

Heart Failure with Preserved Ejection Fraction: *A Clinician's Perspective*

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 - » ABIM, Pulmonary Hypertension Association, American Society of Echocardiography, Heart Failure Society of America, AstraZeneca, Bayer, Novartis, Merck
- We pronounce HFpEF: "*huff-puff*"

Take home messages

- Don't miss the diagnosis of HFpEF
 - » Many patients go undiagnosed for years
 - » Always think of HFpEF in the dyspneic patient
- Your HFpEF patients need help!
 - » High risk for hospitalization and death
 - » Symptomatic, depressed, debilitated
 - » Complex cases in need of multidisciplinary care
 - » Several clinical trials are available

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**MYTHS AND
MISCONCEPTIONS**

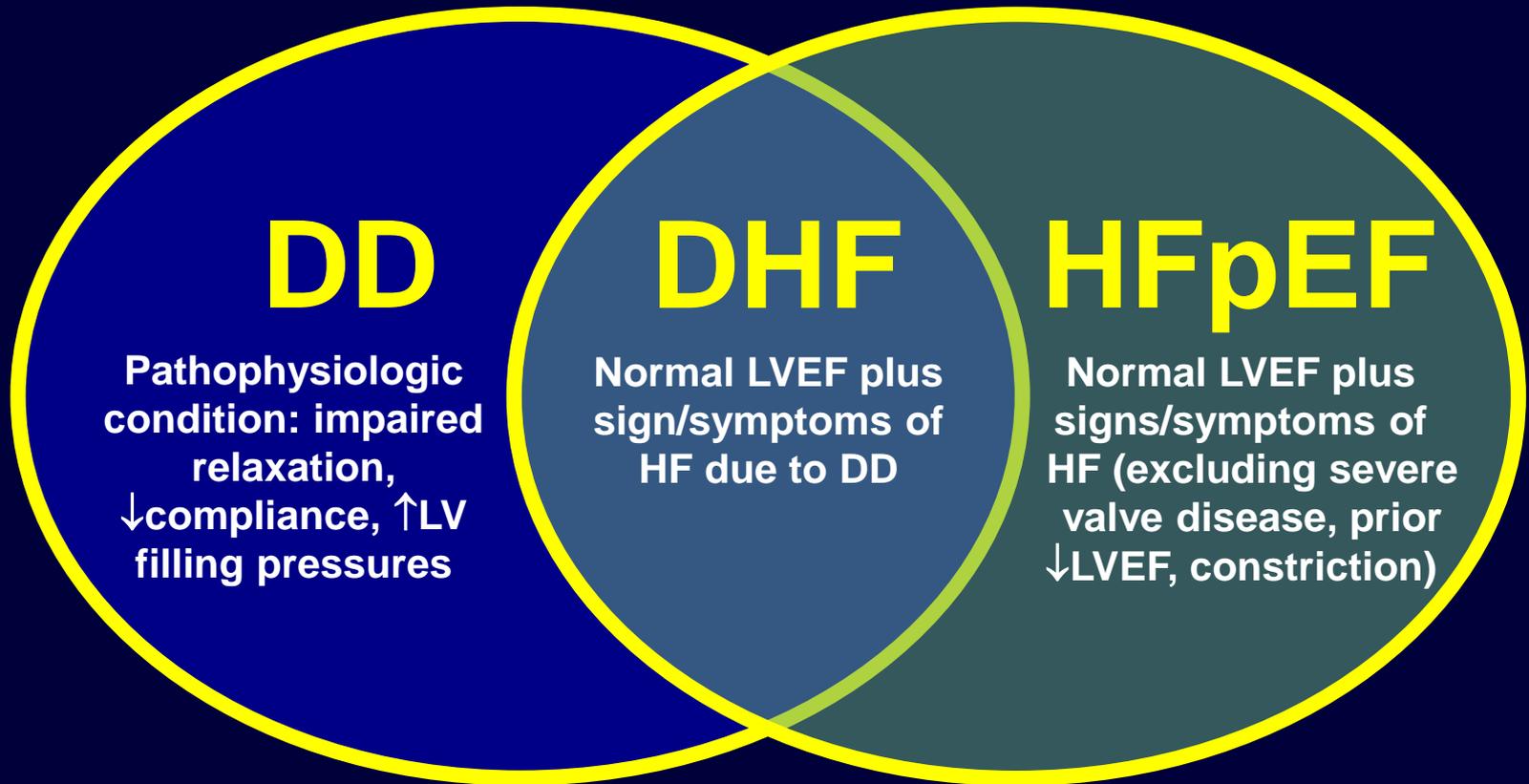
Myth #1:

**Diastolic dysfunction,
diastolic HF, and
HFpEF are all the same**

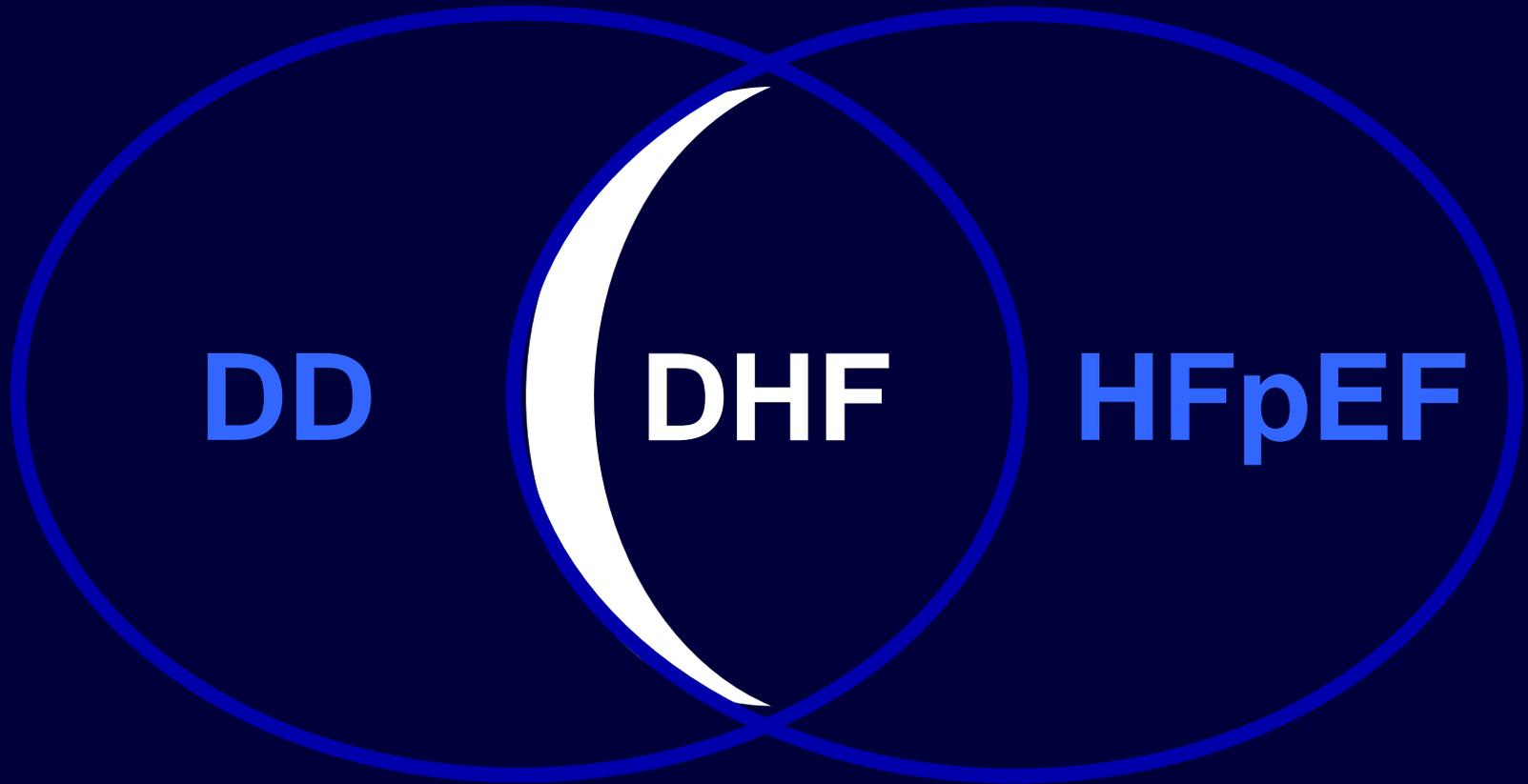
Fact #1:

**HFpEF is more than just
diastolic dysfunction**

DD vs. DHF vs. HFpEF



DD vs. DHF vs. HFpEF



DD vs. DHF vs. HFpEF

*Pure diastolic HF
Is actually a
rare syndrome*

“pure” DHF

Screened 2,054 Patients (age > 65) with a discharge diagnosis of CHF

1,119 patients with a LVEF > 50 %

Reason for exclusion	# of patients excluded
Atrial fibrillation at the time of study	313
Prior CABG	179
Incomplete records	111
Left bundle branch block or paced rhythm	90
No clear documentation of CHF	77
Active malignancy	55
Myocardial ischemia/infarction	53
Dementia/cognitive impairment	44
Deceased prior to enrollment evaluation	41
Dialysis dependant or creatinine (> 2.5 g/dl)	40
Severe COPD/pulmonary disease	39
Warfarin use	30
Moderate to severe valvular heart disease	13
History of organ transplantation	6
Ejection fraction unclear	5
Total Patients Excluded	1096

935 patients with a LVEF ≤ 50 % (excluded)

Diastolic HF study:
*Started with 1,119 patients...
... after exclusions only
23 patients met
enrollment criteria!*

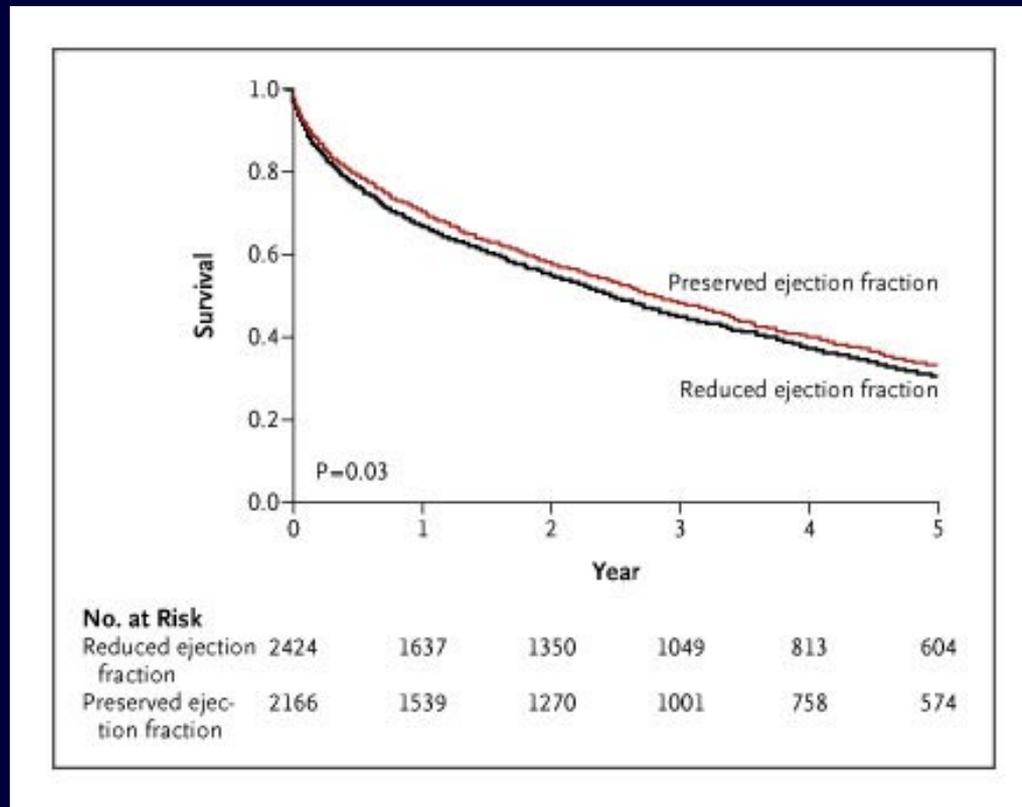
23 patients met criteria for enrollment

11 patients agreed to participate
4 men and 7 women

HFpEF: A debilitating syndrome

- TOPCAT trial (spironolactone vs. placebo) N=3445:
 - » At baseline:
 - Activity level very low (9.3 MET-hr/week)
 - Poor QOL similar to ESRD
 - 27% with moderate or greater depression
 - » Baseline echo:
 - ↑Structural heart disease (LVH, LA enlargement)
 - Diastolic function “normal” in approximately 1/3

HFpEF survival: poor



Owan T et al. N Engl J Med 2006;355:251-259

Dismal 35% survival at 5 years after HF hospitalization, regardless of LVEF

Myth #2:

**Diagnosing HFpEF
is difficult**

Fact #2:

**Diagnosing HFpEF is easy
(if you know what to
look for)**



How is HFpEF
diagnosed?

Keep it simple...

Diagnosis of HFpEF

- Step 1: clinical symptoms/signs of HF
 - » Low CO and/or \uparrow LV filling pressures at rest or with exertion
- Step 2: normal LVEF ($> 50\%$)
- Step 3: objective evidence of cardiac structural and/or functional problem
 - » LVH or LA enlargement or diastolic dysfunction or \uparrow PASP (in absence of PAH)

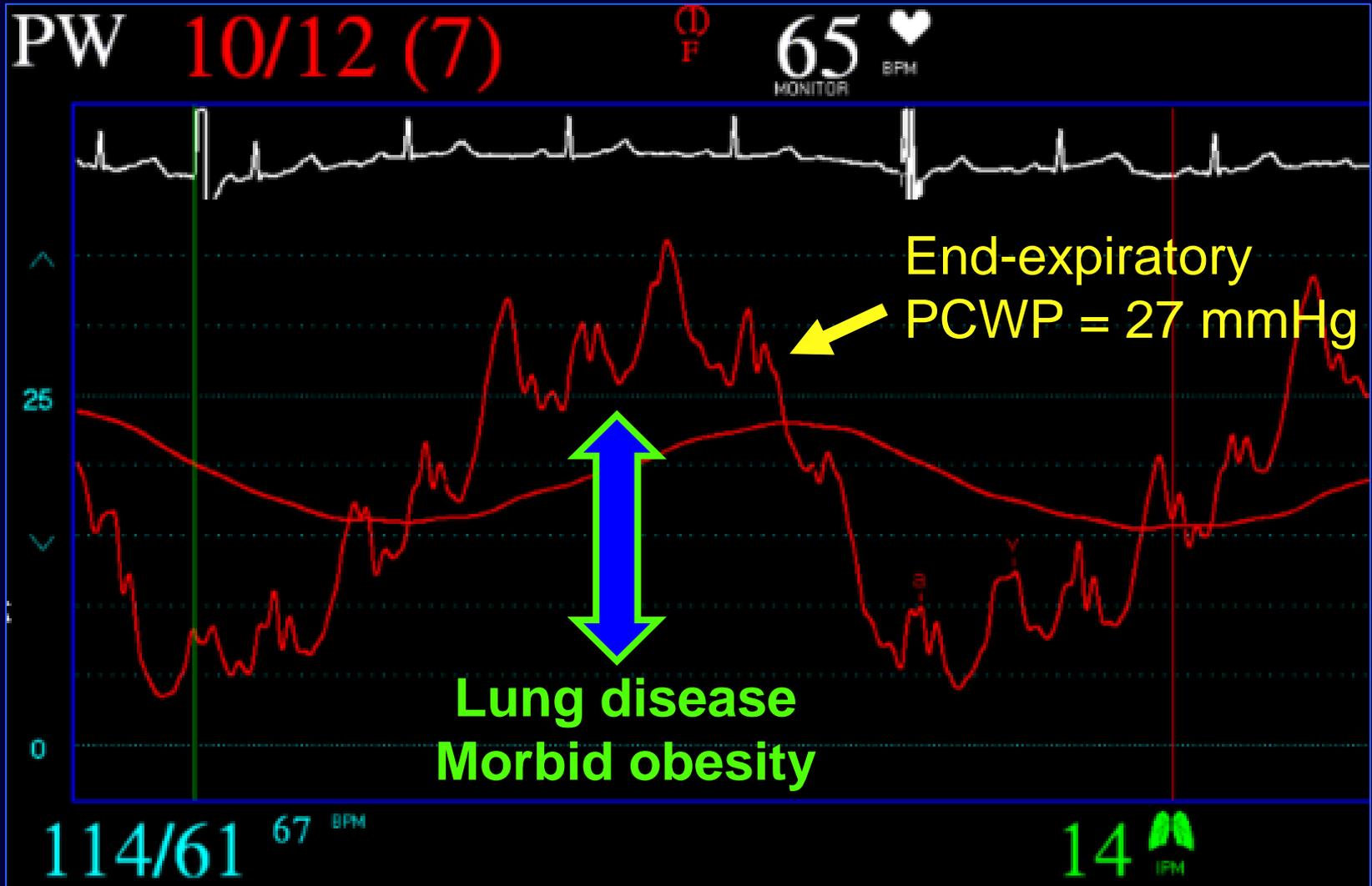
Diagnosis of HFpEF?

- Diastolic dysfunction (DD) on echo:
 - » Not required for the diagnosis
 - » Often uninterpreted or misinterpreted
 - » Grade 2 (moderate) or grade 3 (severe) DD helpful but not required for diagnosis
 - » Patients can have HFpEF with “normal” diastolic function or “mild” DD
- When in doubt: do a right heart cath!

Respiratory variation in PCWP

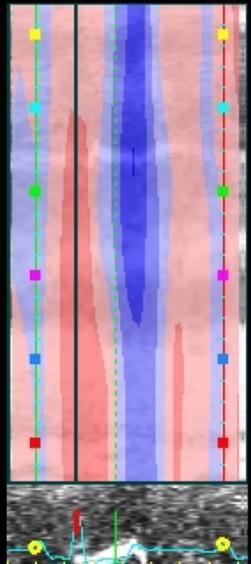
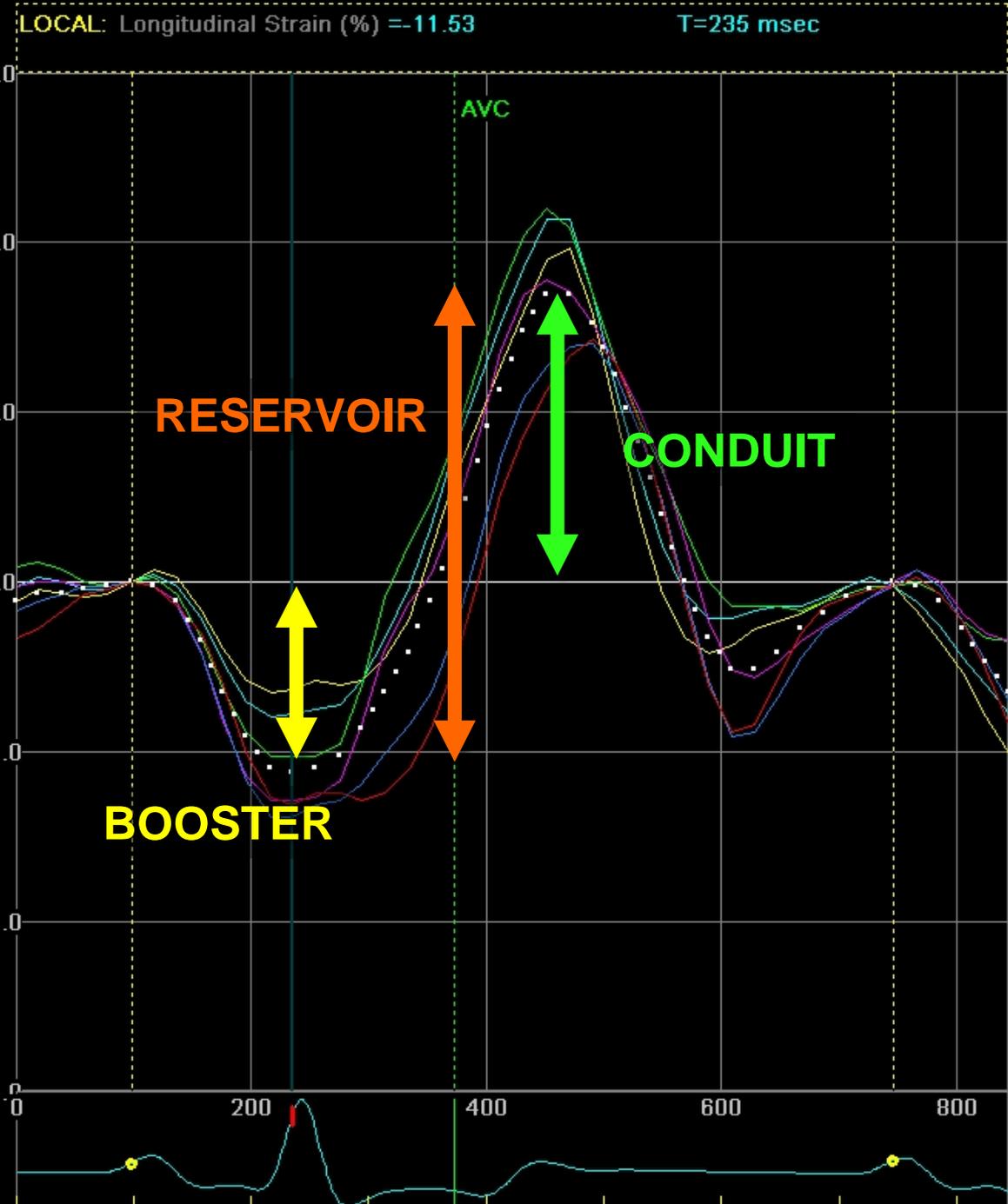
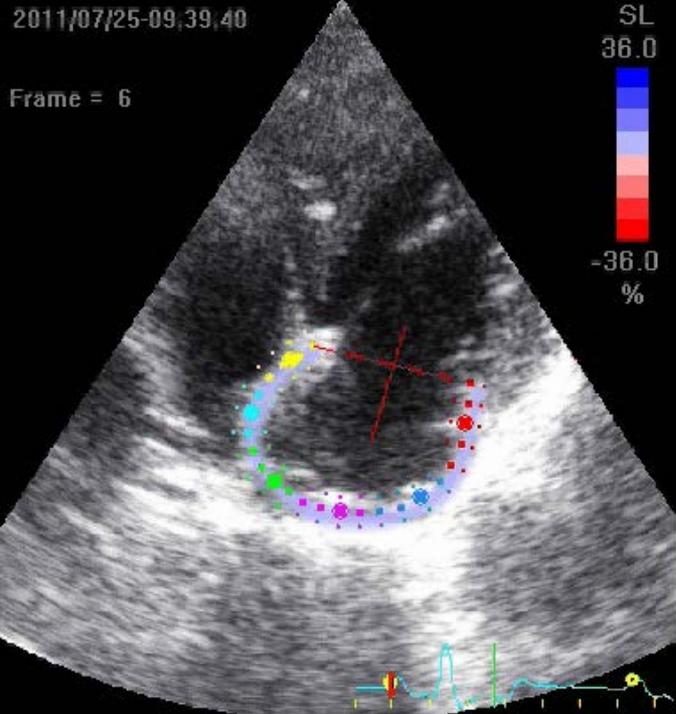


Respiratory variation in PCWP

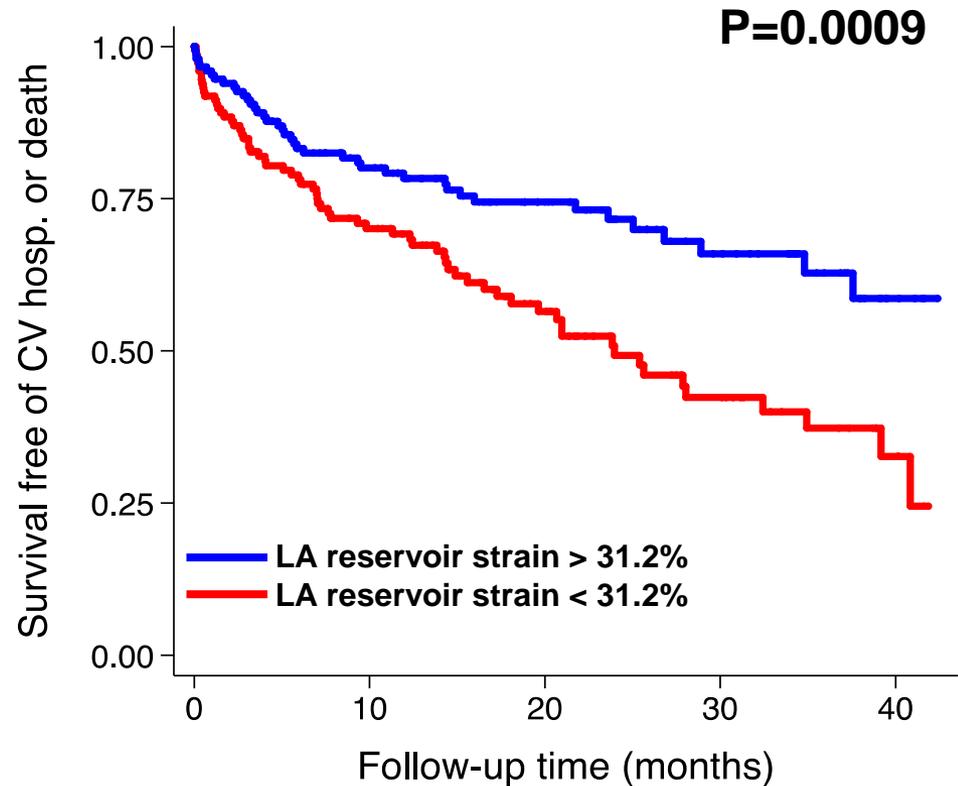
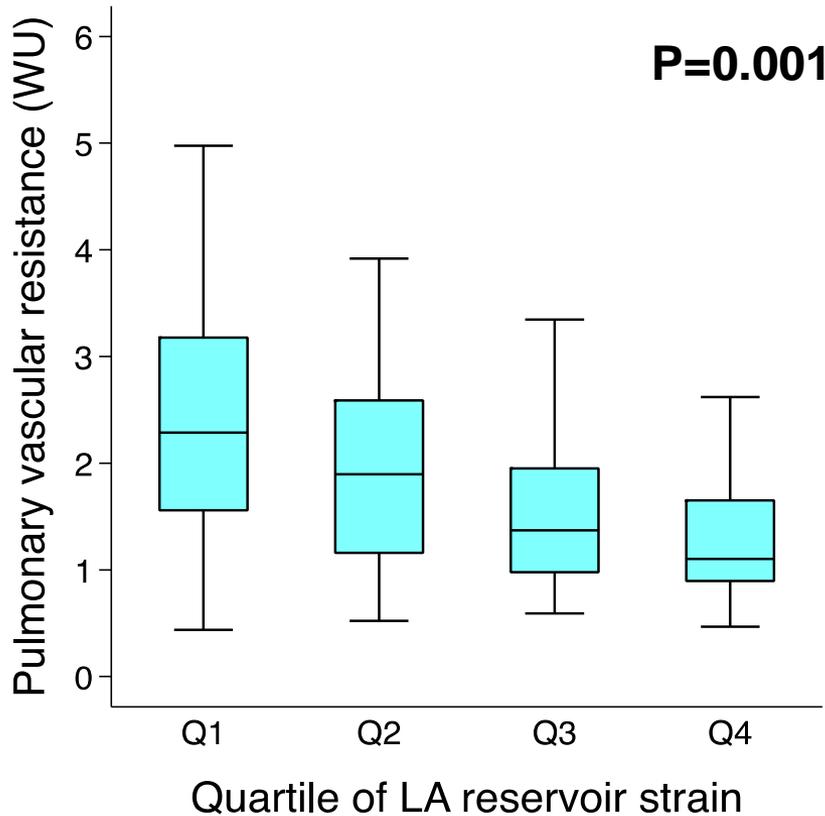


2011/07/25-09,39,40

Frame = 6

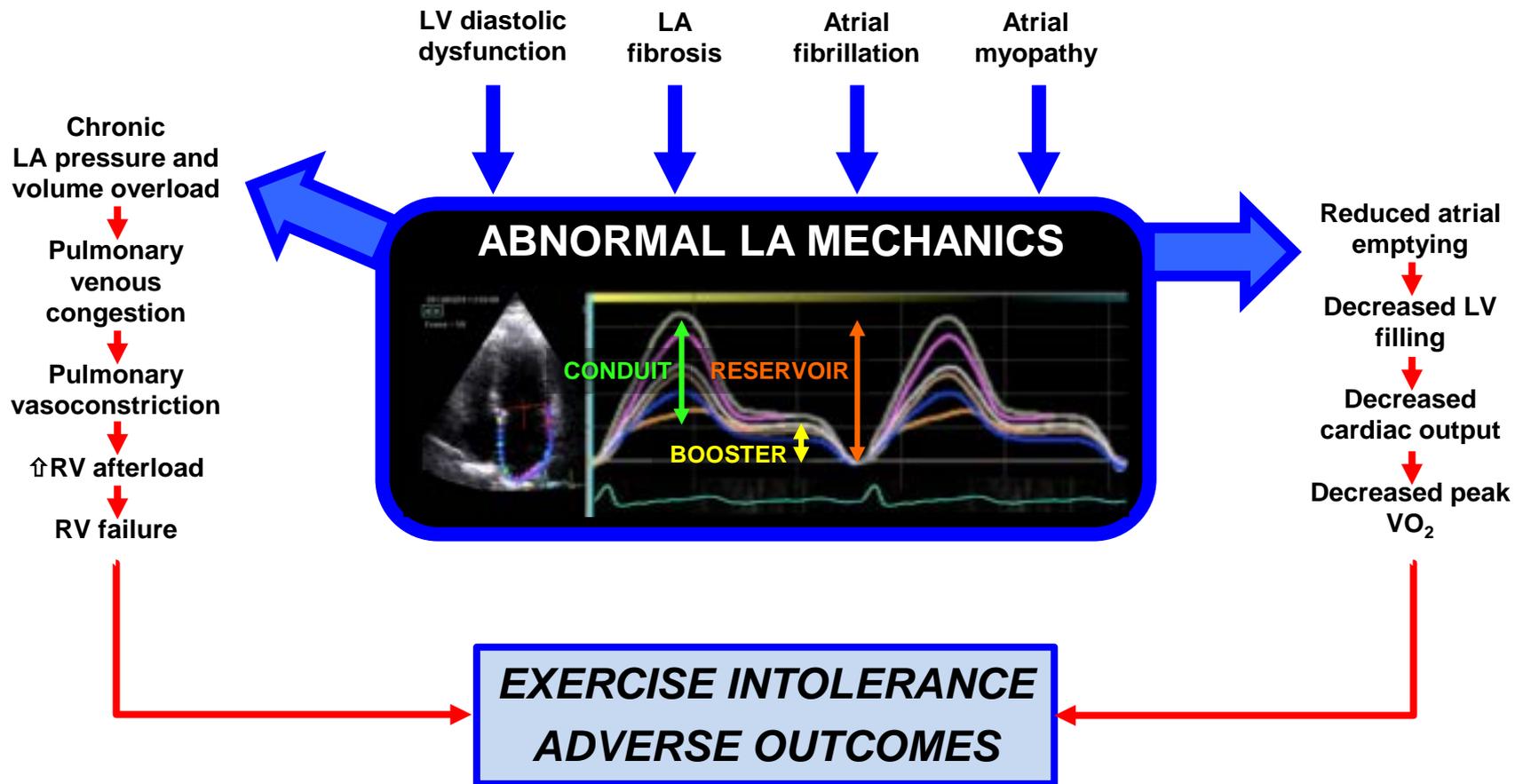


Abnormal LA mechanics in HFpEF



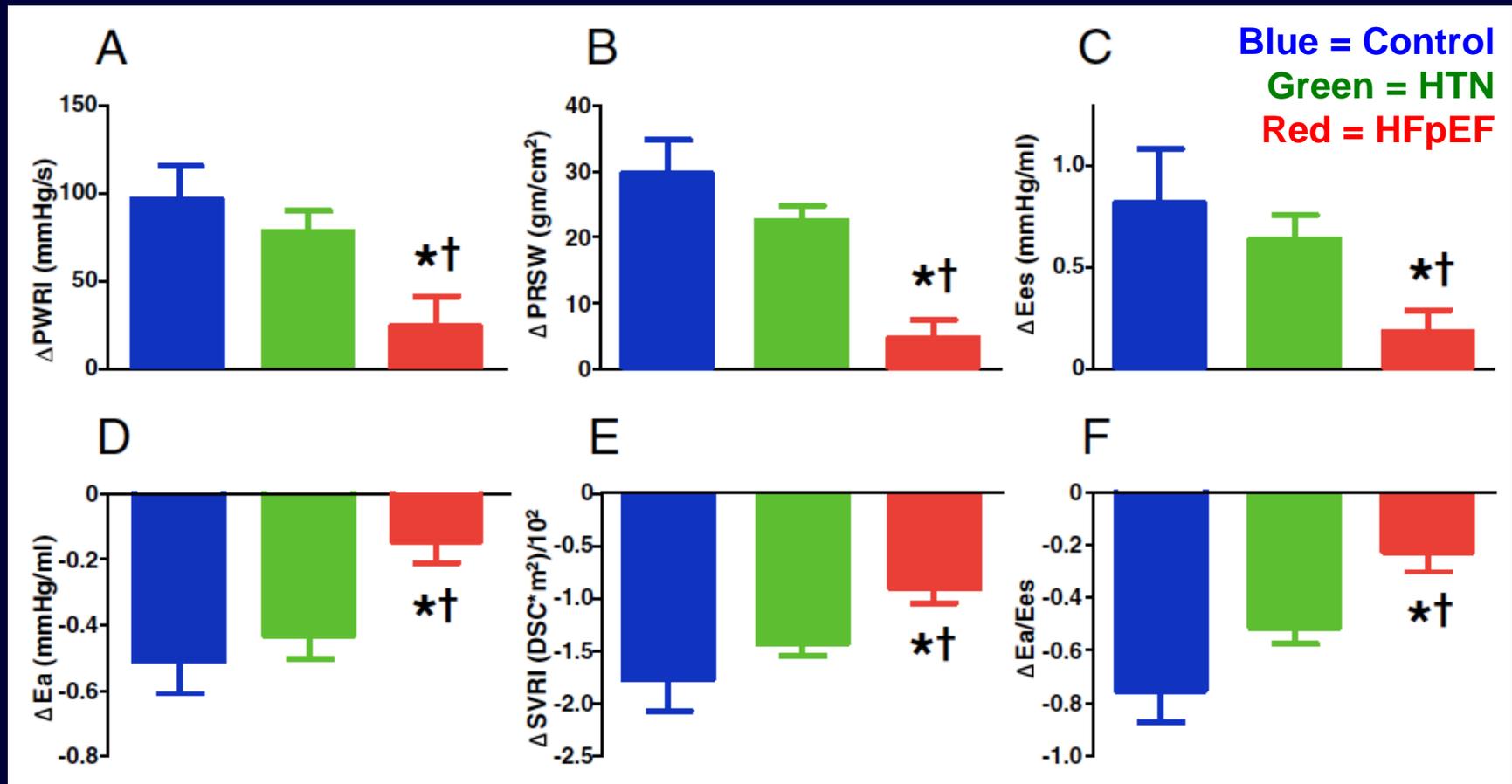
LA strain is a better predictor of outcomes compared to LV or RV longitudinal strain

Abnormal LA mechanics in HFpEF



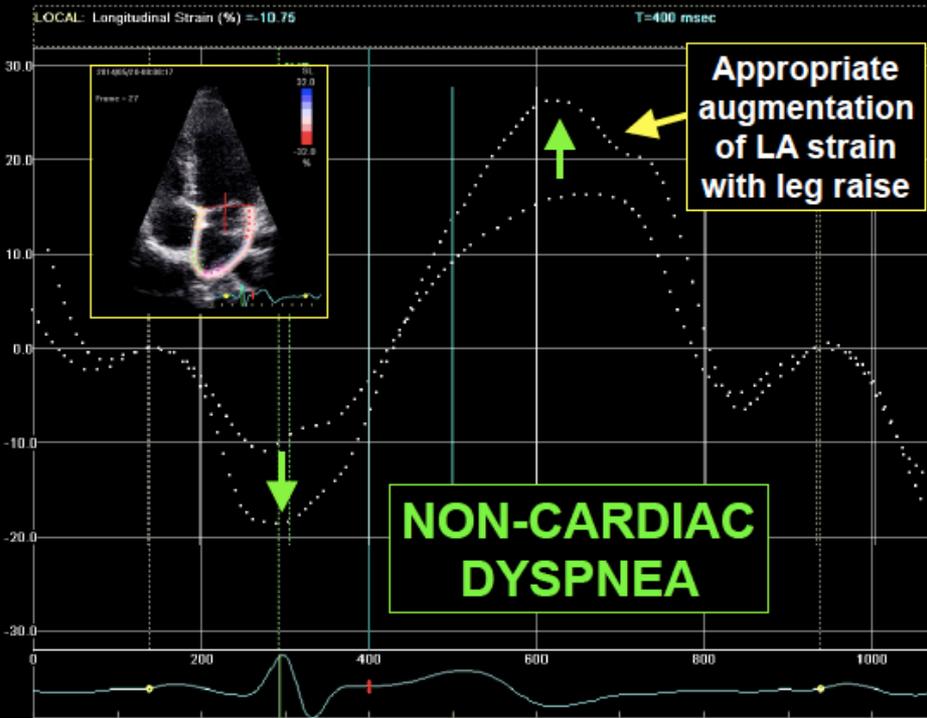
HFpEF: Global CV reserve dysfxn

HFpEF: evidence of impaired CV reserve at 20W exercise



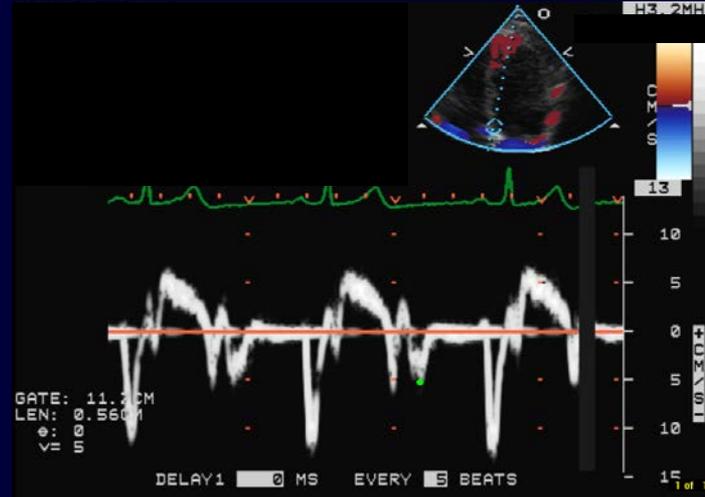
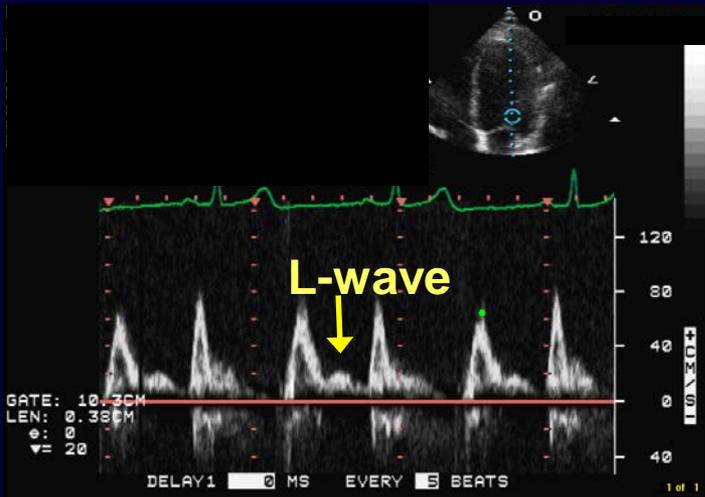
Effect of \uparrow preload on LA strain

HFpEF vs. non-cardiac dyspnea



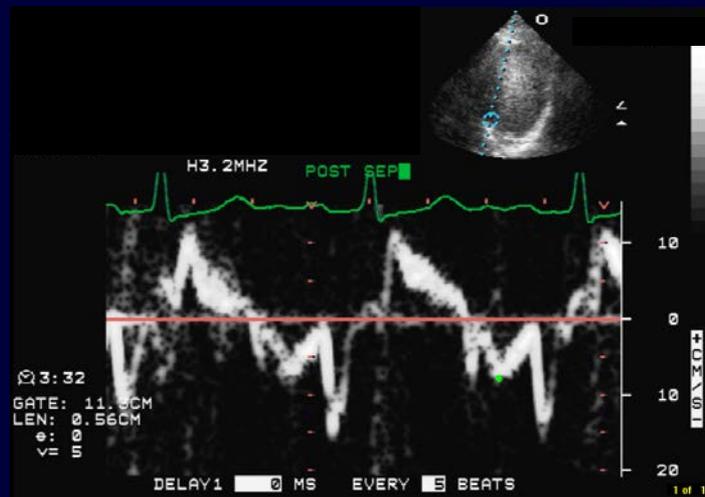
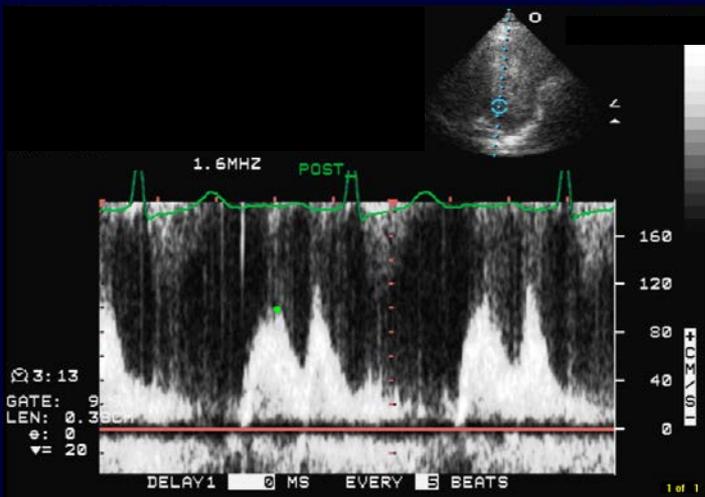
Diastolic stress echo

REST



Rest
 $E/e' = 13.5$

STRESS



Stress
 $E/e' = 16.7$

Myth #3:

**A normal BNP
rules out HFpEF
as a diagnosis**

Fact #3:

**Up to 1/3rd of patients with
confirmed HFpEF have a
normal BNP**

A typical HFpEF patient...

- 63-year-old man
- Morbid obesity, HTN, DM
- Admitted with SOB, DOE, leg swelling
- ?JVP “thick neck”, lungs clear, severe LE edema
- BNP 42 pg/ml, Cr 1.2 mg/dl
- IV diuresis, negative 3L by hospital day #3
- Echo: normal EF, ?filling pressures, ?DD grade
- Hospital day #4: HCO₃ 42, Cr 1.6 mg/dl... stop diuretics??



A typical HFpEF patient...

- Cardiology consult team:
 - » Stop diuretics, give fluids, swelling all lymphedema "he's dry"

A typical HFpEF patient...

- Cardiology consult team:
 - » Stop diuretics, give fluids, swelling all lymphedema "he's dry"
- STOP! Do a cardiac catheterization
 - » RA 18, PA 64/28, PCWP 28, LVEDP 28
 - » Lasix gtt started, diuresed 20L further

A typical HFpEF patient...

- Cardiology consult team:
 - » Stop diuretics, give fluids, swelling all lymphedema "he's dry"
- STOP! Do a cardiac catheterization
 - » RA 18, PA 64/28, PCWP 28, LVEDP 28
 - » Lasix gtt started, diuresed 20L further
- Normal BNP does not rule out HFpEF
- ~30% of HFpEF with \uparrow PCWP: normal BNP

Myth #4:

HFpEF is a single disease

Fact #4:

**HFpEF is a heterogeneous
*syndrome***

The many faces of HFpEF

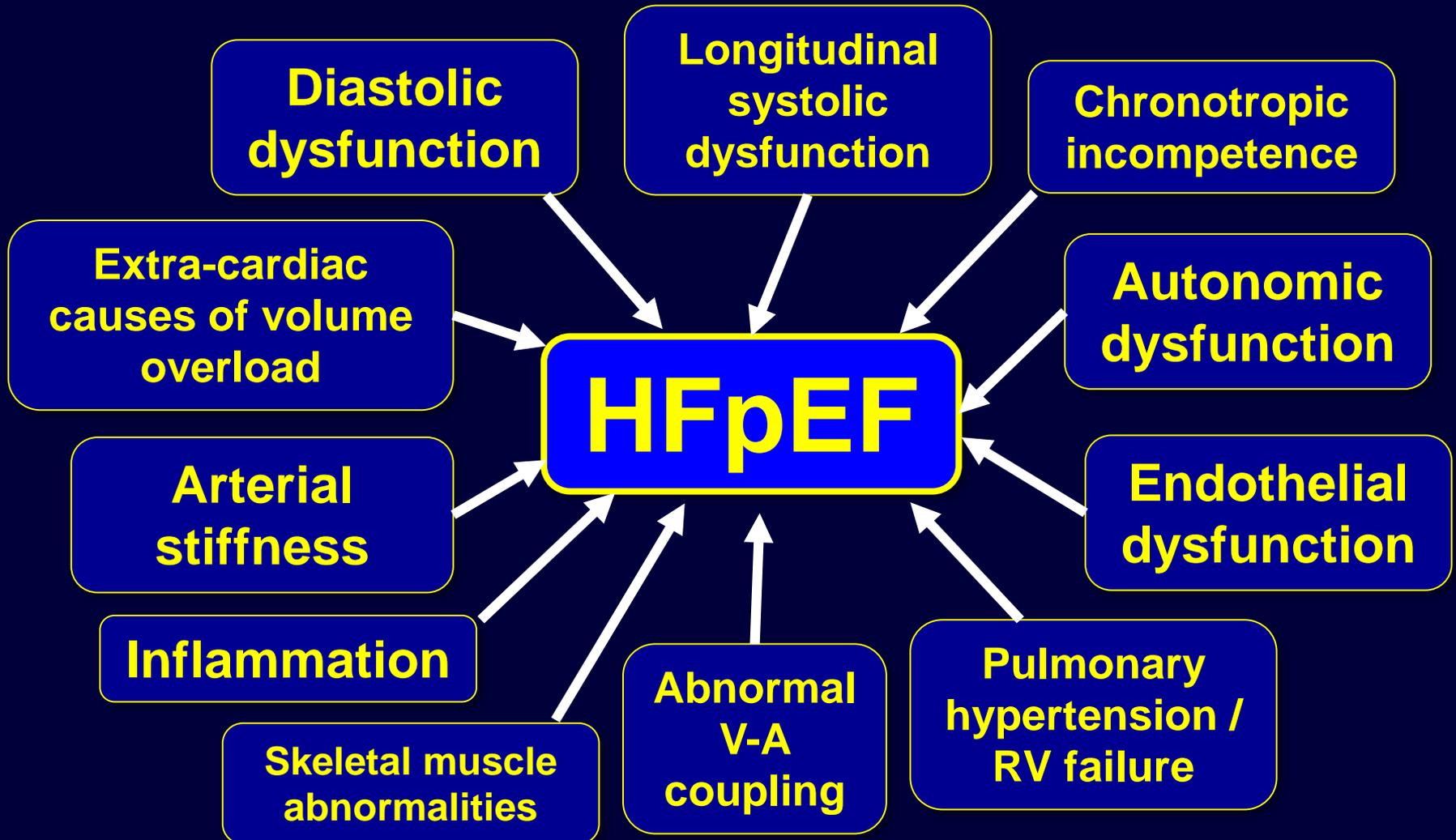


The many faces of HFpEF



**HFpEF: not 1
single "disease,"**

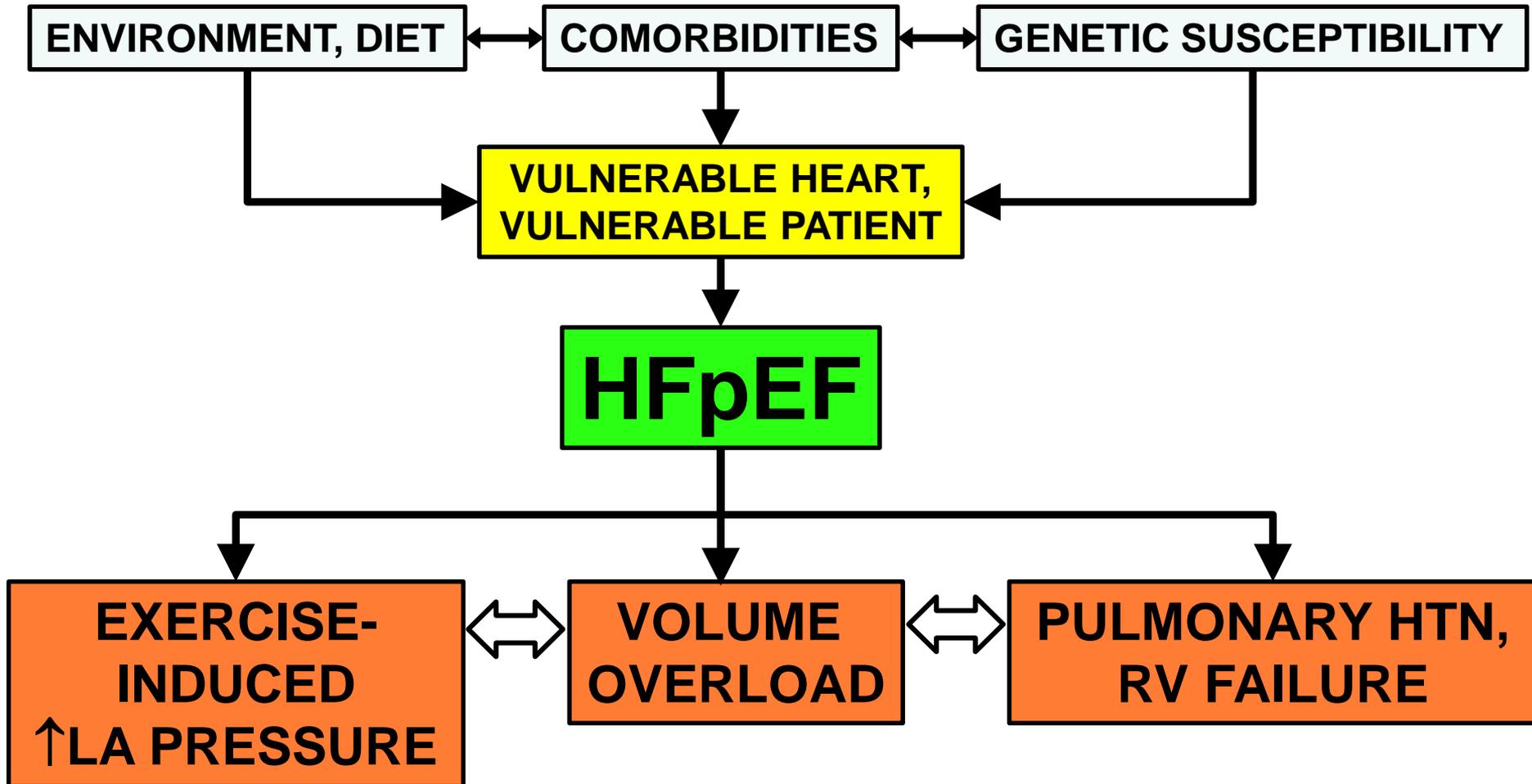
Pathophysiologic contributors to HFpEF



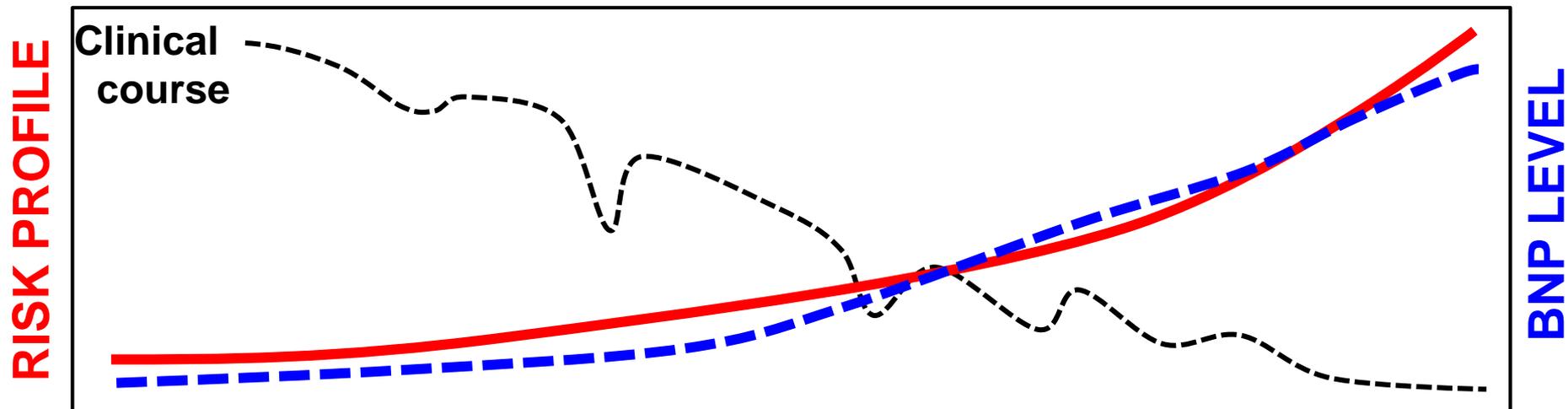
Clinical categories of HFpEF

1. “Garden-variety” HFpEF (HTN, DM, obesity, CKD)
2. CAD-HFpEF
3. Right heart failure-HFpEF
4. A-fib predominant HFpEF
5. HCM-like HFpEF
6. High-output HFpEF
7. Valvular HFpEF (multiple 2+ lesions)
8. Rare causes of HFpEF (“zebras”)

3 types of HFpEF presentation



Risk profile, BNP vary by type of HFpEF presentation



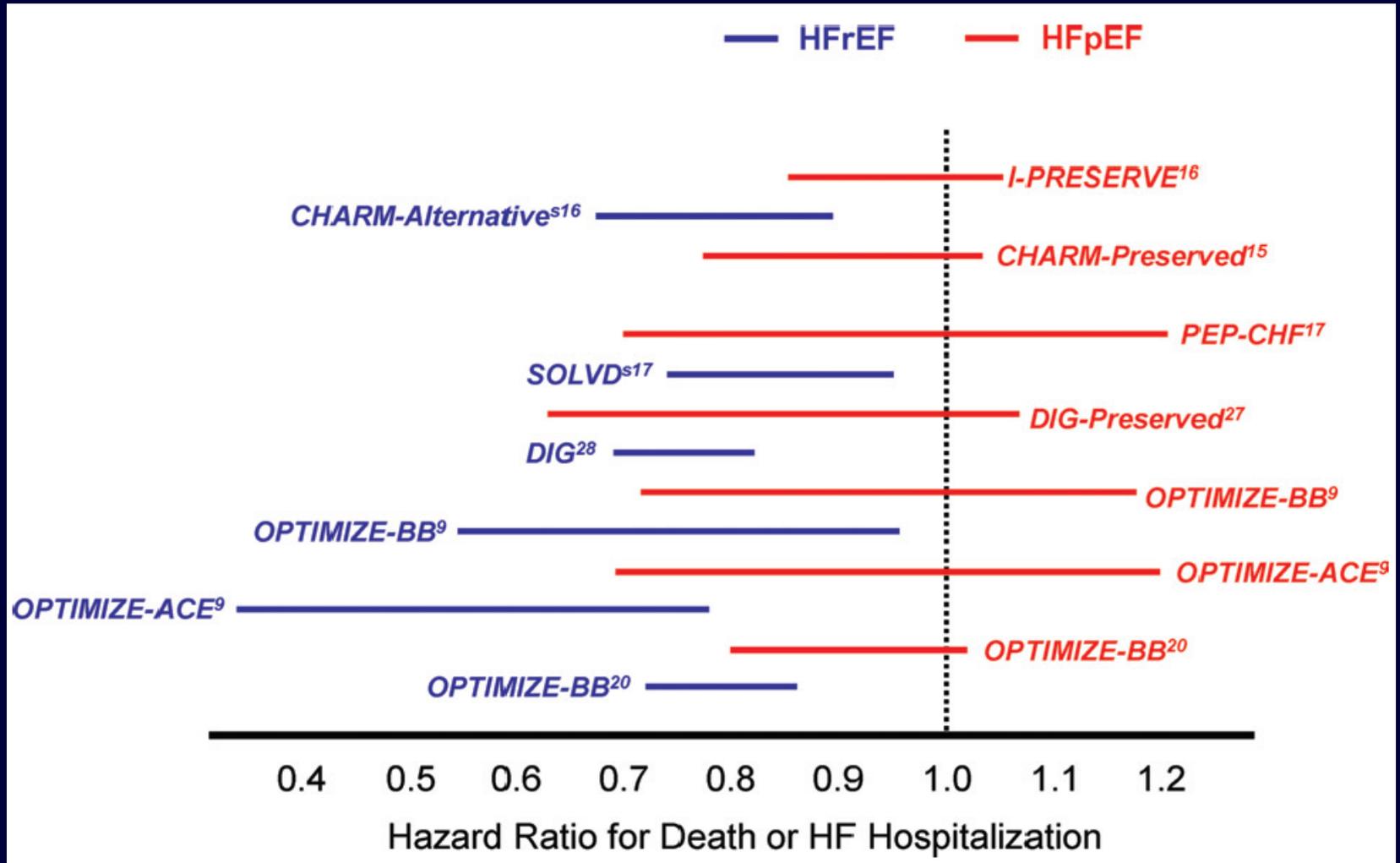
Myth #5:

**There are no proven
treatments for HFpEF**

State-of-the-art in 2016:
Treatment of HFpEF



HFpEF: “no treatments”



Myth #5:

There are no proven treatments for HFpEF

Fact #5:

HFpEF is treatable, but we need to change the treatment paradigm

Why have treatments failed?

- Multiple potential risk factors
- “Difficult diagnosis”
- Poor recognition of presence/prognosis
- Heterogeneity of HFpEF syndrome
 - » Several pathophysiologic mechanisms
- Care by multiple different providers
- Comorbidity burden is high
 - » Cause of death often not related to progressive heart failure



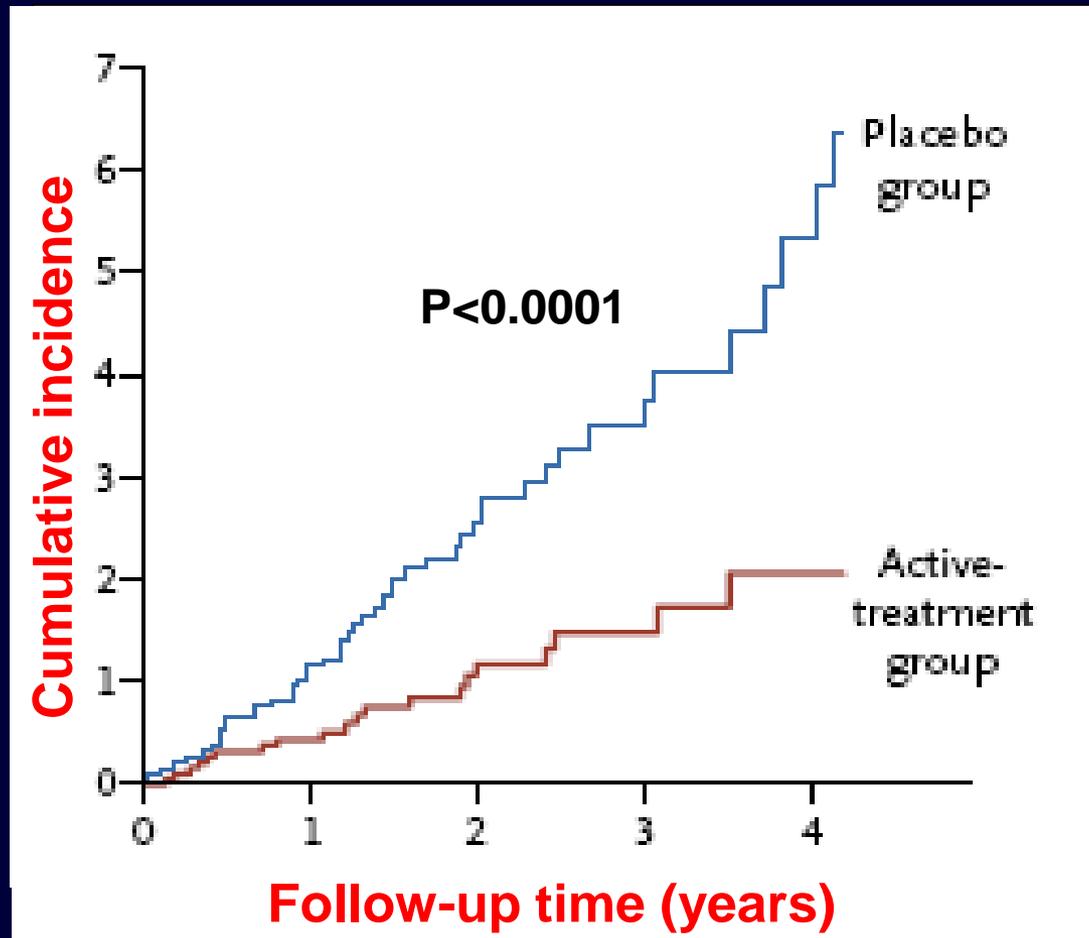
Rx Step #1:

Prevent HFpEF

before it even occurs

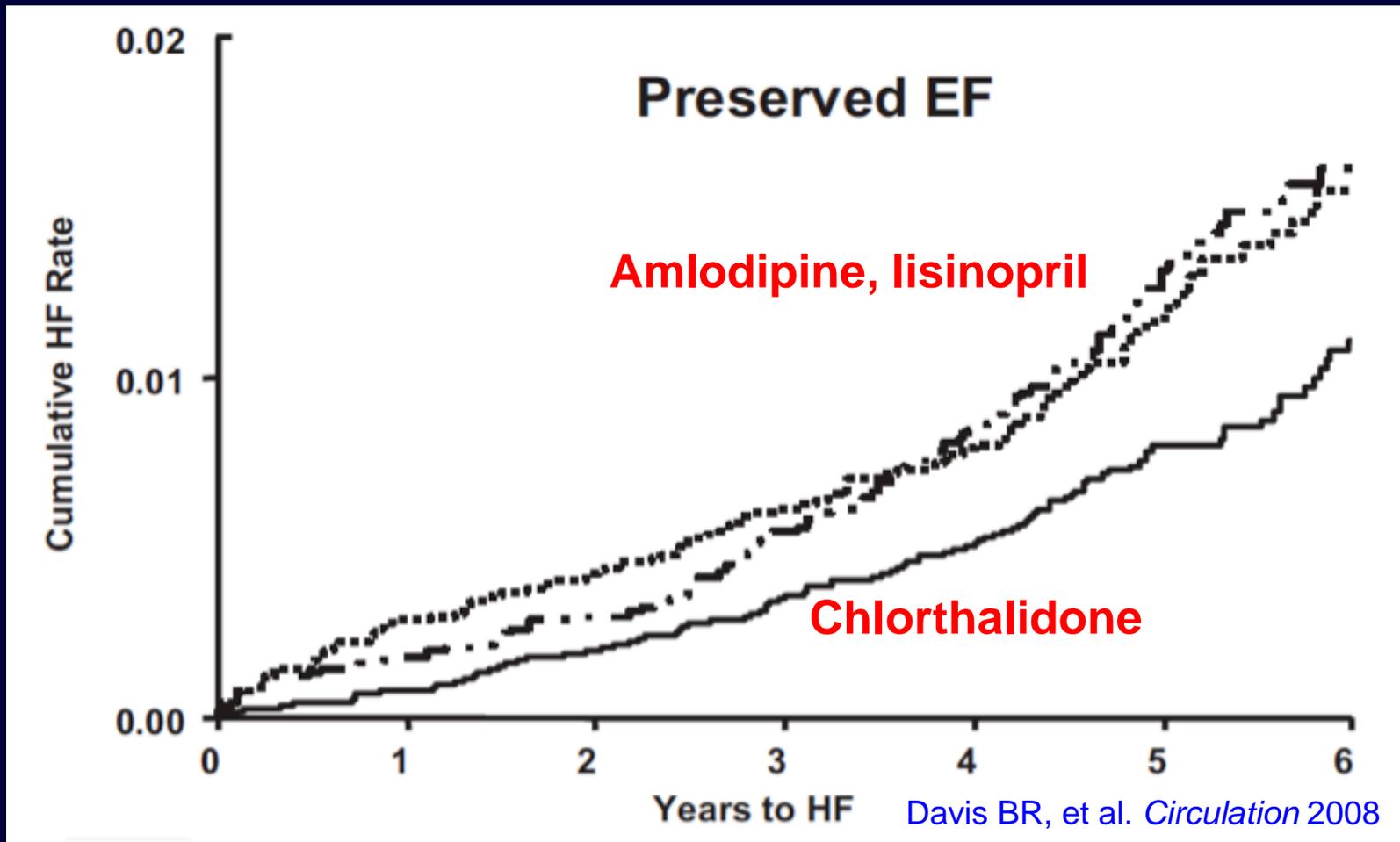
HFpEF can be prevented...

HYVET trial
indapamide
resulted in
64% reduction
in HF hosp.
compared to
placebo



HFpEF can be prevented...

ALLHAT-HFpEF: chlorthalidone best for HFpEF prevention





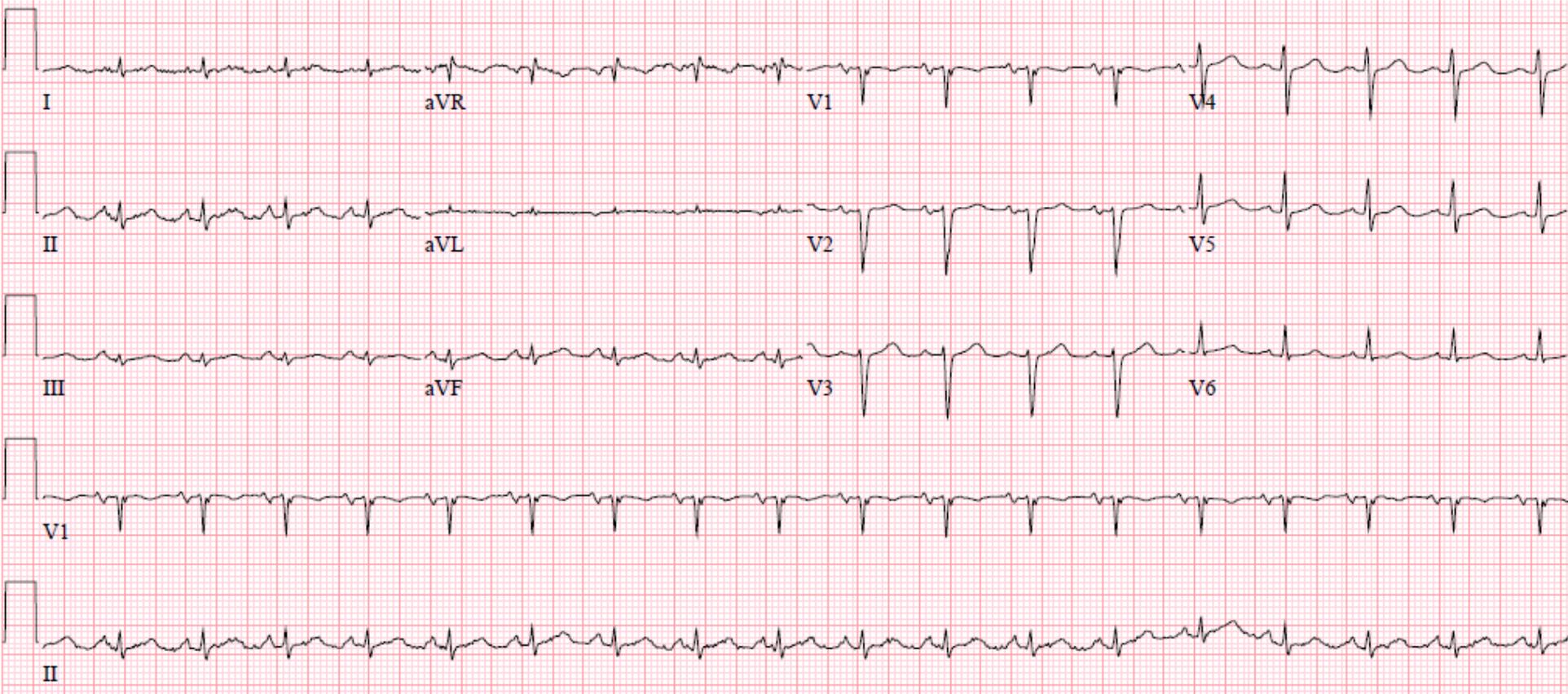
Rx Step #2:

**Before treating,
remember the zebras**

HFpEF: Know your zebras

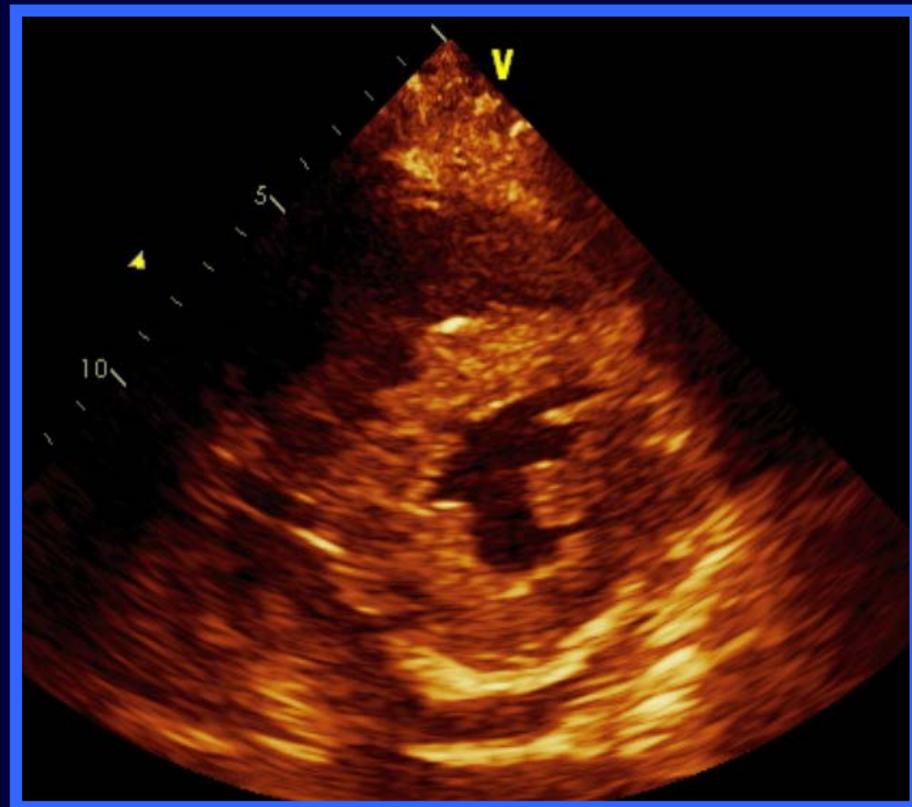
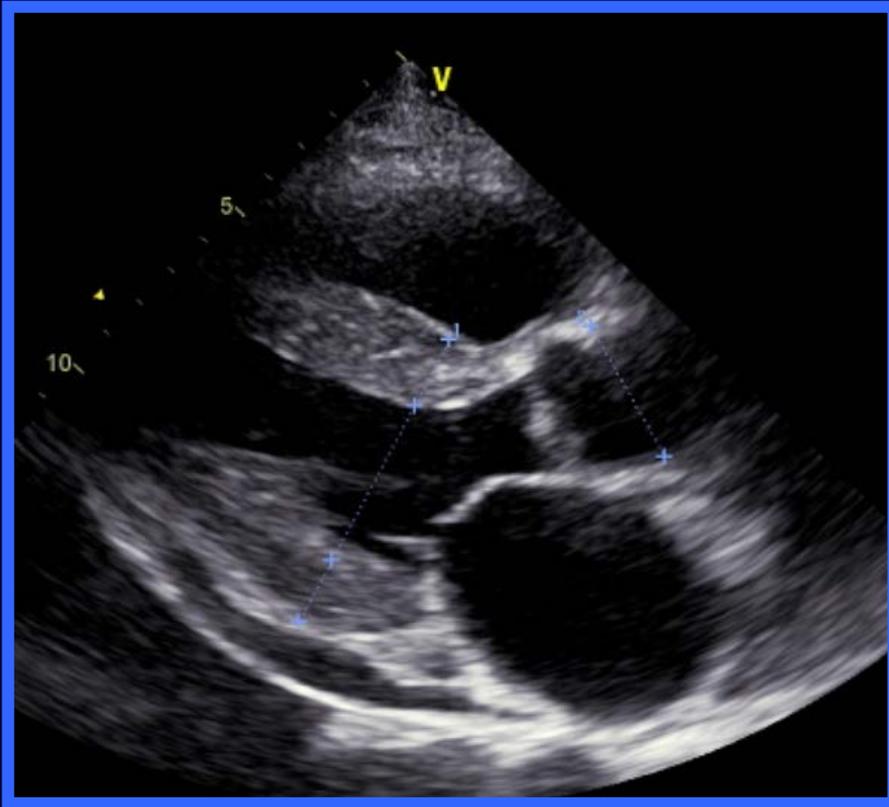
- Assessment of HFpEF: a diagnostic mystery until proven otherwise
- Careful history, physical examination
- Clues to zebras:
 - » Kussmaul's sign: \uparrow JVP with inspiration
 - » \downarrow Voltage ECG with \uparrow LV wall thickness
 - » Careful evaluation of echo is essential

50-year-old woman with SOB



Low voltage, pseudoinfarct pattern

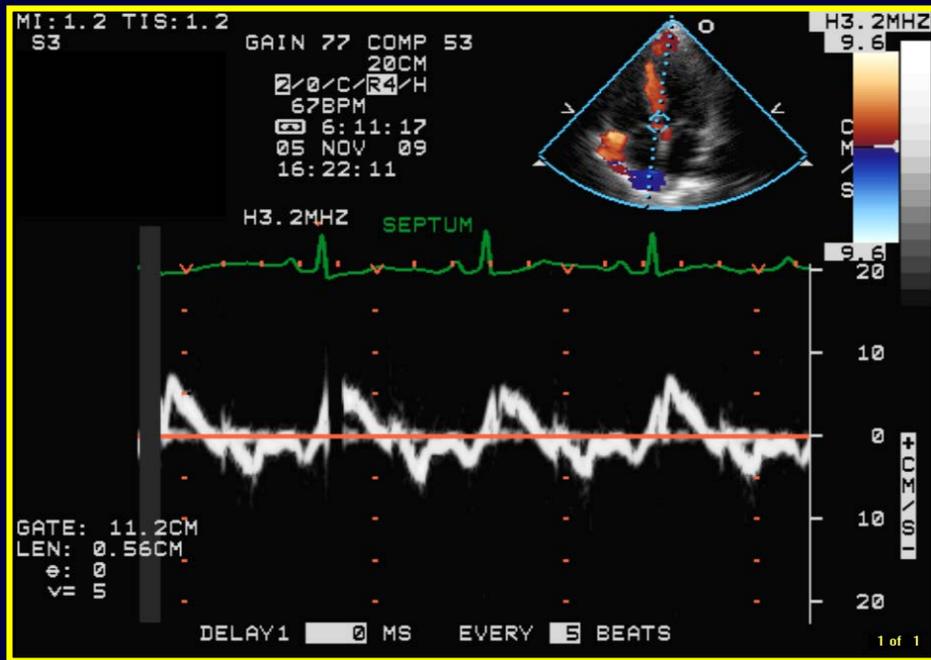
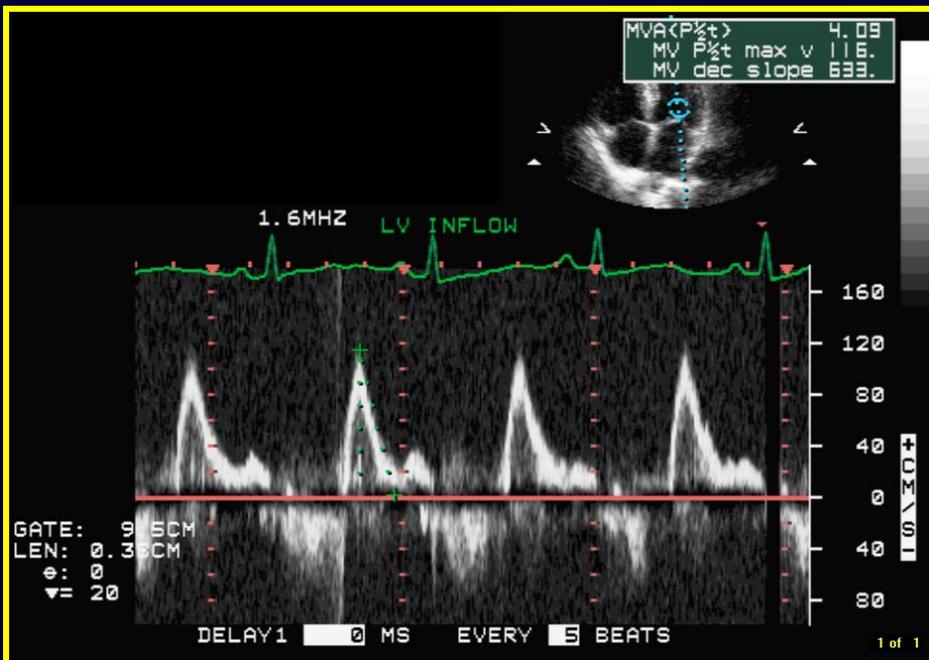
50-year-old woman with SOB



Thick LV, “texture” of myocardium consistent with infiltrative cardiomyopathy

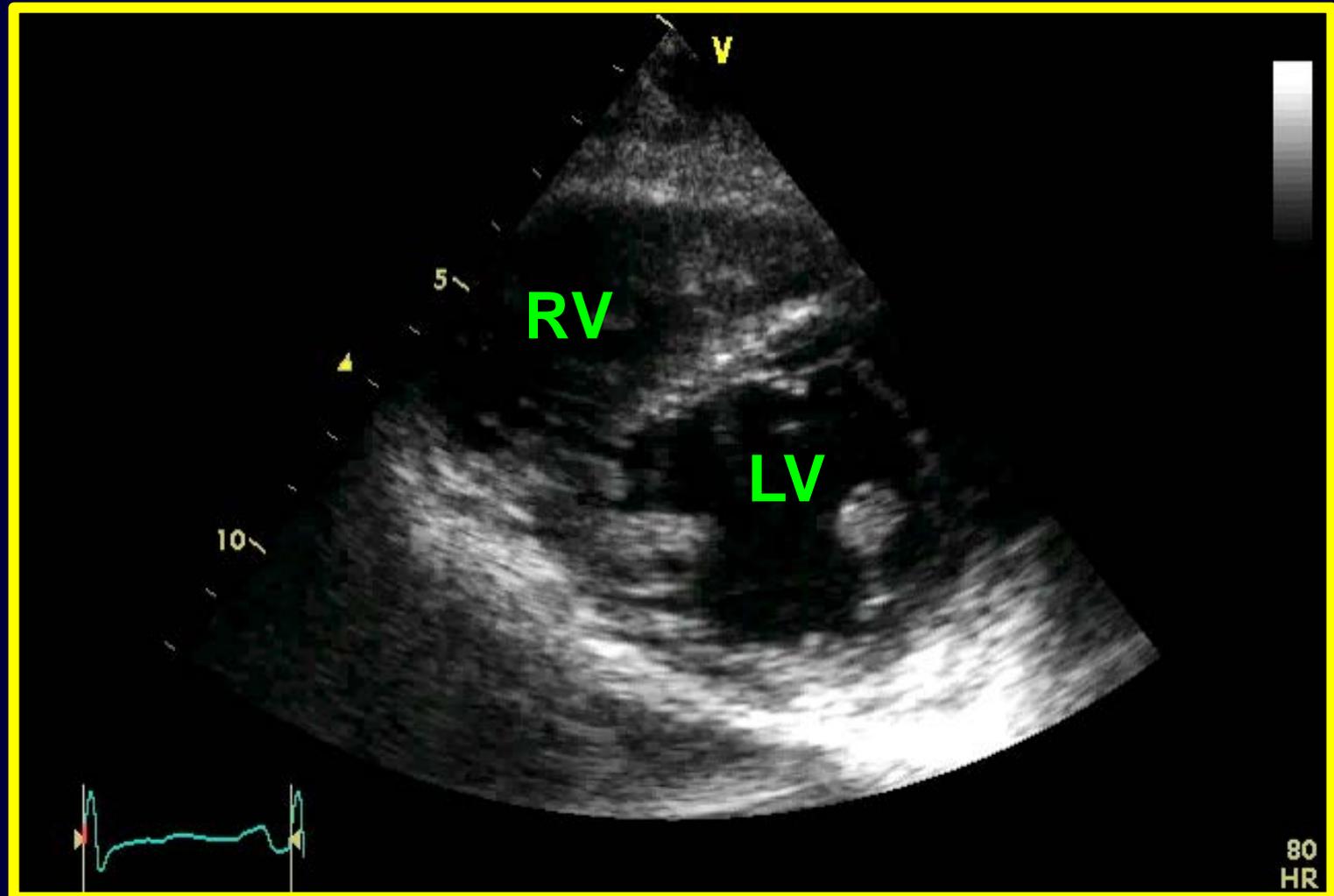
50-year-old woman with SOB

High E velocity, elevated E/A ratio, reduced E', ↓E deceleration time

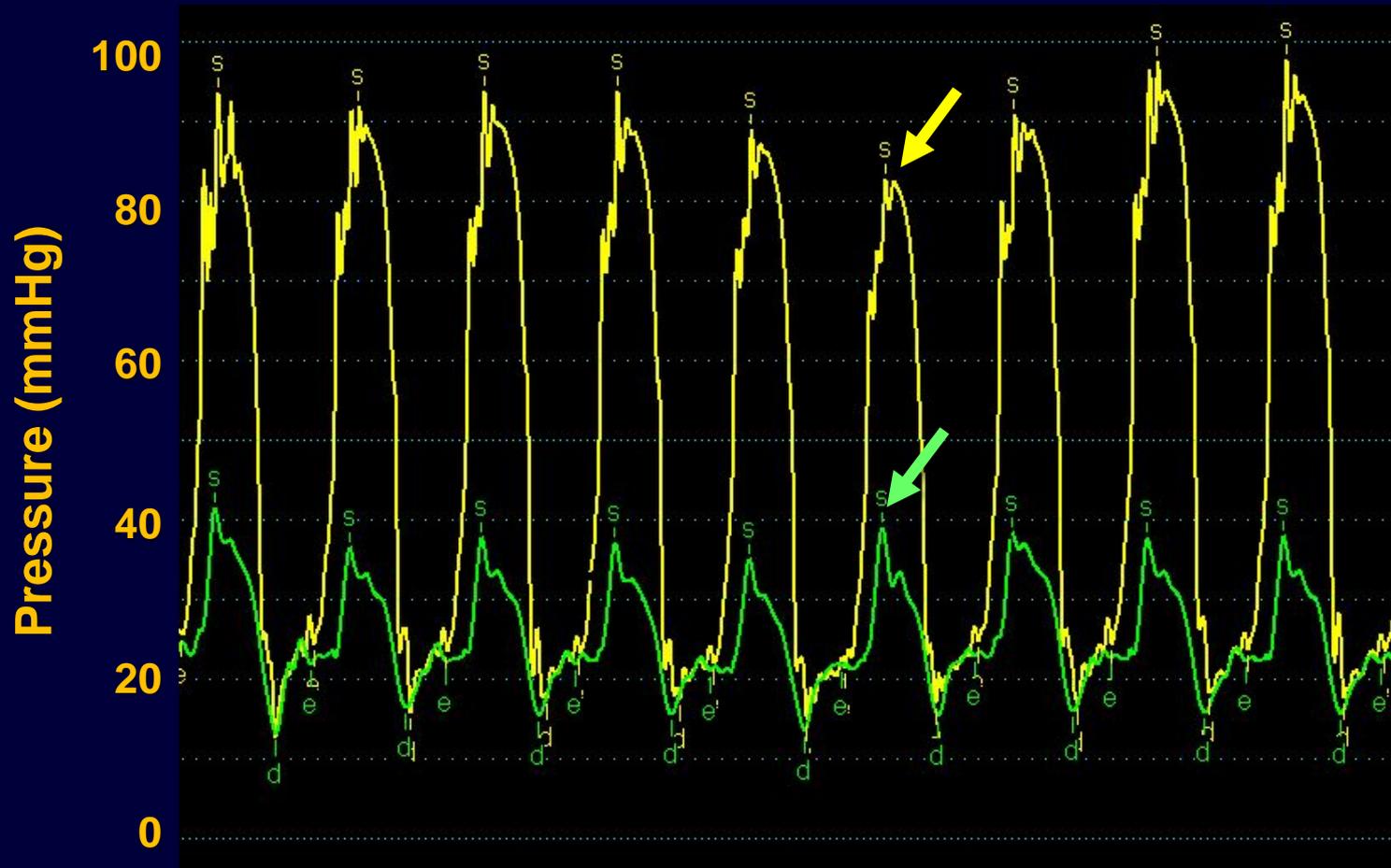


Grade III (severe) LV diastolic dysfunction due to cardiac amyloidosis

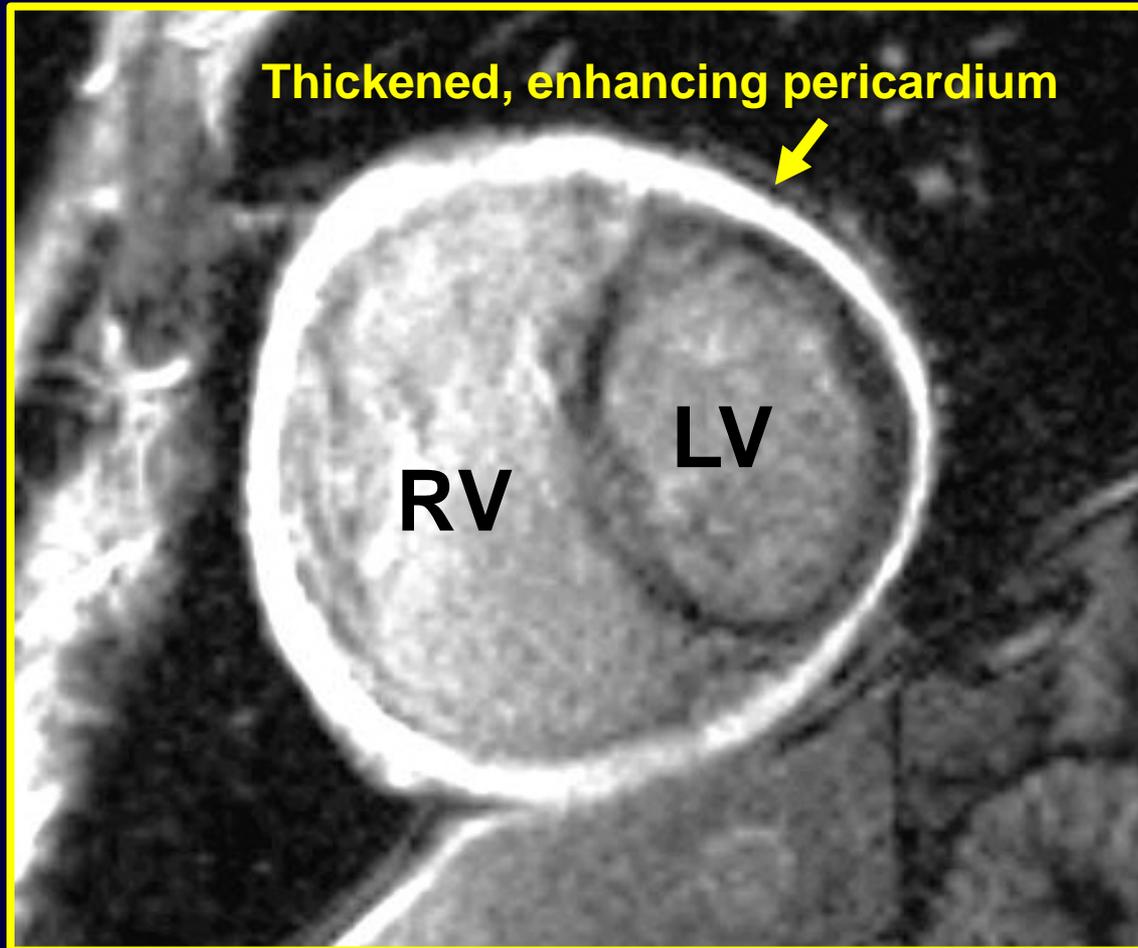
44-year-old man with chronic ascites



44-year-old man with chronic ascites

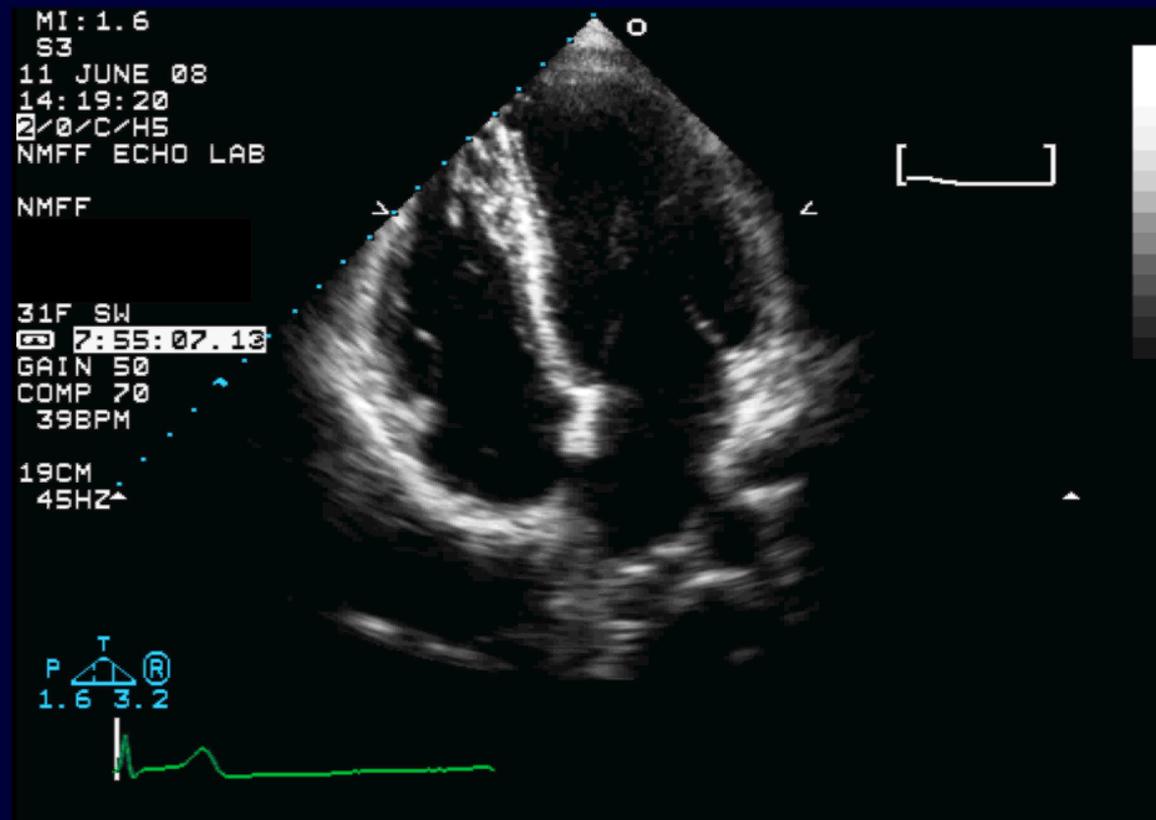


44-year-old man with chronic ascites



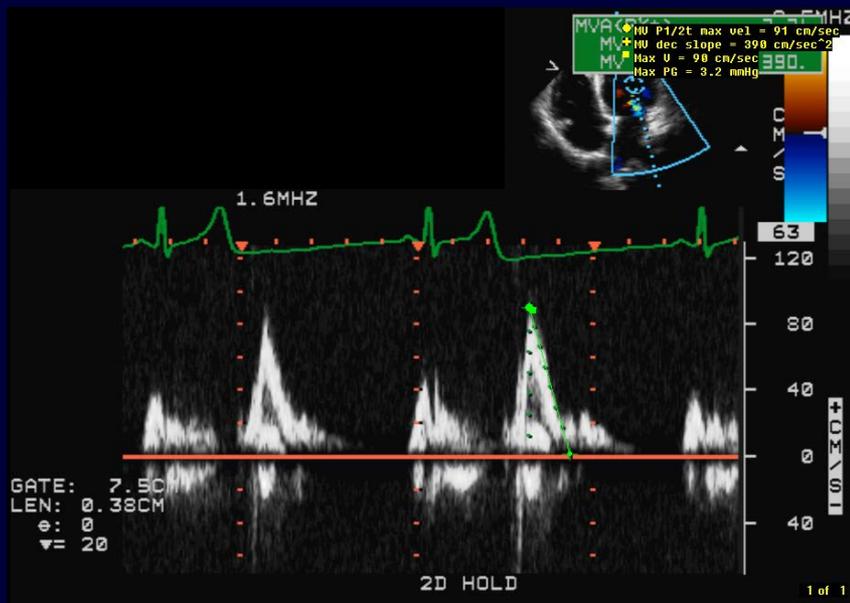
HFpEF pearls: Etiology of HF?

31-year-old woman presents with dyspnea, lower extremity edema, BNP 166 pg/ml (while preparing for marathon)

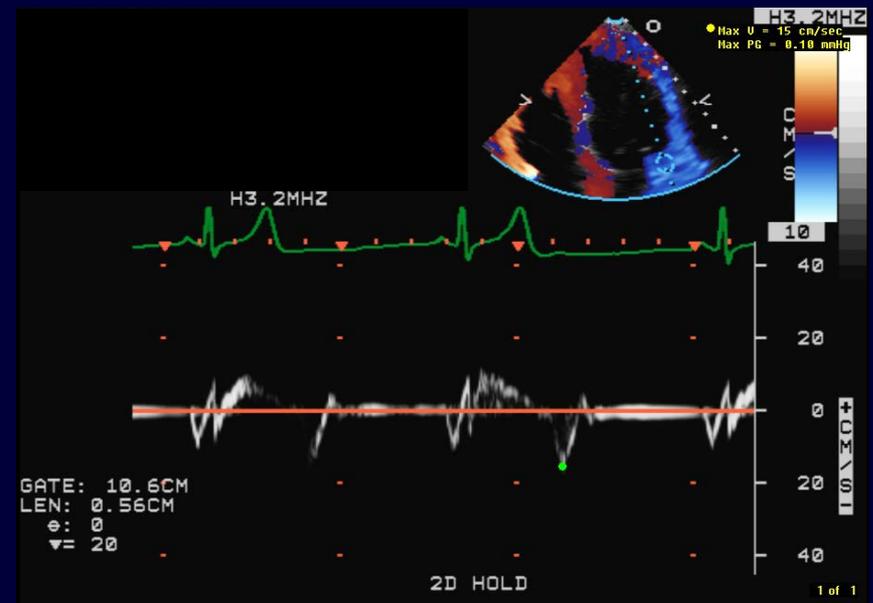


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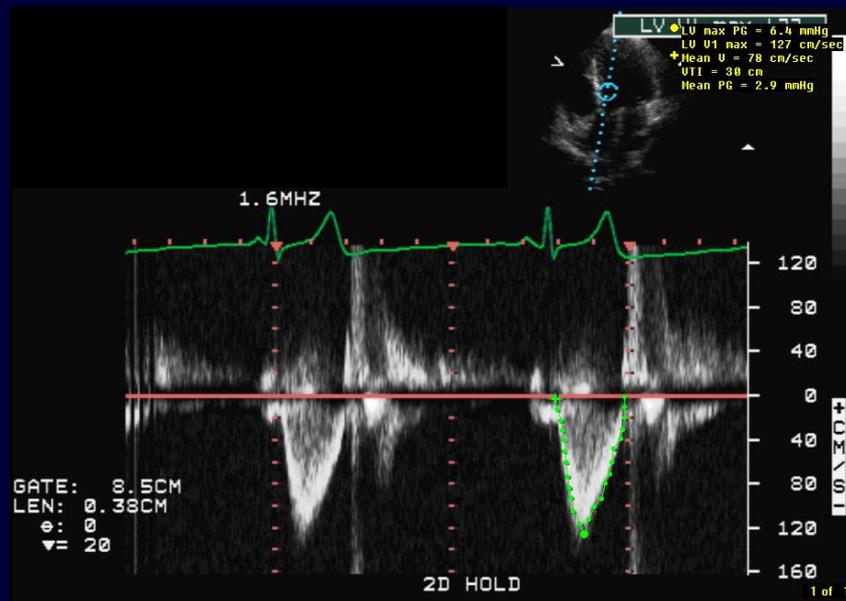
Normal LV diastolic function



$e' = 15$ cm/s; $E/e' = 6$

HFpEF pearls: Etiology of HF?

31-year-old woman presents with dyspnea, lower extremity edema, BNP 166 pg/ml (while preparing for marathon)

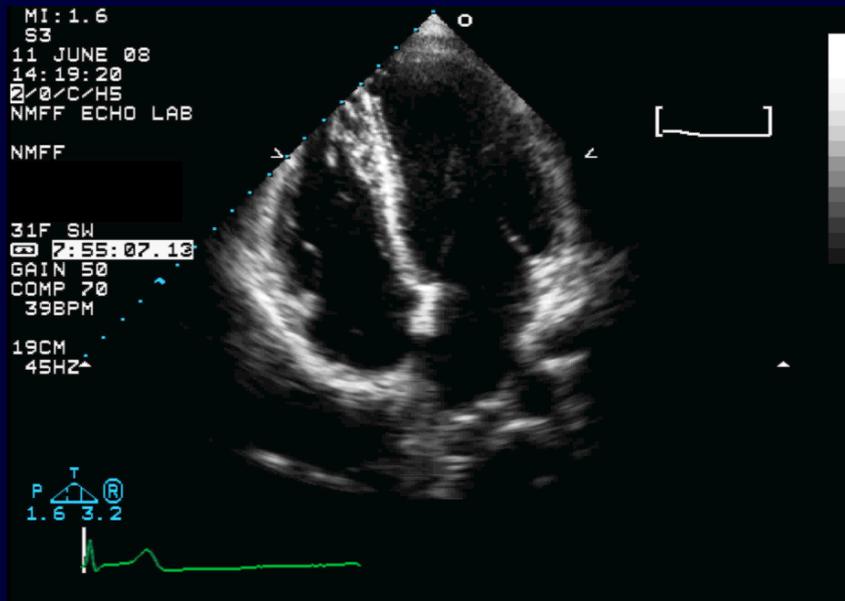


$VTI_{LVOT} = 30 \text{ cm}$

Stroke volume = 100 ml / beat

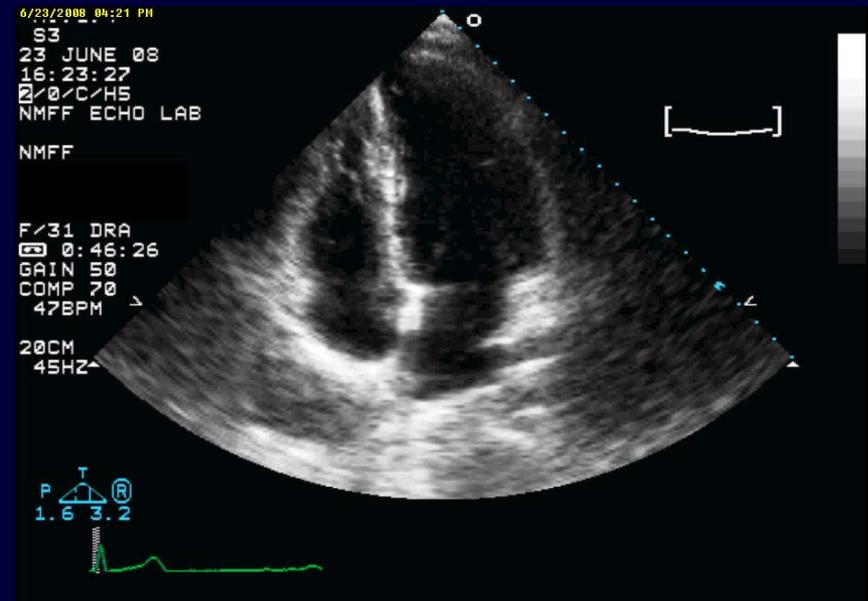
HFpEF pearls: High-output HF

31-year-old woman presents with dyspnea and lower extremity edema
(while preparing for marathon)



BASELINE

LV EDVI = 85 ml/m²
LA volume index = 50 ml/m²

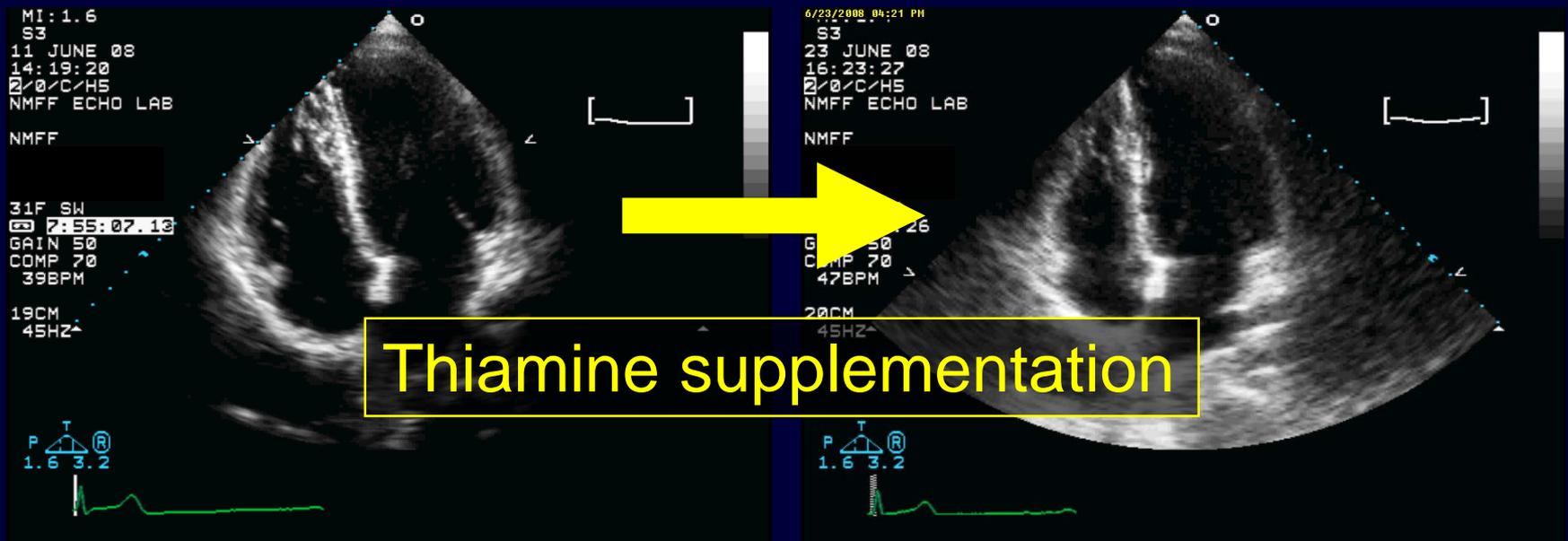


12 DAYS LATER

LV EDVI = 75 ml/m²
LA volume index = 37 ml/m²

HFpEF pearls: High-output HF

31-year-old woman presents with dyspnea and lower extremity edema
(while preparing for marathon)



BASELINE

LV EDVI = 85 ml/m²
LA volume index = 50 ml/m²

12 DAYS LATER

LV EDVI = 75 ml/m²
LA volume index = 37 ml/m²

HFpEF: Know your zebras

- Restrictive cardiomyopathy:
 - » Sparkling myocardium
 - » Severely decreased tissue Doppler s' or e'
 - » Preserved radial function, reduced longitudinal function
- Constrictive pericarditis:
 - » Diastolic septal bounce
 - » Preserved e' velocity
 - » Respiratory variation in mitral inflow

HFpEF: Know your zebras

Parameter	Constriction	Restriction
↑↑E velocity, ↑E/A Short E decel time	Present	Present
Mitral inflow respiratory variation	Present	Absent
Tissue Doppler e' velocity	Normal or increased	Severely reduced
Hepatic vein imaging	Flow reversal during <i>expiration</i>	Flow reversal during <i>inspiration</i>
Simultaneous LV/RV tracings	Discordant	Concordant

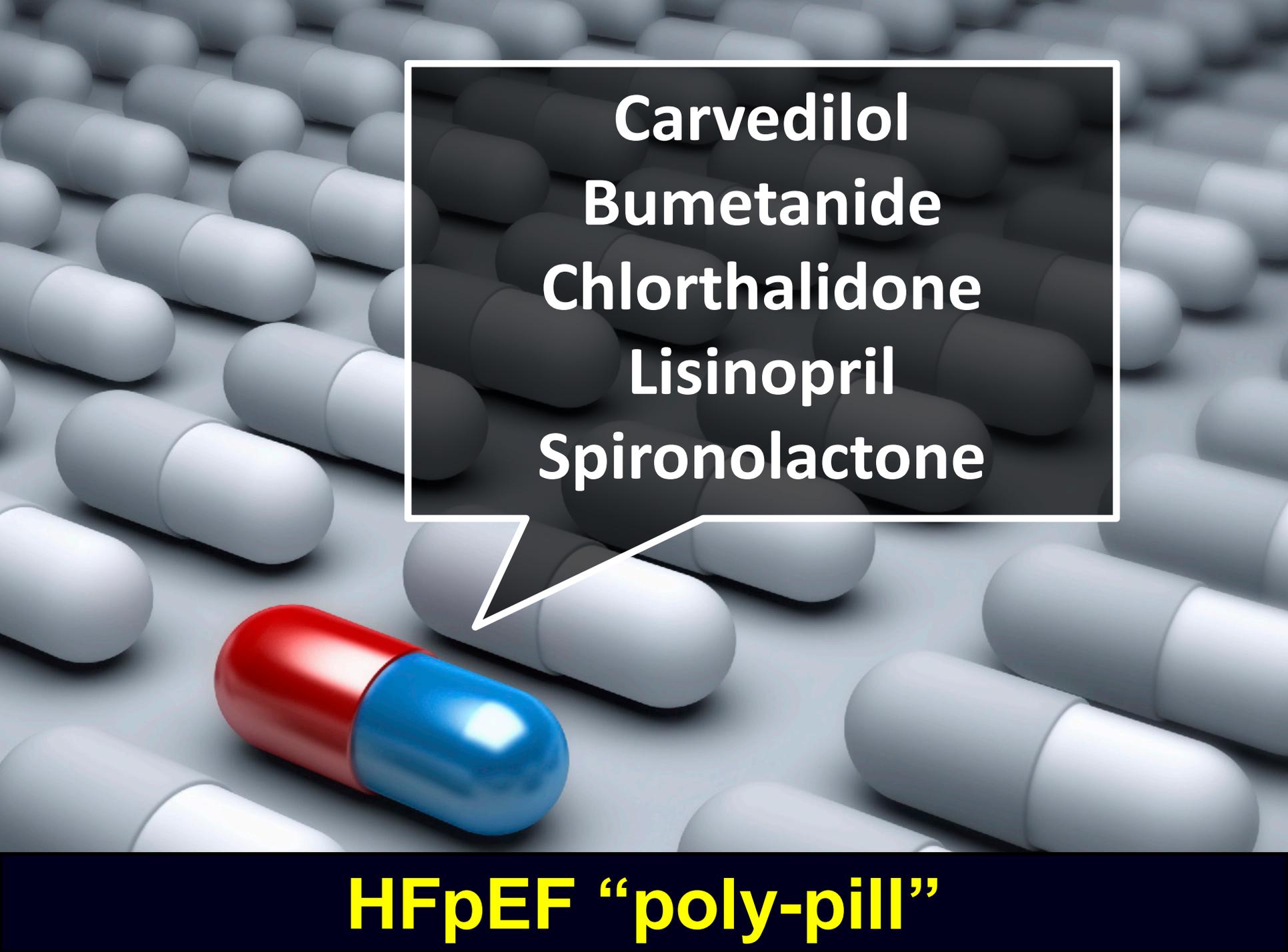


Rx Step #3:

**Treat comorbidities,
BP, fluid overload**

HFpEF treatment algorithm

- Diagnose HFpEF accurately
 - » Remember that HFpEF is extremely common
 - » Make sure you're not dealing with a "zebra"
 - » Low threshold for cardiac cath, CAD eval
- Treat the underlying cause of HFPEF
- Treat BP, fluid overload
- Treat comorbidities aggressively
- CHF education, chronic dz. management



Carvedilol
Bumetanide
Chlorthalidone
Lisinopril
Spironolactone

HFpEF “poly-pill”



Step #4:

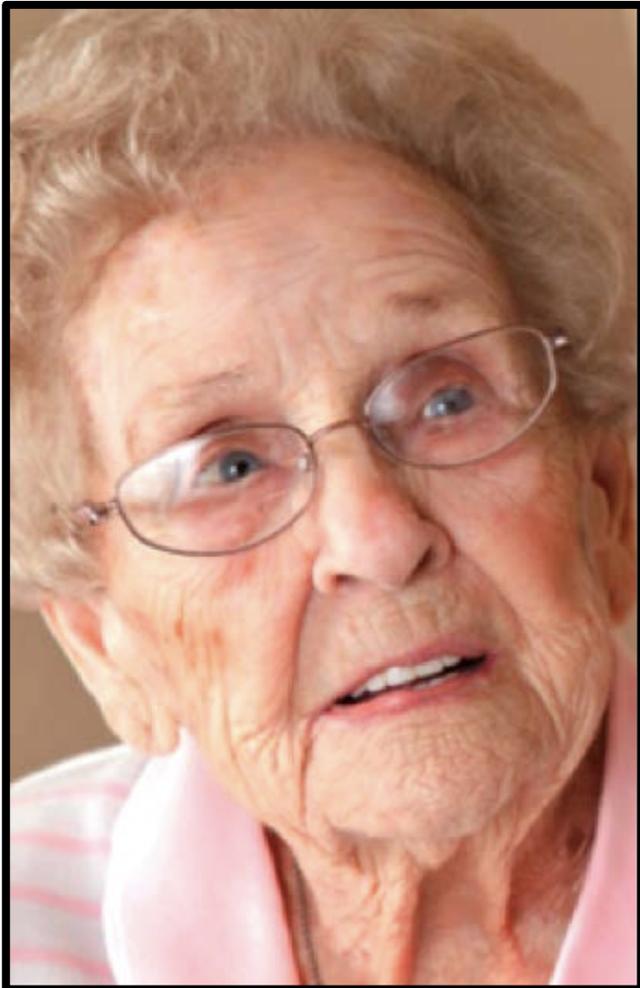
**Tailor treatment to
the type of HFpEF**



Step #4:

**Tailor treatment to
the type of HFpEF**

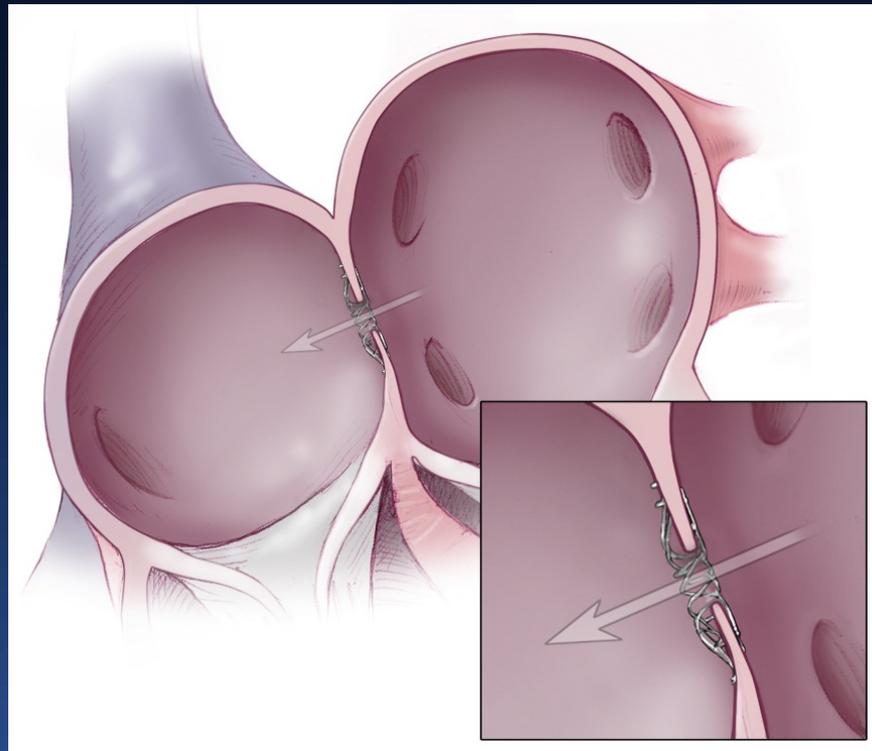
EXERCISE-INDUCED ↑ LA PRESSURE



- Exercise training
- Structure diet/weight loss
- ~~Nitrates/nitrites?~~
- Ivabradine?
- Late Na⁺ current inhibitors (e.g., ranolazine)?

Interatrial shunt device for HFpEF

Creation of L-to-R shunt = $\downarrow\downarrow$ LAp at rest/exercise = $\downarrow\downarrow$ symptoms in HFpEF



Kaye D, Shah SJ... Burkhoff D, et al. J Card Fail 2014

InterAtrial Shunt Device: Concept

Transcatheter implant to create a small permanent interatrial shunt (Qp:Qs ratio 1.2-1.3)

Implant
19mm OD
8 mm ASD

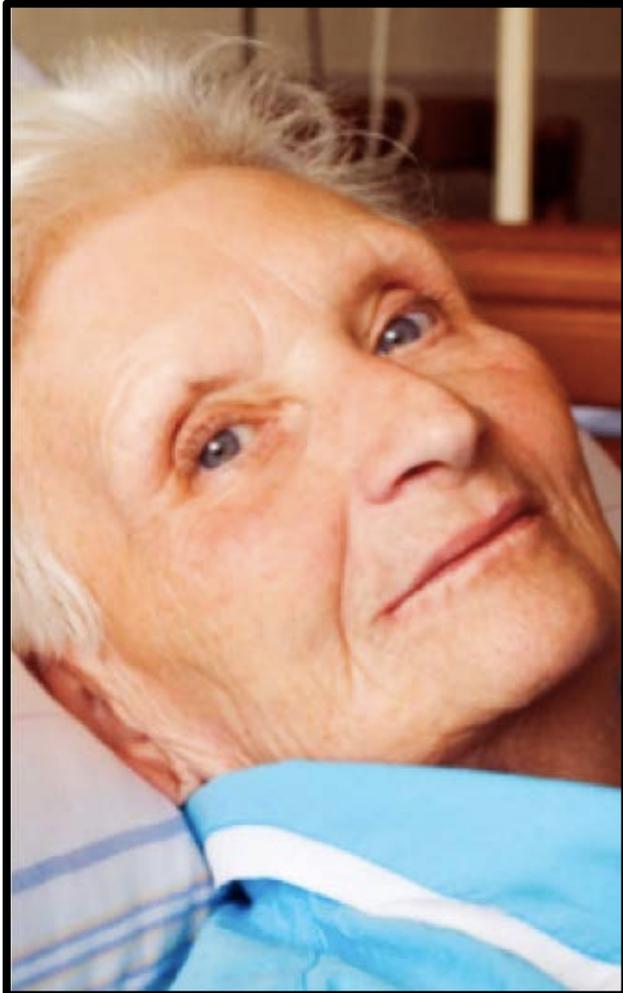


**Animal
explant**



Courtesy of Finn Gustafsson, MD, PhD, DMSci

VOLUME OVERLOAD



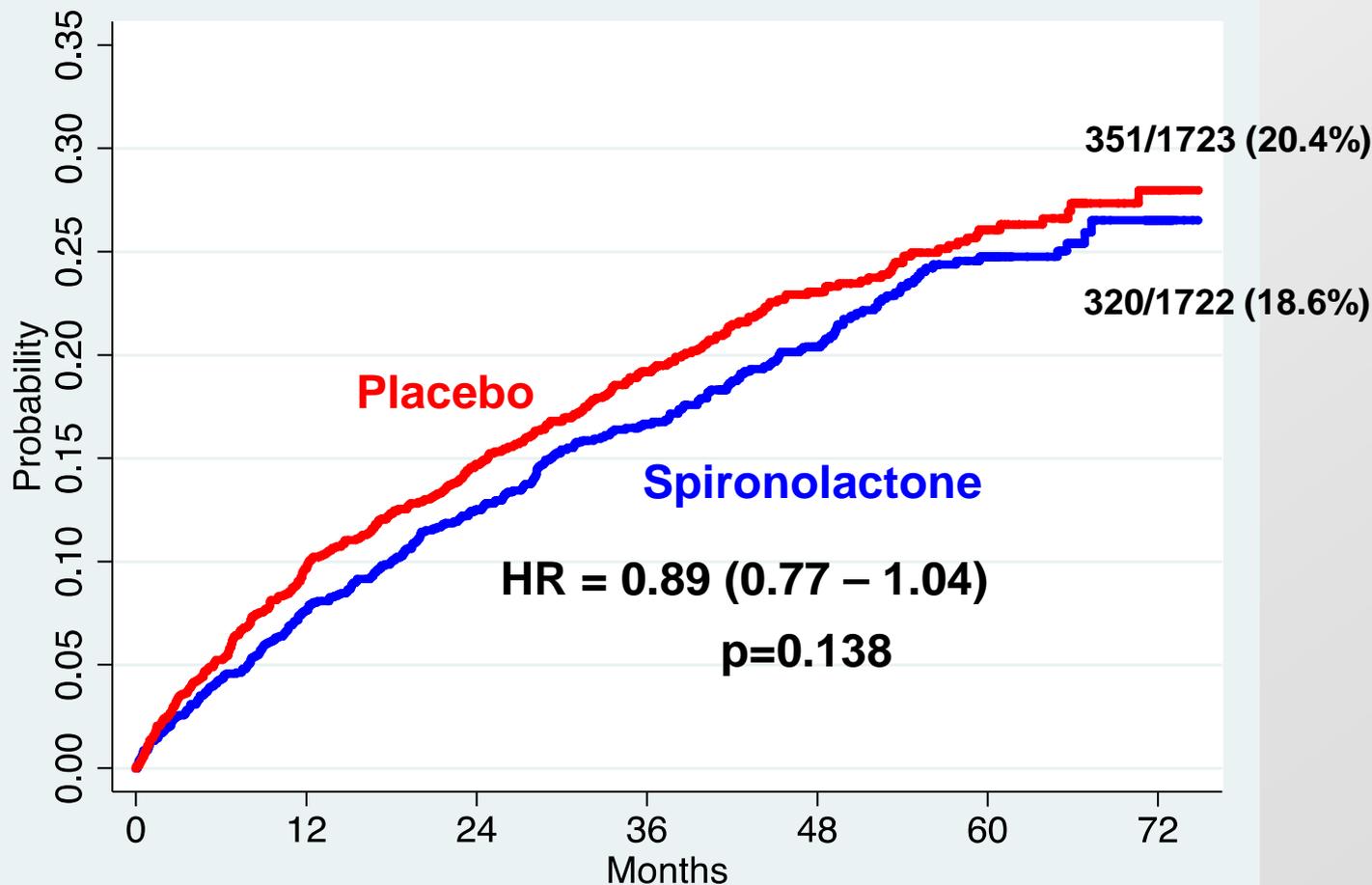
- **Elevated Cr during diuresis? Consider hemoconcentration**
- **Spironolactone**
- **Hemodynamic monitoring for tailored diuretic therapy**
- **Neprilysin inhibition? (PARAGON-HF trial)**
- **sGC stimulator therapy? (SOCRATES trial)**
- **Serelaxin for acute HF? (RELAX-AHF2 trial)**

Spironolactone

- Great for volume overload, RV failure
- ALDO-DHF and RAAM-PEF:
 - » Mineralocorticoid receptor antagonists probably don't work in exercise-induced DD
- TOPCAT (N=3445):
 - » Spironolactone vs. placebo for HFpEF
 - » More volume overloaded than ALDO-DHF
 - » ↓ hospitalization but missed 1° endpoint
 - » *In Americas, spironolactone = better outcomes*

1° Outcome

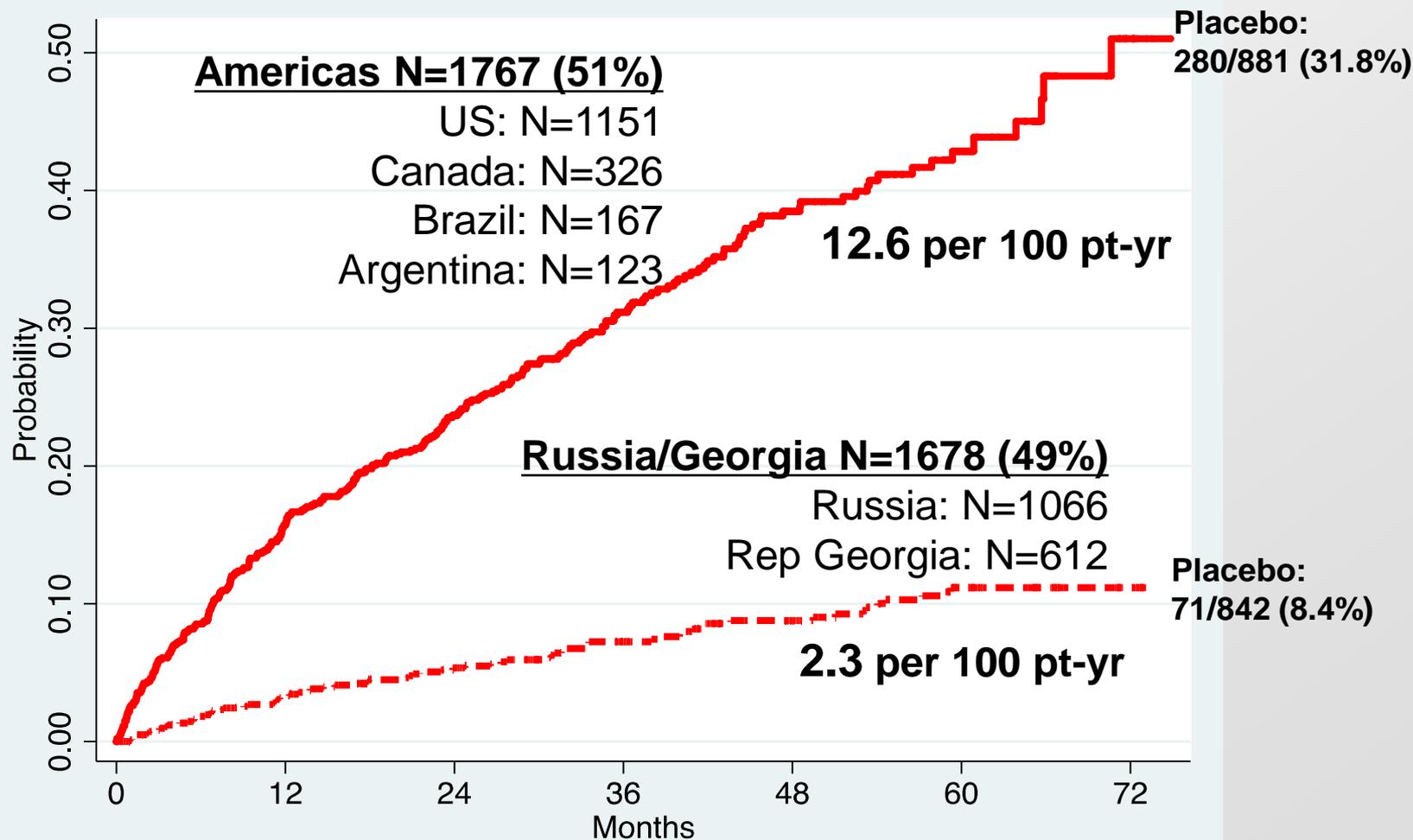
(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)



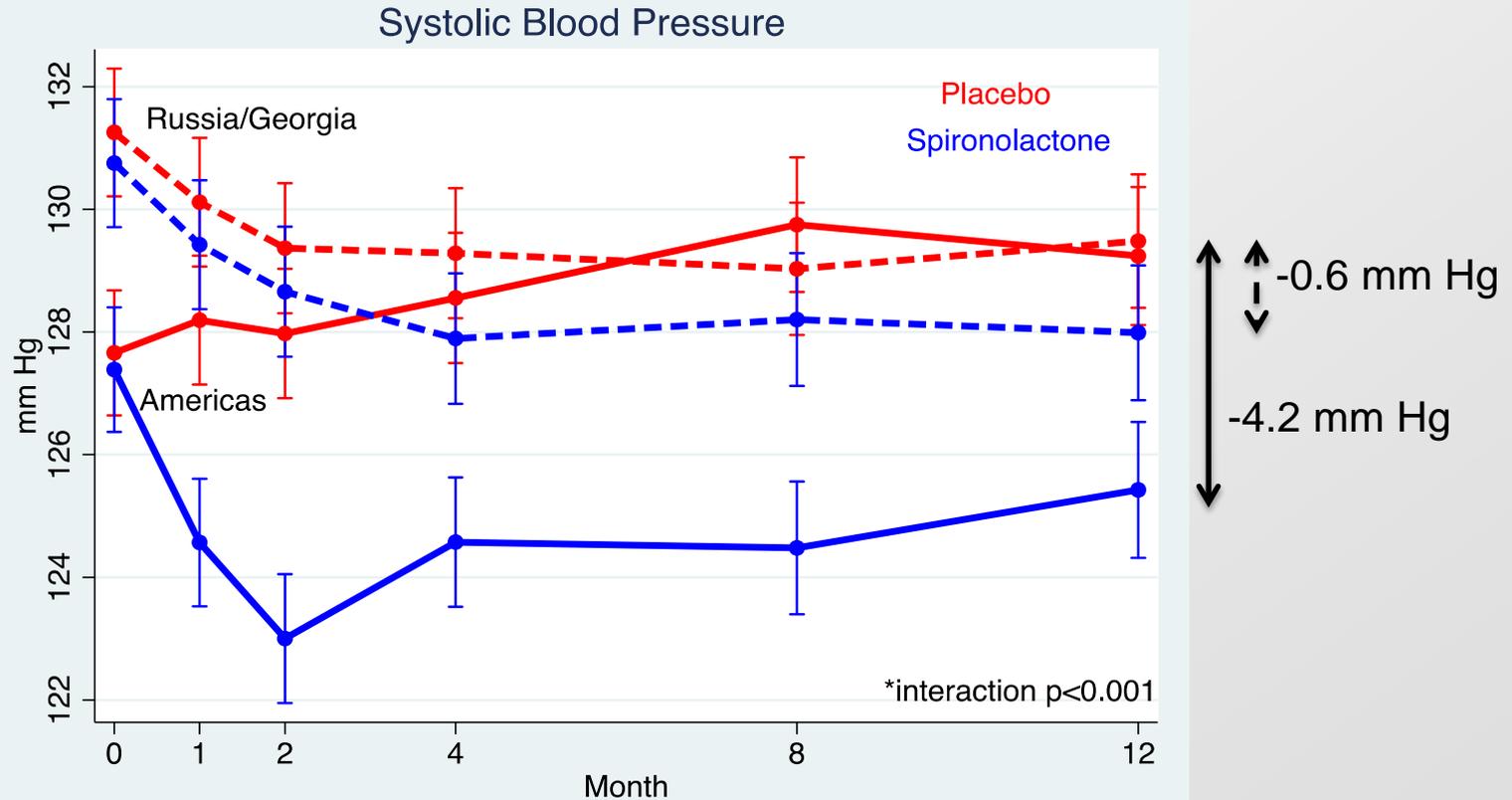
Number at risk

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

Placebo Rates: Primary Outcome, by region



Systolic Blood Pressure Change by Region



Americas
N = 1767

Russia/Georgia
N = 1678

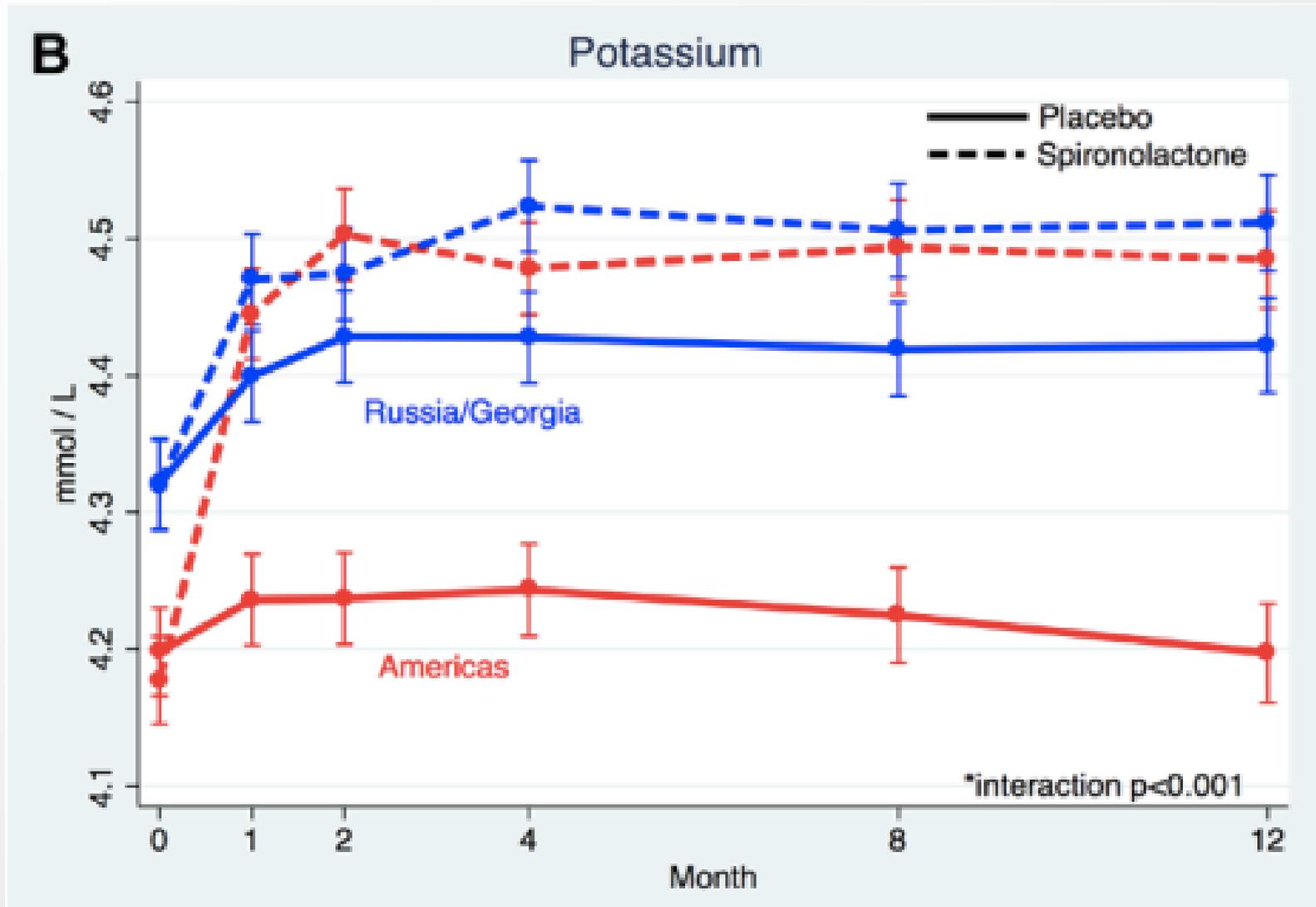
Average SBP Change (Spiro-Placebo)

-4.2 mmHg (p<0.001)

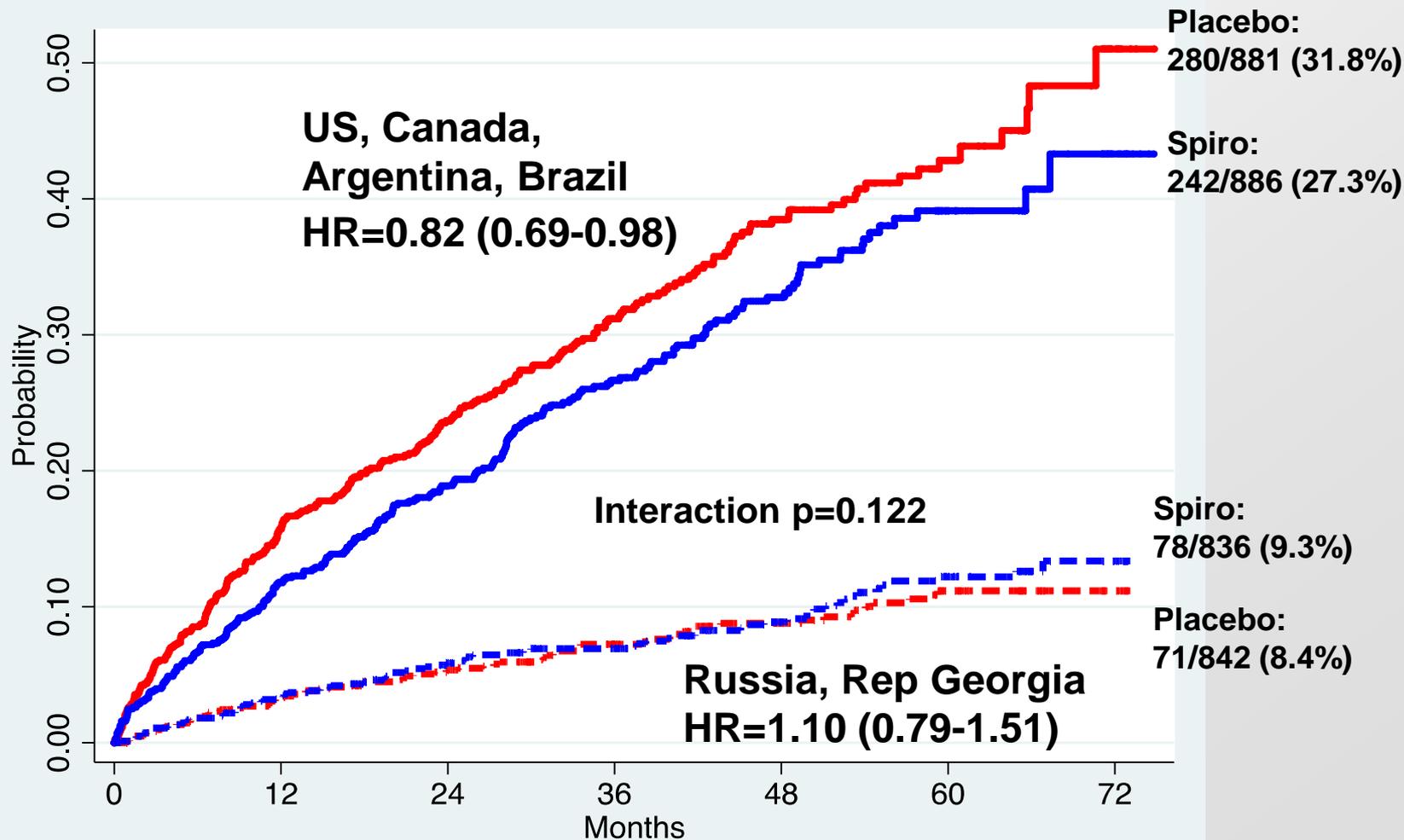
-0.6 mmHg (NS)

SBP delta differed by region (p<0.001), adjusted

Potassium Change by Region

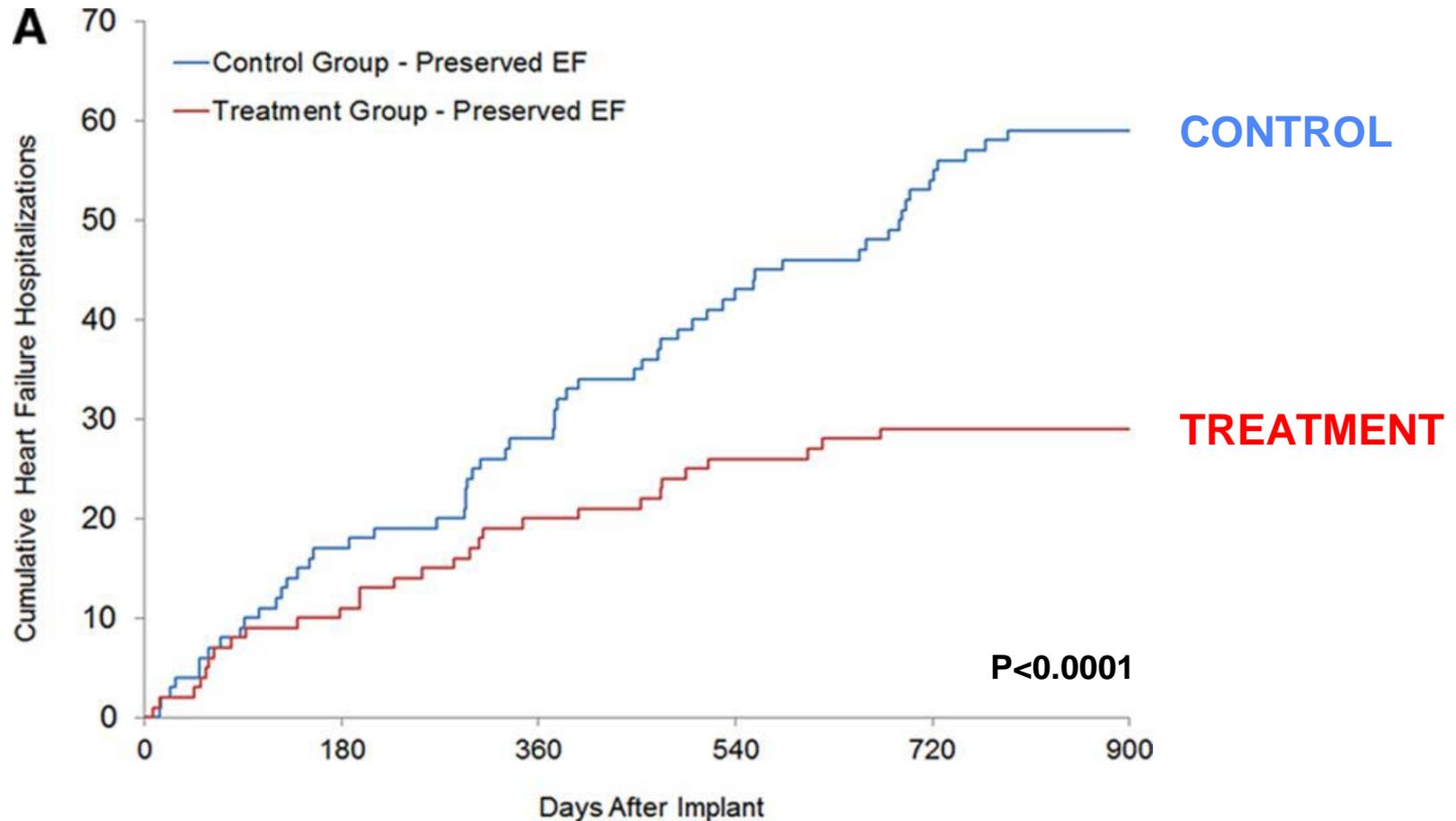


Placebo vs. Spiro by Region



CHAMPION TRIAL

↓ *LA pressure = improved outcomes in HFpEF*



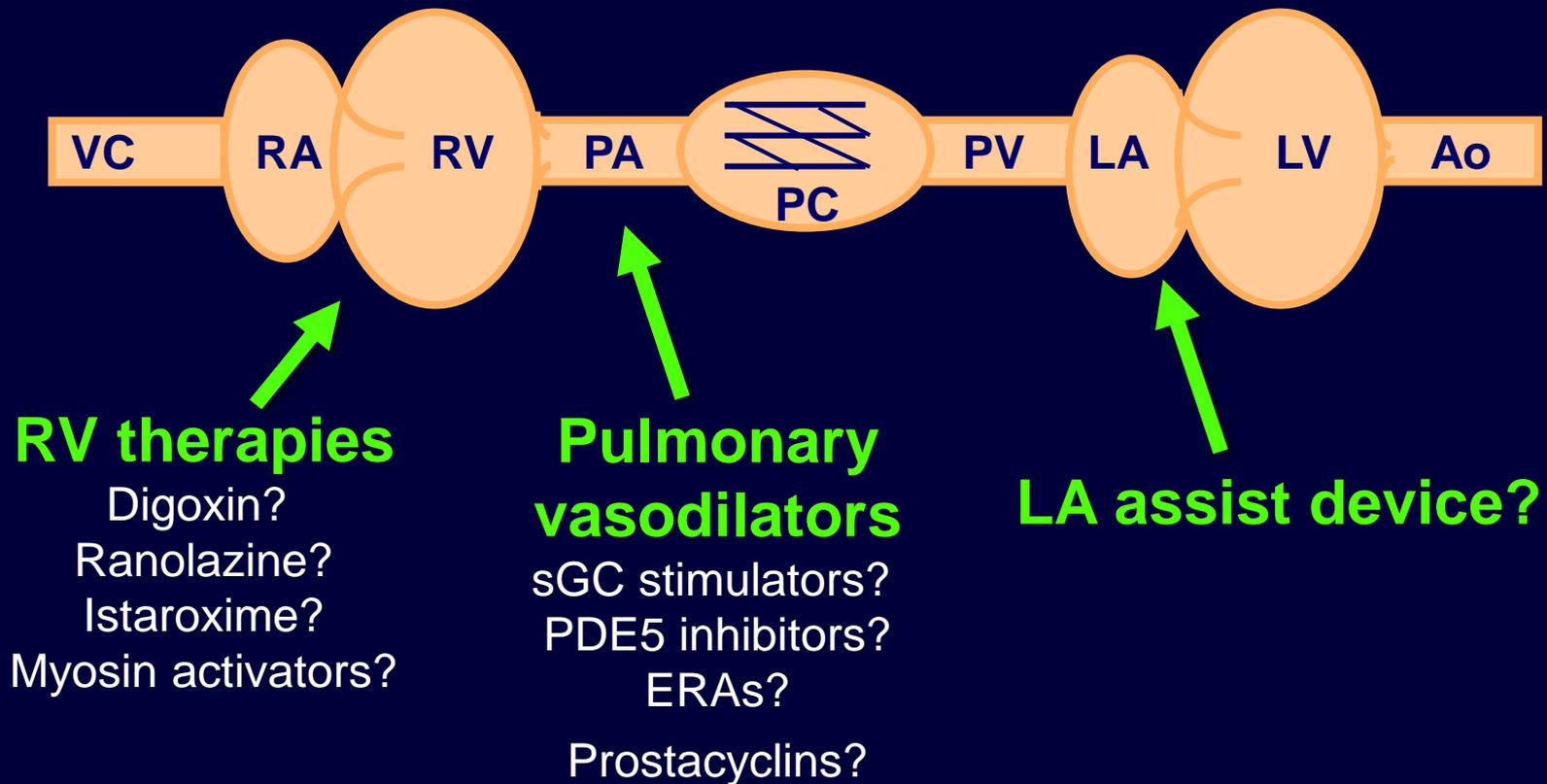
PULMONARY HYPERTENSION RV FAILURE



- Aggressive diuresis, ultrafiltration often needed
- May need to discontinue systemic vasodilators
- Midodrine for low BP during diuresis (if not contraindicated)
- Digoxin to RV inotropy
- PDE5 inhibition if PADP-PCWP gradient > 5 mmHg
- Hemodynamic sensor for careful titration of diuretics

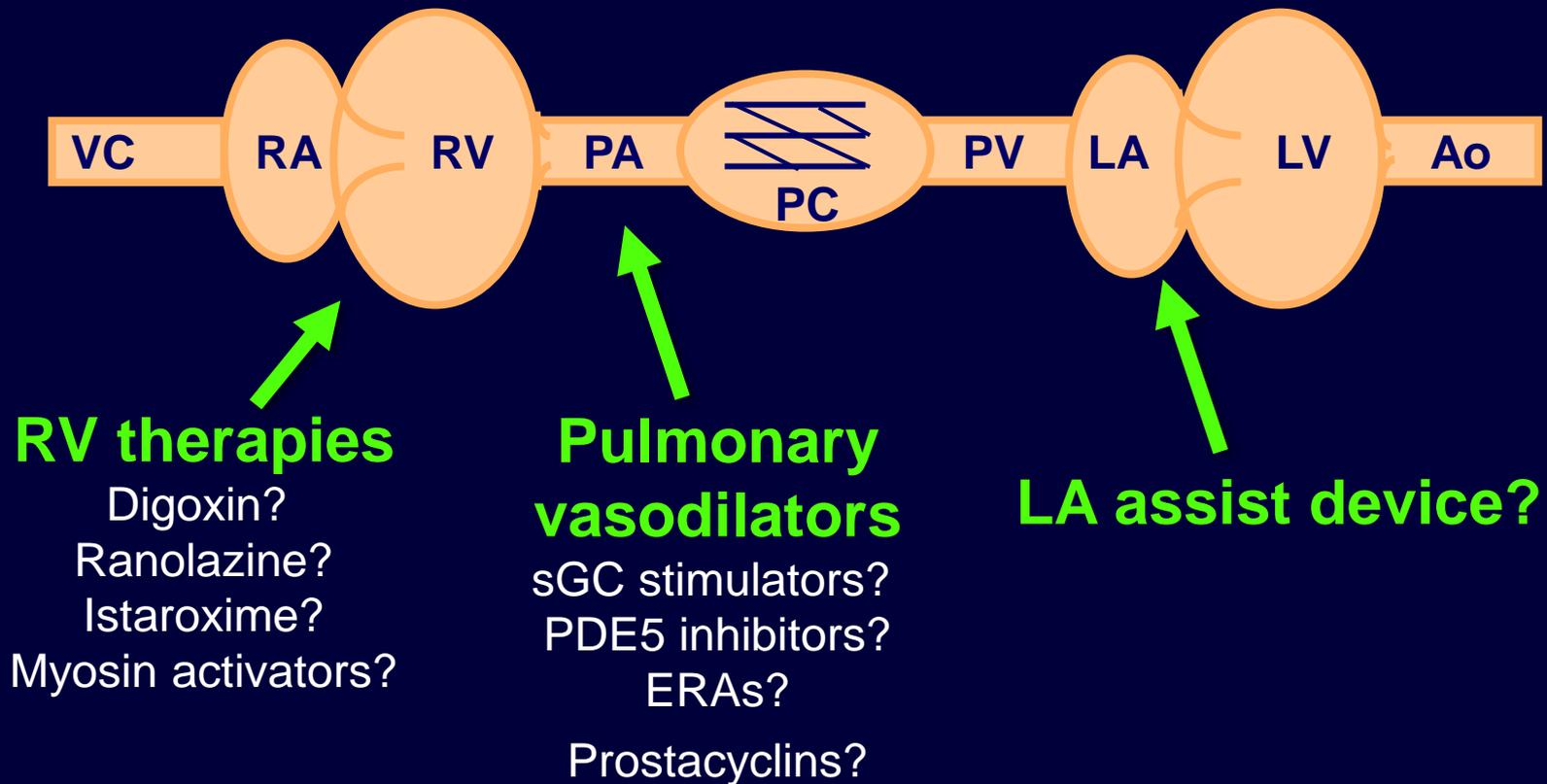
Treatment of PH-HFpEF

Treatment targets: LA, PA, RV



Treatment of PH-HFpEF

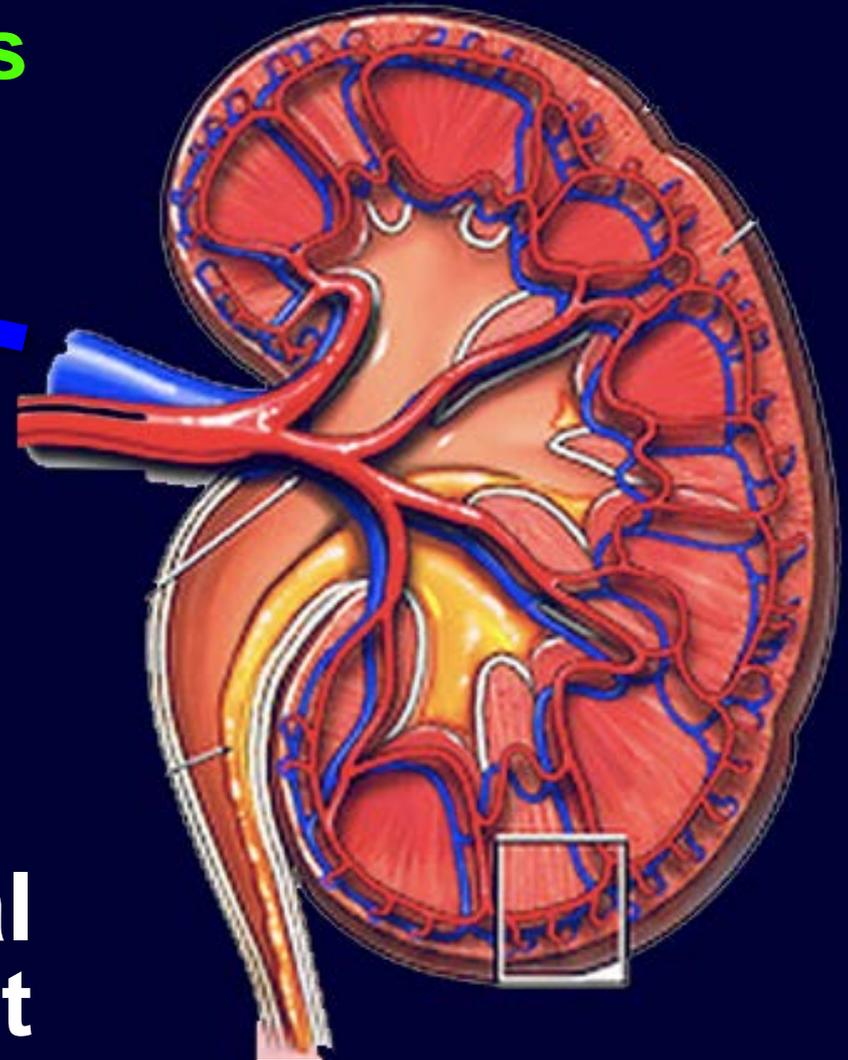
Treatment targets: LA, PA, RV



Renal venous congestion in PH-HFpEF

Many PH-HFpEF patients have RV failure:

\uparrow RA pressure =
 \uparrow renal venous pressure
+
 \downarrow CO =
 \downarrow systemic BP
 \downarrow renal blood flow
= \downarrow transrenal pressure gradient



Renal venous congestion in PH-HFpEF

Many PH-HFpEF patients have RV failure:

↑ RA pressure =
↑ renal venous pressure
+
↓ CO =
↓ systemic BP
↓ renal blood flow
= ↓ transrenal pressure gradient



- *Diuretics*
- *Stop anti-HTN meds*
- *Midodrine*
- *Pulmonary vasodilators?*

HFpEF treatment pearls

1. “Garden-variety” -HFpEF: Rx BP, DM, obesity, refer for clinical trial; If AF → trial of cardioversion
2. CAD-HFpEF: Rx like HF w/reduced EF (BB, ACE-I/ARB, revasc)
3. Right heart failure-HFpEF: diuresis / ultrafiltration, digoxin, sildenafil?
4. HCM-HFpEF: verapamil, diltiazem, long-acting metoprolol
5. High-output HFpEF: Rx underlying cause; diuretics/UF
6. Valvular HFpEF: Rx valve disease if possible
7. Rare causes of HFpEF: clinical trial, Rx underlying cause

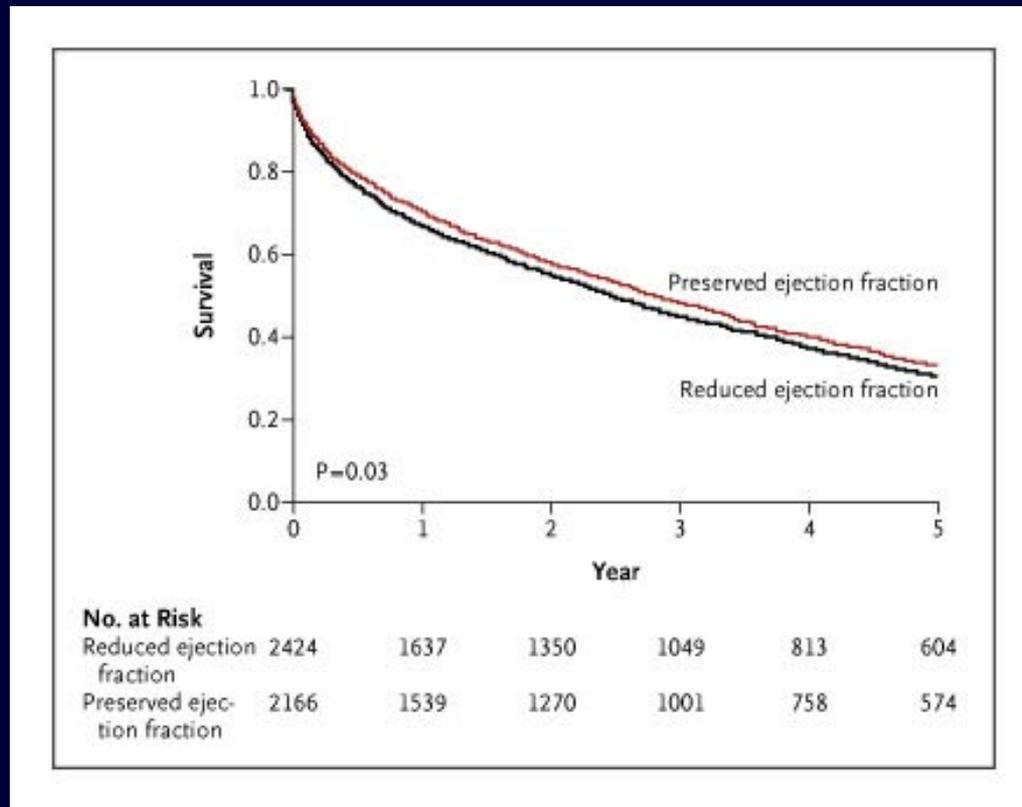
Myth #6:

**HFpEF clinical trials
are doomed**

Fact #6:

**The future is bright for
HFpEF clinical trials**

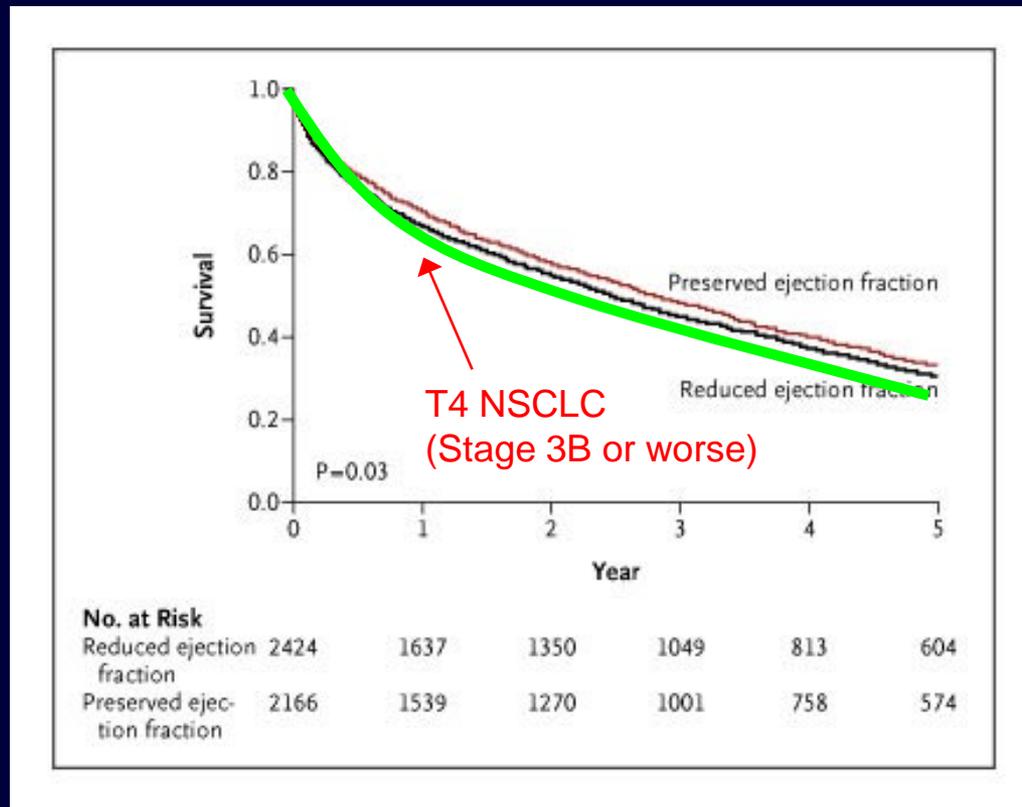
HFpEF survival: poor



Owan T et al. N Engl J Med 2006;355:251-259

Dismal 35% survival at 5 years after HF hospitalization, regardless of LVEF

HFpEF survival: poor



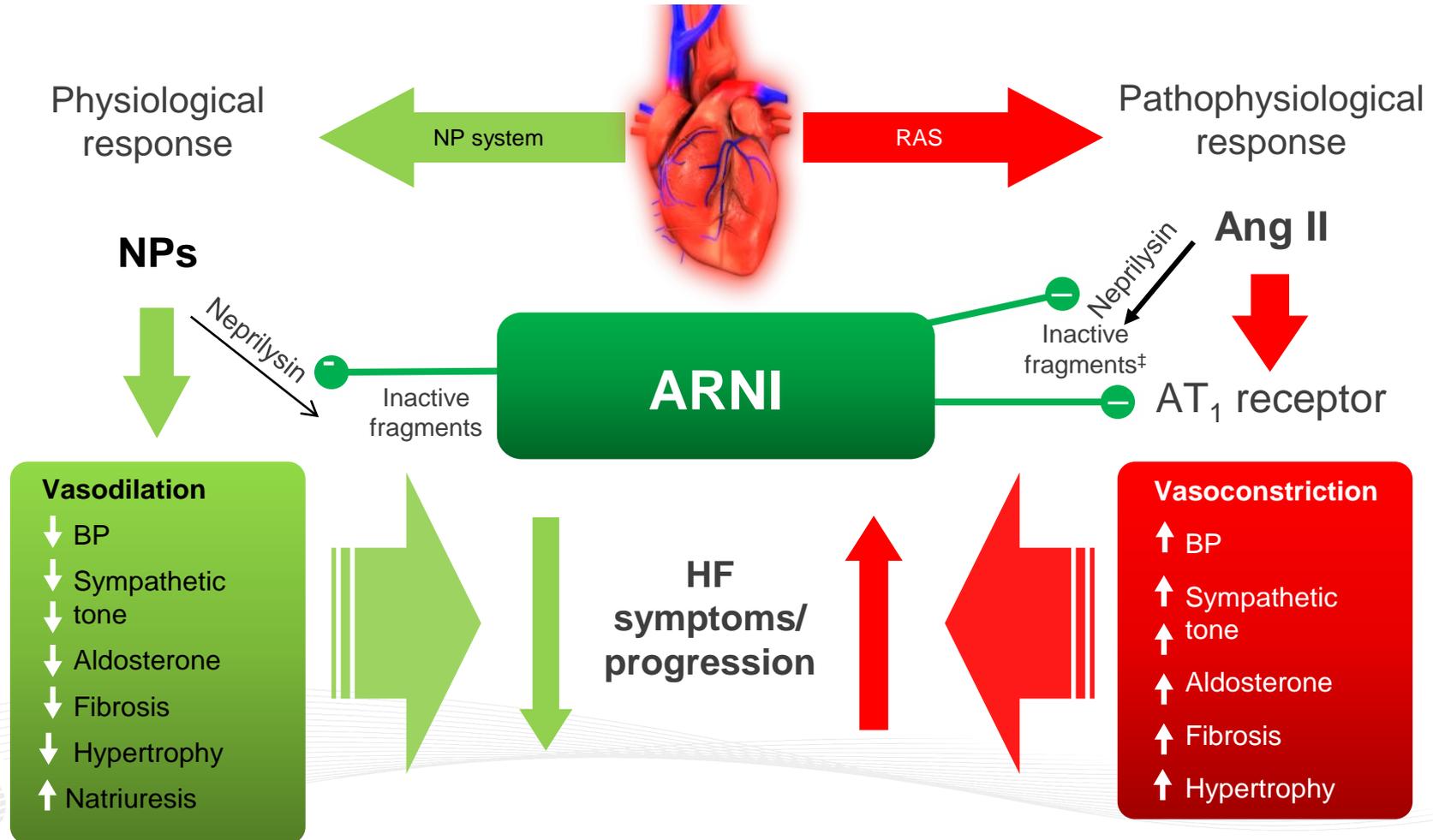
Owan T et al. N Engl J Med 2006;355:251-259; Yang H-X et al. Ann Thoracic Surg 2009.

HFpEF survival: comparable to T4 non-small cell lung cancer, stage 3B or worse

Current HFpEF clinical trials

- PARAGON-HF: *neprilysin inhibition*
- SOCRATES-Preserved: *sGC stimulator*
- ATTR-ACT: *transthyretin stabilizer*
- ENDEAVOUR: *transthyretin RNAi*
- LIBERTY-HCM: *late I_{Na+} inhibitor*
- REDUCE-LAP: *interatrial shunt device*
- (INDIE-HF): *inhaled nitrites*
- (KNO₃CK-OUT): *oral nitrites*

ARNIs: Angiotensin Receptor / Neprilysin Inhibitors



Endothelial Dysfunction

Oxidative Stress

Inflammation

eNOS

sGC Insufficiency

sGC

GTP

cGMP

cGMP Deficiency

Myocardial Dysfunction

Impaired Relaxation, Diastolic Stiffening,
Energy Wastage

Vascular Dysfunction

Disturbed Endothelium-Dependent
Vasotone Regulation

sGC soluble Guanylate Cyclase

NO Nitric Oxide

eNOS Endothelial NO Synthase

cGMP cyclic Guanosine Monophosphate

sGC Stimulators

Endothelial Dysfunction

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Vascular Dysfunction
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sGC soluble Guanylate Cyclase
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cGMP cyclic Guanosine Monophosphate

sGC Stimulators

PDE5
inhibitors

4 Nitrites are very different than nitrates

4 Endothelial dysfunction plays a central role in HFpEF

4 Nitrites improve endothelial function

4 Nitrates may actually *worsen* endothelial function via increased ROS

4 Unlike nitrates, there is strong preliminary data for nitrites in HFpEF (both oral and inhaled forms)

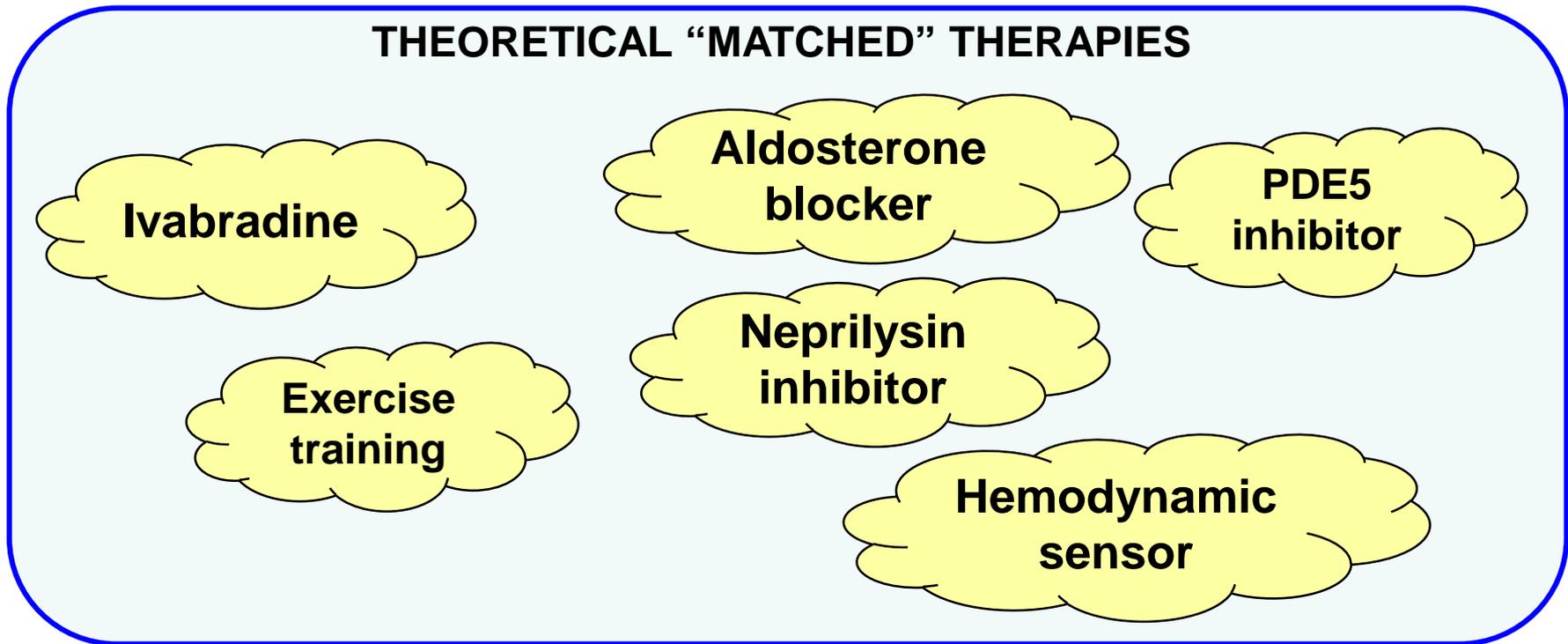
ISMN and Nitrite are very different

	Isosorbide mononitrate (ISMN)	Nitrite
Activation	P450 enzymes in the endoplasmic reticulum	Heme-containing proteins, XO, others
NO elaboration	Tonic - Throughout the day	Intermittent - Coupled to tissue hypoxia, exercise
Tolerance	Yes	No
Endothelial Dysfunction	Yes	No
↑ROS	Yes	No

“Matchmaking” for optimizing HFpEF clinical trials



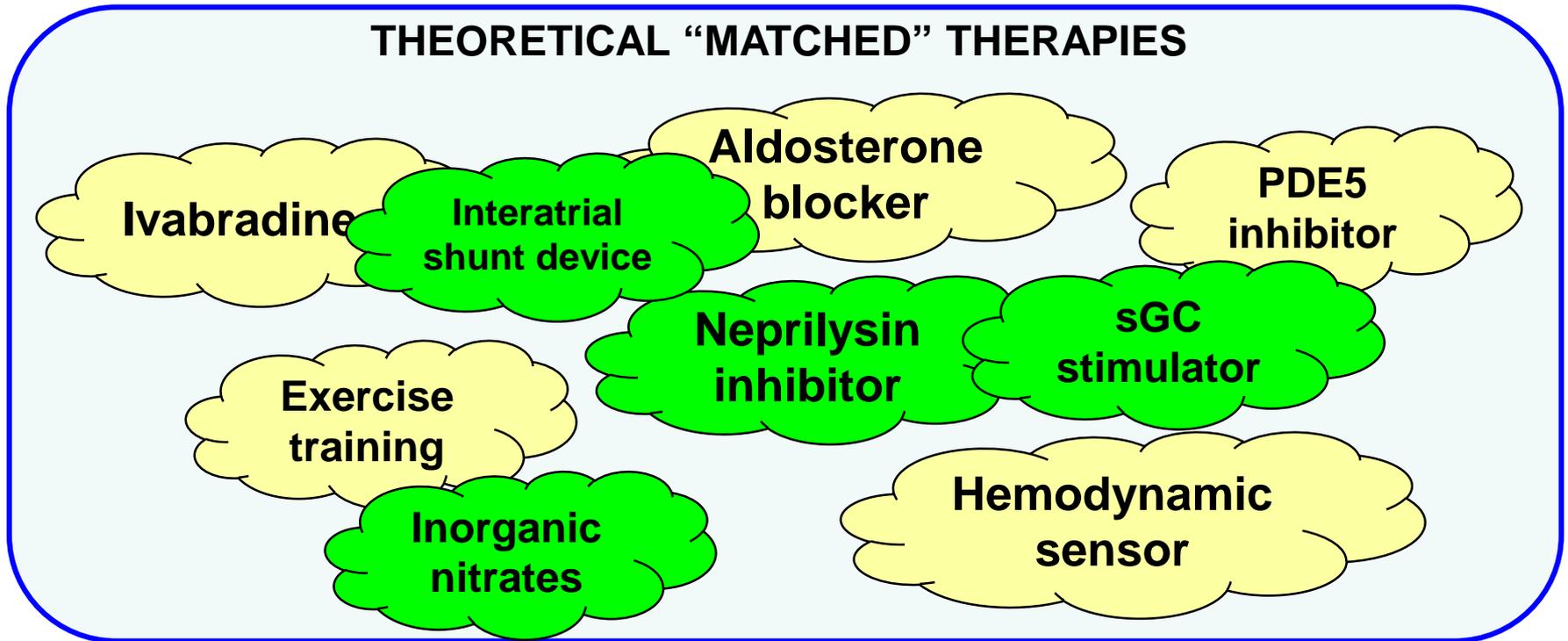
THEORETICAL “MATCHED” THERAPIES



“Matchmaking” for optimizing HFpEF clinical trials



THEORETICAL “MATCHED” THERAPIES



A close-up photograph of a person's hand held palm up, with the word "STOP!" overlaid in large, bold, red capital letters. The background is blurred, showing the person's face and dark clothing. The lighting is soft, highlighting the texture of the skin.

STOP!

1. Make sure you didn't miss dx of HFpEF

2. Don't forget the zebras

3. Categorize by type of HFpEF presentation and tailor treatment

4. There are treatment options for HFpEF!

5. Enroll in HFpEF clinical trials

STOP!





thank you!