Heart failure with preserved ejection fraction

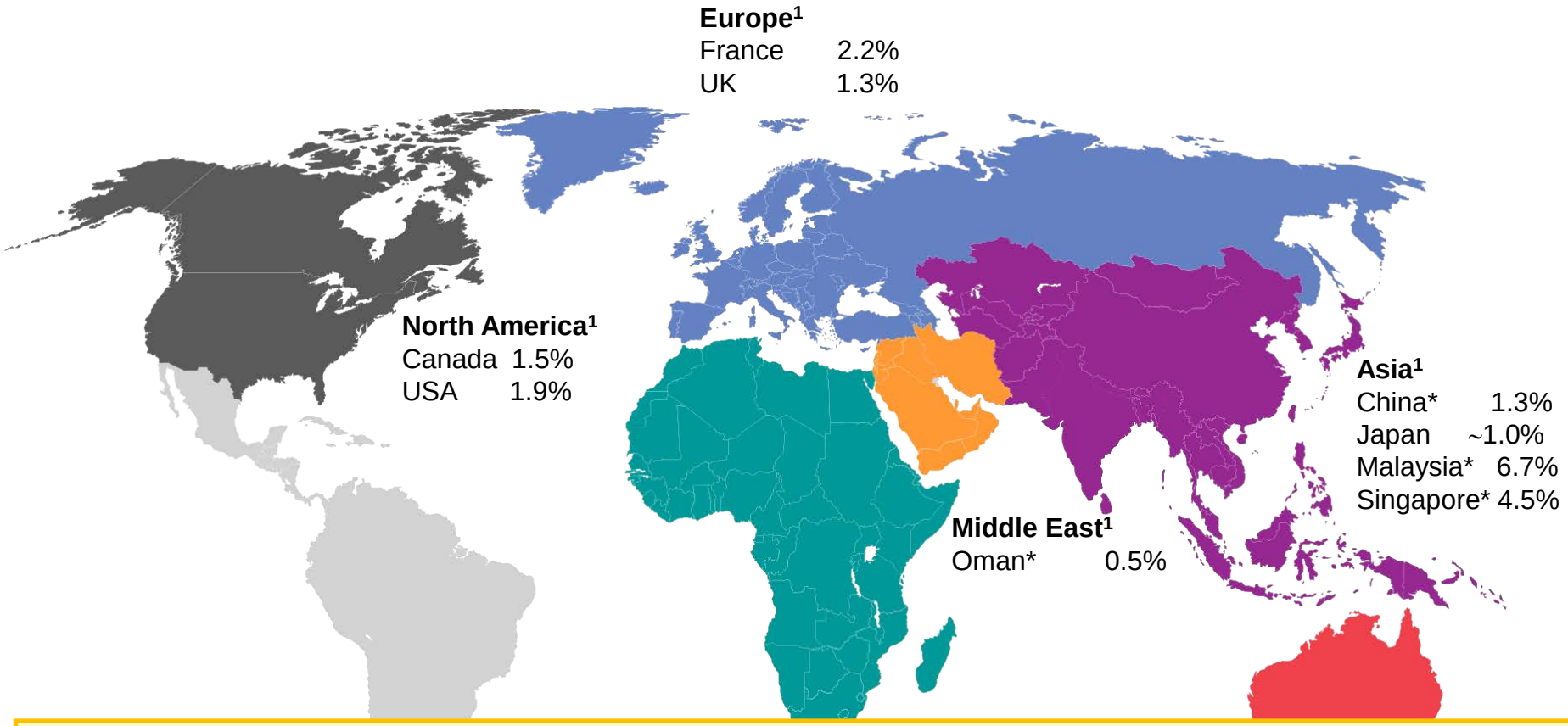
(HFpEF)

CarVasZ 2017

Loek van Heerebeek

Epidemiology of heart failure (HF)

Proportion of the population living with HF in individual countries across the world

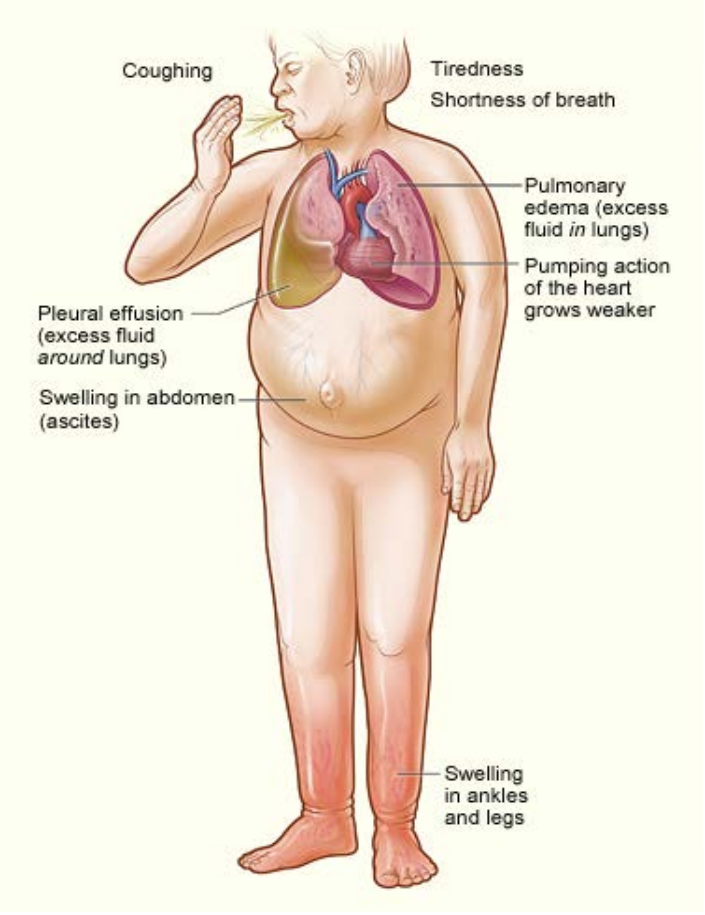


*Most common cause of hospitalization in pts > 65 years
*USA: 5.8 million; 500.000 new cases/yr; *Europe: 6.5 million; 600.000 new cases/yr
*Netherlands: 2008: 120.000 patients; 28000-44000 new cases/yr

Blair JE et al. Curr Cardiol Rev 2013;9:128; Al Shamiri MQ et al. Curr Cardiol Rev 2013;9:174; Guo Y et al. Curr Cardiol Rev 2013;9:122; AHA Heart disease and stroke statistics. Circulation 2017

Heart Failure: Definition and symptoms/signs

Heart Failure (HF): *"HF is a clinical syndrome characterized by symptoms that may be accompanied by signs caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress".* (ESC guidelines Eur Heart J 2016)



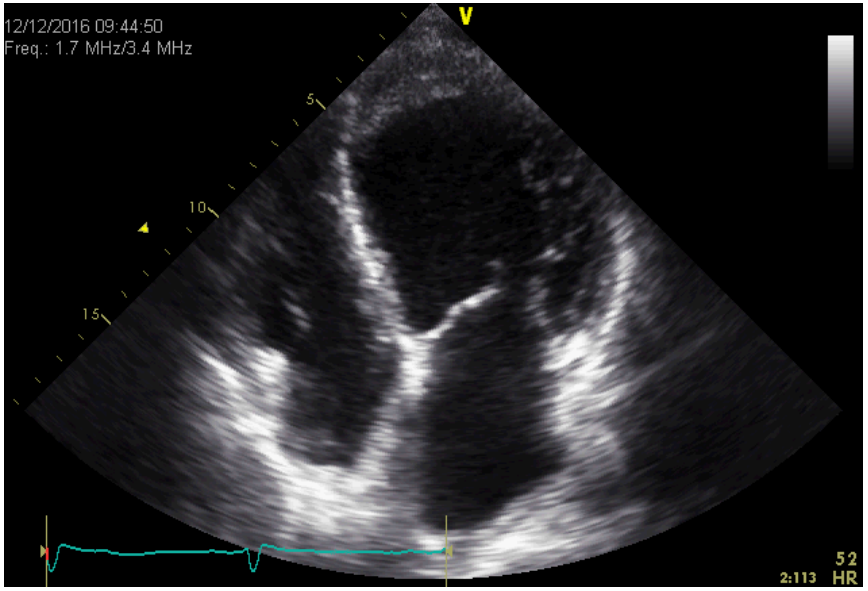
Signs/symptoms of HF; Framingham criteria	
Major criteria	Minor criteria
Orthopnea/nocturnal dyspnea	(Exertional) shortness of breath
↑ central venous pressure	Hepatomegaly
Pulmonary crackles/edema	Pleural effusion; edema
S3 gallop; ↑ circulation time	Hepatomegaly
Hepatojugular reflux	Fatigue
↑ central venous pressure	Tachycardia
	Weight gain or loss >4.5 kg in response to diuretics

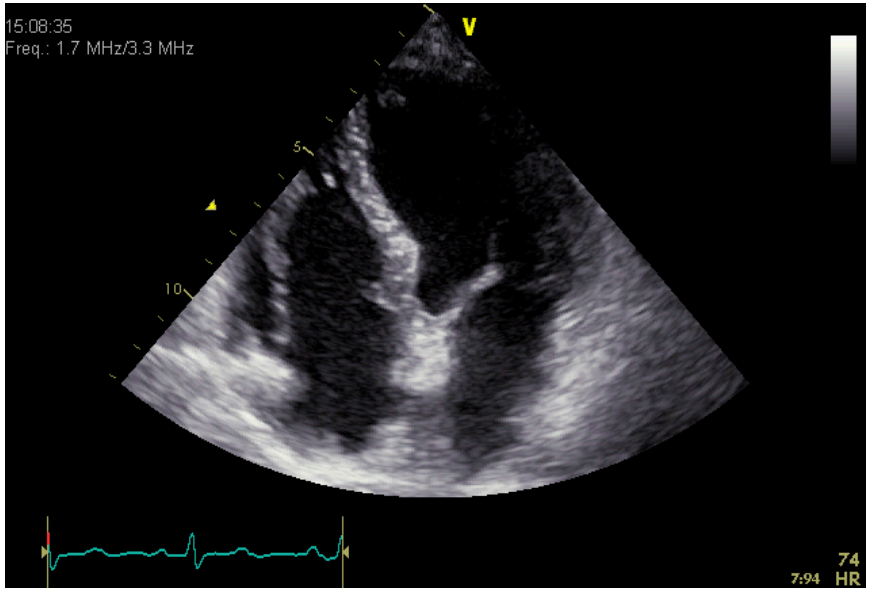
Adapted from ESC guidelines Heart Failure. Eur Heart J 2016;37:2129; Ho KKL et al. Circulation 1993;88:107

HF terminology – based on LV ejection fraction (LVEF)

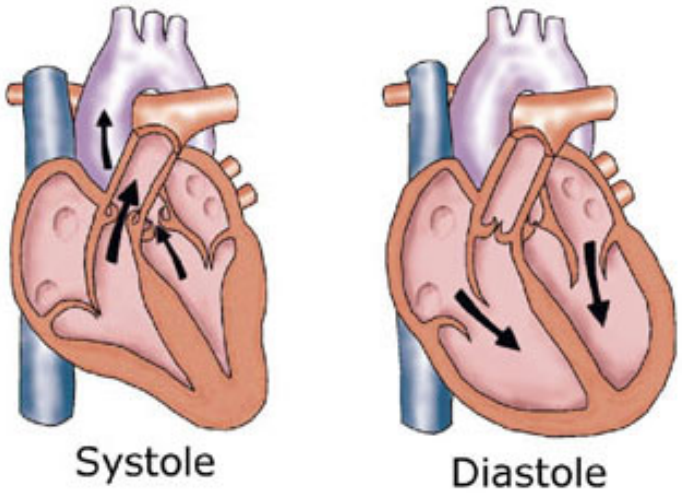
Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).



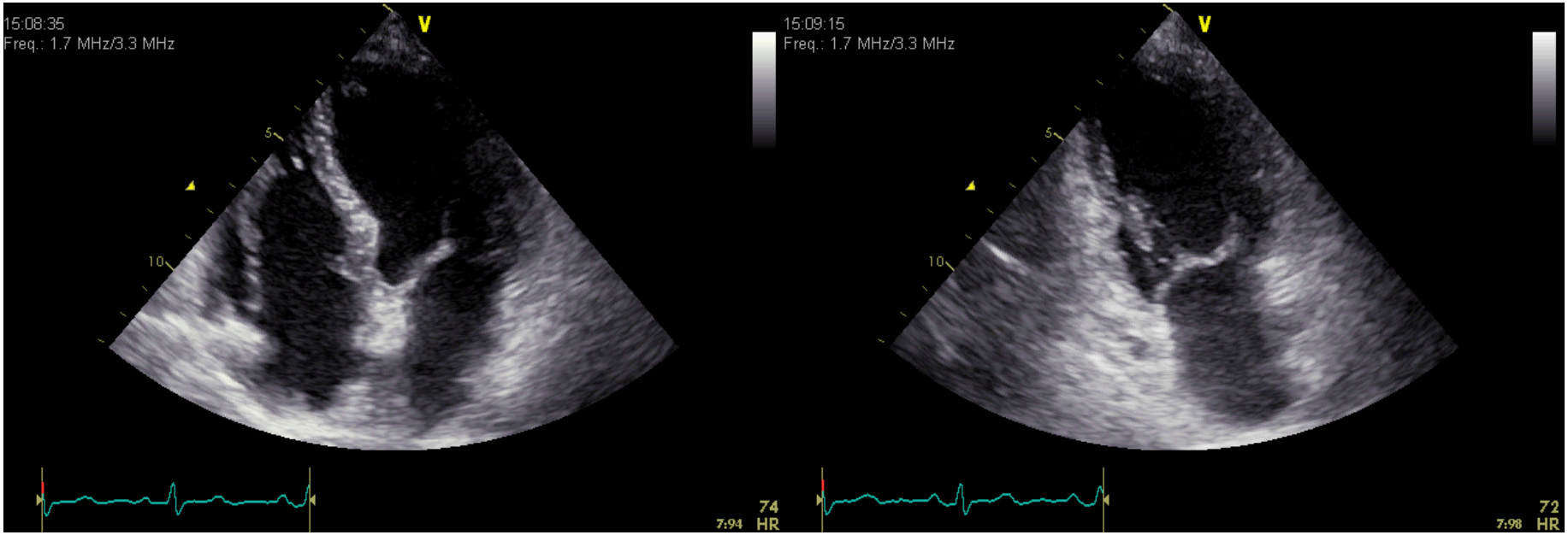


HF terminology – based on LV ejection fraction (LVEF)

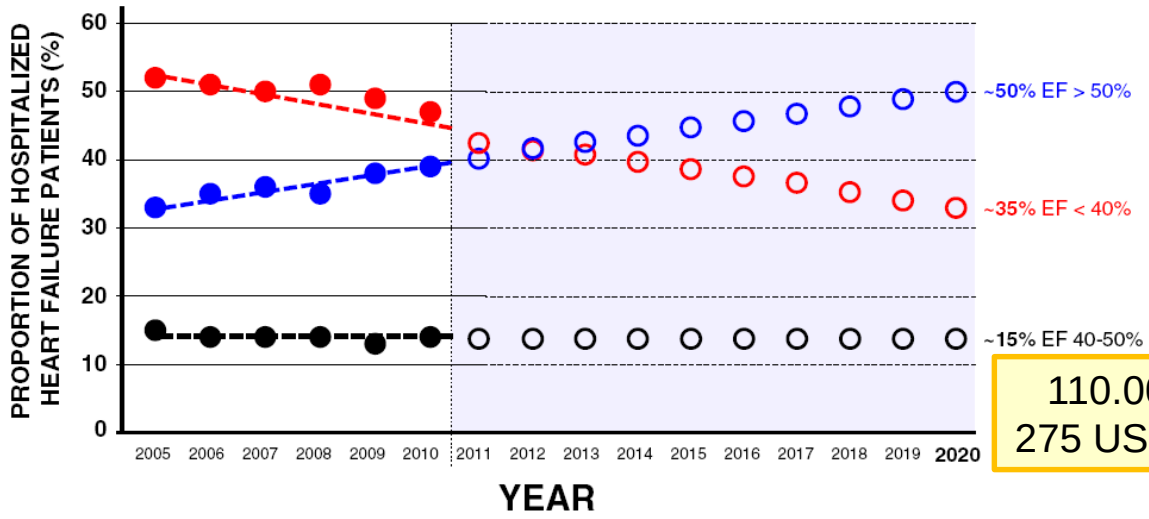


LV ejection fraction =

LV EDV – LV ESV/LV EDV * 100

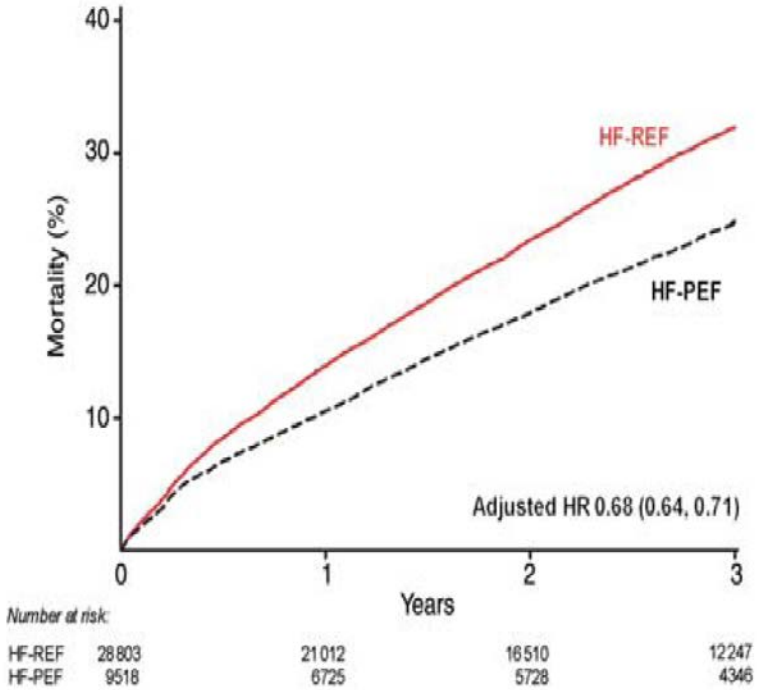


Prevalence, prognosis and treatment of HF with reduced EF (HFrEF) vs HF with preserved EF (HFpEF)



Steinberg BA et al. Circulation 2012;126:65

110.000 pts hosp for HF in 275 US hospitals (2005-2010)



31 HF trials: HFpEF (n=10347) vs HFrEF (n=31625)

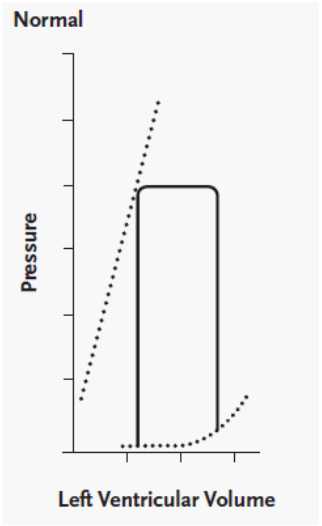
MAGGIC Investigators Eur Heart J 2012,33:1750

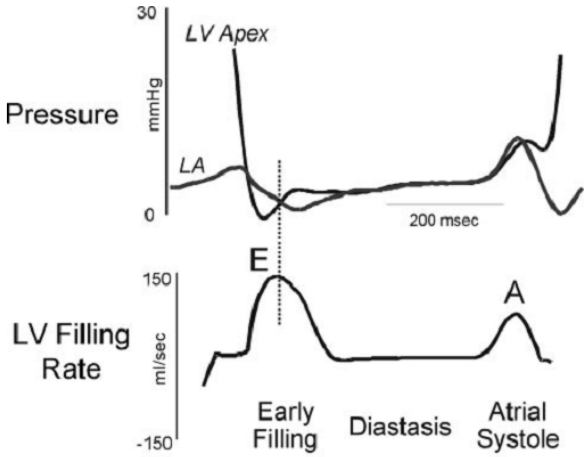
ESC guidelines Heart Failure Eur Heart J 2016;37:2129

ACE-I/ARB *IA/IB*	Betablockers *IA*	MRAs *IA*
Comorbidities *IC* *Diuretics IB*	HFpEF	Valsartan/saccubitril PARADIGM-HF *IB*
Diuretics *IB*	CRT *IA (LBBB)* *IIa (non-LBBB)*	ICD *IA (ischem)* *IB (non-ischem)*

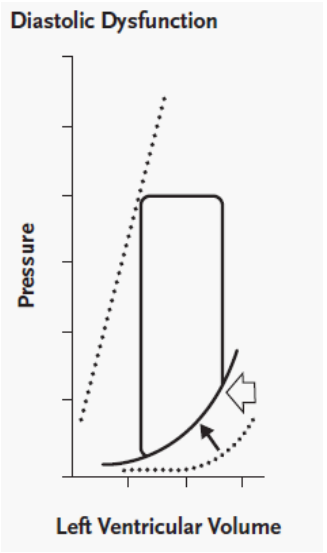
Diastolic LV (dys)function

Normal diastolic function

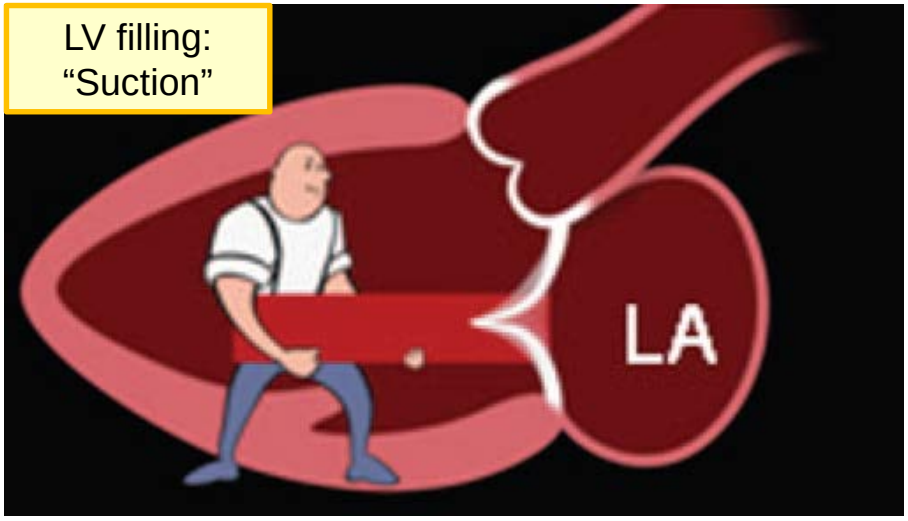




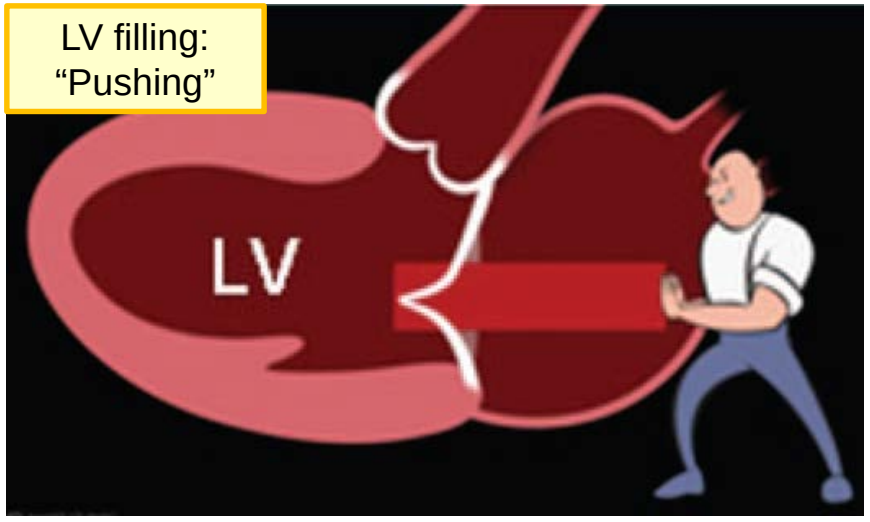
Diastolic dysfunction



LV filling: "Suction"



LV filling: "Pushing"



Nagueh SF et al. Eur J Echocardiogr 2009:10:165; Oh. Circulation 2009;120:802

HFpEF vs HFrEF: Comorbidities

	HFpEF; EF≥50% (n=40354)	HFrEF; EF<40% (n=55083)
Age (yrs)	78 (67-85)	70 (58-80)
Female, %	63	36
BMI, kg/m2	29 (24-35)	27 (23-32)
BMI >30 kg/m2, %	33	25
LVEF (%)	60 (55-63)	25 (20-30)
Hypertension, %	80	72
Diabetes mellitus (oral), %	24	22
Diabetes mellitus (insulin), %	22	18
Anemia, %	22	14
Chronic kidney disease, %	52	48
Pulmonary disease, %	33	27
Atrial fibrillation, %	34	28
Coronary artery disease, %	44	52
Peripheral vasc disease, %	12	11.5
CVA/TIA, %	15	13
ntproBNP (pg/ml)	3401 (1389-8046)	6847 (2888-14019)

Steinberg BA et al. Circulation 2012

How to diagnose HFpEF

Symptoms and signs of heart failure

Normal or mildly reduced LV systolic function
LVEF >50% and LVEDVI ≤ 97 ml/m^2

Evidence of abnormal LV relaxation, filling, diastolic distensibility and stiffness

Invasive hemodynamic measurements

mPCWP > 12 mmHg
Or
LVEDP > 16 mmHg
Or
τ > 48 ms
Or
b > 0.27

Tissue Doppler

E/e' > 15

15 > E/e'> 8

Biomarkers
NT-proBNP >220 pg/ml
Or
BNP > 200 pg/ml

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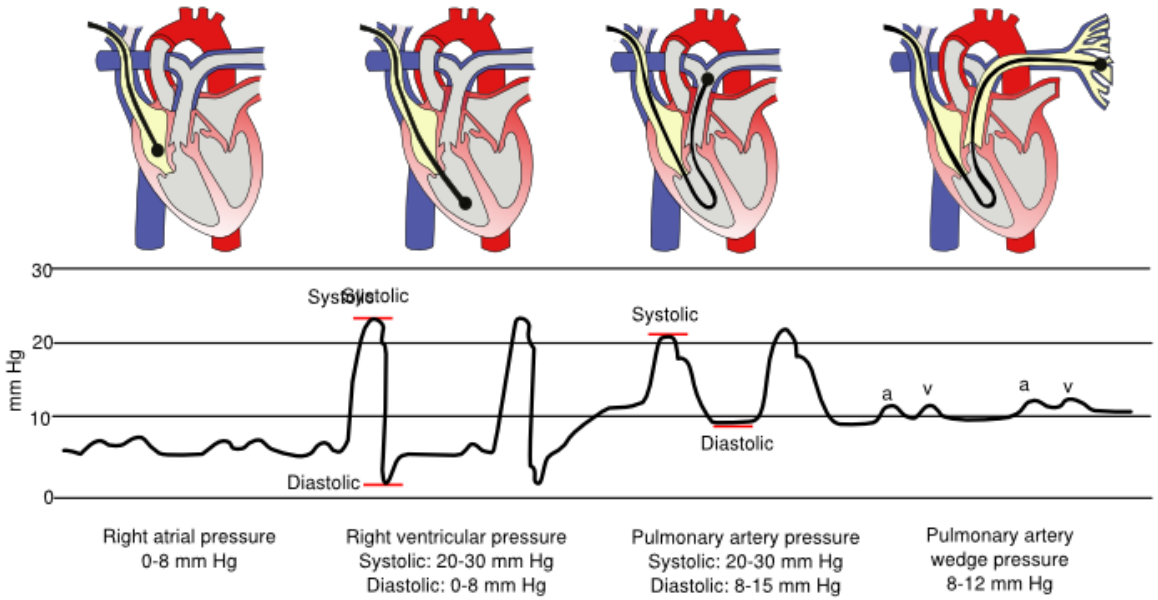
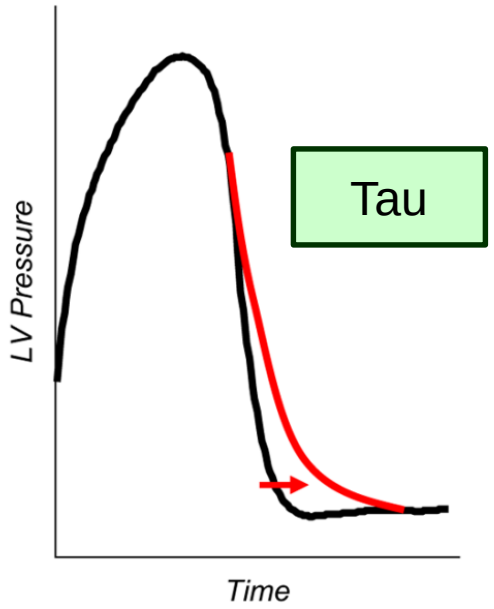
Echo blood flow Doppler
$E/A_{>50yr}$ <0.5 and $DT_{>50y}$ >280 ms
Or
Ard-Ad > 30 ms
Or
LAVI > 40 ml/m^2
Or
LVMI > 122 g/m^2 (women); 149 g/m^2 (men)
Or
Atrial fibrillation

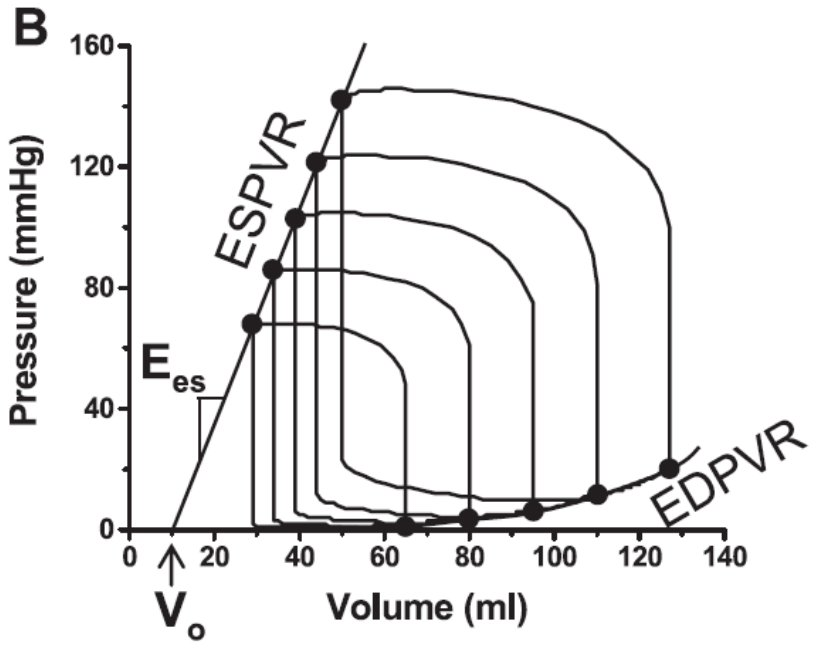
TD
E/e' > 8

HFpEF

Invasive diagnosis of HF





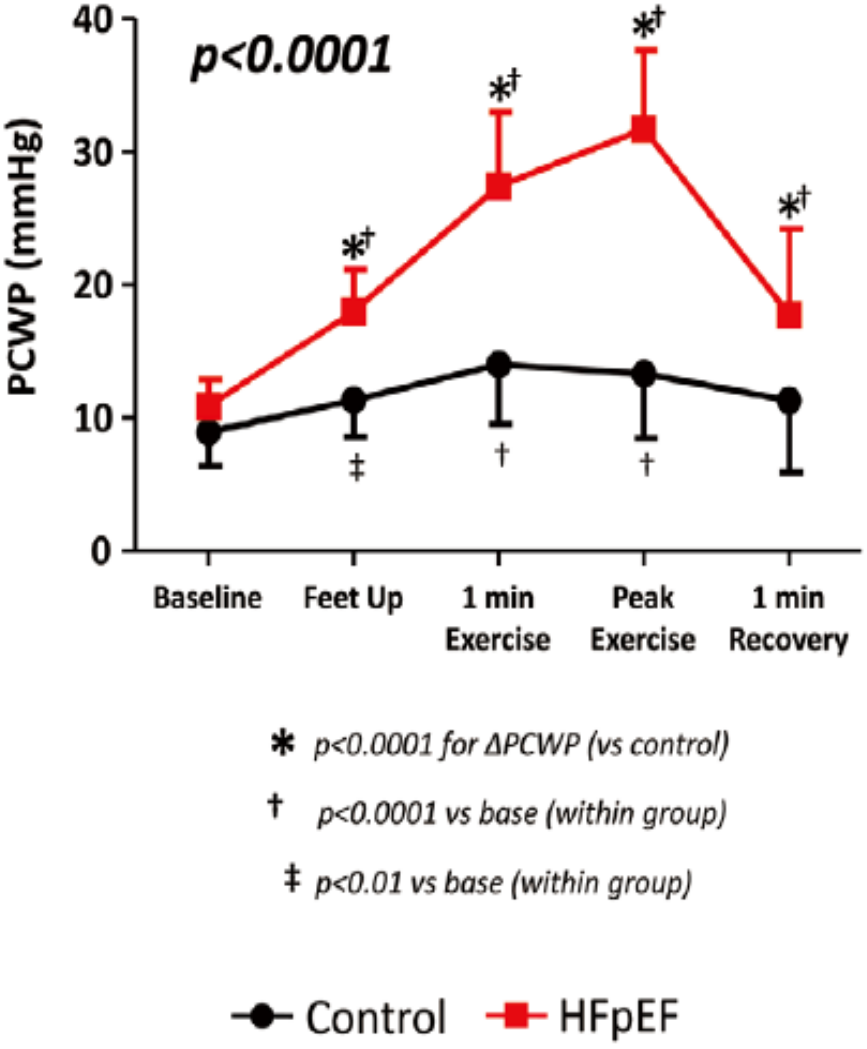


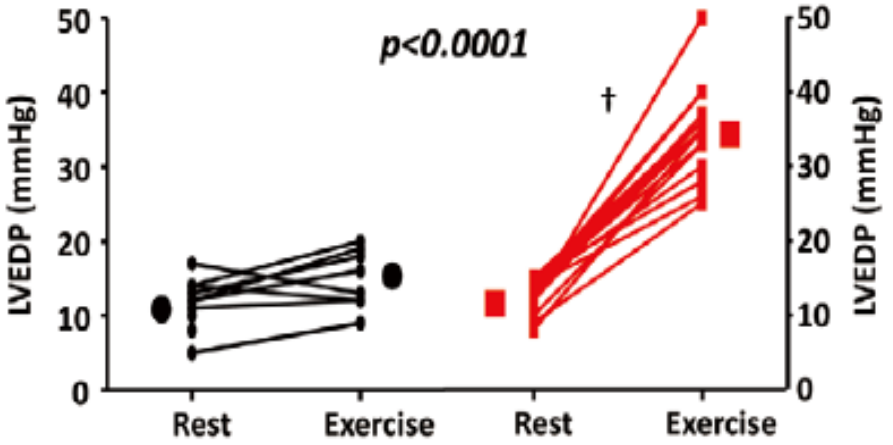
HFpEF: Impaired exercise tolerance

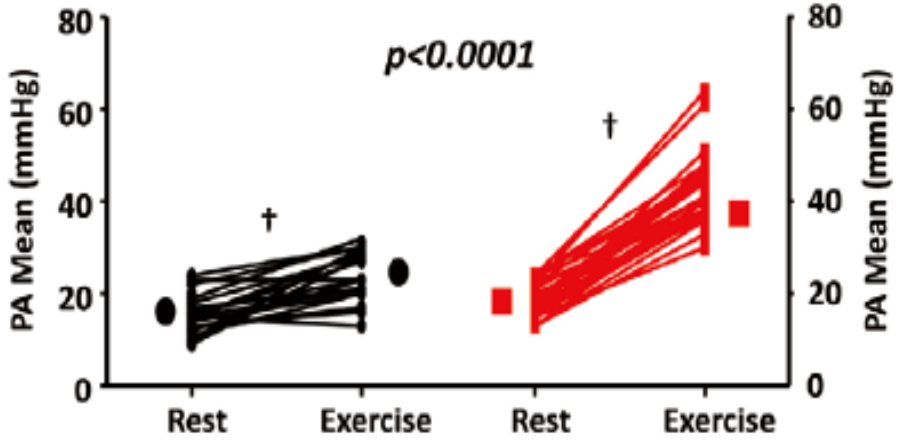
HFpEF signs/symptoms
Shortness of breath/edema
Fatigue
Chest pain
Peripheral muscle weakness

Right heart catheterization (RHC) with exercise in NYHA II-III HFpEF pts normal filling pressures rest but sharp ↑ with exercise

55 pts, EF≥50%,NYHA II-III, normal BNP, no CAD, normal HD rest; Ri/Le heart cath;







Borlaug BA, Circ J 2014;78:20

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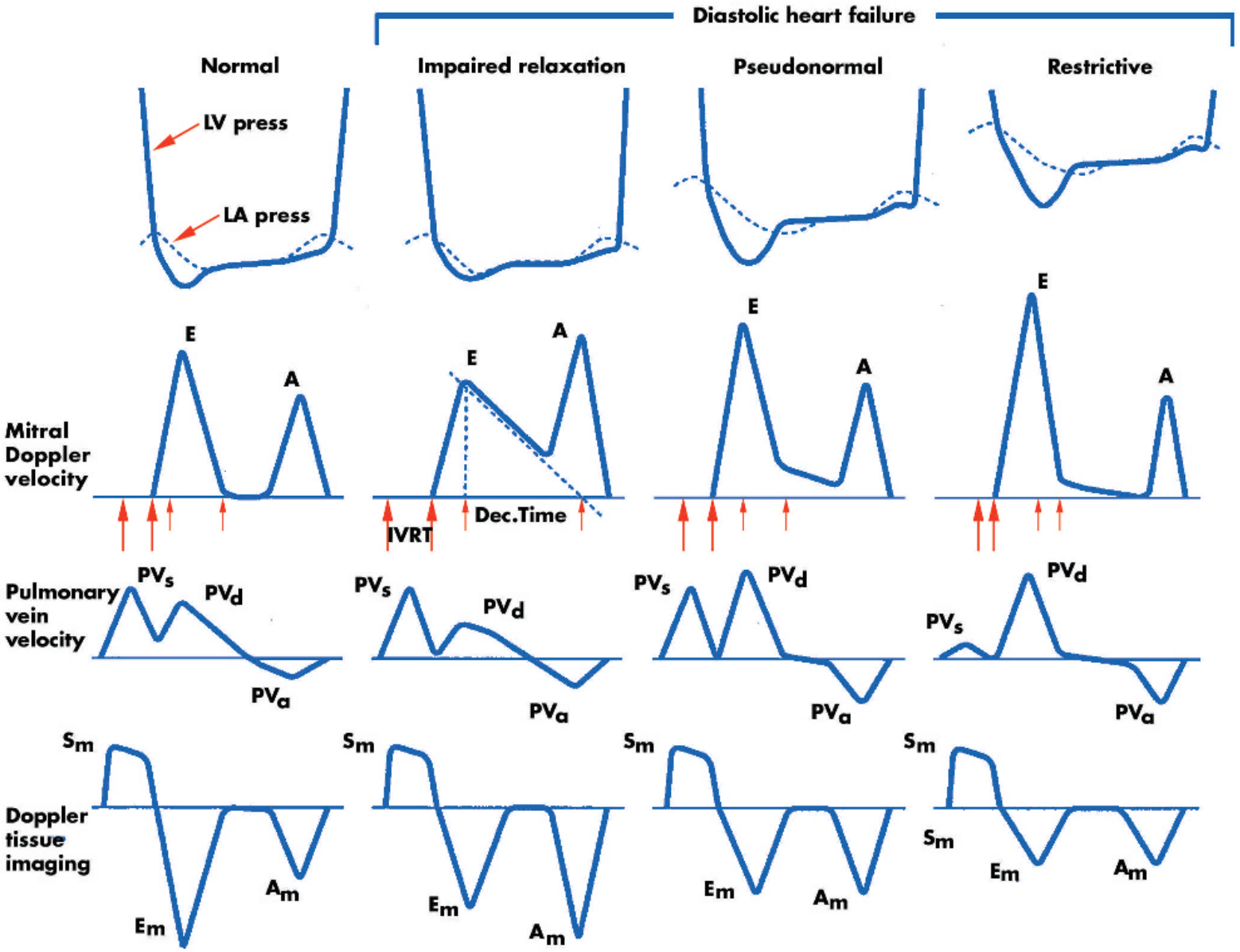
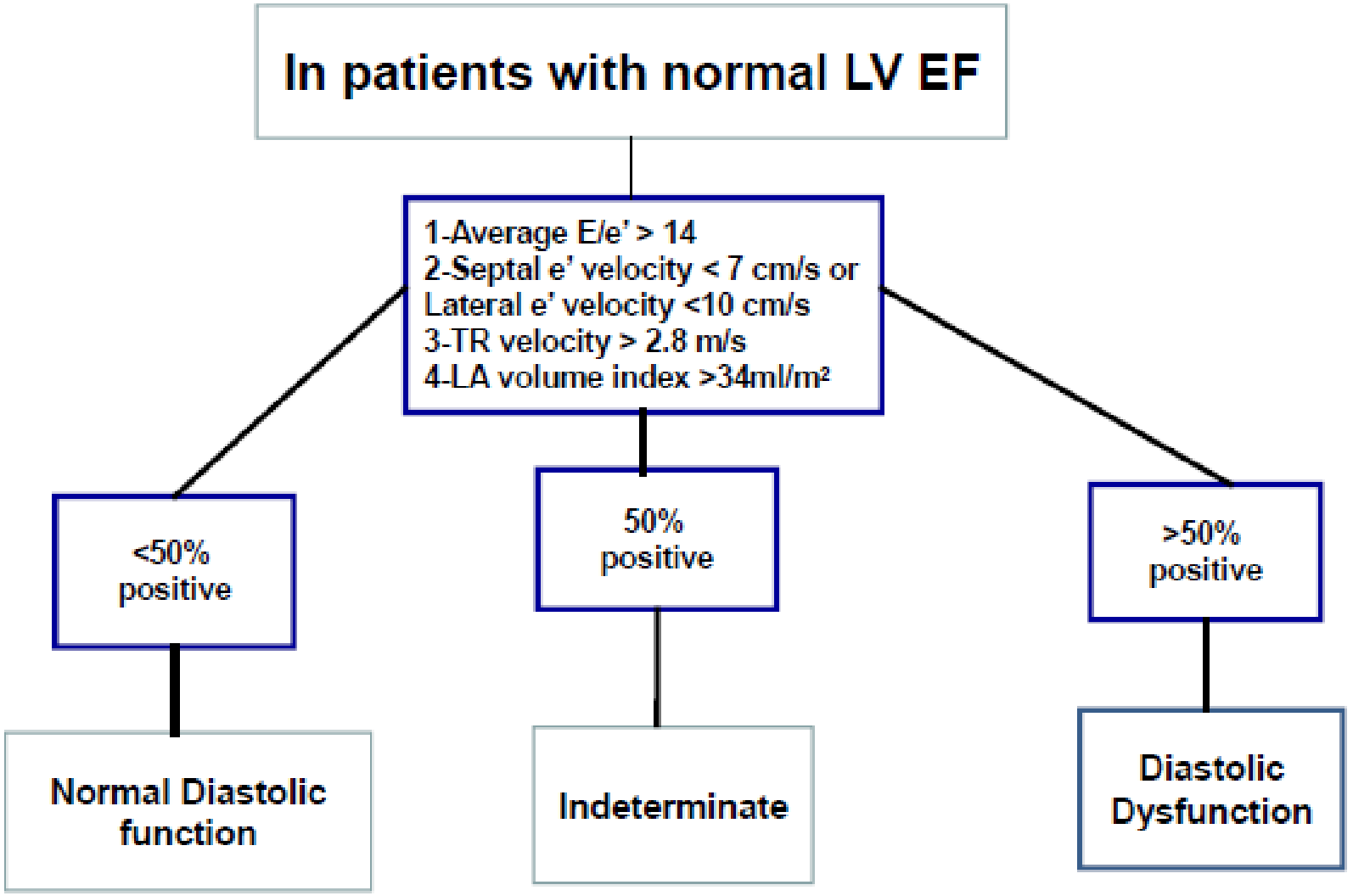
HFpEF

Grading LV diastolic dysfunction



Leite Moreira AF. Heart 2006:92:712

ASE/EACVI Recommendations for evaluation of diastolic function



Nagueh SF et al, J Am Soc Echocardiogr 2016;29:277

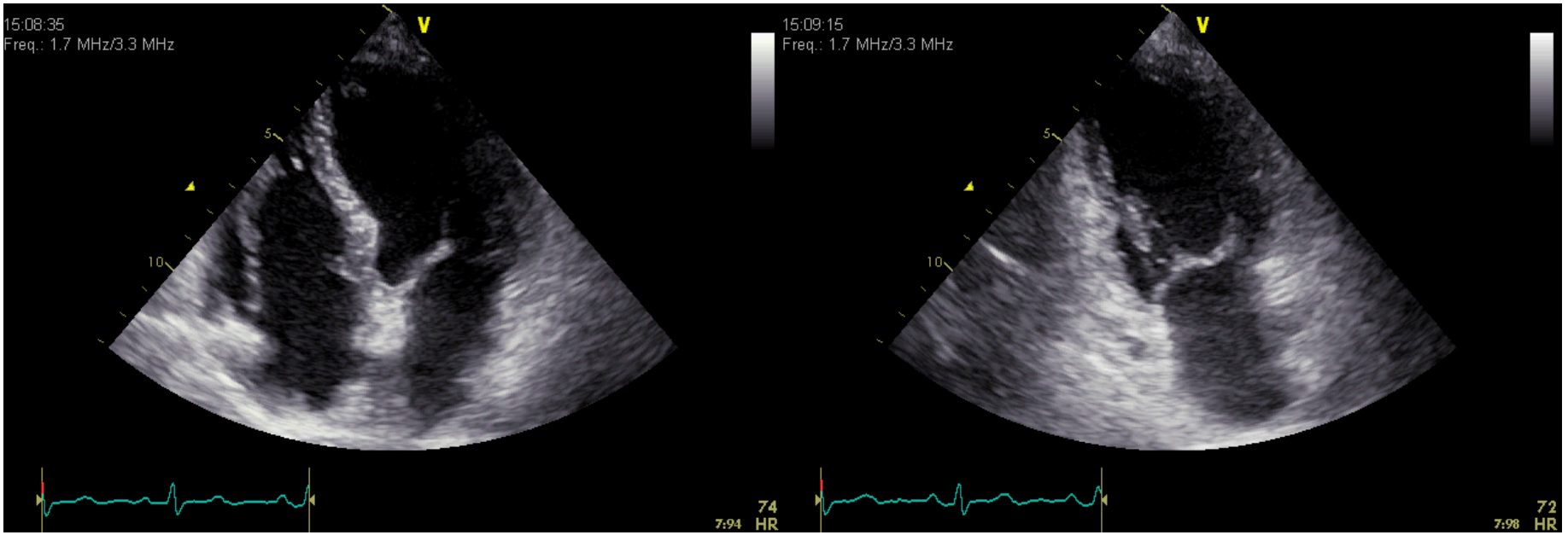
Case

Female, Age 77 yrs

Hx: Hypertension, mild astma, peripheral vascular disease
Rx: Ascal, candesartan, metoprolol, simvastatin

Exertional tiredness and shortness of breath
150/80 mmHg, Height 160 cm, Weight 55 kg,
BMI 21.5 kg/m2, waist circumference 90 cm.

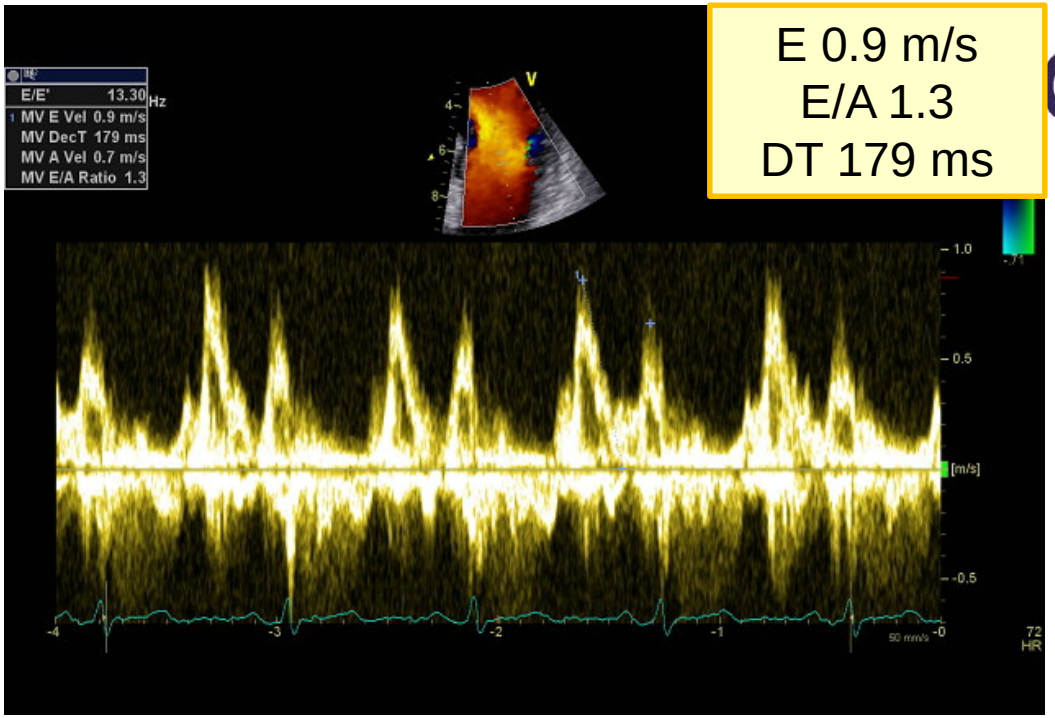
SPECT: no ischemia



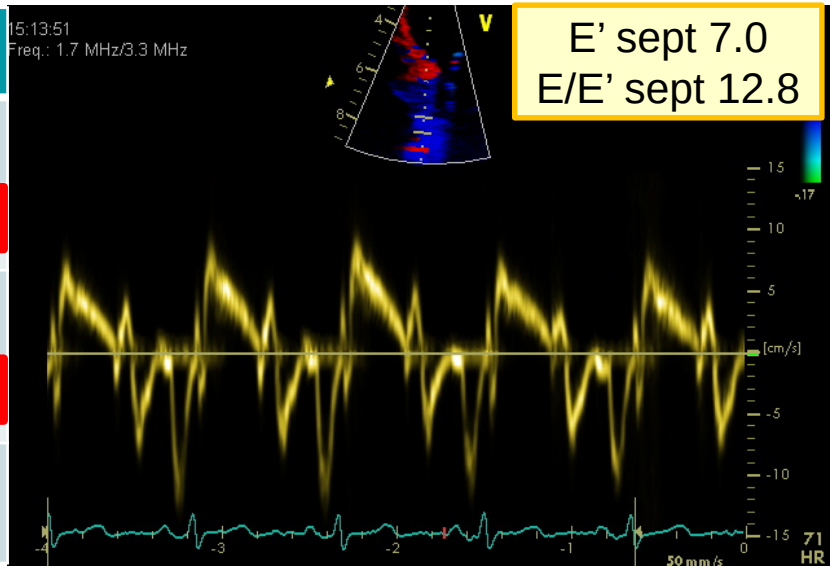
LVEF 64%

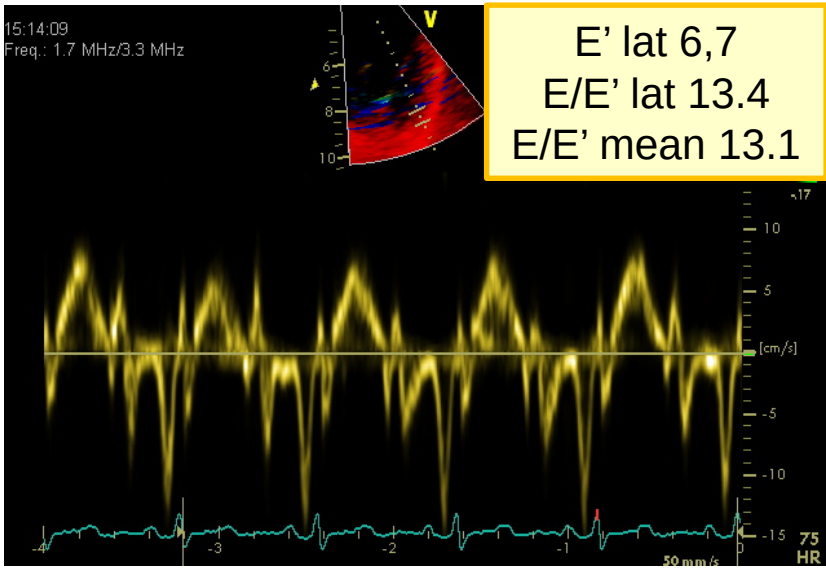
Recommendations diastolic fx
Nagueh SF Eur J Echocardiogr 2009

Grade 1	Grade 2	Grade 3
E/A <0.8	E/A 0.8-1.5	E/A ≥ 2
DT > 200 ms	DT 160-200 ms	DT < 160 ms



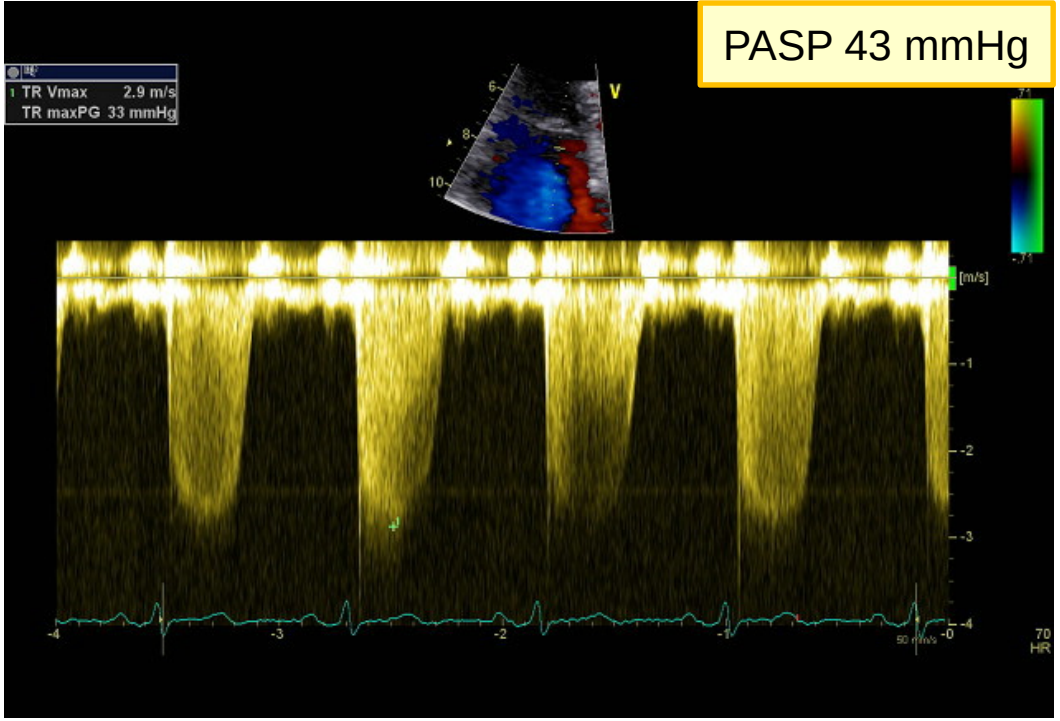
Tissue Doppler
E' sept < 7 cm/s
E' lat < 10 cm/s
E/E' sept > 15
E/E' lat >13
E/E' mean >14

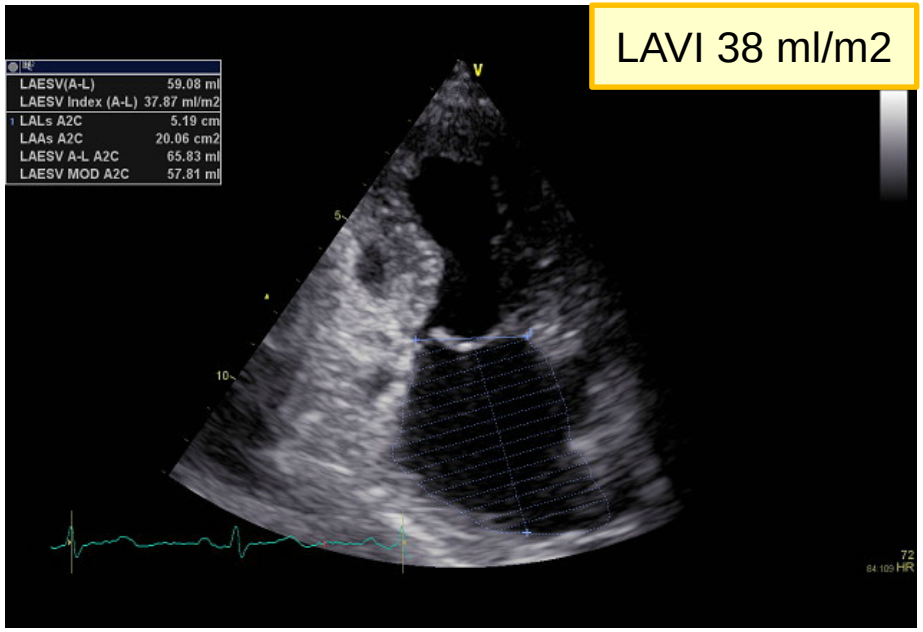


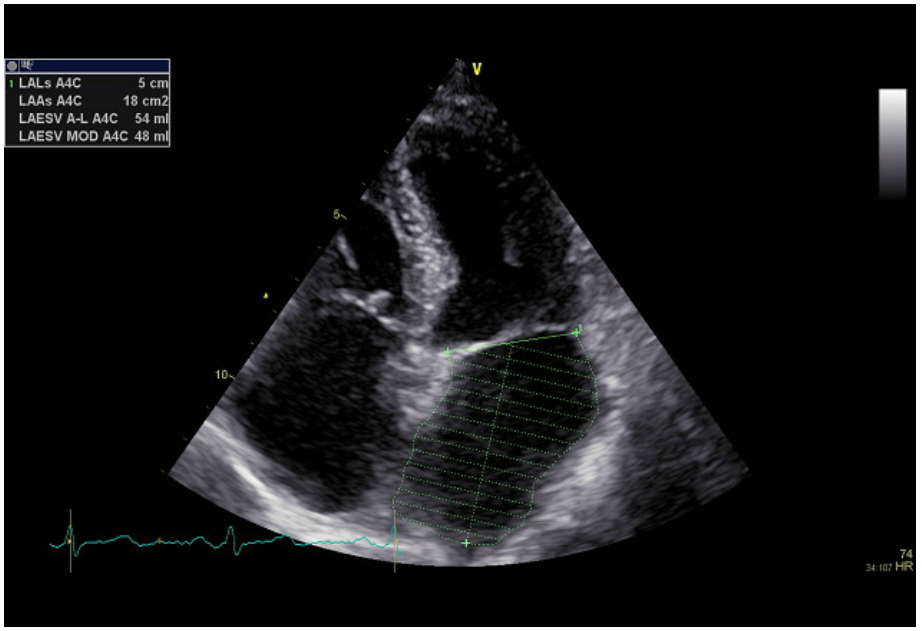


Nagueh SF et al. Eur Heart J Cardiovasc Imaging 2016,17:1327; Nagueh SF et al. Eur J Echocardiogr 2009;10:165

Recommendations
PASP > 35 mmHg
LAVI > 34 ml/m^2

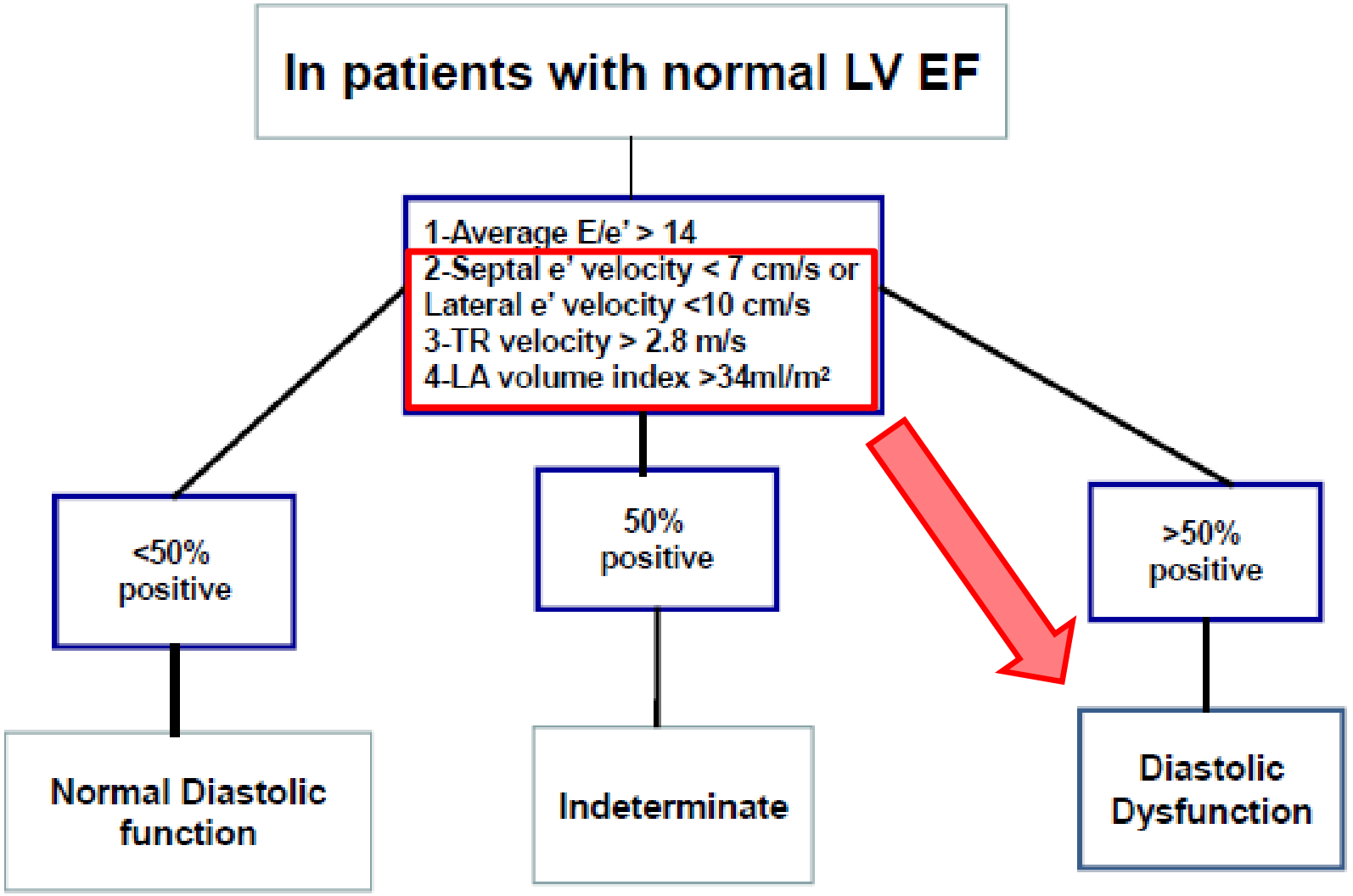






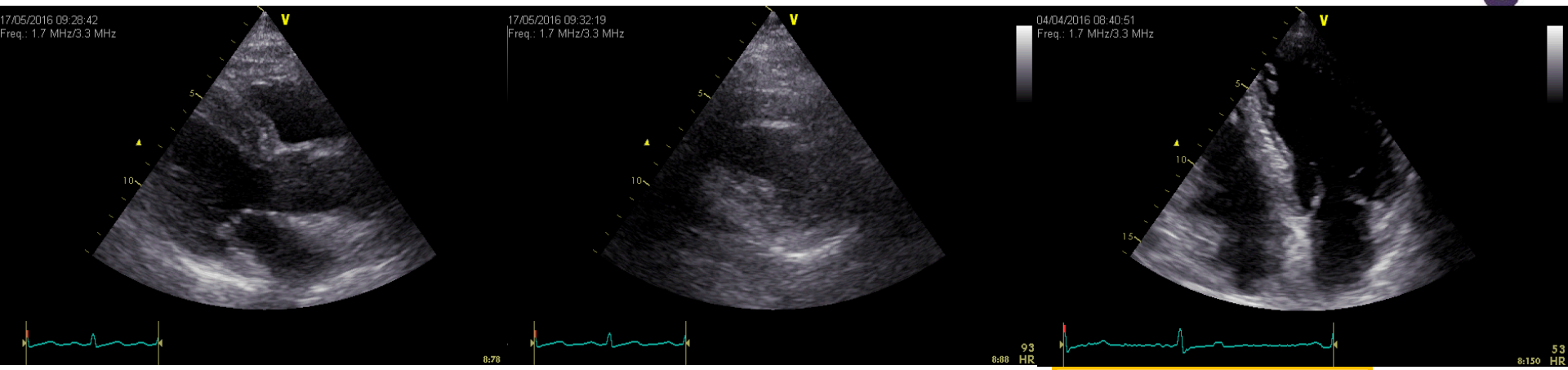
Nagueh SF et al. Eur Heart J Cardiovasc Imaging 2016,17:1327; Nagueh SF et al. Eur J Echocardiogr 2009;10:165

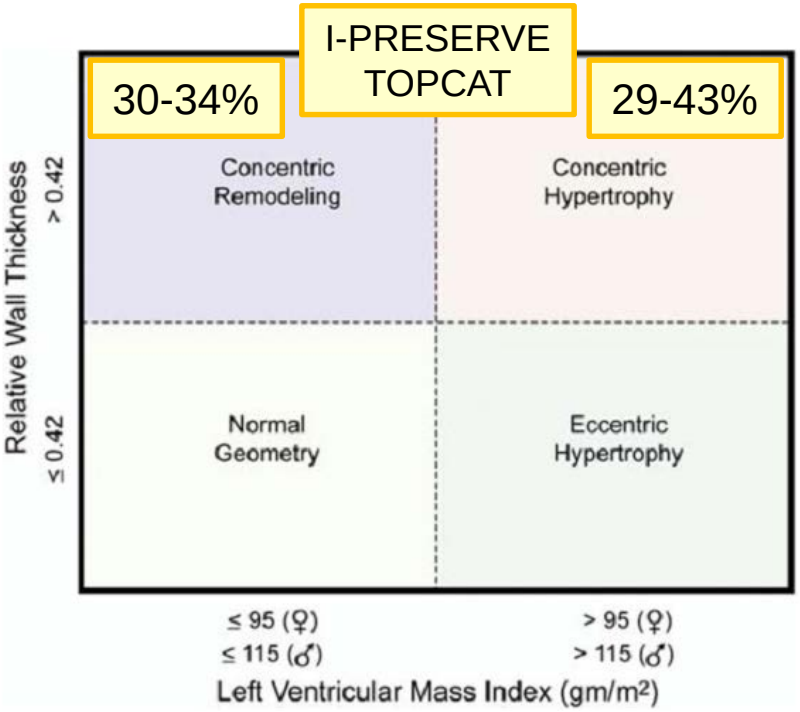
ASE/EACVI Recommendations for evaluation of diastolic function

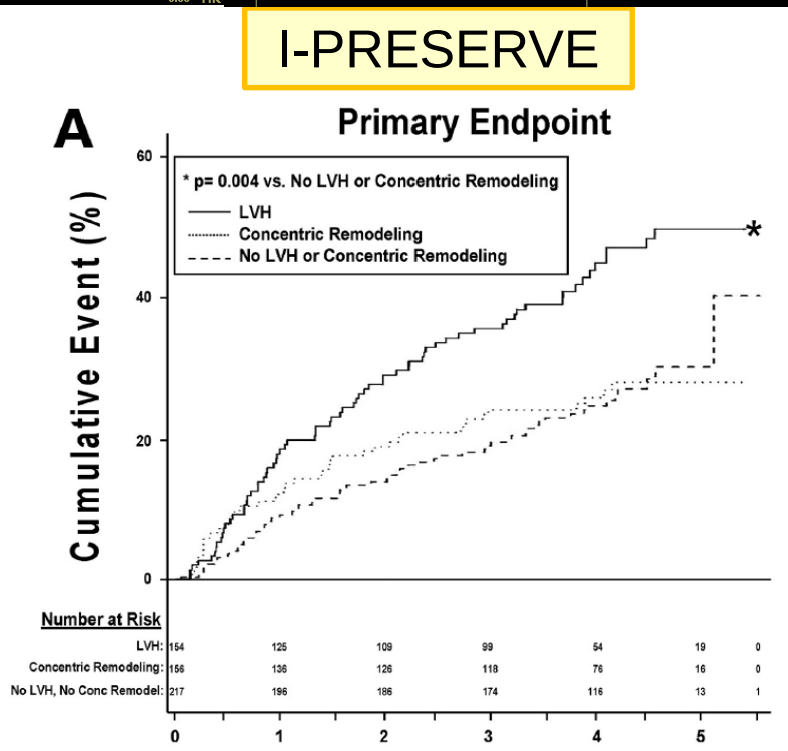


Nagueh SF et al, J Am Soc Echocardiogr 2016;29:277

Diagnosing HFpEF: Structural LV remodeling

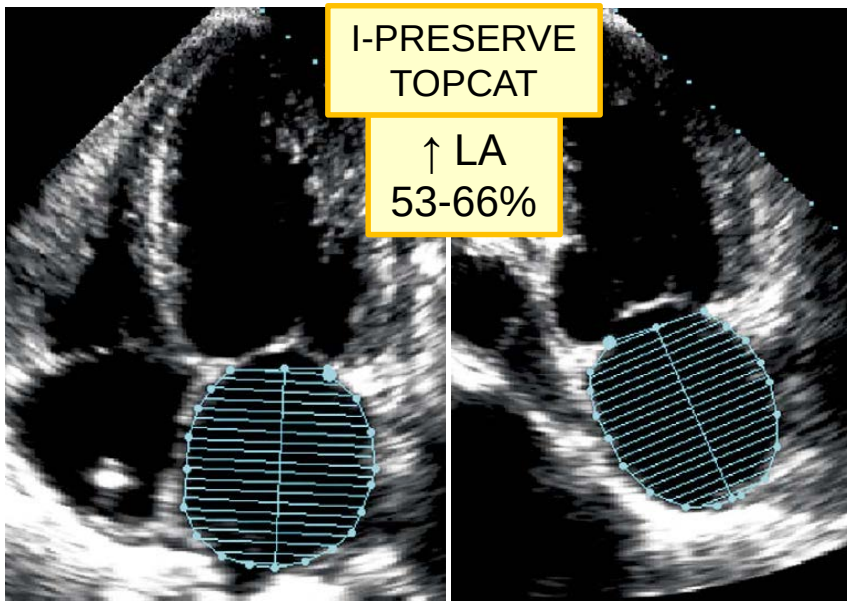


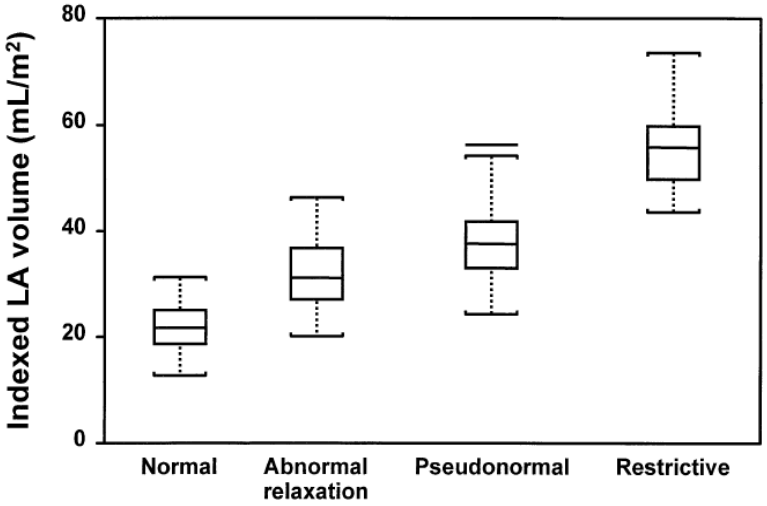


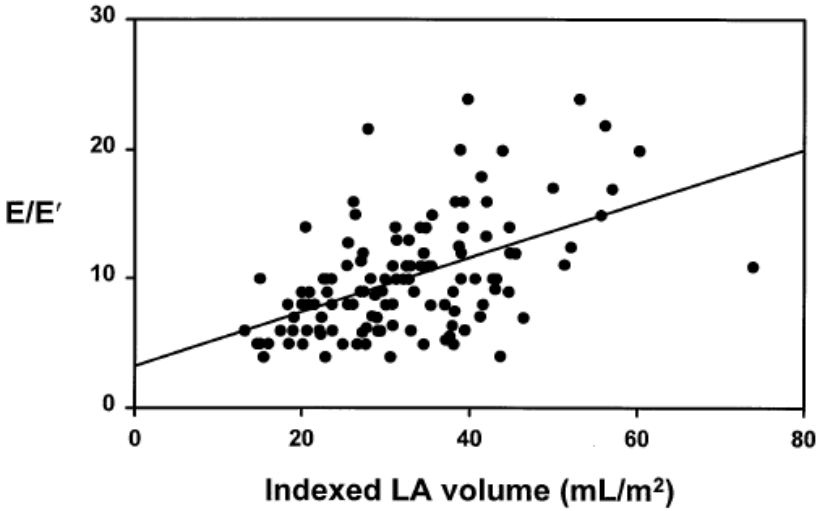


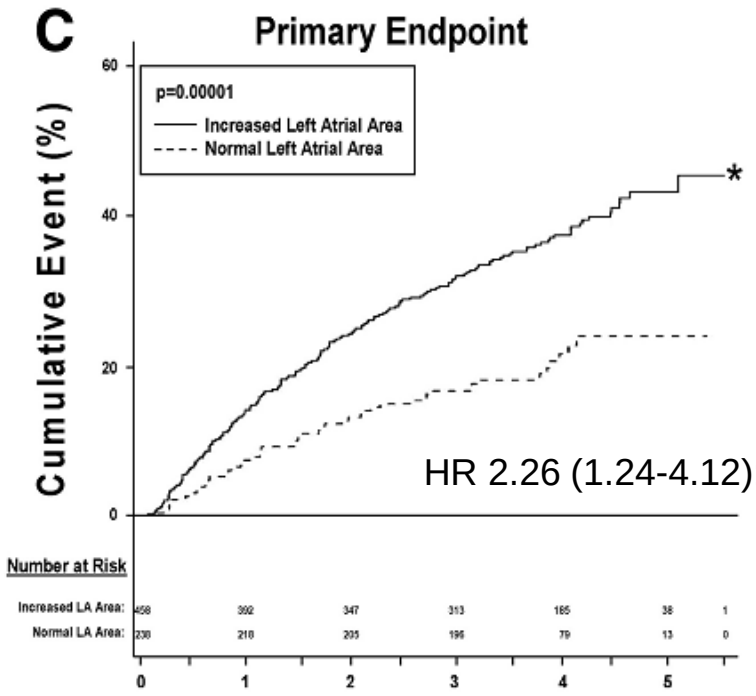
Konstam MA et al. JACC Img 2011;4:98; Zile MR, Circulation 2011; Shah AM, Circ Heart Fail 2014

LA dimensions and function: “HbA1c” of diastolic function





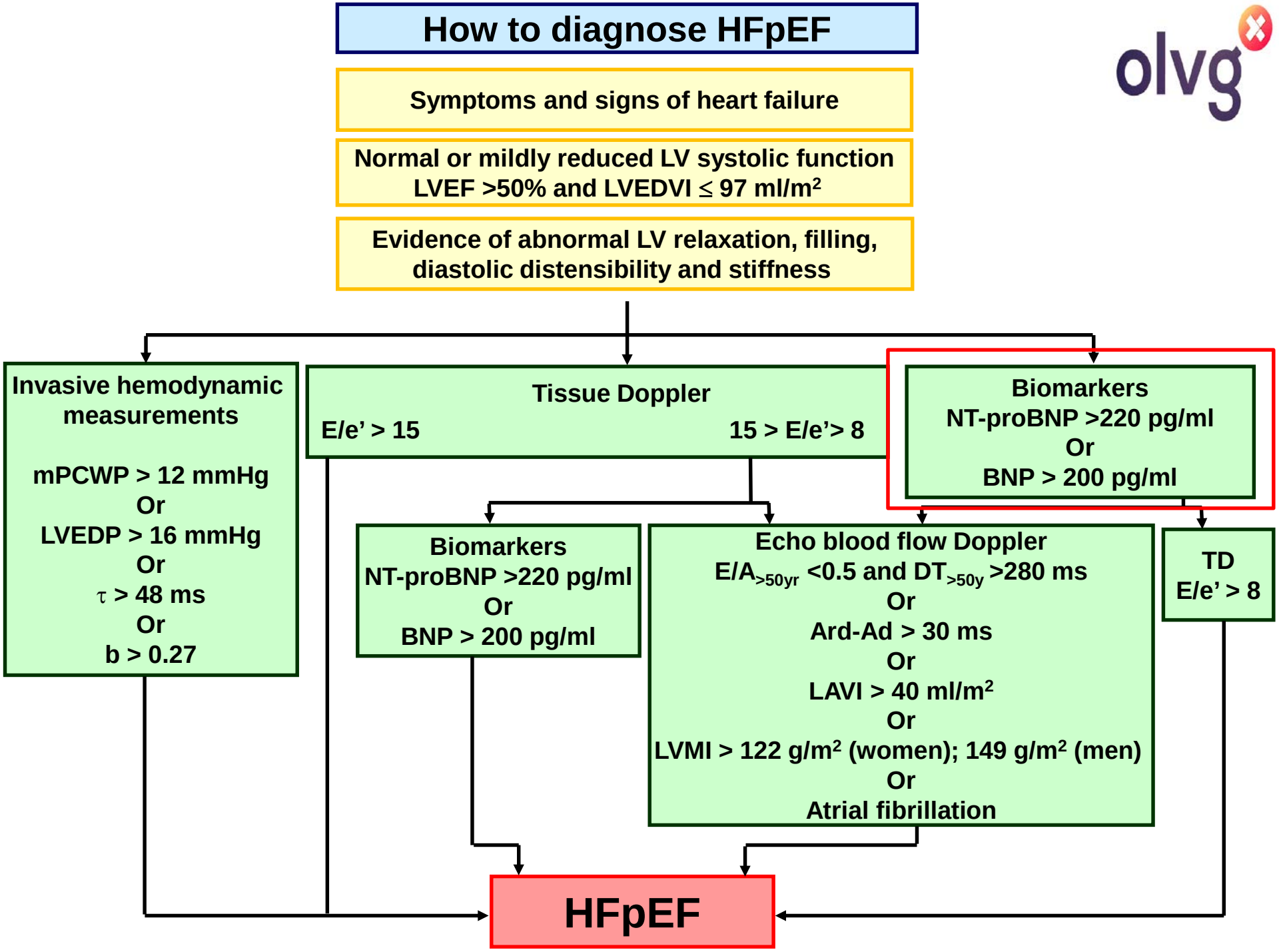




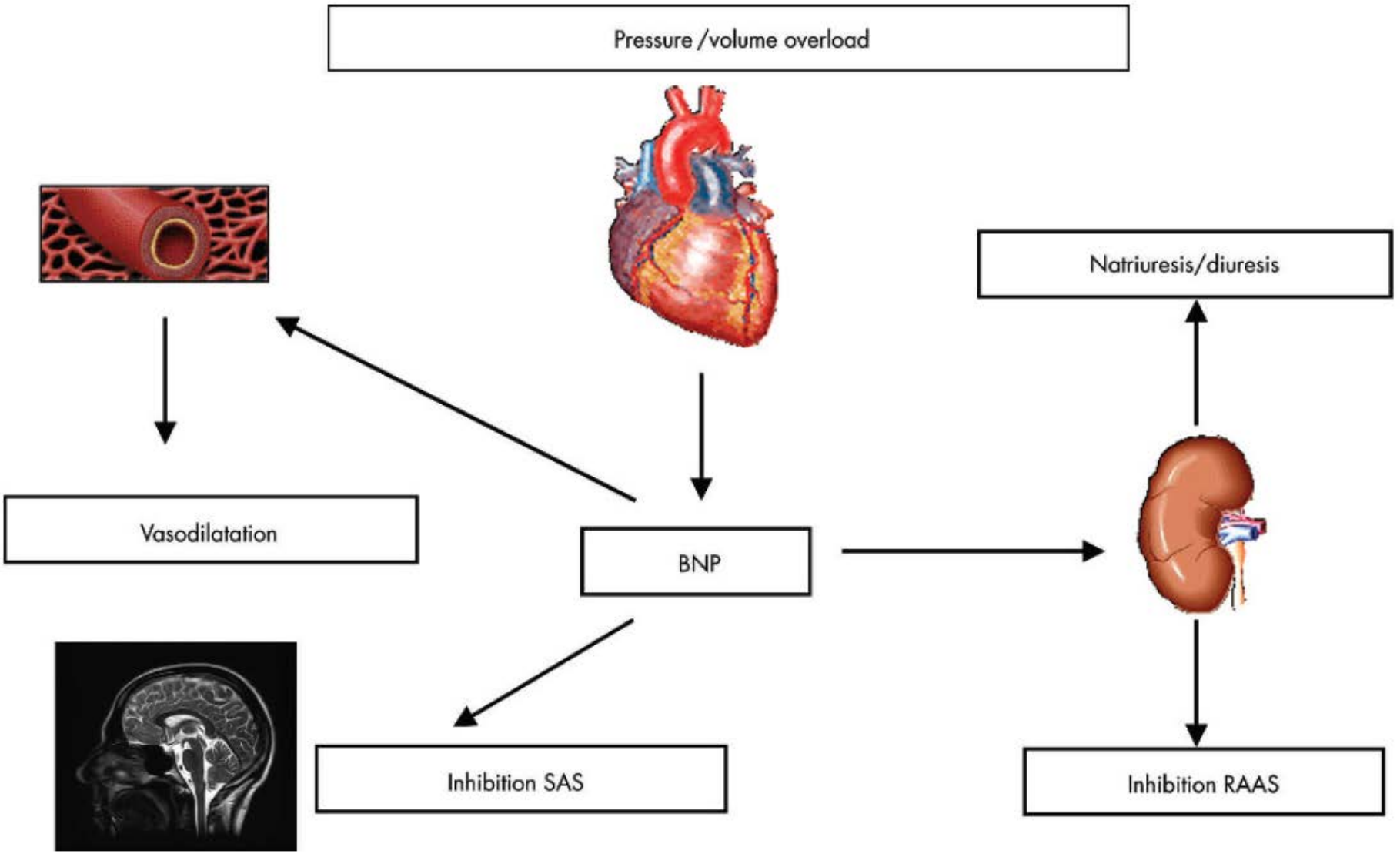
HR 2.26 (1.24-4.12); p=0.008

Lang R Eur J Echocardiogr 2009;7:79; Tsang Am J Cardiol 2002;90:1284; Zile MR Circulation 2011;124:2491

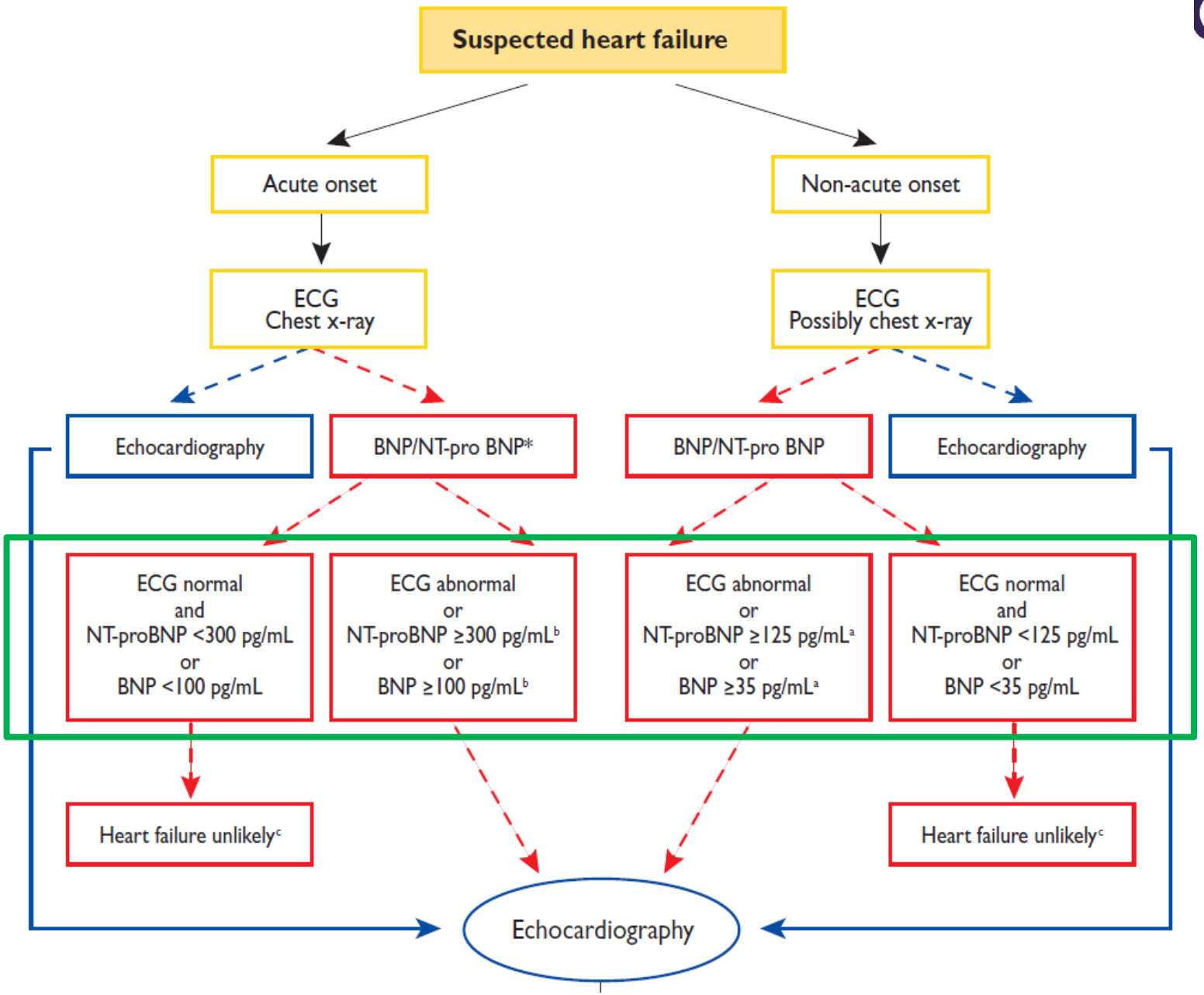
How to diagnose HFpEF



Biomarkers: Natriuretic peptides

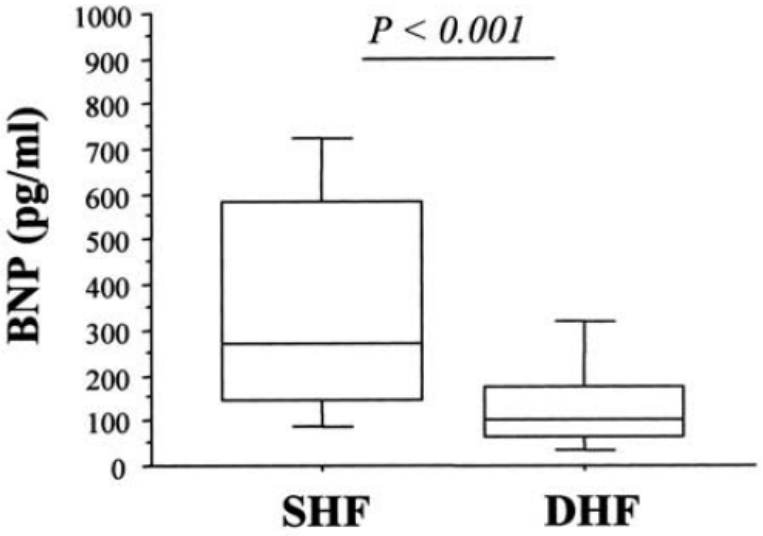


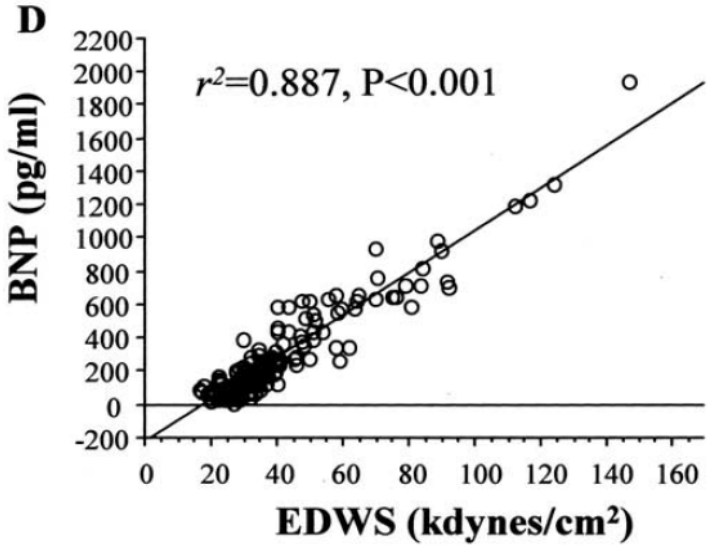
Diagnosis of HF

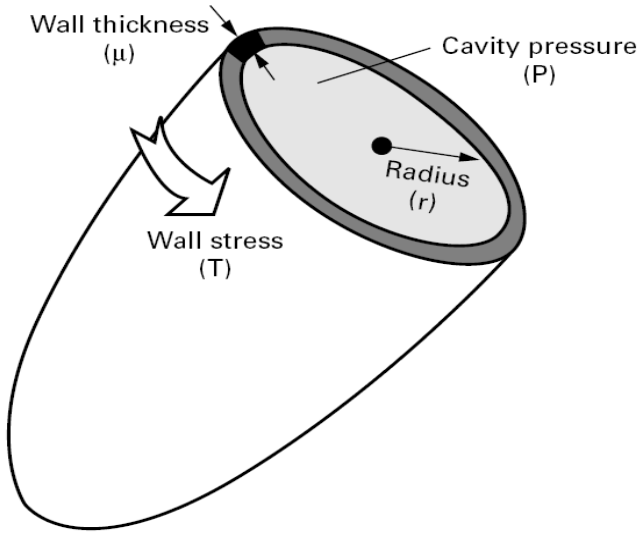


McMurray JJ et al. Eur Heart J. 2012;33:1787

(ntpro)BNP for pathophysiological stratification







The law of Laplace:

$$\text{Wall stress (T)} = \frac{[\text{cavity pressure (P)}] \times [\text{radius (r)}]}{2 \times [\text{wall thickness (}\mu\text{)}]}$$

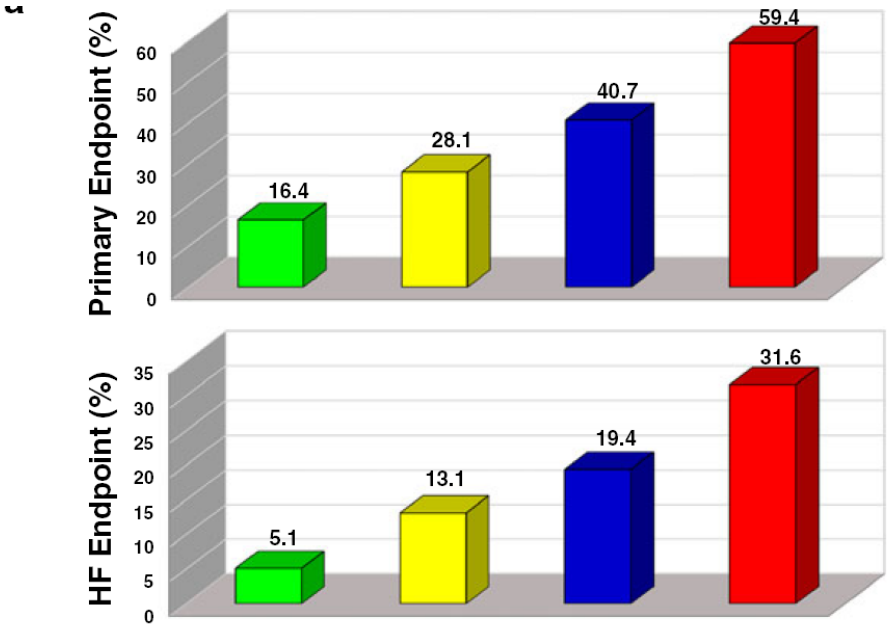
In addition to LV wall stress, (ntpro)BNP levels influenced by:

Gender
Renal function
Age
Body mass index

Iwanaga et al, JACC 2006;47:742; Shuai et al. Eur J HF 2011;7:737

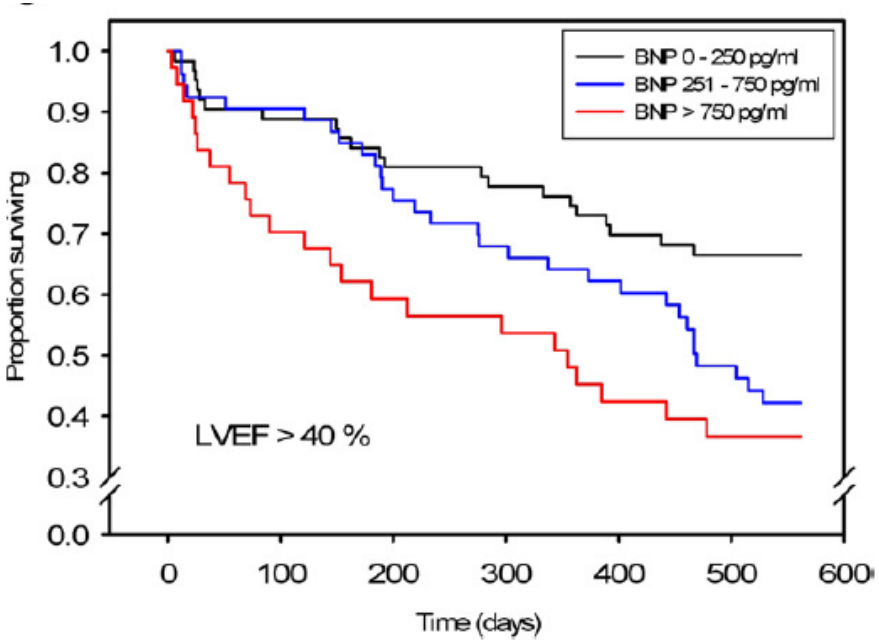
(ntpro)BNP correlates with worse outcome in HFpEF

I-Preserve



NT-pro BNP (pg/mL)	< 133	134 – 338	339 – 963	> 964
Median NT-pro BNP (pg/mL)	73	214	551	1720
# of Patients	870	867	873	870

Coach



Zile et al. J Cardiovasc Trans Res 2013;6:501

van Veldhuisen DJ et al, JACC 2013;61:1498

Causes of elevated natriuretic peptides

Cardiac	Heart failure Acute coronary syndromes Pulmonary embolism Myocarditis Left ventricular hypertrophy Hypertrophic or restrictive cardiomyopathy Valvular heart disease Congenital heart disease Atrial and ventricular tachyarrhythmias Heart contusion Cardioversion, ICD shock Surgical procedures involving the heart Pulmonary hypertension
Non-cardiac	Advanced age Ischaemic stroke Subarachnoid haemorrhage Renal dysfunction Liver dysfunction (mainly liver cirrhosis with ascites) Paraneoplastic syndrome Chronic obstructive pulmonary disease Severe infections (including pneumonia and sepsis) Severe burns Anaemia Severe metabolic and hormone abnormalities (e.g. thyrotoxicosis, diabetic ketosis)

Acute HF unlikely if

BNP < 100 pg/ml
Nt-proBNP <300 pg/ml

*High NPs
Not always HF!!!

Unexpectedly low NPs:

*Decomp endstage HF
*Flash pulm edema
*Right-sided HF

Diagnostic value of natriuretic peptides in outpatient HFpEF

	BNP ≤ 100 pg/ml (n=46)	BNP > 100 pg/ml (n=113)	P value
Age	62 ± 11	66 ± 12	0.038
Female, %	72	55	0.049
NYHA I II III IV	 4 (9%) 22 (48%) 20 (43%) 0	 8 (7%) 46 (41%) 57 (50%) 2 (2%)	0.63
Exertional dyspnea	43 (93%)	102 (90%)	0.52
Orthopnea	22 (48%)	54 (48%)	0.99
Nocturnal dyspnea	13 (28%)	33 (29%)	0.91
Crackles	13 (28%)	32 (28%)	0.99
Peripheral edema	30 (65%)	75 (66%)	0.89
BMI (kg/m2)	35 ± 9	31 ± 9	0.005
CKD	13 (28%)	75 (66%)	<0.001
Atrial fibrillation	5 (11%)	44 (39%)	0.001
Creatinine (mg/dl)	1.0 (0.8-1.2)	1.2 (1.0-1.8)	0.0001
Hb (g/dl)	12.2 ± 1.4	11.6 ± 1.9	0.0002
RA pressure (mmHg)	12 ± 5	15 ± 6	0.02
PASP (mmHg)	46 ± 11	55 ± 18	0.008
MPAP (mmHg)	33 ± 8	37 ± 11	0.045
PCWP (mmHg)	25 ± 8	27 ± 9	0.42
Cardiac index (L/min/m2)	3.1 ± 0.8	2.9 ± 0.9	0.28
PVR (dyne.s/cm5)	87 (64-112)	142 (90-229)	0.0005
SVR (dyne.s/cm5)	1227 ± 507	1292 ± 566	0.55

Outpatient HFpEF (n=159), EF>50%, prior HF hosp, PCWP >15 mmHg; NYHA II-III

Exertional dyspnea: 91%; orthopnea 48%; nocturnal dyspnea (29%); elevated CVP 72%; crackles 28%; periperhal edema 66%

29% of outpatient HFpEF patients had BNP <100 pg/ml!!!

Anjan VY et al. Am J Cardiol 2012;110:870

Figure I. Distribution of the HFpEF patients according to NT-proBNP value

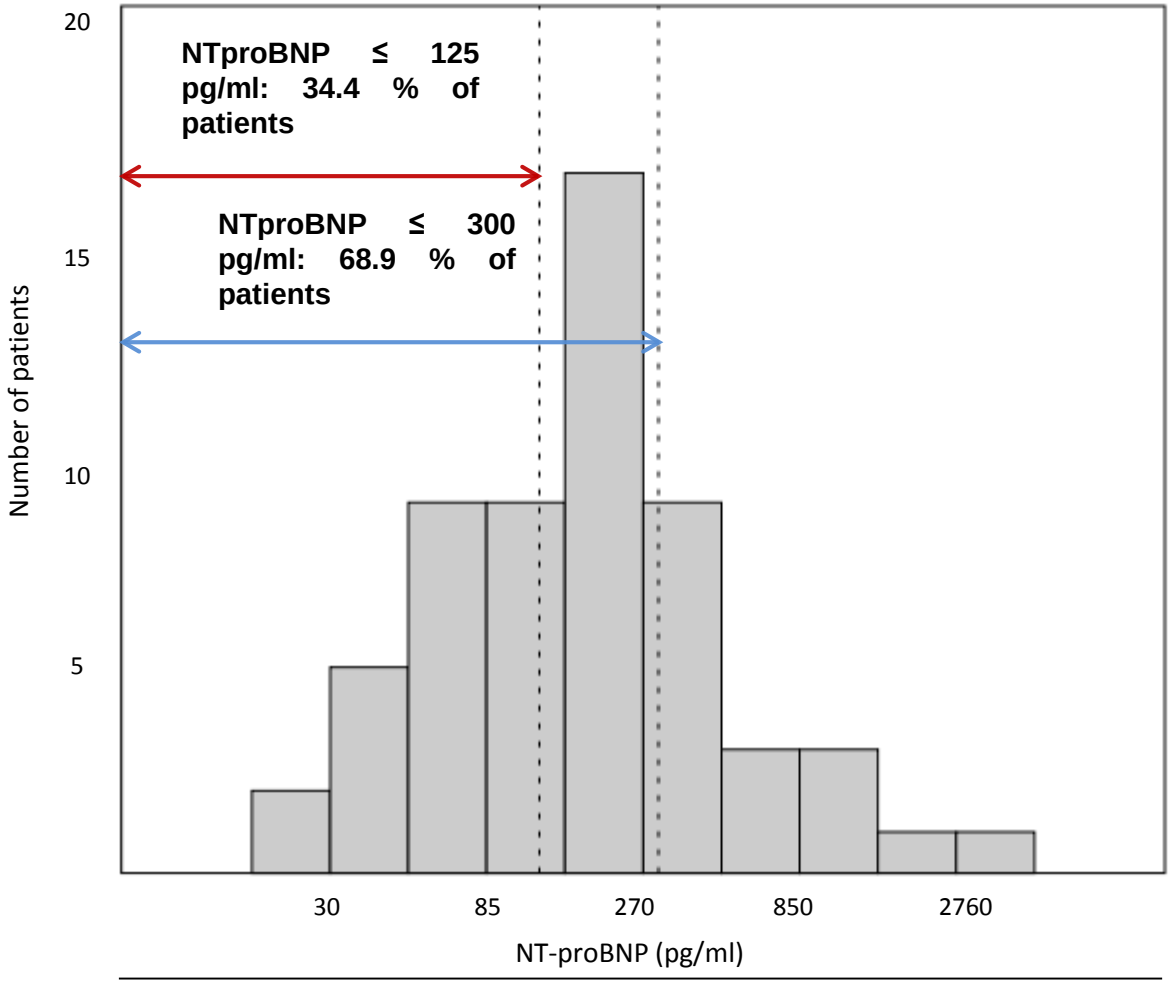
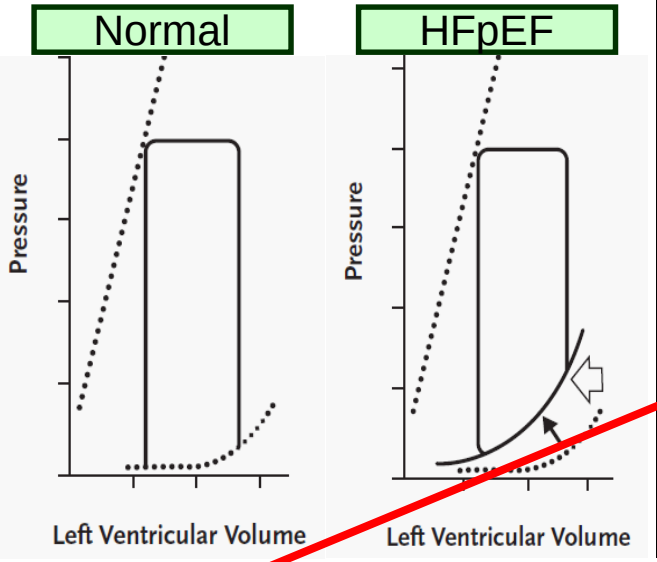
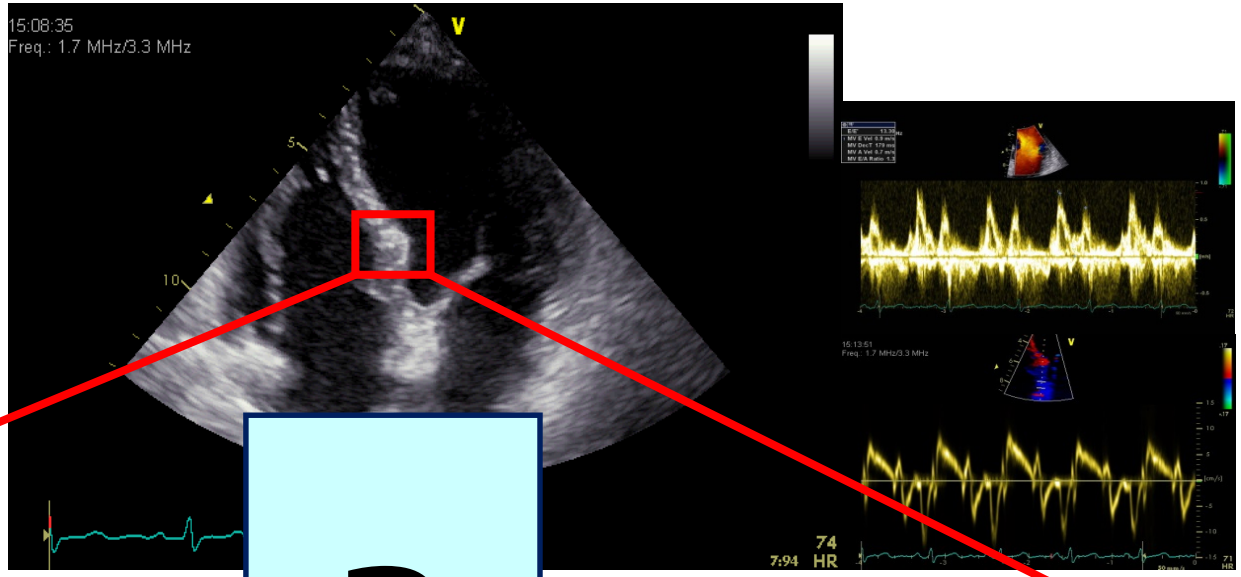


Figure 1. HFpEF patients are distributed according to the NT-proBNP value. NT-proBNP was log-transformed and then the correspondent values were used to build the graph.

HFpEF: Structural and functional myocardial abnormalities





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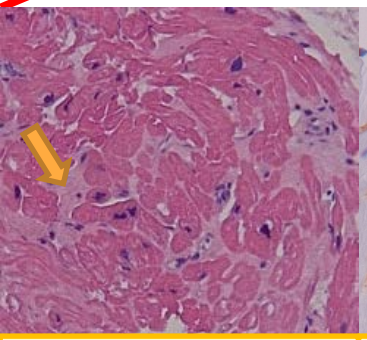
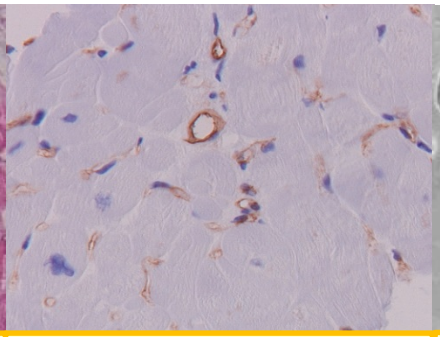
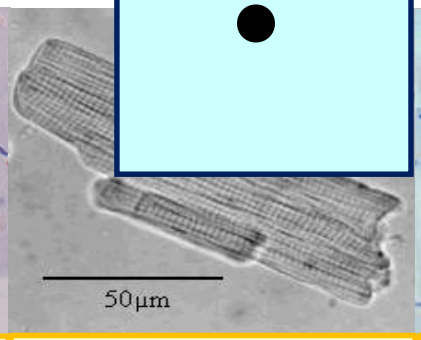
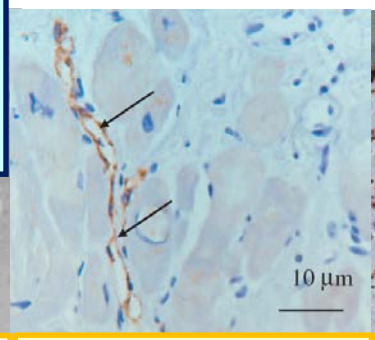
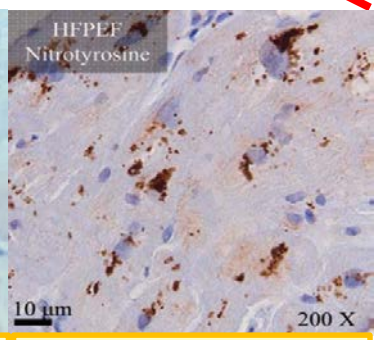










Fibrosis	↓ capillary density	↑ CM stifness	Inflammation	Oxidative stress

The “typical” HFpEF patient

HFpEF: Demographics and comorbidities	
Older age	Hypertension (75%)
Female gender	Renal insufficiency (26-53%)
Overweight/obesity (80%)	COPD (30%)
Metabolic syndrome (85%)	Anemia (35%)
Diabetes mellitus type II (30-40%)	OSAS (40%)

HFpEF: both a cardiometabolic and inflammatory disorder

olvg

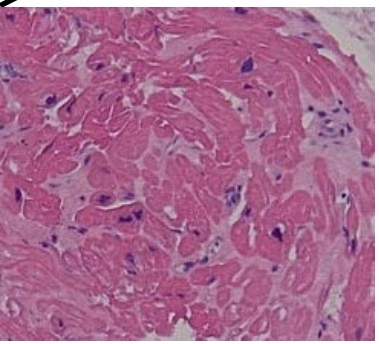
*Cardiometabolic risk factors
*Salt sensitive hypertension
*Chronic kidney disease
*Anemia/iron deficiency

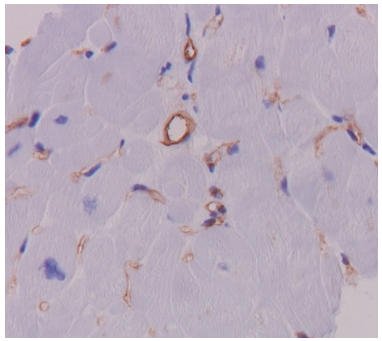
*↑ Age
*Female/Estrogen deficiency
*COPD
*OSAS

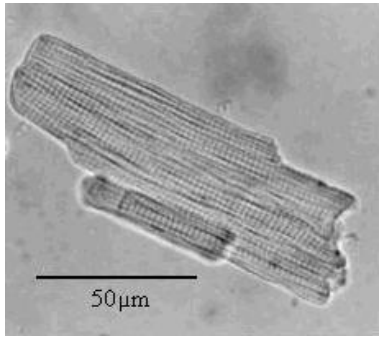
Inflammation

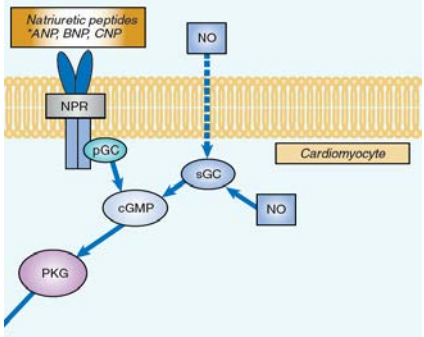
Oxidative stress

Endothelial dysfunction







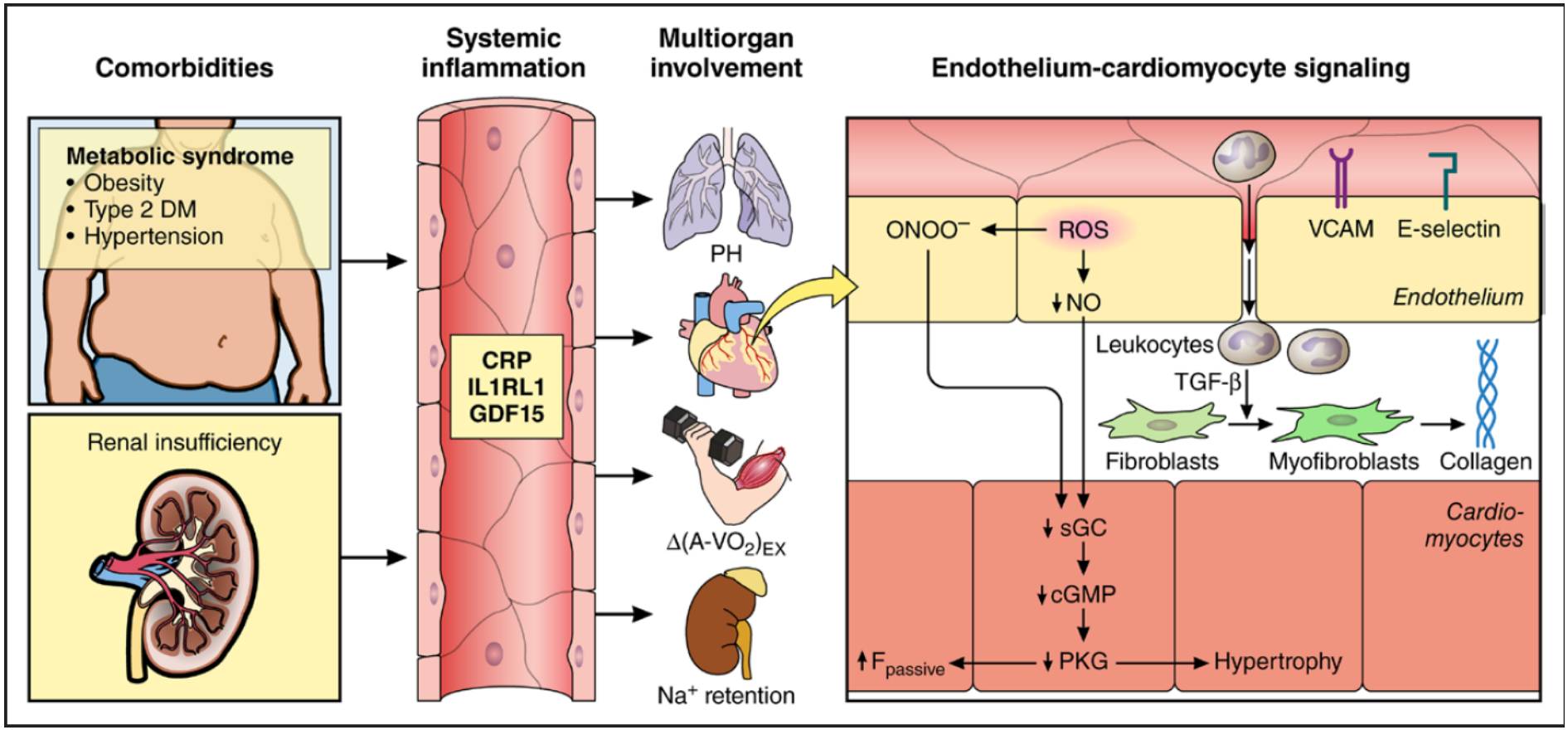


ECM	Microvasculature	Cardiomyocyte	Impaired signaling	Metabolic
Interstitial fibrosis	Microvascular dysfunction	Impaired relaxation	↓ NP/NO-cGMP-PKG	Mito dysfx
Perivascular fibrosis	Capillary rarefaction	↑ CM stiffness	Altered redox signaling	Glucose and lipotoxicity
Protein changes		CM hypertrophy	Neurohumoral activation	Impaired energetics
Cross-linking				

HFpEF: The novel paradigm

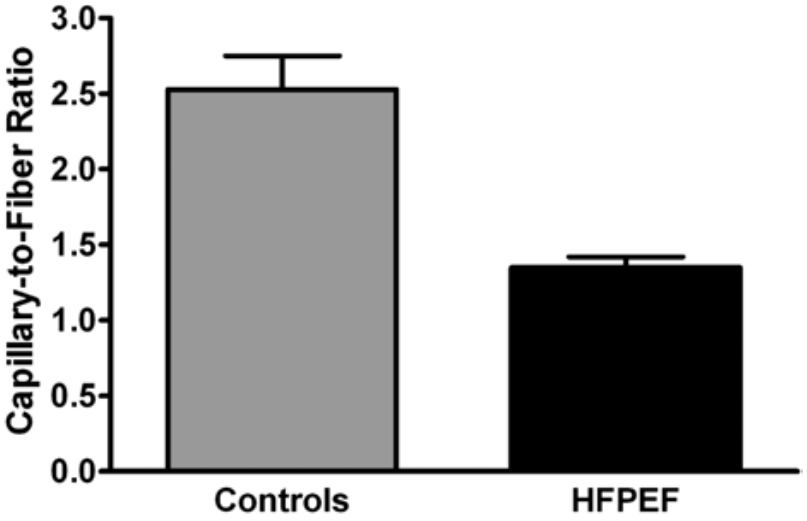
*Comorbidities drive myocardial remodeling and dysfunction through coronary microvascular endothelial inflammation and dysfunction → interstitial fibrosis and CM hypertrophy and stiffening through downregulation of myocardial cGMP-PKG signaling

*Because of systemic inflammation, other organs than the heart are also involved.

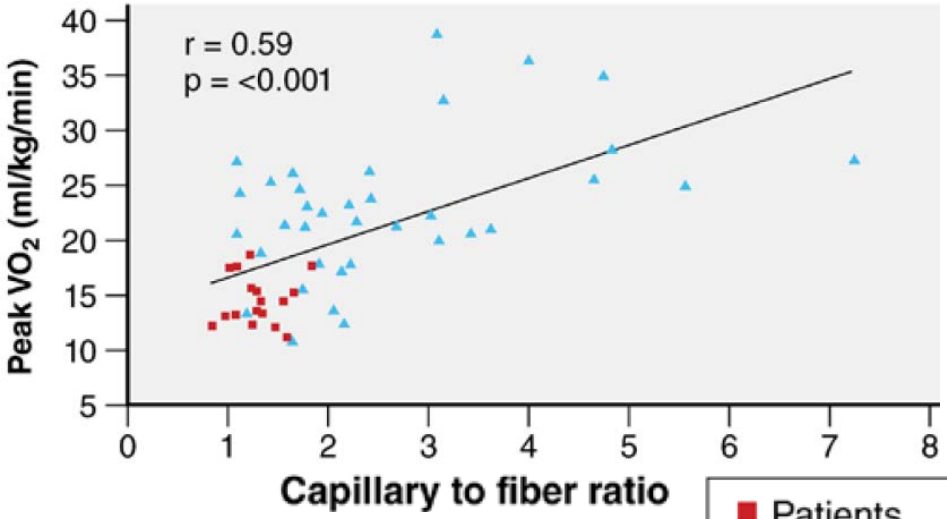


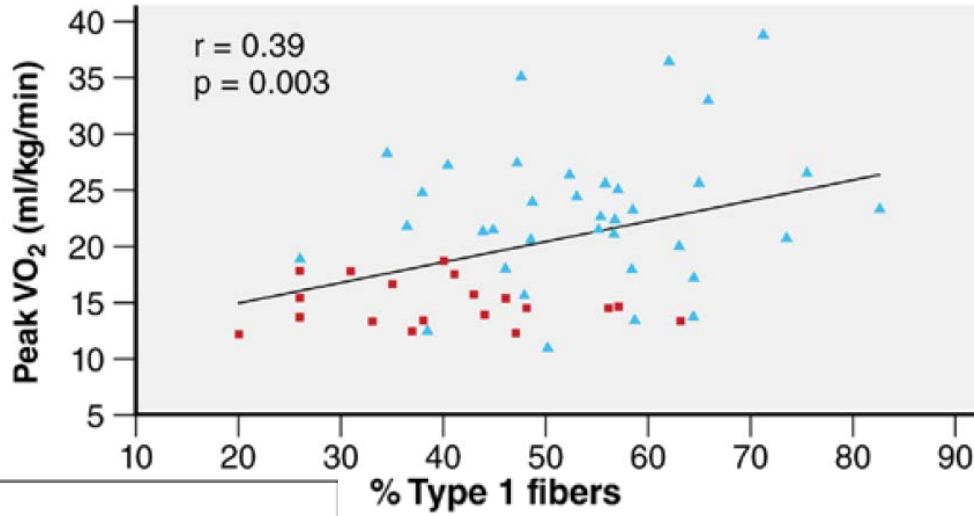
Shah S…van Heerebeek L, Paulus WJ. Circulation 2016;134:73

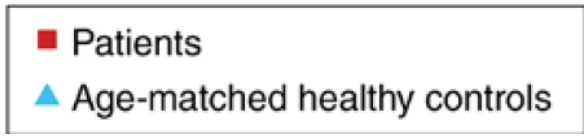
HFpEF: Skeletal muscle abnormalities



Kitzman DW et al. Circulation 2015;131:522

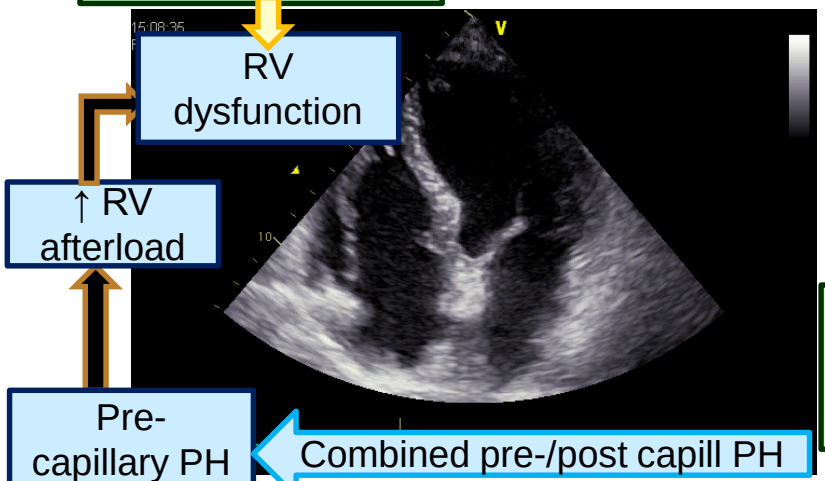






Upadhya B et al. Curr Heart Fail Rep 2015;12:205; Shah S et al. Circulation 2016;134:73

HFpEF: Pulmonary hypertension



Intrinsic myocardial disease

RV dysfunction

↑ RV afterload

Pre-capillary PH

Combined pre-/post capill PH

Longstanding post-capillary PH:
→Vasoconstriction/Inflammation
Pulmonary arterial remodeling

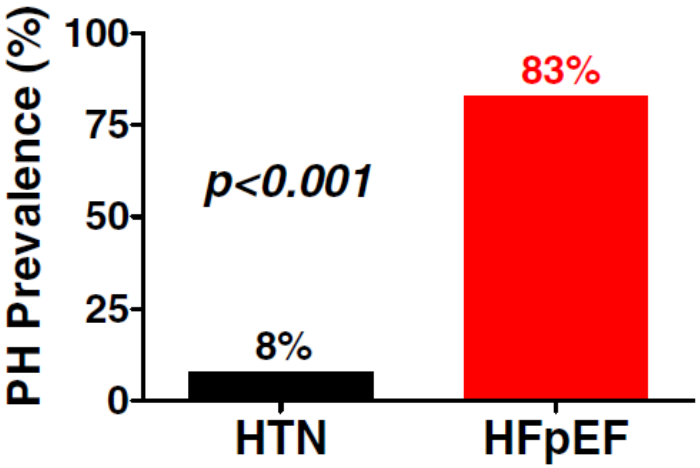
↑ LV stifness
Impaired relaxation
→ ↑ LVDP

↑ LA pressure

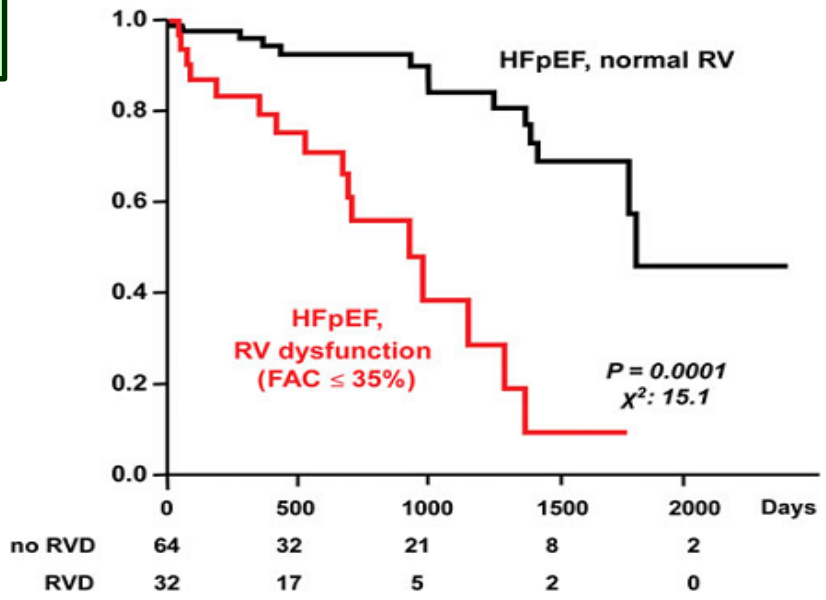
↑ PCWP

Passive backward pressure transmission

Post-capillary PH



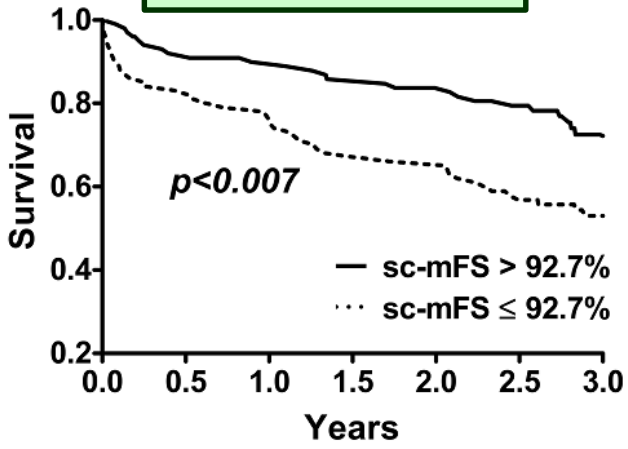
Lam CS et al. JACC 2009;53:1119



Melenovsky V et al. Eur Heart J 2014;35:3452

HFpEF: Phenotypic stratification

Systolic dysfunction

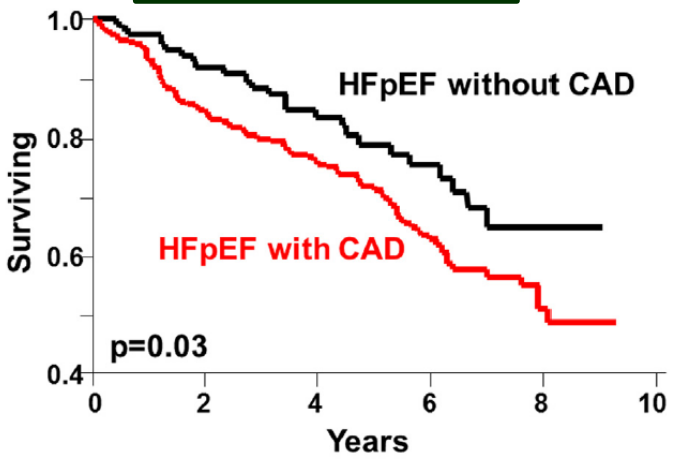


Number at risk

sc-mFS > 92.7%	100	91	87	83	79	70	42
sc-mFS ≤ 92.7%	100	83	76	68	65	54	36

Borlaug, JACC 2009;54:410

Coronary disease

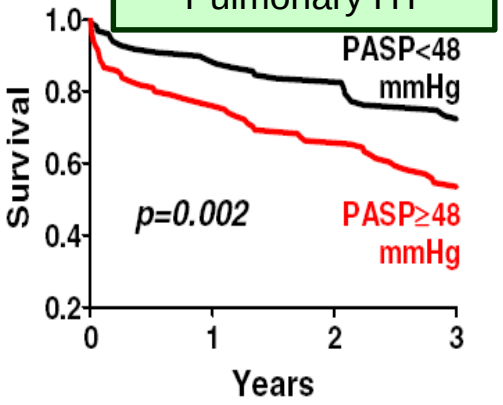


Number remaining

CAD (-)	121	90	60	34	14
CAD (+)	255	193	129	83	23

Hwang, JACC 2014;63:2817

Pulmonary HT

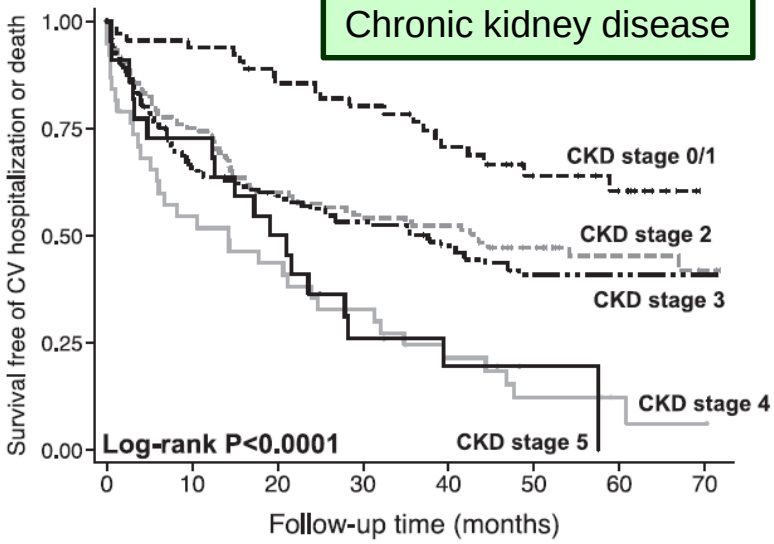


Number remaining

PASP<48 mmHg	98	86	80	44
PASP≥48 mmHg	105	78	67	38

Lam, JACC 2009;53:1119

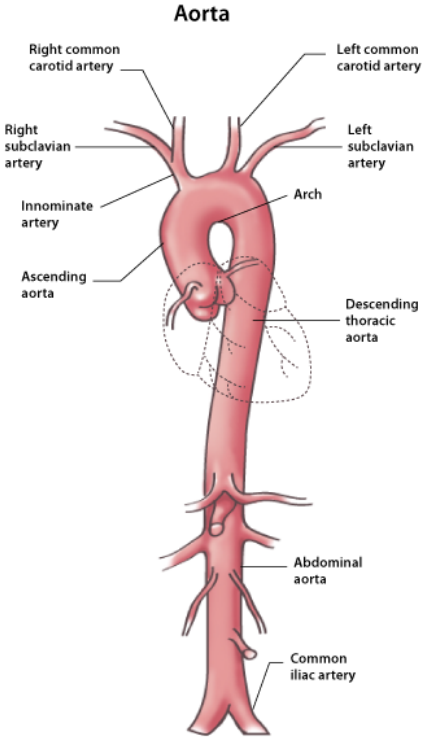
Chronic kidney disease

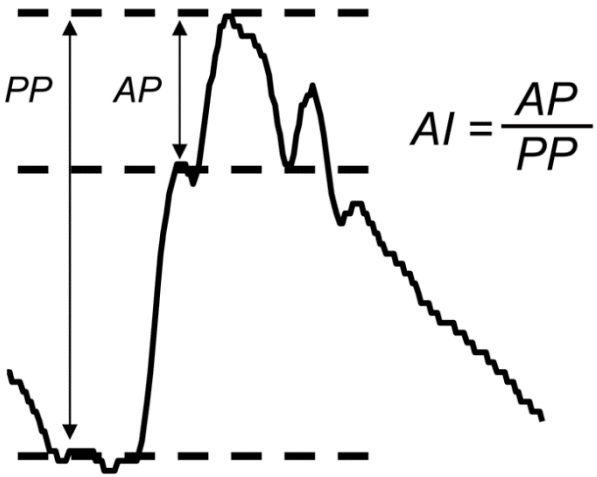


Unger ED et al, Eur J Heart Fail 2016;18:103

Treatment of HFpEF

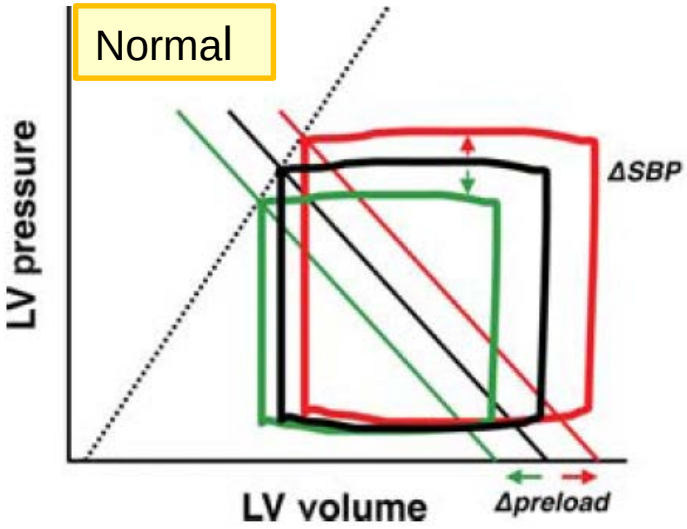
HFpEF: increased arterial stiffness

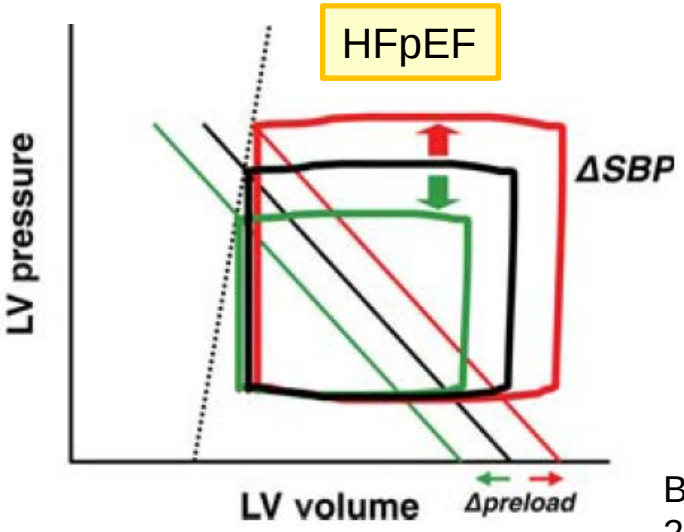




HFpEF: Stiff heart coupled to stiff arteries

Borlaug et al Heart Fail Clin 2008;4:23

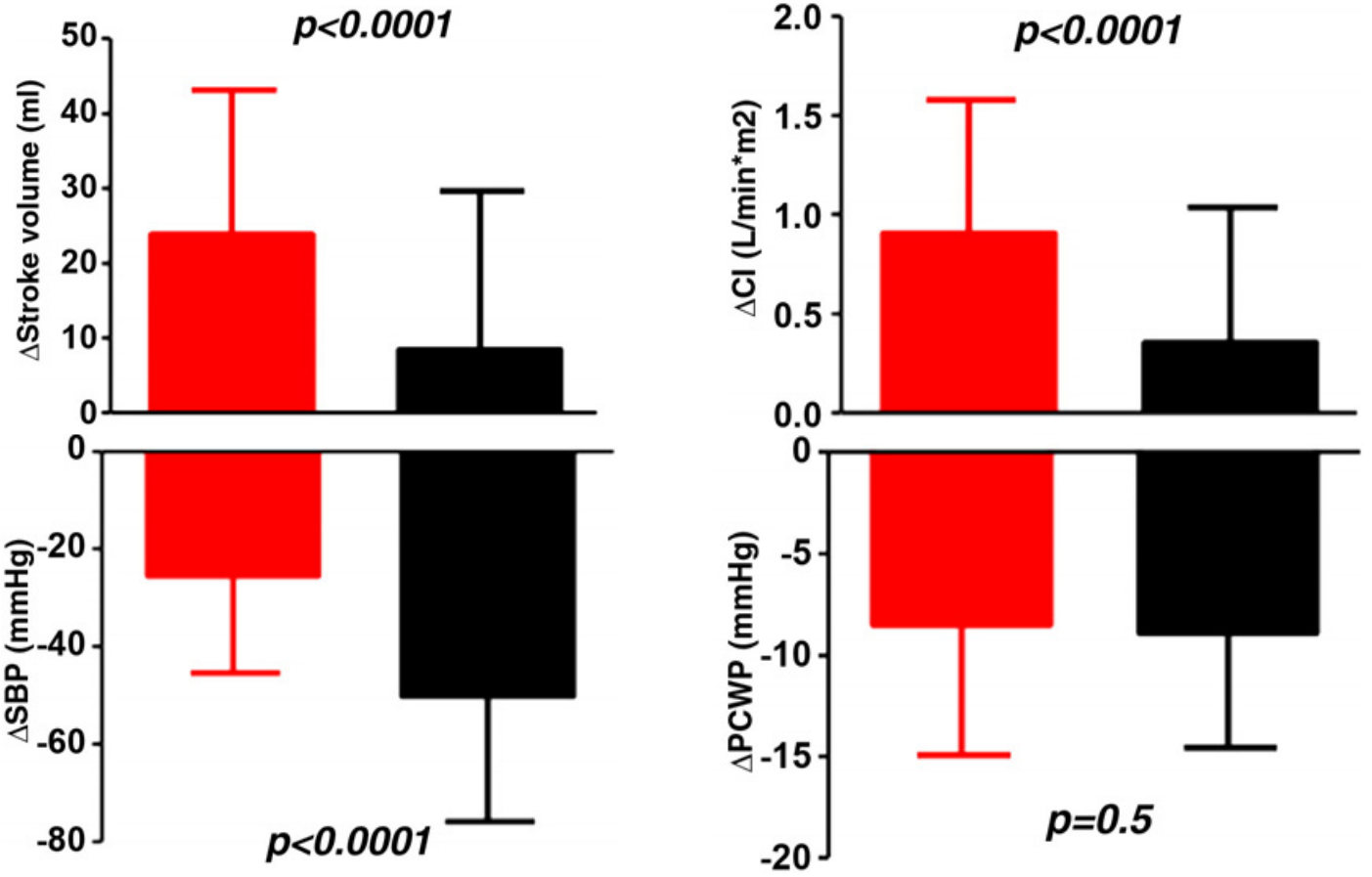




Borlaug, Eur Heart J 2011;32:670

Effects of arterial vasodilation in HFpEF and HFrEF

Nitroprusside infusion in HFpEF (n=83) vs HFrEF (n=174) pts:
*In HFpEF profound ↓ in SBP and MAP; 2.6-fold larger than in HFrEF
*In HFpEF 60% lower increment in SV and CO; SV actually ↓ in 35% of HFpEF pts vs 9% of HFrEF pts



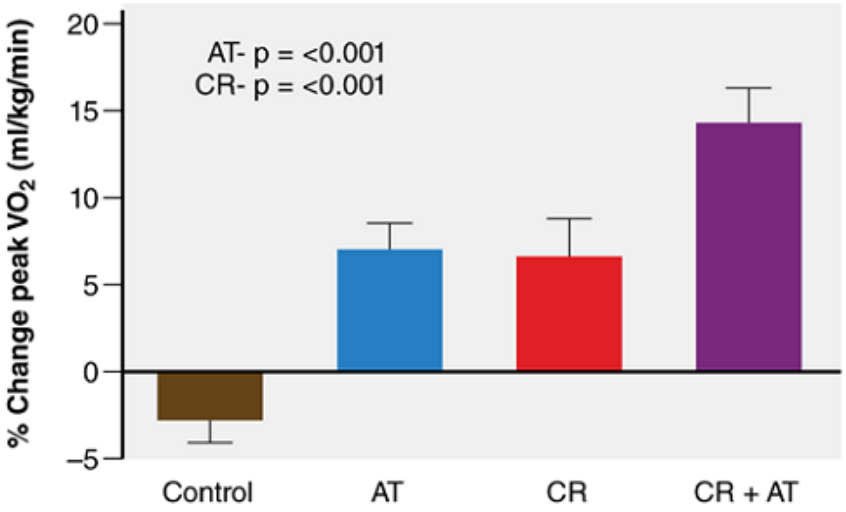
Schwartzenberg et al, JACC 2012;59:442

Trial	EF (%)	Sample size	Drug	Result
CHARM-Preserved	>40	3023	Candesartan	Neutral
PEP-CHF	>40	850	Perindopril	Neutral
DIG-PEF	>45	988	Digoxin	Neutral
SENIORS	>35	752	Nebivolol	Neutral
I-PRESERVE	≥45	4133	Irbesartan	Neutral
ELANDD	>45	116	Nebivolol	Neutral
J-DHF	>40	245	Carvedilol	Neutral
ALDO-DHF	≥50	422	Spironolacton	Neutral
Ex-DHF	**≥50**	**64**	**Exercise**	**Peak VO2 ↑**
PARAMOUNT	≥45	300	Valsartan/sacubitril	ntproBNP ↓
RELAX	≥50	216	Sildenafil	Neutral
RELAX-AHF	≥50	300	Serelaxin	Neutral
RAAM-PEF	≥50	44	Eplerenon	Neutral
EDIFY	≥50	400	Ivabradine	Neutral
TOPCAT	≥45	3445	Spironolactone	Neutral
PARAGON-HF	≥45	4600	Valsartan/sacubitril	Recruiting
SOCRATES-PRESERVED	≥45	477	Vericiguat	Completed
ADHERE	≥40	>50000	Registry	
OPTIMIZE-HF	≥40; >50	21150	Registry	
MAGGIC	≥50	10347	Registry	
GWTG-HF	≥50; 40-49	40354	Registry	

HFpEF anti-inflammatory therapy: Life style changes

Obese (BMI 39 kg/m2) HFpEF pts(n=100) randomized to aerobic exerc training (AT) caloric restriction (CR) or both for 20 weeks;

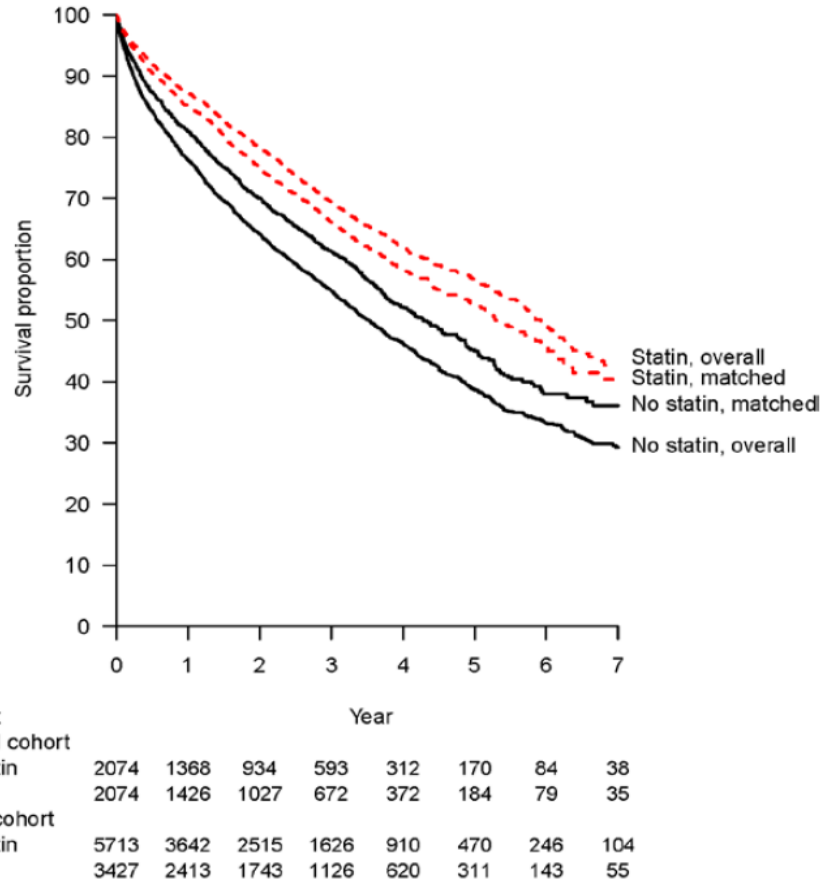
prim EP: peak VO2 and quality of life



Kitzman JAMA 2016;315:36

Prospective Swedish HF Registry, HFpEF pts (n=9140; age 77 ±11 yrs; 54% women);

Statin in 37.5% (n=3427) of HFpEF pts
Association between statin use and outcome

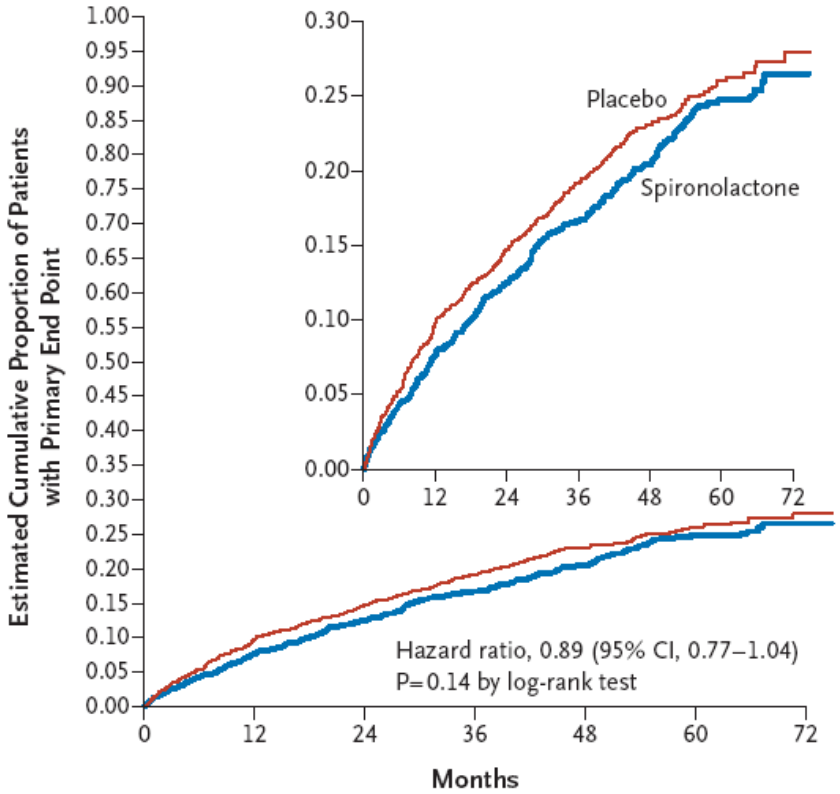


No. at risk								
Matched cohort								
No statin	2074	1368	934	593	312	170	84	38
Statin	2074	1426	1027	672	372	184	79	35
Overall cohort								
No statin	5713	3642	2515	1626	910	470	246	104
Statin	3427	2413	1743	1126	620	311	143	55

Alehagen U et al. Circ Heart Fail 2015;8:862

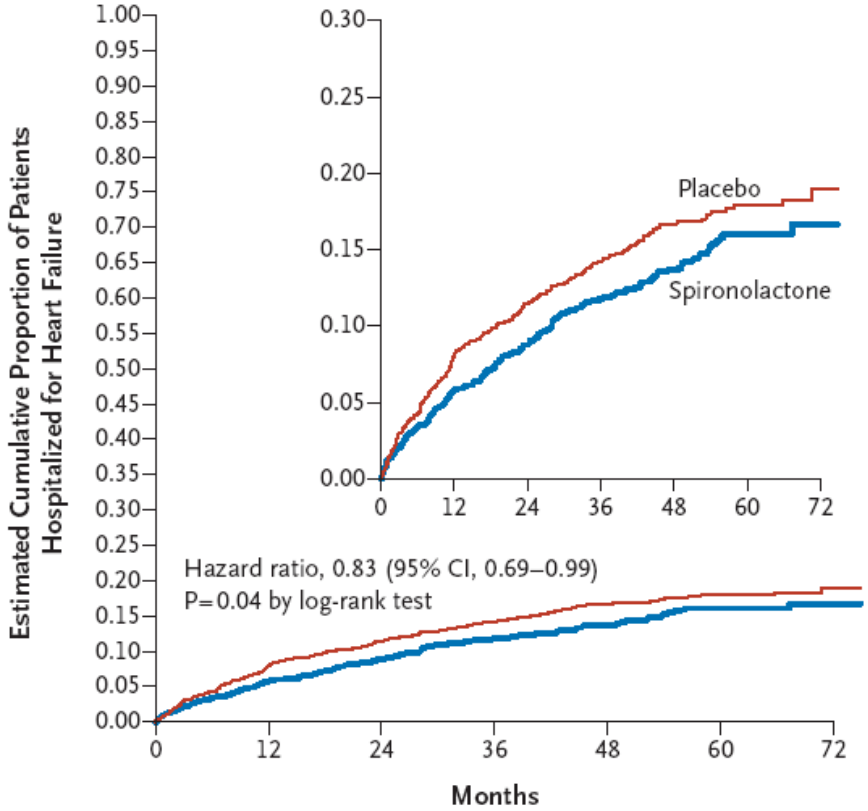
Spironolactone in HFpEF: TOPCAT

Phase III; Randomised; double blind; placebo-controlled; multicenter trial; 2006-2012
HFpEF patients (n=3445 pts); ≥50 yrs;NYHA II-III; EF≥45%; prior HF hosp/↑ntproBNP
Randomisation 1:1 to spironolacton (15-45 mg od) vs placebo;mean FUP 3.3 yrs
Prim Endp: composite of CV death/cardiac arrest or HF hospitalization
Sec Endp: all cause death, hospitalization



No. at Risk

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



No. at Risk

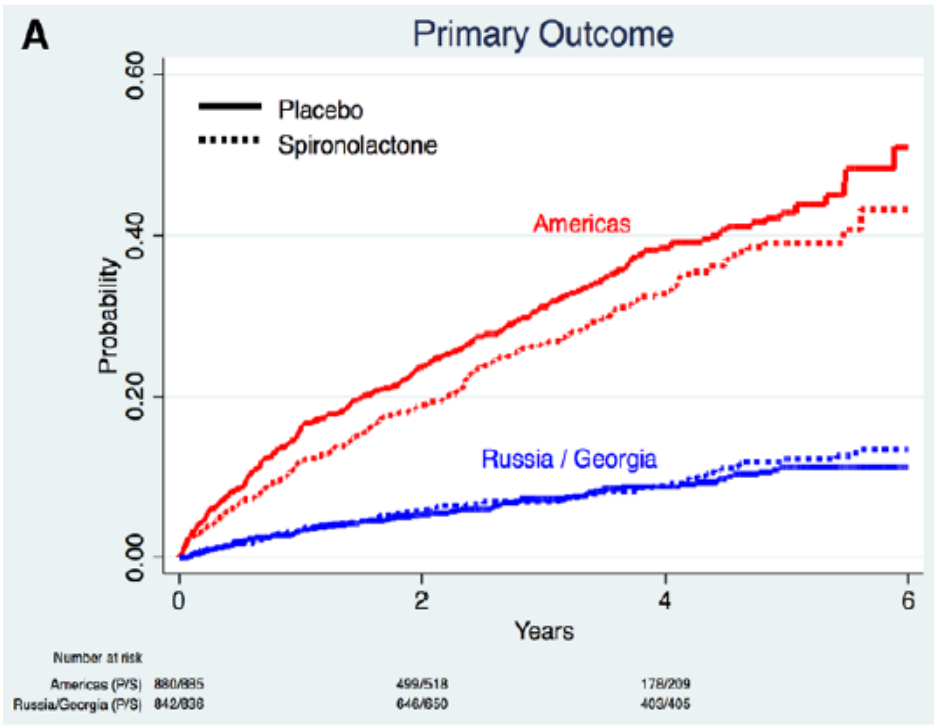
Spironolactone	1722	1502	1167	869	613	330	53
Placebo	1723	1464	1148	837	583	332	53

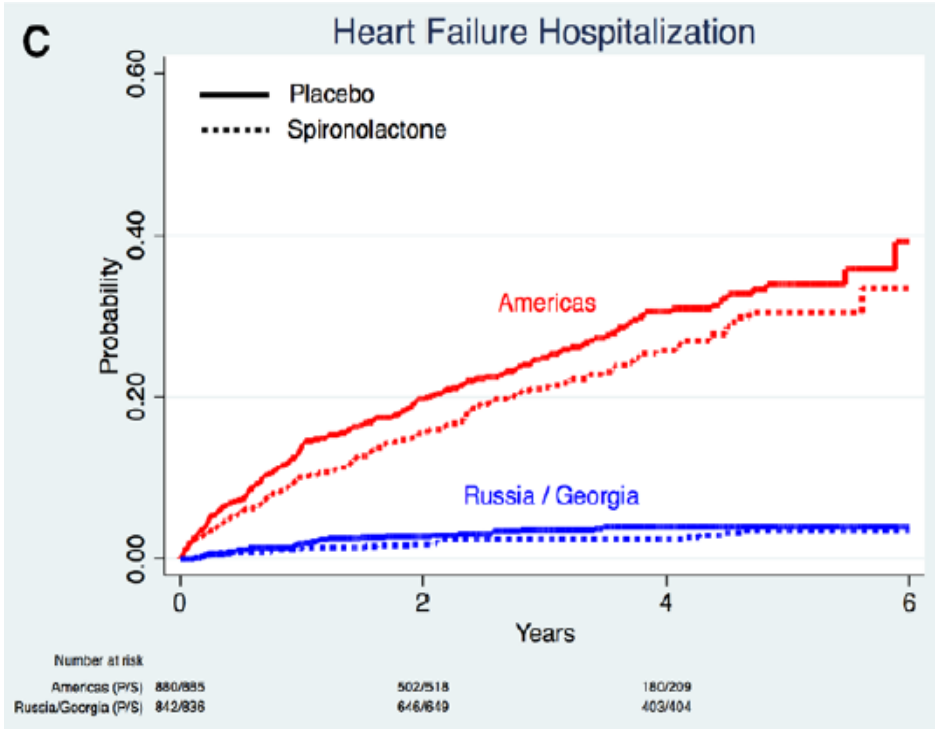
Pitt B et al, NEJM 2014;370:1383

TOPCAT: Regional variation

TOPCAT: 3445 HFpEF patients;
Entry through either prior HF hosp. or nt-proBNP
North/South America: 1767 (51%); Russia/Georgia: 1678 (49%)

Americas: 55% prior HF hosp. and 45% elevated BNP
Russia/Georgia: 89% prior HF hosp. and 11% elevated BNP



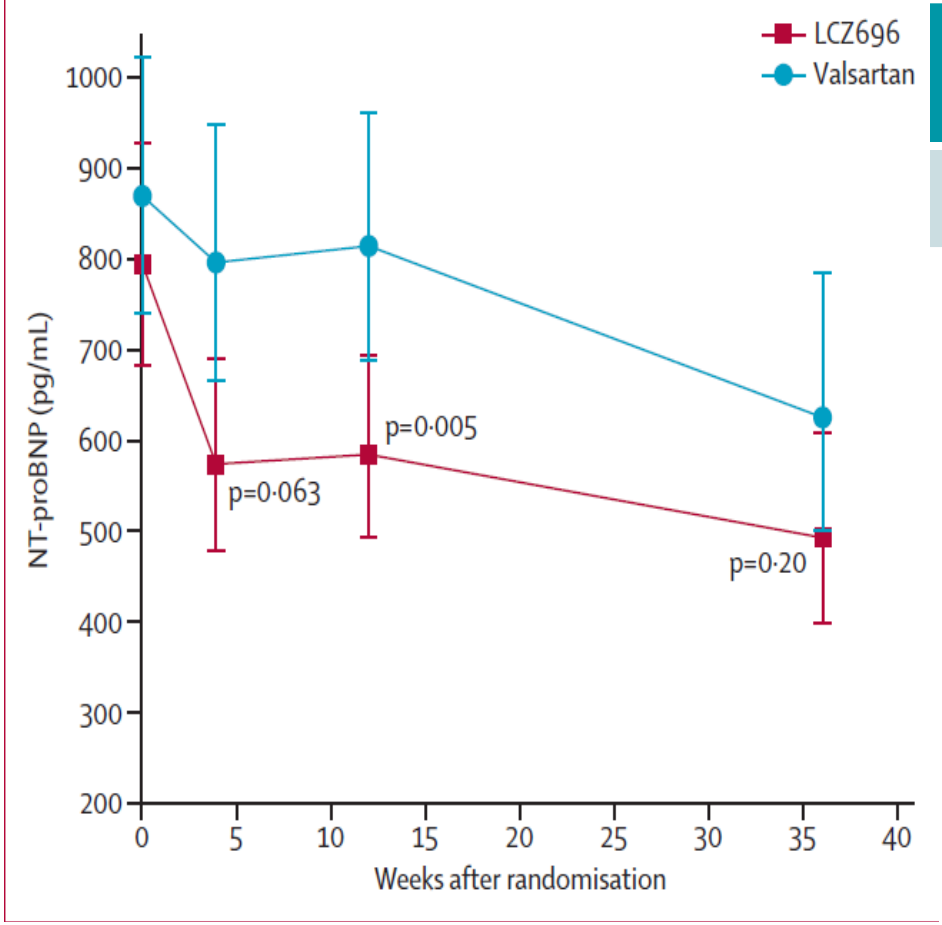


Pfeffer MA et al, Circulation 2015;131:34

ARNI: LCZ696 (Entresto): PARAMOUNT

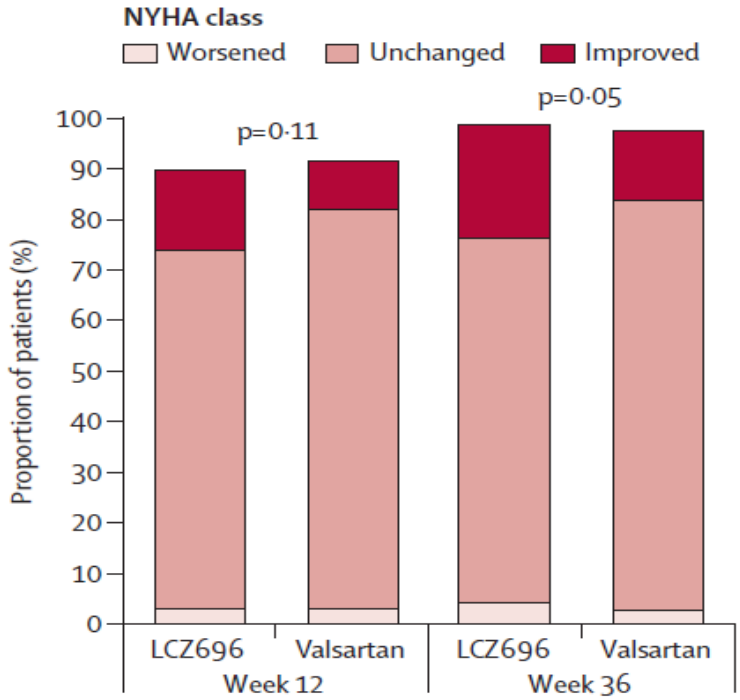
Phase II RCT 2009-2011; HFpEF (n=266 pts); NYHA II-III; EF≥45%; ntproBNP ≥400pg/ml
1:1 to LCZ696 (200 mg bid) vs valsartan (160 mg bid) for 36 wks.

Primary endpoint: Δ in ntproBNP baseline to 12 wks



Secondary endpoint: Δ in Echo parameters and functional class

	LCZ baseline	LCZ Δ from baseline	Valsart baseline	Valsart Δ from baseline	P-value
LAVI	35 ± 11.7	-2.6 ± 7.3	36.8 ± 14.8	0.31 ± 9.3	0.007

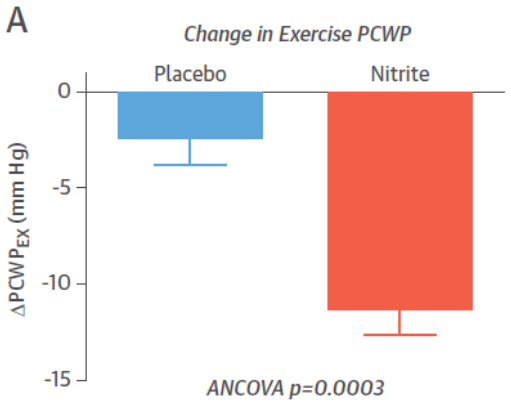


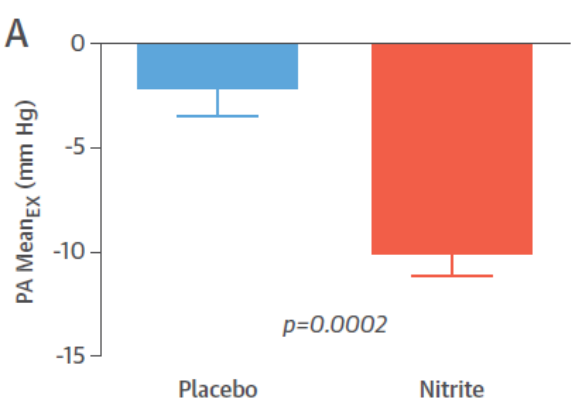
Solomon S et al. Lancet 2012;380:1387

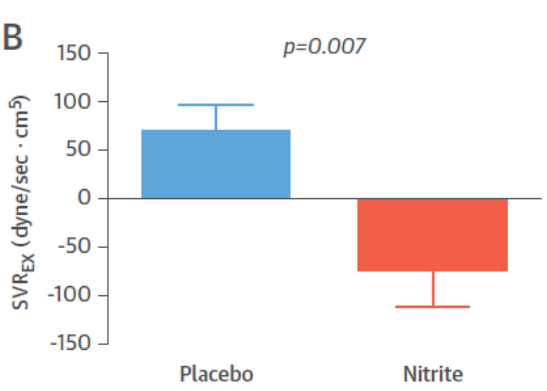
Inorganic nitrite improves cardiac output and LV stiffness

HFpEF (n=28) (PCWP rest ≥ 15 mmHg and/or exercise >25 mmHg) randomized 1:1 to Inorganic nitrite (NO2; reduced to bioactive NO under hypoxia/tissue acidosis) or placebo underwent RHC exercise with simultaneous expired gas analysis

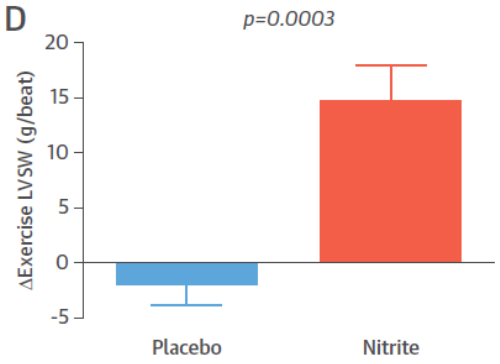
Nitrite lowers PCWP, mPAP and SVR

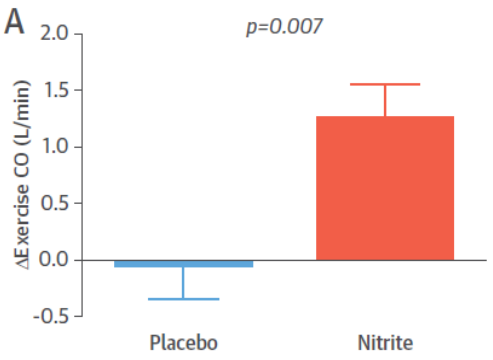


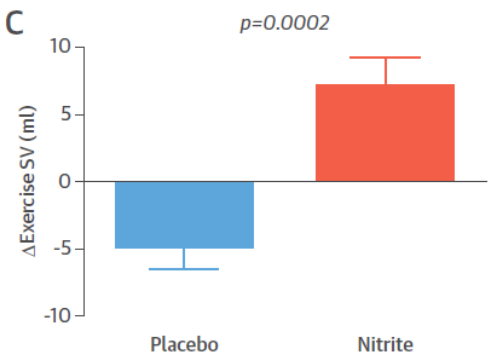




Nitrite improves LV systolic function, CO and SV





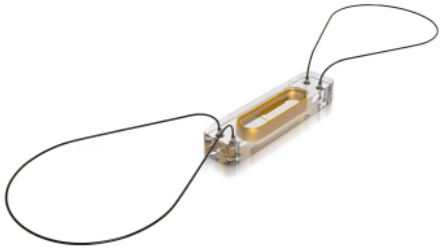


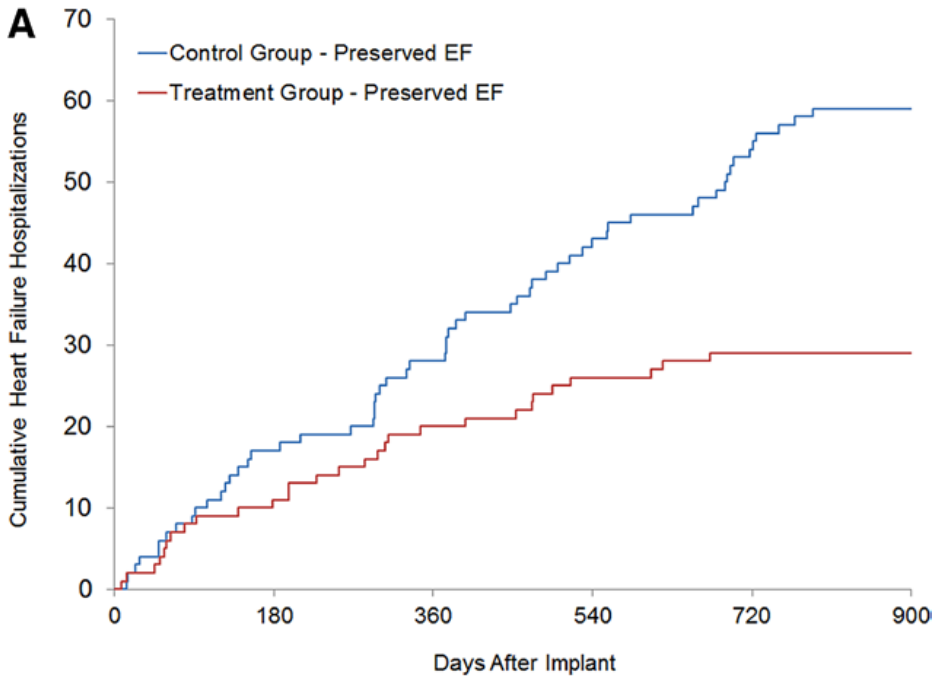
Borlaug JACC 2015;66:1672

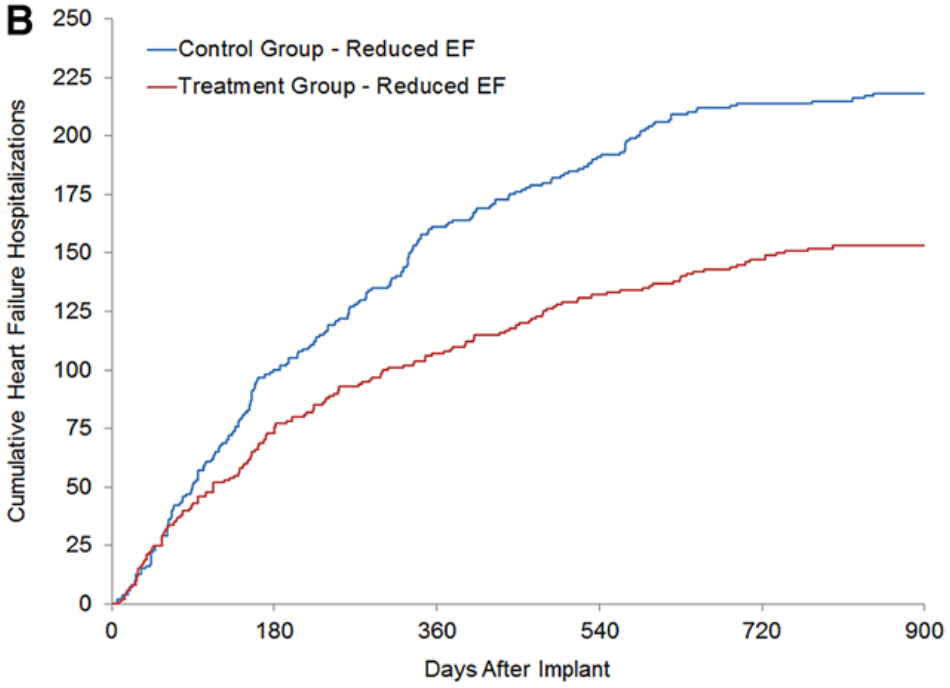
Treatment of HFpEF

HFpEF – HD monitoring devices

CardioMEMS HD guided HF management improves HF hosp in HFpEF
*Hosp rate >6 mths: 46% lower; hosp rate at 18 mths: 50% lower
*More therapeutic changes in vasodilators/diuretics in HD guided group

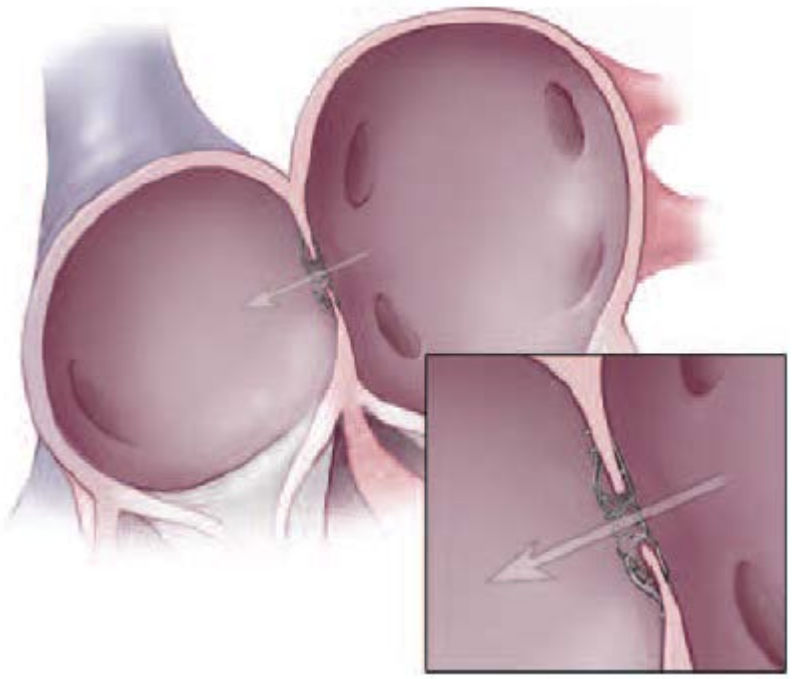


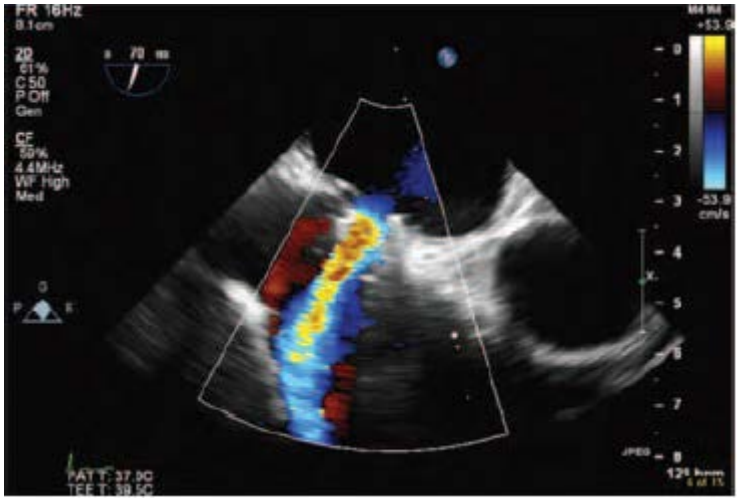


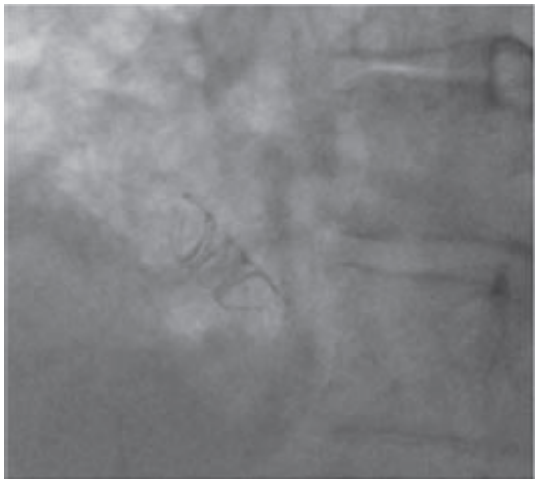


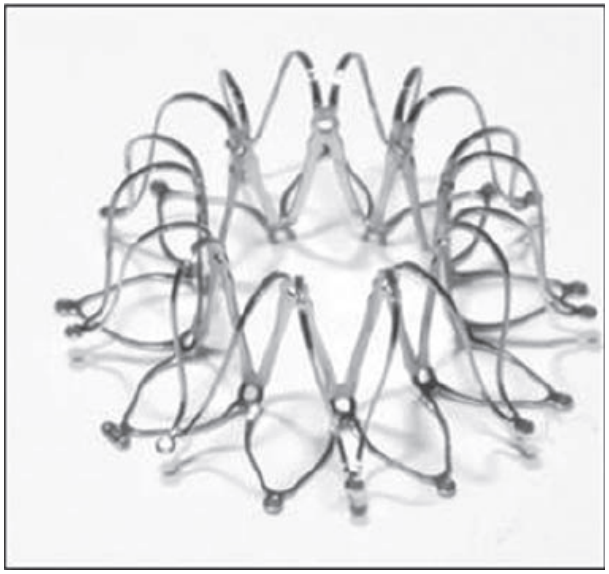
Adamson Circ Heart Fail 2014;7:935

Interatrial shunt device to lower LA pressures







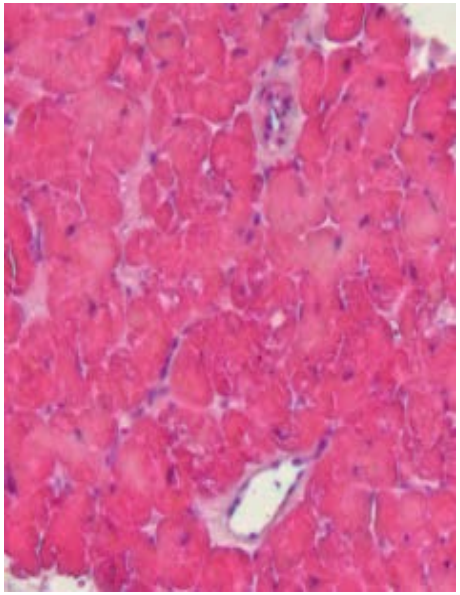


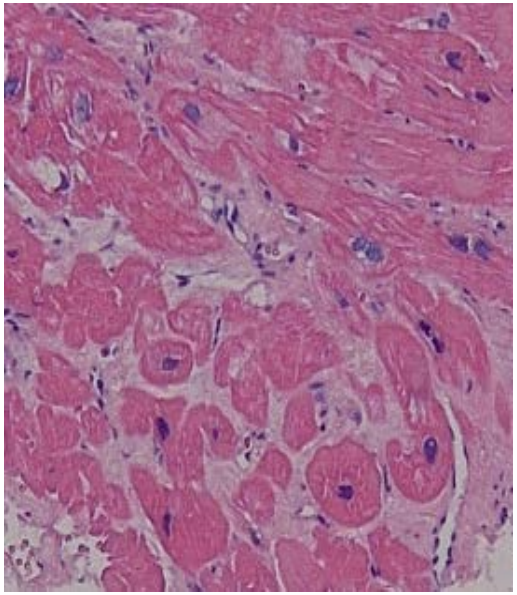
Sondergaard et al. Eur J Heart Fail 2014;16:796

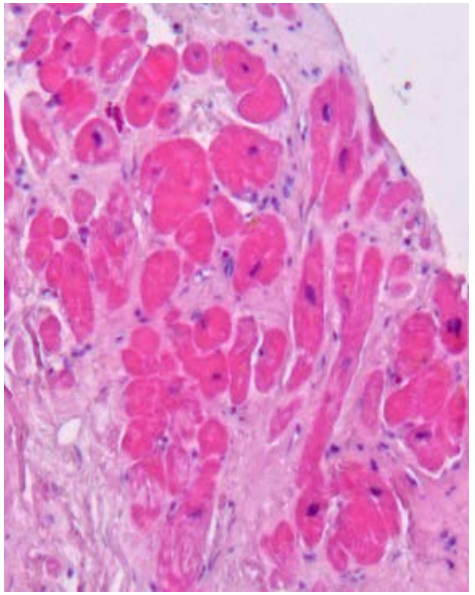
HFpEF: “One size fits all strategy” does not work
→Importance of determining “stage of disease”

“Early HFpEF”

“Advanced HFpEF”







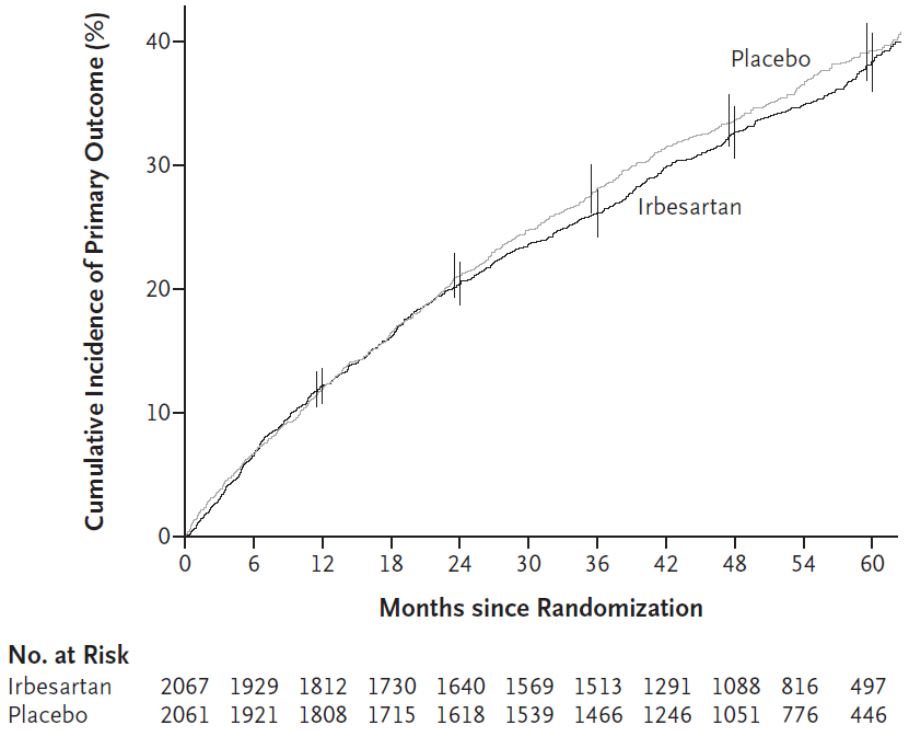
“Early HFpEF”

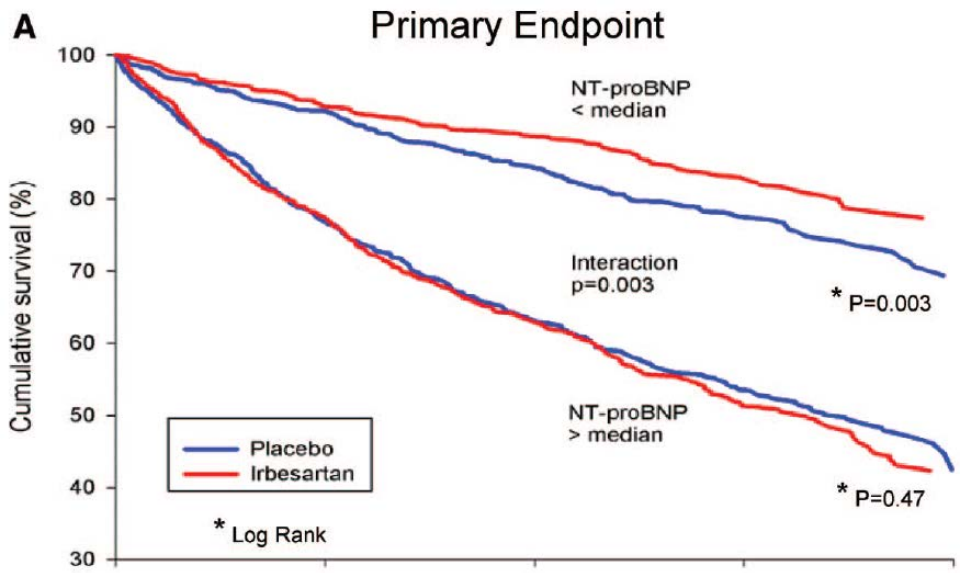
*Neutral results → “Improve pa“Advanced HFpEF”atient stratification alized treatment”

Irbesartan in HFpEF: I-PRESERVE trial

I-Preserve: Neutral prim EP (composite all-cause mortality and CV hospitalization…

…but positive in HFpEF pts with ntproBNP < median





Massie BM et al, NEJM 2008;359:2456

Anand et al, Circ Heart Failure 2011;4:569

HFpEF : a heterogeneous disease: we should enhance insight into pathophysiological diversity and clinical diversity

olvg

Pathophysiological diversity

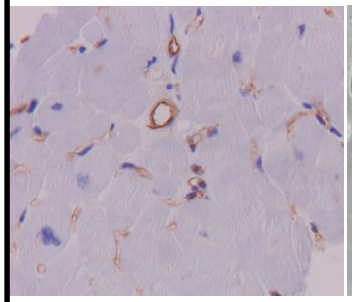
Clinical phenotypic diversity

Therapeutic stratification according to cardiac struct/funct remodeling

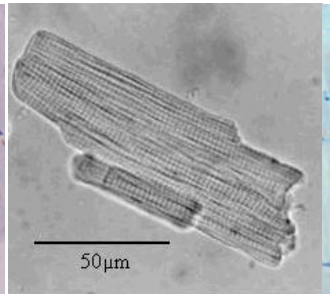
Therapeutic stratification acc to comorbidities

Therapeutic stratification acc to ancillary mechanisms

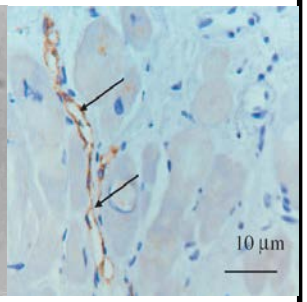
Capillary rarefaction



Cardiomyocyte stifness

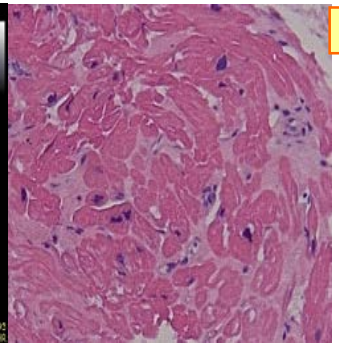


MVD and inflammation

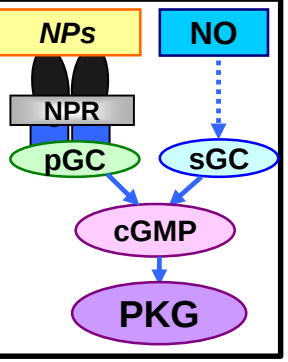


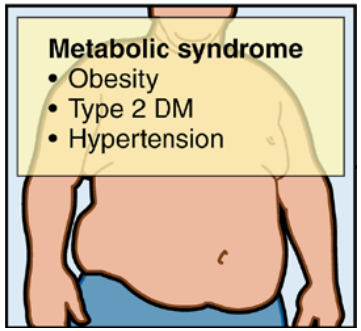
Hypertrophy

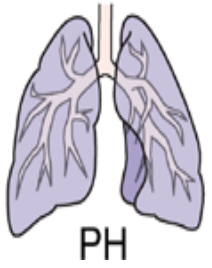
Fibrosis

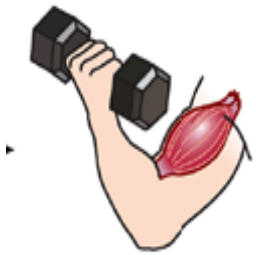


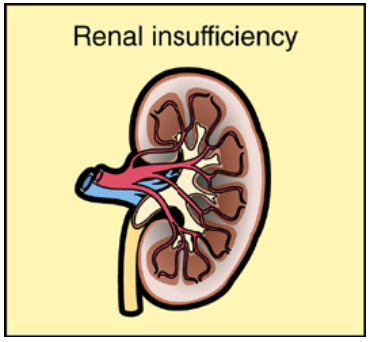
Impaired signaling



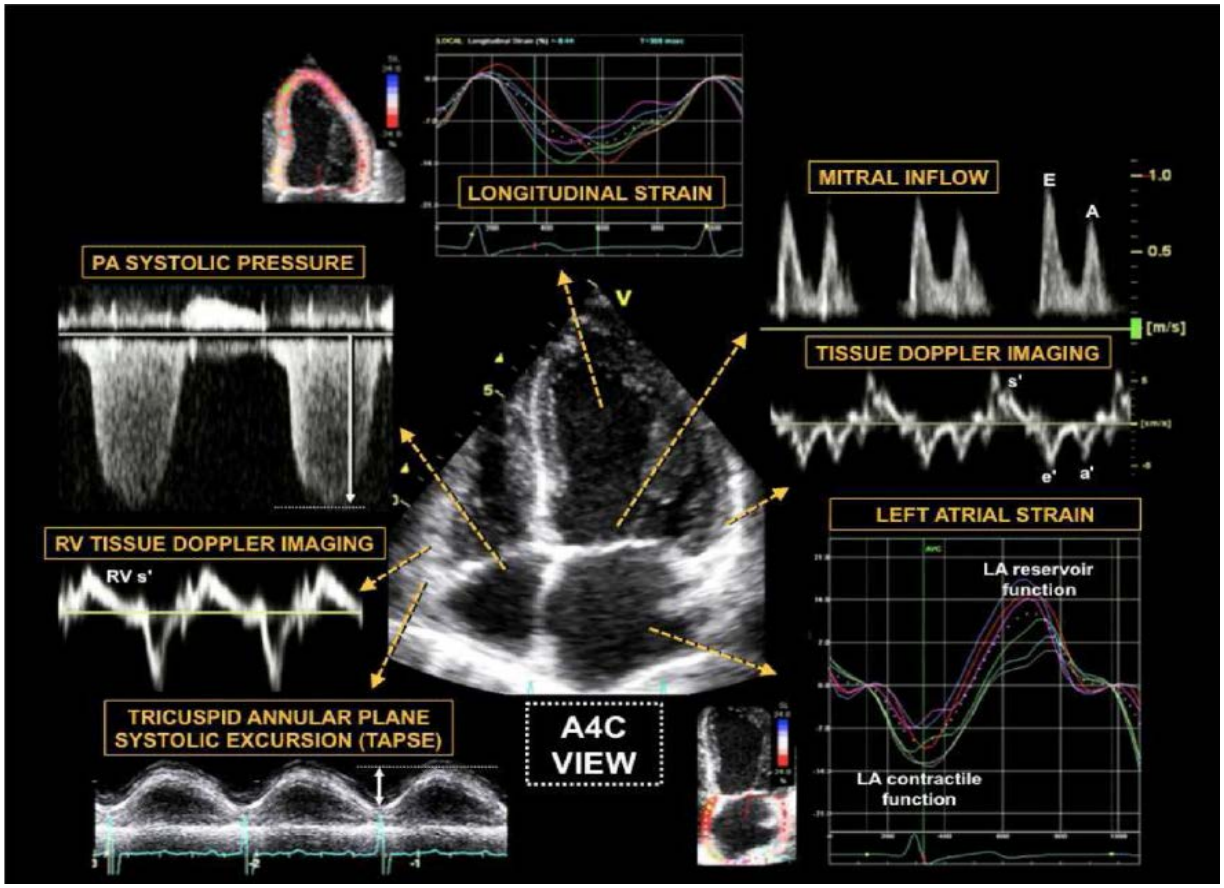


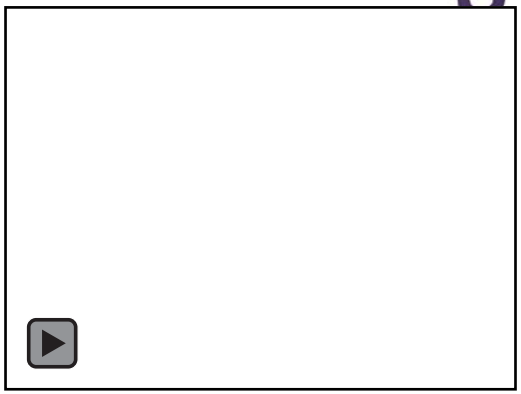


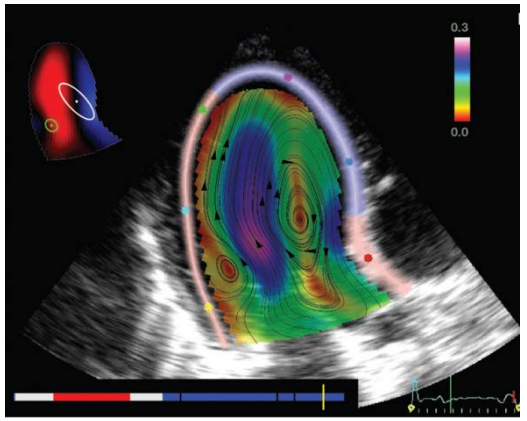


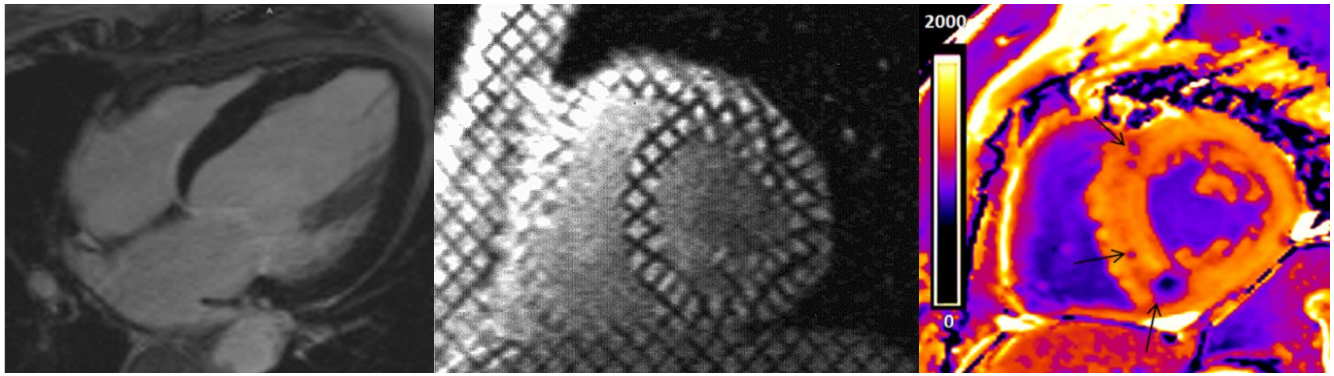


Imaging in HFpEF: Integrative multimodality imaging approach to improve phenotypic stratification



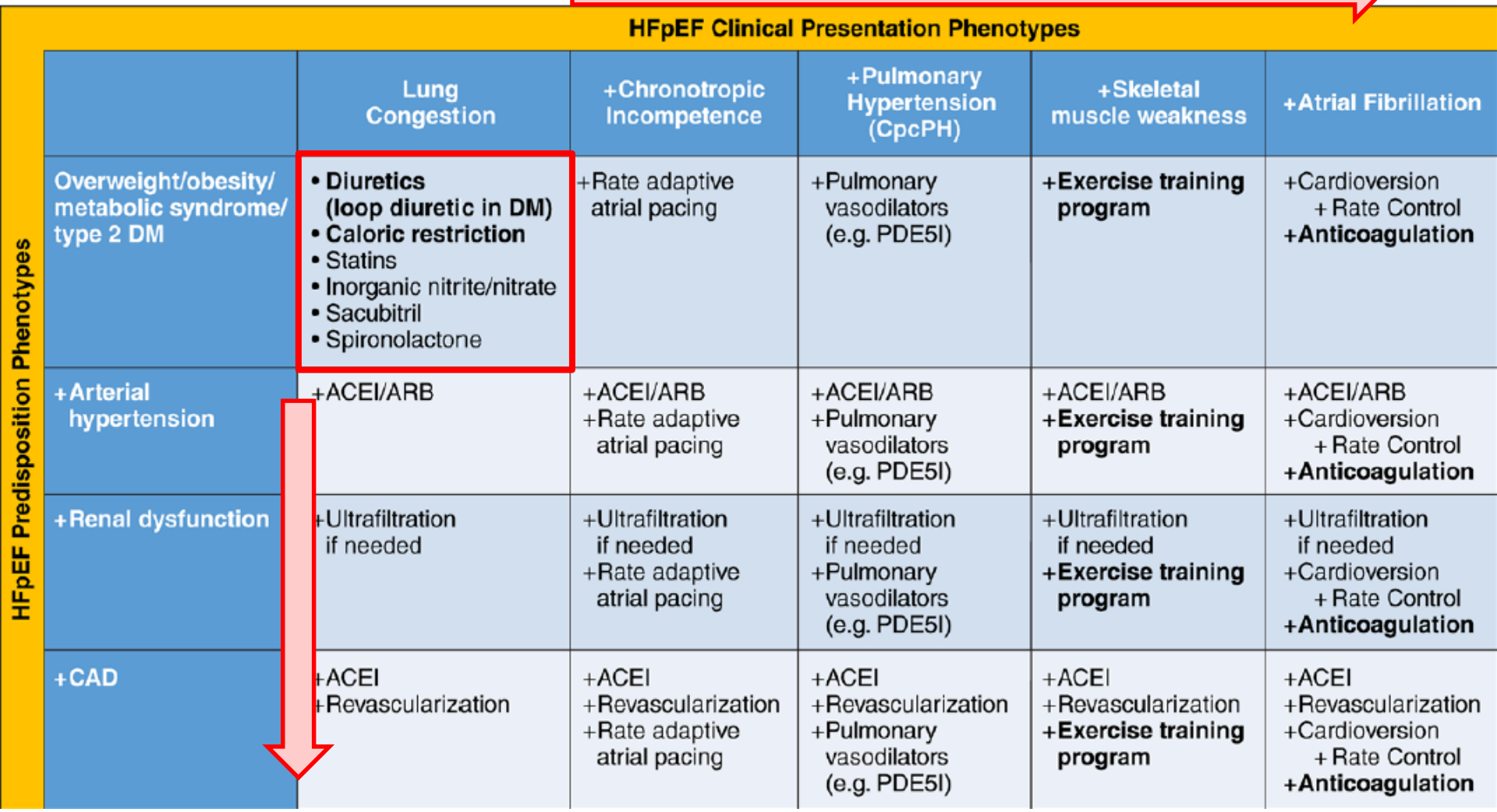






Shah SJ et al, Heart Fail Clin 2014;10:407; Munoz DR et al Eur Heart J Cardiovasc Img 2013;14:1029; Perea JR Insights imaging 2015;6:189

Phenotypic stratification might pave the way for effective patient tailored therapy in HFpEF



HFpEF Predisposition Phenotypes	Lung Congestion	+Chronotropic Incompetence	+Pulmonary Hypertension (CpcPH)	+Skeletal muscle weakness	+Atrial Fibrillation
Overweight/obesity/ metabolic syndrome/ type 2 DM	• **Diuretics (loop diuretic in DM)** • **Caloric restriction** • Statins • Inorganic nitrite/nitrate • Sacubitril • Spironolactone	+Rate adaptive atrial pacing	+Pulmonary vasodilators (e.g. PDE5I)	**+Exercise training program**	+Cardioversion + Rate Control **+Anticoagulation**
+Arterial hypertension	+ACEI/ARB	+ACEI/ARB +Rate adaptive atrial pacing	+ACEI/ARB +Pulmonary vasodilators (e.g. PDE5I)	+ACEI/ARB **+Exercise training program**	+ACEI/ARB +Cardioversion + Rate Control **+Anticoagulation**
+Renal dysfunction	+Ultrafiltration if needed	+Ultrafiltration if needed +Rate adaptive atrial pacing	+Ultrafiltration if needed +Pulmonary vasodilators (e.g. PDE5I)	+Ultrafiltration if needed **+Exercise training program**	+Ultrafiltration if needed +Cardioversion + Rate Control **+Anticoagulation**
+CAD	+ACEI +Revascularization	+ACEI +Revascularization +Rate adaptive atrial pacing	+ACEI +Revascularization +Pulmonary vasodilators (e.g. PDE5I)	+ACEI +Revascularization **+Exercise training program**	+ACEI +Revascularization +Cardioversion + Rate Control **+Anticoagulation**

Shah S…van Heerebeek L, Paulus WJ. Circulation 2016;134:73

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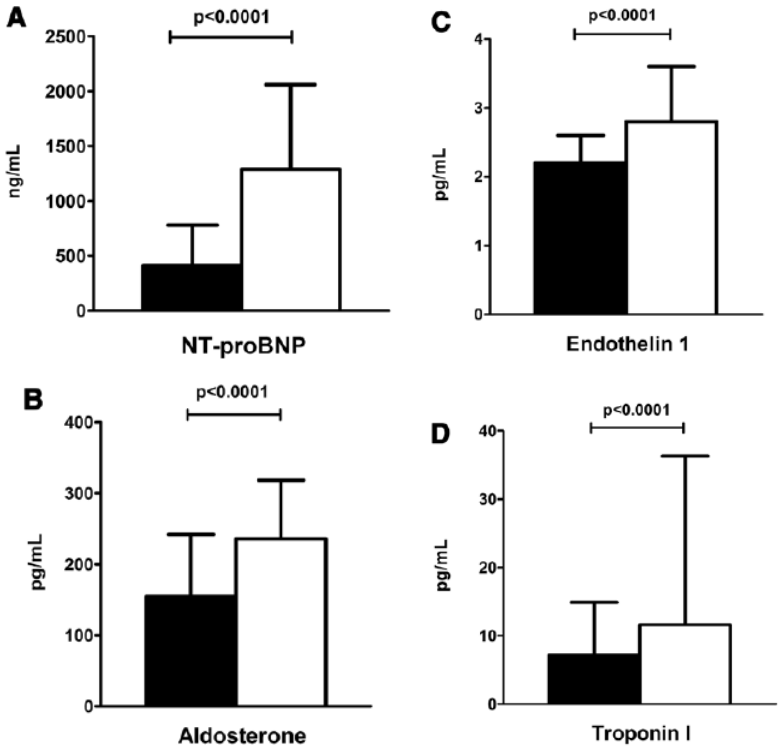
HFpEF: Prognostic impact of phenotypic diversity – RELAX trial

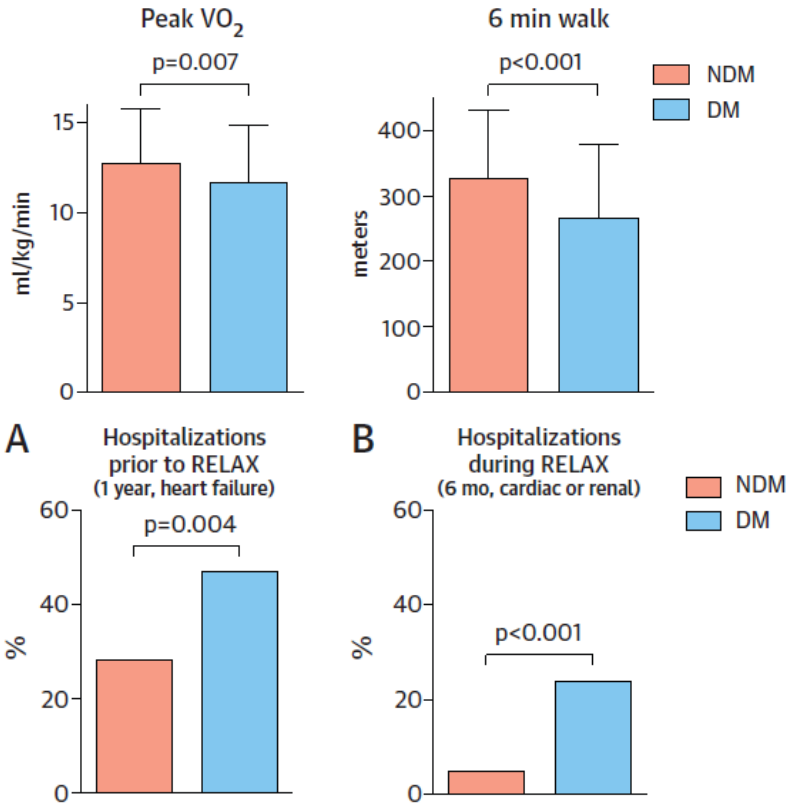
Atrial fibrillation

	Afib (n=79)	SR (n=124)	P-value
Age, y	73 ± 9	66 ± 10	<0.001
LVEF, %	59 ± 8	63 ± 7	0.002
LAVI, ml/m2	62 ± 25	41 ± 13	<0.001
E/E'	18.6 ± 9.2	18.2 ± 9.7	0.74
RA pressure, mmHg	11 ± 5	7 ± 4	<0.001
Peak VO2	11.7 ± 2.7	12.8 ± 3.2	0.008



Diabetes mellitus

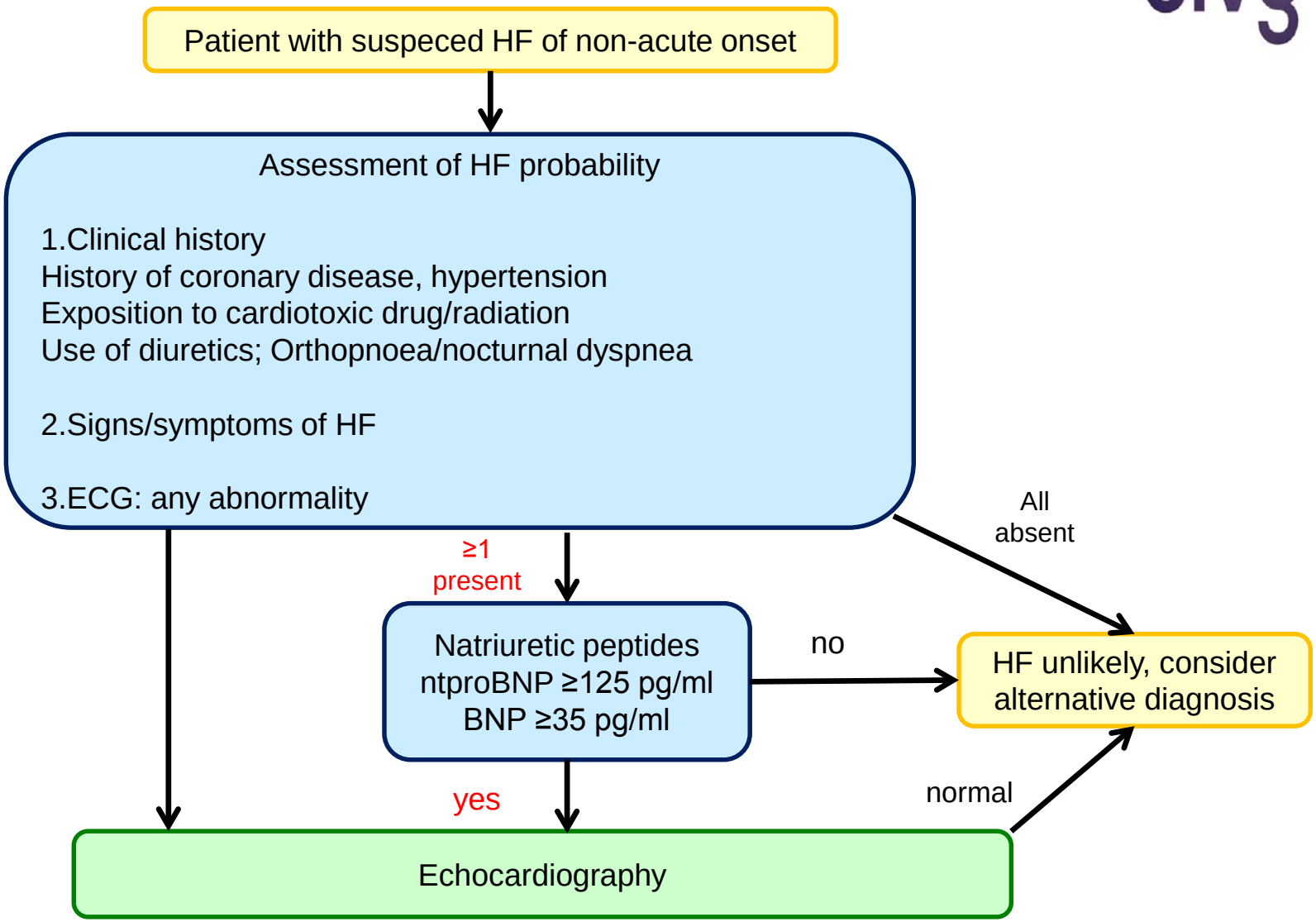
	nonDM (n=79)	DM (n=124)	P-value
Age, y	71 (63,79)	66 (62,73)	0.003
E/E'	14.6 (11,22)	18 (13,25)	0.054
Galectin-3	13.1 (10.6-16)	15.5 (12.2-21.4)	<0.001
CITP	5.7 (4.5,7.5)	7.8 (5.5,12.4)	<0.001
Uric acid	6.8 (6.3,9.4)	7.8 (6.3,9.4)	0.005
CRP	3.3 (1.6,7.3)	4.5 (2.1,10)	0.015



Zakeri R et al Circ Heart Fail 2014;7:123

Lindman BR et al JACC 2014;64:541

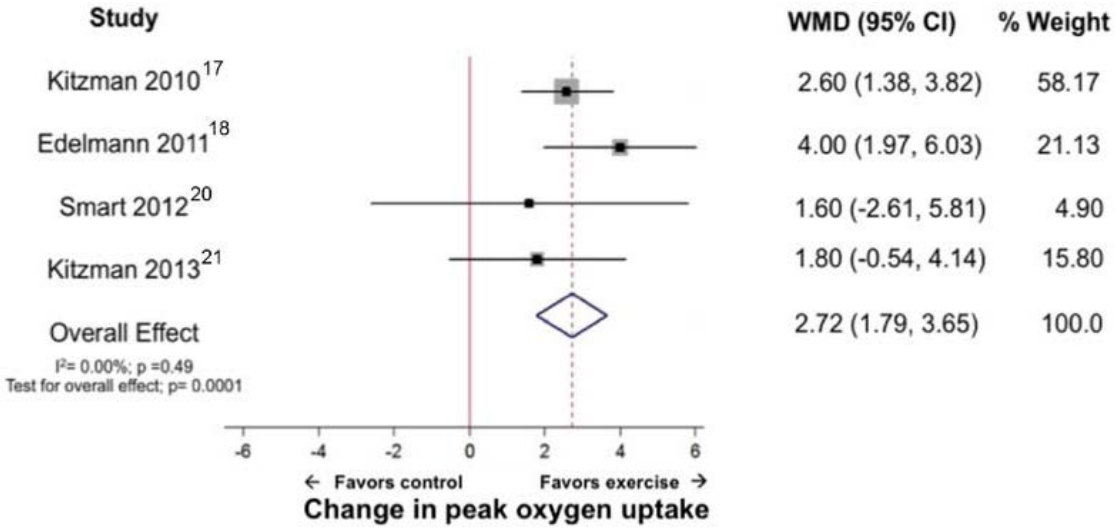
Diagnosis of HF

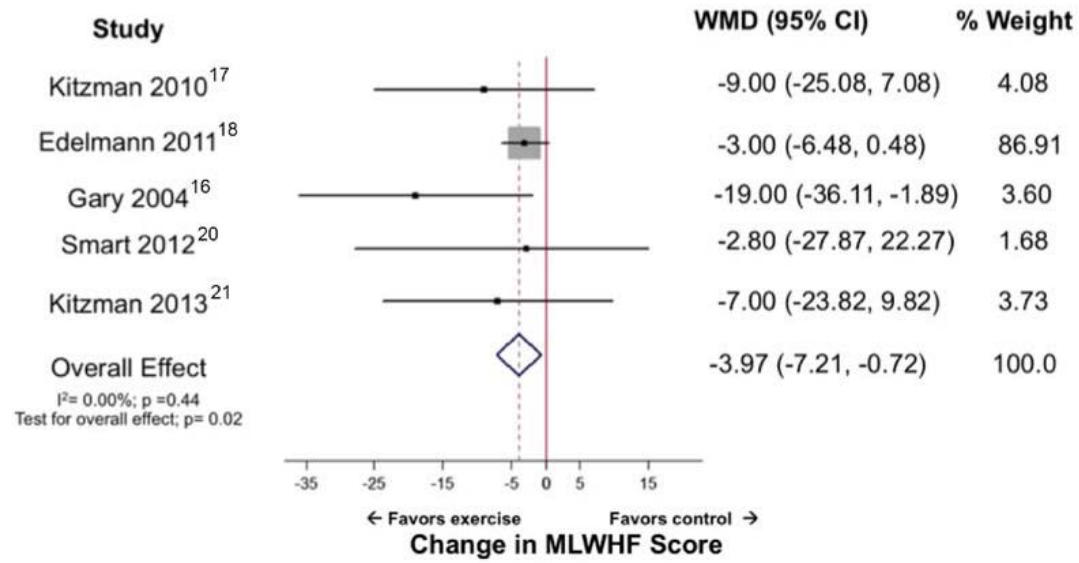


ESC guidelines Heart Failure. Eur Heart J 2016;37:2129

Therapy for HFpEF: Physical exercise

Exercise training in HFpEF improves cardiorespiratory fitness and QoL, but no improvement of systolic/diastolic function





Pandey A et al. Circ Heart Fail 2014;8:33

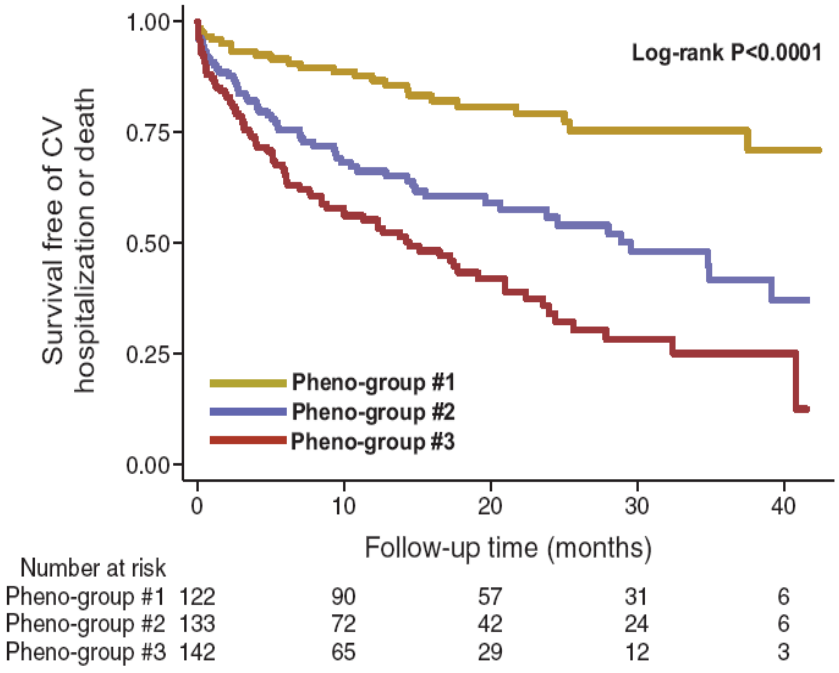
HFpEF: Phenotypic diversity

Unbiased hierarchical cluster analysis of phenotypic data in HFpEF (n=397): 3 phenogroups

1)Younger, less remod.

2)Metabolic risk profile; ↓↓ relaxation, ↑↑ PCWP

3)Oldest, CKD++, RV dysf, ↑↑BNP, ↑↑ E/E'

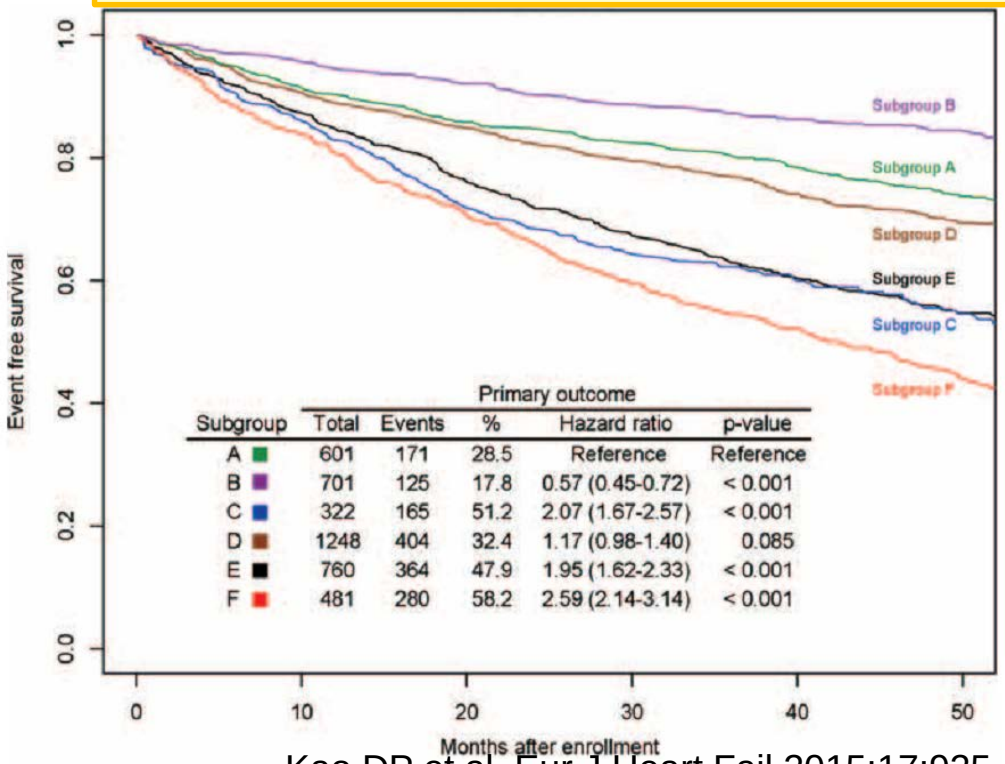


Shah SJ et al. Circulation 2015;131:269

Latent class analysis in I-Preserve (n=4113) characterized according to 11 clinical features.

6 subgroups with differences in outcome (p<0.001)

1)Obesity, DM, hyperlipidemia, anaemia and CKD (Subgroup C)
2)Advanced age, lower BMI, Afib, valvular disease, CKD and anaemia (Subgroup F)



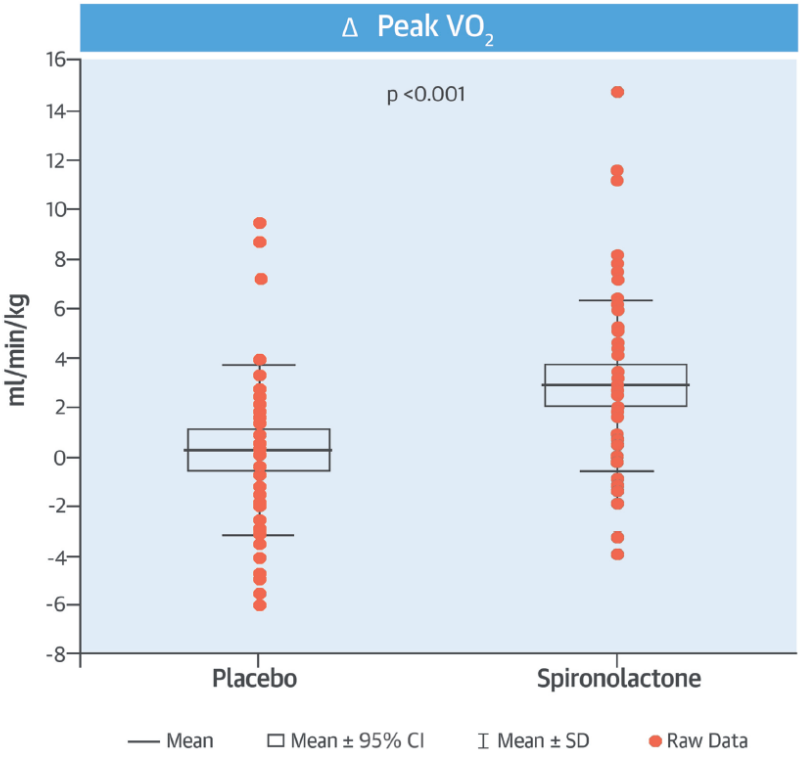
Kao DP et al. Eur J Heart Fail 2015;17:925

Effect of spironolactone on exercise tolerance in HFpEF

Spironolactone (25 mg od) vs placebo (6 mths) HFpEF pts (n=159); NYHA II/III dyspnea (exercise E/E' >13); EF>50%; DD; prim EP: peak VO2 and exertional E/E'

Spironolactone improved:
*peak VO2 (Δ2.9 vs Δ0.3 ml/min/kg;p<0.001)
*exercise E/E' (Δ -3.0 vs 0.5; p<0.001)

	Spironolactone (n=64)	Placebo (n=67)	P
Age, yrs	66.3 ± 7.7	67.6 ± 9.1	0.37
Female	56 (88)	54 (81)	0.28
BMI, kg/m2	30.7 ± 4.5	29.7 ± 4.6	0.22
BNP, pg/ml	40 (26-63)	54 (27-99)	0.44
Galectin-3, ng/ml	11.1 (8.4-13.5)	12.2 (8.2-14.7)	0.53



	Spironolactone (n=64) Baseline	Spironolactone 6 mth FUP	Placebo (n=67) Baseline	Placebo 6 mth FUP	P
LVMI, g/m2.7	55 (52-58)	52 (49-55)	56 (53-60)	56 (53-59)	0.04
LAVI, ml/m2	36.8 (34.9-38.7)	35.1 (33.2-36.9)	36.0 (33.6-38.4)	36.2 (33.9-38.5)	0.01
Peak VO2, mL/kg.min	14.5 (13.4, 15.4)	Δ2.9 (2.5, 3.3)	15.0 (14.0, 16.1)	Δ0.3 (-0.5, 1.1)	<0.001
E/E' mean (rest)	12.2 (11.2-13.2)	11.4 (10.7-12.2)	11.9 (11.0-12.8)	12.5 (11.5-13.4)	0.01
E/E' mean (exercise)	Δ4.4 (3.9-4.8)	Δ2.0 (1.5-2.5)	Δ4.9 (4.3-5.6)	Δ4.9 (4.1-5.7)	<0.001

Kosmala W et al, JACC 2016;68:1823

Treatment effects in TOPCAT stratified to LVEF and gender

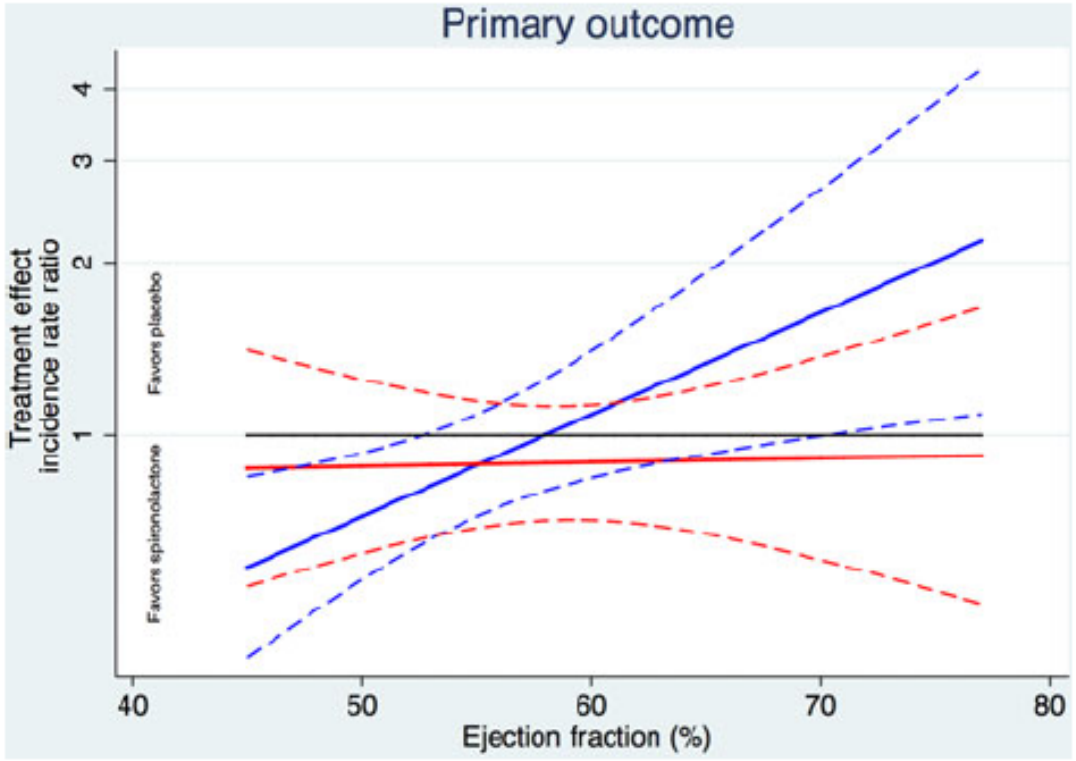
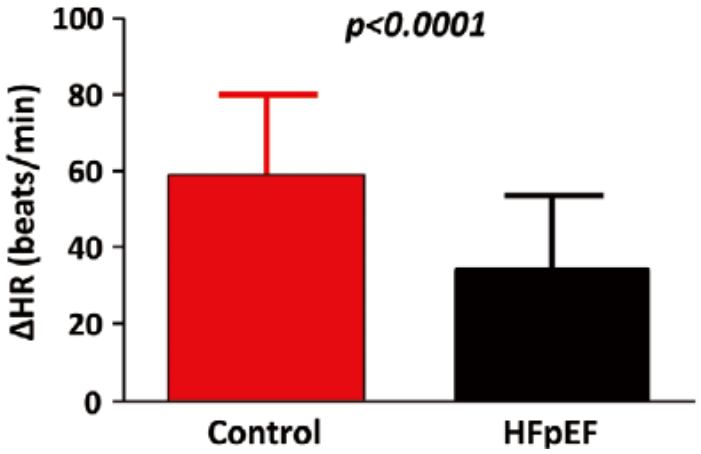
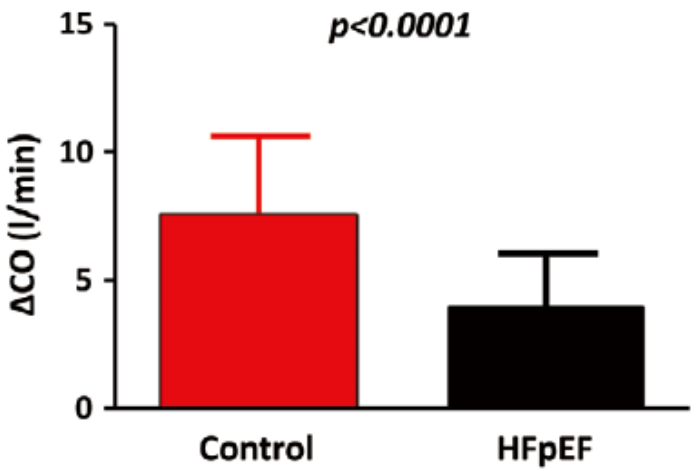


Figure 4 Treatment effect for the primary outcome in men (blue) and women (red). $P_{interaction} = 0.077$.

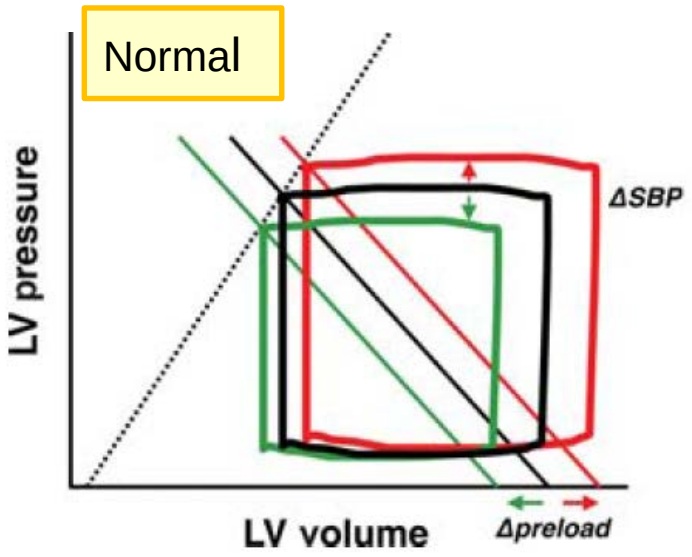
Solomon SD et al. Eur Heart J. 2015

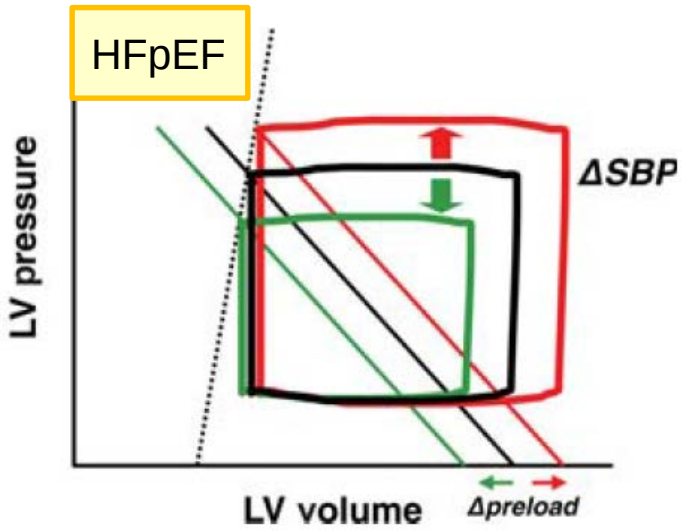
HFpEF: blunted chronotropy and CO reserve and ventr.-vasc. stiffening





Borlaug Circ J 2014;78:20

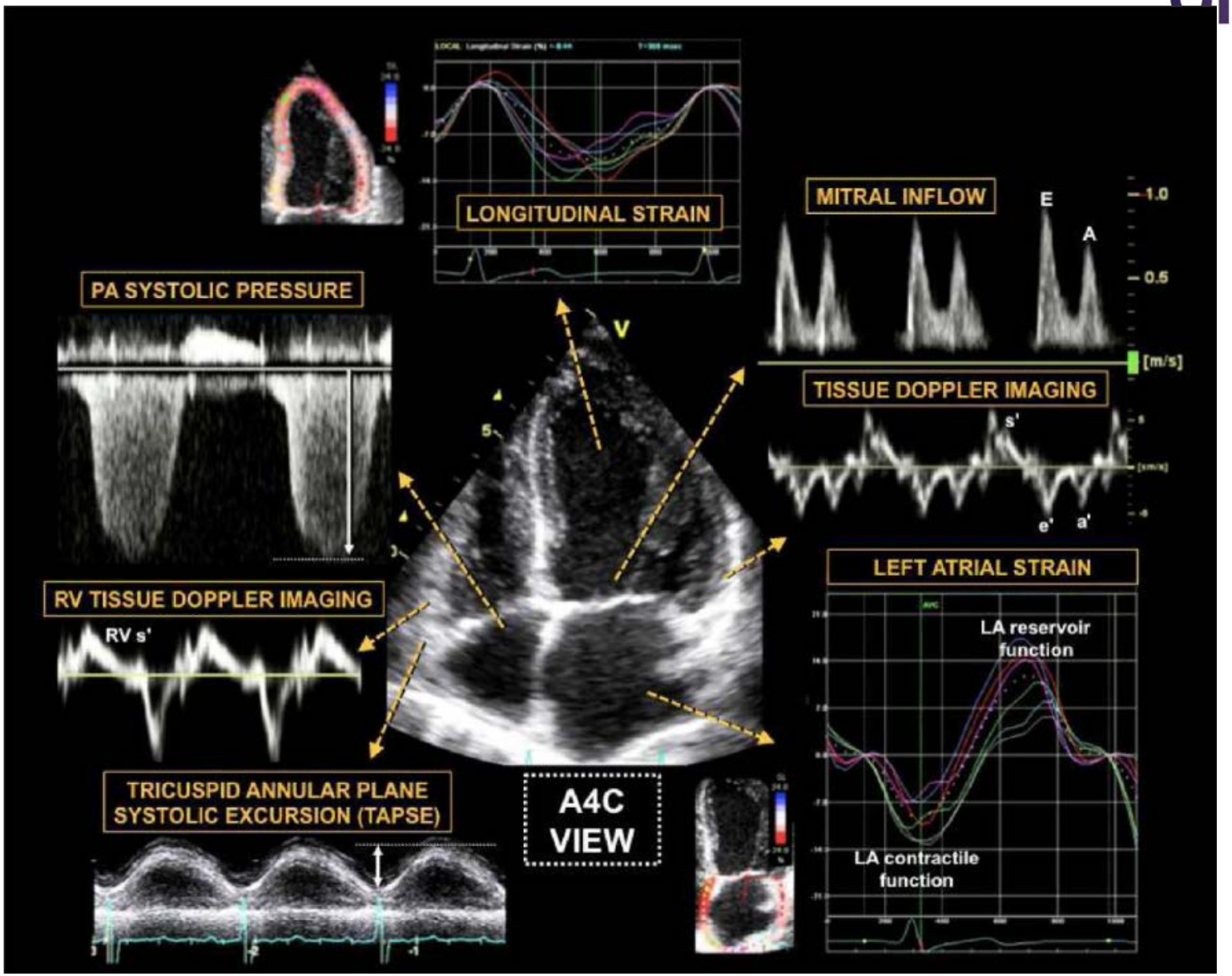




Borlaug, Eur Heart J 2011;32:670

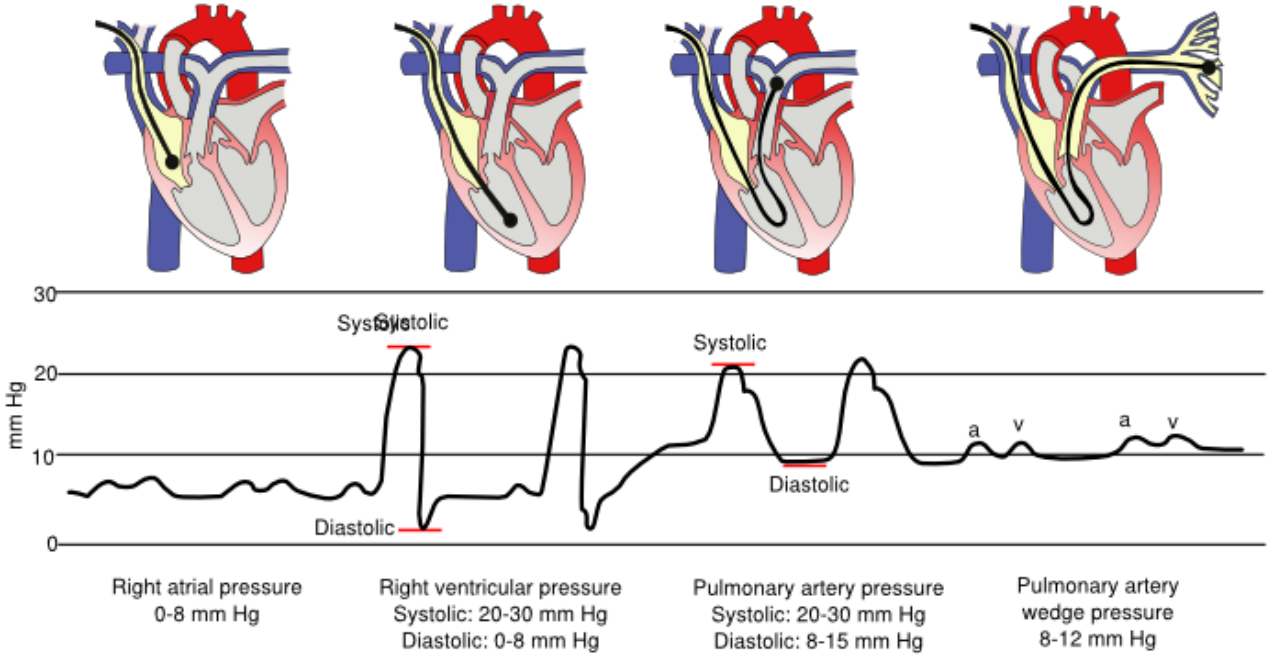
*HFpEF: Fixed and blunted CO reserve combined with ventricular-vascular stiffening result in preload dependency and potential detrimental response to arterial vasodilation resulting in low BP and renal dysfunction

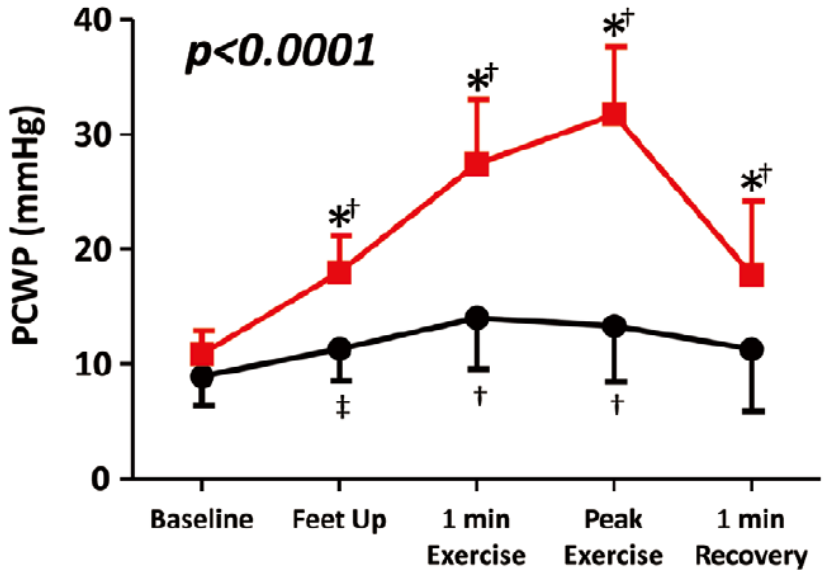
Integrated echocardiography in HFpEF

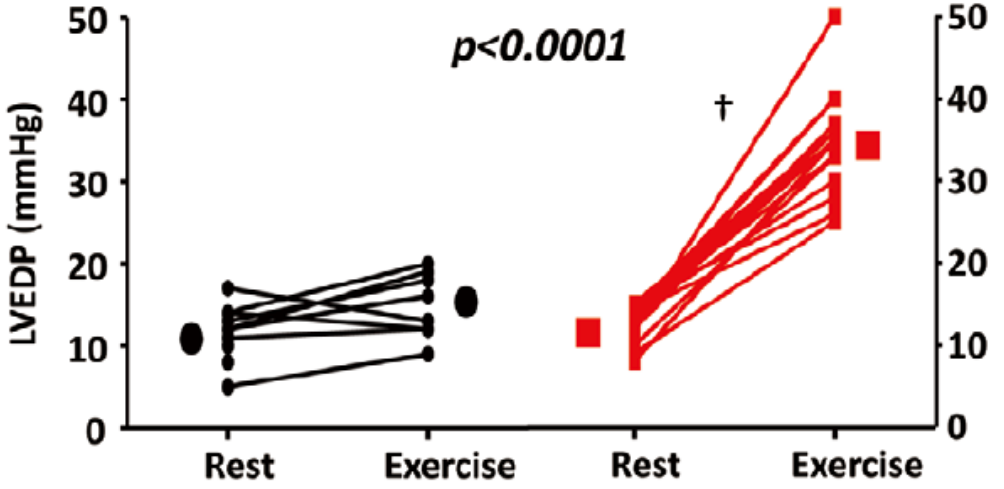


Shah SJ et al, Heart Fail Clin 2014;10:407

Diastolic dysfunction: high LV filling pressures



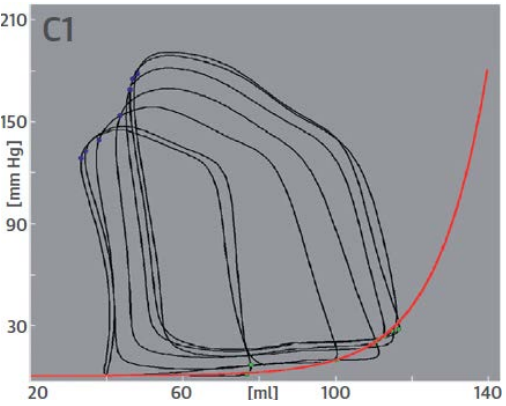


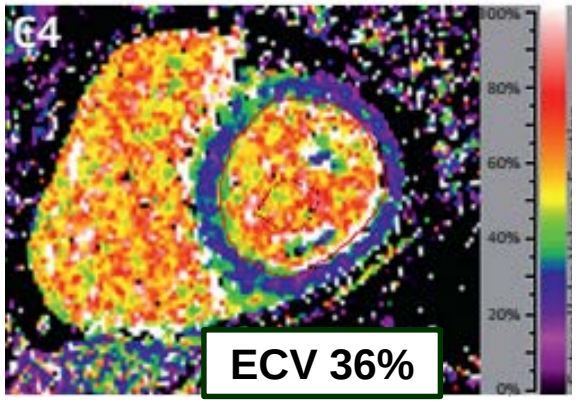


Borlaug BA, Circ J 2014;78:20

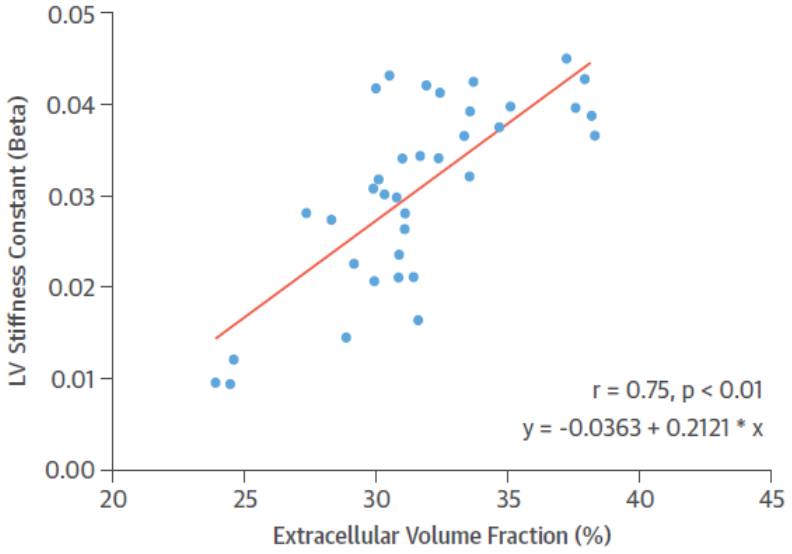
HFpEF: Interstitial fibrosis

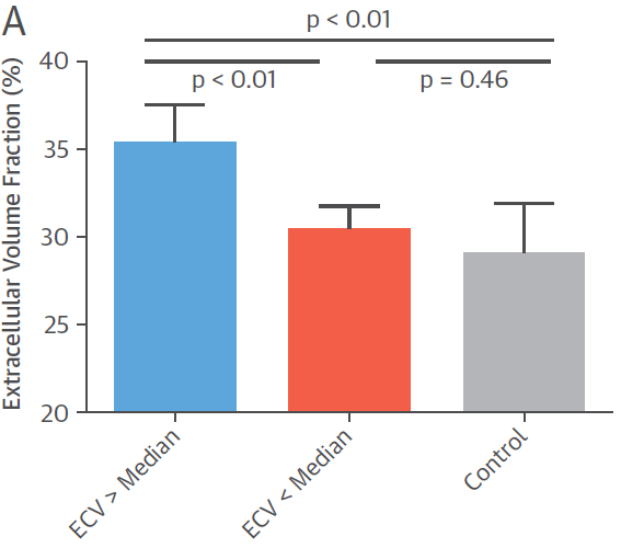
cMRI with T1 mapping and LV PV loops in HFpEF (n=24) and C (n=12)

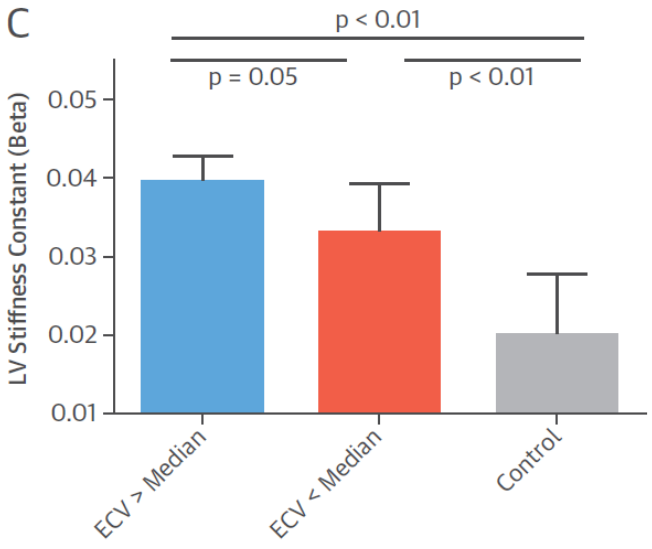


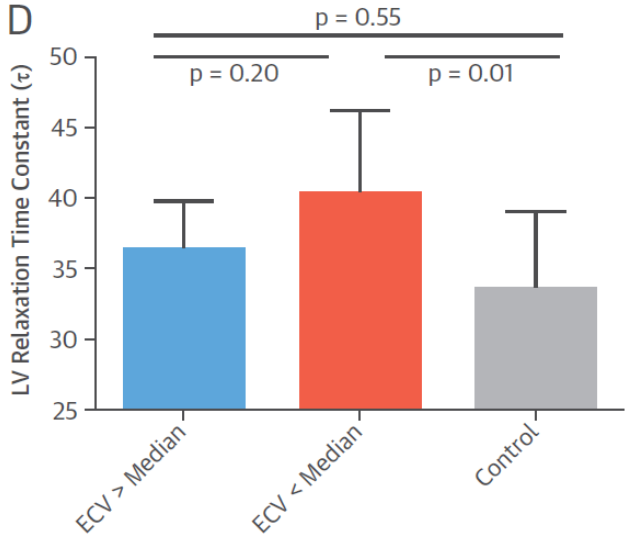


Rommel KP et al. JACC 2016;67:1815

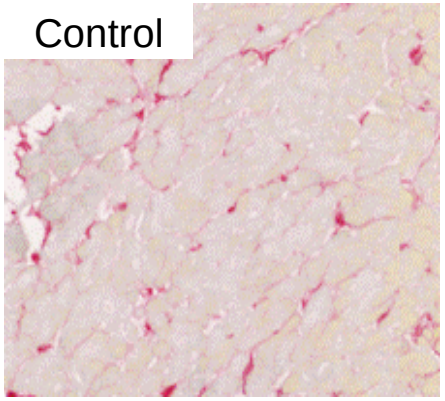


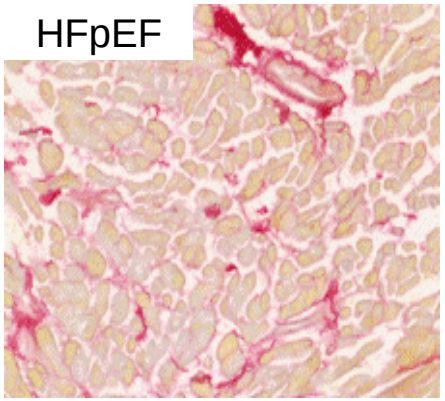




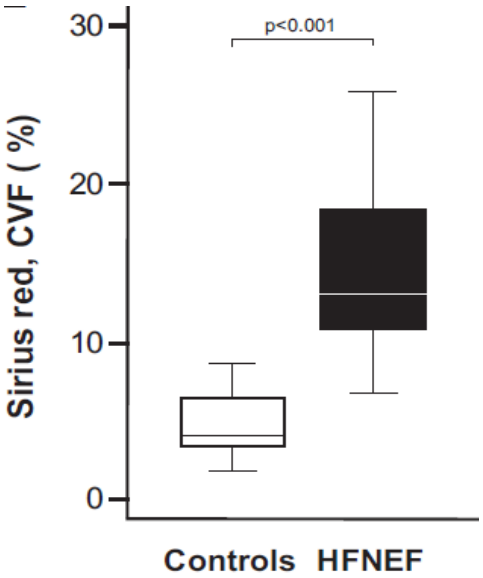


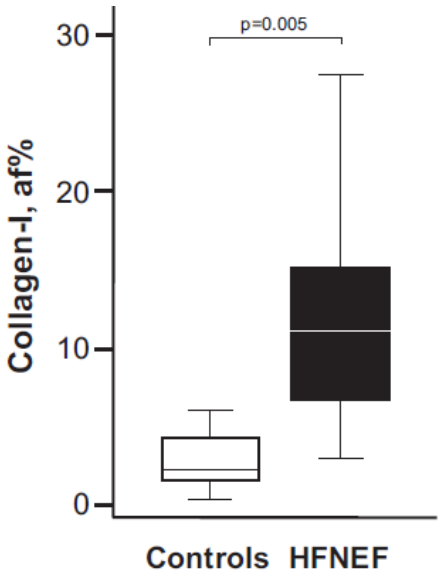
HFpEF: Interstitial fibrosis

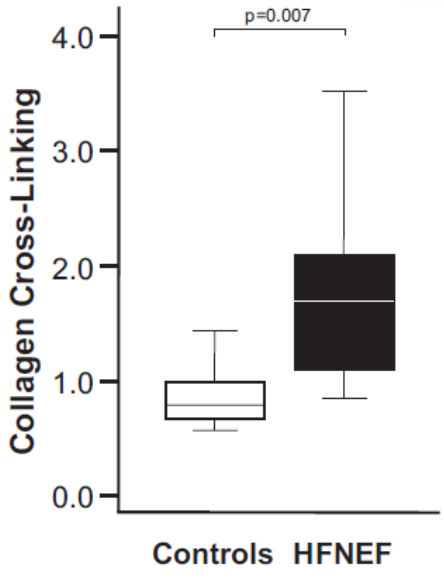


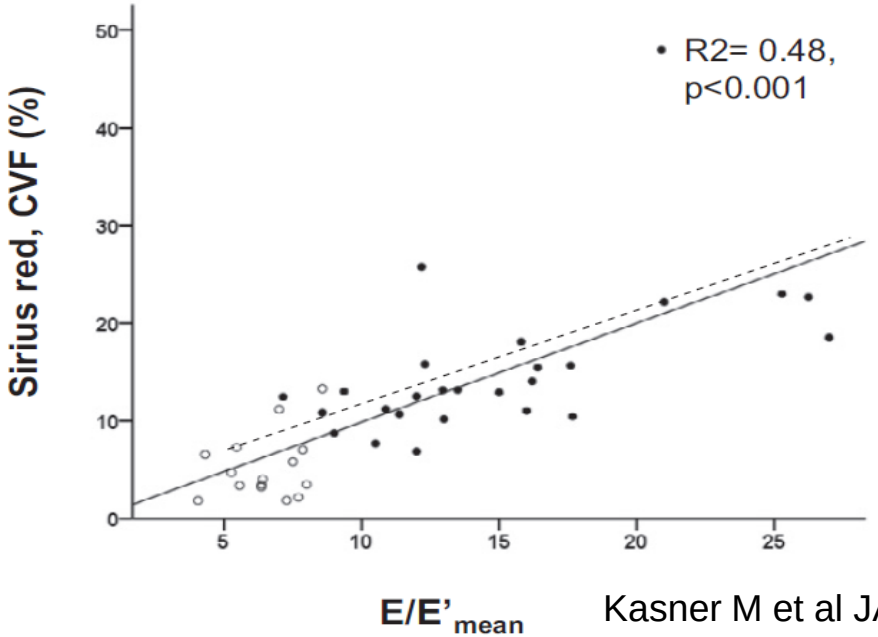


RV EMBs and echo in HFpEF (n=26) and C (n=15)





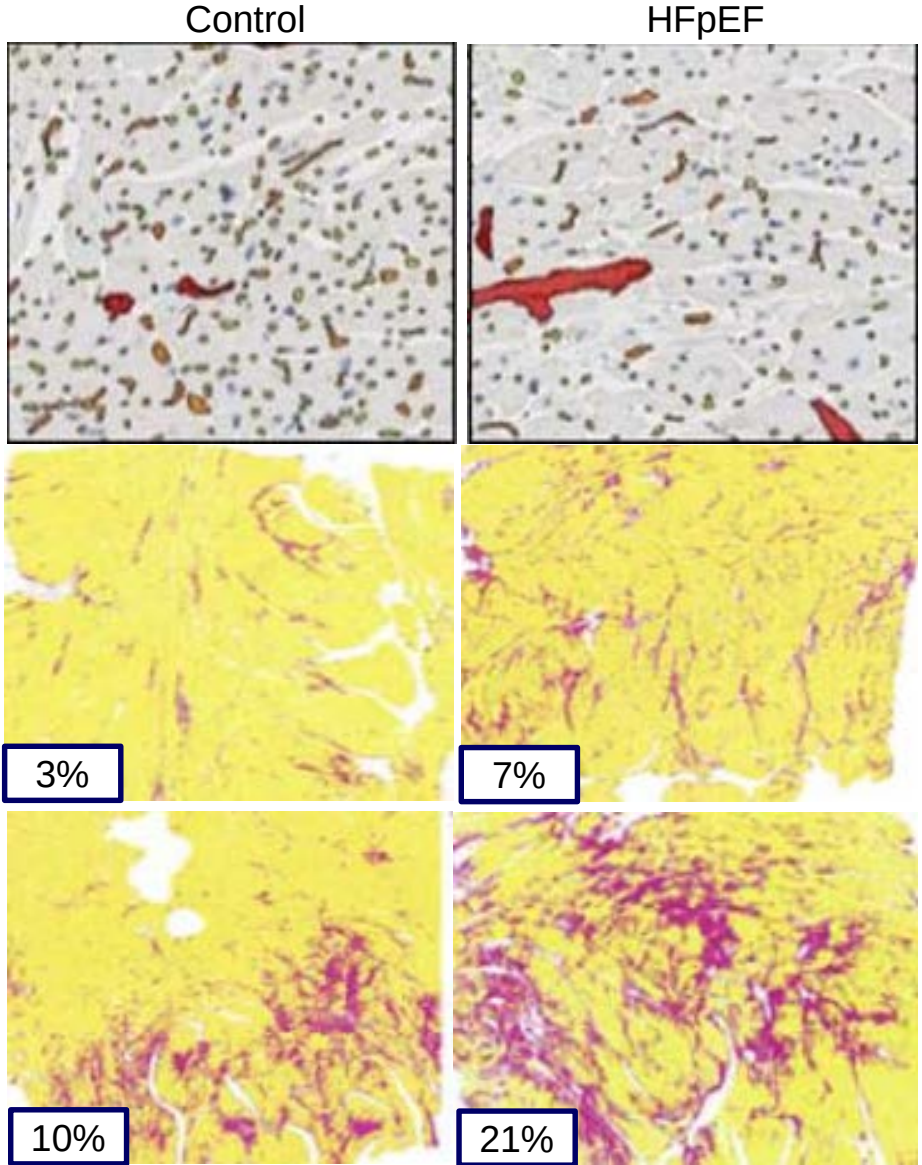




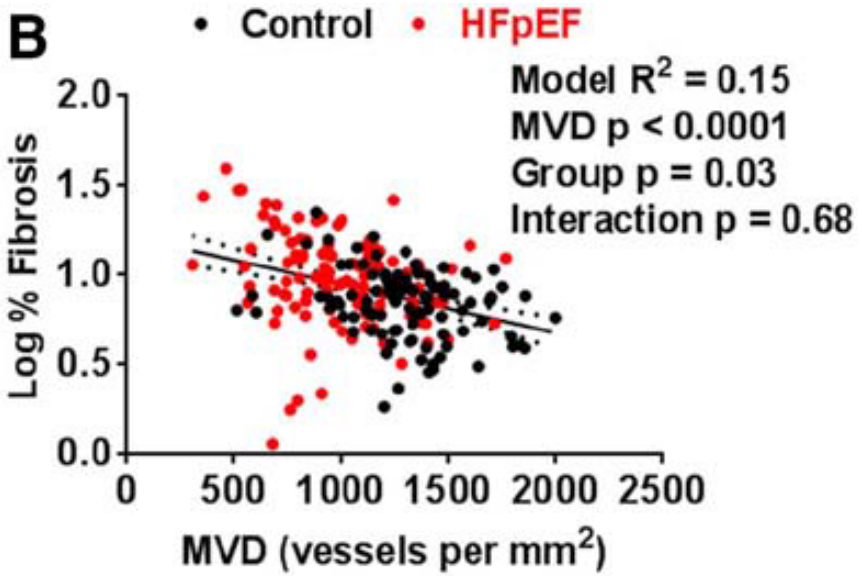
Kasner M et al JACC 2011;57:977

HFpEF: Myocardial fibrosis and capillary rarefaction

Autopsy study HFpEF (n=124) and age-appropriate control subjects (non-cardiac death, no HF;n=104)



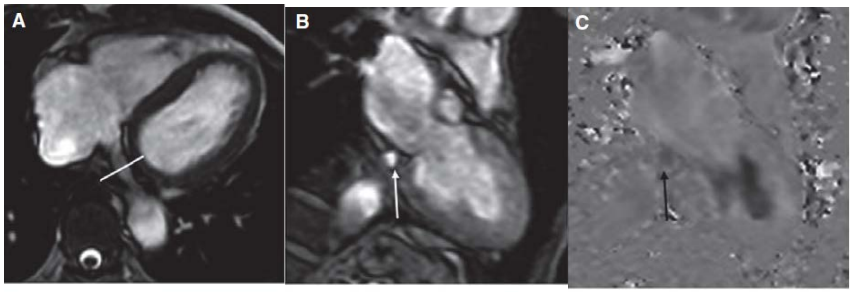
	Control	HFpEF	P value
Microvessels /mm2	1316 (1148-1467)	961 (800-1370)	<0.001
% area fibrosis	7.1 (5.1-9.0)	9.6 (6.8-13.5)	<0.001

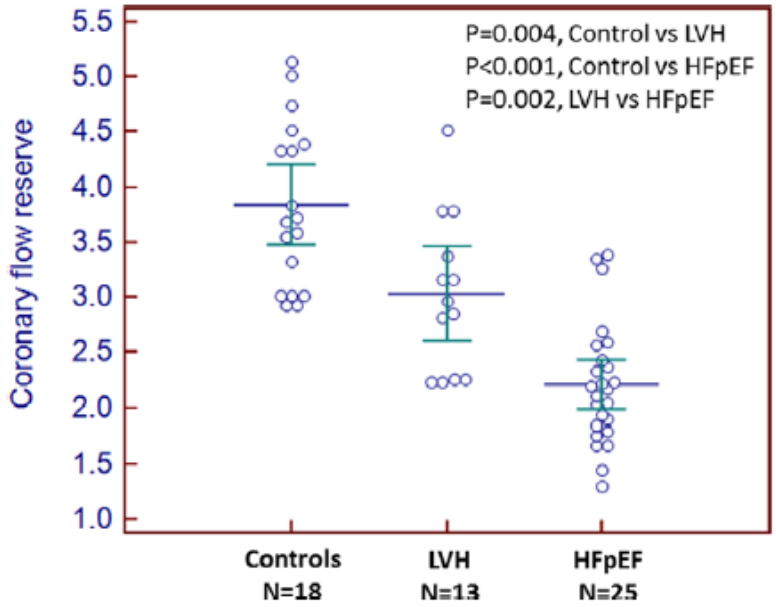


Mohammed SF et al., Circulation 2015;131:550

HFpEF: Impaired coronary and myocardial flow reserve

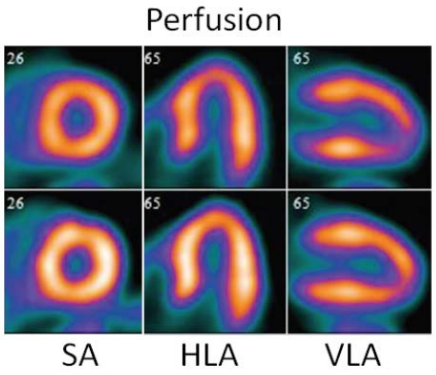
cMRI/adenosine: coronary flow reserve in HFpEF (n=25; 2.21 ±0.55) vs HHD (n=13; 3.05±0.74) and C (n=18; 3.83±0.73;p<0.001)

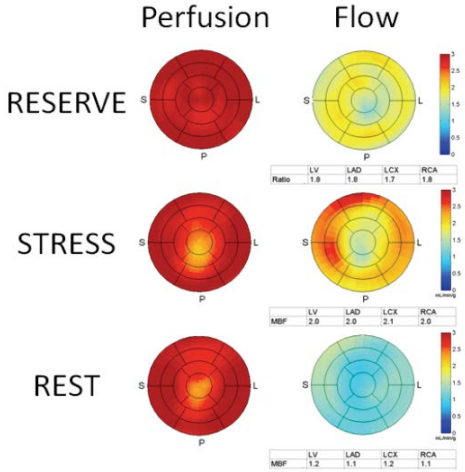




Kato, J Am Heart Assoc 2016;5:e002649

Rb-82 PET myocardial flow reserve (MFR) in HFpEF (n=78) vs Con/HT+ (n=186) and Con/HT- (n=112)

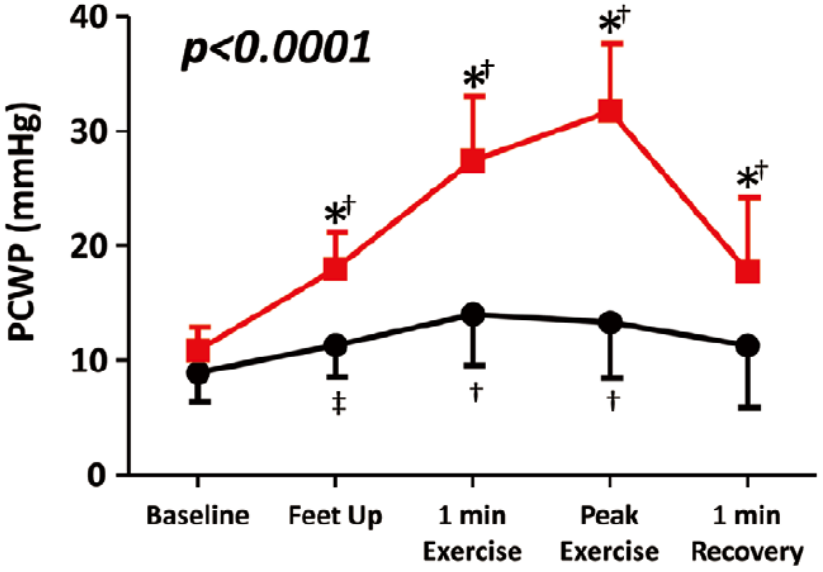


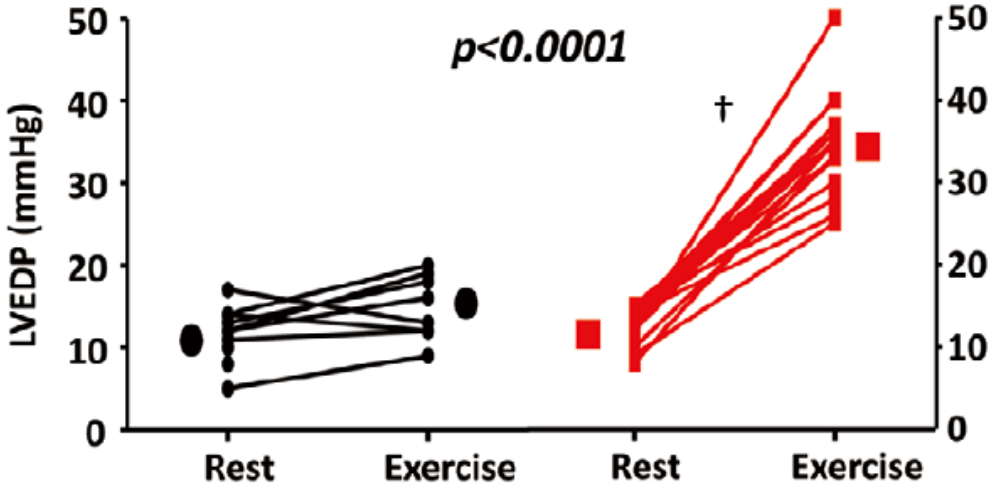


	HFpEF (n=78)	Con/HT + (n=186)	Con/HT – (n=112)	P value
Age, y	68 ± 9	63 ± 11	58 ± 10	<0.001
Resting LVEF, %	62 ± 7	61 ± 7	62 ± 7	0.883
E/E'	14.7 ± 5.8	11.5 ± 3.1	10.2 ± 3.1	0.883
Resting MBF, mL/min/g	0.92 ± 0.26	0.84 ± 0.35	0.79 ± 0.25	0.021
Stress MBF, mL/min/g	1.90 ± 0.61	1.99 ± 0.65	2.16 ± 0.54	<0.001
Global MFR, stress/rest ratio	2.16 ± 0.69	2.54 ± 0.80	2.89 ± 0.70	<0.001

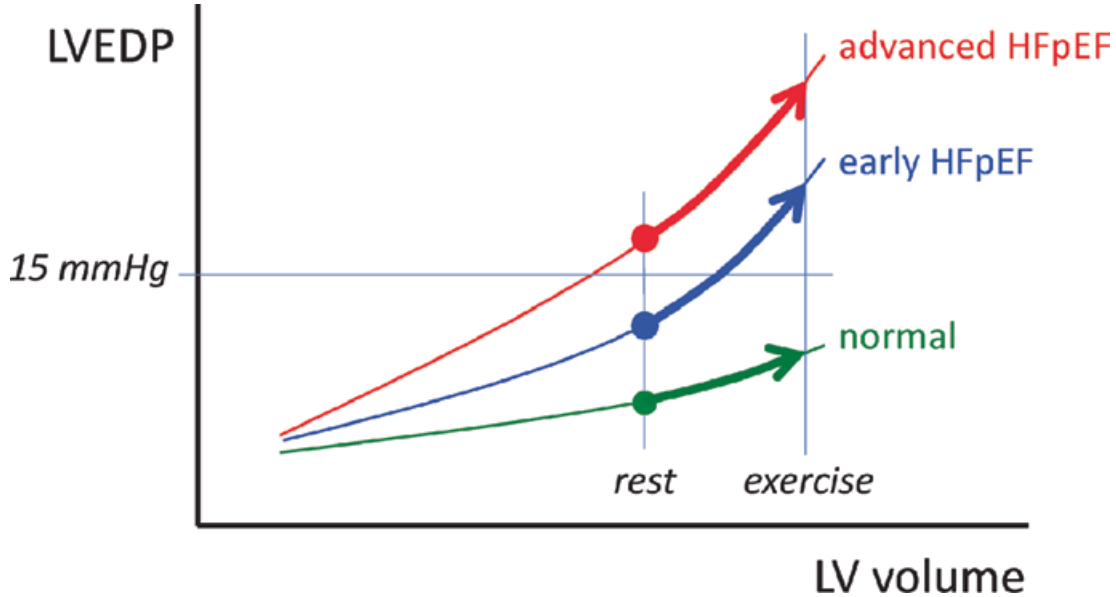
Srivaratharajah K et al. Circ Heart Fail 2016;9:e002562

HFpEF: exercise RHC: identification of non-cardiac dyspnea vs early vs advanced HFpEF





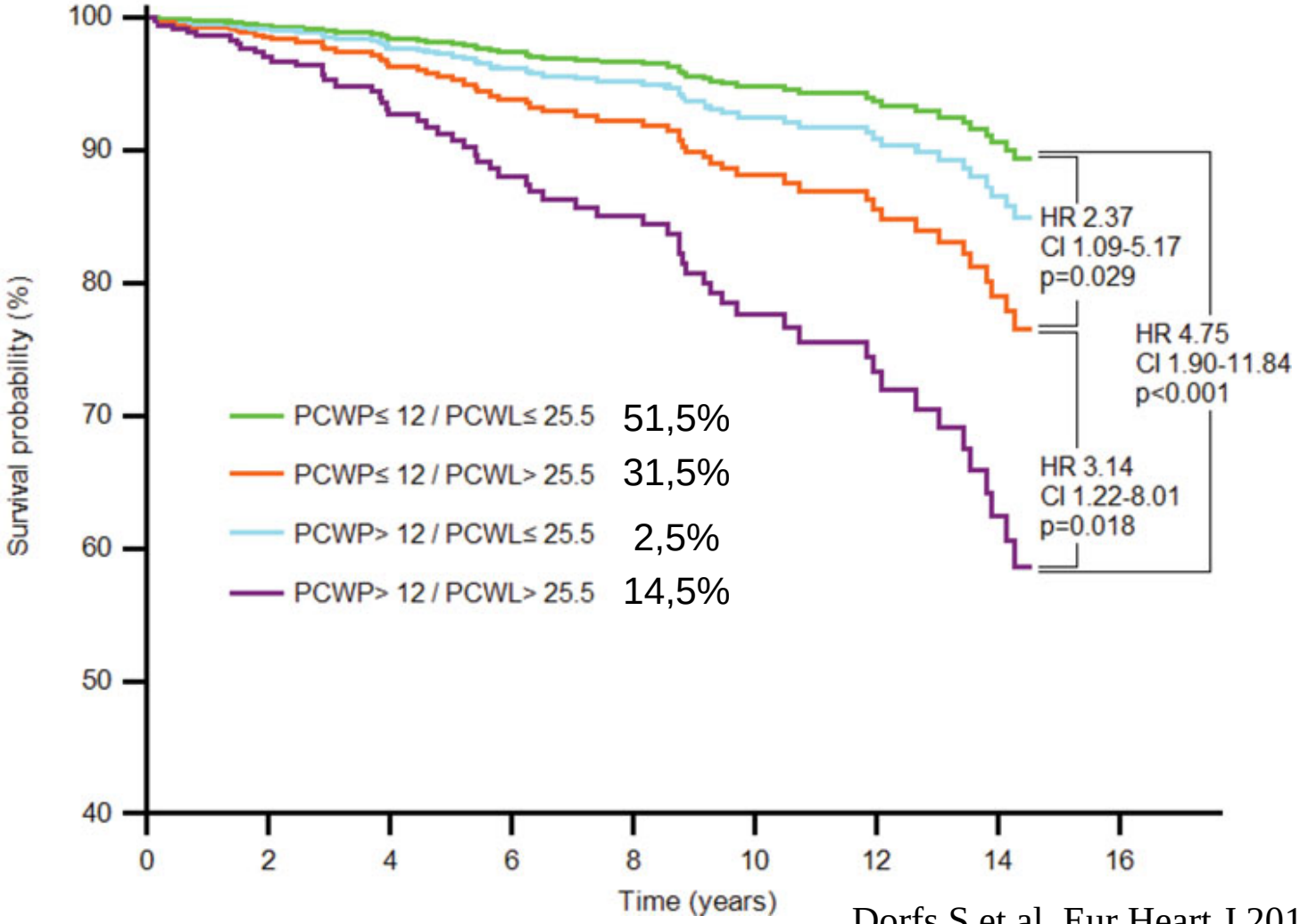
Borlaug BA, Circ J 2014;78:20



Huis in t Veld, Neth Heart J 2016;24:244

HFpEF: ↑ PCWP at rest and with exercise predict outcome

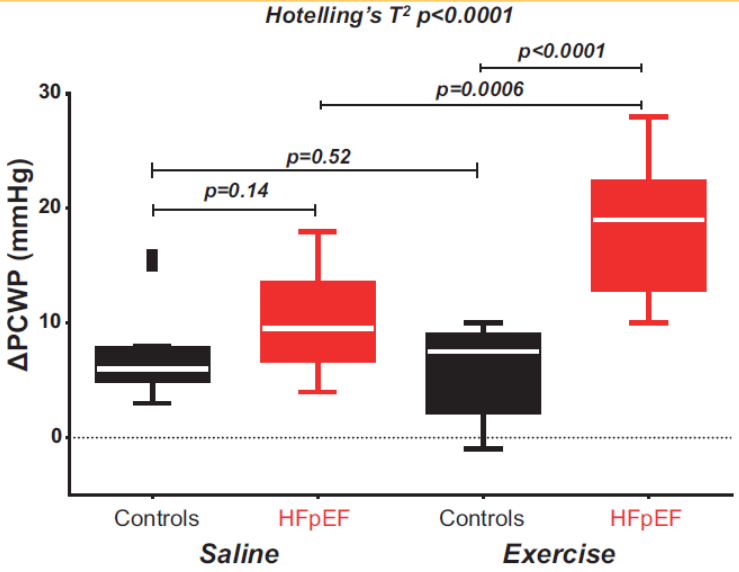
355 pts unexplained dyspnea, suspected HFpEF; no CAD; EF>50%
Right heart cath. at rest (PCWP) and with exercise (ratio of PCWP at peak exercise to workload normalized to body weight; PCWL)

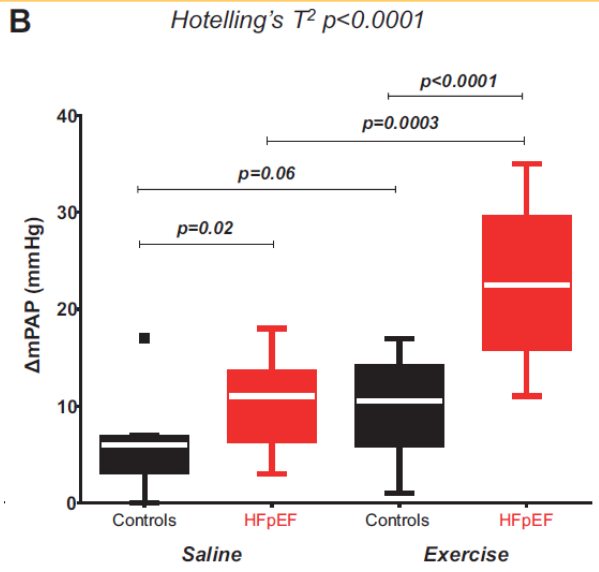


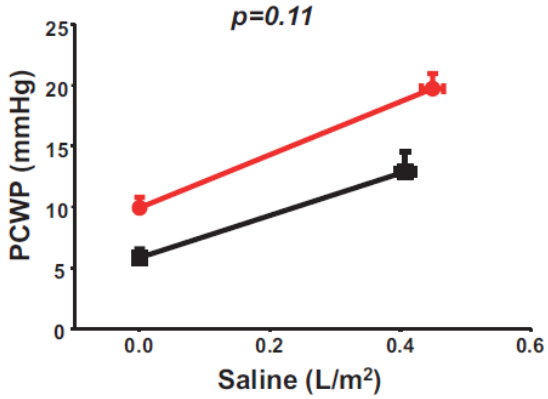
Dorfs S et al, Eur Heart J 2014;35:3103

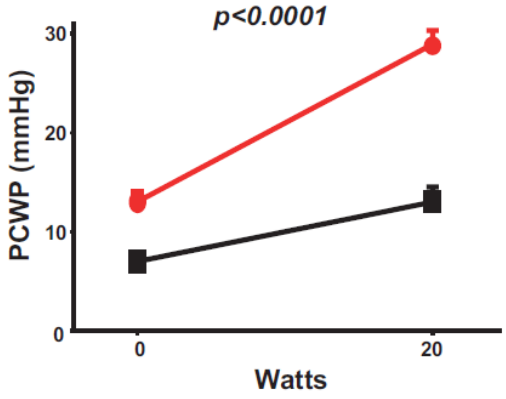
Diastolic stress testing: saline loading vs exercise

RHC rest+exercise study in HFpEF (n=14) and control (n=12); compared to saline loading; exercise led to ≈ 2-fold greater increases in PAP (22±8 vs 11±4 mmHg;p=0.001) and PCWP (18±5 vs 10±4 mmHg;p<0.001)





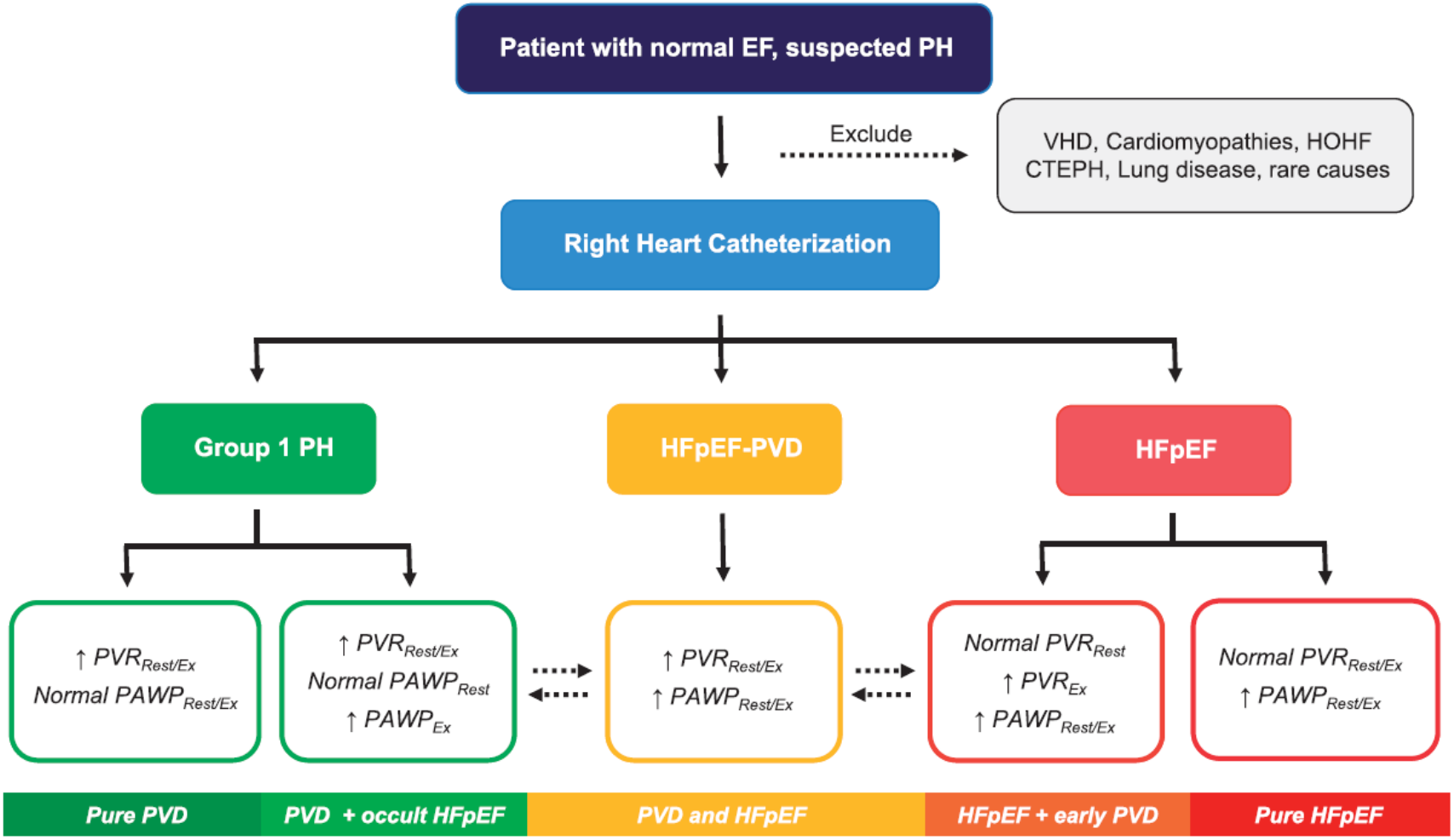




Controls HFpEF

Andersen MJ, Circ Heart Fail 2015;8:41

Invasive stratification of PH in HFpEF



Borlaug BA et al, Eur Heart J 2017;Apr

Table 1. Clinical characteristics.

Parameters	HFpEF patients (n = 67)
Demographics	
Age (yr)	71 ± 9
Women, n (%)	63 (94)
BMI (kg/m²)	32.2 ± 6.11
Hemodynamics	
Systolic BP (mmHg)	147 ± 24
Diastolic BP (mmHg)	76 ± 11
Heart rate (bpm)	71 ± 12
Medical hystory	
T2DM	24 (35.8)
Hypertension	54 (80.6)
COPD	14 (20.9)
Haematology and biochemistry	
MDRD derived eGFR (ml/min/1.73m²)	60.8 ± 15.4
NT-proBNP (pg/ml)	161 (76 – 347)
Haemoglobin (mmol/L)	8.17 ± 0.66
Medications	
ACE inhibitors or ARBs	34 (50.7)
Loop diuretics	23 (34.3)
Thiazide diuretics	17 (25.4)
Aldosteron antagonists	8 (11.9)
Calcium channels-blockers	24 (35.8)
Beta-blockers	38 (56.7)
Oral Hypoglycaemic Agents	21 (31.3)
Insulin	9 (13.4)
Statins	47 (70.1)

Data are shown as n (%) or mean ± SD or median (interquartile range). BMI: Body Mass Index. BP: Blood Pressure. T2DM: Type 2 Diabetes Mellitus. COPD: Chronic Obstructive Pulmonary Disease. MDRD: Modification of Diet in Renal Disease. eGFR: estimated Glomerular Filtration Rate. NT-proBNP: N-terminal pro Brain Natriuretic Peptide. ACE inhibitors: Angiotensin-Converting-Enzyme inhibitors. ARBs: Angiotensin II Receptor Blockers.

Table 2. Echocardiographic characteristics of the HFpEF and controls groups.

Parameters	Controls (n= 58)	HFpEF patients (n = 67)	p value
LVMI (g/m²)	78.1 ± 16.0	86.0 ± 16.5	**0.008**
PWTd (mm)	9.33 ± 1.08	10.4 ± 1.35	**< 0.001**
RWT	0.41 ± 0.04	0.45 ± 0.06	**< 0.001**
LV EDVI (ml/m²)	40.1 (36.0 - 44.5)	40.9 (33.9 – 45.9)	0.941
LV EF (%)	60.0 (58.0 – 63.0)	55.0 (53.0 – 58.0)	**< 0.001**
LV GLS (%)	20.7 ± 1.90	18.6 ± 2.31	**< 0.001**
E/A	0.99 ± 0.23	1.01 ± 0.39	0.662
DT (ms)	174 ± 26.0	208 ± 34.6	**< 0.001**
E' lateral (cm/s)	10.0 ± 2.15	7.17 ± 1.51	**< 0.001**
E' septal (cm/s)	7.62 ± 2.03	5.54 ± 1.10	**< 0.001**
E' mean (cm/s)	8.89 ± 1.94	6.35 ± 1.17	**< 0.001**
E/E' lateral	7.81 ± 2.10	13.0 ± 5.76	**< 0.001**
E/E' septal	10.4 ± 3.02	16.7 ± 5.96	**< 0.001**
E/E' mean	8.83 ± 2.53	14.5 ± 5.24	**< 0.001**
A' mean (cm/s)	10.1 ± 1.83	8.64 ± 2.29	**0.002**
LAVI max (ml/m²)	26.2 ± 5.19	41.4 ± 10.9	**< 0.001**
LAVI pre-A (ml/m²)	18.2 ± 4.53	30.1 ± 8.08	**< 0.001**
LAVI min (ml/m²)	11.6 ± 3.24	22.8 ± 7.24	**< 0.001**
LA global ef (%)	59.8 ± 4.87	46.6 ± 7.08	**< 0.001**
LA passive ef (%)	33.6 ± 5.99	27.3 ± 6.78	**< 0.001**
LA active ef (%)	39.3 ± 6.25	26.4 ± 7.11	**< 0.001**
TR velocity (m/s)	2.50 ± 0.31	2.64 ± 0.37	0.087
TAPSE (mm)	24.2 ± 2.10	23.0 ± 2.72	**0.015**

Data are shown as mean ± SD or median (interquartile range). LVMI: Left Ventricular Mass Index. PWTd: Posterior Wall Thickness in diastole. RWT: Relative Wall Thickness. LV EDVI: Left Ventricular End-diastolic Volume Index. EF: Ejection Fraction. GLS: Global Longitudinal Strain. E/A: peak early filling – E wave – over late diastolic filling – A wave – velocities ratio. DT: Deceleration Time. E': peak early diastolic tissue velocity. A' mean: peak late diastolic tissue velocity. E/E': peak early filling over early diastolic tissue velocities ratio. LAVI max, pre-A, min: Left Atrium Volume Index maximal, at the onset of A wave, minimal. ef: emptying fraction. TR: Tricuspid Regurgitation. TAPSE: Tricuspid Annular Plane Systolic Excursion.

Table 3. Echocardiographic characteristics of controls and HFpEF patients with low NT-proBNP (< median).

Parameters	Controls (n = 58)	Low NT-proBNP (n = 32)	p value
LVMI (g/m²)	78.1 ± 16.0	85.6 ± 13.7	**0.028**
PWTd (mm)	9.33 ± 1.08	10.4 ± 1.22	**< 0.001**
RWT	0.41 ± 0.04	0.44 ± 0.05	**0.002**
LV EDVI (ml/m²)	40.1 (36.0 - 44.5)	41.7 (37.3 – 47.2)	0.193
LV EF (%)	60.0 (58.0 – 63.0)	55.0 (54.0 – 58)	**< 0.001**
LV GLS (%)	20.7 ± 1.90	18.5 ± 2.42	**< 0.001**
E/A	0.99 ± 0.23	0.96 ± 0.26	0.563
DT (ms)	174 ± 26.0	214 ± 32.4	**< 0.001**
E' lateral (cm/s)	10.0 ± 2.15	7.43 ± 1.30	**< 0.001**
E' septal (cm/s)	7.62 ± 2.03	5.77 ± 1.01	**< 0.001**
E' mean (cm/s)	8.89 ± 1.94	6.47 ± 1.18	**< 0.001**
E/E' lateral	7.81 ± 2.10	11.5 ± 3.56	**< 0.001**
E/E' septal	10.4 ± 3.02	14.5 ± 3.43	**< 0.001**
E/E' mean	8.83 ± 2.53	12.7 ± 3.26	**< 0.001**
A' mean (cm/s)	10.1 ± 1.83	9.60 ± 1.94	0.429
LAVI max (ml/m²)	26.2 ± 5.19	39.9 ± 8.34	**< 0.001**
LAVI pre-A (ml/m²)	18.2 ± 4.53	28.5 ± 6.39	**< 0.001**
LAVI min (ml/m²)	11.6 ± 3.24	20.9 ± 4.86	**< 0.001**
LA global ef (%)	59.8 ± 4.87	49.1 ± 7.04	**< 0.001**
LA passive ef (%)	33.6 ± 5.99	28.7 ± 5.61	**< 0.001**
LA active ef (%)	39.3 ± 6.25	28.3 ± 7.49	**< 0.001**
TR velocity (m/s)	2.50 ± 0.31	2.62 ± 0.38	0.237
TAPSE (mm)	24.2 ± 2.10	23.4 ± 3.04	0.813

Data are shown as mean ± SD or median (interquartile range). LVMI: Left Ventricular Mass Index. PWTd: Posterior Wall Thickness in diastole. RWT: Relative Wall Thickness. LV EDVI: Left Ventricular End-diastolic Volume Index. EF: Ejection Fraction. GLS: Global Longitudinal Strain. E/A: peak early filling – E wave – over late diastolic filling – A wave – velocities ratio. DT: Deceleration Time. E': peak early diastolic tissue velocity. A' mean: peak late diastolic tissue velocity. E/E': peak early filling over early diastolic tissue velocities ratio. LAVI max, pre-A, min: Left Atrium Volume Index maximal, at the onset of A wave, minimal. ef: emptying fraction. TR: Tricuspid Regurgitation. TAPSE: Tricuspid Annular Plane Systolic Excursion.

Table 4. Echocardiographic and clinical characteristics of controls and HFpEF patients with low (< median) and high (> median) NT-proBNP.

Parameters	Low NT-proBNP (n = 32)	High NT-proBNP (n = 35)	p value
Age (yr)	70 ± 9	72 ± 8	0.272
BMI (kg/mq)	33.4 ± 5.78	31.2 ± 6.31	0.150
T2DM	11 (34.4)	13 (37.1)	0.813
Hypertension	26 (81.2)	28 (82.8)	0.844
MDRD derived eGFR (ml/min/1.73mq)	66.8 ± 11.6	54.4 ± 16.5	**0.004**
Use of loop diuretics	4 (12.5)	19 (54.3)	**<0.001**
LVMI (g/m²)	85.6 ± 13.7	86.4 ± 18.9	0.855
PWTd (mm)	10.4 ± 1.22	10.4 ± 1.48	0.836
RWT	0.44 ± 0.05	0.45 ± 0.07	0.5393
LV EDVI (ml/m²)	41.7 (37.3 – 47.2)	37 (30.7 – 43.9)	0.076
LV EF (%)	55.0 (54.0 – 58)	55.0 (52.0 – 58.0)	0.899
LV GLS (%)	18.5 ± 2.42	18.7 ± 2.22	0.806
E/A	0.96 ± 0.26	1.06 ± 0.49	0.272
DT (ms)	214 ± 32.4	204 ± 36.2	0.251
E' lateral (cm/s)	7.43 ± 1.30	6.92 ± 1.66	0.174
E' septal (cm/s)	5.77 ± 1.01	5.33 ± 1.16	0.127
E' mean (cm/s)	6.47 ± 1.18	6.09 ±1.30	0.092
E/E' lateral	11.5 ± 3.56	14.4 ± 7.07	**0.040**
E/E' septal	14.5 ± 3.43	18.9 ± 7.02	**0.004**
E/E' mean	12.7 ± 3.26	16.2 ± 6.18	**0.009**
A' mean (cm/s)	9.60 ± 1.94	7.61 ± 2.10	**<0.001**
LAVI max (ml/m²)	39.9 ± 8.34	42.8 ± 12.8	0.277
LAVI pre-A (ml/m²)	28.5 ± 6.39	31.6 ± 9.25	0.125
LAVI min (ml/m²)	20.9 ± 4.86	24.5 ± 8.61	**0.041**
LA global ef (%)	49.1 ± 7.04	44.2 ± 6.34	**0.004**
LA passive ef (%)	28.7 ± 5.61	25.9 ± 7.56	0.104
LA active ef (%)	28.3 ± 7.49	24.6 ± 6.52	**0.035**
TR velocity (m/s)	2.62 ± 0.38	2.66 ± 0.37	0.797
TAPSE (mm)	23.4 ± 3.04	22.7 ± 2.40	0.319

Data are shown as n (%) or mean ± SD or median (interquartile range). BMI: Body Mass Index. T2DM: Type 2 Diabetes Mellitus. MDRD: Modification of Diet in Renal Disease. eGFR: estimated Glomerular Filtration Rate. LVMI: Left Ventricular Mass Index. PWTd: Posterior Wall Thickness in diastole. RWT: Relative Wall Thickness. LV EDVI: Left Ventricular End-diastolic Volume Index. EF: Ejection Fraction. GLS: Global Longitudinal Strain. E/A: peak early filling – E wave – over late diastolic filling – A wave – velocities ratio. DT: Deceleration Time. E': peak early diastolic tissue velocity. A' mean: peak late diastolic tissue velocity. E/E': peak early filling over early diastolic tissue velocities ratio. LAVI max, pre-A, min: Left Atrium Volume Index maximal, at the onset of A wave, minimal. ef: emptying fraction. TR: Tricuspid Regurgitation. TAPSE: Tricuspid Annular Plane Systolic Excursion

Figure 3. Relationship between NT-proBNP and echocardiographic indices.

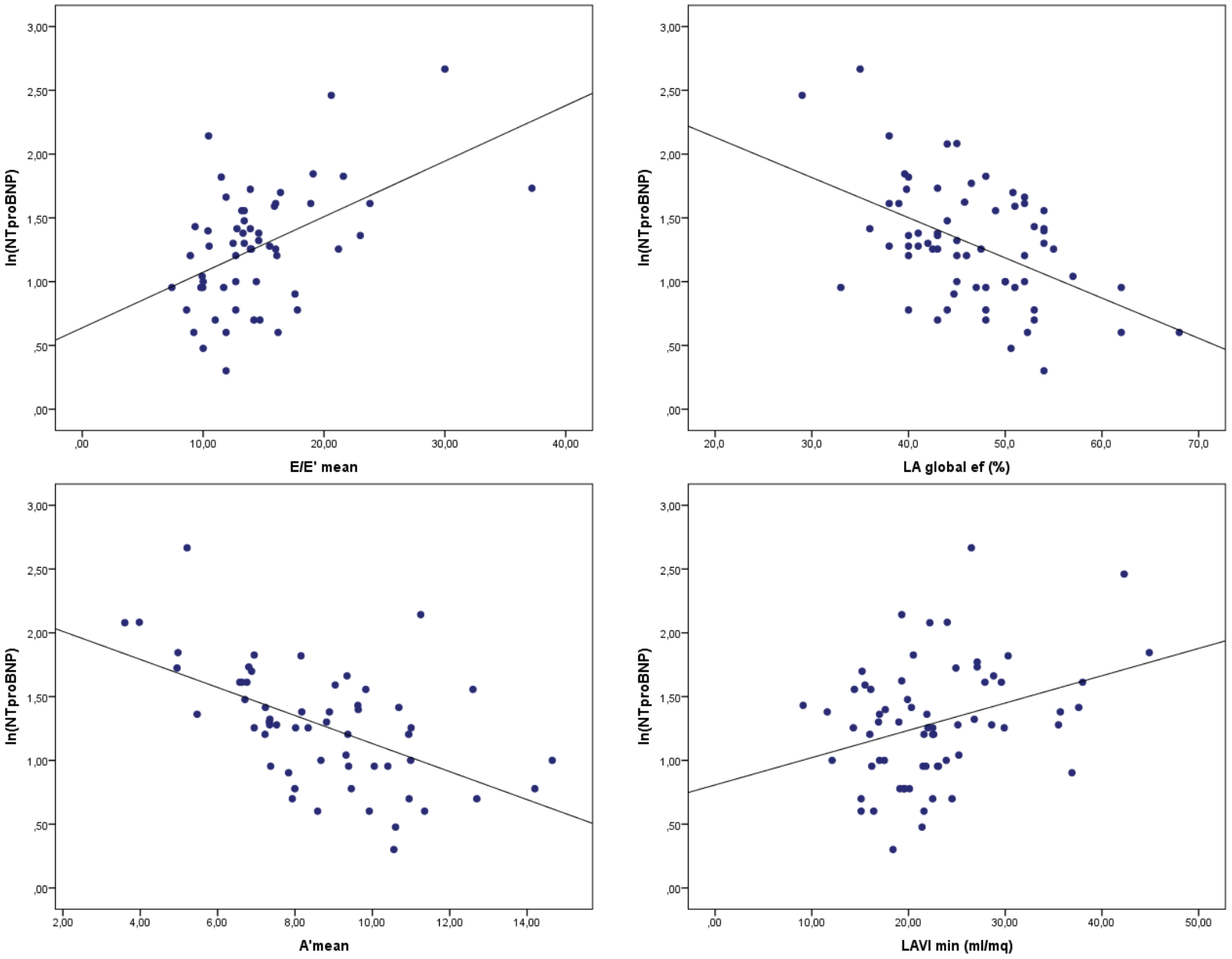
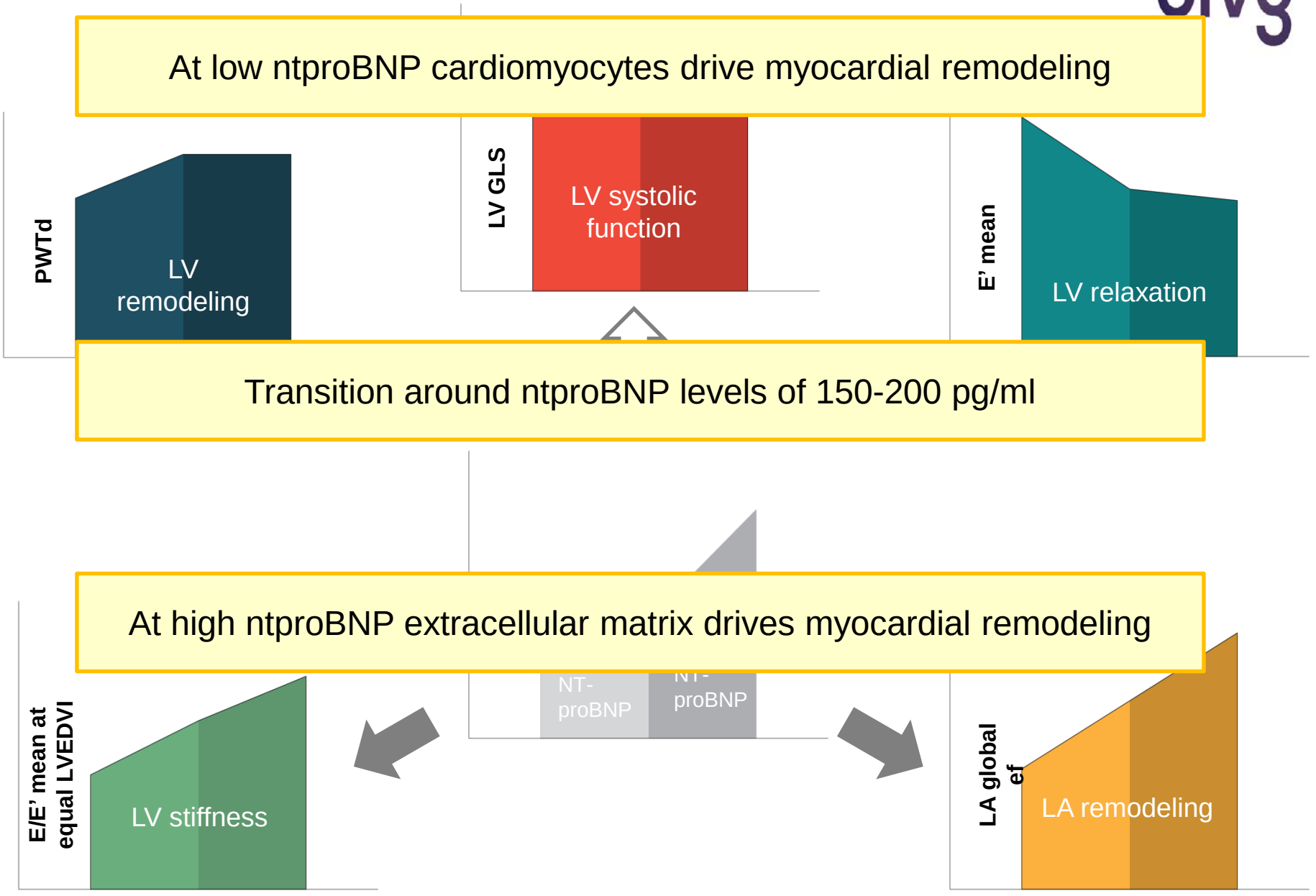


Figure 4. Cardiac remodeling and dysfunction with rising NT-proBNP



Can Exercise Teach Us How to Treat Heart Disease?
Fig1 misschien Fig2

Mann N et al, Circulation 2012;126:2625

Exercise effects in TOPCAT
Poor intermediate ideal

Hegde SM et al, Circulation 2017;136:982