Hartfalendag 2014

Medicamenteuze Therapie van HFpEF

Prof. Adriaan A. Voors, cardiologist

University Medical Center Groningen

Heart Failure Guidelines

"No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF. Diuretics are used to control sodium and water retention and relieve breathlessness and oedema as in HF-REF. Adequate treatment of hypertension and myocardial ischaemia is also considered to be important, as is control of the ventricular rate in patients with AF."

ESC HF Guidelines 2012; EJHF 2012

Treatment of HFpEF

	Rec	LOE
Control of BP according to Hypertension guidelines	I	B
Diuretics to reduce symptoms due to volume overlaod	I	C
Coronary revascularization for patients with CAD in whom angina/ischemia is present despite GDMT	IIa	C
Management of AF according to current guidelines to improve symptoms	IIa	C
Using beta-blockers, ACEi and/or ARBs for hypertension	IIa	C
ARBs might be consider to decrease hospitalizations	IIb	B
Nutritional supplementation is not recommended	III	C

2013 ACCF/AHA Heart Failure Guidelines; JACC 2013

Use of Diuretics in HFpEF

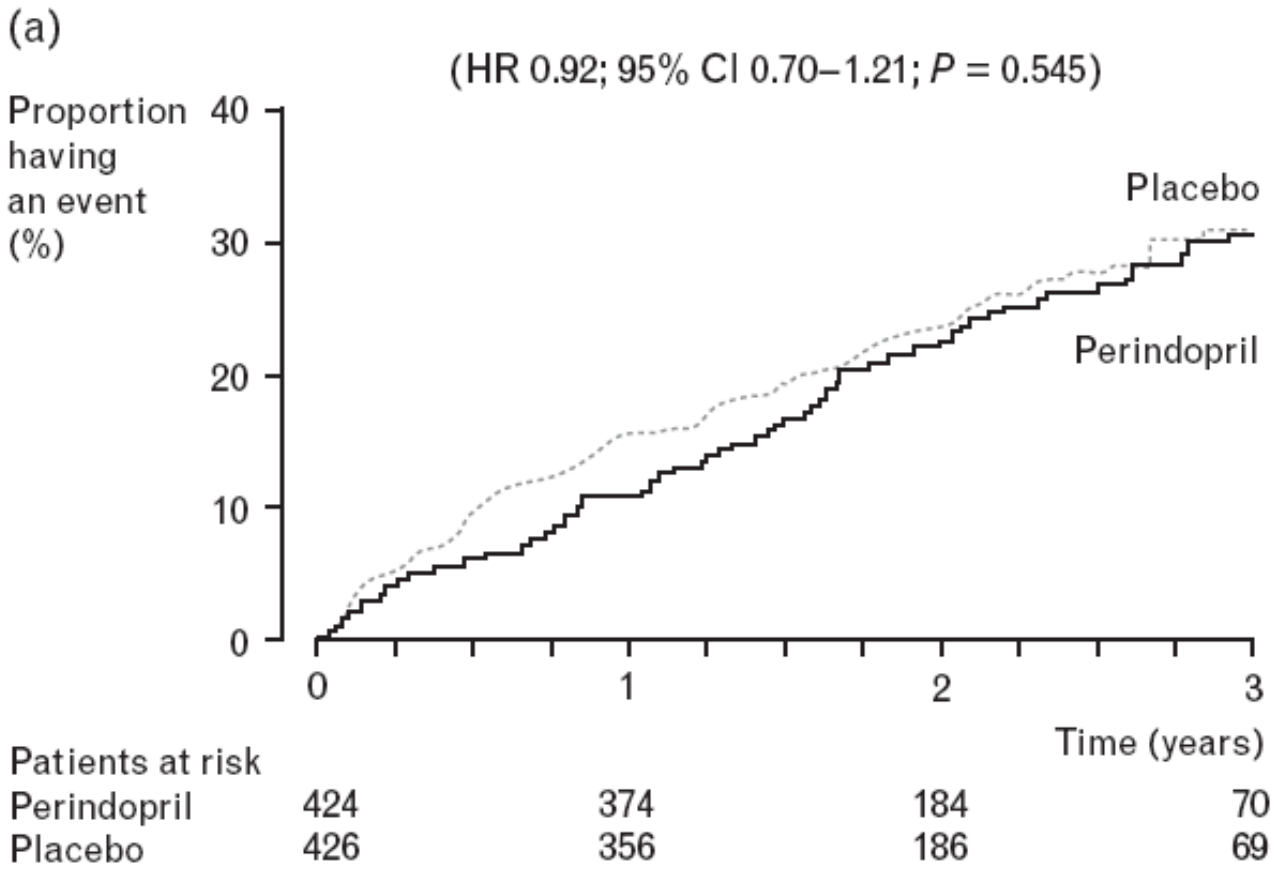
- Main aim: achieve and maintain euvolaemia (‘dry weight’) at lowest achievable dose.
- Dose must be adjusted, particularly at dry body weight, to avoid the risk of dehydration leading to hypotension and renal dysfunction.
- This may reduce cardiac output in patients with HF-PEF and often needlessly prevents the use of (or achievement of the target dose of) other disease-modifying therapies

ESC HF Guidelines 2012; EJHF 2012

Randomized Clinical Trials in HFpEF

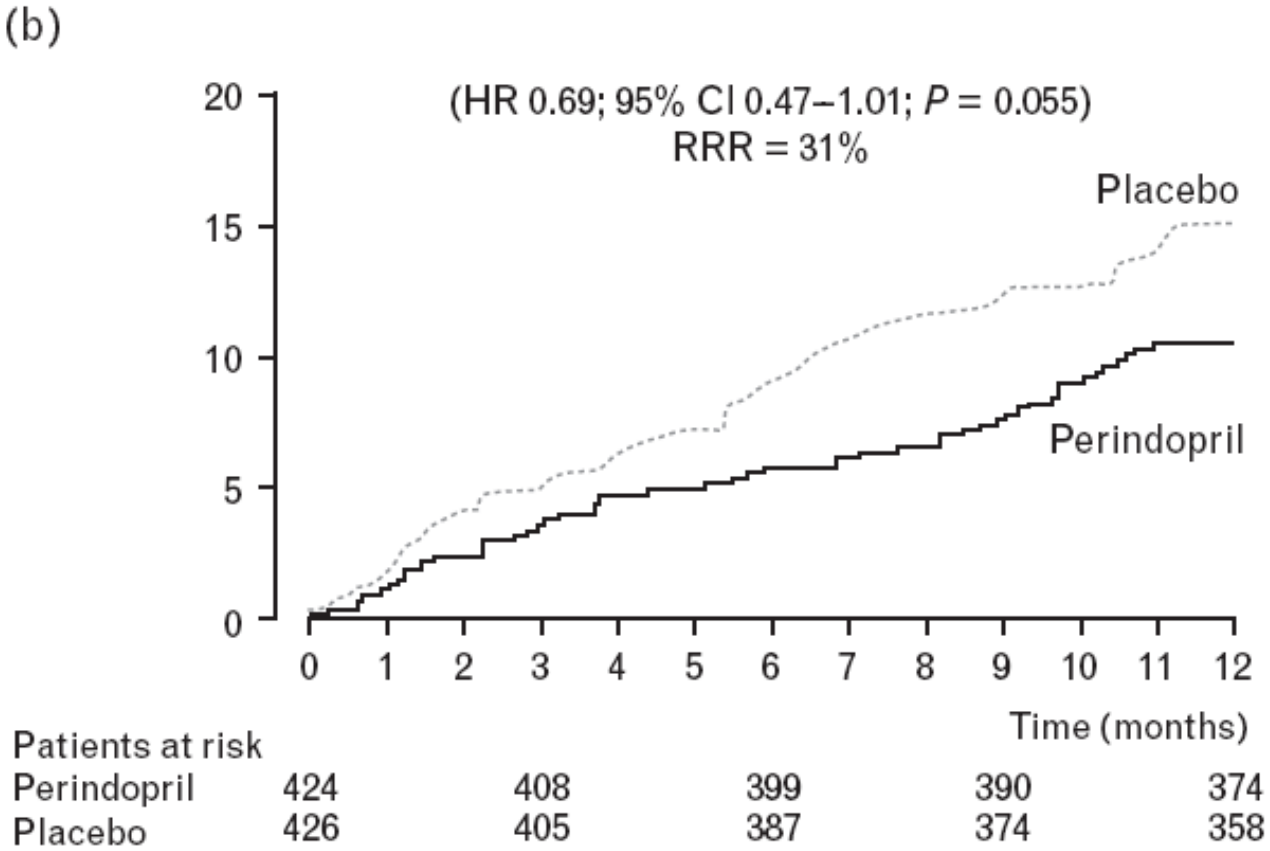
	Charm-Preserved	PEP-CHF	I-PRESERVE
Drug	Candesartan 32 mg vs. Placebo	Perindopril 4 mg vs. Placebo	Irbesartan 300 mg vs. Placebo
Number	3023	850	4128
Age	67 years	75 years	72 years
% Female	40	55	60
LVEF	>40% (54)	>40% (64)	>45% (60)
Primary Outcome	CV-death or HF-hosp	Death or HF-hosp	Death or CV-hosp
Follow-up	37 months	25 months	50 months

Effect of ACEi in HFpEF: PEP-CHF



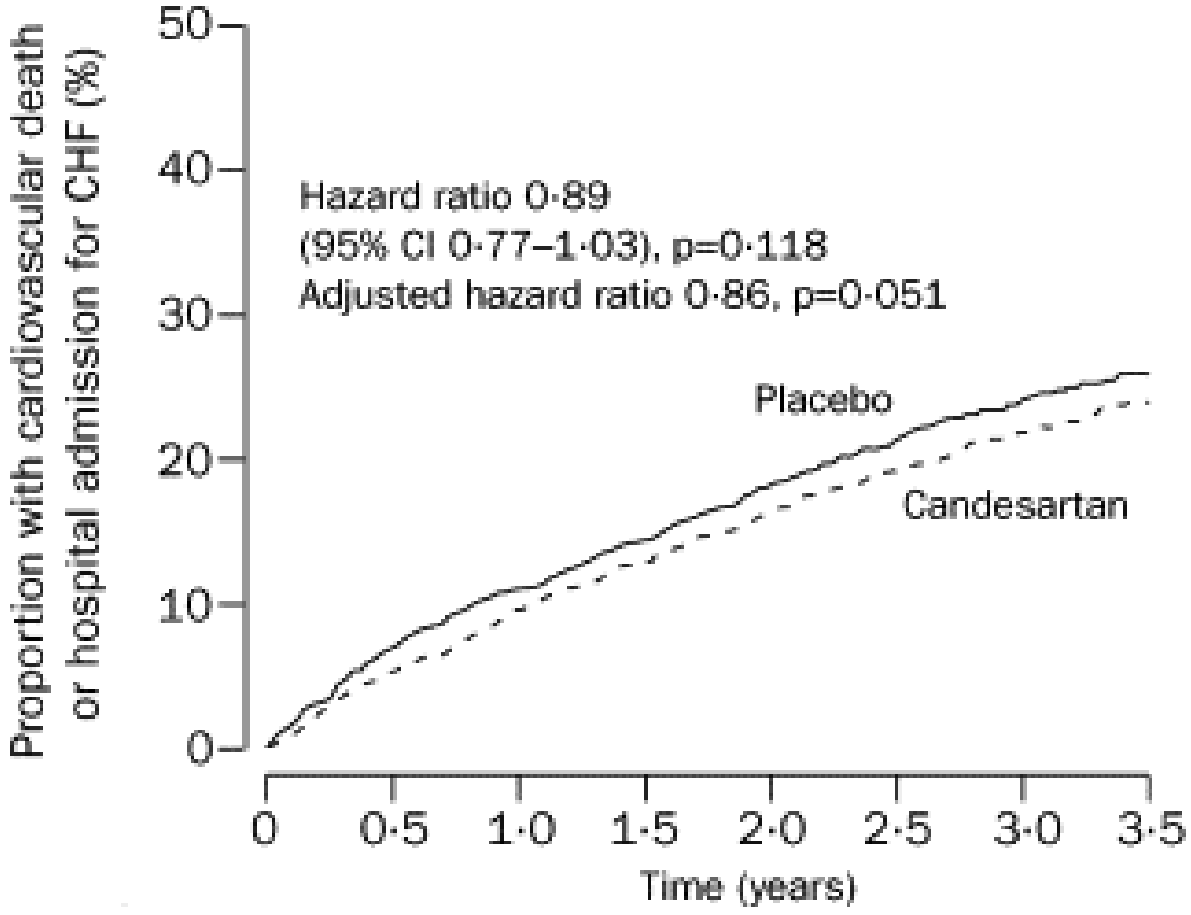
Cleland et al. EJHF 2006

Effect of ACEi in HFpEF: PEP-CHF



Cleland et al. EJHF 2006

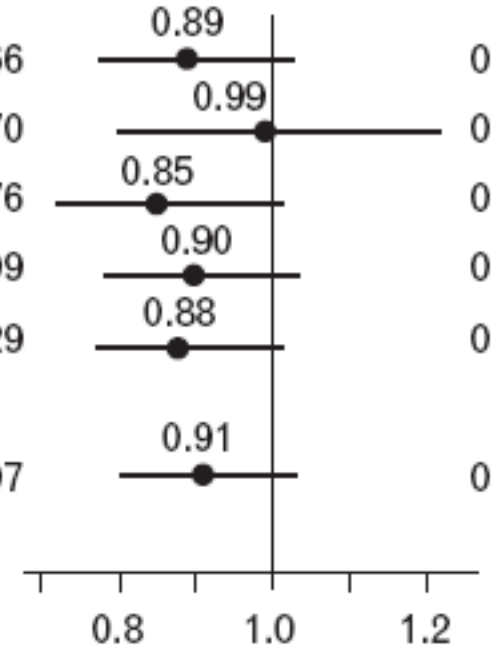
Effects of ARB in HFpEF: CHARM-preserved



Yusuf et al. Lancet 2003

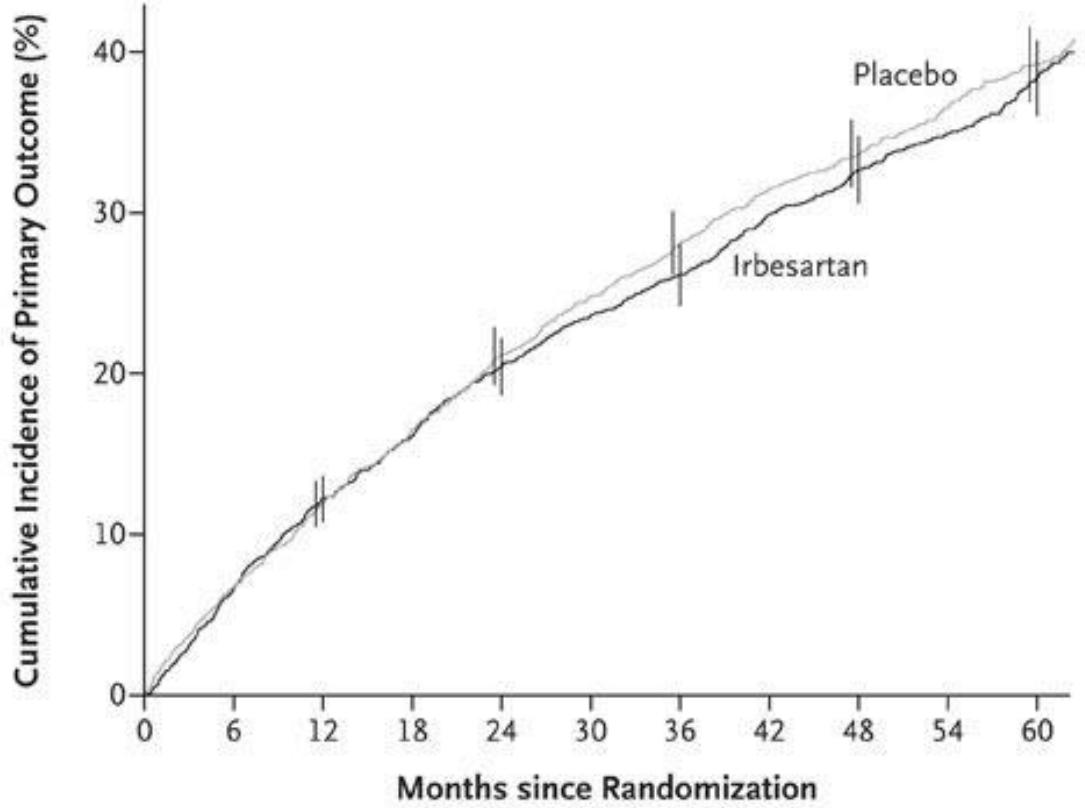
Effects of ARB in HFpEF: CHARM-preserved

	Candesartan	Placebo	HR	*P*-value	Covariate-adjusted *P*-value
CV death, HF hosp	333	366	0.89	0.118	0.051
CV death	170	170	0.99	0.918	0.635
HF hospitalization	241	276	0.85	0.072	0.047
CV death, HF hosp, MI	365	399	0.90	0.126	0.051
CV death, HF hosp, MI, stroke	388	429	0.88	0.078	0.037
CV death, HF hosp, MI, stroke, revascularization	460	497	0.91	0.123	0.13



Yusuf et al. Lancet 2003

Effects of ARB in HFpEF: I-PRESERVE



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

Massie et al. NEJM 2008

The NEW ENGLAND JOURNAL of MEDICINE

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Spironolactone for Heart Failure with Preserved Ejection Fraction

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TOPCAT: methods

- Objective: to determine effects of spironolactone on composite endpoint of CV-mortality, aborted cardiac arrest or HF-hospitalization in HFpEF patients
- Inclusions: Symptomatic HF, Age ≥50, LVEF ≥45%, stratified according to:
  - HF-hospitalization in past year
  - Elevated NPs (BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL)
- Major exclusions: eGFR <30 ml/min/1.73m^2, K^+ ≥5 mmol/L, AF >90/min, recent ACS.

Variable	Spironolactone (n=1722)	Placebo (n=1723)
Age	69 years	69 years
Female	52%	51%
LVEF	56%	56%
Stratum HF hospitalization Natriuretic Peptide	 71.5% 28.5%	 71.5% 28.5%
Hypertension	91%	92%
NYHA class II NYHA class III	63.3% 33.8%	64.3% 32.2%
Coronary Artery Disease	57%	60%
Atrial Fibrillation	35%	35%
Diabetes Mellitus	33%	32%

Variable	Spironolactone (n=1722)	Placebo (n=1723)
Systolic Blood Pressure	130 mmHg	130 mmHg
Diastolic Blood Pressure	80 mmHg	80 mmHg
Heart rate	68 bpm	68 bpm
eGFR (ml/min/1.73m^2)	65	66
Serum Potassium	4.3 mmol/L	4.3 mmol/L
Medications		
ACE-i of ARB	84%	84%
Beta-blocker	78%	77%
Diuretic	81%	82%
Statin	53%	52%
Anticoagulant	23%	22%

Primary outcome

Mean follow-up 3.3 years

Outcome	Spironolactone	Placebo	HR (95%CI) and p-value
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=0.483
HF Hospitalization	206 (12.0%) 3.8/100pt-yr	245 (14.2%) 4.6/100pt-yr	0.83 (0.69-0.99) P=0.042

Safety

Total number of SAE's:

spironolactone 835 (48.5%)

placebo 855 (49.6%)

However… Doubling Creatinine above ULN

HR=1.49 (1.18-1.87); P<0.001

	Spironolactone	Placebo	P-value
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

TOPCAT: Subgroups

- Of 22 pre-specified subgroups, only 1 showed a significant interaction with treatment

Enrolled by:	Spironolactone	Placebo	HR (95% CI) P-value
Natriuretic Peptide	78/490 (15.9%)	116/491 (23.6%)	0.65 (0.49-0.87) P=0.003
Heart Failure Hospitalization	242/1232 (19.6%)	235/1232 (19.1%)	1.01 (0.84-1.21) P=0.923

TOPCAT: Conclusions

- Treatment with spironolactone did not alter the primary composite endpoint, but reduced hospitalizations for heart failure
- Use of spironolactone in these patients requires careful monitoring of K^+ and creatinine

Why novel therapies in HFpEF?

- HFpEF increasingly prevalent
- Prognosis as poor as systolic heart failure
- Different pathophysiology and different patient characteristics
- Drugs that are beneficial in HFrEF do not seem to be beneficial in HFpEF
- As yet, no proven pharmacological therapy for HFpEF

HFpEF: what's in the pipeline?

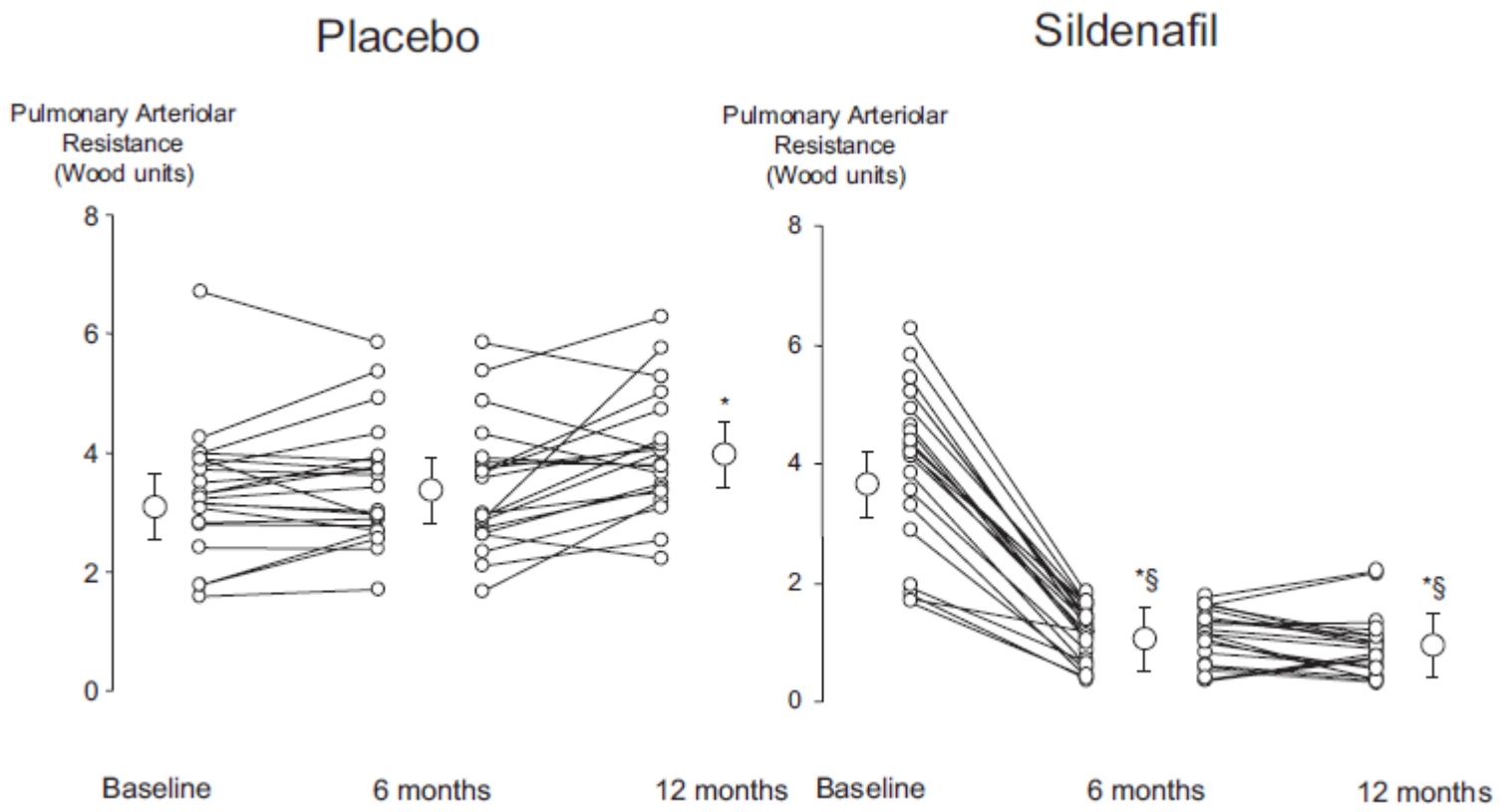
- PDE-5 inhibition (sildenafil)
- Sinus node inhibition (ivabradine)
- Soluable Guanylate Cyclase stimulation (vericiguat)
- Beta-blockade
- Angiotensin Receptor Neprilysin Inhibition (LCZ696)
- Exercise

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction : A Target of Phosphodiesterase-5 Inhibition in a 1-Year Study

Marco Guazzi, Marco Vicenzi, Ross Arena and Maurizio D. Guazzi



Guazzi et al. Circulation 2011

ONLINE FIRST

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

A Randomized Clinical Trial

Methods 216 stable outpatients with HF, LVEF 50%, elevated NT-proBNP or elevated invasively measured filling pressures, and reduced exercise capacity were randomized to Sildenafil (n=113) or placebo (n=103)

Main Outcome Measures Primary end point was change in peak oxygen consumption after 24 weeks of therapy.

RELAX: main outcomes

Table 3. Primary, Secondary, and Safety End Points

	Placebo		Sildenafil		
	No. of Patients	Variable	No. of Patients	Variable	*P* Value
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)	.89
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

Abbreviations: IQR, interquartile range; MLHFQ, Minnesota Living with Heart Failure Questionnaire.
[a] A mean value of 95 in each group is expected under the null hypothesis of no treatment effect.
[b] Site investigator identified causes of death were sudden death (n=1), progressive cardiorenal failure (n=1), and noncardiovascular (n=1).

HFpEF: PDE-5 inhibitors

Study Drug	N	Patients	1e Endpoint	Institution
Sildenafil	44	LVEF>50% PAP>40 mmHg	PAP, RVF	University of Milano (Guazzi)
Udenafil	52	LVEF ≥50% NYHA II-IV	ΔVO2max	Seoul National Univesity Hospital (Kim)
Sildenafil	50	LVEF≥50% PAP>40 mmHg	PAP, PCWP	University Medical Center Groningen (Hoendermis)

HFpEF: what's in the pipeline?

- PDE-5 inhibition (sildenafil)
- Sinus node inhibition (ivabradine)
- Soluable Guanylate Cyclase stimulation (vericiguat)
- Beta-blockade
- Angiotensin Receptor Neprilysin Inhibition (LCZ696)
- Exercise

Why Ivabradine in HFpEF?

- Heart Rate independent risk factor for mortality in HFpEF
- Ivabradine Effective in HFrEF
- Ivabradine improves diastolic function in experimental and human studies
- Ivabradine lowers myocardial and vascular collagen content
- Ivabradine improves vascular stiffness in experimental studies

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Heart Failure

Effect of I_f-Channel Inhibition on Hemodynamic Status and Exercise Tolerance in Heart Failure With Preserved Ejection Fraction

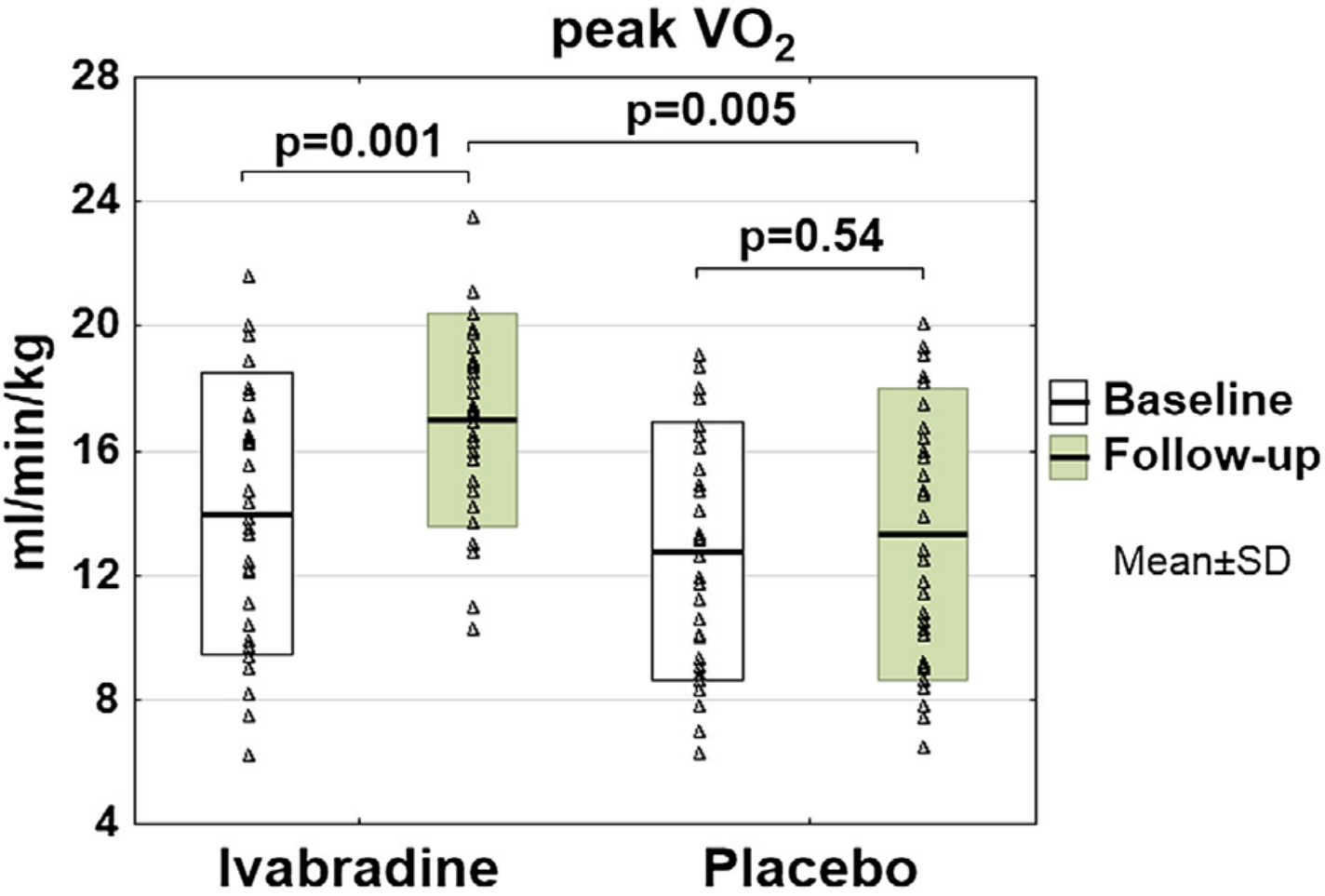
A Randomized Trial

Wojciech Kosmala, MD, PHD,* David J. Holland, PHD,† Aleksandra Rojek, MD,* Leah Wright, BS,‡ Monika Przewlocka-Kosmala, MD, PHD,* Thomas H. Marwick, MD, PHD‡

Wroclaw, Poland; and Brisbane and Hobart, Australia

- 61 patients with HFpEF were randomly assigned to ivabradine 5 mg twice daily (n=30) or placebo (n=31) for 7 days in this double-blind trial.
- CPX with echo of myocardial function and left ventricular filling were undertaken at rest and after exercise.

Ivabradine improves exercise capacity in HFpEF



Kosmala et al. JACC 2013

EDIfY

PrEserveD left ventricular ejectIon fraction
chronic heart Failure with ivabradine studY

Effect of ivabradine *versus* placebo on cardiac function, exercise capacity, and neuroendocrine activation in patients with Chronic Heart Failure with Preserved left ventricular Ejection Fraction

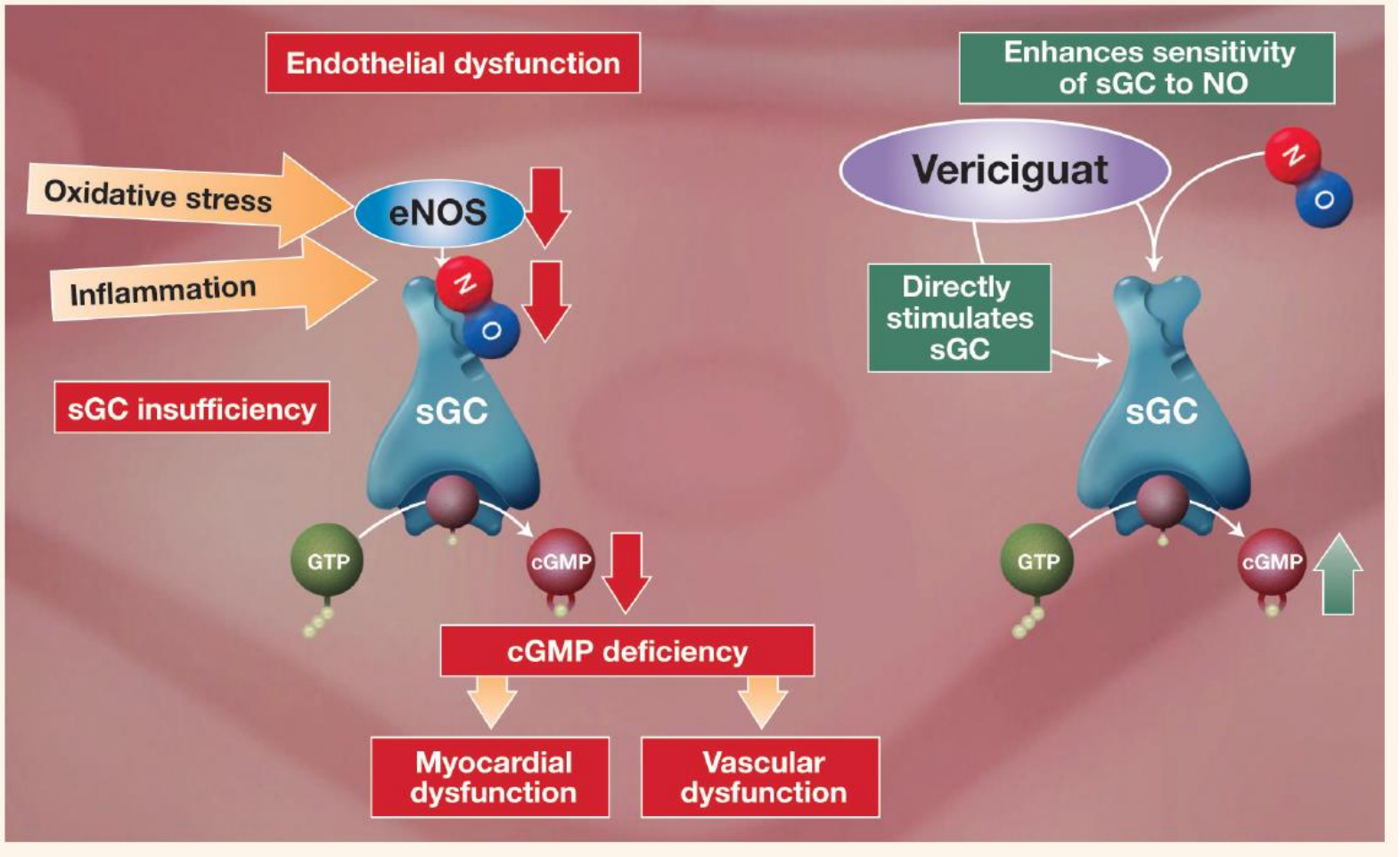
An 8-month, randomised double-blind, placebo controlled, international, multicentre study

- Primary objective± to assess the effect of ivabradine compared to placebo on the diastolic function, exercise capacity, and the neuroendocrine activation over an 8-month treatment period in 400 patients with HF-PEF

HFpEF: what's in the pipeline?

- PDE-5 inhibition (sildenafil)
- Sinus node inhibition (ivabradine)
- Soluable Guanylate Cyclase stimulation (vericiguat)
- Beta-blockade
- Angiotensin Receptor Neprilysin Inhibition (LCZ696)
- Exercise

Soluble guanylate cyclase – a novel target for the treatment of heart failure



cGMP, cyclic guanosine monophosphate; eNOS, endothelial nitric oxide synthase; GTP, guanosine triphosphate; NO, nitric oxide; sGC, soluble guanylate cyclase.

Soluble Guanylate ***C***yclase stimulato***r*** He***art*** Failur***e*** ***S***tudies:

The **SOCRATES** Program

	SOCRATES-REDUCED	SOCRATES-PRESERVED
Design	2 randomized parallel-group, placebo-controlled, double-blind, dose finding Phase IIb studies of 4 dose regimens of the oral sGC stimulator vericiguat over 12 weeks	
Inclusion Criteria	**Worsening chronic heart failure requiring hospitalization (or IV diuretic for HF) with initiation after clinical stabilization**	
	LVEF <45%	LVEF ≥45% Left atrial (LA) enlargement
Primary Outcome	NT-proBNP at 12 weeks	NT-proBNP / LA vol. at 12 weeks (split α: each $p<0.025$)
Enrollment	410 patients in 5 arms	470 patients in 5 arms
Study status	FPFV Nov 29, 2013	FPFV Nov 6, 2013
CT.gov ID	NCT01951625	NCT01951638

HFpEF: what's in the pipeline?

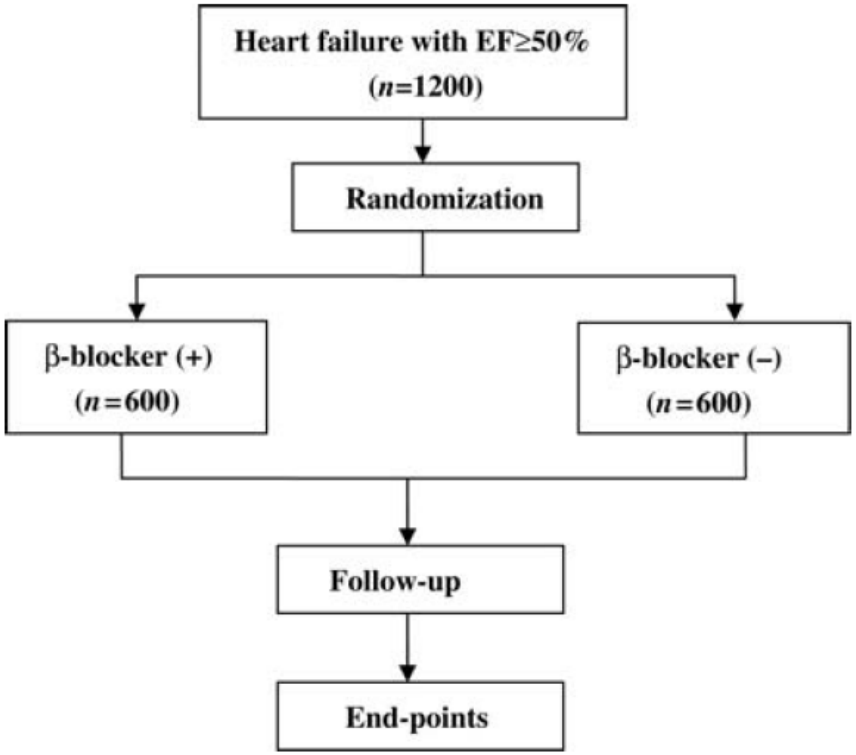
- PDE-5 inhibition (sildenafil)
- Sinus node inhibition (ivabradine)
- Soluable Guanylate Cyclase stimulation (vericiguat)
- Beta-blockade
- Angiotensin Receptor Neprilysin Inhibition (LCZ696)
- Exercise

Rationale and design of the β-blocker in heart failure with normal left ventricular ejection fraction (β-PRESERVE) study

Jingmin Zhou, Haiming Shi, Jian Zhang, Yongxin Lu, Michael Fu, and Junbo Ge* for the β-PRESERVE Study Investigators

Table 1 Key inclusion criteria

Male or female aged ≥40 years
Left ventricular ejection fraction (LVEF) ≥50%
Consistent with current symptoms of NYHA II or highe 3 months prior to enrolment
NT-proBNP ≥1500 pg/mL
Health status suitable for outpatient follow-up
Written informed consent obtained

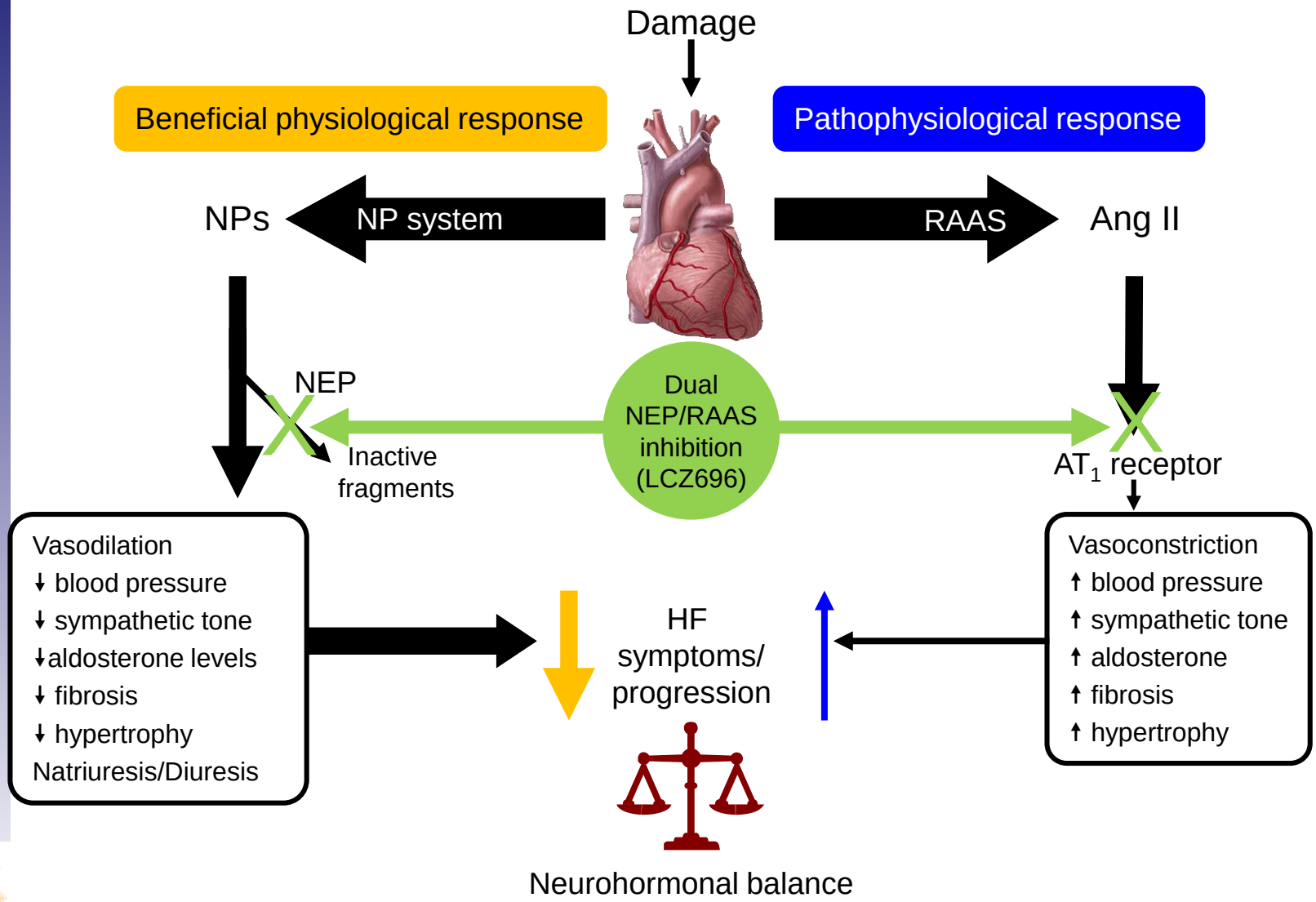


1e endpoint: CV death and/or HF admission

HFpEF: what's in the pipeline?

- PDE-5 inhibition (sildenafil)
- Sinus node inhibition (ivabradine)
- Soluable Guanylate Cyclase stimulation (vericiguat)
- Beta-blockade
- Angiotensin Receptor Neprilysin Inhibition (LCZ696)
- Exercise

LCZ696 has the potential to restore the appropriate balance of the RAAS and natriuretic peptides in HF

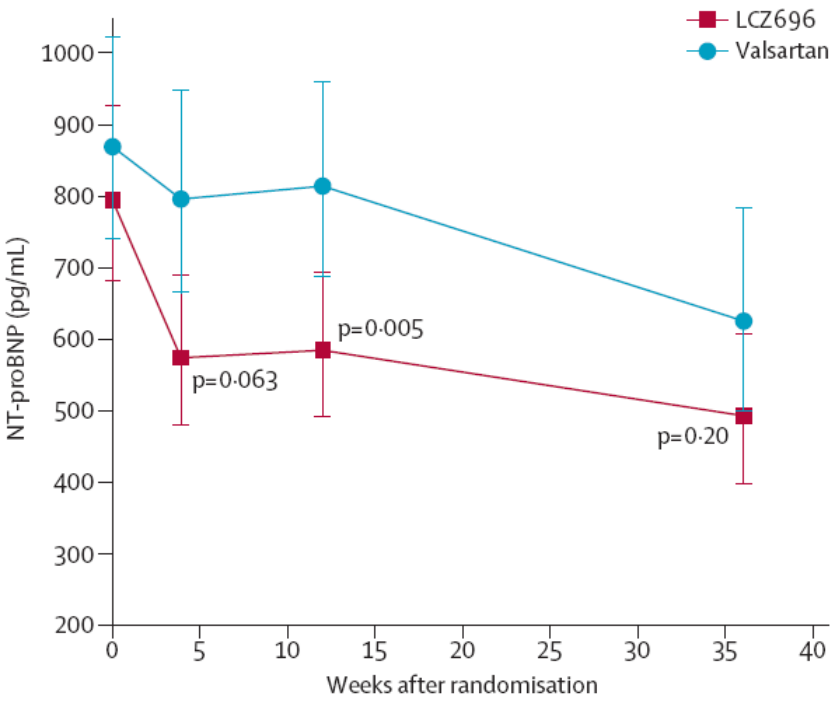


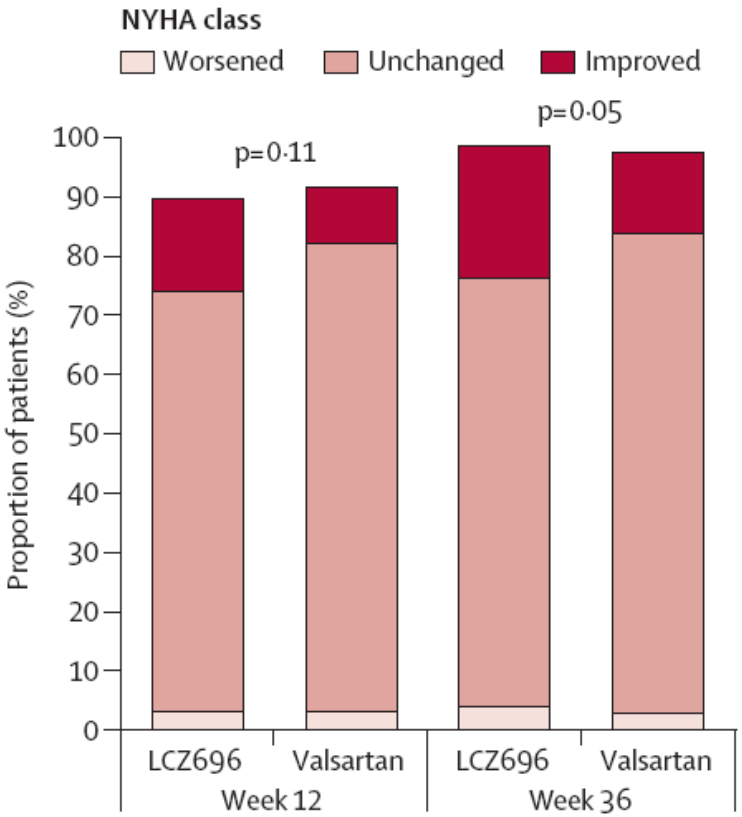
THE LANCET

The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

*Scott D Solomon, Michael Zile, Burkert Pieske, Adriaan Voors, Amil Shah, Elisabeth Kraigher-Krainer, Victor Shi, Toni Bransford, Madoka Takeuchi, Jianjian Gong, Martin Lefkowitz, Milton Packer, John J V McMurray, for the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators**

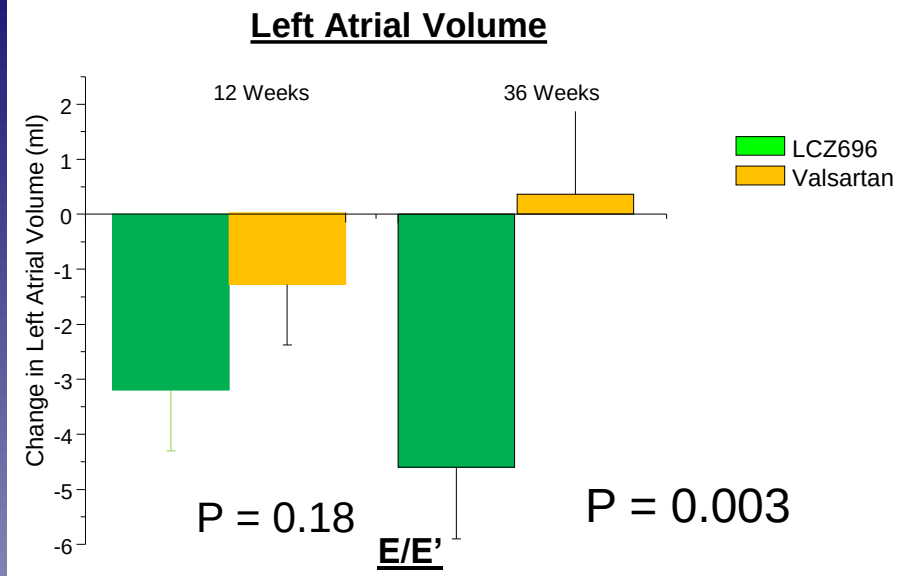
PARAMOUNT: main results

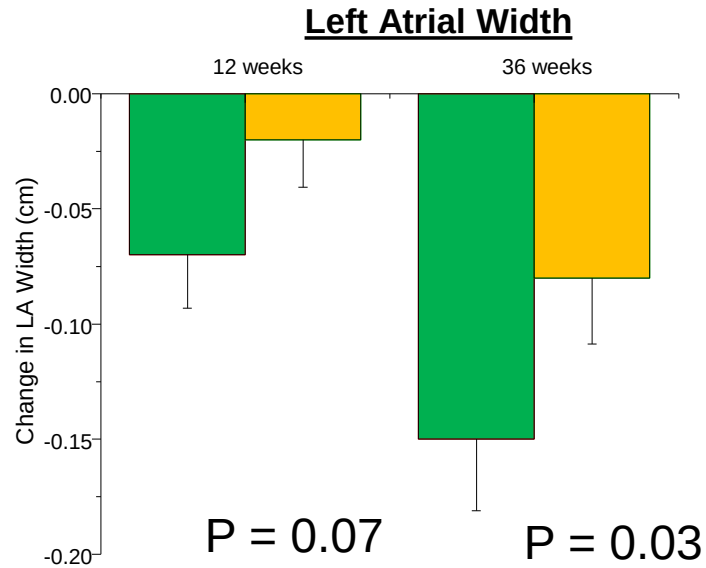


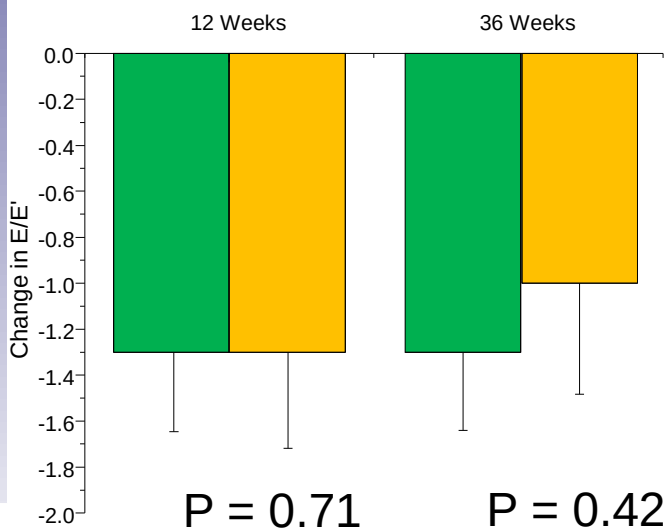


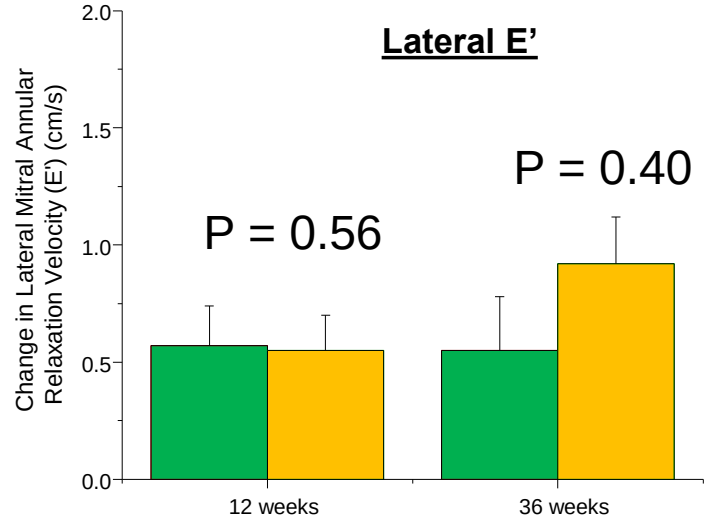
Solomon et al. Lancet 2012

Changes in Echocardiographic Measures





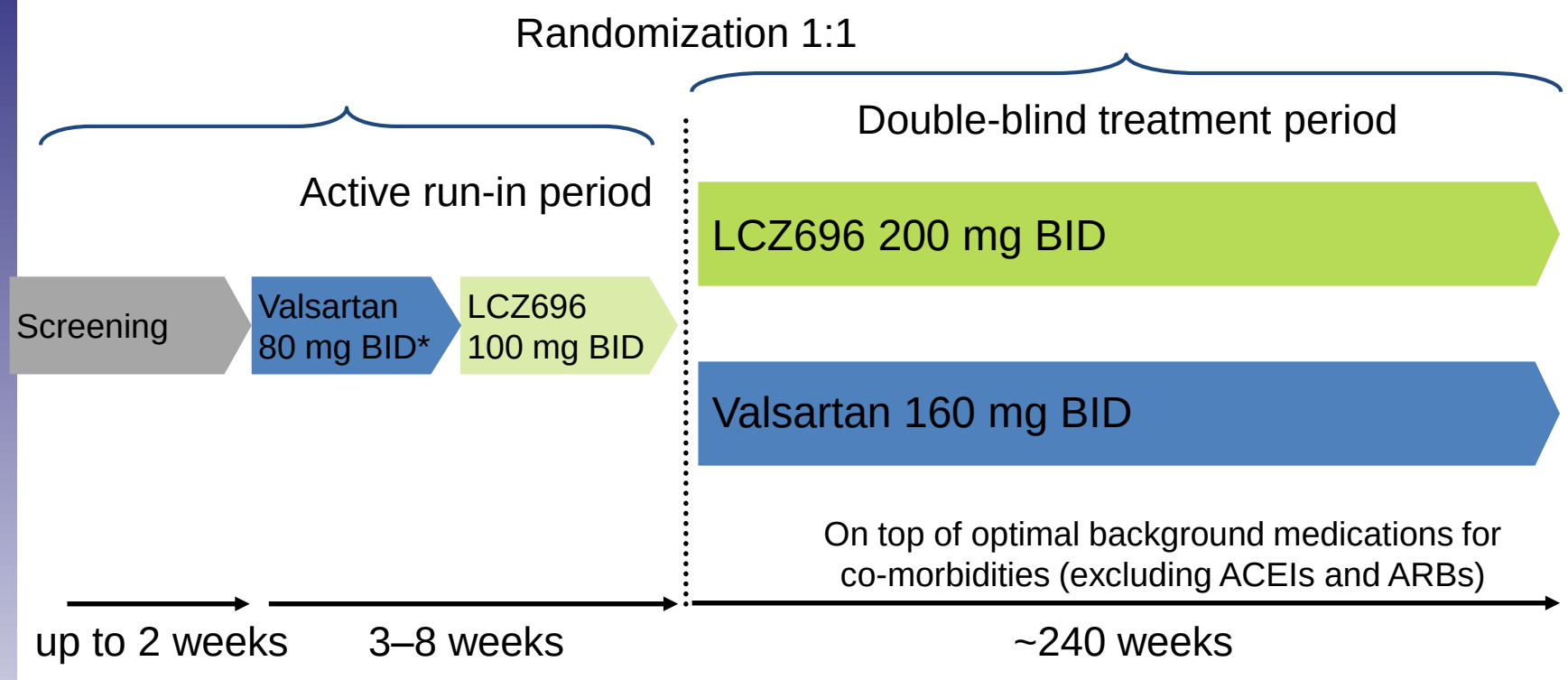




Solomon et al. Lancet 2012

PARAGON-HFPEF: study design

- 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)

*Valsartan 40 mg BID (up to 2 weeks) followed by valsartan 80 mg BID as an optional starting run-in dose for those patients being treated with less than the minimum dose of ACEI or ARB at Visit 1

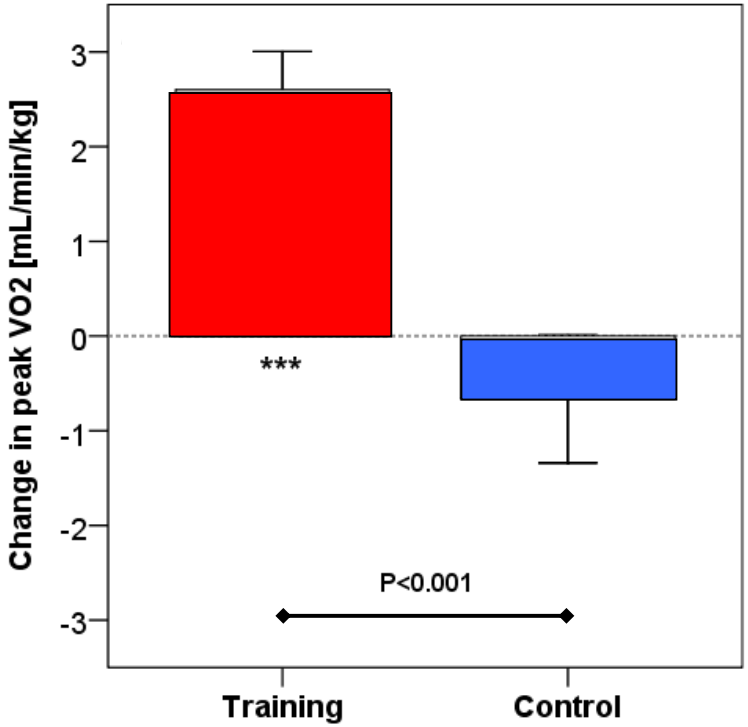
Solomon SD, et al. Poster presentation at ESC-HF Congress, 25 May 2013; Clinicaltrials.gov NCT01920711;accessed March 2014

HFpEF: what's in the pipeline?

- PDE-5 inhibition (sildenafil)
- Sinus node inhibition (ivabradine)
- Soluable Guanylate Cyclase stimulation (vericiguat)
- Beta-blockade
- Angiotensin Receptor Neprilysin Inhibition (LCZ696)
- Exercise

Exercise Training Improves Exercise Capacity and Diastolic Function in Patients With Heart Failure With Preserved Ejection Fraction

Results of the Ex-DHF (Exercise training in Diastolic Heart Failure) Pilot Study



Screened for eligibility n=71

(Age ≥ 45 years, dyspnea at exertion, preserved systolic function & echo signs of DDys, presence of at least one risk factor, written informed consent)

Primary Endpoint:
peak VO2

Edelman et al. JACC 2011

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Heart Failure

Effect of Endurance Exercise Training on Endothelial Function and Arterial Stiffness in Older Patients With Heart Failure and Preserved Ejection Fraction

A Randomized, Controlled, Single-Blind Trial

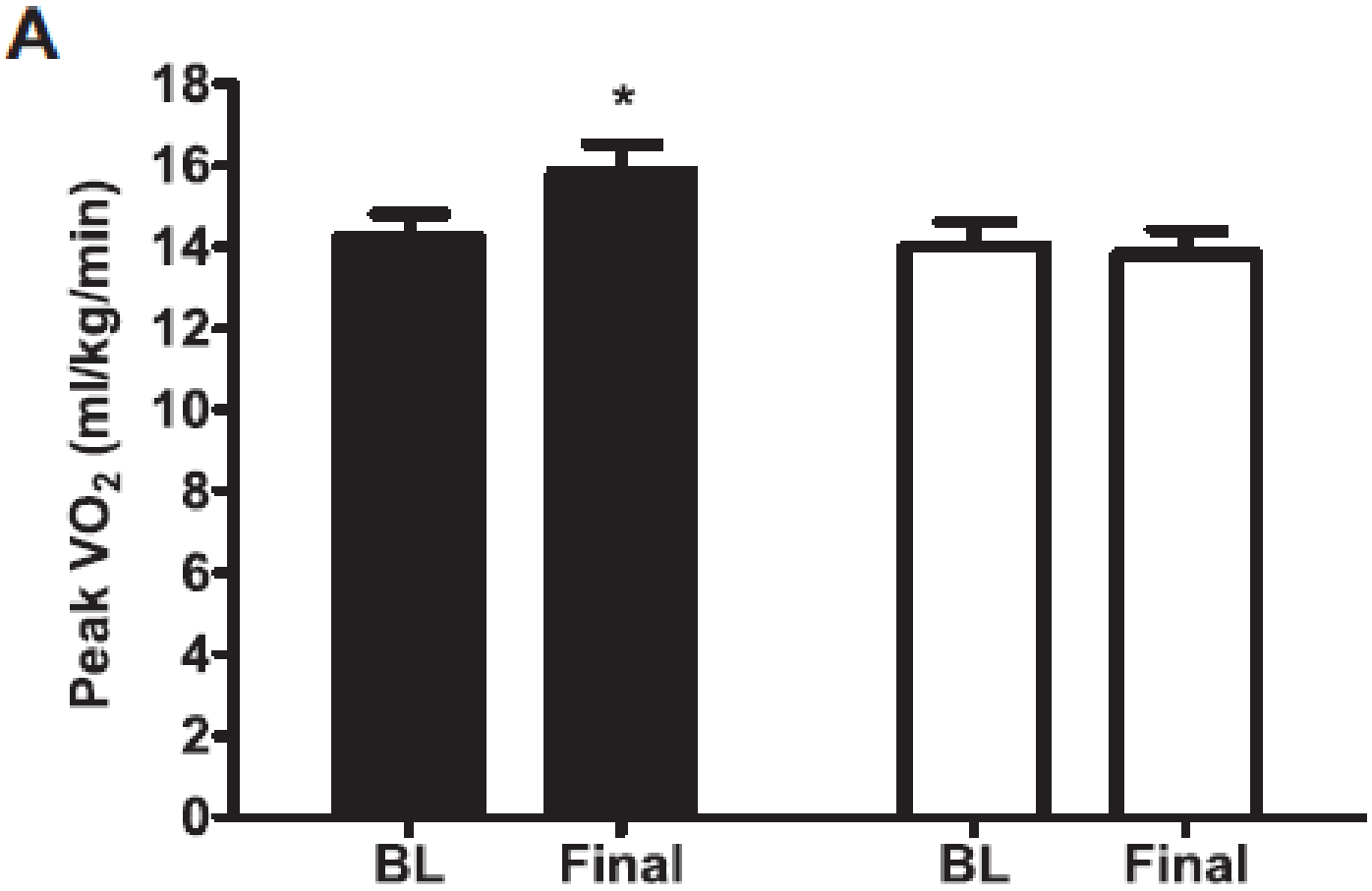
Dalane W. Kitzman, MD,* Peter H. Brubaker, PHD,† David M. Herrington, MD,*
Timothy M. Morgan, PHD,‡ Kathryn P. Stewart, RT, RDMS,* W. Gregory Hundley, MD,*
Abdelhamed Abdelhamed, MD,§ Mark J. Haykowsky, PHD||

Winston-Salem, North Carolina; Fairborn, Ohio; and Edmonton, Alberta, Canada

- 63 HFpEF patients (70 years) were randomized to 16 weeks of ET (walking, arm and leg ergometry, n=32) or attention control (CT) (n=31)

Kitzman et al. JACC 2013

ET increased peak VO2 (ET: 15.8 ml/kg/min vs. CT: 13.8 ml/kg/min, p<0.0001)



Kitzman et al. JACC 2013

HFpEF: Exercise training

Study Drug	N	Patients	1e Endpoint	Institution
Exercise training (EX-DHF)	340	LVEF>50% Diastolic dysfunction	Combined Clinical Endpoint	Multicenter
Exercise training	50	LVEF ≥50% Echo: diastolic dysfunction	∆6MWT	University of Michigan (Alexander)
Exercise Training	80	LVEF >50%	∆VO2max	Hadassah University Hospital (Gotsman)
Exercise Training (EXEC)	100	LVEF ≥50%	Observational	Mayo Clinic (Borlaug)

Conclusions: treatment of HFpEF

- Limited evidence
- Careful diuretic treatment
- RAAS-inhibitor inevitable, but limited evidence
- Spironolactone? Potential risks and benefits..
- A lot in the pipeline
  - LCZ696?
  - Ivabradine?
  - Sildenafil?
  - Soluable Guanyl Cyclase stimulator?
  - Devices?

Most important…..