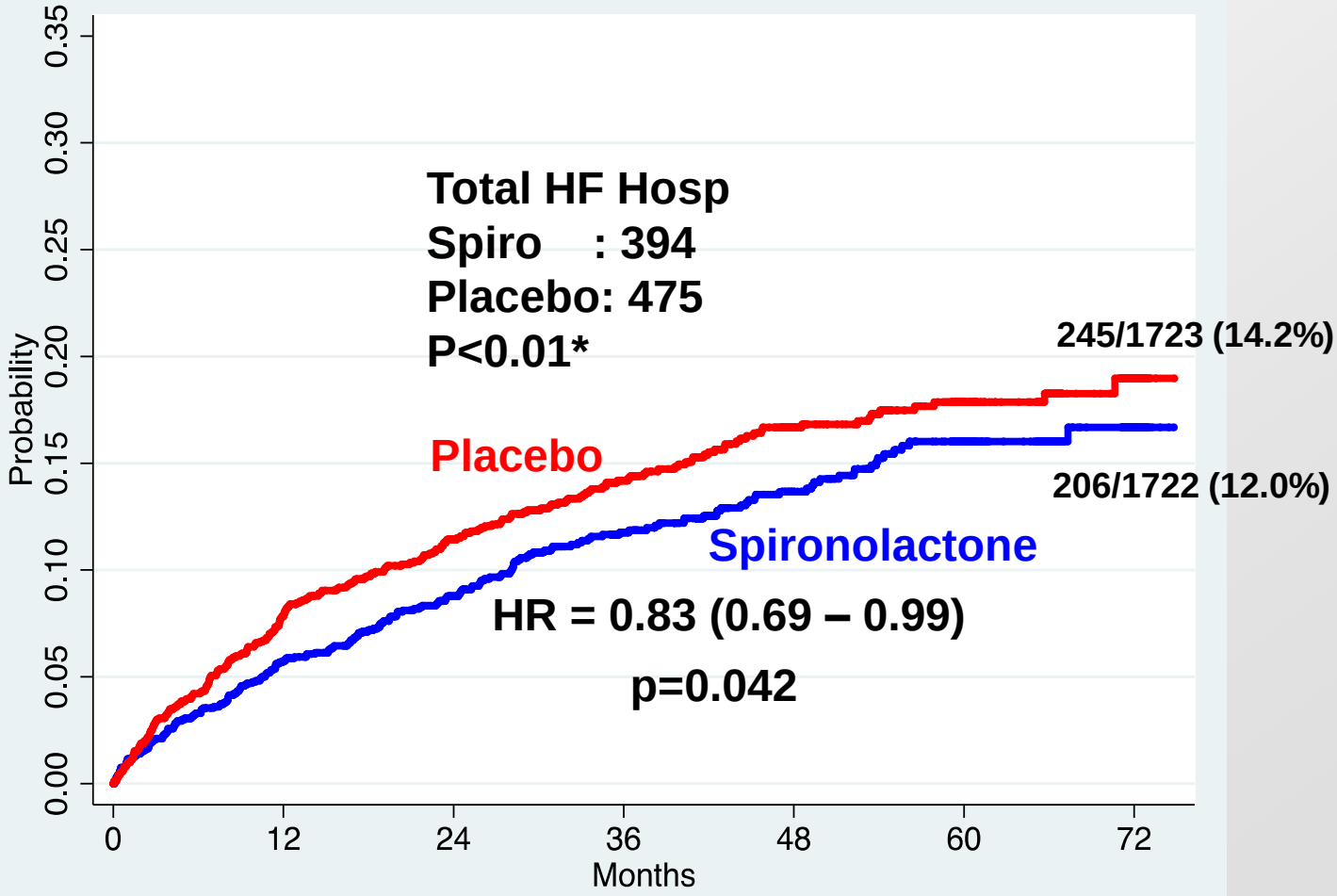
TOPCAT
Funded by the NHLBI

1° and Components

Outcome	# and % of Subjects with Event, and Event Rate		Hazard Ratio (95% CI) p-value
	Spironolactone (N = 1722)	Placebo (N = 1723)	
Primary Outcome	**320 (18.6%)** 5.9/100pt-yr	**351 (20.4%)** 6.6/100pt-yr	**0.89** (0.77-1.04) P=0.138
Primary Components			
CV Mortality	**160 (9.3%)** 2.8/100pt-yr	**176 (10.2%)** 3.1/100pt-yr	**0.90** (0.73-1.12) P=0.354
Aborted Cardiac Arrest	**3 (<1%)** 0.05/100pt-yr	**5 (<1%)** 0.09/100pt-yr	**0.60** (0.14-2.50) P=0.482
Hospitalization for Heart Failure	**206 (12.0%)** 3.8/100pt-yr	**245 (14.2%)** 4.6/100pt-yr	**0.83** (0.69-0.99) P=0.042

Funded by the NHLBI

Heart Failure Hospitalizations



*poisson regression

TOPCAT
Funded by the NHLBI

Serum Potassium*

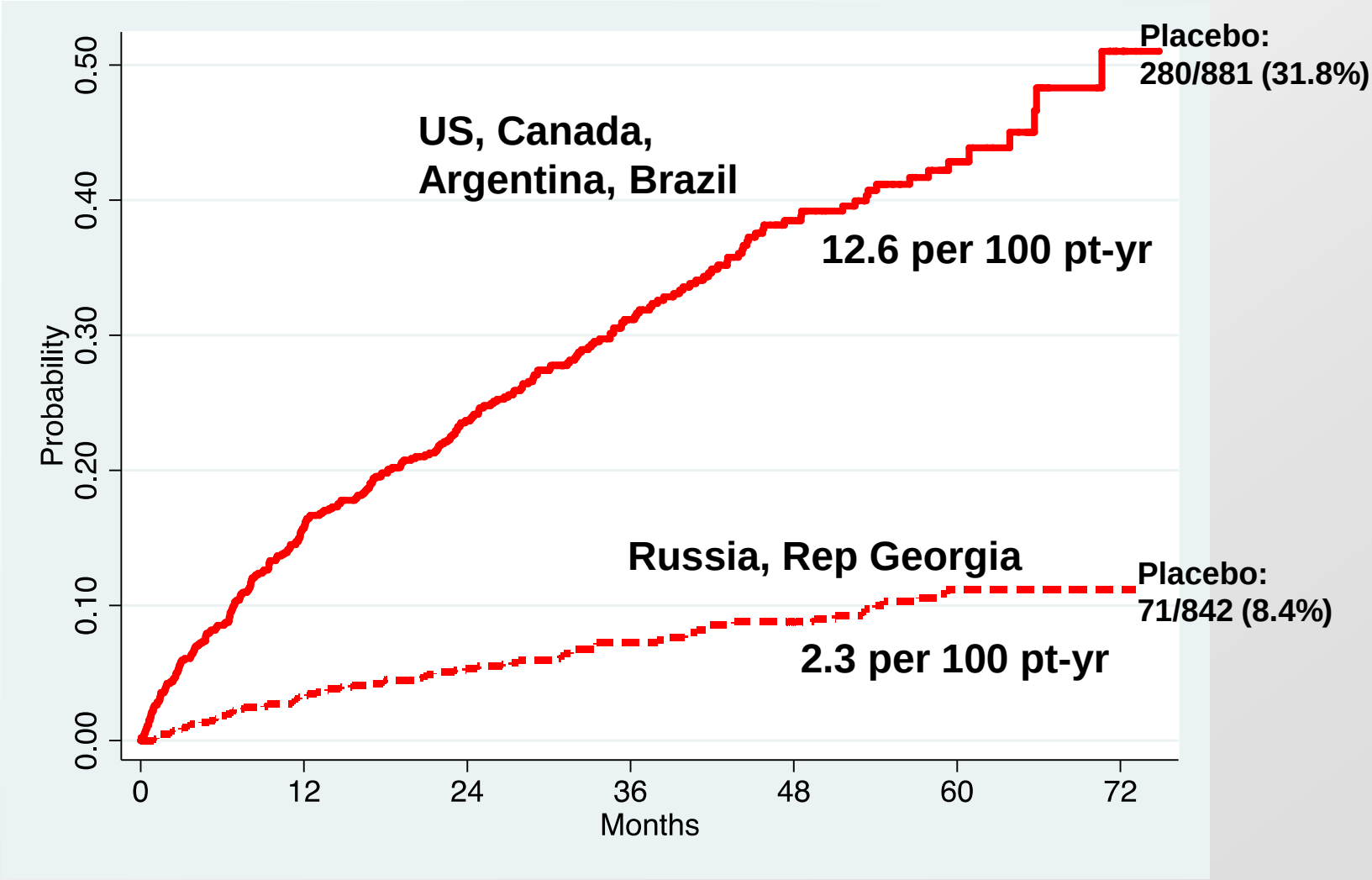
Potassium	Spiro	Placebo	P (chi-sq)
Hyperkalemia (≥ 5.5 mmol/L)	**322** (18.7%)	**157** (9.1%)	**<0.001**
Hypokalemia (<3.5 mmol/L)	**279** (16.2%)	**394** (22.9%)	**<0.001**

No deaths related to hyperkalemia were reported.

***Monitoring at each dose change and visit (algorithm in Desai Am Heart J 2011)**

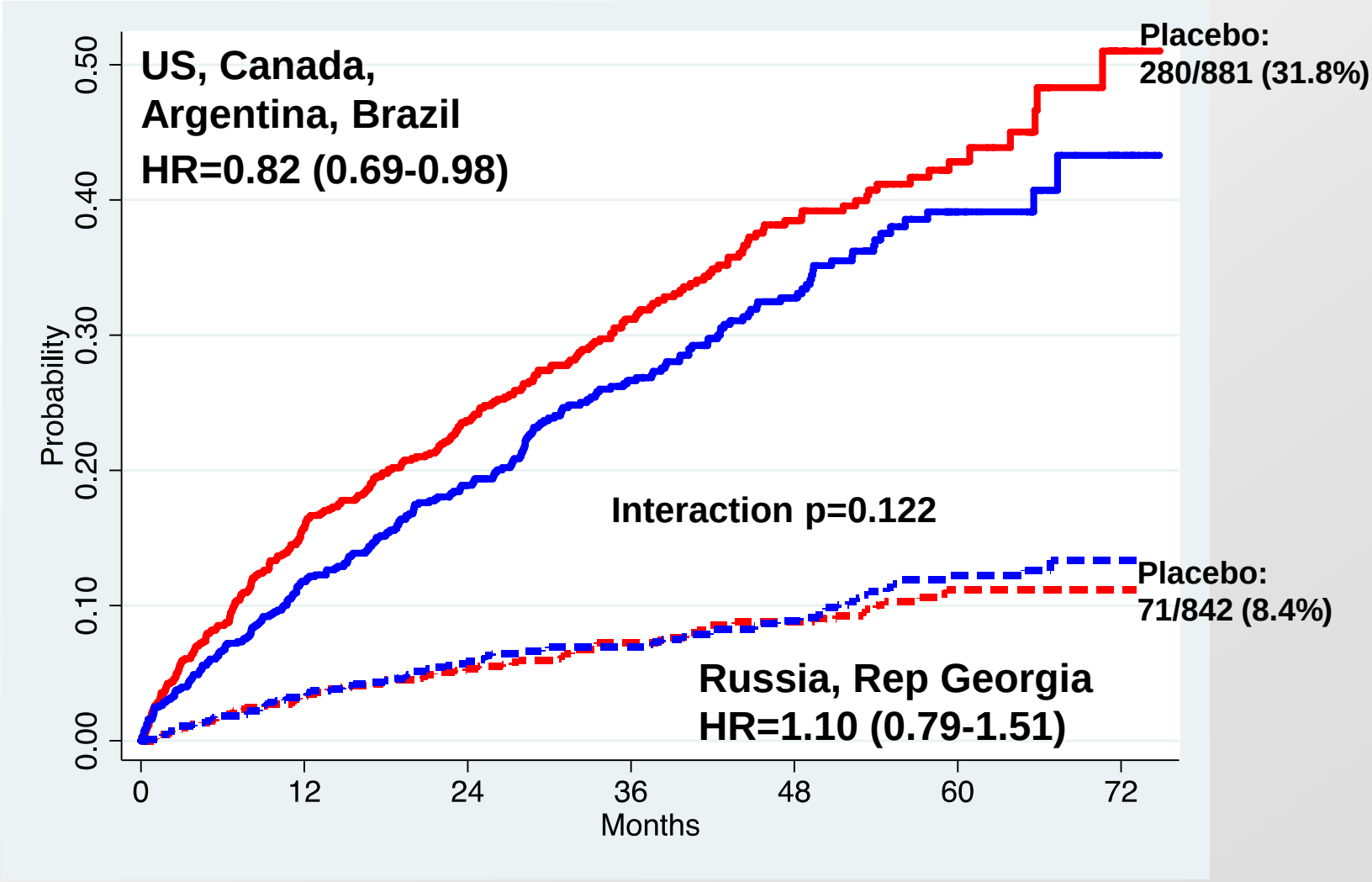
Placebo Rates:
Primary Outcome, by region

TOPCAT
Funded by the NHLBI



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

TOPCAT
Funded by the NHLBI



Echocardiographic parameters in select HFpEF trials.

Anderson and Vasan. Heart Fail Clin. 2014 July ; 10(3)

Table 2	TOPCAT(62)	PARAMOUNT(63)	RELAX(20)	I-PRESERVE(17,64)	CHARMES(65,66)	Aldo-DHF(6)	PEP-CHF(18)
N	935	292	216	745	312	422	850
Definition of diastolic heart failure	LVEF ≥45%, HF hospitalization, or BNP ≥100 or NT-proBNP ≥360 pg/mL	LVEF ≥45%, NT-pro-BNP >400 pg/mL	LVEF ≥50%, NT-pro-BNP >400, pVO2 <60% of predicted	LVEF ≥45%, recent HF hospitalization or other objective signs of HF	LVEF >40%	LVEF ≥50%, echocardiographic diastolic dysfunction or AF pV02 ≤25	LVEF >40%, HF by clinical criteria
Age (years)	70±10	71±9	69 (62–77)	72±7	66±11	67±8	75 (72–79)
Women	49%	56%	48%	62%	34%	52%	56%
LV structure							
EDD (cm)	4.80±0.58	4.64±0.48	4.6 (4.3–5.1)	4.8±0.6	5.4±0.7	4.65±0.62	4.6 (4.2–5.1)
EDVi (mL/m2)	49.9±15.5	61.4±15.4	NA	49±14	NA	NA	NA
MWT (cm)	1.18±0.20	0.91±0.16	NA	0.93±0.15	NA	NA	1.3 (1.2–1.5)
LVMI (g/m2)	111±31	79.1±22.2	78 (62–94)	NA	117±42	109±28	NA
RWT	0.49±0.10	0.38±0.08	NA	0.40±0.08	NA	NA	NA
LV geometry							
Normal	14%	72%	NA	46%	NA	NA	NA
Concentric remodeling	34%	14%	NA	25%	NA	NA	NA
Concentric hypertrophy	43%	7%	NA	29%	NA	NA	NA
Eccentric hypertrophy	9%	7%	NA	0%	NA	NA	NA
LV systolic function							
EF (%)	59.6±8.0	57.7±7.9	60 (56–65)	64±9	50 (18–65)	67±8	65 (56–66)
LV diastolic function							
LAVi (mL/m2)	29.8±12.5	35.9±13.5	44 (36–59)	NA	41.3±14.7	28.0±8.4	NA
LA diameter (cm)	4.3±0.6	3.7±0.5	NA	NA	NA	NA	4.5 (4.1–4.8)
E/A ratio	1.2±0.7	1.1±0.62	1.5 (1.0–2.1)	1.05±0.74	1.1±0.7	0.91±0.33	0.7 (0.6–0.9)
TDI E− septal (cm/s)	6.1±2.2	5.8±2.0	6 (5–8)	7.2±2.9	NA	5.9±1.3	NA
TDI E− lateral (cm/s)	8.2±3.2	7.5±2.8	NA	9.1±3.4	NA	NA	NA
E/E− ratio (septal)	15.6±6.8	15.9±7.3	16 (11–24)	NA	NA	12.8±4.0	NA

Echocardiographic parameters in select HFpEF trials. Cont'

Table 2	TOPCAT(62)	PARAMOUNT(63)	RELAX(20)	I-PRESERVE(17,64)	CHARMES(65,66)	Aldo-DHF(6)	PEP-CHF(18)
E/E− ratio (lateral)	11.8±5.9	12.7±7.4	NA	10.0±4.5	NA	NA	NA
Diastolic dysfunction, any	66%	92%	NA	69%	67%	100%	NA
None	34%	8%	31%	33%	NA	0%	NA
Grade 1	22%	31%	NA	29%	22%	77%	NA
Grade 2	34%	43%	NA	36%	37%	21%	NA
Grade 3	10%	18%	NA	4%	7%	2%	NA
Pulmonary pressure	2.8±0.5 (TR [m/s])	2.5±0.4 (TR [m/s])	41 (33–53) (RVSP [mmHg])	37±13 (RVSP [mmHg])	NA	NA	NA
Mortality rate in placebo-group	176/1723 (10.2%)*	NA	0/103 (0%)	436/2061 (21%)	170/1509 (11.3%)*	0/209 (0%)	53/426 (12.4%)
Length of follow-up	Mean 3.3 years	12 weeks	24 weeks	Mean 49.5 months	Mean 36.6 months	12 months	Mean 2.1 years
Annual mortal ity rate¶	3.1%	NA	0%	5.1%	12%	0%	5.8%

Anderson and Vasan. Heart Fail Clin. 2014 July ; 10(3)

Atrial fibrillation

- **Often coexists with HFpEF presentation**
- **May be the causation of decompensation**
- **Meta-analysis of > 54,000 patients,**
- **A significantly higher risk of death in AF patients with HFrEF compared to those with HFpEF.**
  - **There was a crude mortality rate of 24% *versus* 18% respectively, over 2 years.**
  - **no significant difference in incident stroke or heart failure hospitalization between the two groups.**

Kotecha D. et al. Int J of Cardiol 2016 Jan 15;203:660-6

Exercise Training in Older Patients With Heart Failure and Preserved Ejection Fraction

A Randomized, Controlled, Single-Blind Trial

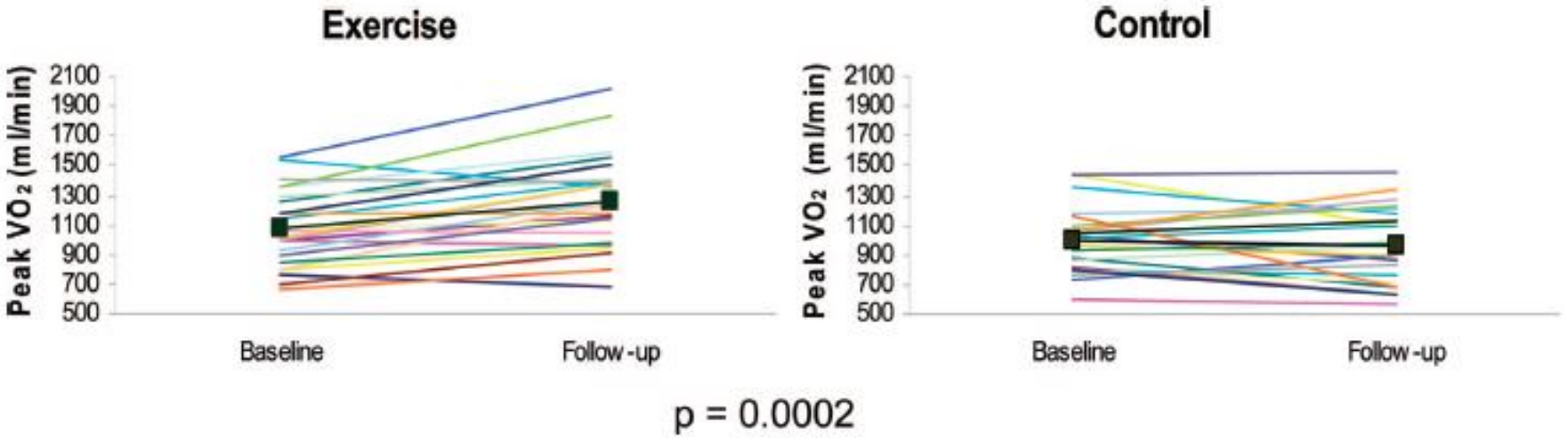


Figure. Individual and mean (■) responses of peak exercise $\dot{V}O_2$ following 16 weeks of supervised exercise training. Results are displayed in raw, nonindexed peak $\dot{V}O_2$, as this is uninfluenced by weight.

Kitzman et al. Circ Heart Fail. 2010;3:659-667.

Pharmacological Treatment for Stage C HF With Preserved EF

COR	LOE	Recommendations	Comment/ Rationale
I	B	Systolic and diastolic blood pressure should be controlled in patients with HF*p*EF in accordance with published clinical practice guidelines to prevent morbidity	2013 recommendation remains current.
I	C	Diuretics should be used for relief of symptoms due to volume overload in patients with HF*p*EF.	2013 recommendation remains current.

Pharmacological Treatment for Stage C HF With Preserved EF

COR	LOE	Recommendations	Comment/ Rationale
IIa	C	Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic HF*p*EF despite GDMT.	2013 recommendation remains current.
IIa	C	Management of AF according to published clinical practice guidelines in patients with HF*p*EF is reasonable to improve symptomatic HF.	2013 recommendation remains current.
IIa	C	The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HF*p*EF.	2013 recommendation remains current.

Pharmacological Treatment for Stage C HF With Preserved EF

COR	LOE	Recommendations	Comment/ Rationale
IIb	**B-R**	In appropriately selected patients with HF*p*EF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations.	NEW: Current recommendation reflects new RCT data.
IIb	**B**	The use of ARBs might be considered to decrease hospitalizations for patients with HF*p*EF.	2013 recommendation remains current.

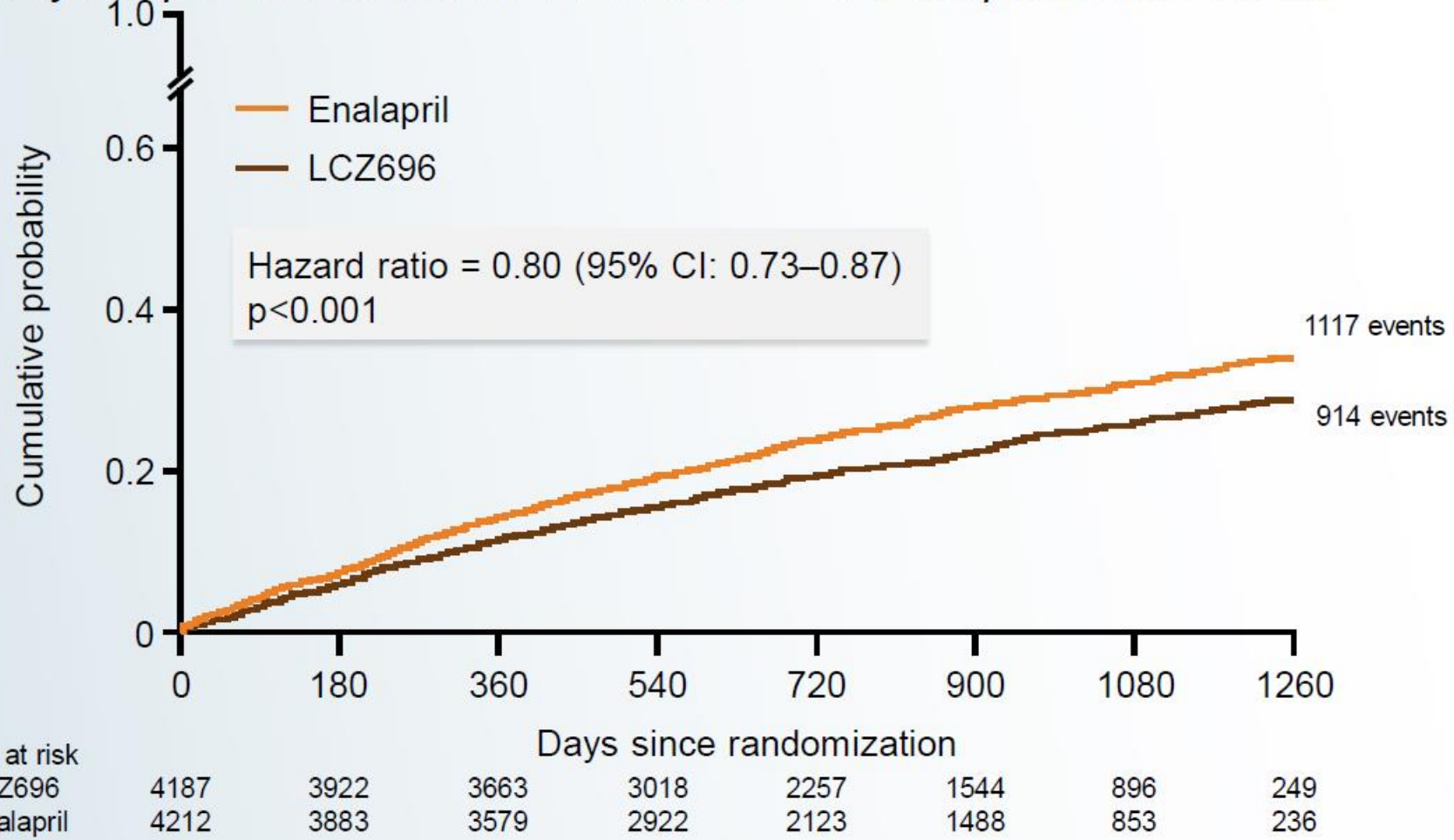
Pharmacological Treatment for Stage C HF With Preserved EF

COR	LOE	Recommendations	Comment/ Rationale
III: No Benefit	**B-R**	Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HF*p*EF is ineffective.	NEW: Current recommendation reflects new data from RCTs.
III: No Benefit	**C**	Routine use of nutritional supplements is not recommended for patients with HF*p*EF.	2013 recommendation remains current.

PARADIGM-HF

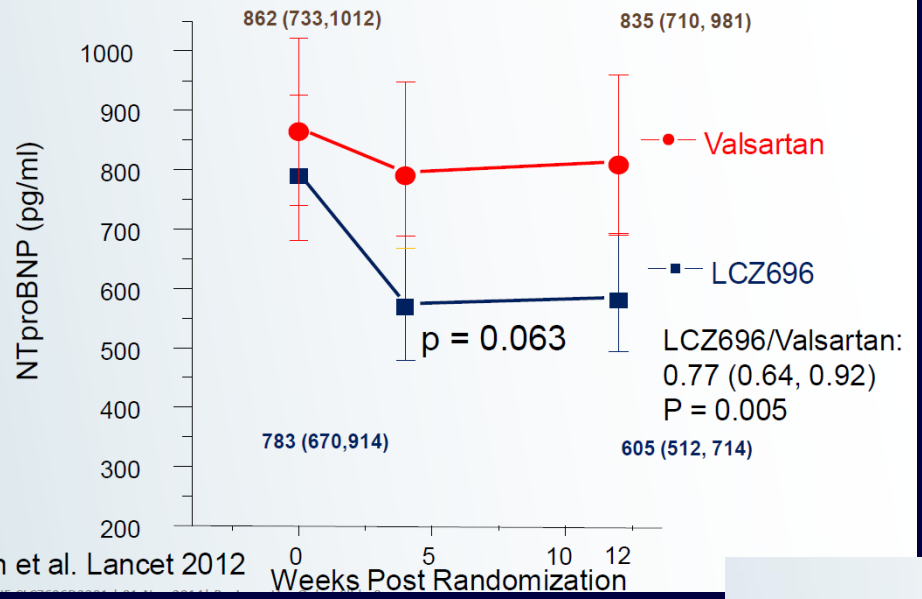
PARAGONHF

Primary endpoint: Death from CV causes or first hospitalization for HF



McMurray, et al. N Engl J Med 2014 Sep 11:371(11):993-1004

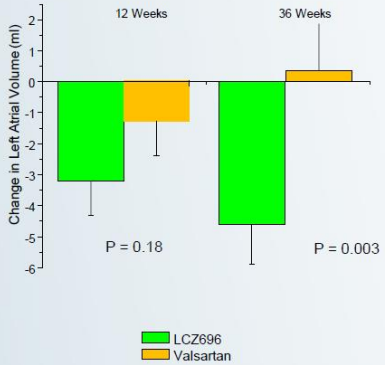
Primary Endpoint: NT-proBNP at 12 Weeks



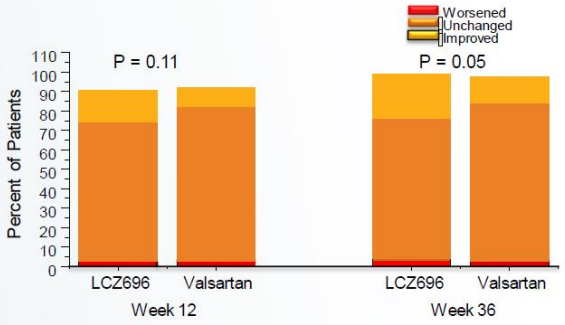
Solomon et al. Lancet 2012

PARAMOUNT: Improvement in LA Volume and NYHA Class at 36 weeks

Left Atrial Volume



NYHA Class

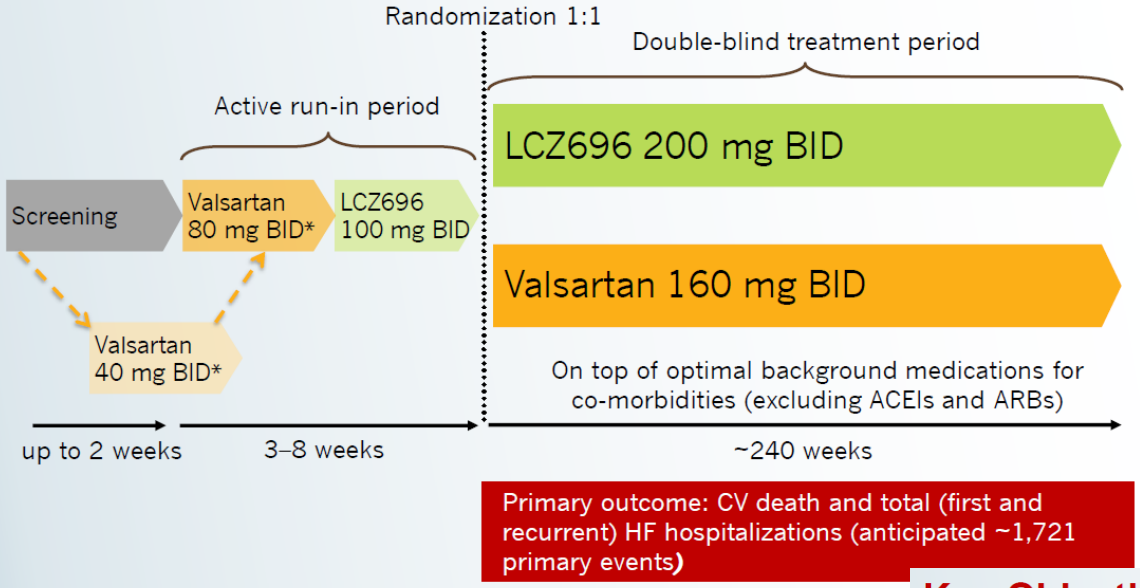


No Significant Changes in LV volumes, Ejection Fraction, or LV mass at 12 or 36 weeks

Study Design

PARAGONHF

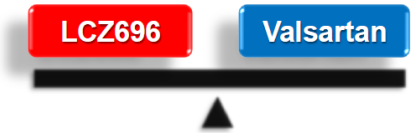
Target patient population: ~4,300 patients with symptomatic HF (NYHA Class II–IV) and LVEF ≥45%



Primary outcome: CV death and total (first and recurrent) HF hospitalizations (anticipated ~1,721 primary events)

Key Objectives

PARAGONHF



Primary Objective
↓ CV Mortality and (total) HF hospitalization

Secondary Objectives
[↓CV Mortality, HF Hospitalization, stroke, MI]
↑ NYHA Classification
→ New onset AF
→ All-cause mortality

Key points

- Heart failure with preserved ejection fraction (HFPEF) is a common disease, especially among the elderly and in women.
- With an increasing prevalence of hypertension, obesity, atrial fibrillation, and diabetes, and the growing elderly segment of the general population, the prevalence of HFPEF is projected to increase in the future.
- HFPEF presents a diagnostic challenge and studies differ widely in their reported incidence and mortality rates associated with this condition.
- There is agreement that between a third and one half of heart failure patients in the community have HFPEF.
- Prognosis is overall poor. Patients with HFPEF have substantial comorbidity, high rates of repeated hospitalizations, and a high mortality.
- Is the mortality often not related to the HFPEF but to the comorbidities?
- Are there different groups within the phenotypes?

Gracias!