

# Disclosures

(potentiële) belangenverstremgeling	Zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
<ul style="list-style-type: none"><li>• Sponsoring of onderzoeksgeld</li><li>• Honorarium of andere (financiële) vergoeding</li><li>• Aandeelhouder</li><li>• Andere relatie, namelijk ...</li></ul>	<ul style="list-style-type: none"><li>•</li><li>• Sprekersvergoeding Novartis, Boehringer Ingelheim, Servier, Bayer</li><li>•</li><li>•</li></ul>

# Assessments in Diastolic Heart Failure

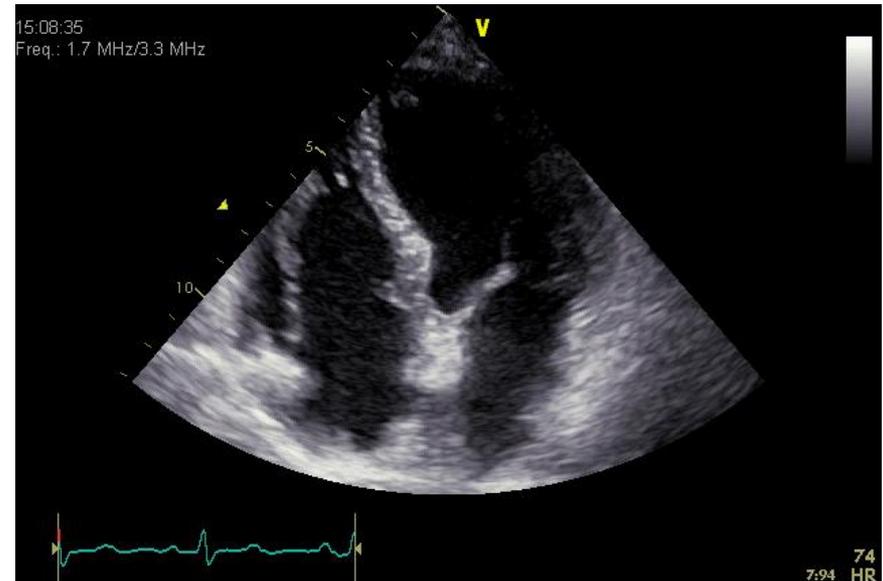
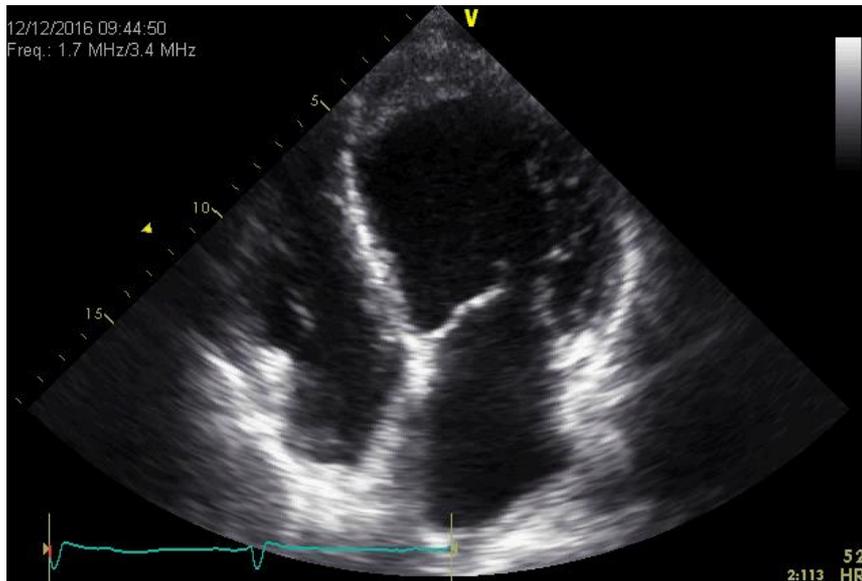


Loek van Heerebeek, Cardiologist, MD, PhD, FESC

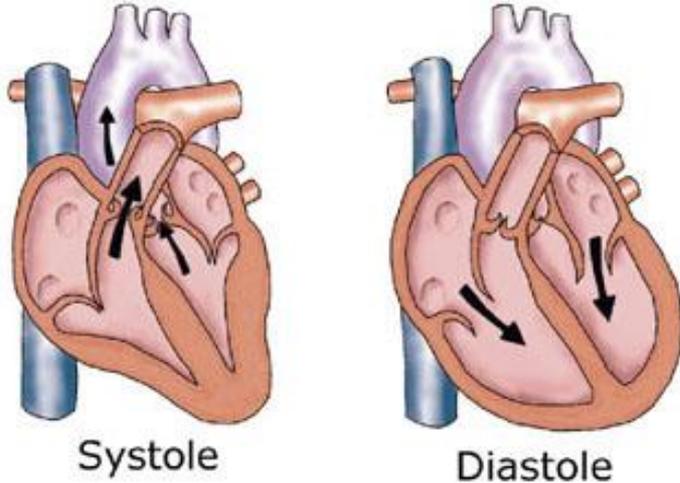
**Table 3.1** Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF	HFrEF	HFmrEF	HFpEF
<b>CRITERIA</b>	<b>1</b>	Symptoms ± Signs <sup>a</sup>	Symptoms ± Signs <sup>a</sup>
	<b>2</b>	LVEF <40%	LVEF 40–49%
	<b>3</b>	–	1. Elevated levels of natriuretic peptides <sup>b</sup> ; 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).

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

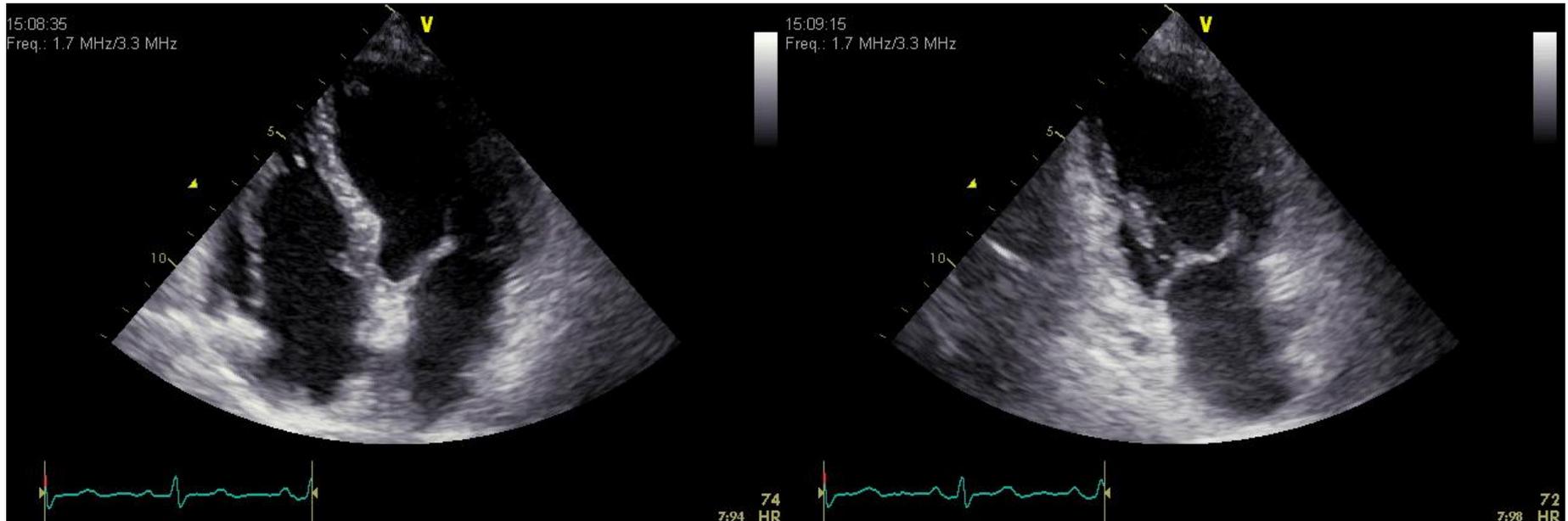


# HF terminology – based on LV ejection fraction (LVEF)

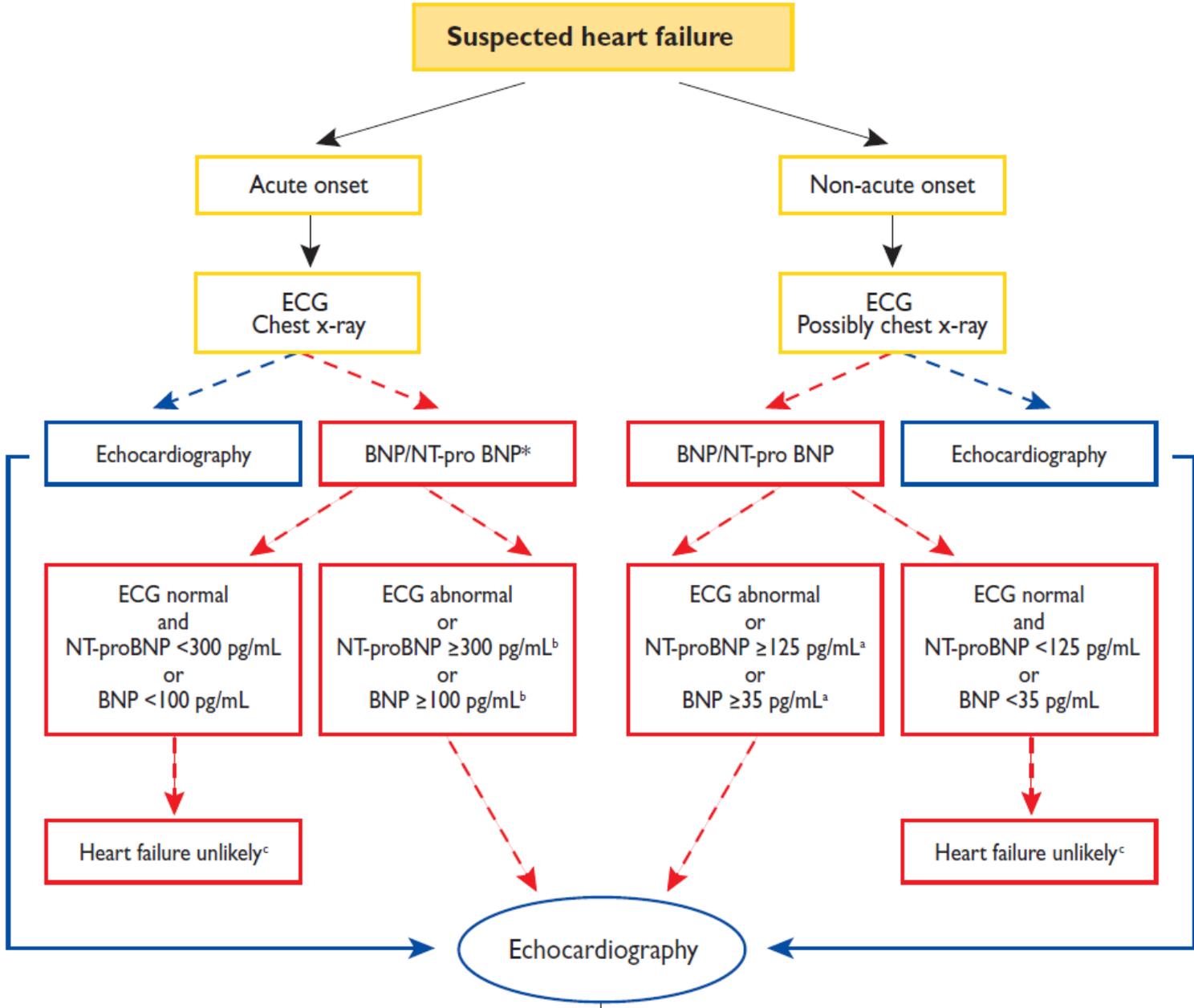


LV ejection fraction =

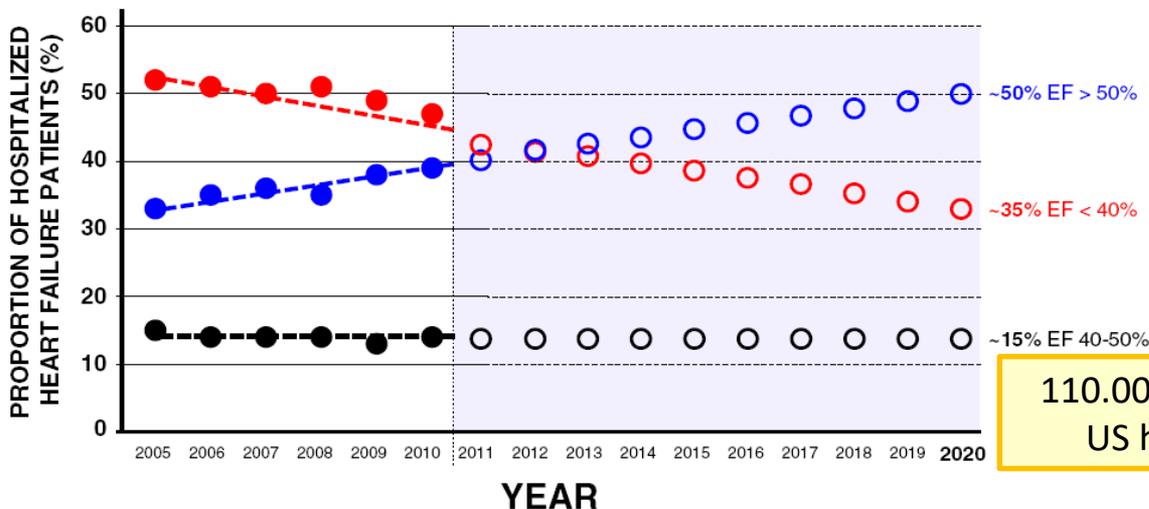
$$\frac{\text{LV EDV} - \text{LV ESV}}{\text{LV EDV}} * 100$$



# Diagnosis of HF

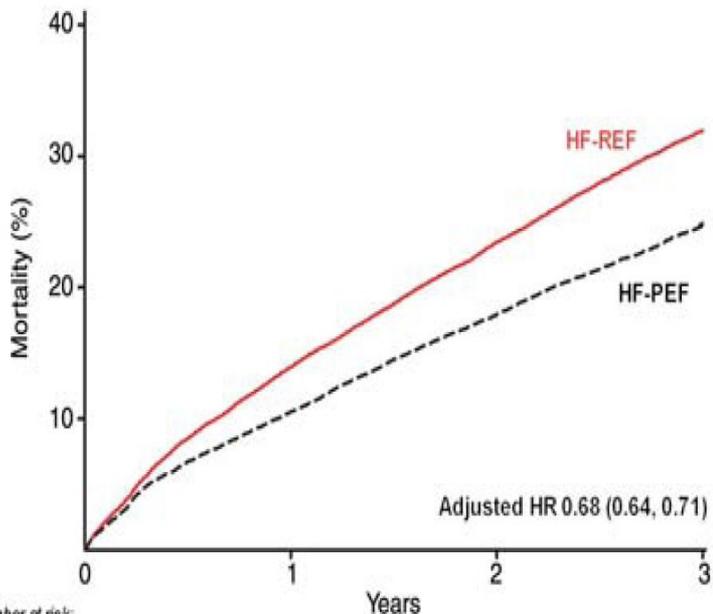


# Prevalence, prognosis and treatment of HFrEF vs HFpEF

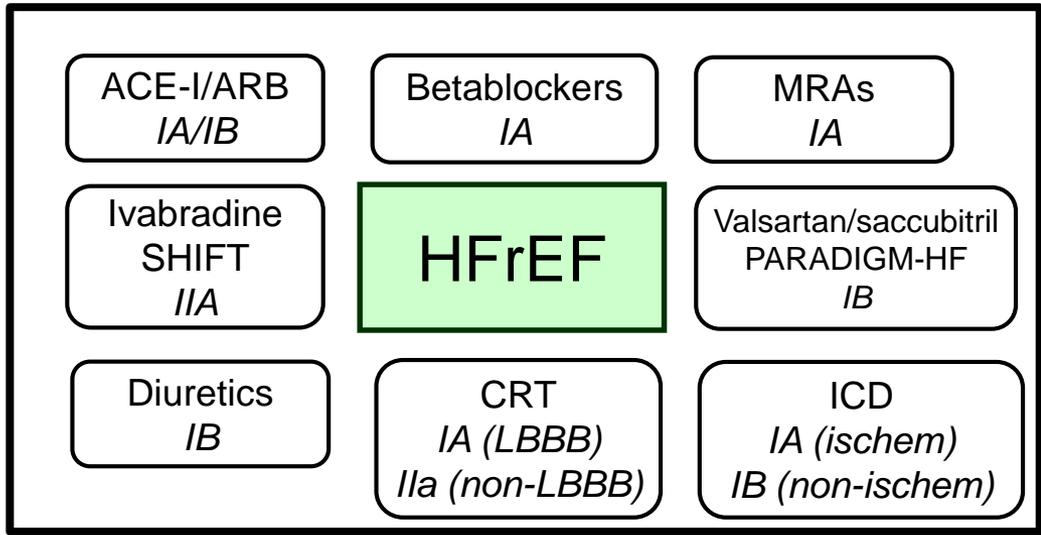


Steinberg BA et al.  
Circulation  
2012;126:65

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

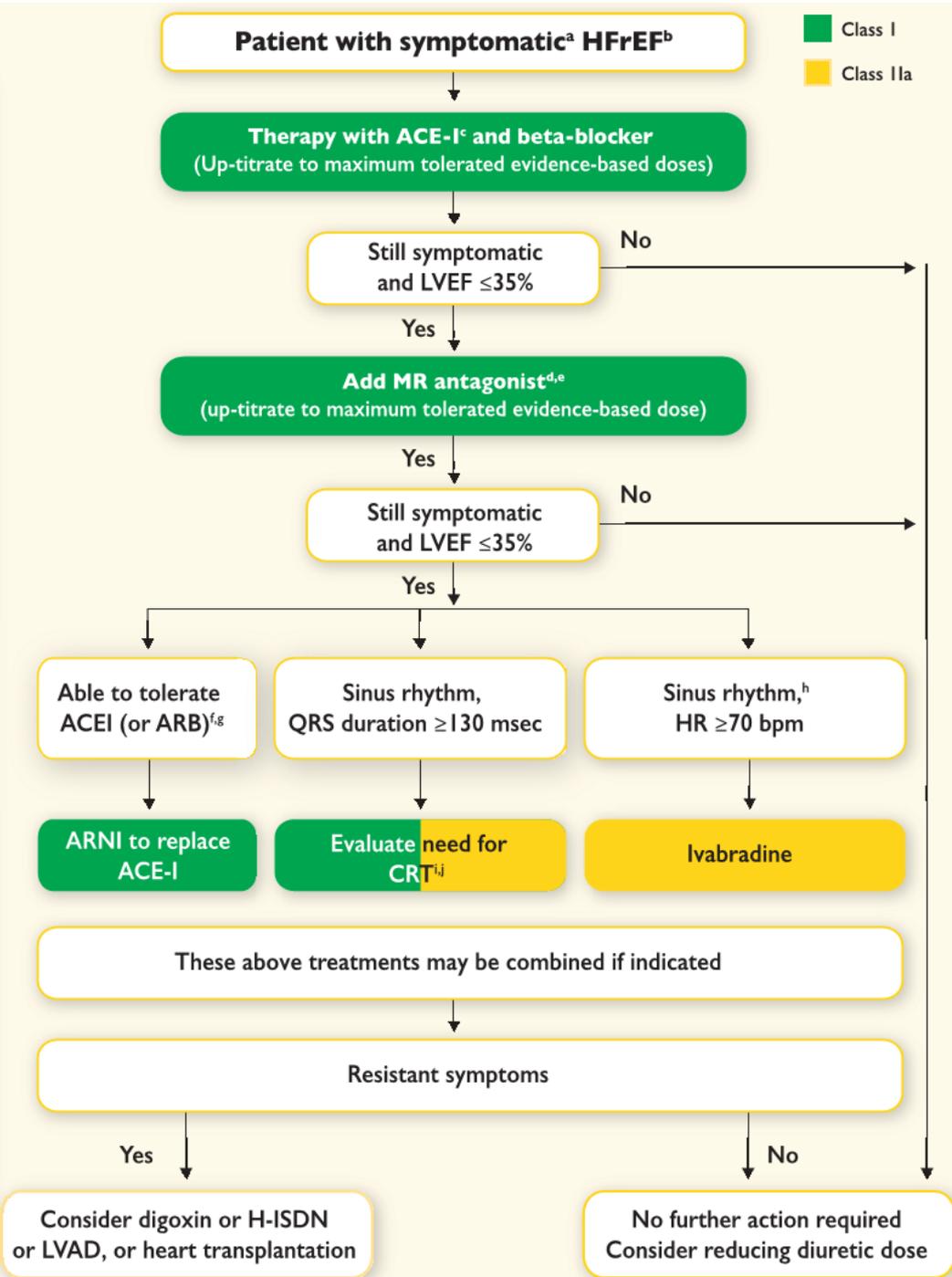


	0	1	2	3
Number at risk:				
HF-REF	28803	21012	16510	12247
HF-PEF	9518	6725	5728	4346



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

Diuretics to relieve symptoms and signs of congestion  
 If LVEF  $\leq 35\%$  despite OMT or a history of symptomatic VT/VF, implant ICD

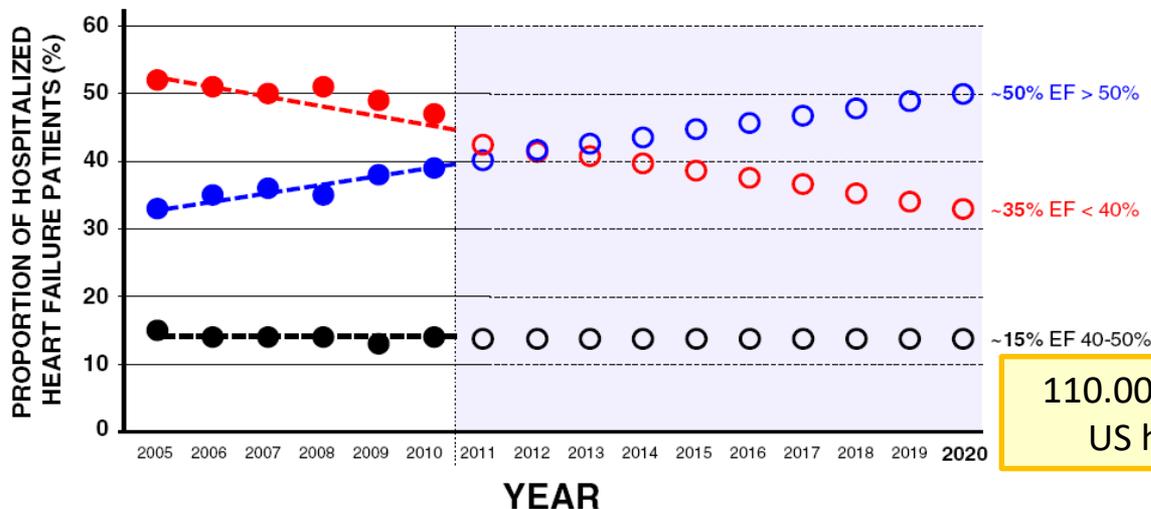


■ Class I  
■ Class IIa

Consider digoxin or H-ISDN  
 or LVAD, or heart transplantation

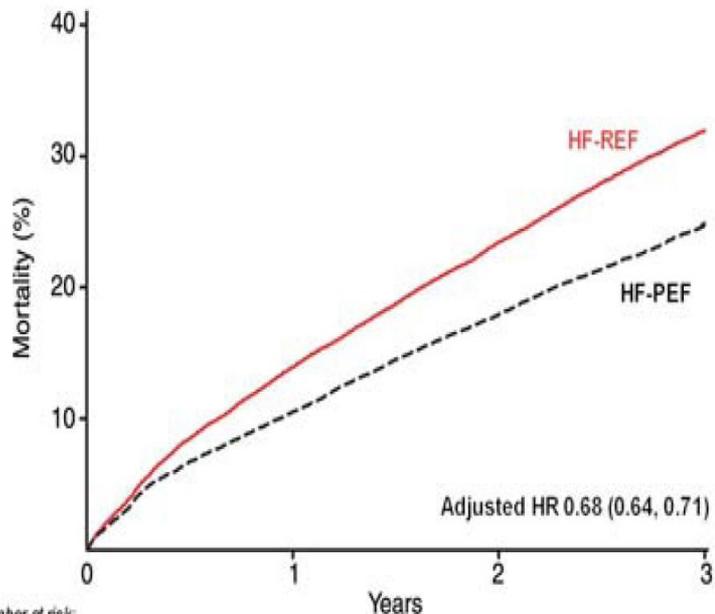
No further action required  
 Consider reducing diuretic dose

# Prevalence, prognosis and treatment of HFrEF vs HFpEF

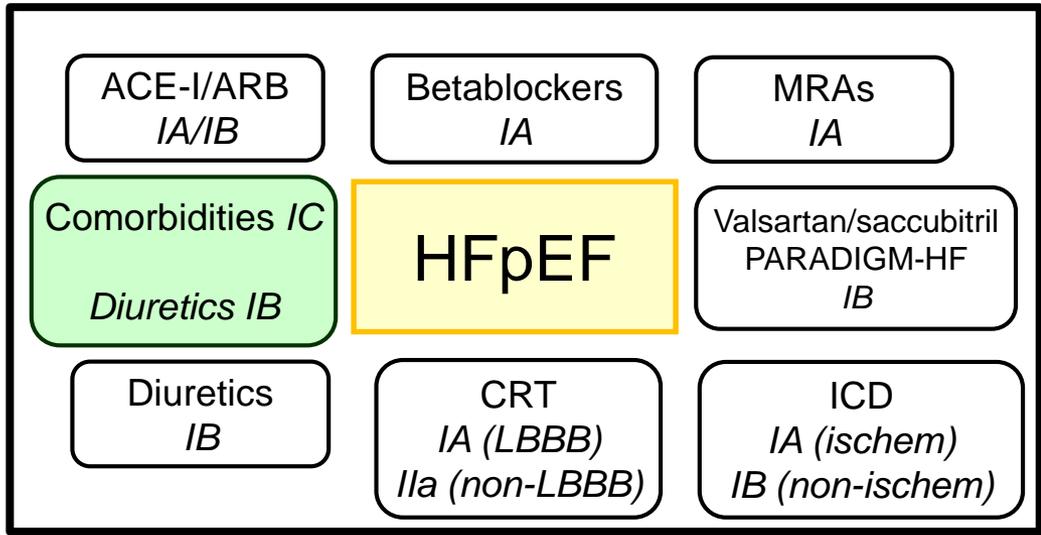


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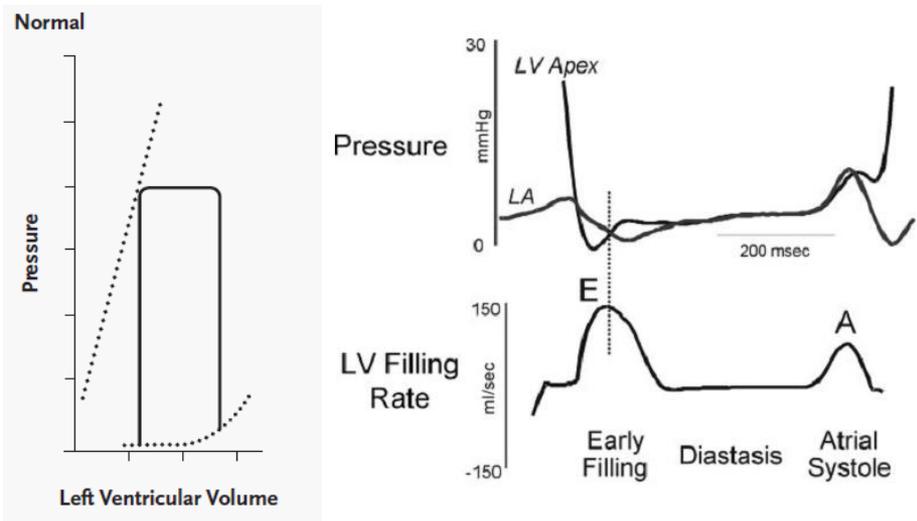


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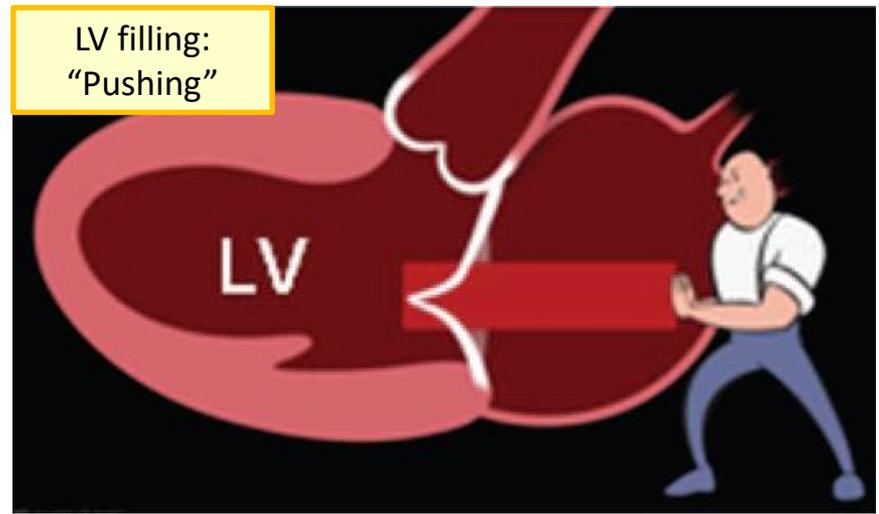
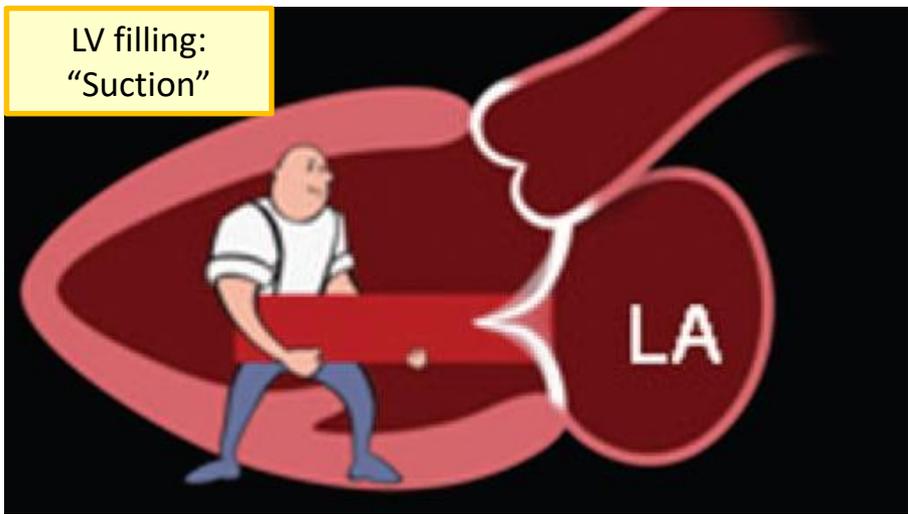
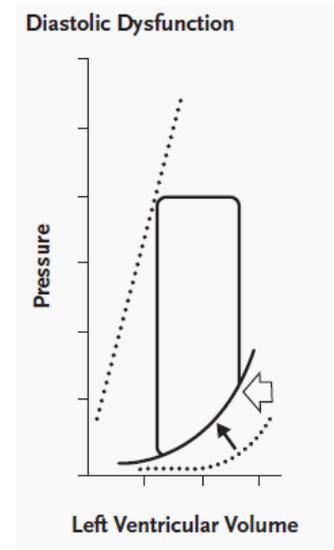


31 HF trials: HFpEF (n=10347) vs HFrEF (n=31625)

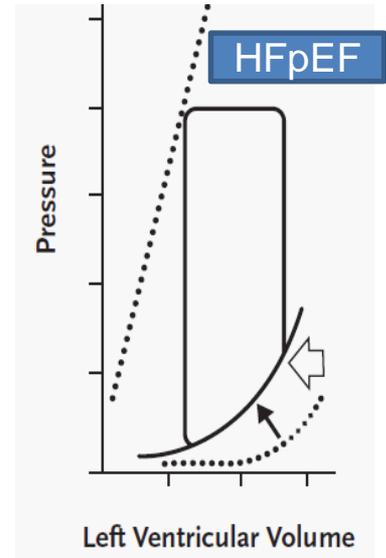
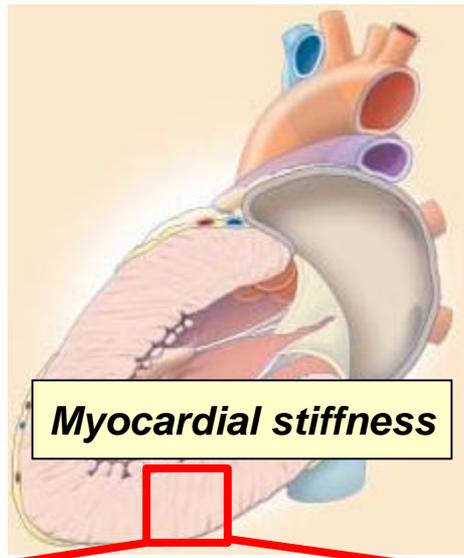
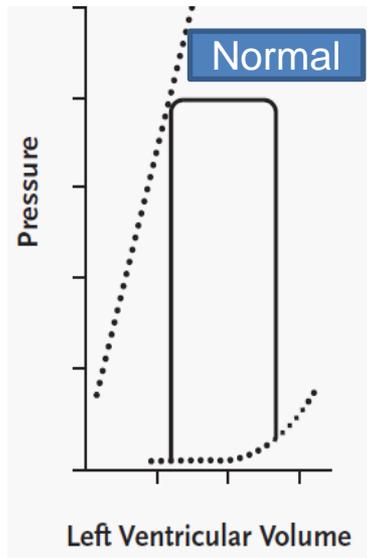
## Normal diastolic function



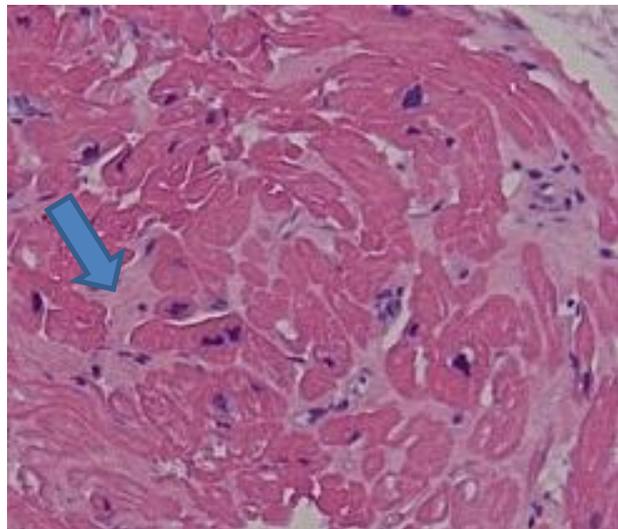
## Diastolic dysfunction



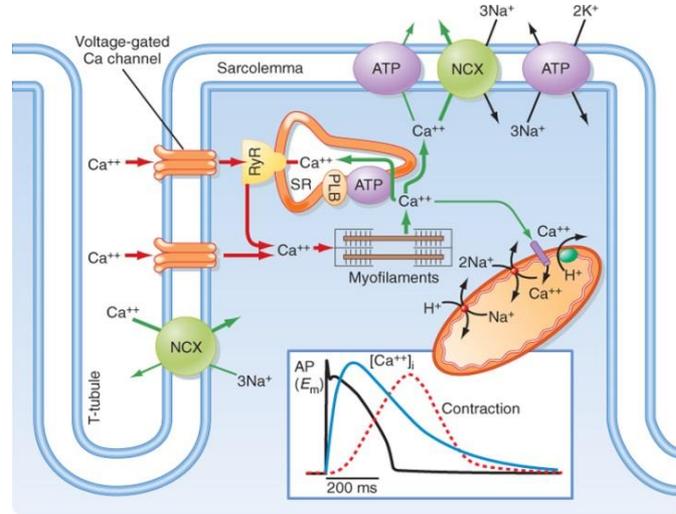
# HFpEF: High diastolic LV stiffness



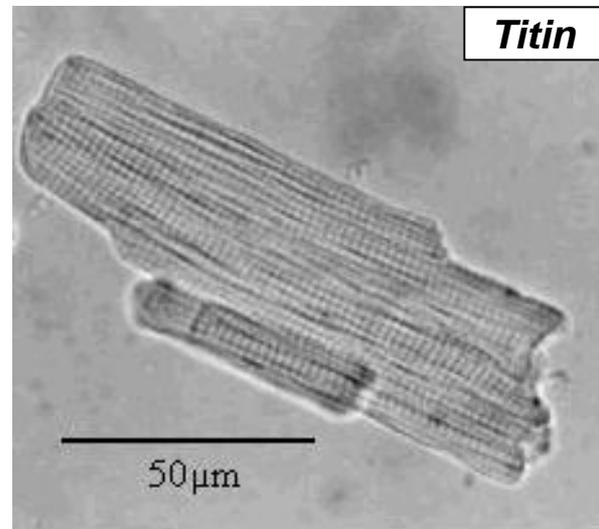
## ECM - Collagen



## Impaired relaxation



## ↑ CM stiffness



# “The typical HFpEF patient”

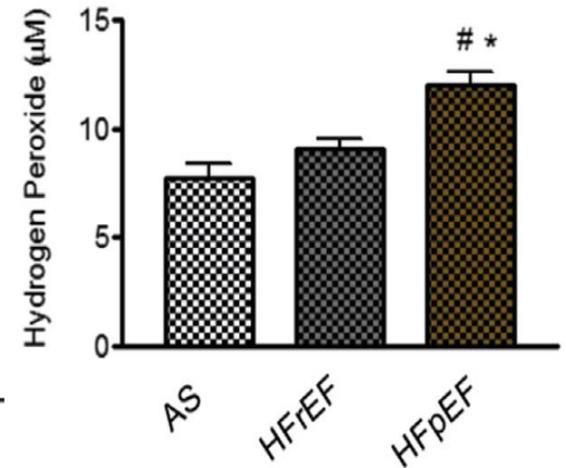
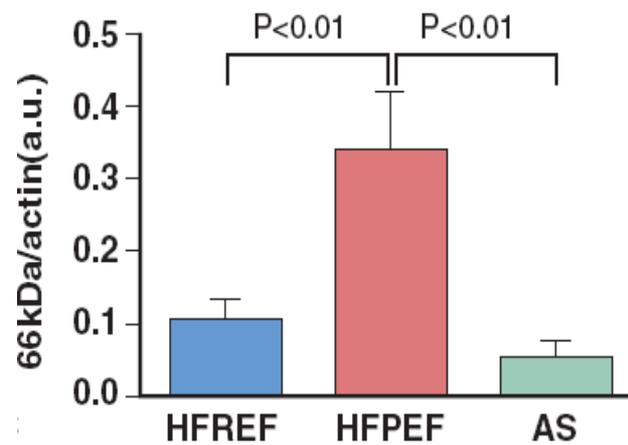
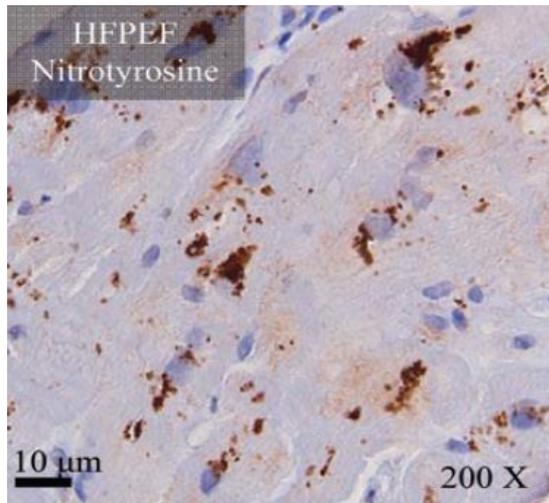
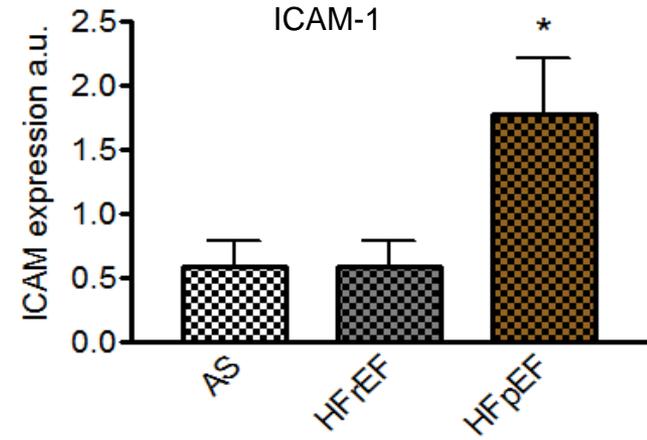
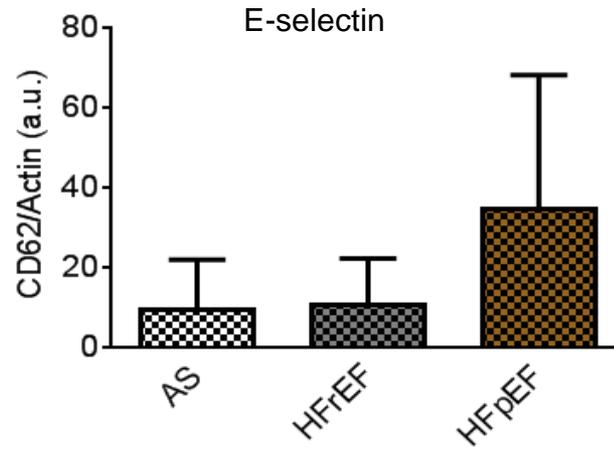
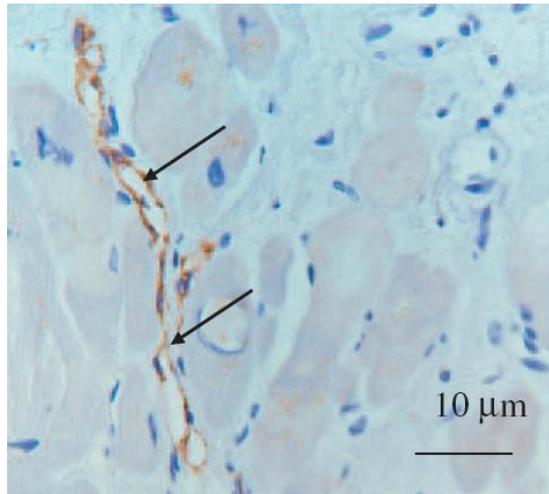


Systemic inflammation

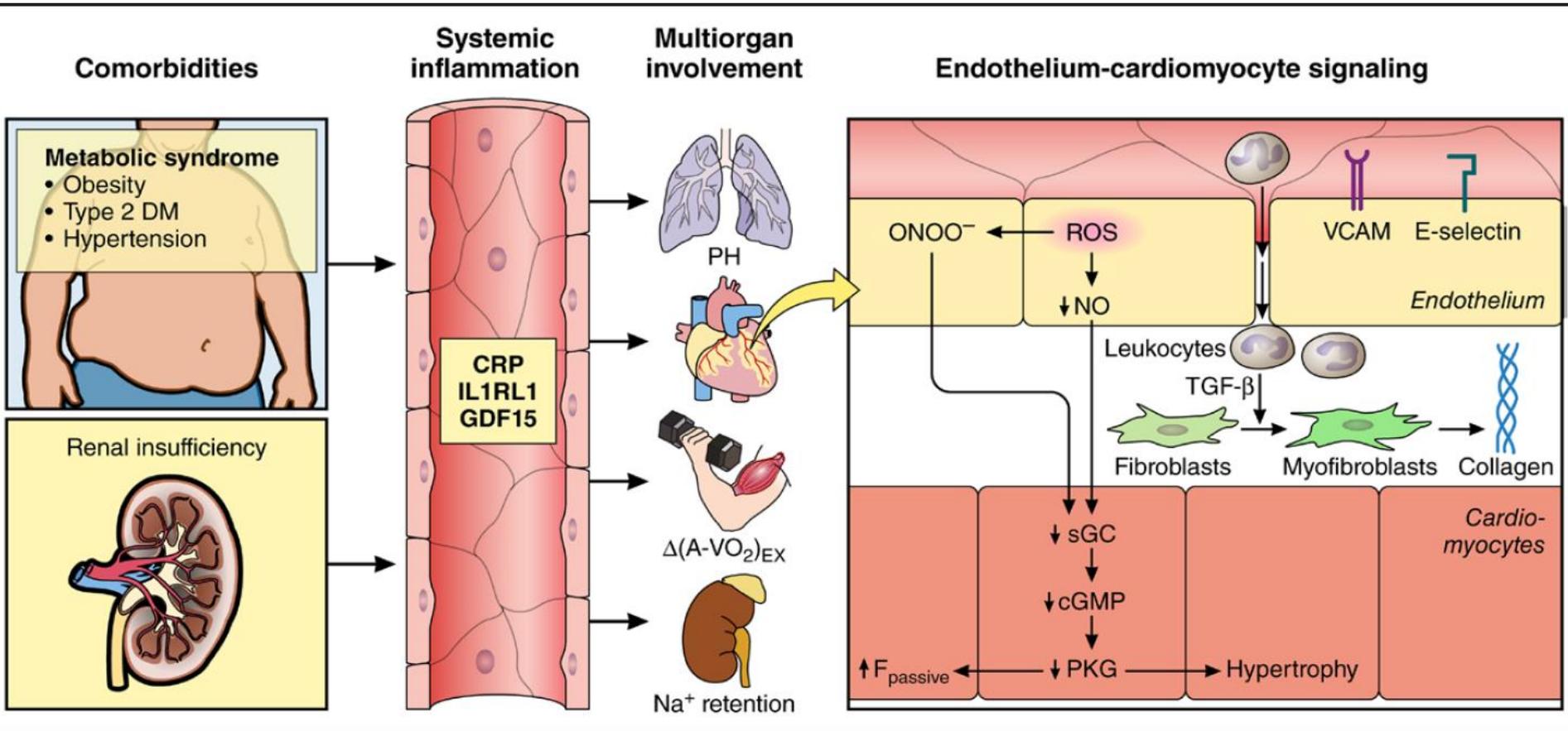
## HFpEF: Demographics and comorbidities

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: coronary microvascular endothelial inflammation



# The new HFpEF paradigm



# Diagnosis



# HFpEF: Diagnosis

Symptoms and signs of heart failure

Normal or mildly reduced LV systolic function  
LVEF >50% and LVEDVI  $\leq$  97 ml/m<sup>2</sup>

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

Invasive hemodynamic  
measurements

Echocardiography

Biomarkers  
(NT-proBNP >220 pg/ml)

mPCWP > 12 mmHg  
Or  
LVEDP > 16 mmHg

E/E' >15

15 > E/E' > 8

NT-proBNP  
>220 pg/ml

\*E/A ratio <0.5; DT >280 ms  
\*LA volume index (>40 ml/m<sup>2</sup>)  
\*LV mass index >122 or 149 g/m<sup>2</sup>  
\*Atrial fibrillation

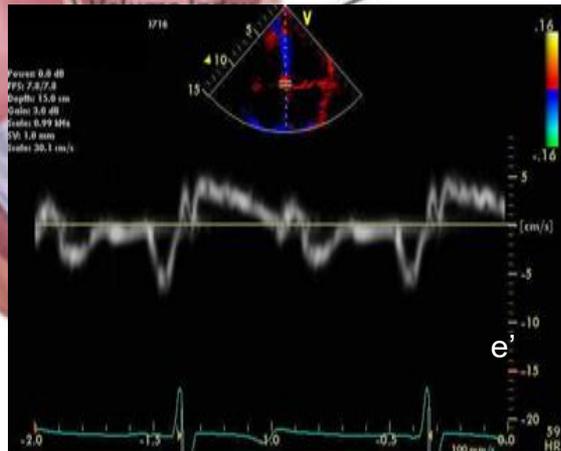
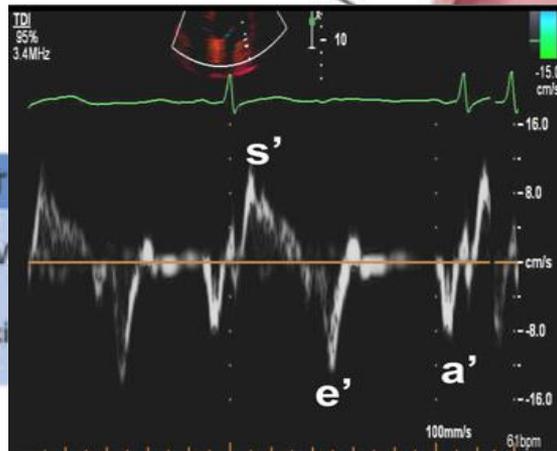
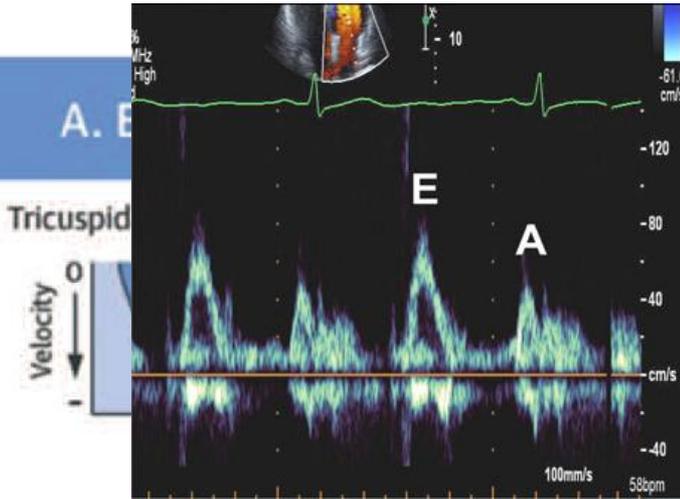
E/E' >8

**HFpEF**

# HFpEF: Diagnosis - Echo

Control

HFpEF

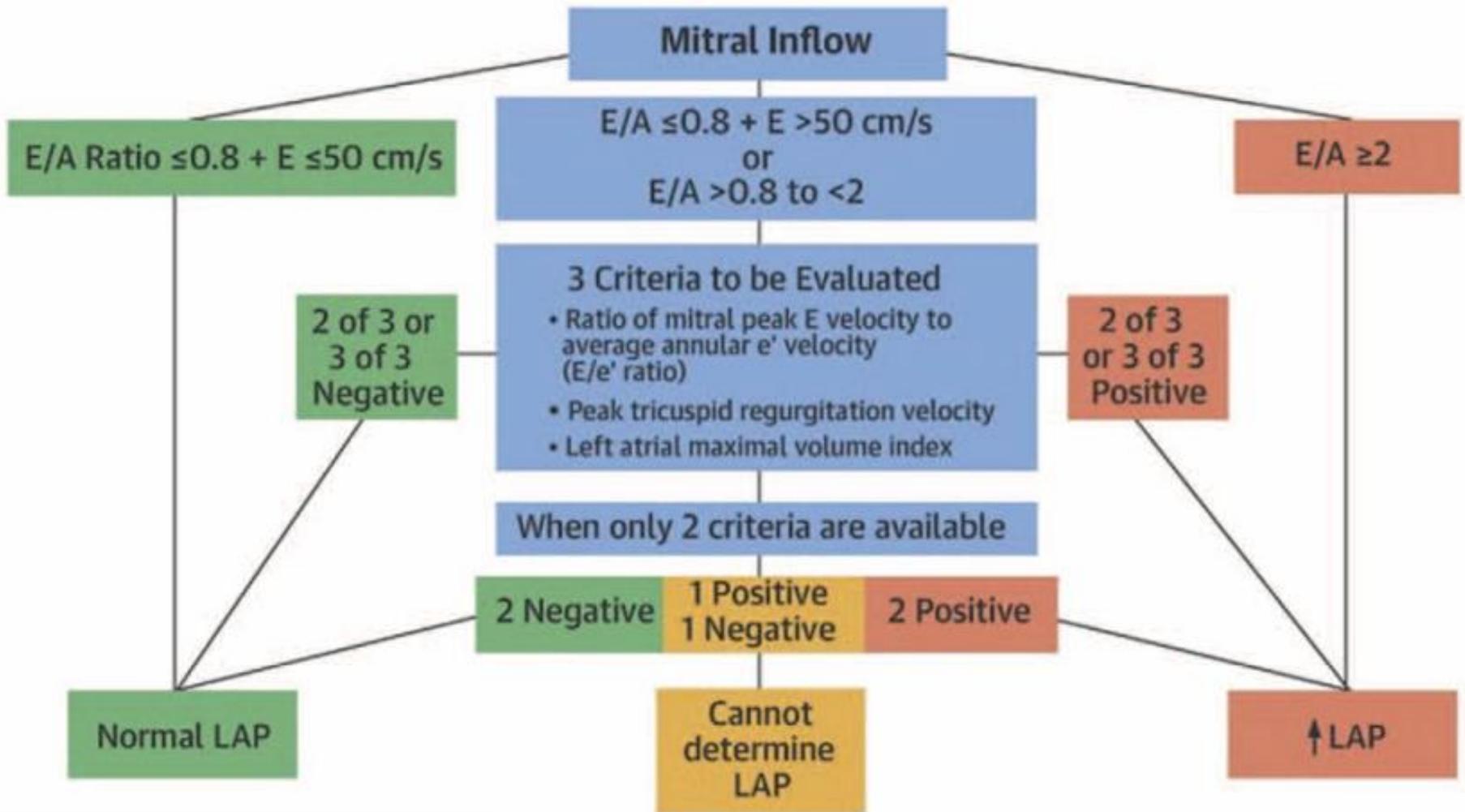


- Parameter
- Peak Tricuspid Regurgitation Velocity
  - E/e'
  - Left Atrial Maximal Volume Index

$E/e' = 80/12 = 6.67$

$E/e' = 80/4 = 20$

# Algorithm for estimating LV filling pressure



\*Peak TR  $\geq 2.8$  m/s  
\*E/E'  $> 14$   
\*LAVI  $> 34$  ml/m<sup>2</sup>

# Case – Female 77 yrs

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

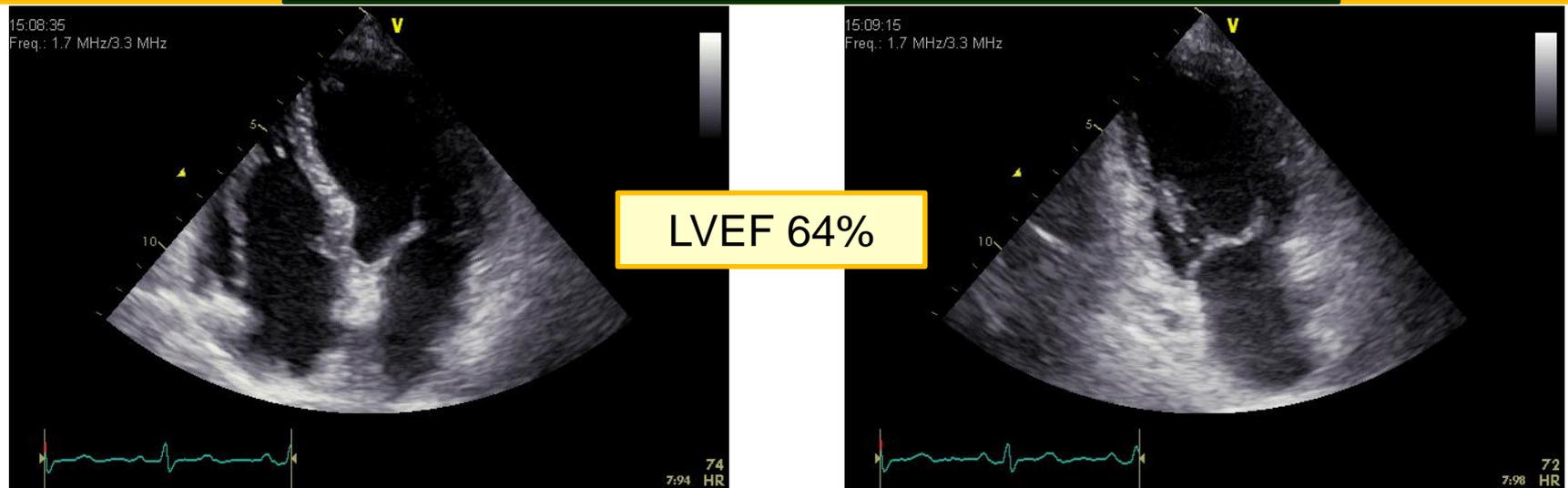
Exertional tiredness and shortness of breath; 150/80 mmHg, Height 160 cm, Weight 55 kg, BMI 21.5 kg/m<sup>2</sup>, waist circumference 90 cm.

ECG: SR 70 bpm, no abnormalities; Chest X-ray: no abnormalities

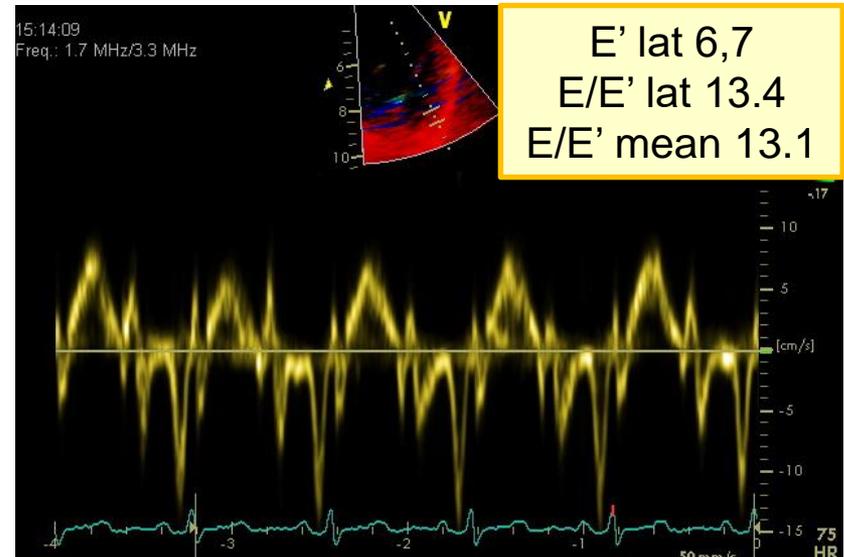
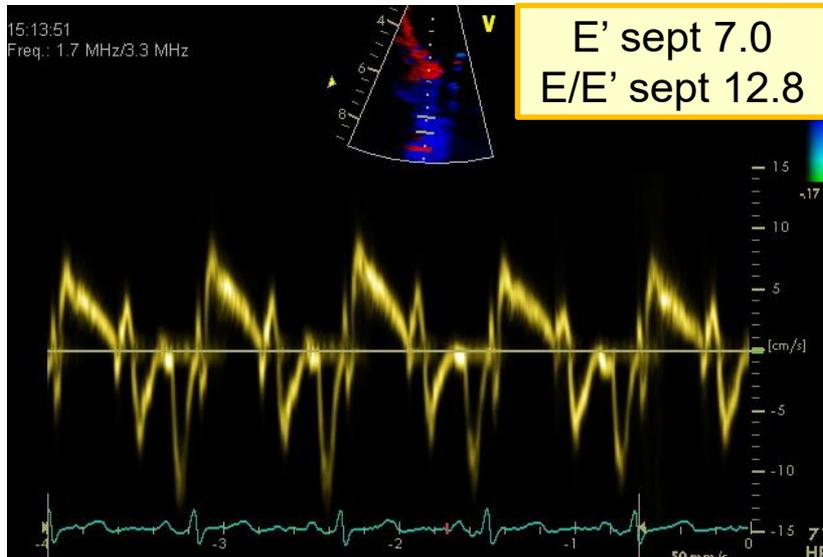
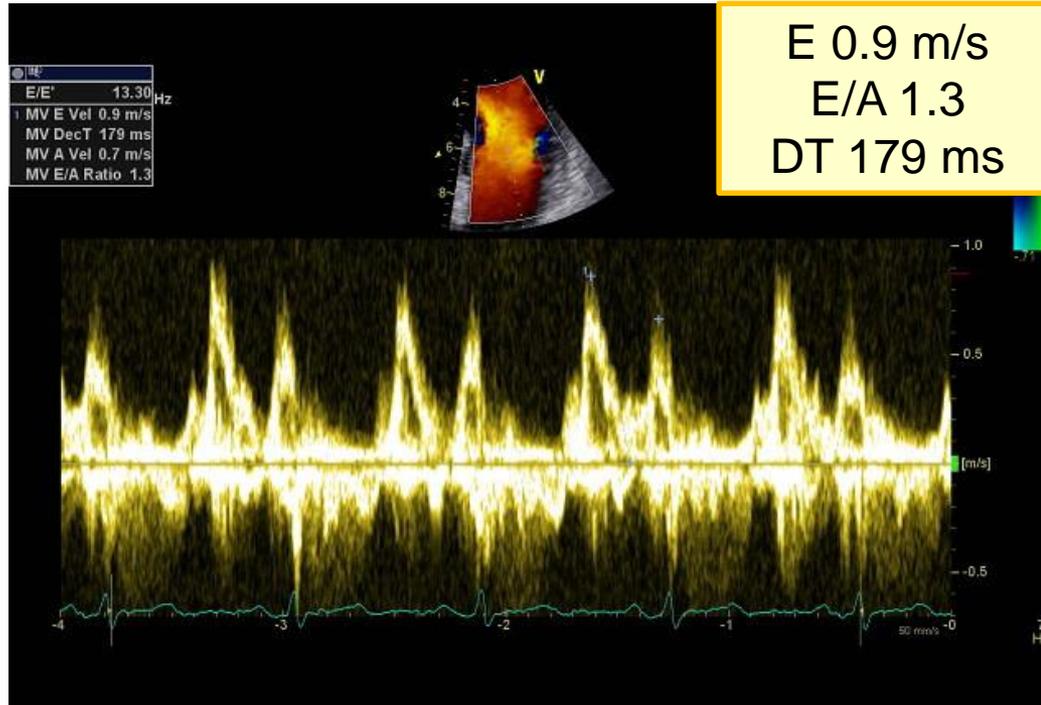
Pulmonary function test: mild obstruction; COPD GOLD I

Lab: Hb 7.6 mmol/l (12.2 g/dl), eGFR 68 ml/min, NT-proBNP 10 pmol/l (84 pg/ml)

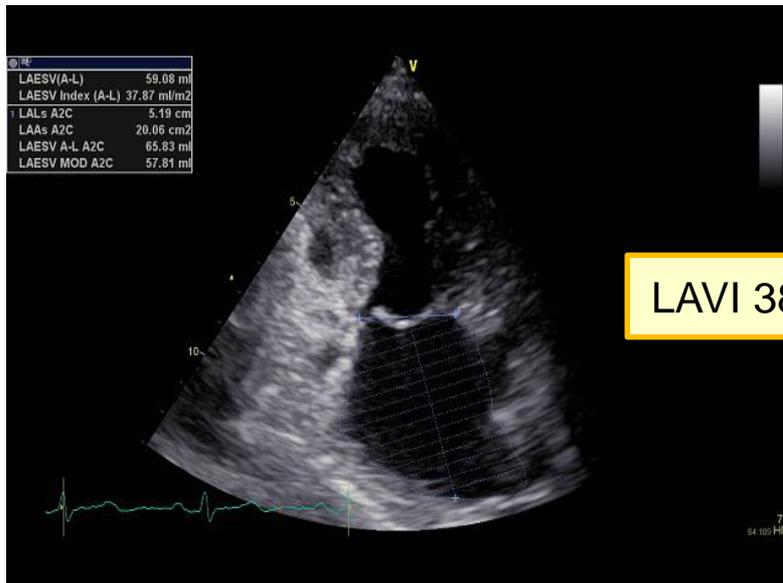
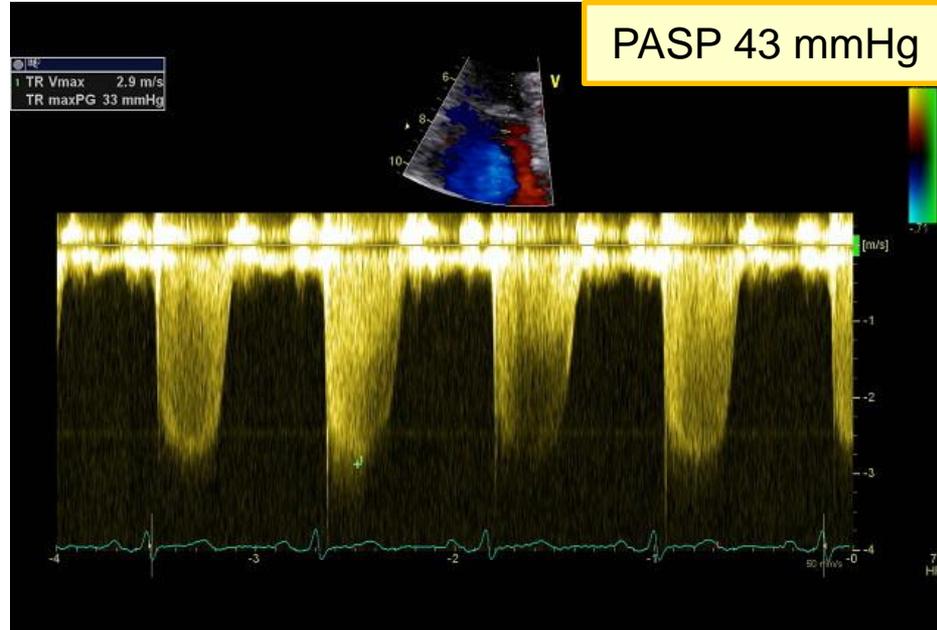
COPD? Deconditioning? Heart failure (HFpEF)?



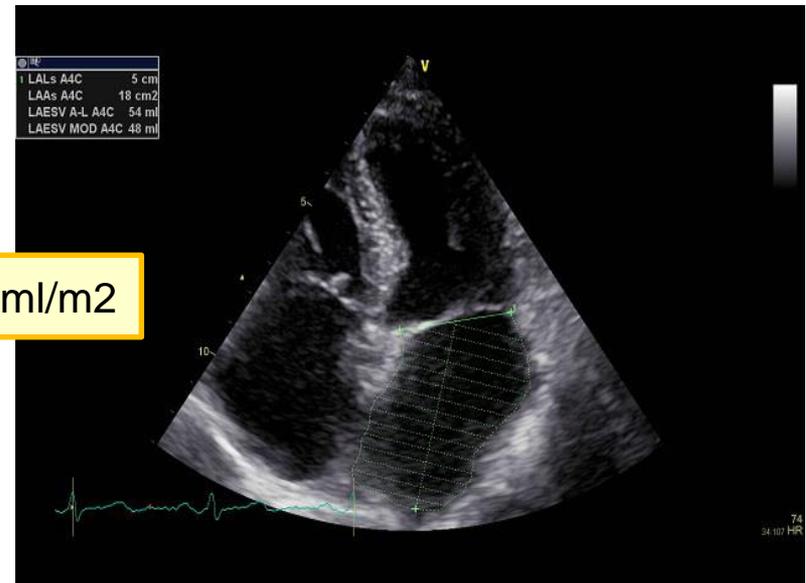
# Case – Female 77 yrs



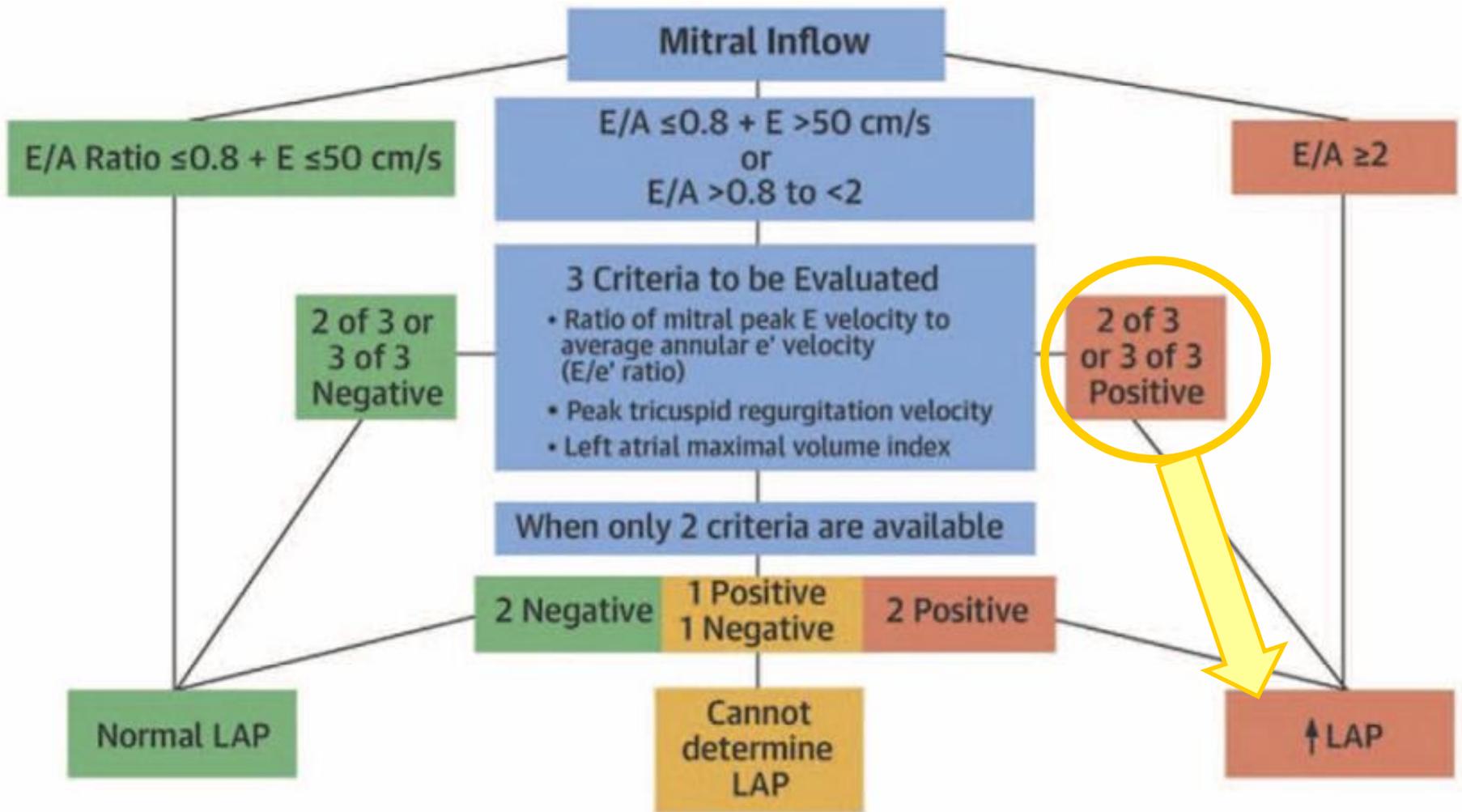
# Case – Female 77 yrs



LAVI 38 ml/m<sup>2</sup>



# Algorithm for estimating LV filling pressure



\*Peak TR  $\geq 2.8$  m/s  
\*E/E'  $> 14$   
\*LAVI  $> 34$  ml/m<sup>2</sup>

**RvK:** Exertional Dyspnea, NYHA III

**VG:**

2001: T2DM, hypertension, dyslipidemia

2016: OSAS, CPAP

**Rx:** Losartan 1 dd 50 mg, amlodipine 1 dd 5 mg, simvastatine 1 dd 40 mg, gliclazide 3 dd 80 mg, metformine 2 dd 850 mg, insuline lantus, omeprazol

**A:** Progressive exertional dyspnea, NYHA III; ↓ exercise tolerance. Intermittent minor edema. Nycturia 0-2x. During exercise training saturation drop to 89-90%. After training session completely exhausted.

**LO:** RR 150/70 mmHg; Length 167 cm Weight 93 kg, BMI 33.3 kg/m<sup>2</sup>; waist 104 cm.  
**CVD:** normal; **Cor:** S1S2 cresc/decrec systol murmur; 2/6 ao trajectory  
**Pulm:** VAG; **extrem:** normal

**ECG:** SR, normal axis/conduction, no ST deviations

**Laboratory: Hemoglobine 7.2 mmol/l\***; Leukocytes  $7.6 \times 10^9/l$ ; M.C.V. 97.3 fl; Trombocytes  $304 \times 10^9/l$ ; Sodium 138 mmol/l; Potassium 4.4 mmol/l; Creatinin 73  $\mu\text{mol/l}$ ; **eGFR (MDRD formule) 70  $\text{kl}/1,73\text{m}^2$** ; **nt-proBNP 4 pmol/l**; ASAT 26 IU/l; ALAT 34 IU/l\*; gamma-GT 25 IU/l; TSH 1.5 mIU/l

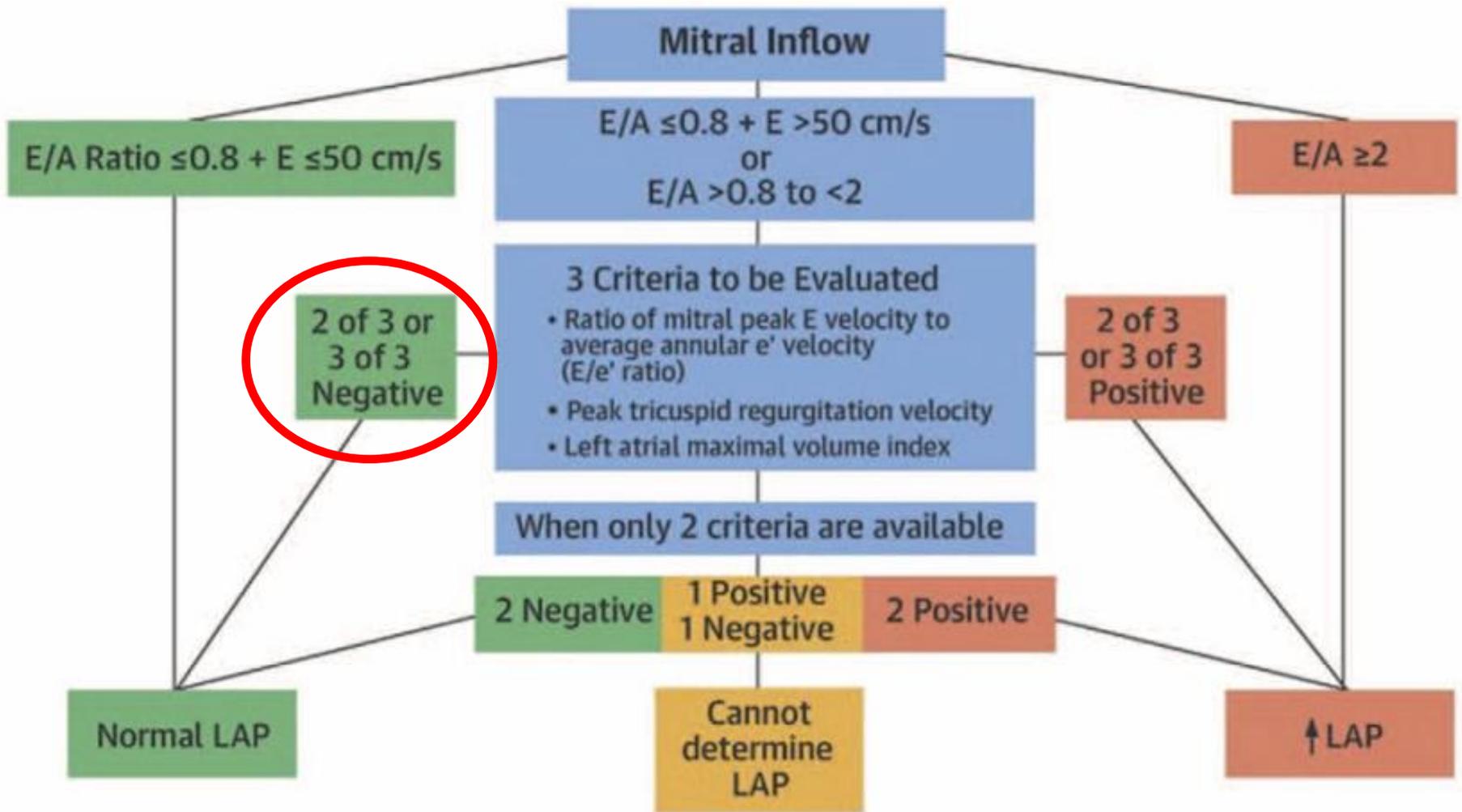
**Ergo:** HF max 160/min (101%). No ST deviations. Stopped because of dyspnea; RR rest 140/60 to 220/60 mmHg. **Ergo:** Hartfrequentie stijgt naar 160/min bij max inspanning (101% van max hartfrequentie); 150 Watt gefietst; voorspeld = 127 W di  
**CT hart:** Agatston 16.6 (16%). RCA: C/NS prox; LCA: n.a. No additional pathology.

**Longfunctie:**

		Meting	Pred	% Pred	z score
FVC	L	<b>2,06</b>	3,24	64	
FEV1	L	<b>1,84</b>	2,53	73	
FEV1/FVC%	%	<b>89,2</b>	78,7	113	
PEF	L/s	<b>4,92</b>	-	-	-
FEV1/VCmax%	%	<b>89,2</b>	78,7	113	

**Echo:** Good systolic LV function. Normal dimensions. E 67 cm/s; E/A ratio 0.8; E' 8.9 cm/s, DecT 207 ms, E/E' 7.51. TR veloc 2.55 m/s; SPAP 26+3 mmHg. Normal RV. Dilated LA. LAVI 42 ml/m<sup>2</sup>. AoV: minor calcification. Normal VCI.

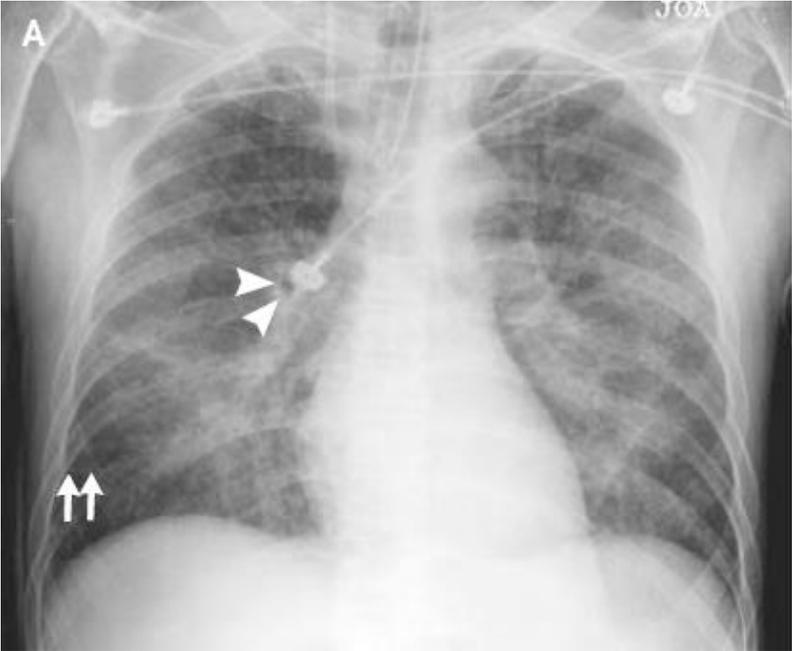
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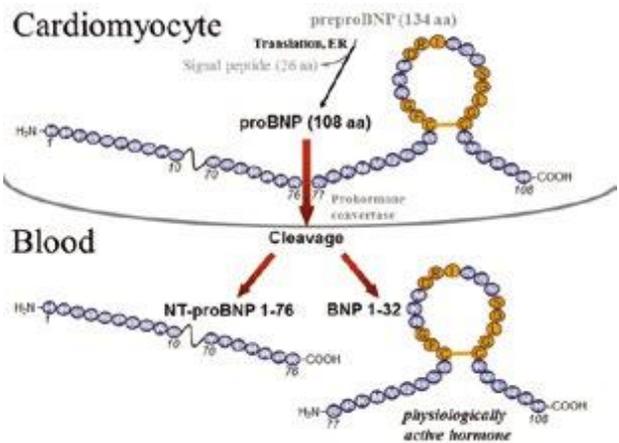
\*Peak TR  $\geq 2.8$  m/s  
\*E/E'  $> 14$   
\*LAVI  $> 34$  ml/m<sup>2</sup>

# Diagnosis of HFpEF is challenging!!

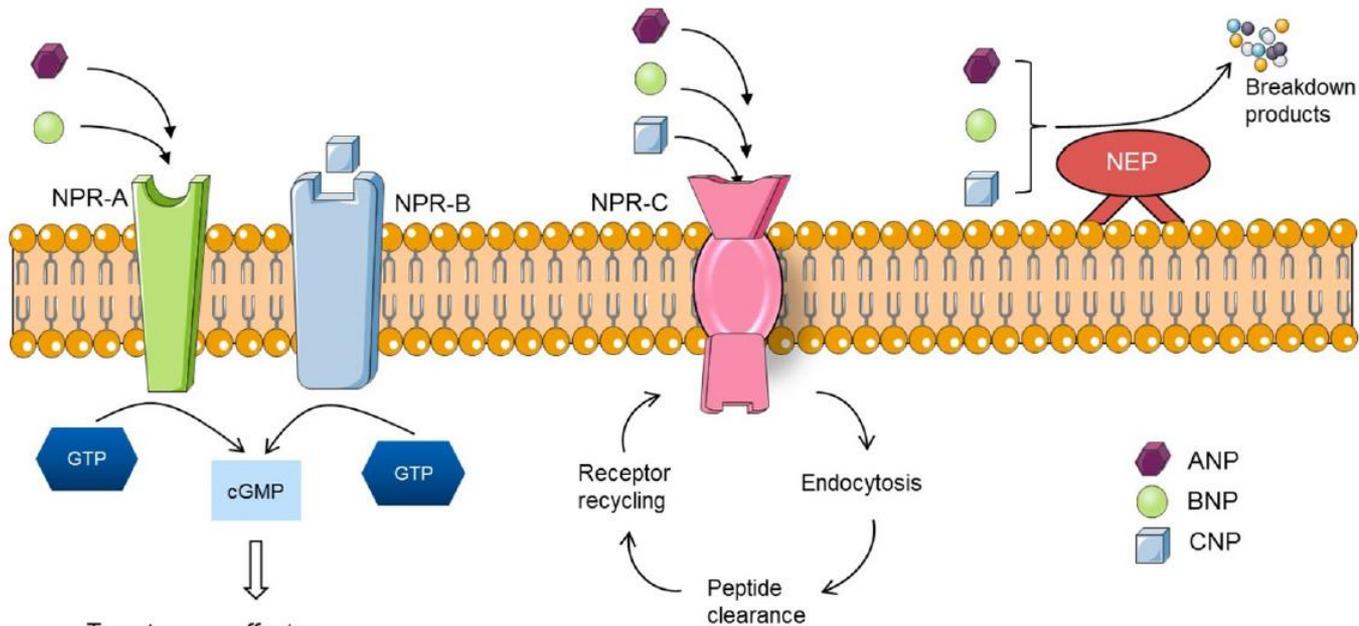
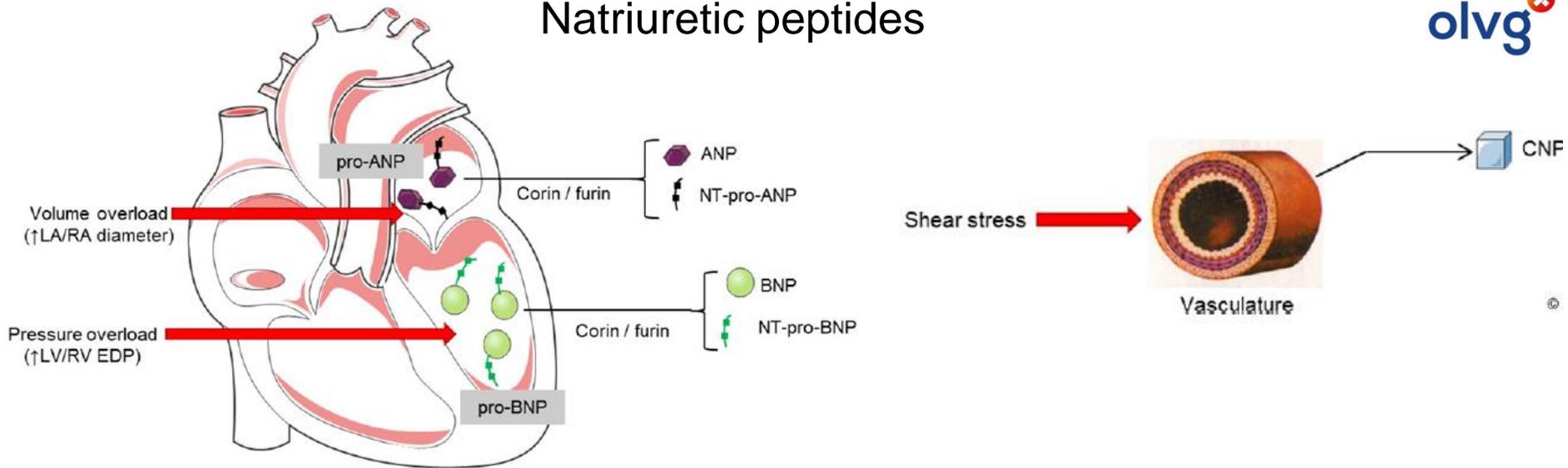
NYHA IV



NYHA II-III

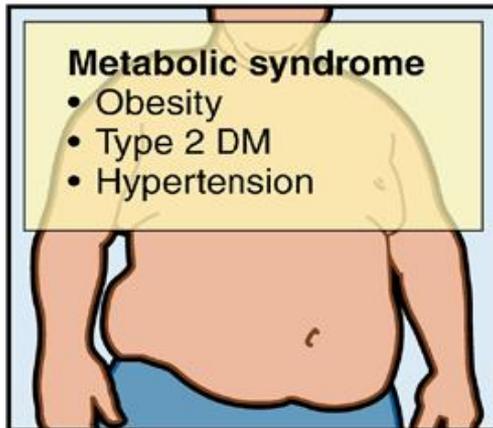
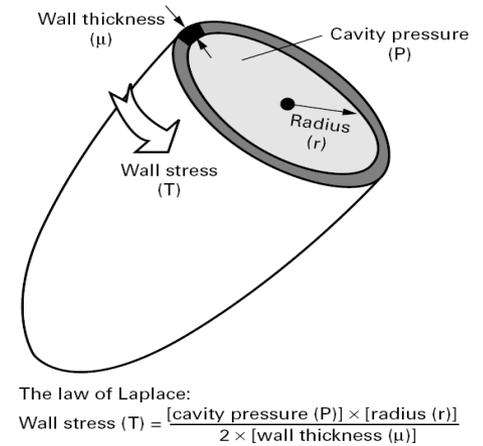
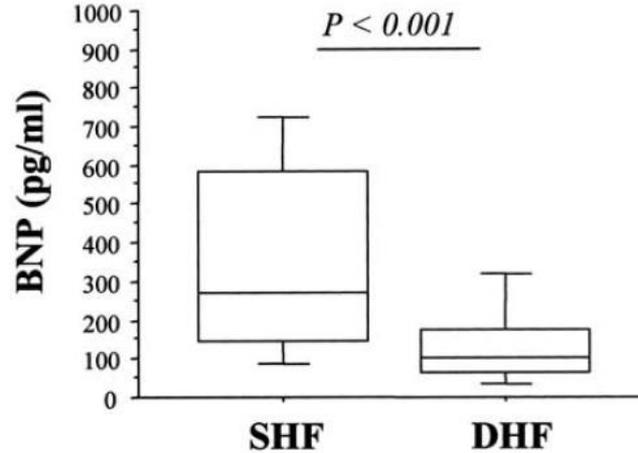
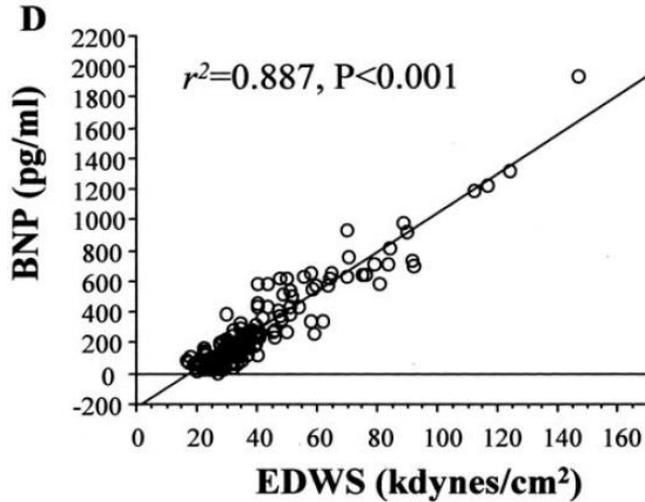


# Natriuretic peptides

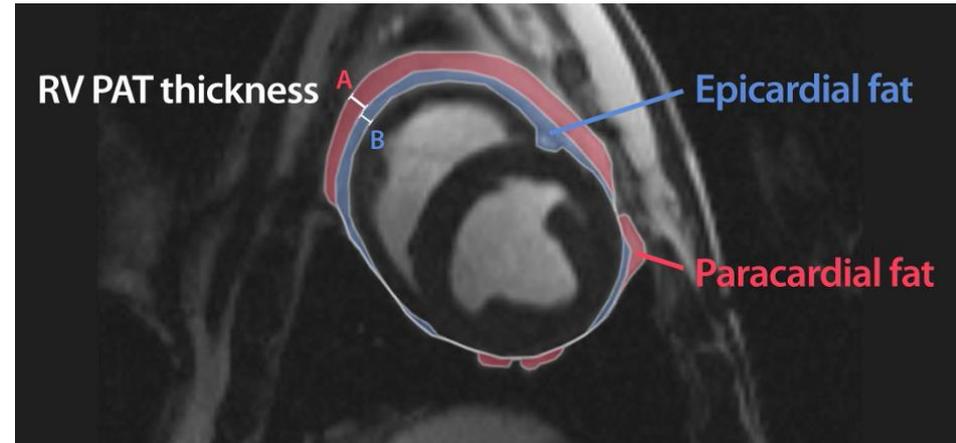


- Target organ effects:
- Vasodilatation
  - Natriuresis
  - Anti-proliferative effects
  - Reduced CV remodelling

# HFpEF: frequently low NT-proBNP



Androgens/adipokines  
 Insulin resistance  
 Epicardial fat induced inflammation



Epicardial fat raises intrapericardial pressure, dampening transmural LVP and lowering LV distending pressure



**Normal NT-proBNP in 20-30%  
of invasively proven NYHA II-III  
HFpEF patients!!**



Diagnostic tests:  
Laboratory/  
Echocardiography/Catheterization

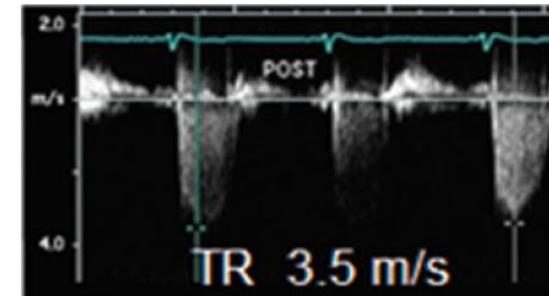
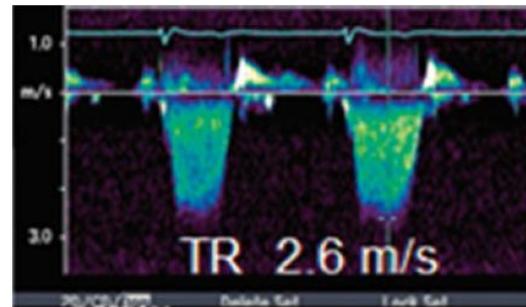
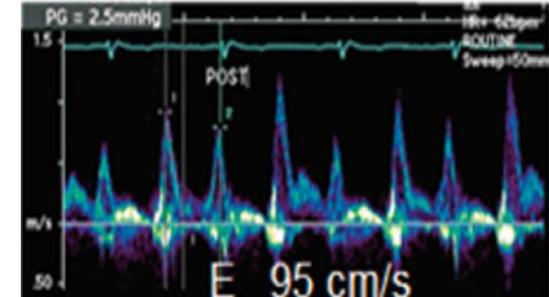
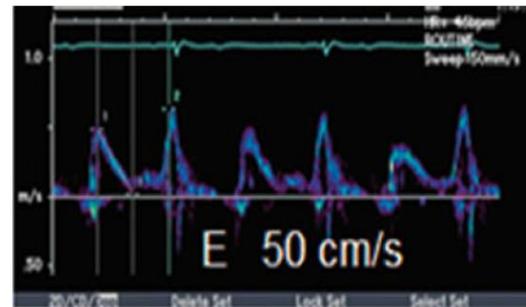
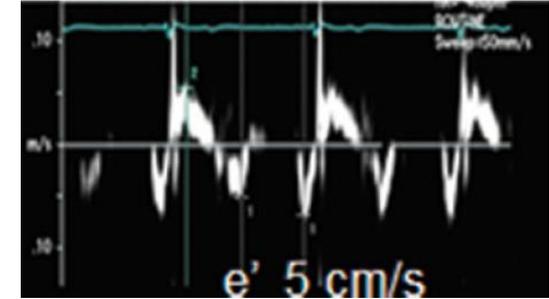
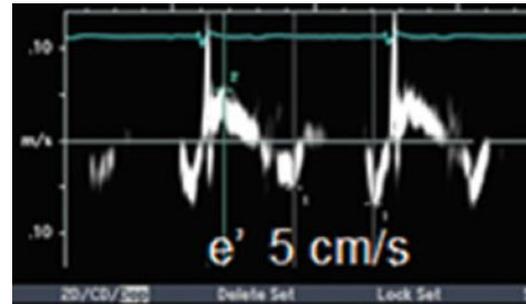
→ predominantly performed at rest,  
when patient is asymptomatic



Patient with NYHA II-III dyspnea?

→ Perform diagnostic tests at exercise!

# Exercise echocardiography



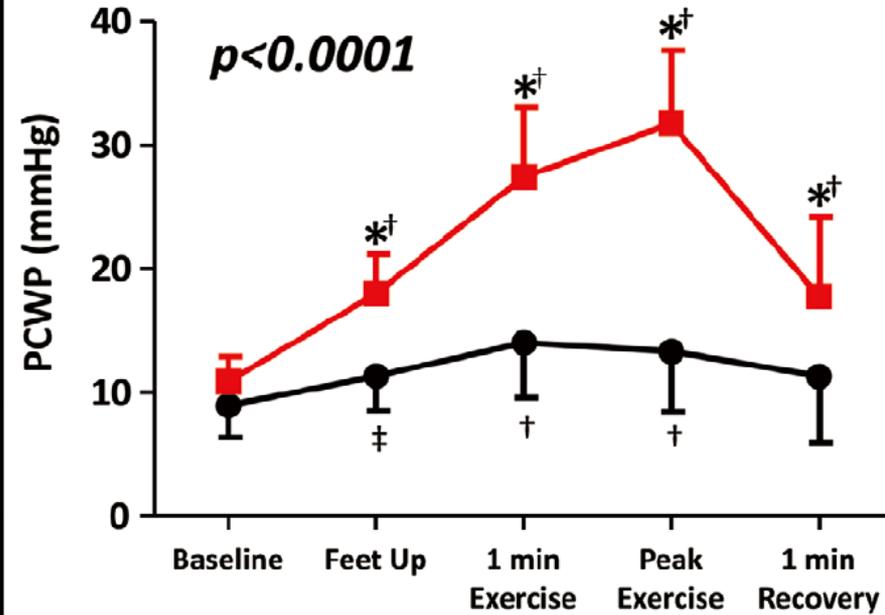
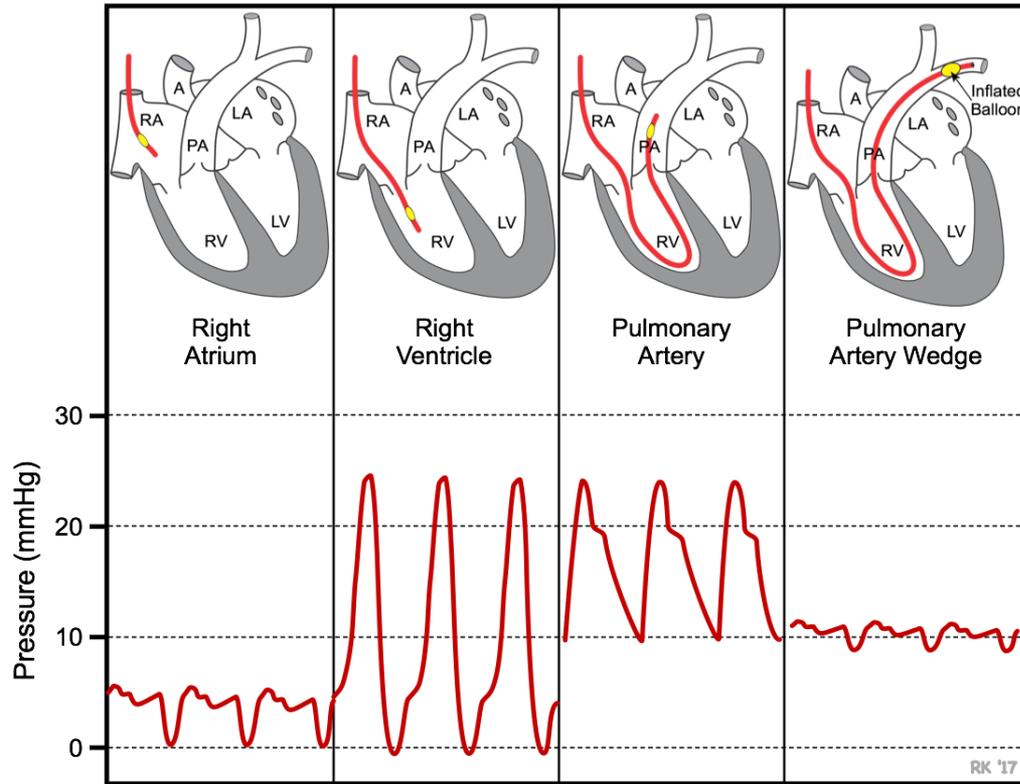
Exercise echo:

Diagnostic of diastolic LV dysfunction when  $E/E' > 14$

Rest  
 $E/E' 10$

Exercise  
 $E/E' 19$

# Right heart catheterization: Rest/exercise



\*  $p < 0.0001$  for  $\Delta$ PCWP (vs control)

†  $p < 0.0001$  vs base (within group)

‡  $p < 0.01$  vs base (within group)

● Control    ■ HFpEF

**Conclusion:**

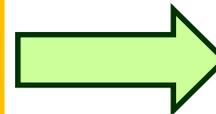
- 1) Exertional dyspnea, NYHA III/IV, normal ntnoBNP;
- 2) No obstructive coronary disease.
- 3) Good LV/RV function, no sign valve disease
- 4) Increased cardiovascular risk profile
- 5) Restrictive spirometry; DD/obesity

DD?

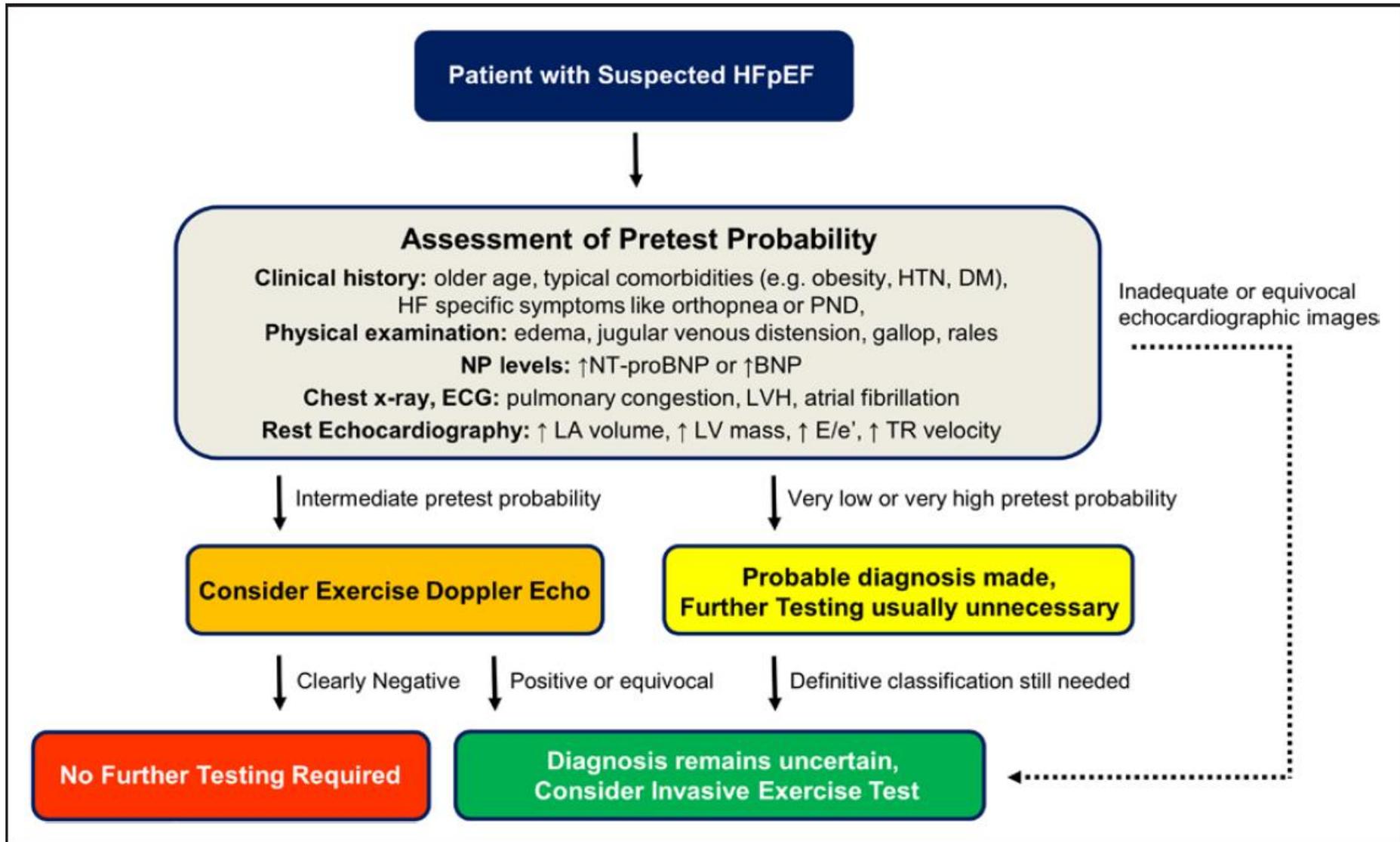
“Early stage” HFpEF; pulm; deconditioning/obesity

**RHC rest/exercise:**

PCWP rest: 16 mmHg; exercise: 30 mmHg.



**HFpEF !**



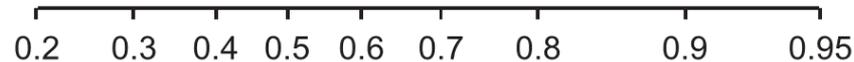
# H2FPEF score for probability of HFpEF

	Clinical Variable	Values	Points
<b>H<sub>2</sub></b>	<b>H</b> heavy	Body mass index > 30 kg/m <sup>2</sup>	2
	<b>H</b> ypertensive	2 or more antihypertensive medicines	1
<b>F</b>	Atrial <b>F</b> ibrillation	Paroxysmal or Persistent	3
<b>P</b>	<b>P</b> ulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
<b>E</b>	<b>E</b> lder	Age > 60 years	1
<b>F</b>	<b>F</b> illing Pressure	Doppler Echocardiographic E/e' > 9	1
<b>H<sub>2</sub>FPEF score</b>			<b>Sum (0-9)</b>

Total Points



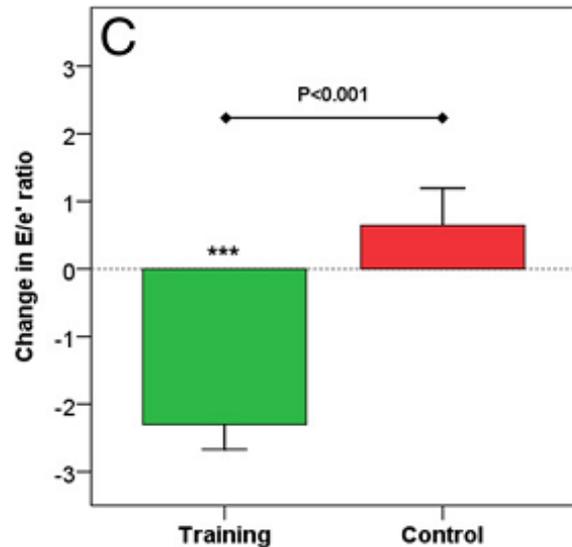
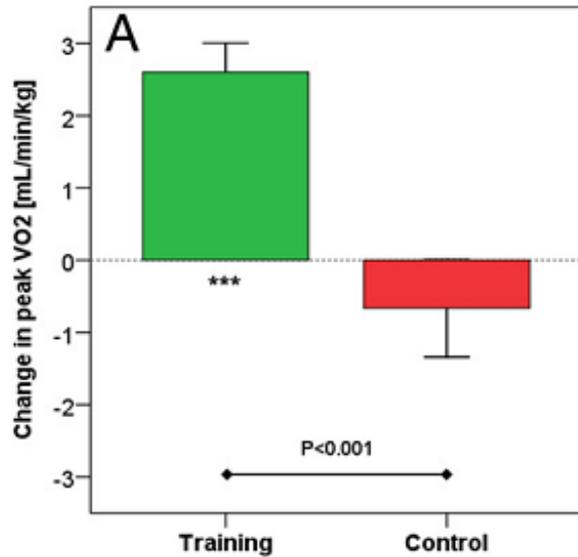
Probability of HFpEF



# Treatment of HFpEF

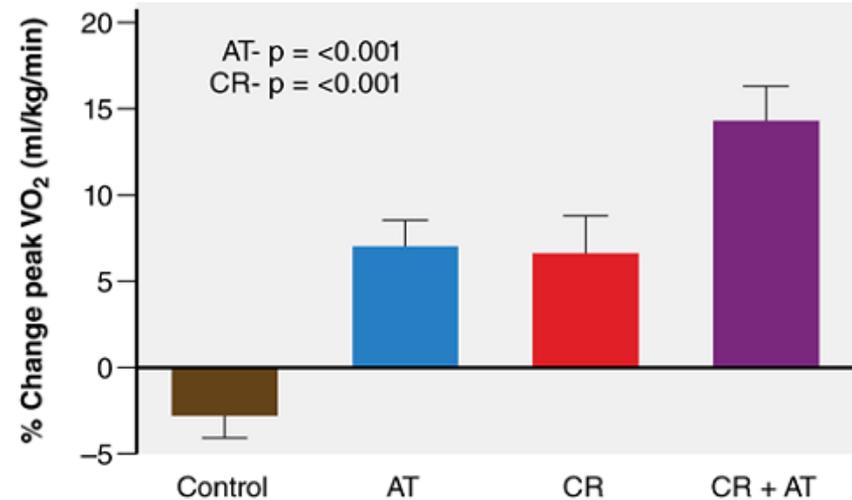


# HFpEF: Exercise training and caloric restriction



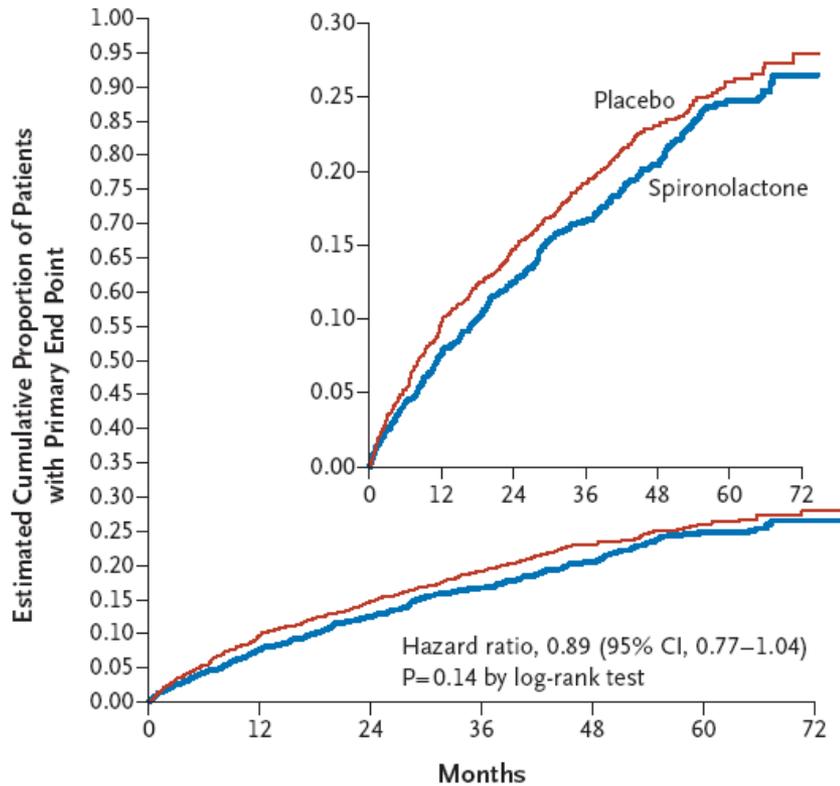
Obese (BMI 39 kg/m<sup>2</sup>) HFpEF pts(n=100) randomized to aerobic exerc training (AT) caloric restriction (CR) or both for 20 weeks;

prim EP: peak VO<sub>2</sub> and quality of life

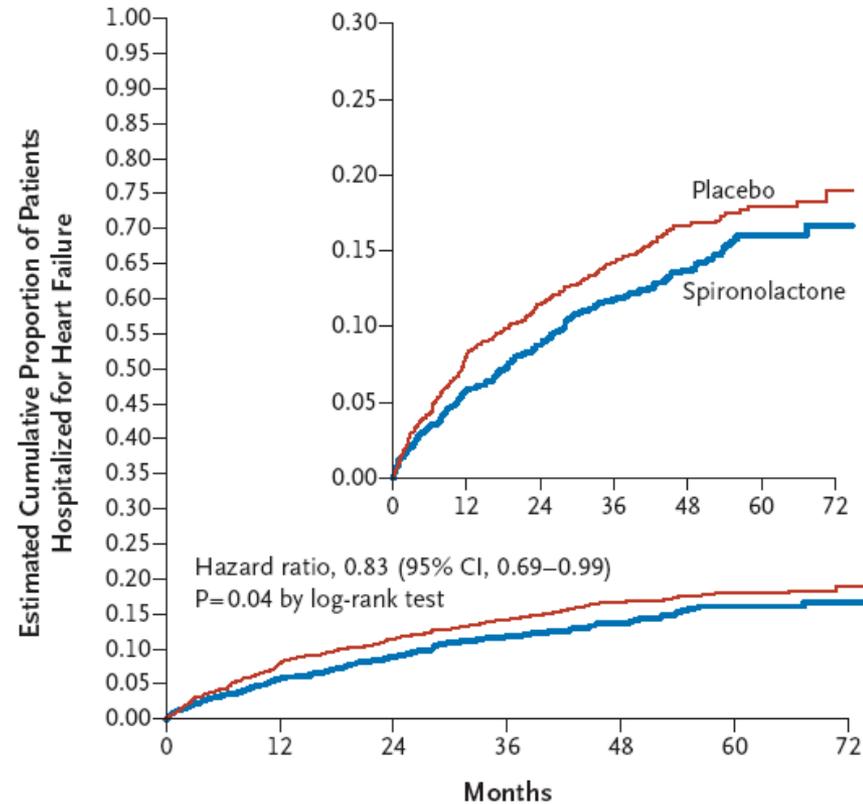


# Spirolactone in HFpEF: TOPCAT

Phase III; Randomised; double blind; placebo-controlled; multicenter trial; 2006-2012  
 HFpEF (n=3445);  $\geq 50$  yrs; NYHA II-III; EF  $\geq 45\%$ ; prior HF hosp/ $\uparrow$ 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



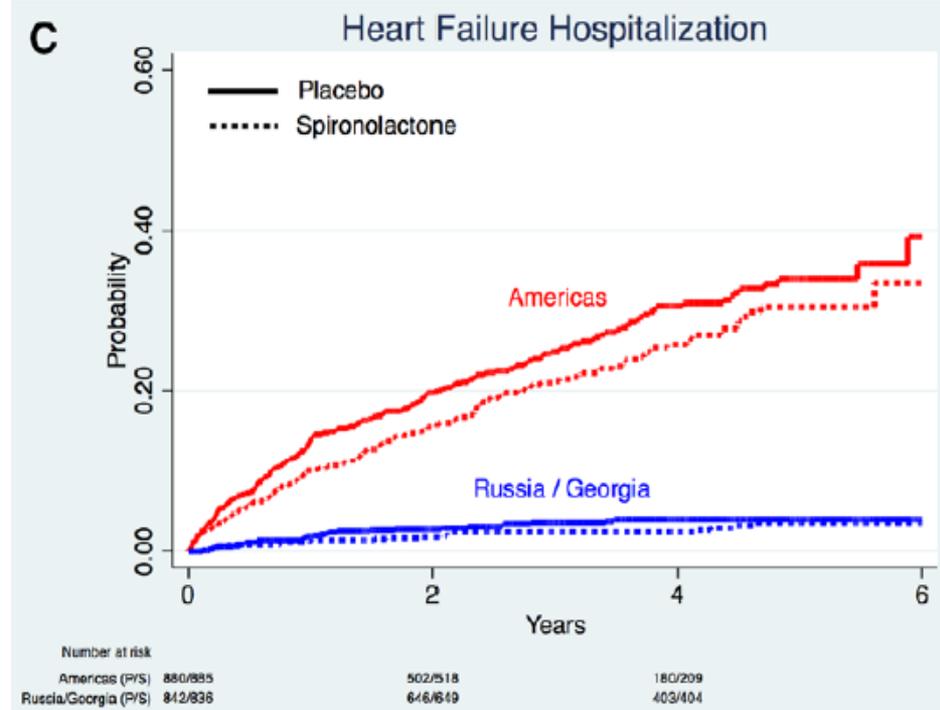
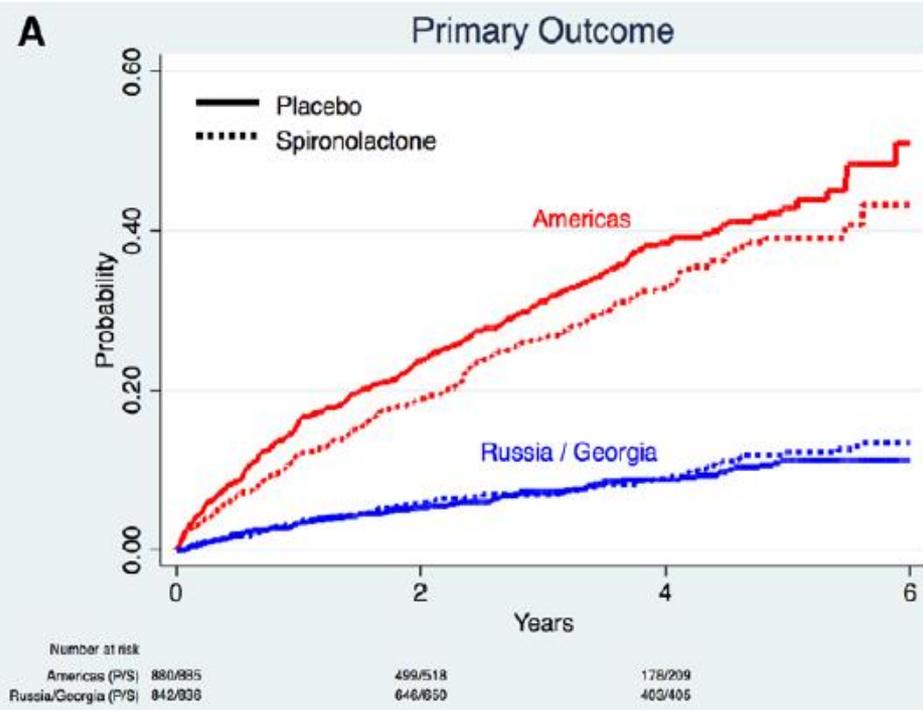
No. at Risk	0	12	24	36	48	60	72
Spirolactone	1722	1502	1168	870	614	330	53
Placebo	1723	1462	1145	834	581	331	53



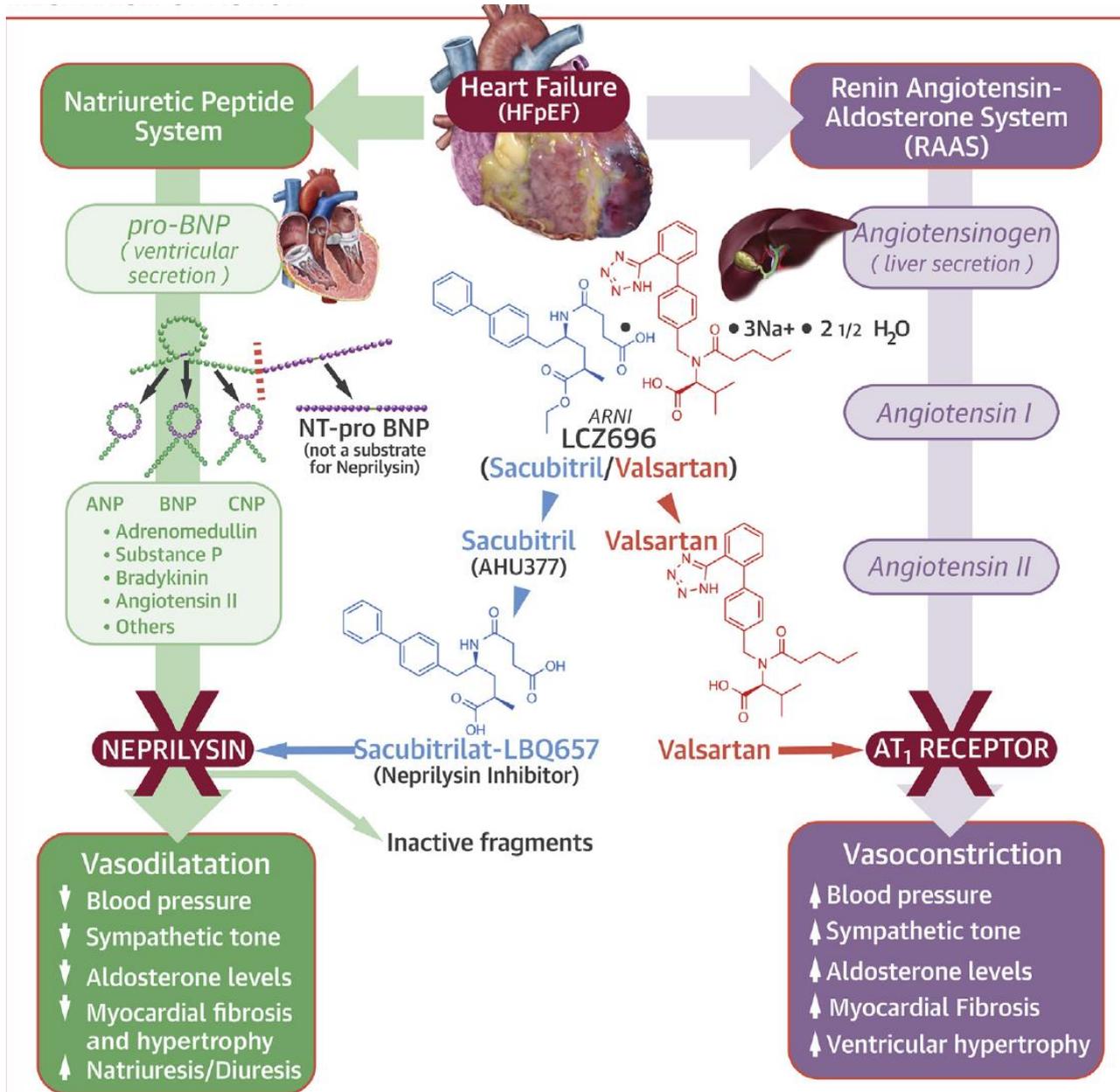
No. at Risk	0	12	24	36	48	60	72
Spirolactone	1722	1502	1167	869	613	330	53
Placebo	1723	1464	1148	837	583	332	53

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



# Sacubitril/valsartan

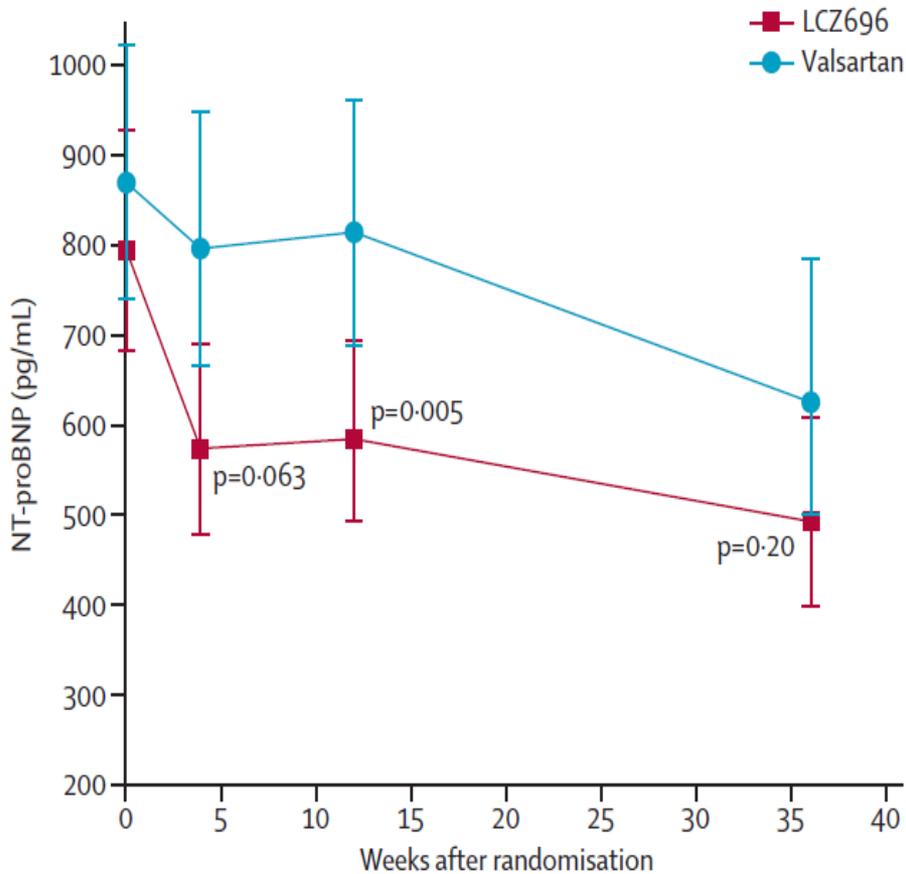


# ARNI: LCZ696 (Entresto): PARAMOUNT

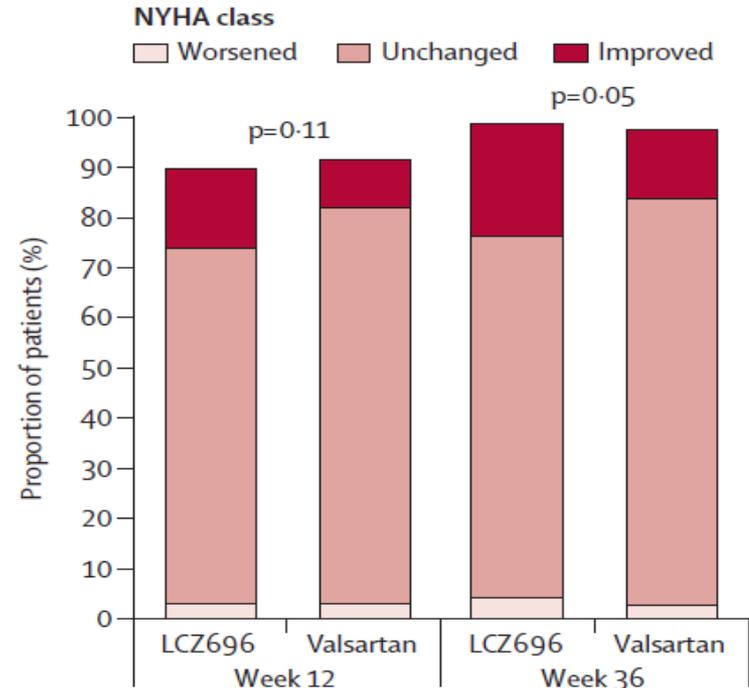
Phase II RCT 2009-2011; HFpEF (n=266 pts); NYHA II-III; EF $\geq$ 45%; nproBNP  $\geq$ 400pg/ml  
1:1 to LCZ696 (200 mg bid) vs valsartan (160 mg bid) for 36 wks.

Primary endpoint:  $\Delta$  in nproBNP baseline to 12 wks

Secondary endpoint:  $\Delta$  in Echo parameters and functional class



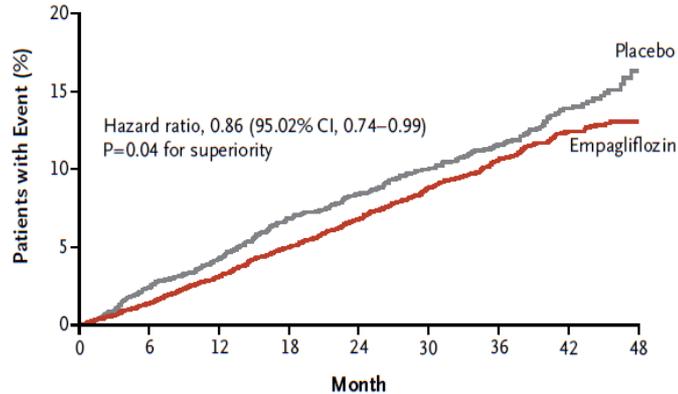
	LCZ baseline	LCZ $\Delta$ from baseline	Valsart baseline	Valsart $\Delta$ from baseline	P-value
LAVI	35 $\pm$ 11.7	-2.6 $\pm$ 7.3	36.8 $\pm$ 14.8	0.31 $\pm$ 9.3	0.007



# Sodium glucose co-transporter 2 (SGLT2)-inhibitors

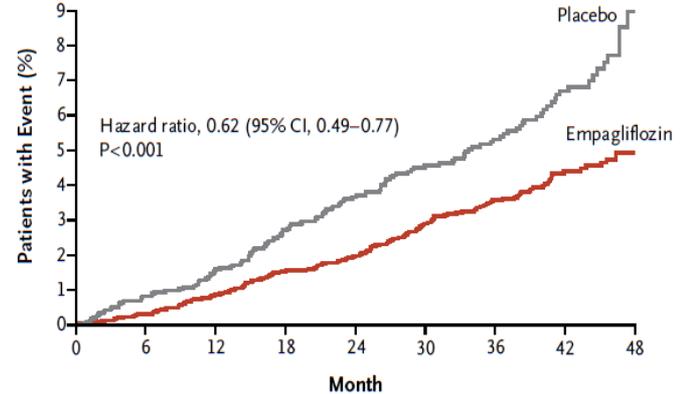
**EMPAREG trial– empagliflozin in DM**  
 T2DM pts (n=7020) at high risk for CV outcomes, FUP 3.1 yrs  
 Prim EP: composite of CV death, non-fatal MI or stroke (Zinman et al. NEJM 2015;373:2117)

**A Primary Outcome**



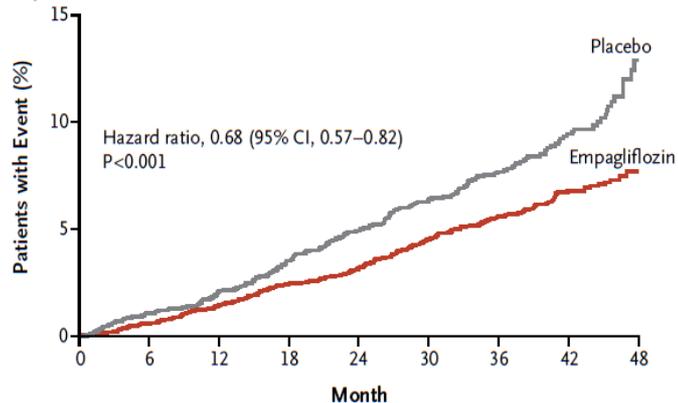
No. at Risk	0	6	12	18	24	30	36	42	48
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

**B Death from Cardiovascular Causes**



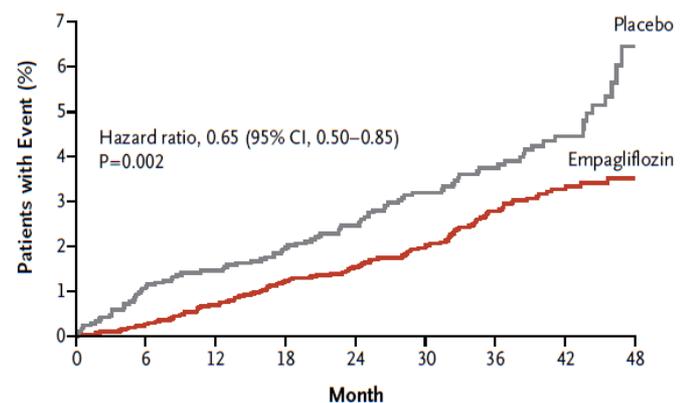
No. at Risk	0	6	12	18	24	30	36	42	48
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

**C Death from Any Cause**



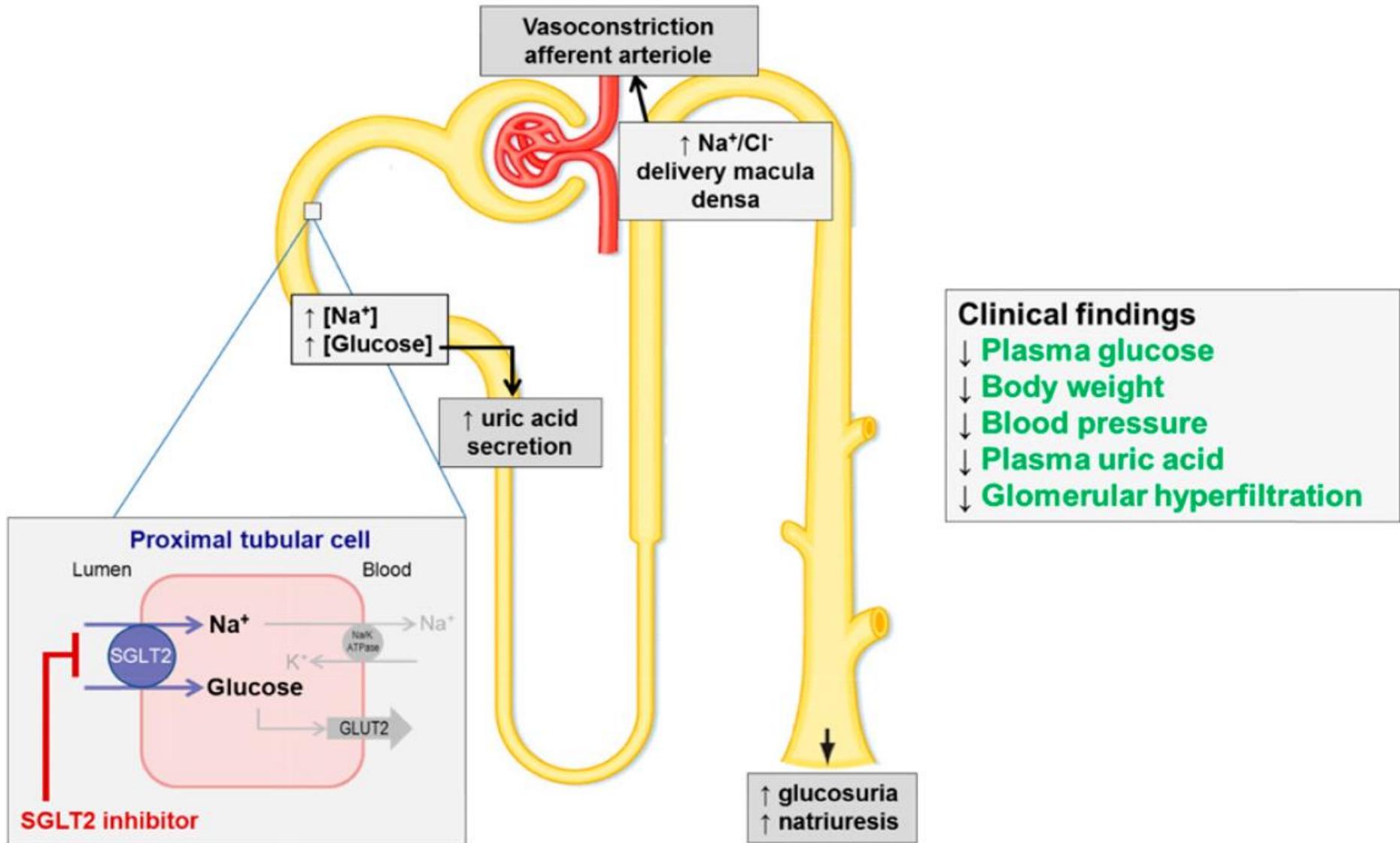
No. at Risk	0	6	12	18	24	30	36	42	48
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

**D Hospitalization for Heart Failure**

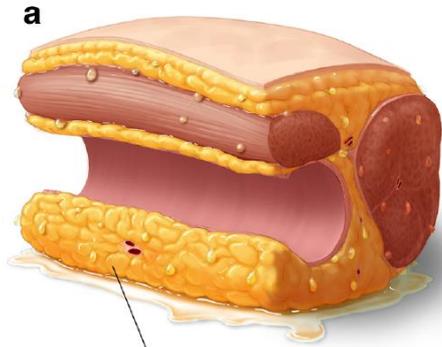


No. at Risk	0	6	12	18	24	30	36	42	48
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

# SGLT2-inhibitors



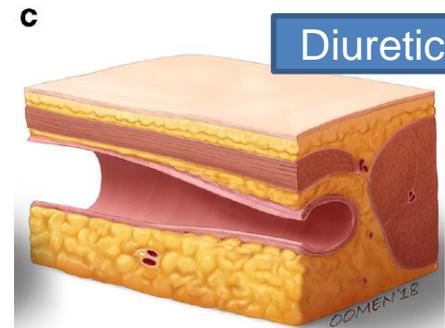
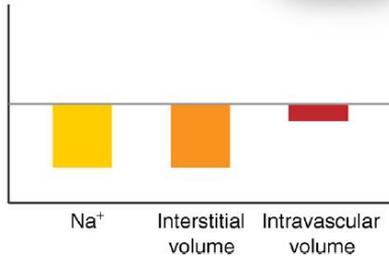
# SGLT2-inhibitors



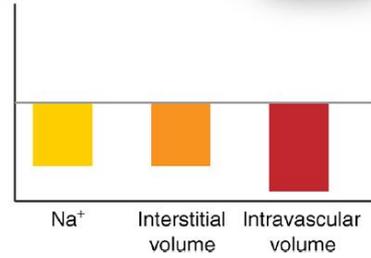
Interstitial oedema in congestive heart failure



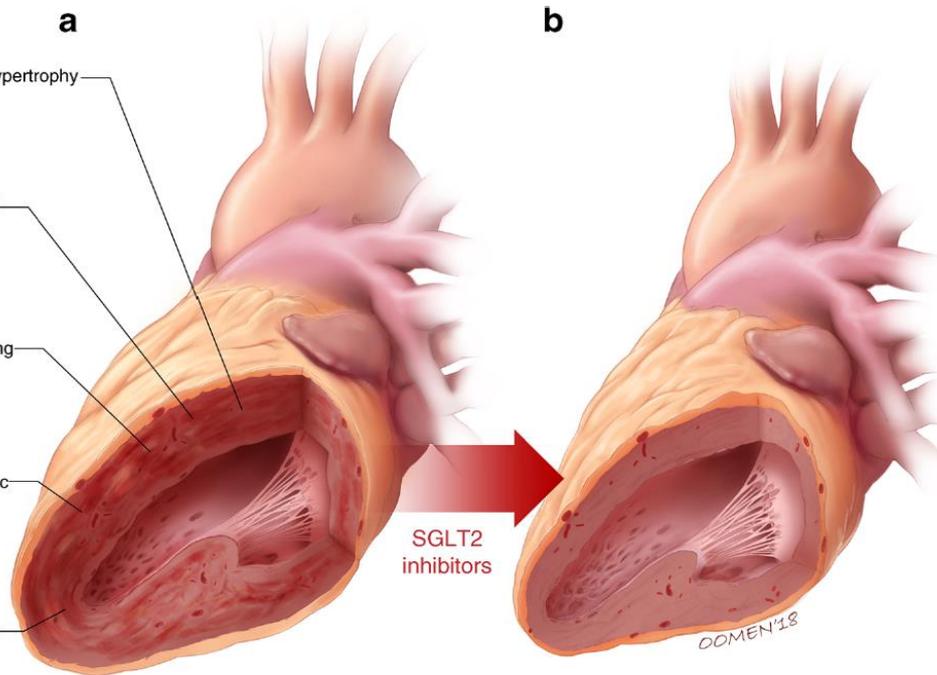
SGLT2-I



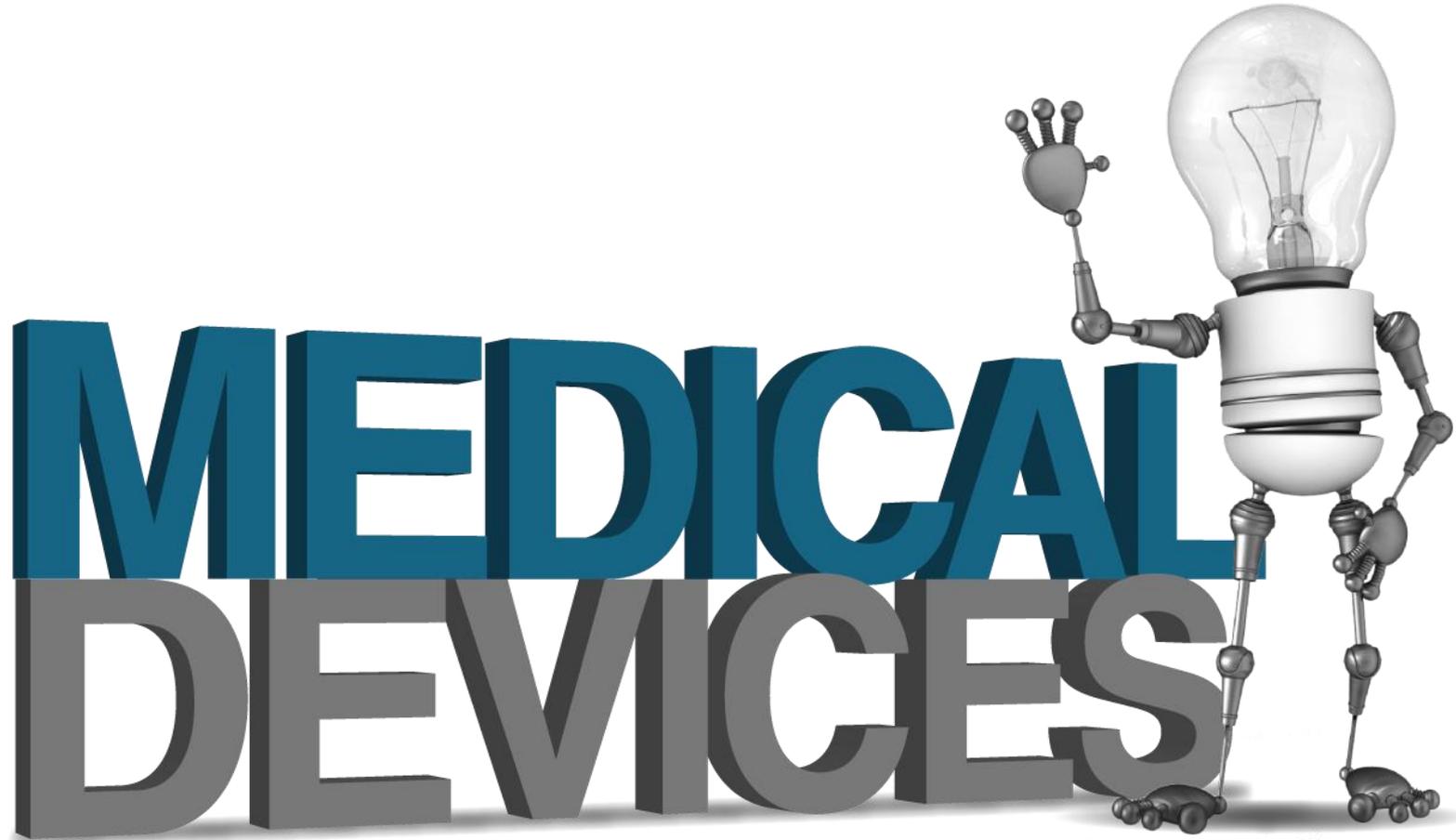
Diuretic



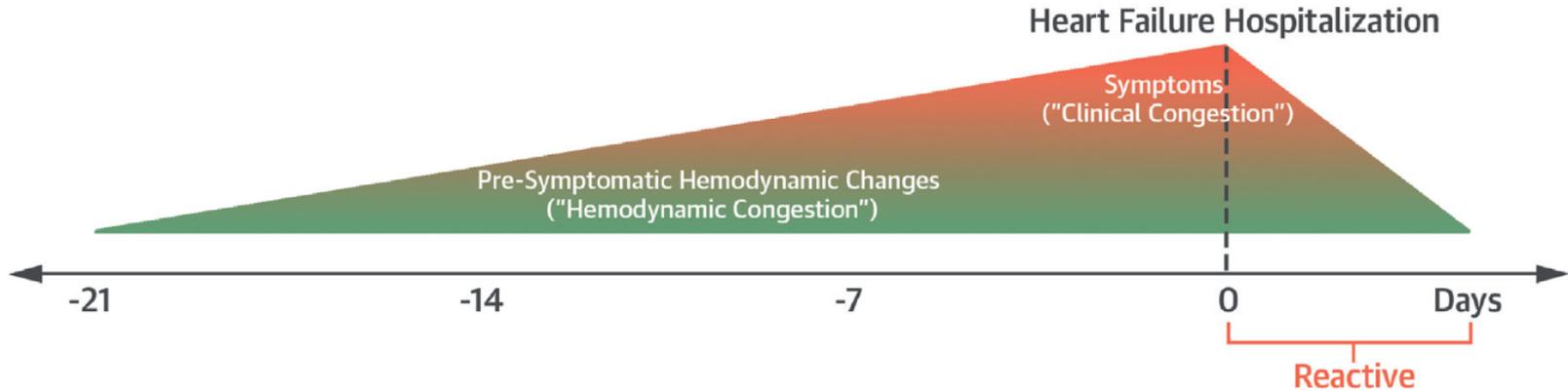
- Left ventricle hypertrophy
- ↑ Cytokines and inflammation
- ECM remodelling
- Impaired cardiac metabolism
- CMC apoptosis



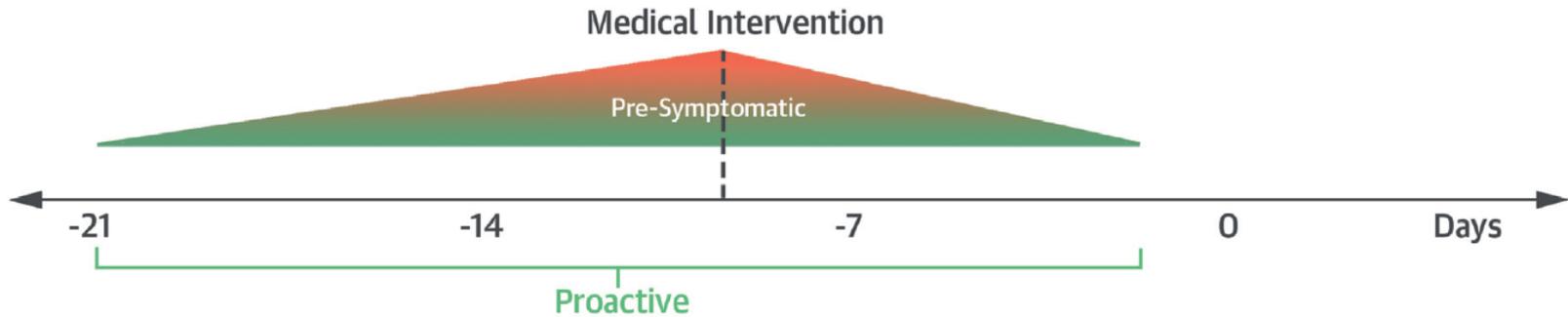
SGLT2 inhibitors



## Heart Failure Hospitalization



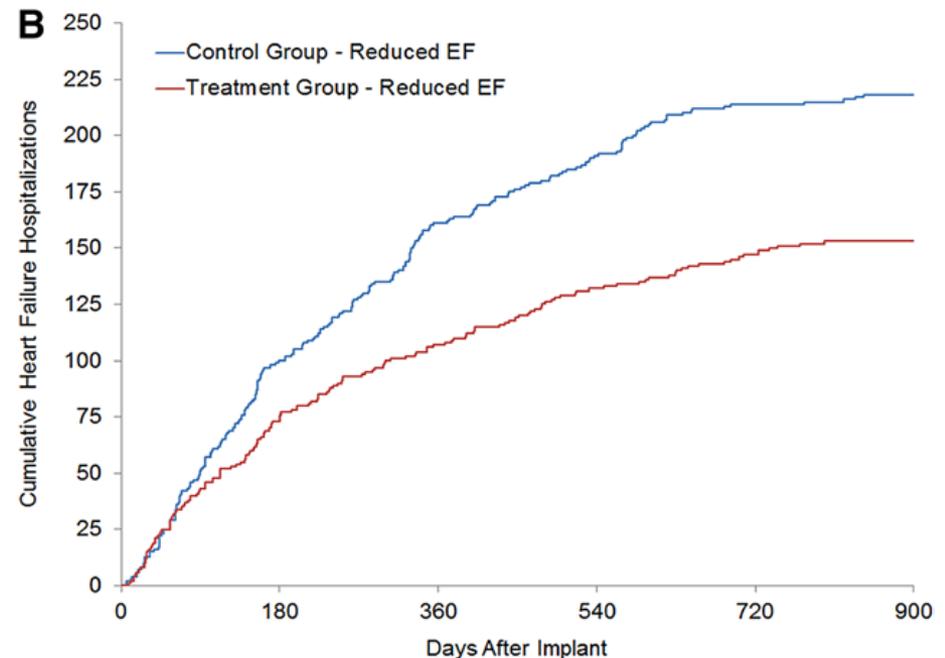
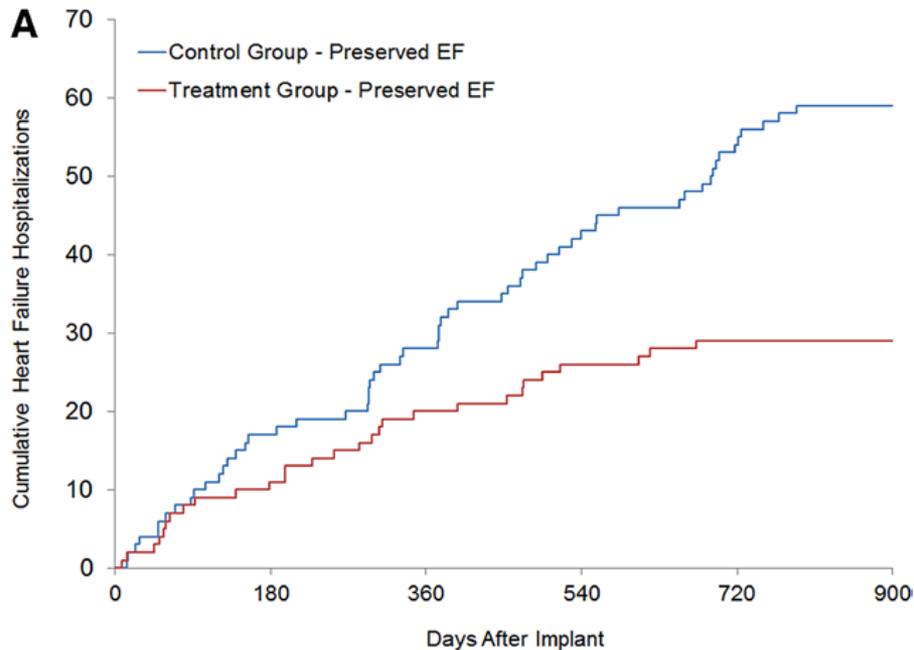
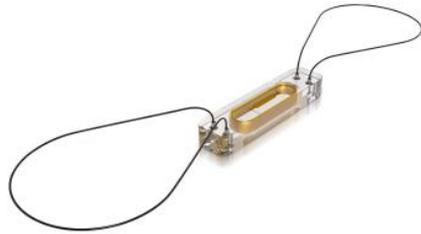
## Averted Heart Failure Hospitalization



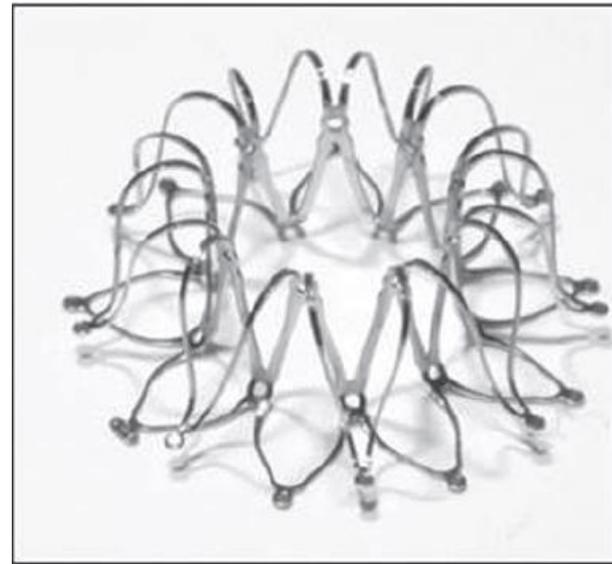
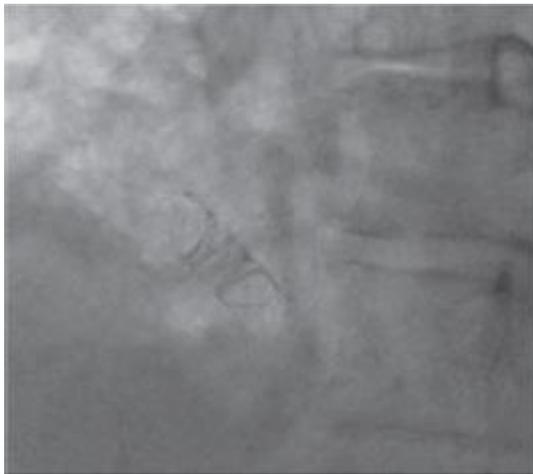
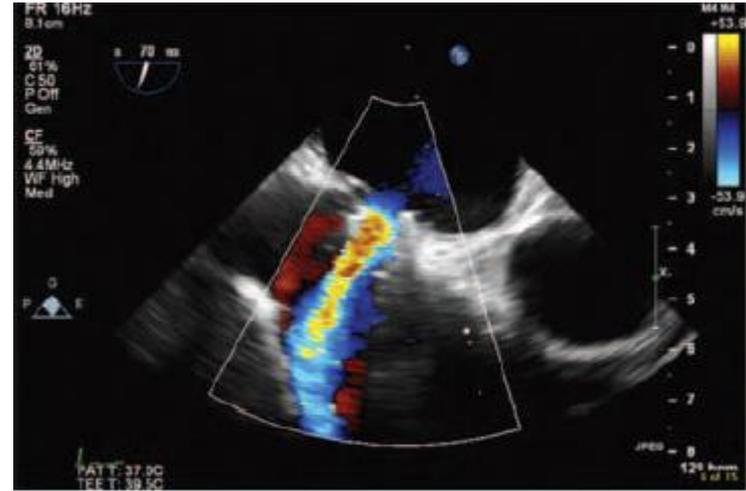
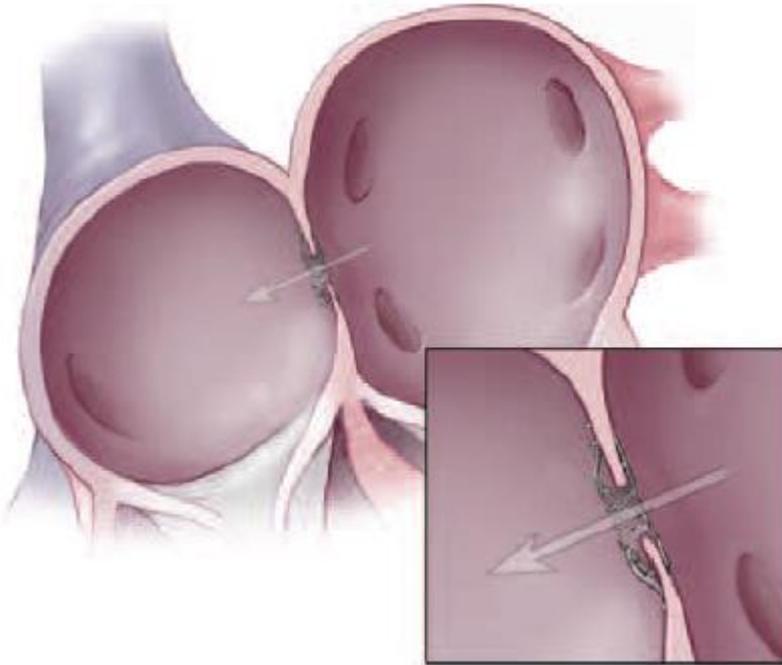
CardioMEMS HD guided HF management improves HF hosp in HFpEF

\*Hosp rate >6 mths: 46% lower; hosp rate at 18 mths: 50% lower

\*More therapeutic changes in vasodilators/diuretics in HD guided group



# Interatrial shunt device to lower LA pressures



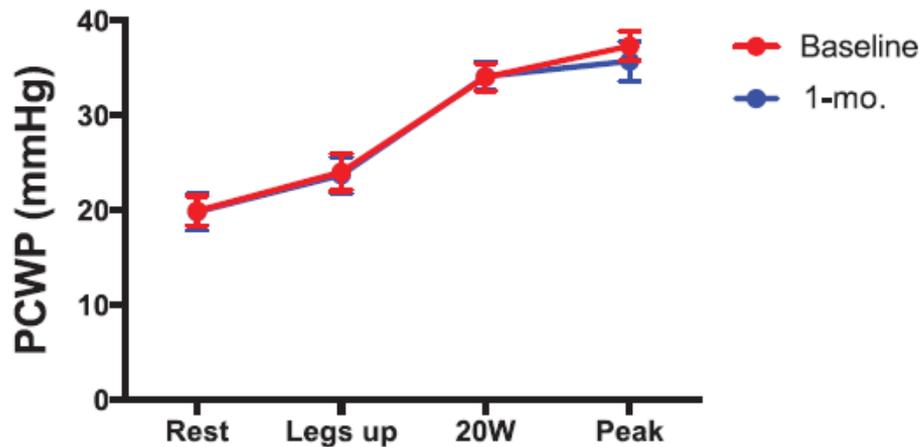
# REDUCE LAP-HF I

Phase 2, multicenter RCT; HF pts(n=44; EF  $\geq$ 40%), NYHA III-IV, exercise PCWP  $\geq$ 25 mmHg 1:1 to IASD vs sham procedure.

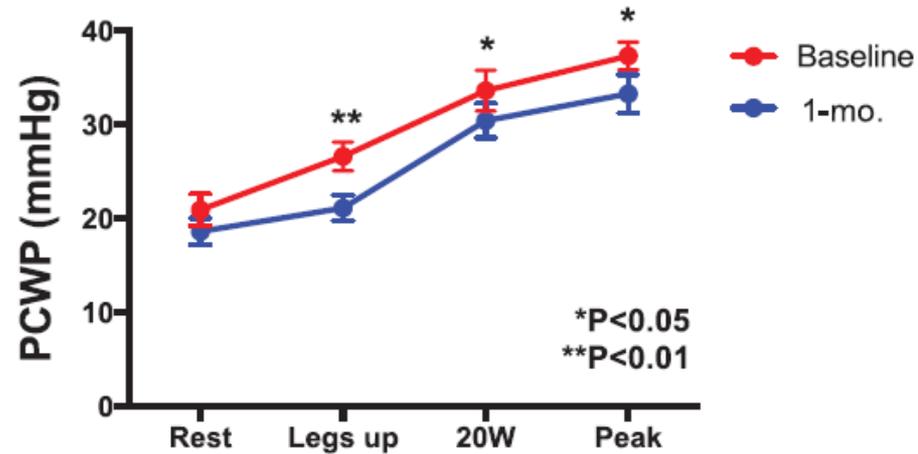
Prim EP: exercise PCWP 1 mth

Results: IASD resulted in greater reduction in exercise PCWP (p=0.028)

No peri-procedural or 1-mth MACE



Control group: Baseline vs. 1-month PCWP

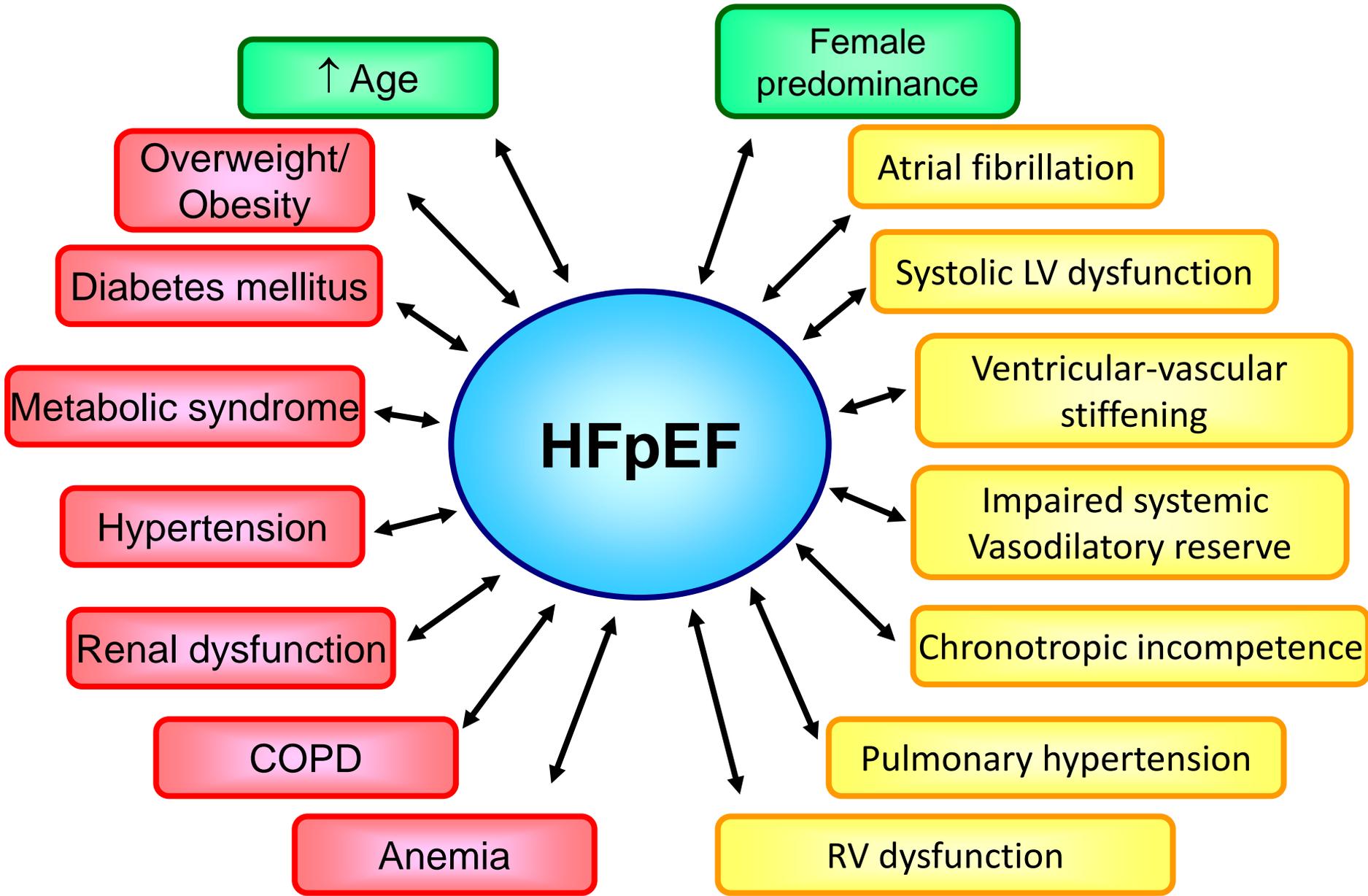


IASD group: Baseline vs. 1-month PCWP

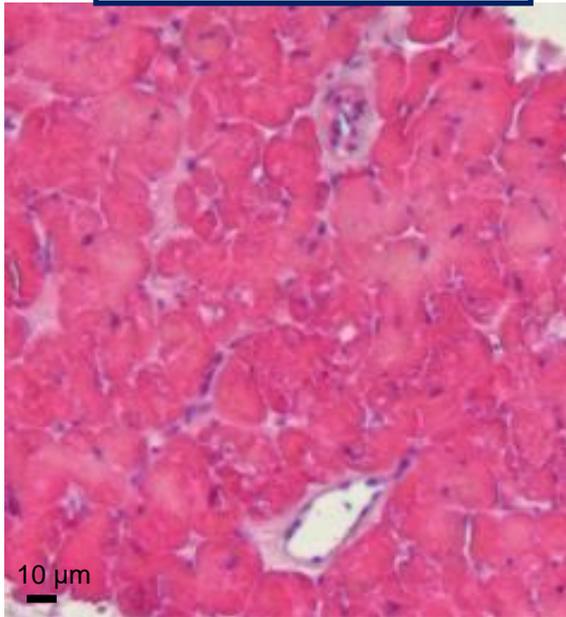
# Enhance pathophysiological insight



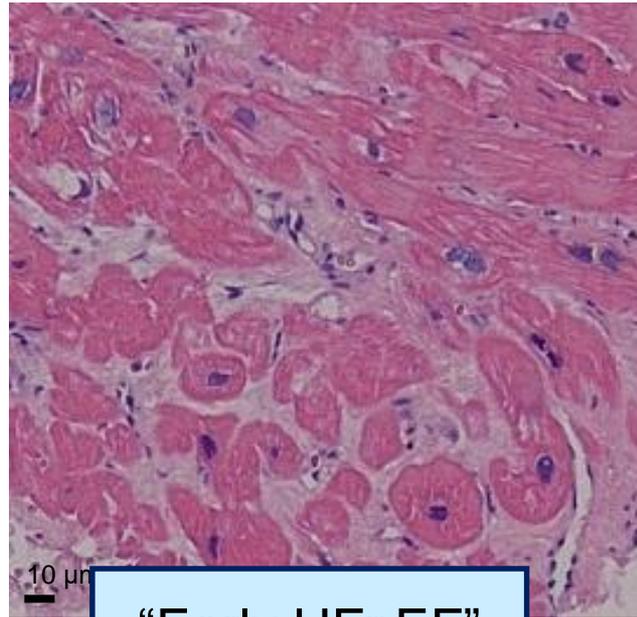
# HFpEF – a heterogeneous disease



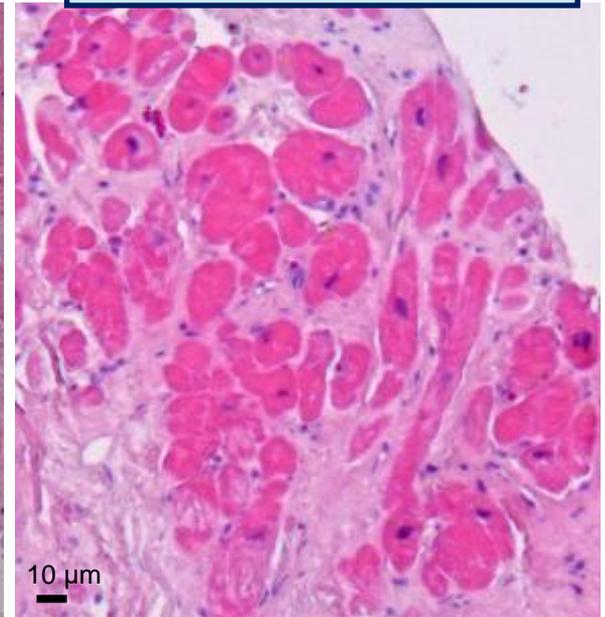
A “Early HFpEF”



B



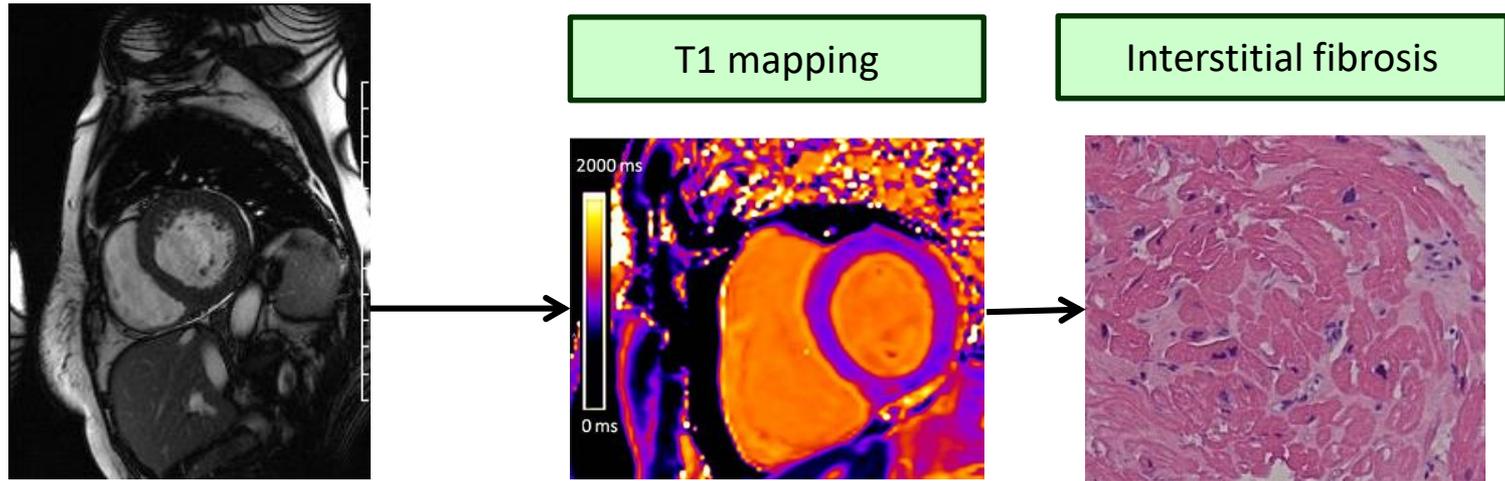
C “Advanced HFpEF”



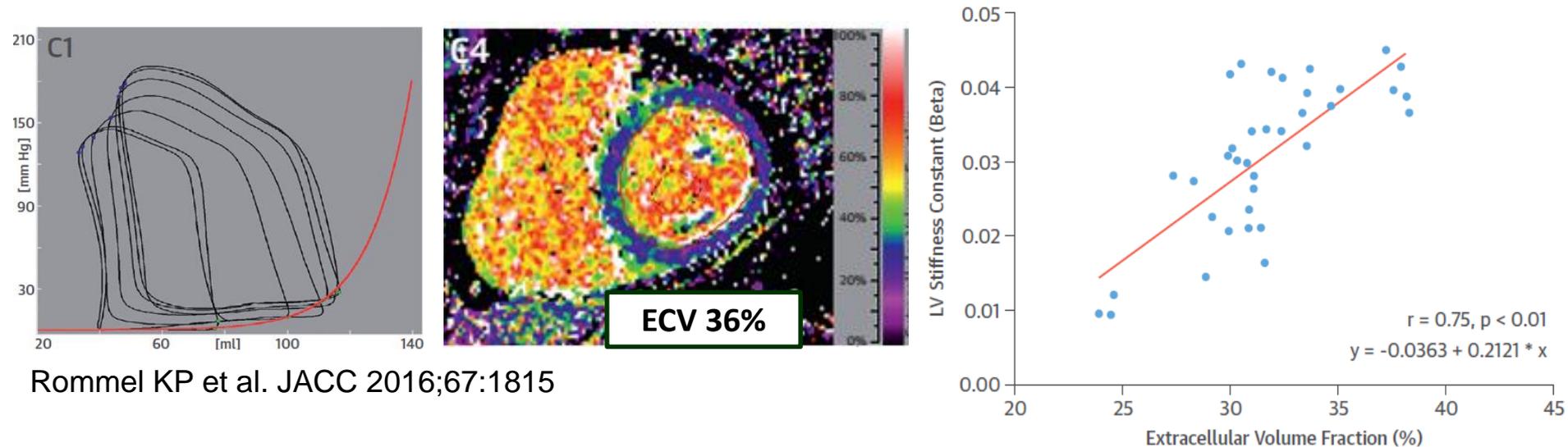
“Early HFpEF”

\*Neutral results → “Improve patient stratification  
→ “Improve patient stratification → “Advanced HFpEF” personalized treatment”

# Cardiac MRI – Characterization of myocardial tissue

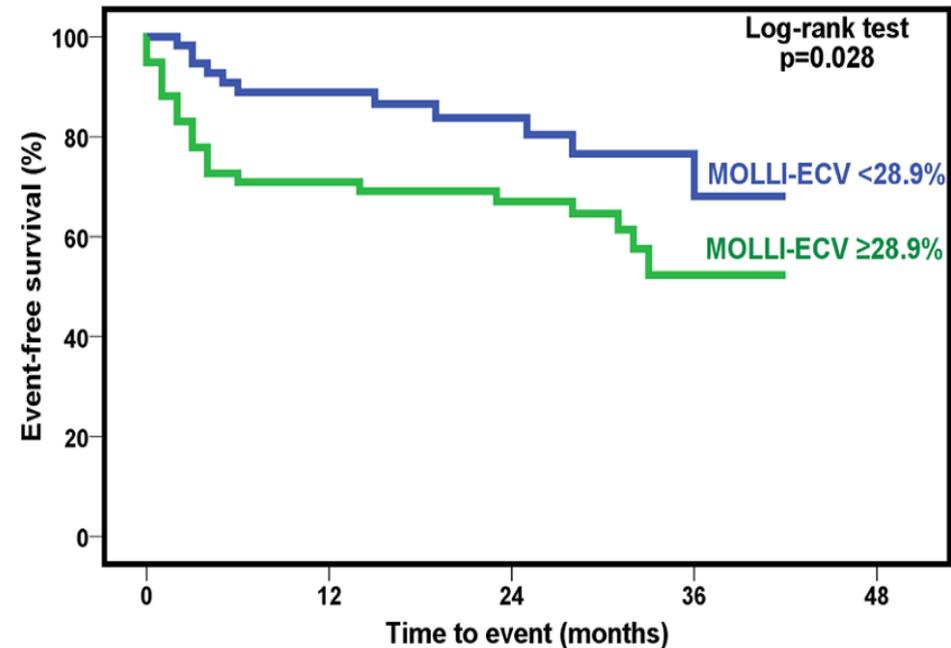
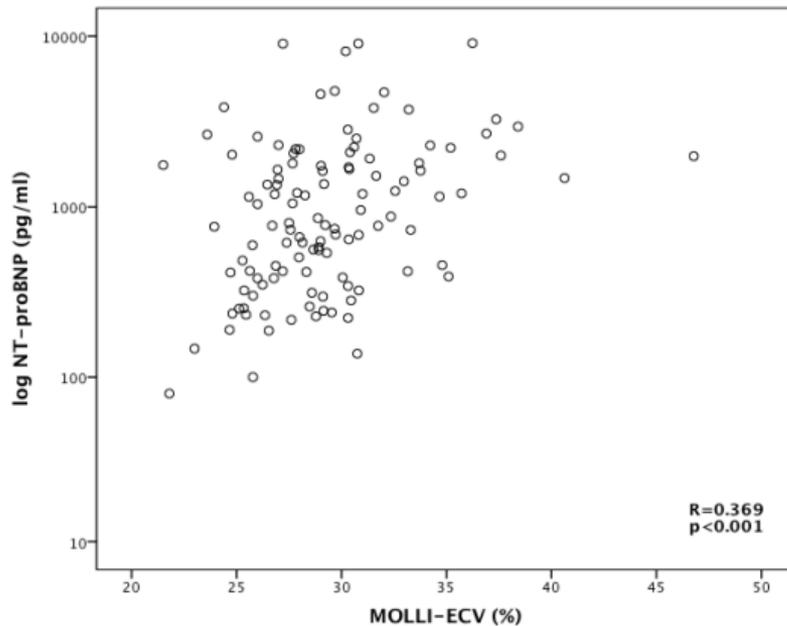


cMRI with T1 mapping and LV PV loops in HFpEF (n=24) and C (n=12)



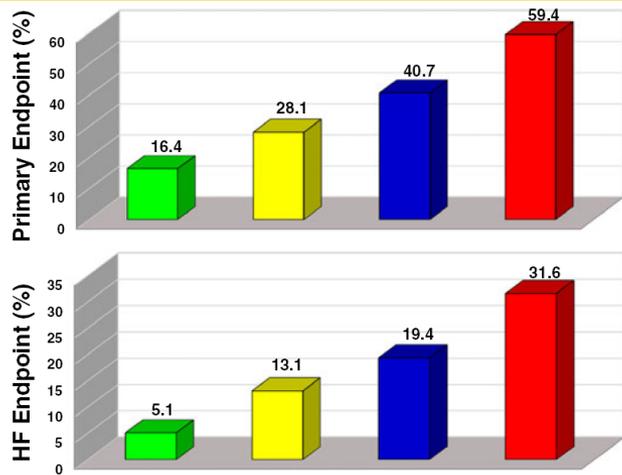
# HFpEF: NT-proBNP: marker of disease progression

	Total HFpEF (n=117)	HFpEF ECV <28.9% (n=58)	HFpEF ECV >28.9% (n=59)	P-value
Age	73.6 ± 7.8	73.6 ± 7.8	73.6 ± 7.8	0.402
Cardiac event, n (%)	34 (29.1)	11 (19.0)	23 (39.0)	0.017
ntproBNP (pg/ml)	833 (396-1892)	616 (308-1349)	1362 (582-2240)	0.001
MOLLI ECV (%)	29.3 ± 3.9	26.4 ± 1.7	32.1 ± 3.4	<0.001



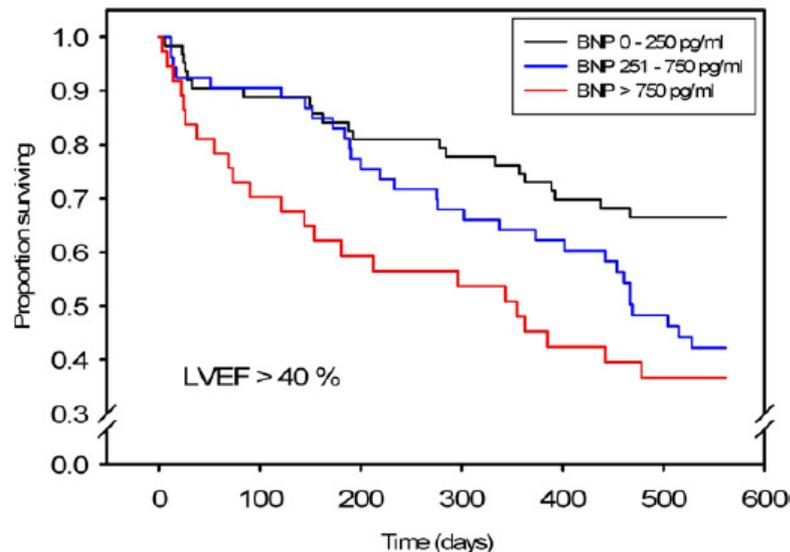
# (NT-pro)BNP correlates with worse outcome in HFpEF

## I-Preserve (Zile MR et al. Cardiovasc Trans Res 2013;6:501)

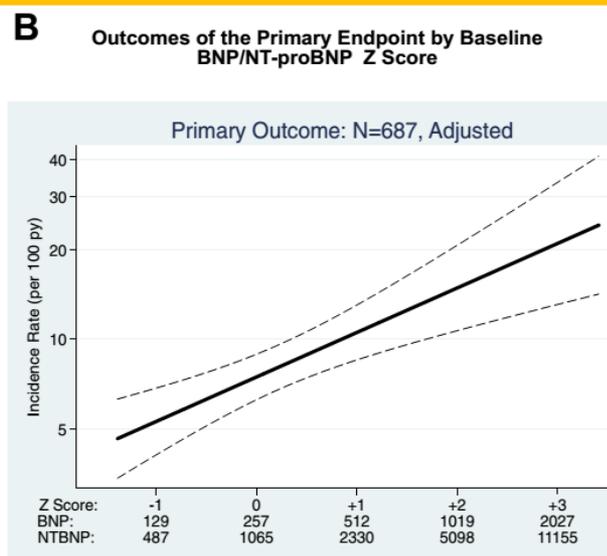
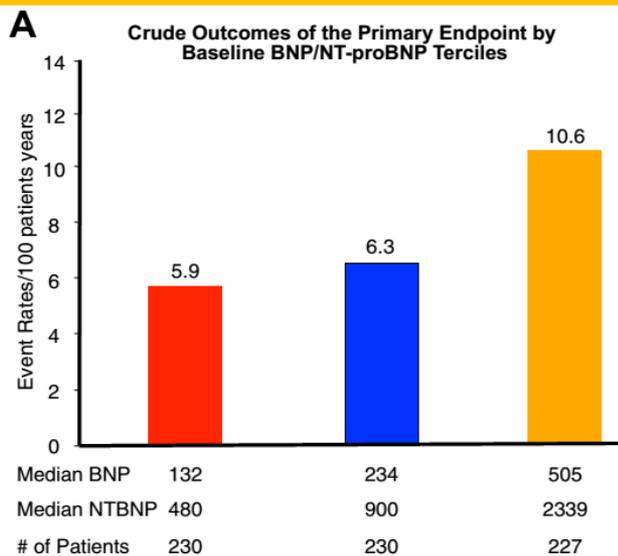


NT-pro BNP (pg/mL)	< 133	134 – 338	339 – 963	> 964
Median NT-pro BNP (pg/mL)	73	214	551	1720
# of Patients	870	867	873	870

## Coach (van Veldhuisen DJ et al. JACC 2013;61:1498)

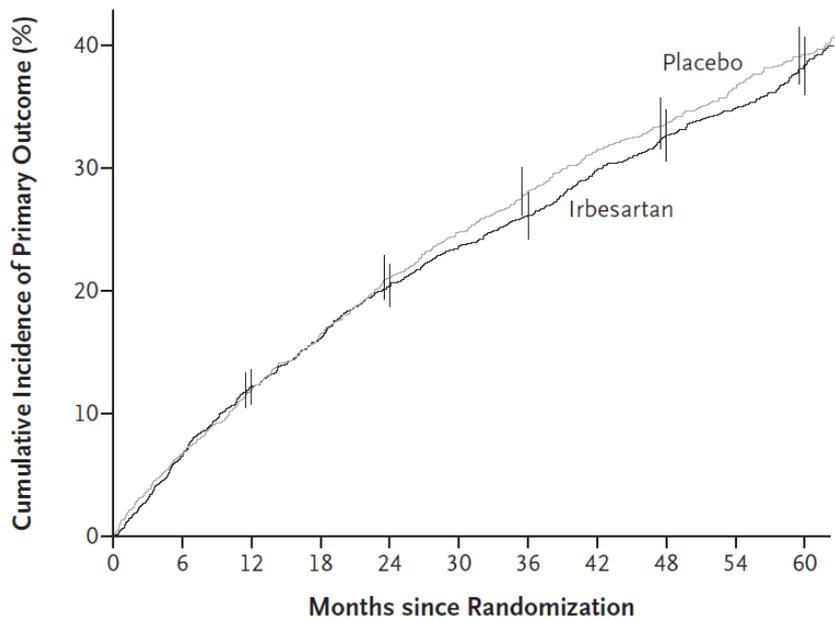


## TOPCAT (Anand IS et al. JACC Heart Fail 2017;5:241)



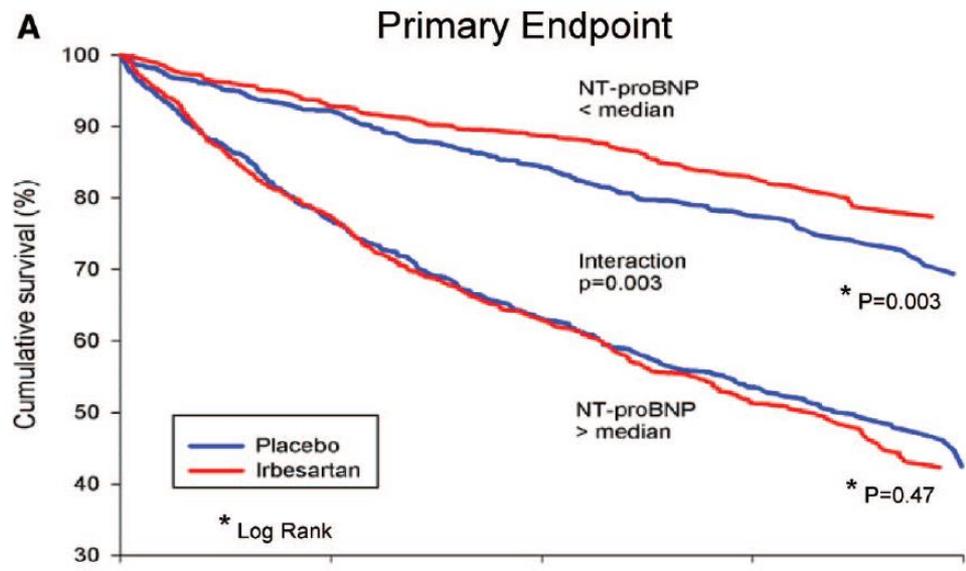
I-Preserve: Neutral prim EP (composite all-cause mortality and CV hospitalization...

...but positive in HFpEF pts with ntproBNP < median

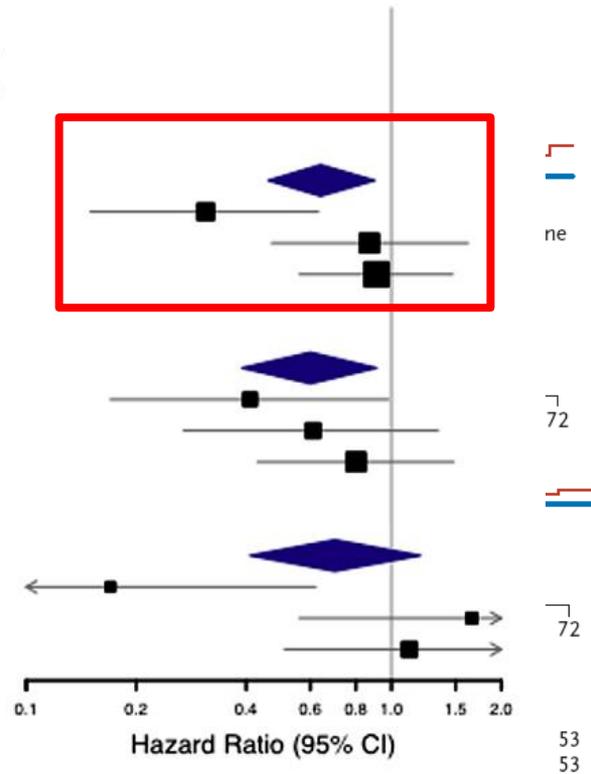


No. at Risk

Irbesartan	2067	1929	1812	1730	1640	1569	1513	1291	1088	816	497
Placebo	2061	1921	1808	1715	1618	1539	1466	1246	1051	776	446



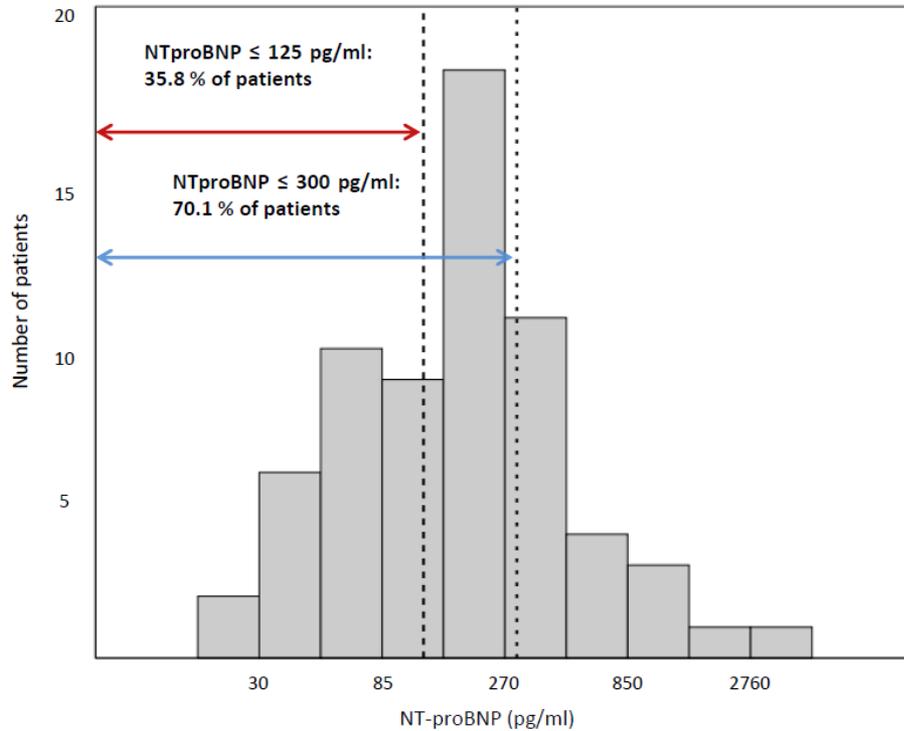
Subgroup	Placebo No. of Events/Patients	Spirolactone No. of Events/Patients	Hazard Ratio (95% CI)	P Value for Interaction
<b>BNP/NTBNP (n=687)</b>				
Overall	91/355 (25.6%)	57/332 (17.2%)	0.64 (0.46, 0.90)	0.017
Tertile 1	30/117 (25.6%)	10/113 (8.8%)	0.31 (0.15, 0.63)	
Tertile 2	21/110 (19.1%)	19/120 (15.8%)	0.87 (0.47, 1.62)	
Tertile 3	40/128 (31.2%)	28/99 (28.3%)	0.91 (0.56, 1.47)	
<b>BNP (n=430)</b>				
Overall	60/224 (26.8%)	34/206 (16.5%)	0.60 (0.39, 0.91)	0.216
Tertile 1	19/79 (24.1%)	7/65 (10.8%)	0.41 (0.17, 0.98)	
Tertile 2	16/70 (22.9%)	10/74 (13.5%)	0.61 (0.27, 1.34)	
Tertile 3	25/75 (33.3%)	17/67 (25.4%)	0.80 (0.43, 1.48)	
<b>NTBNP (n=257)</b>				
Overall	31/131 (23.7%)	23/126 (18.3%)	0.70 (0.41, 1.20)	0.027
Tertile 1	11/38 (28.9%)	3/48 (6.2%)	0.17 (0.05, 0.62)	
Tertile 2	5/40 (12.5%)	9/46 (19.6%)	1.66 (0.56, 4.97)	
Tertile 3	15/53 (28.3%)	11/32 (34.4%)	1.12 (0.51, 2.46)	



No.  
Spird  
Place

Anand IS et al, JACC Heart Fail 2017;5:241

# HFpEF: NT-proBNP



HFpEF pts (n=83), without Afib or CAD,  
 NYHA II-III, age 70 ± 9, BMI 31.6 ± 6.2;  
 median NT-proBNP 161pg/ml

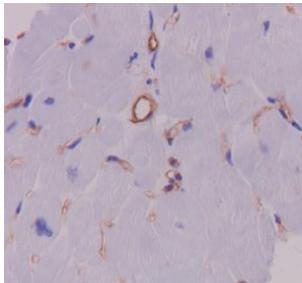
	NT-proBNP trial entry criteria	NT-proBNP (pg/ml)
RELAX	> 400 pg/ml	700 (283-1553)
PARAMOUNT	> 400 pg/ml	884 (521-1416)
TOPCAT	>360 pg/ml	900 (557-1920)
SOCRATES-PRESERVED	>300 pg/ml	1174 (433-2576)
EMPEROR-PRESERVED	>300 pg/ml	recruiting
PARAGON	>300 pg/ml	pending

Pathophysiological diversity

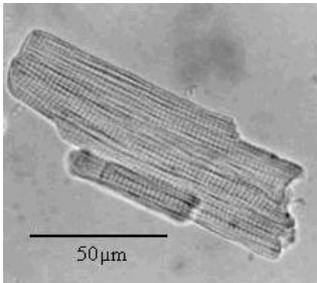


Therapeutic stratification according to cardiac struct/func remodeling

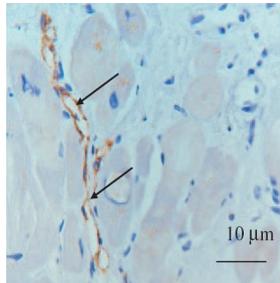
Capillary rarefaction



CM stiffness



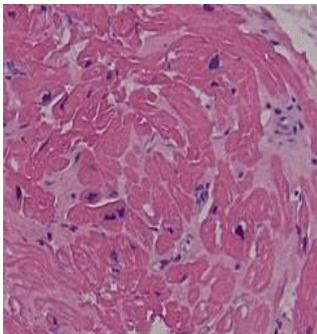
MVD and inflammation



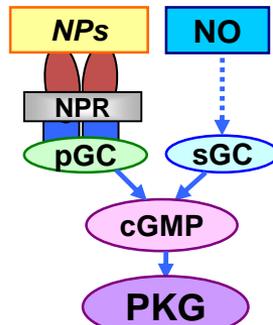
Hypertrophy



Fibrosis



Impaired signaling



Clinical phenotypic diversity



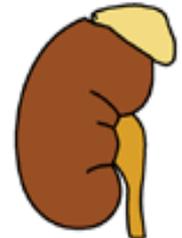
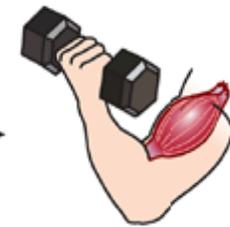
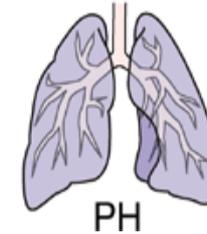
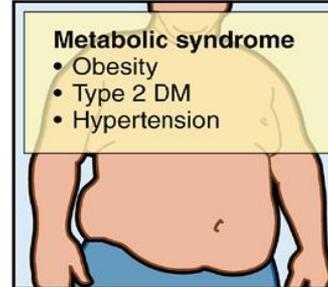
Therapeutic stratification acc to comorbidities



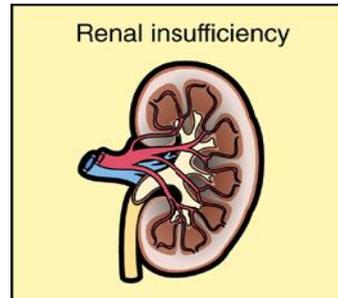
Therapeutic stratification acc to ancillary mechanisms

Metabolic syndrome

- Obesity
- Type 2 DM
- Hypertension



Renal insufficiency



Suspicion heart failure: symptoms/signs + risk factors (age, DM, HT, obesity, sedentary lifestyle)

Dyspnea outpt clinic; 1st consult

TTE, Ergometry, Lab, Urine, Pulmonary function, Chest X-ray

LV/RV dimensions  
LV/RV systolic + diastolic fx  
LV strain  
LV twist/untwist/torsion  
LA/RA volume + fx  
LV/RV 3D volumes/EF

Nt-proBNP/BNP

LVEF  $\leq$  45%? Valve dis?

eGFR  $<$  60 ml/min?

DM de novo?

Pulmonary dysfx? osas?

Elderly? Frail? Multi Rx

Regular outpatient clinic

Nephrologist

Internist

Pulmonologist

Geriatrician

Entry from 2nd line

2nd consult

No HFpEF

Exit or regular outpt clinic

HFpEF possible

2) Pulm

CPET

VO<sub>2</sub>  
VE/CO<sub>2</sub>

1) Stress-MRI

T1 mapping  
Perfusion  
CFR  
LV/RV vol/fx  
LA/RA vol/fx  
PA:Ao ratio  
Diastology

Ischemia?

no

yes

CAG

no

yes

+RHC

Revascularize

3) RHC (+ exerc)

PCWP  
PAP (S,M,D)  
RAP, RVP  
PVR/SVR  
PAC  
CO  
AVO2 diff

Biomarkers

CV stress  
Inflamm.  
Fibrosis  
Endoth dysfx  
Neurohum  
Adipose

HFpEF confirmed  
2nd outpt clinic consult

Research program

Clinical program

\*Stratification strategy  
MRI, RHC, TTE, biomarkers  
(CV stress, inflamm, fibrosis, ED,  
neurohum, adipose)  
\*Grants; Reconnect, etc.

Congestion/HT: diuret, RAAS-I, CCB  
Metabolic abnormalities: statin  
Obesity: Calory restriction  
Endurance training  
Comorbidity treatment

THANK YOU!!



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				Neutral
I-PRESERVE				Neutral
ELANDD				Neutral
J-DHF				Neutral
<b>ALDO-DHF</b>				<b>Neutral</b>
<b>Ex-DHF</b>				<b>Peak VO2 ↑</b>
PARAMOUNT			ubitril	ntproBNP ↓
<b>RELAX</b>				<b>Neutral</b>
<b>RELAX-AHF</b>				<b>Neutral</b>
<b>RAAM-PEF</b>				<b>Neutral</b>
EDIFY				Neutral
TOPCAT	≥45	3445	Spironolactone	Neutral
PARAGON-HF			acubitril	Pending
SOCRATES-PRESERVED				Neutral
ADHERE				
OPTIMIZE-HF				
MAGGIC				
GWTG-HF	≥50; 40-49	40354	Registry	

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
it is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.	I	C
Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.	I	B

HFpEF pathophysiology?

# The new ESC HFA PEFF score (0-6)

MAJOR CRITERIA: 2 points; MINOR CRITERIA: 1 point

## *Functional*

## *Morphological*

## *Biomarker*

MAJOR

Septal  $e' < 7$ ,  
Lateral  $e' < 10$   
Or  
 $E/e' (Avg) \geq 15$

LAVI  $> 34$   
Or  
LVMI  $> 149/122$  (M/F)  
And  
RWT  $> 0.42$

NTproBNP  $> 220/660$  (SR/AF)  
Or  
BNP  $> 80/240$  (SR/PAF)

MINOR

$E/e' (Avg)$  9-14  
Or  
TR vel  $> 2.8$  m/s  
Or  
GLS  $< 16\%$

LAVI  $> 29-34$   
Or  
LVMI  $> 115/95$  (M/F)  
Or RWT  $> 0.42$   
Or LVWT  $> 12$  mm

NTproBNP  $> 115-220$  or  
BNP  $> 35-80$  (SR)  
Or  
NTproBNP  $> 365-660$  or  
BNP 105-240 (AF)

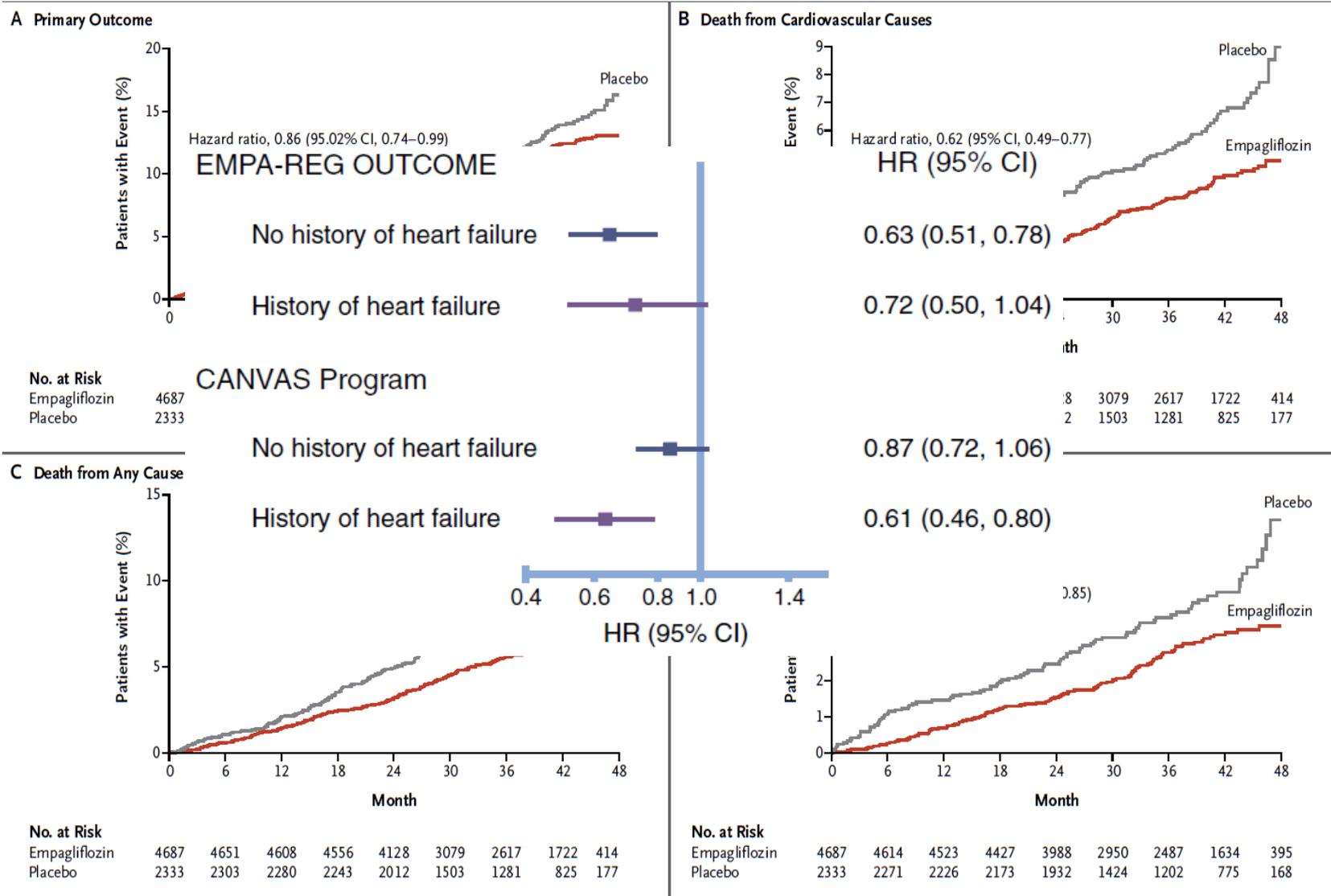
### **HFA-PEFF score:**

$\geq 5$  points: HFpEF

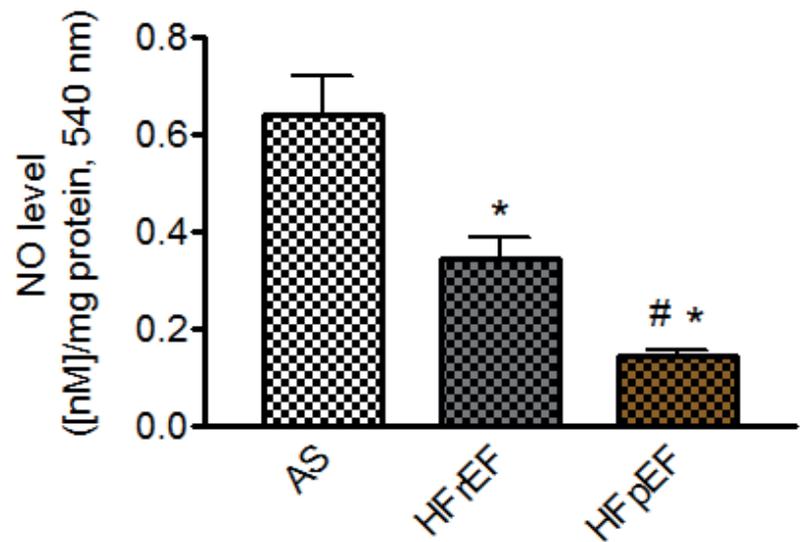
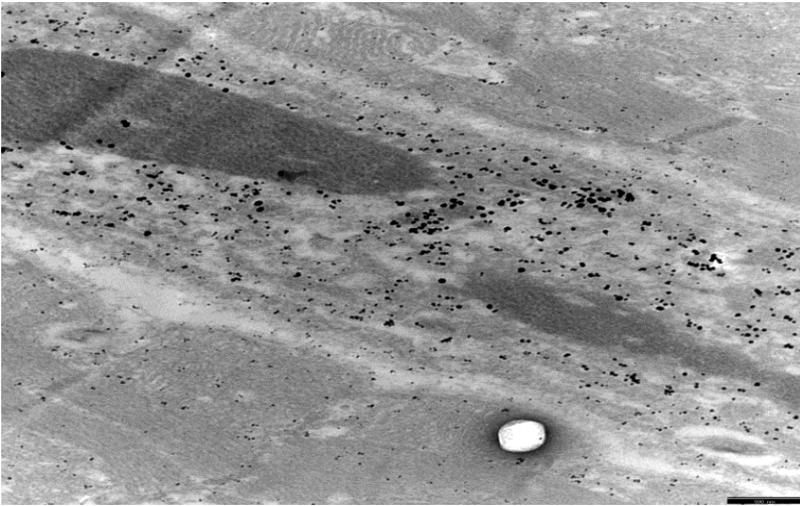
2-4 points: Diastolic stress test or invasive hemodynamics

$< 2$  points: no HFpEF

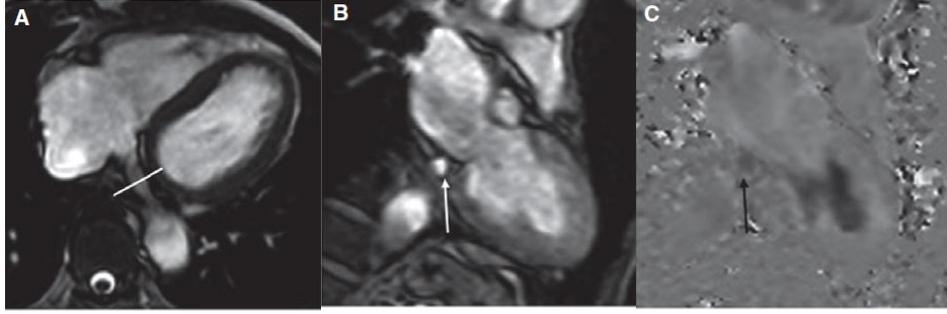
**EMPAREG trial– empagliflozin in DM**  
**T2DM pts (n=7020) at high risk for CV outcomes, FUP 3.1 yrs**  
**Prim EP: composite of CV death, non-fatal MI or stroke (Zinman et al. NEJM 2015;373:2117)**



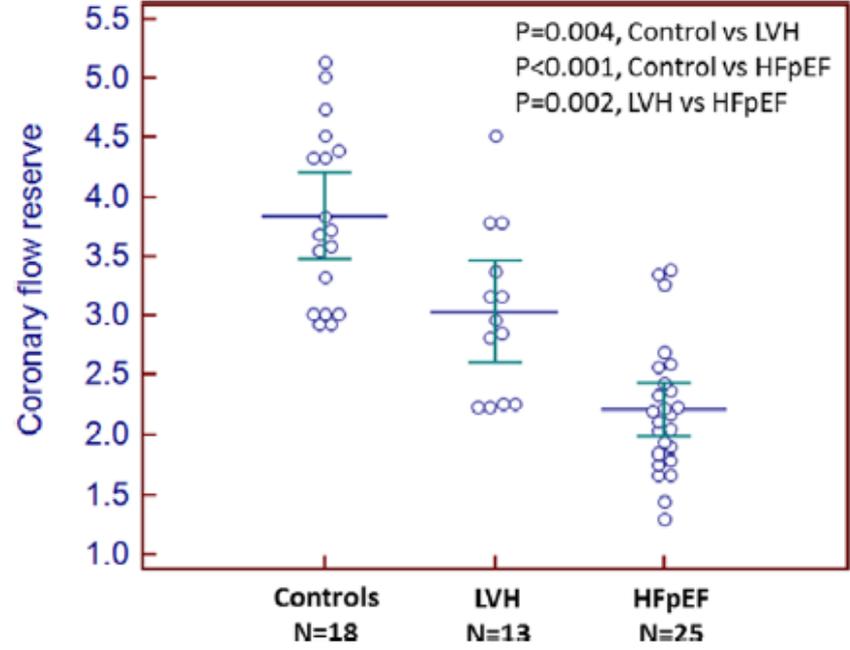
Immunolabeling electron microscopy



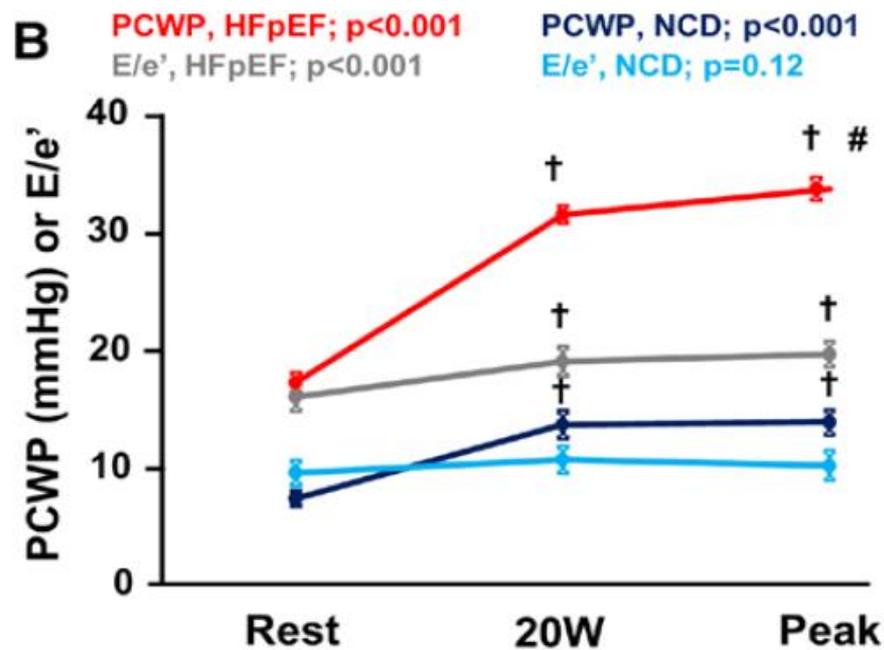
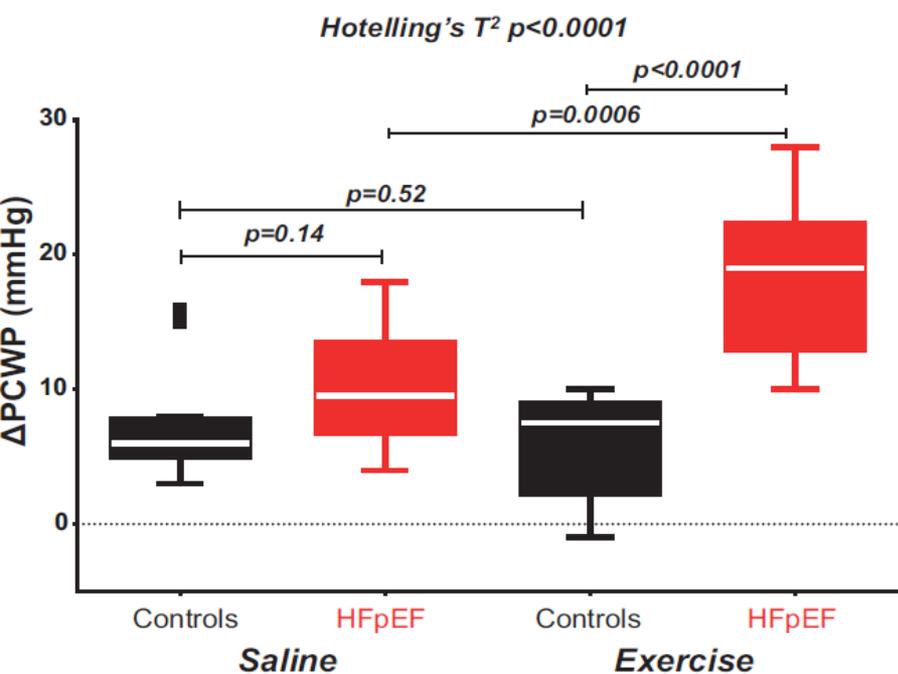
cMRI/adenosine: coronary flow reserve in HFpEF (n=25; 2.21 ±0.55 ) vs HHD (n=13; 3.05±0.74 ) and C (n=18; 3.83±0.73;p<0.001)



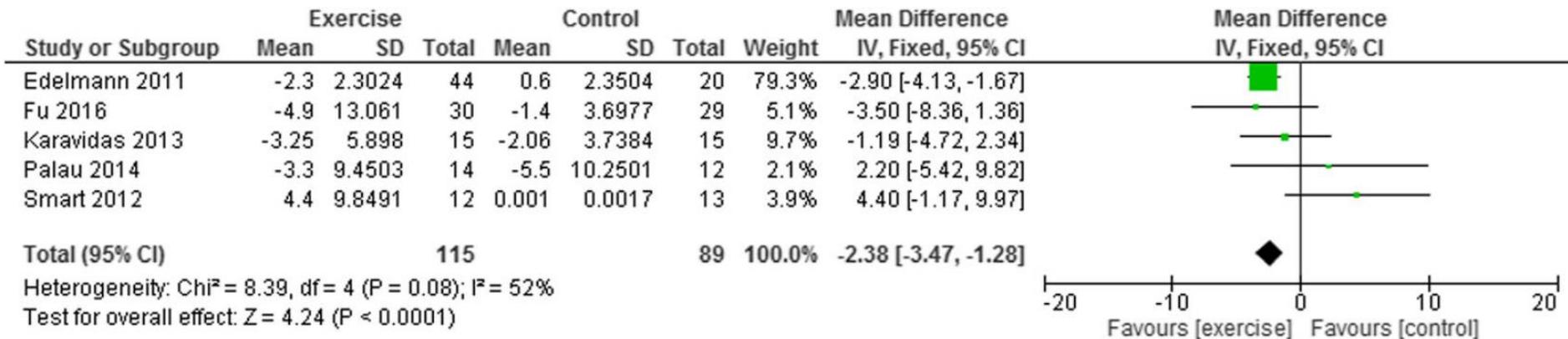
Cine MRI      Magnitude image      Phase contrast image



# HFpEF: Exercise induced increase in LV filling pressures



# Exercise training in HFpEF



# HFpEF – HD monitoring devices - CardioMems

