

Diagnosis Heart Failure:
How do we treat them?

MAY 4, 2018

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Heart Failure with Preserved Ejection Fraction (HFpEF): *Who are they?* *How do we treat them?*

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Disclosures

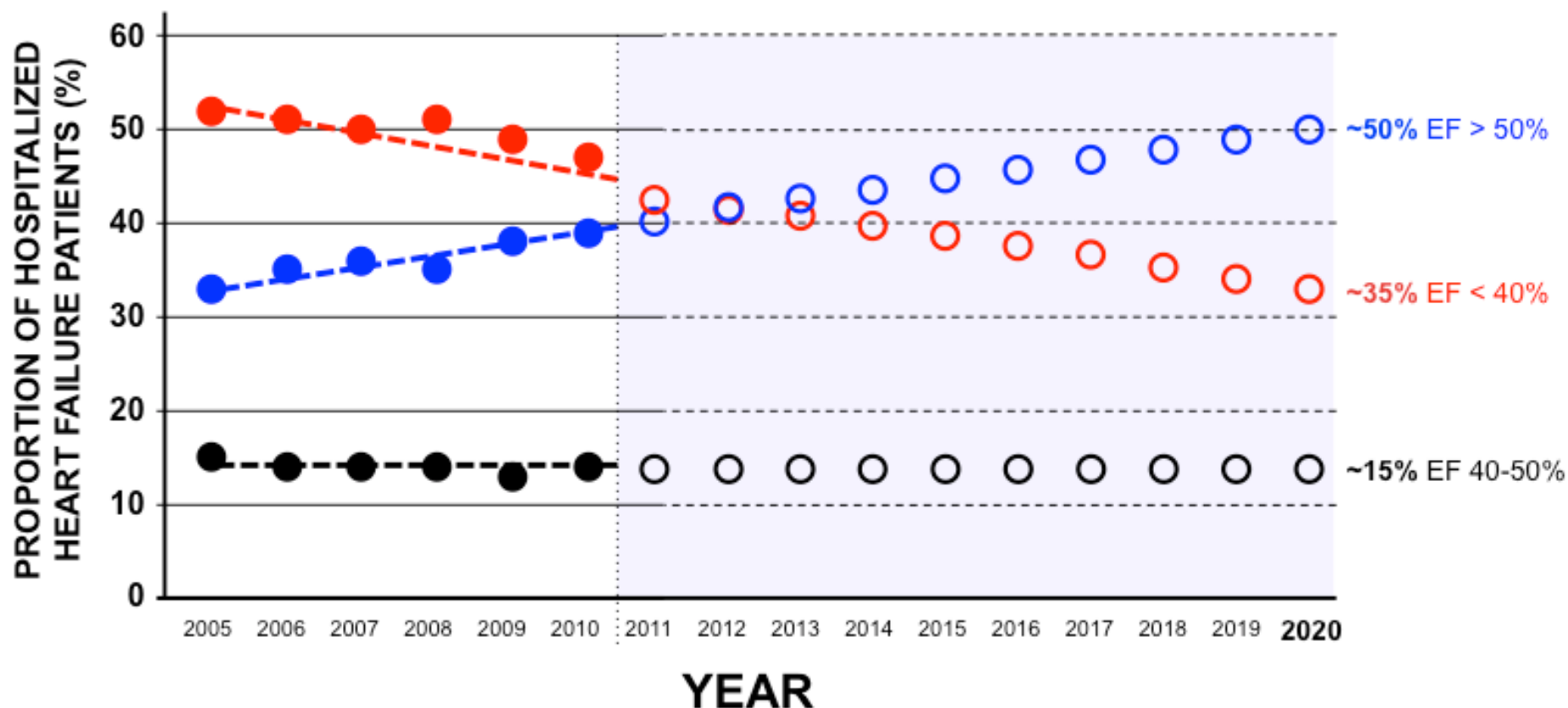
- Research funding:
 - » NIH R01 HL107577, R01 HL127028
 - » AHA #16SFRN28780016, #15CVGPS27260148
 - » Actelion, AstraZeneca, Corvia, Novartis
- Consulting/advisory board/steering committee:
 - » Actelion, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Cardiora, Eisai, Gilead, Ironwood, Merck, MyoKardia, Novartis, Pfizer, Sanofi, United Therapeutics

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- We pronounce HFpEF: “huff-puff”

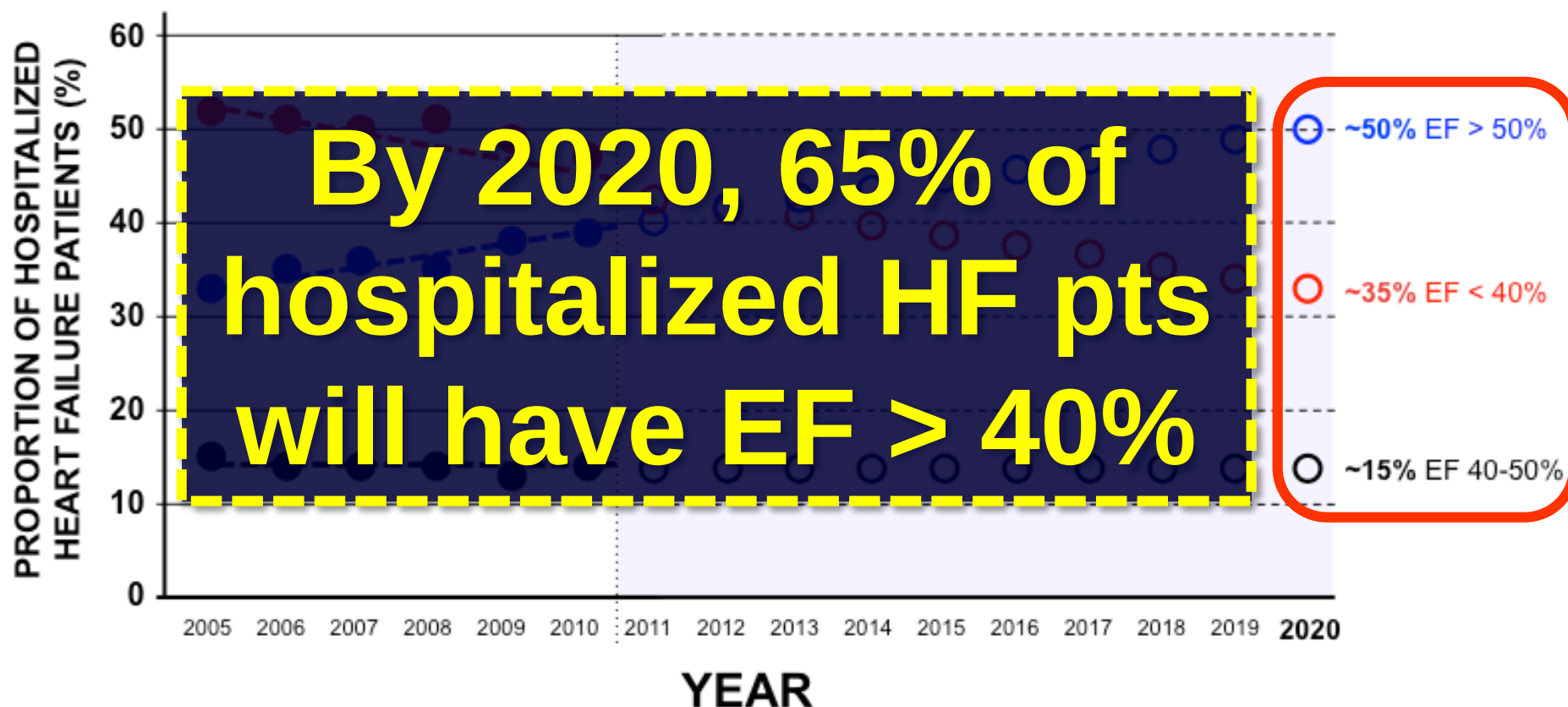
HFpEF: prevalence increasing

GWTG-HF: N=110,621 patients hospitalized with HF
 $P < 0.0001$ for trend of increased HFpEF prevalence

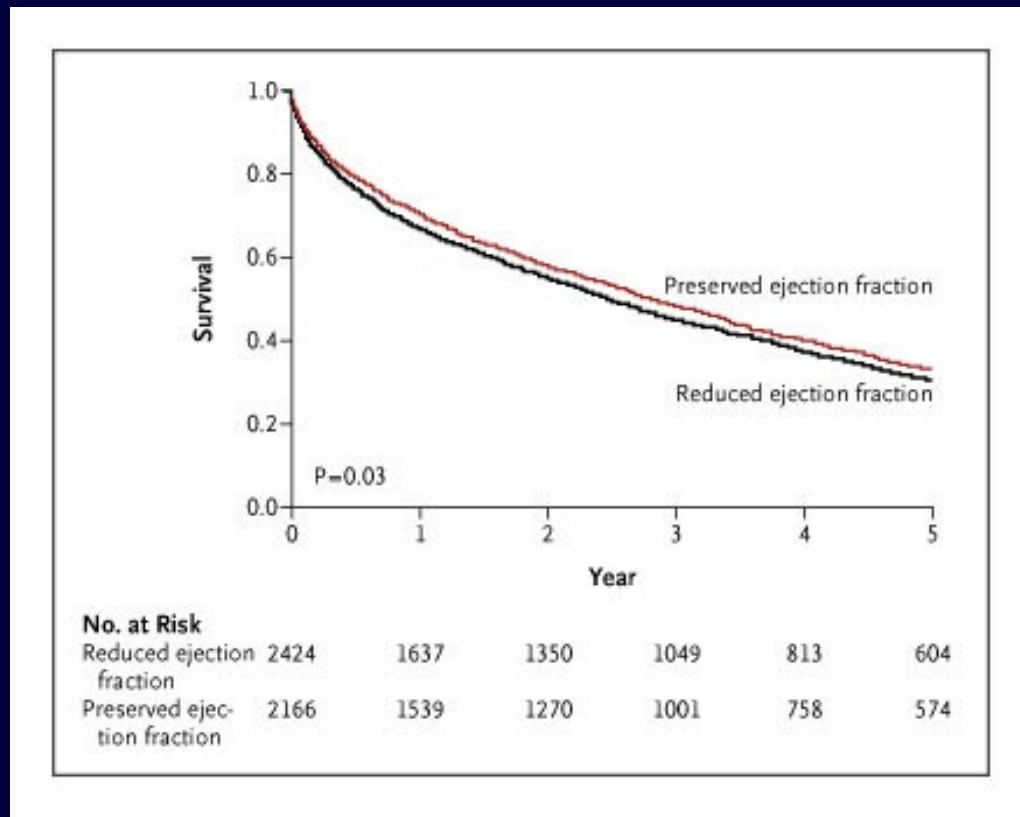


HFpEF: prevalence increasing

GWTG-HF: N=110,621 patients hospitalized with HF
 $P < 0.0001$ for trend of increased HFpEF prevalence



HFpEF survival: poor



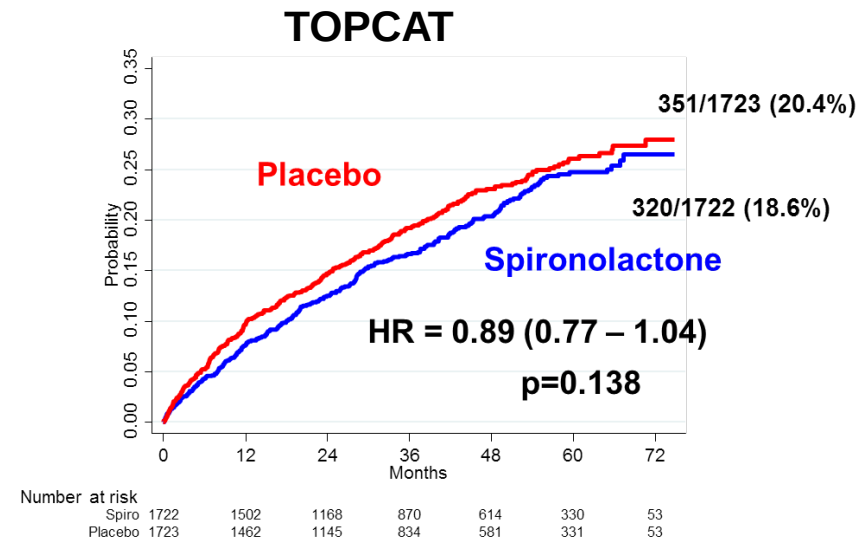
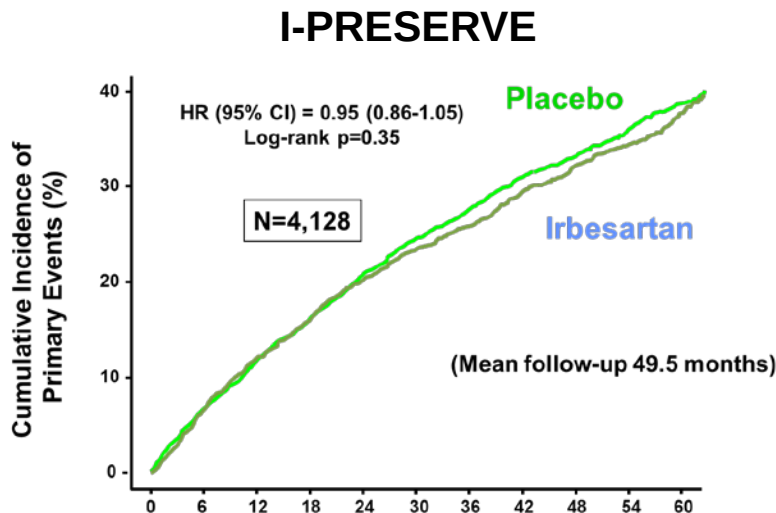
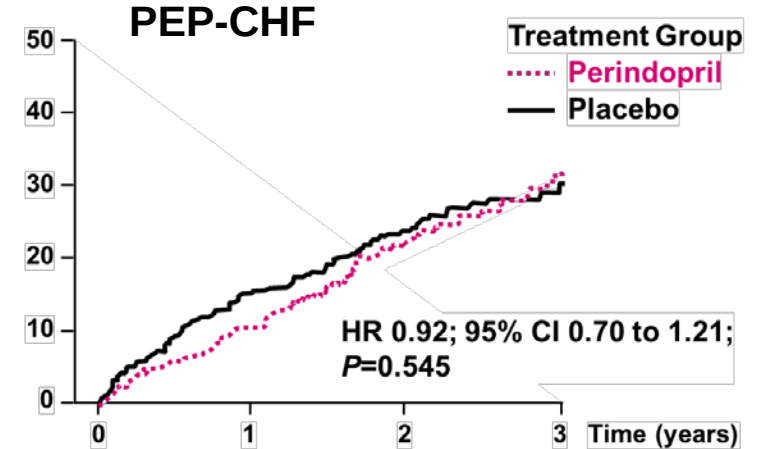
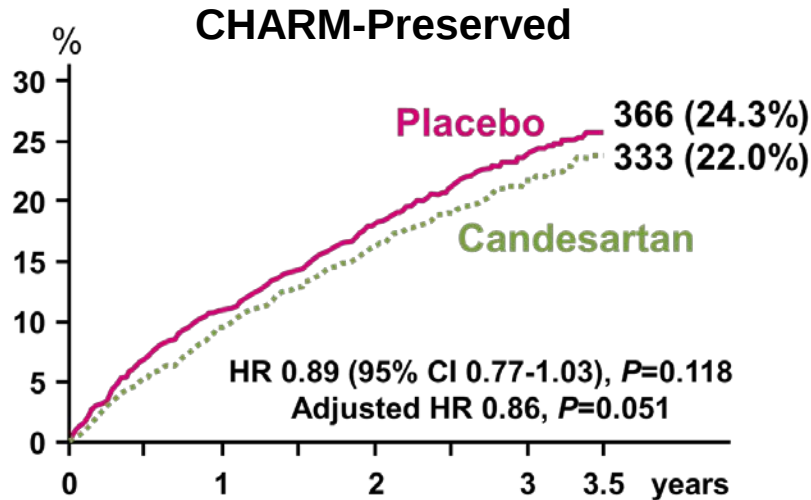
Owan T et al. N Engl J Med 2006;355:251-259

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

HFpEF: 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
 - » In the Americas (n=1758):
 - Mean BMI: 34 ± 8 kg/m²
 - 88% with BMI > 25 kg/m²
 - 65% with BMI > 30 kg/m²

HFpEF trials: disappointing results



HFpEF challenges

- Rising prevalence
- High morbidity
- High mortality
- Multiple pathophysiologic contributors
- Few available therapies
- *Need new solutions...*

Solution: dedicated HFpEF program

Curr Cardiol Rep (2016) 18:122
DOI 10.1007/s11886-016-0802-1



HEART FAILURE (MR MEHRA AND E JOYCE, SECTION EDITOR)

How to Develop and Implement a Specialized Heart Failure with Preserved Ejection Fraction Clinical Program

Sanjiv J. Shah¹ • Rebecca Cogswell² • John J. Ryan³ • Kavita Sharma⁴

Shah SJ, et al. *Curr Cardiol Rep* 2016

Myth #1:

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

Fact #1:

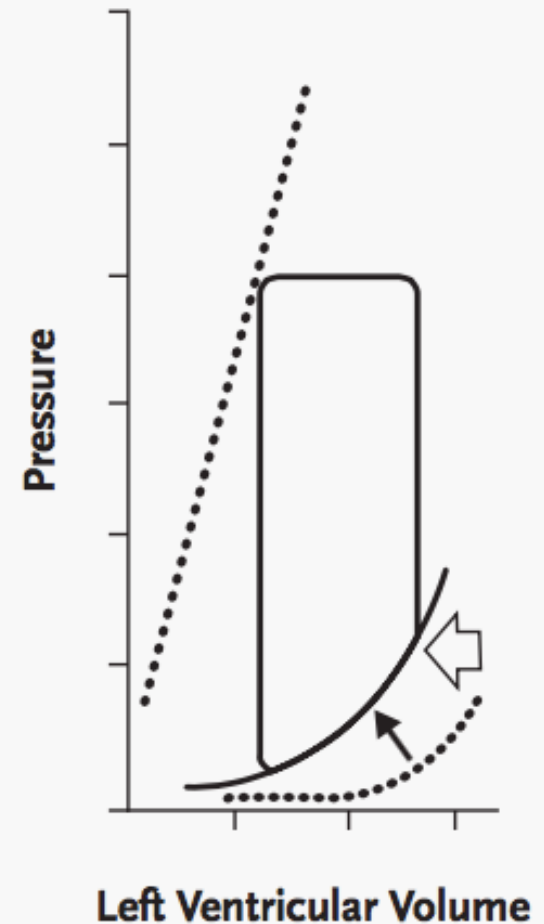
**HFpEF is more than just
diastolic dysfunction**

“Diastolic HF” c.2004

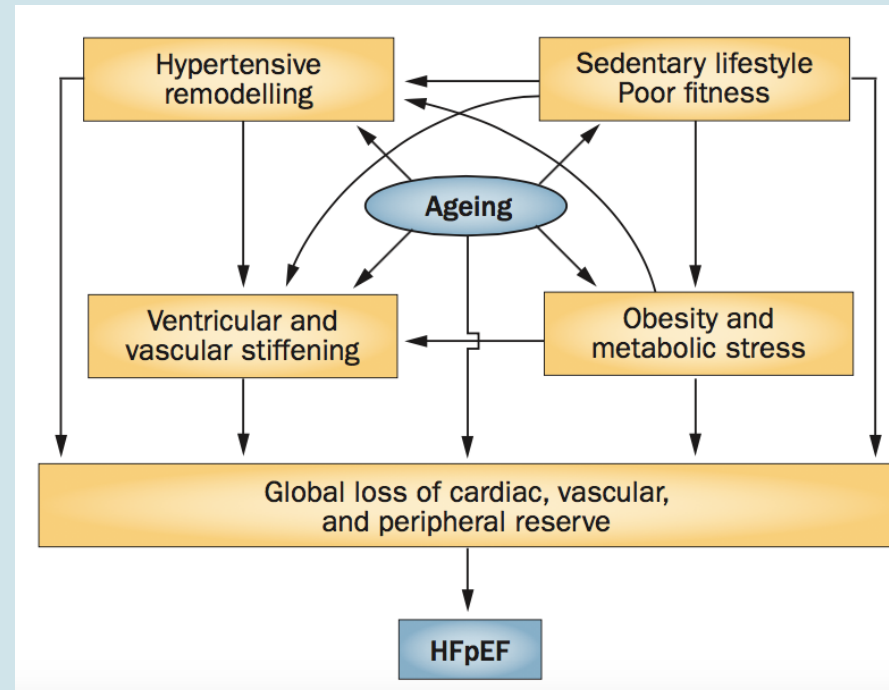
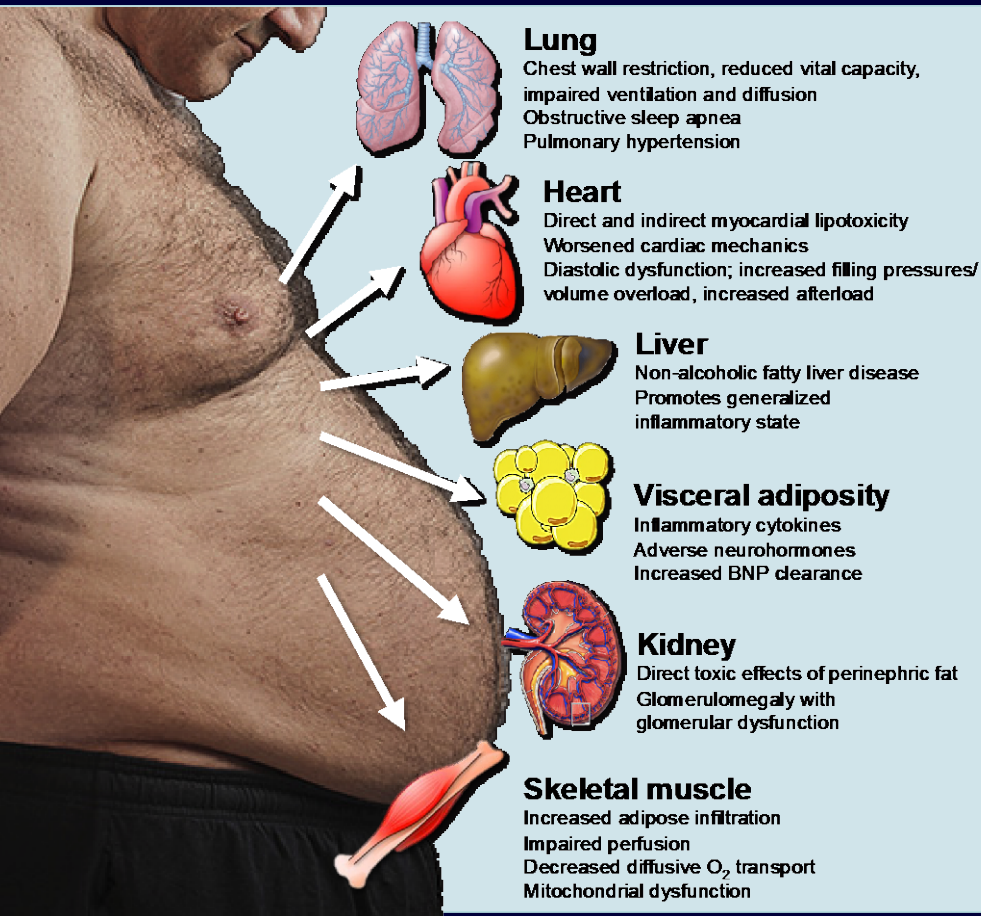


Aurigemma G, et al. *NEJM* 2004

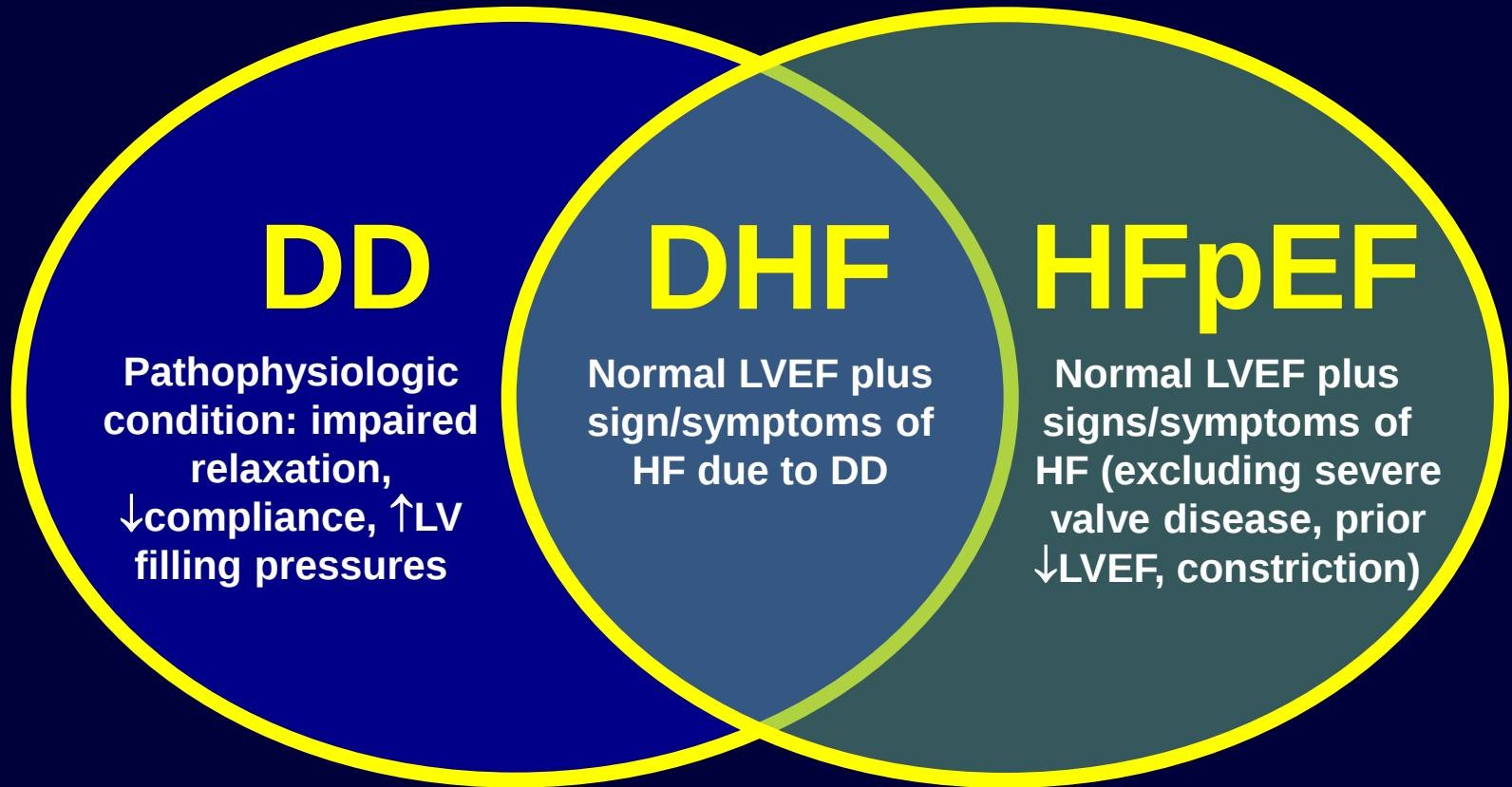
Diastolic Dysfunction



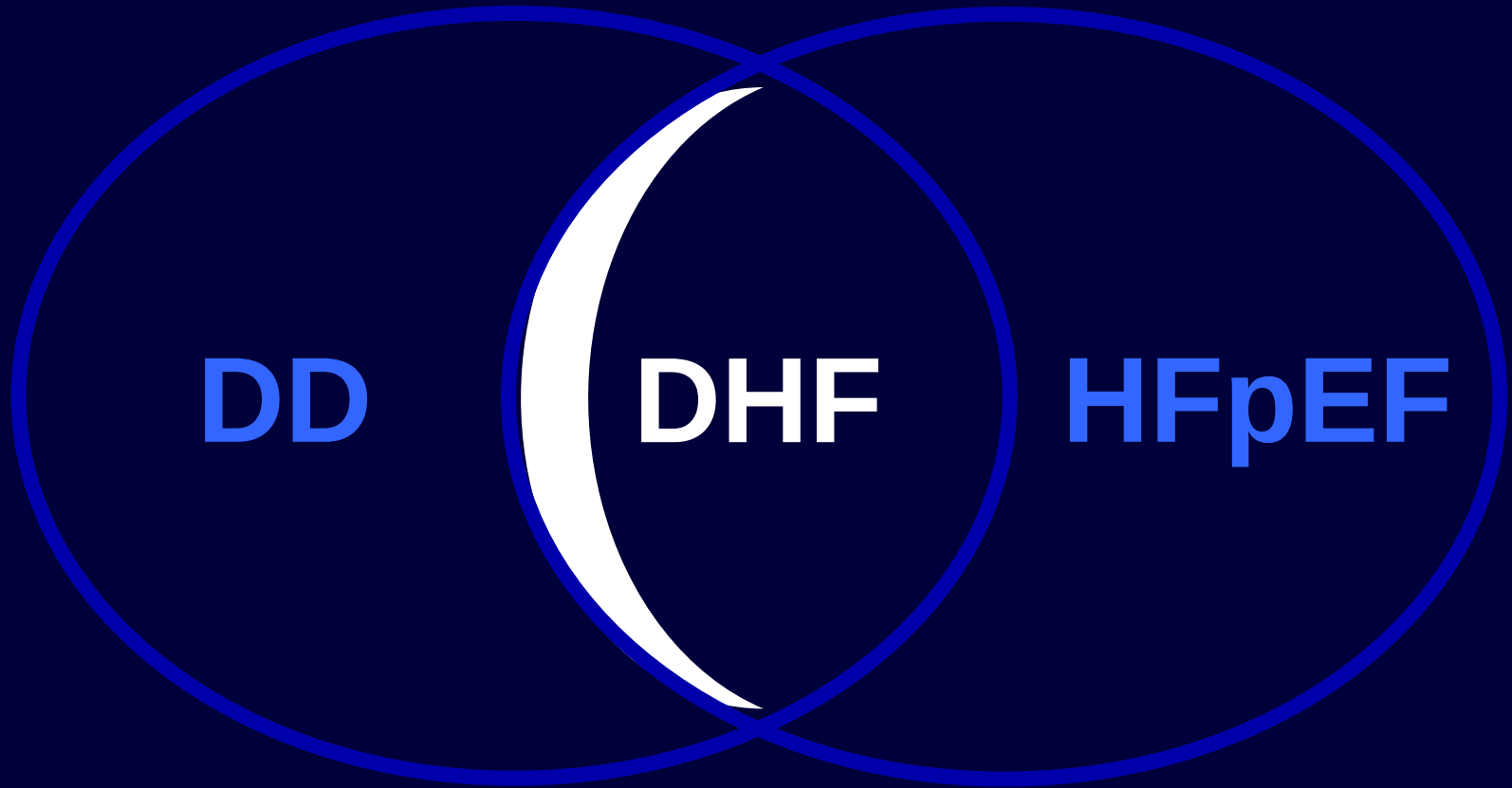
HFpEF in 2017



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

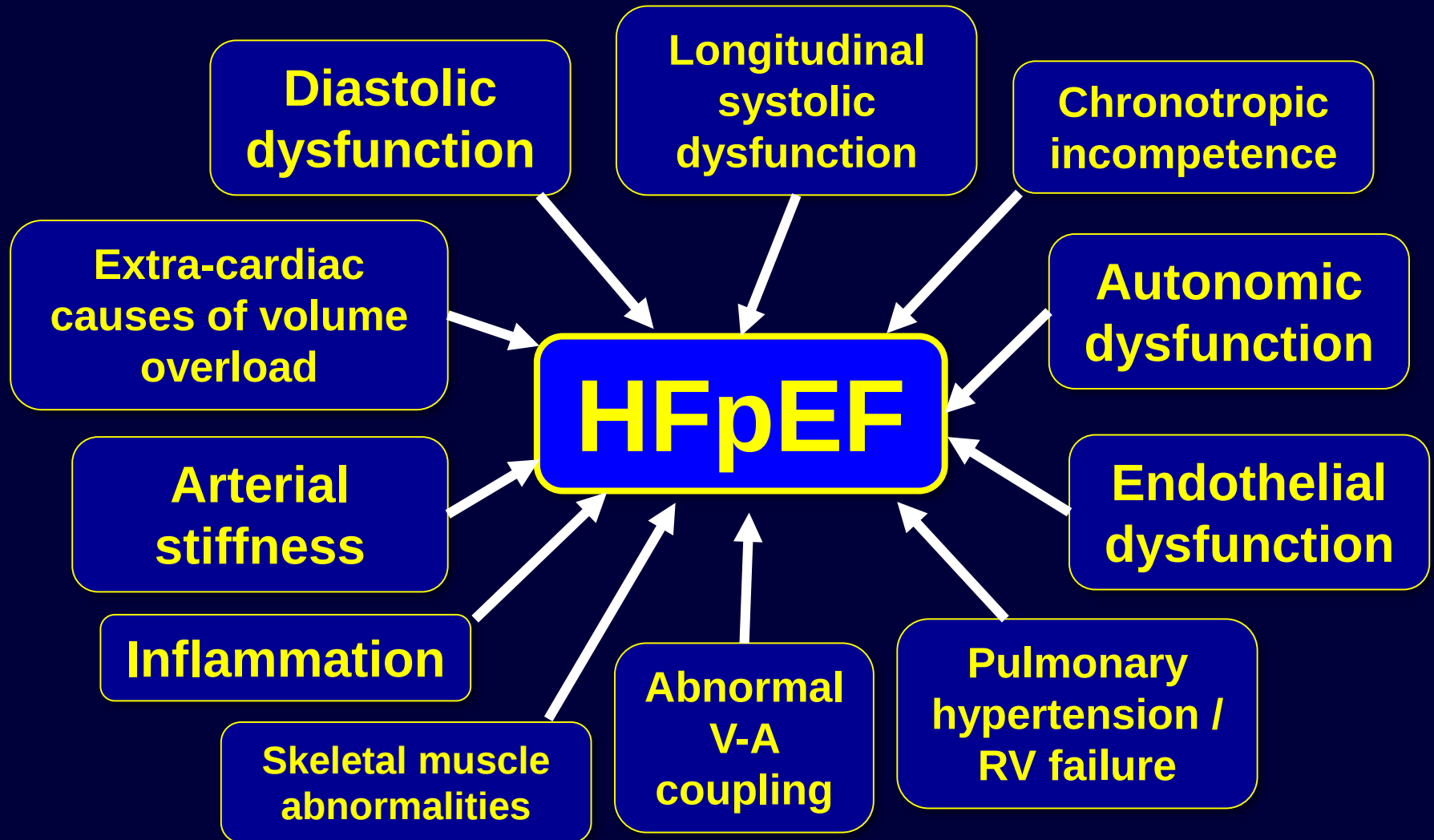
935 patients with a LVEF ≤ 50 % (excluded)

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

Pathophysiologic contributors to HFpEF



Myth #2:

**Diagnosing HFpEF
is difficult**

Fact #2:

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

Diagnosis of HFpEF: 5 Lessons

1. Don't use BNP to rule out HFpEF
2. Echocardiography is the cornerstone, use it to guide next steps
3. Know your zebras
4. Perturb the system
5. Everyone has HFpEF until proven otherwise

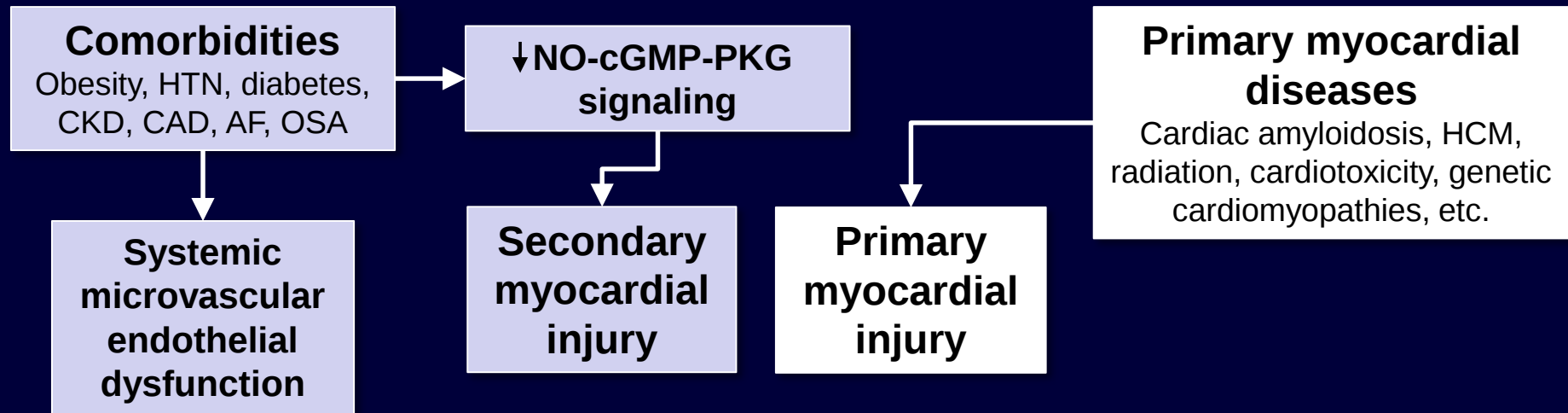
What is HFpEF?

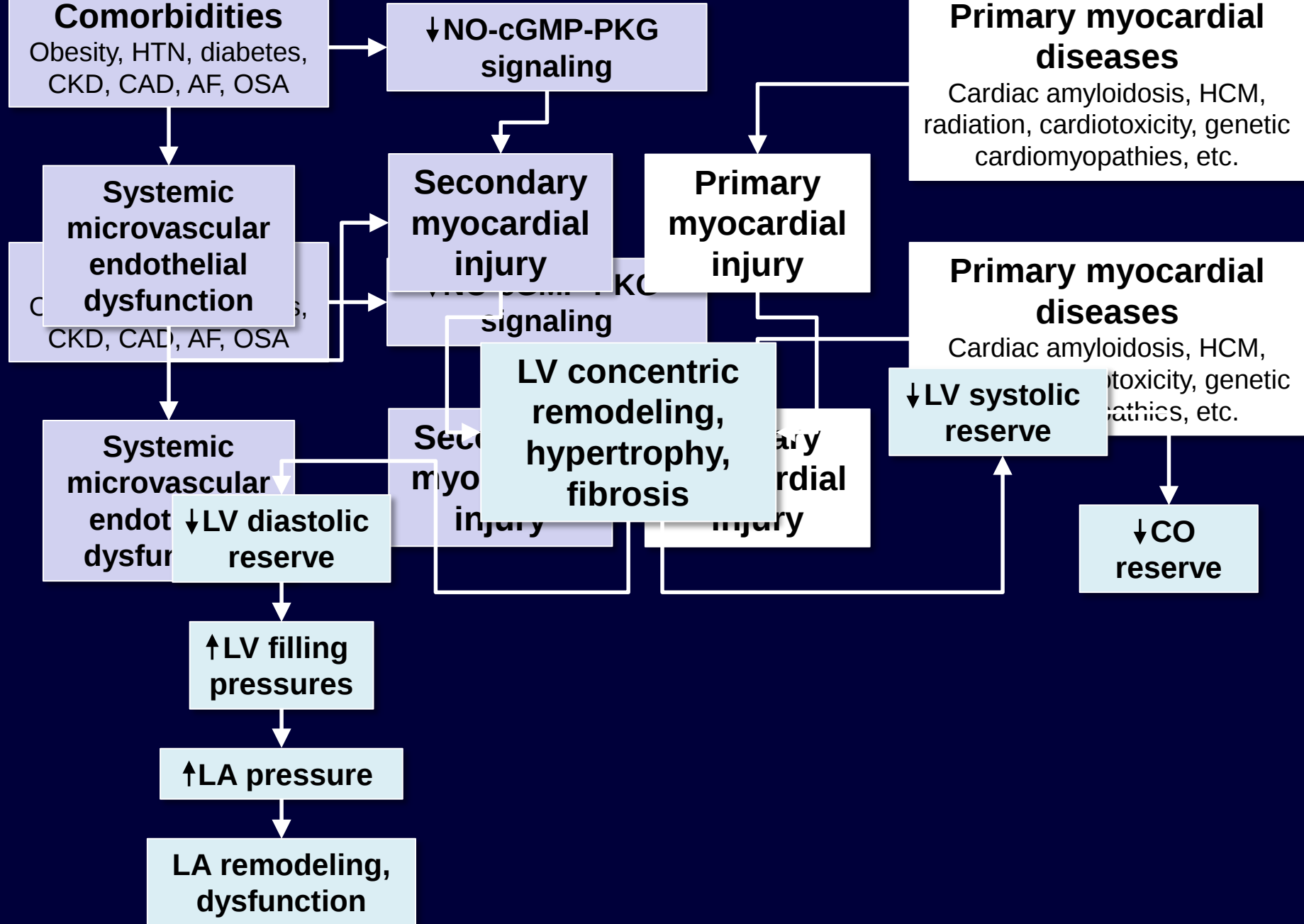
- Signs and symptoms of HF (dyspnea, exercise intolerance, fluid retention)
- Preserved LVEF (>45-50%)
- Evidence of elevated LV filling pressures at rest or during exercise

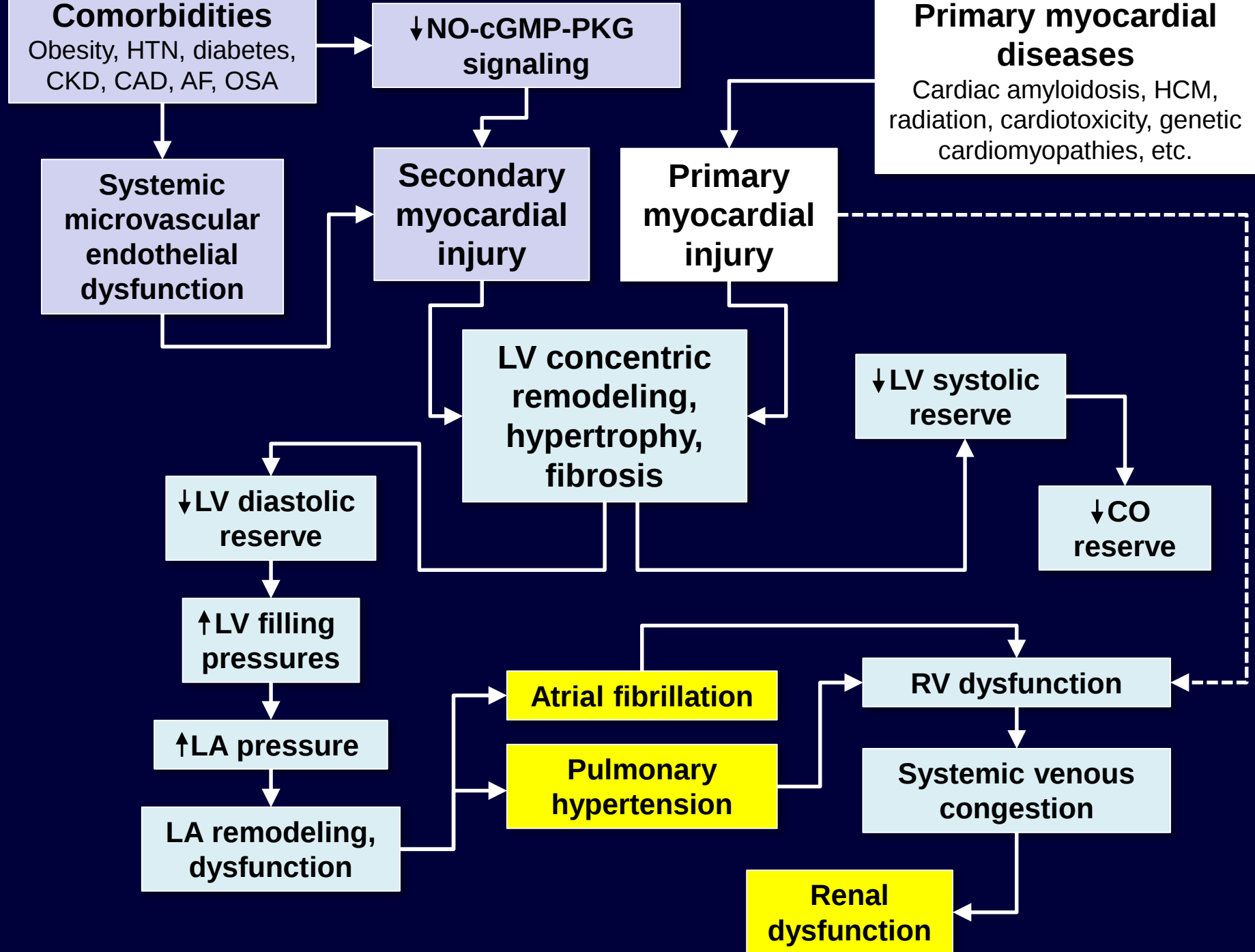
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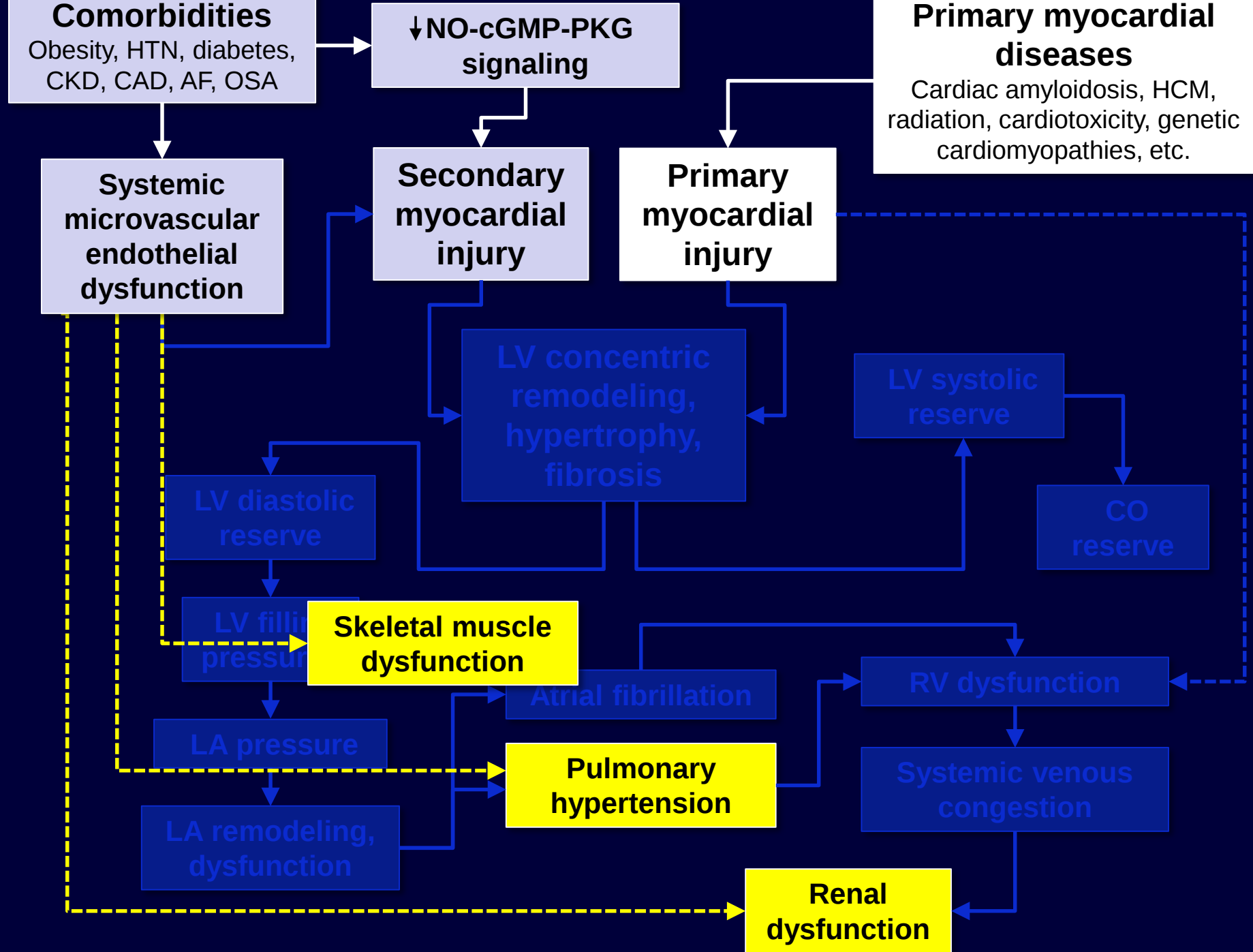
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- Evidence of elevated LV filling pressures at rest or during exercise
- Evidence of a cardiac-predominant problem (not an extra-cardiac cause)

What is HFpEF?

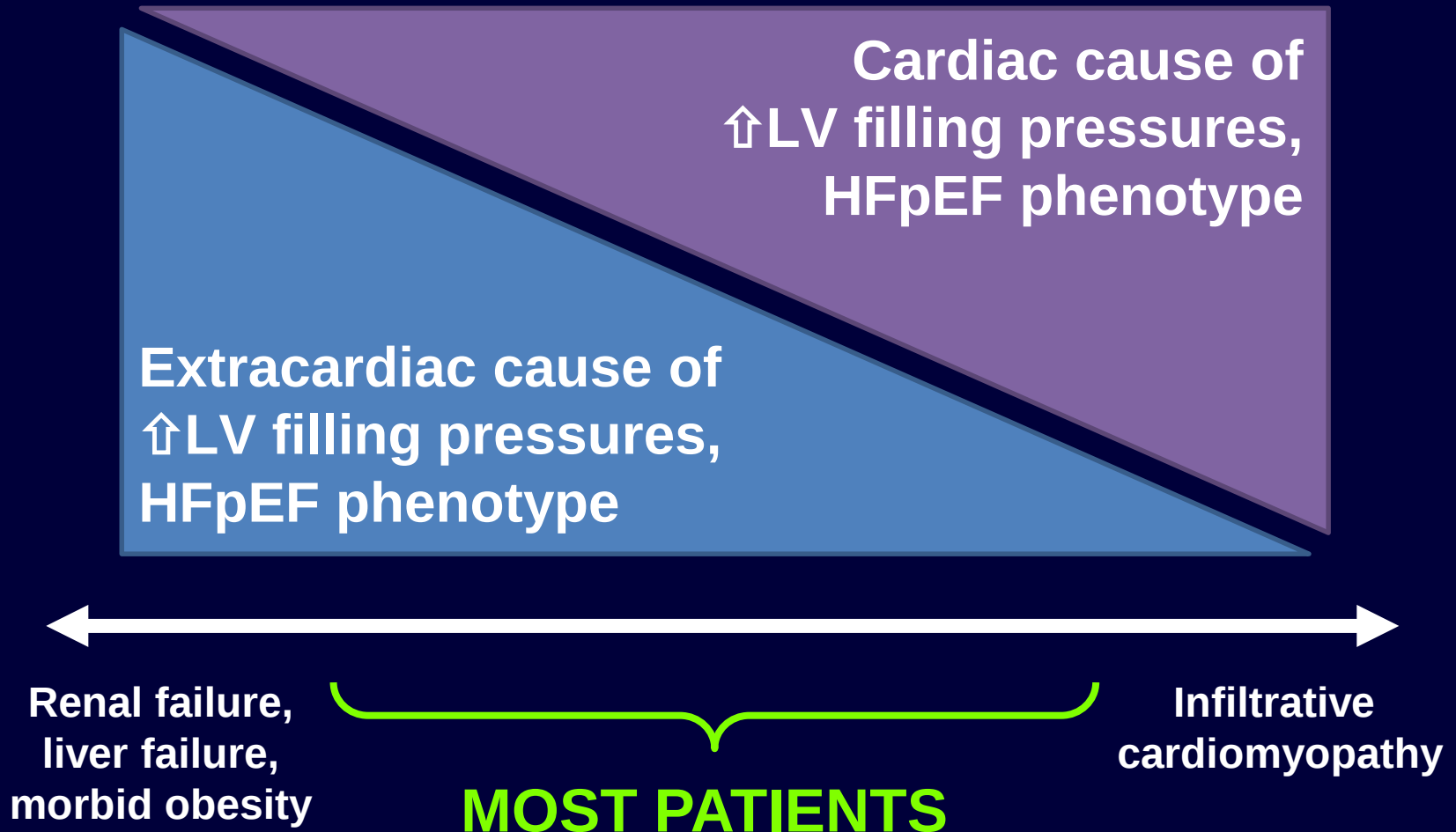




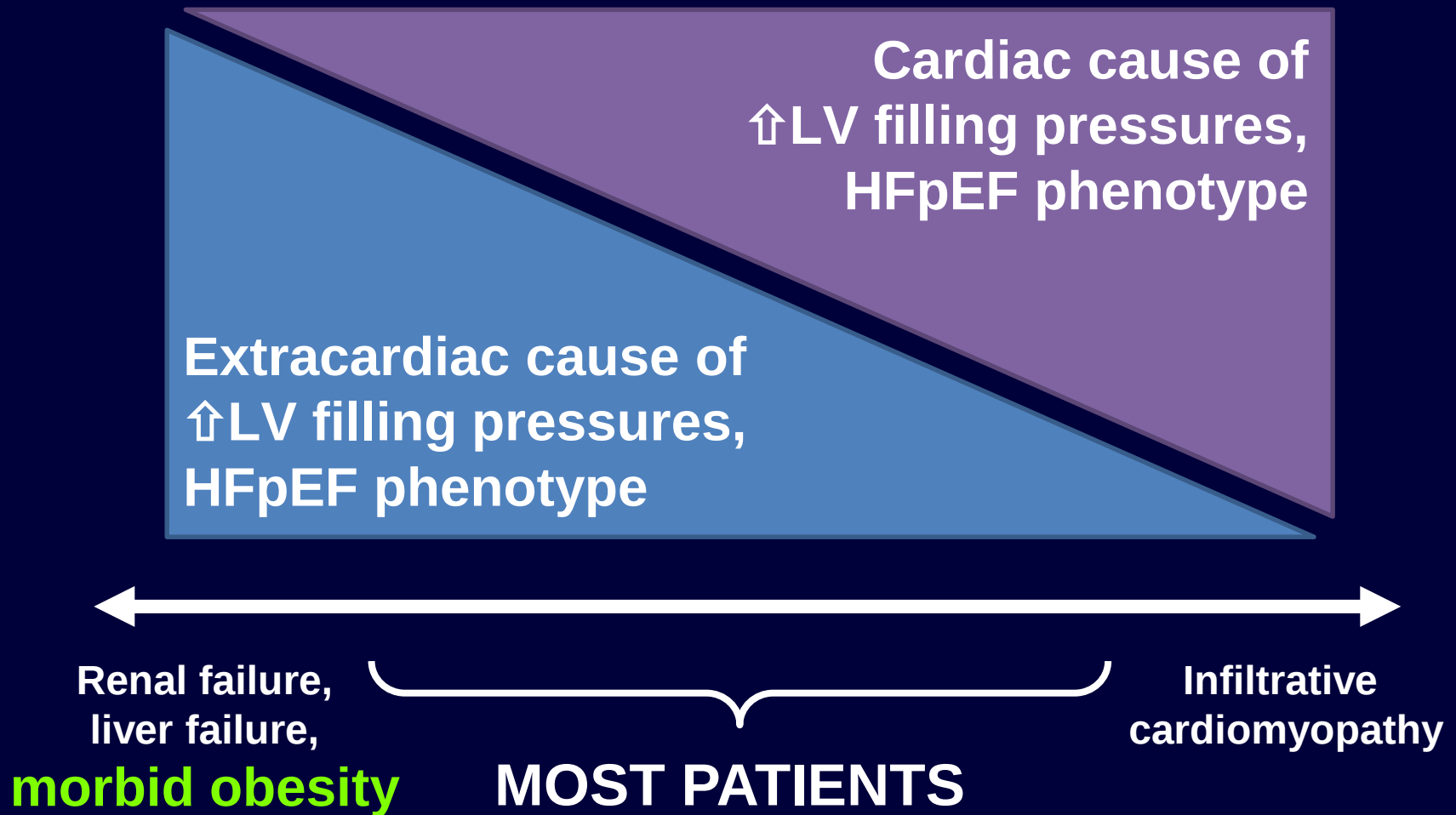




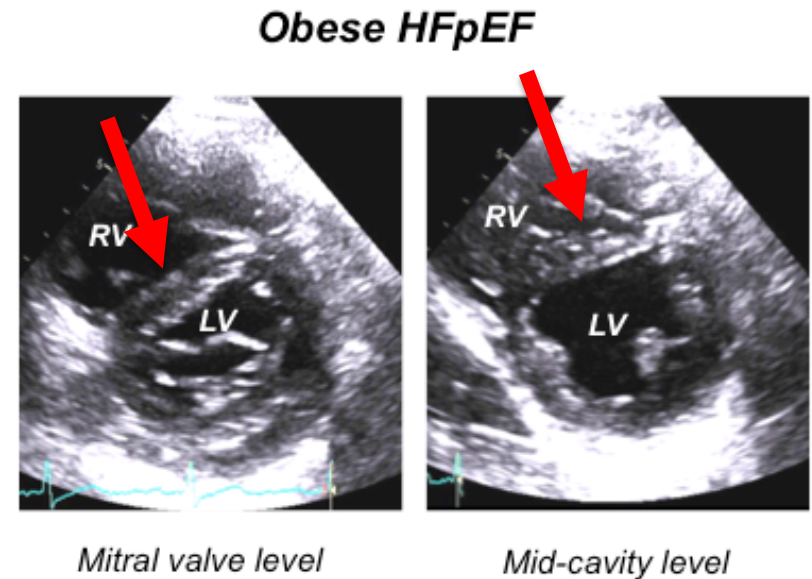
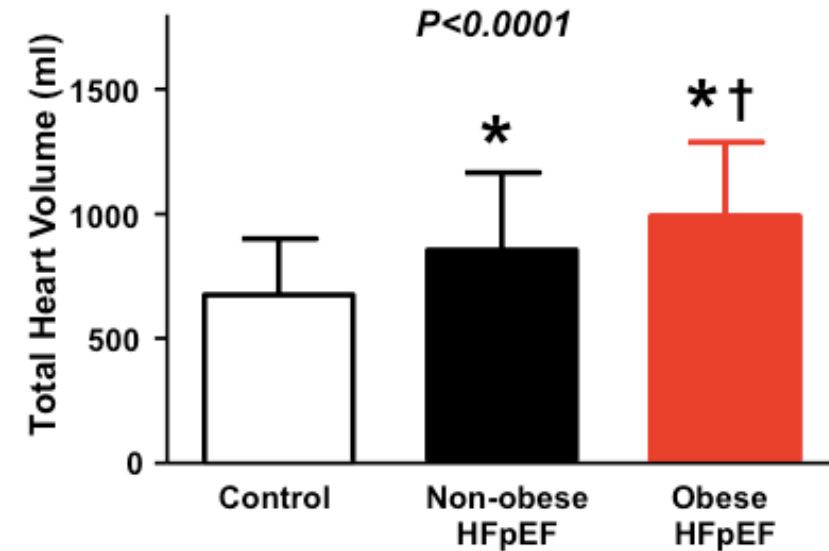
What is HFpEF?



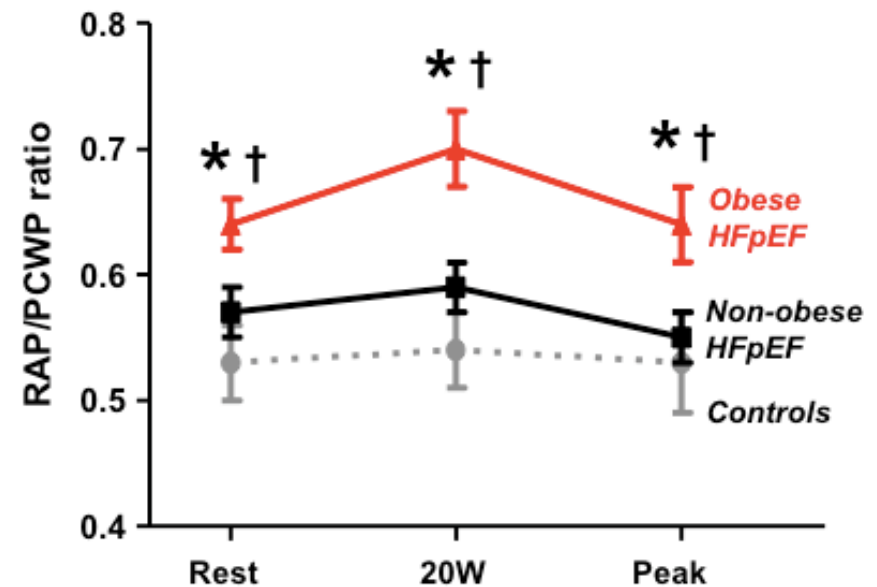
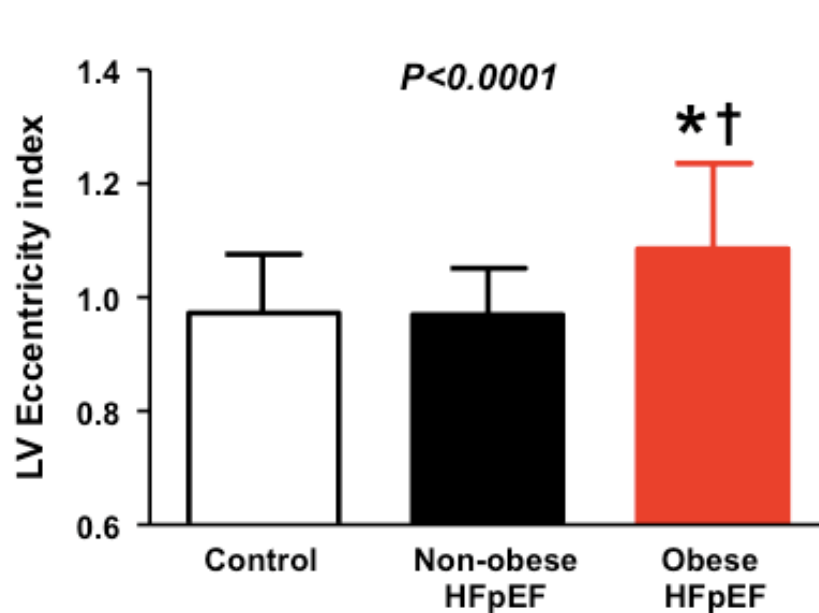
What is HFpEF?



Obese HFpEF phenotype

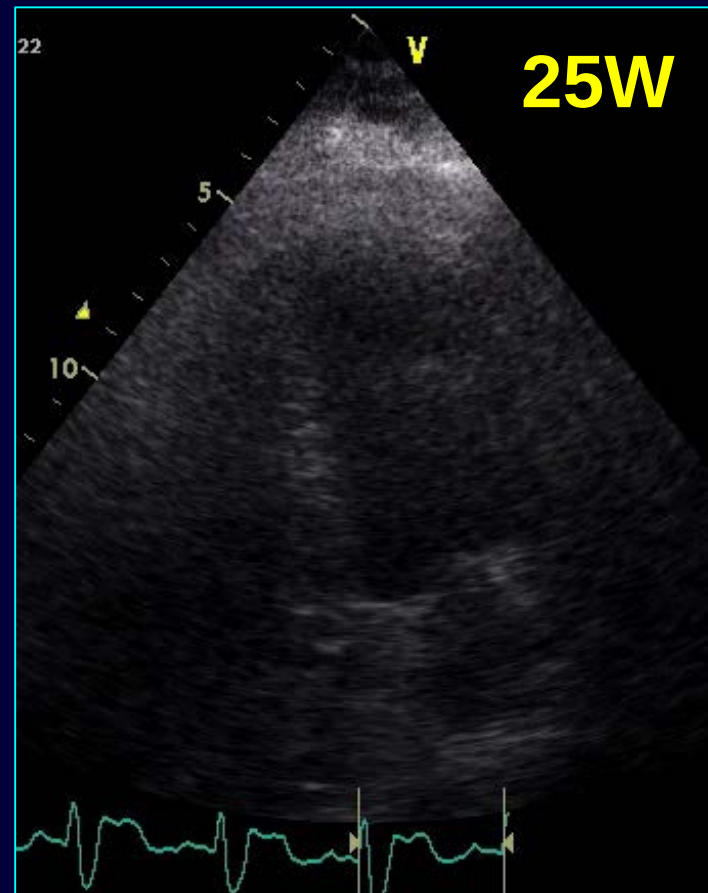


Obese HFpEF phenotype

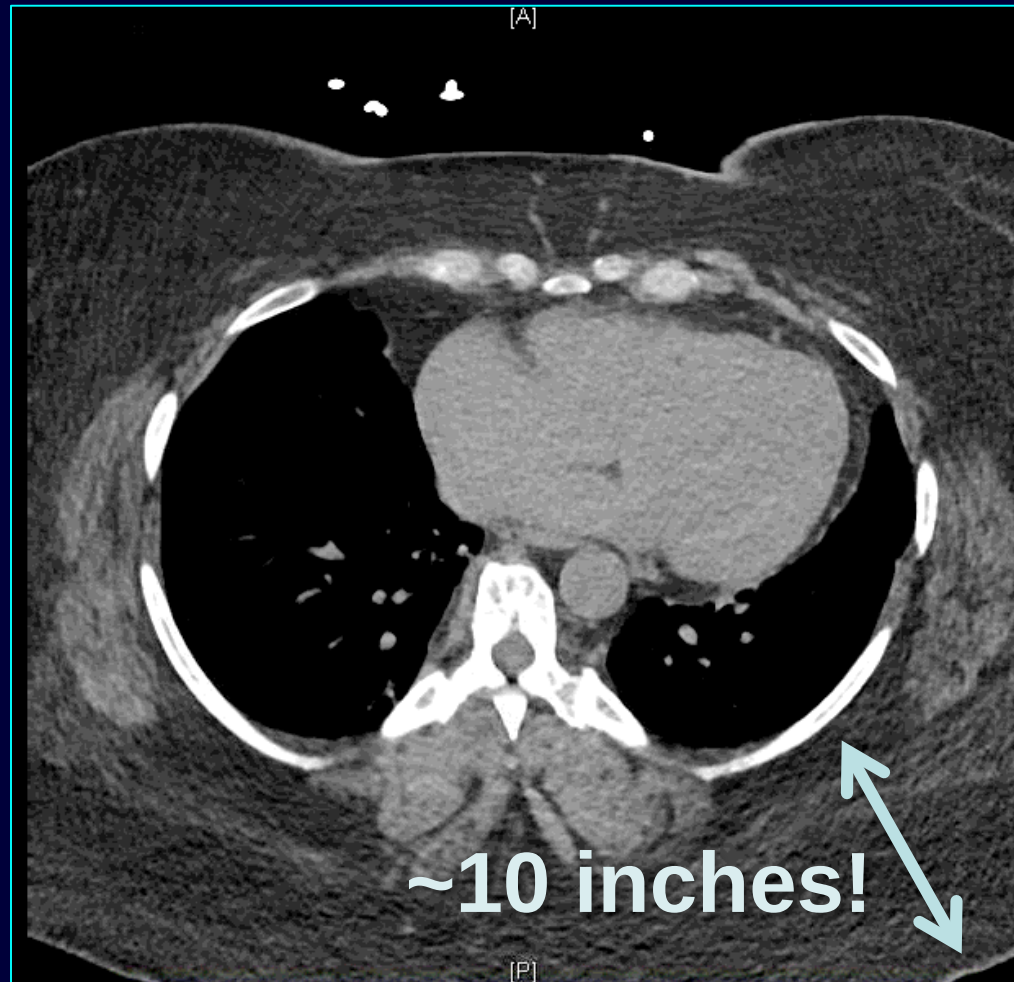


61-year-old woman with HFpEF

BMI = 56 kg/m², RAP = 18 mmHg, PCWP = 26 mmHg



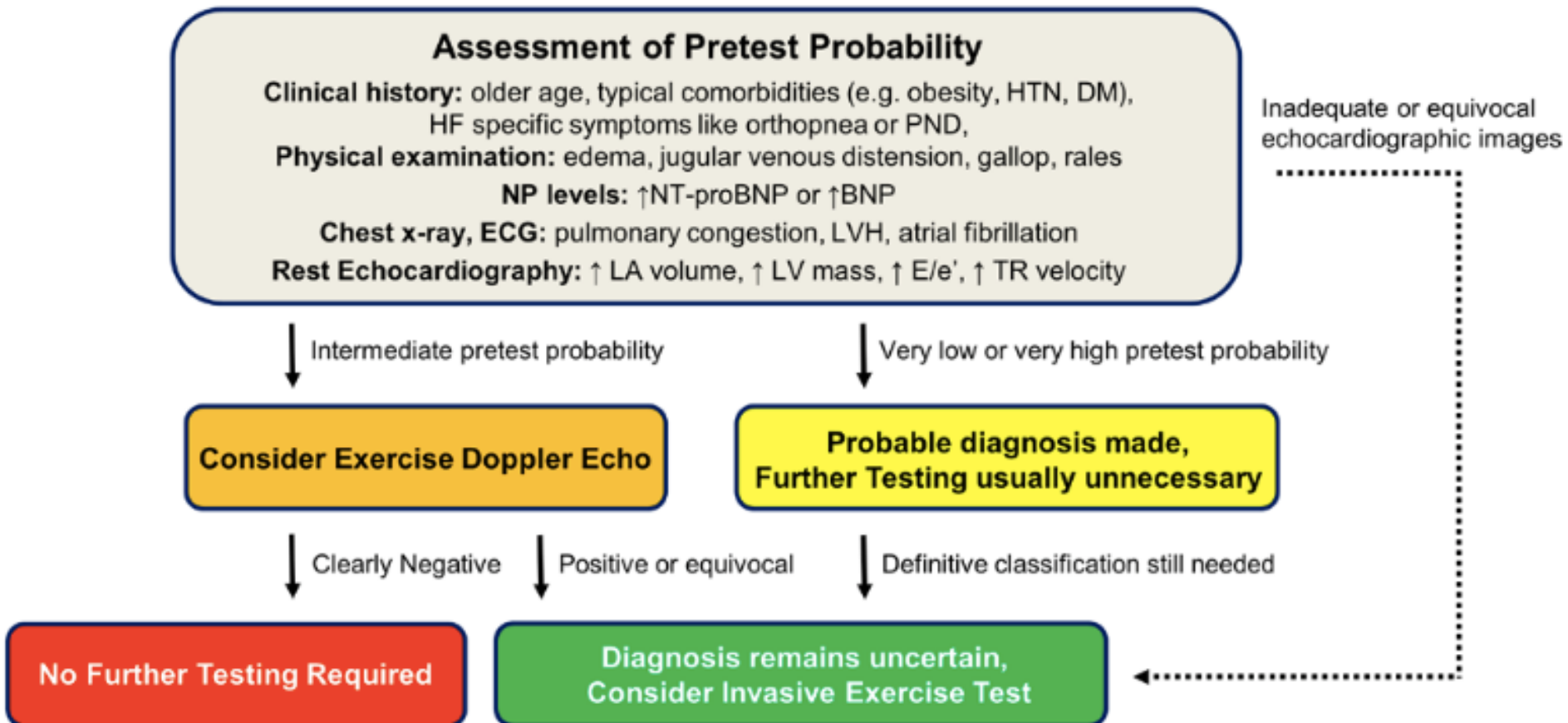
61-year-old woman with HFpEF



What is HFpEF?

- Signs and symptoms of HF (dyspnea, exercise intolerance, fluid retention)
- Preserved LVEF (>45-50%)
- Evidence of elevated LV filling pressures at rest or during exercise
- Evidence of a cardiac-predominant problem (not an extra-cardiac cause)
- Exclude: infiltrative, genetic, valvular, toxin, pericardial, ischemic etiology

Diagnostic approach to HFpEF



Diagnostic approach to HFpEF

Assessment of Pretest Probability

Clinical history: older age, typical comorbidities (e.g. obesity, HTN, DM),
HF specific symptoms like orthopnea or PND,

Physical examination: edema, jugular venous distension, gallop, rales

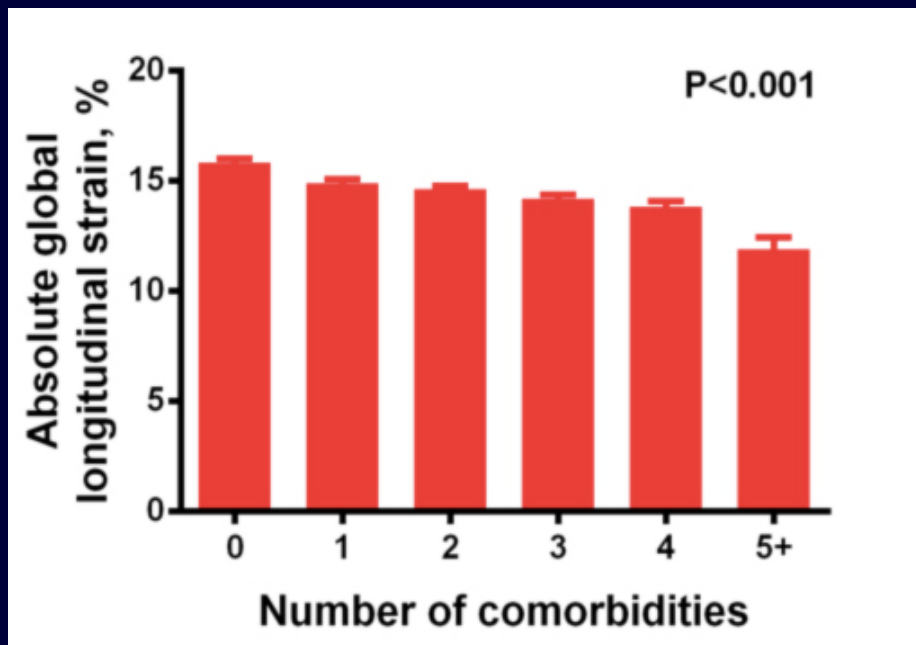
NP levels: ↑NT-proBNP or ↑BNP

Chest x-ray, ECG: pulmonary congestion, LVH, atrial fibrillation

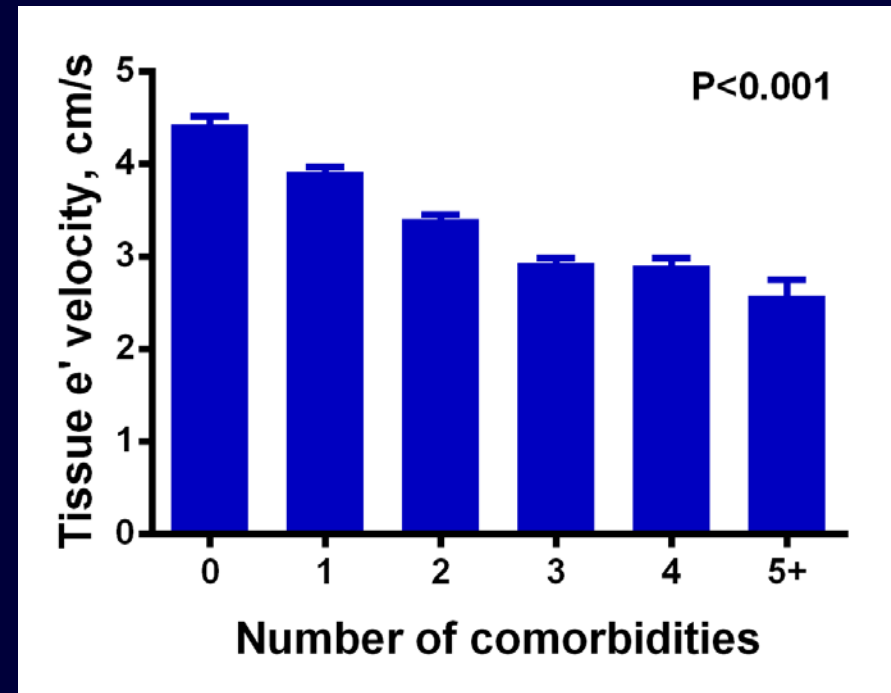
Rest Echocardiography: ↑ LA volume, ↑ LV mass, ↑ E/e', ↑ TR velocity

Comorbidity burden → myocardial dysfunction

Longitudinal systolic function worsens with increasing number of risk factors



Diastolic function worsens with increasing number of risk factors



Diagnosis of HFpEF is easy

- Signs and symptoms of HF
- LVEF $>45-50\%$
- Evidence of increased left-sided filling pressures at rest or with stress
 - » Elevated BNP
 - » Left atrial enlargement/dysfunction
 - » Elevated E/e' ratio (at rest or with exercise)
 - » $\uparrow$ PCWP or LVEDP (at rest or with exercise)

ESC criteria for HFpEF Dx

- Signs and symptoms of HF
- LVEF $>50\%$
- BNP >35 pg/ml or NTproBNP >125 pg/ml
- At least one of the following
 - » LVH and/or LAE
 - » LV diastolic dysfunction
 - Average $E/e' \geq 13$ or
 - Average $e' < 9$ cm/s

ASE/EACVI “diastolic dysfunction”

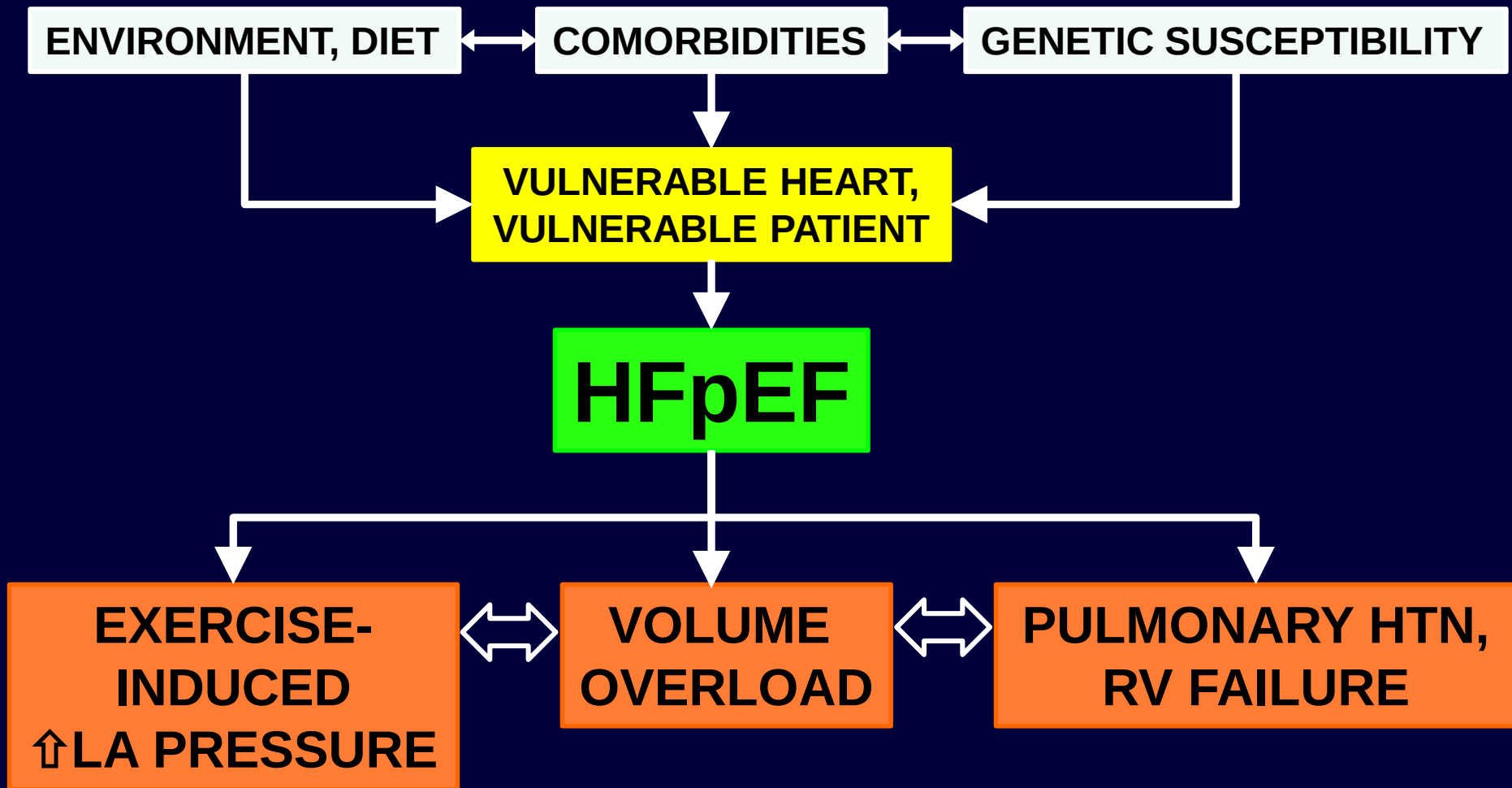
- 4 key criteria:
 - » Average $E/e' > 14$
 - » Septal $e' < 7$ cm/s *or* lateral $e' < 10$ cm/s
 - » Peak TR velocity > 2.8 m/s
 - » LA volume index > 34 ml/m²
- 0-1 criteria: No HFpEF
- 2 criteria: indeterminate HFpEF
- 3-4 criteria: HFpEF

HFpEF diagnostic toolbox



- Physical exam
- Biomarkers
- Echocardiography
- Invasive exercise hemodynamics
- Coronary evaluation
- Cardiac MRI
- Cardiopulmonary exercise test

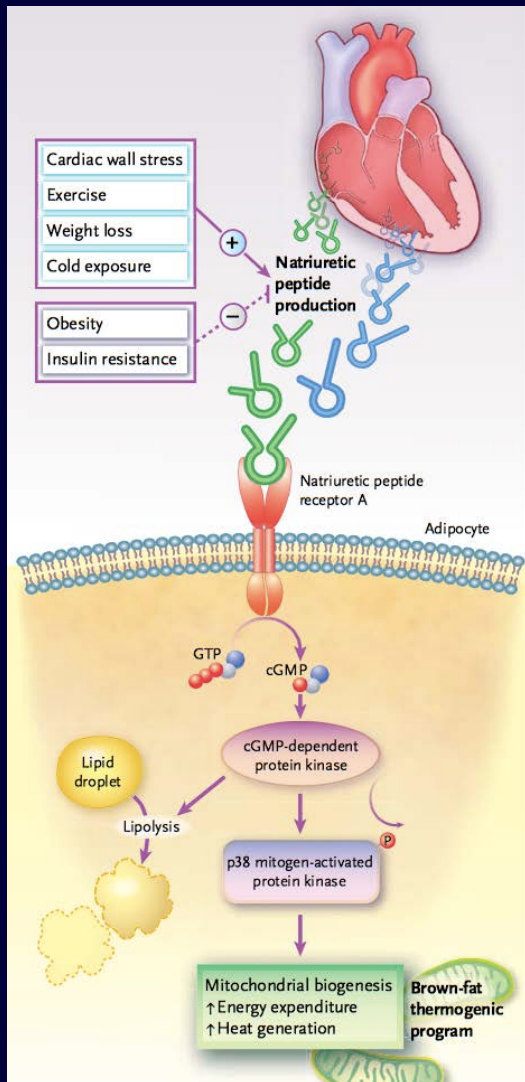
Types of HFpEF presentation



Lesson #1:

**Don't use BNP
to rule out
HFpEF**

BNP deficiency syndrome

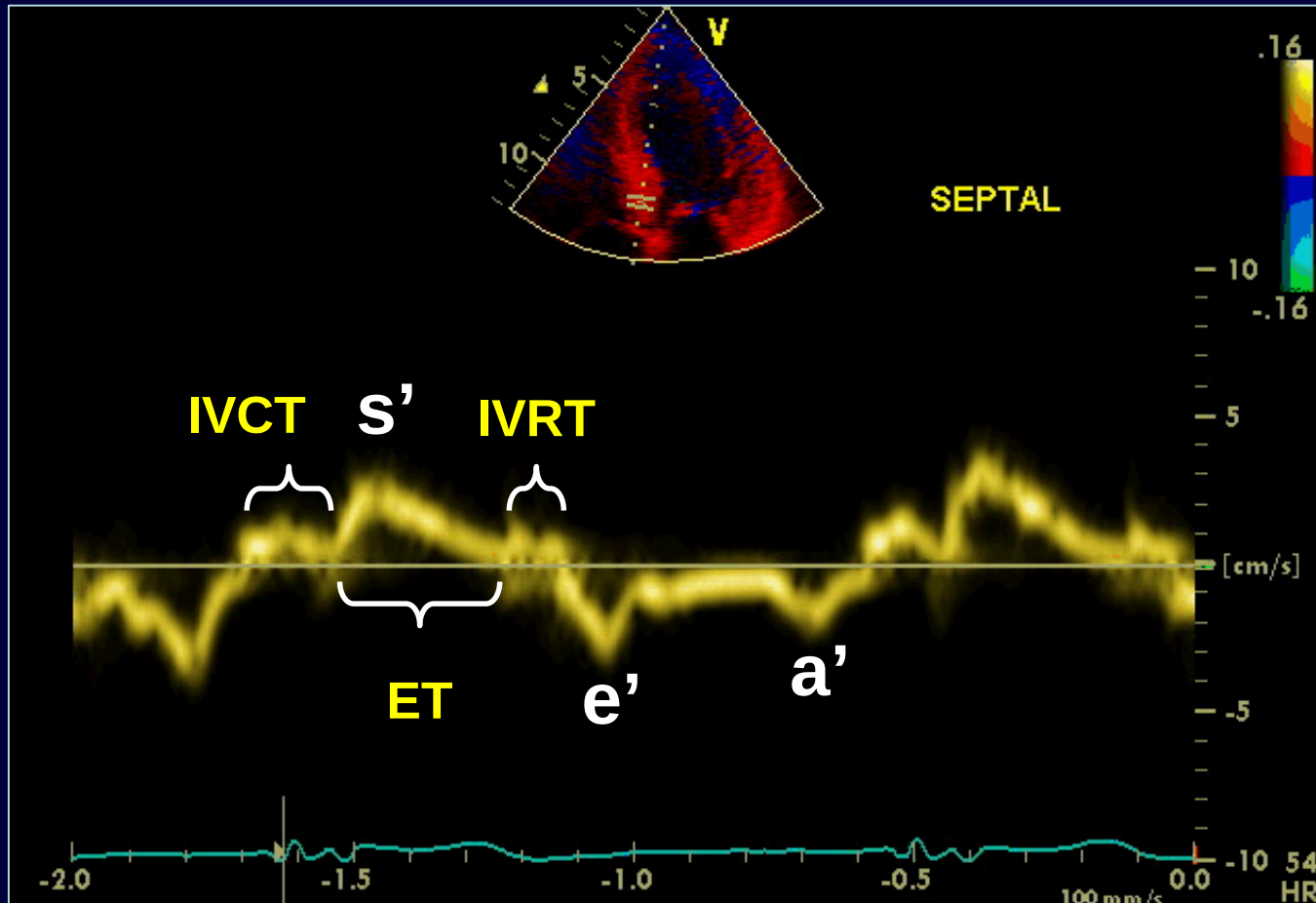


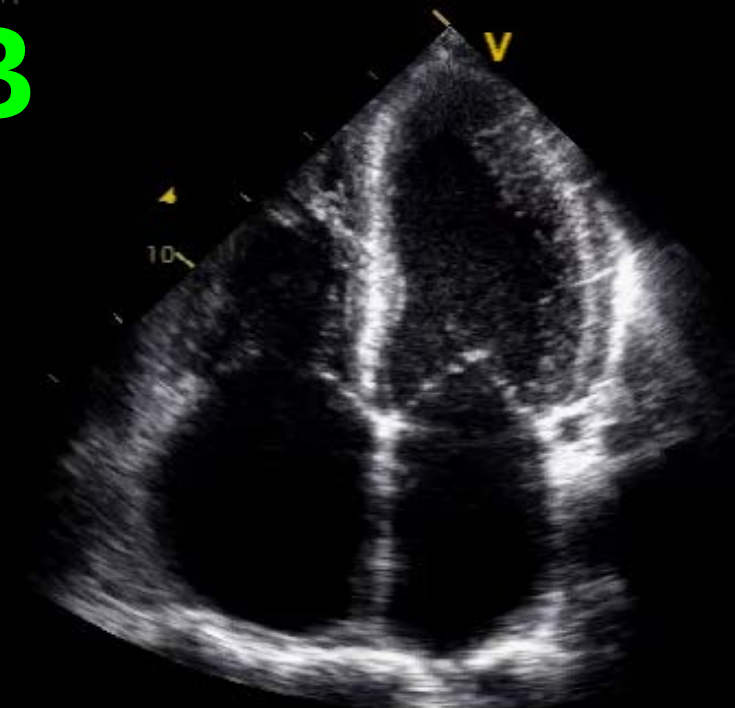
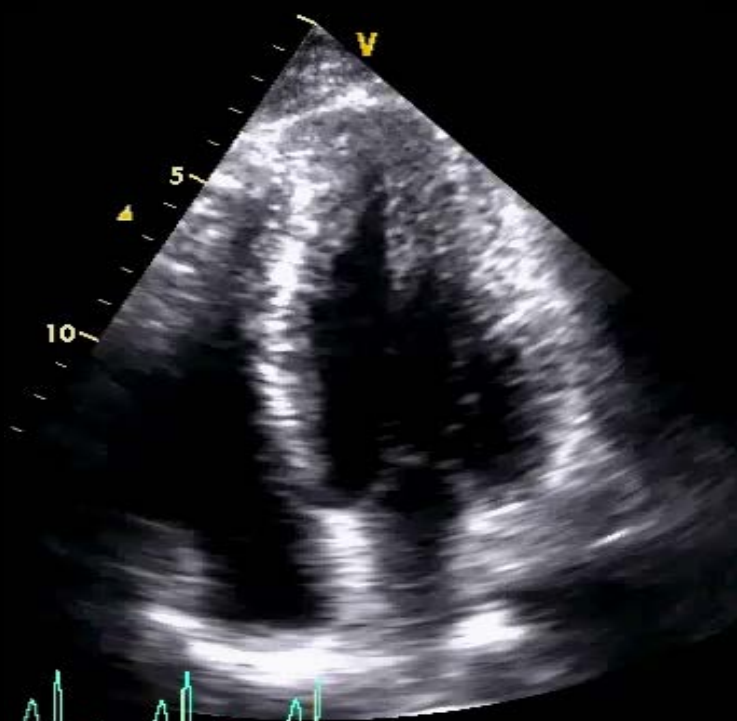
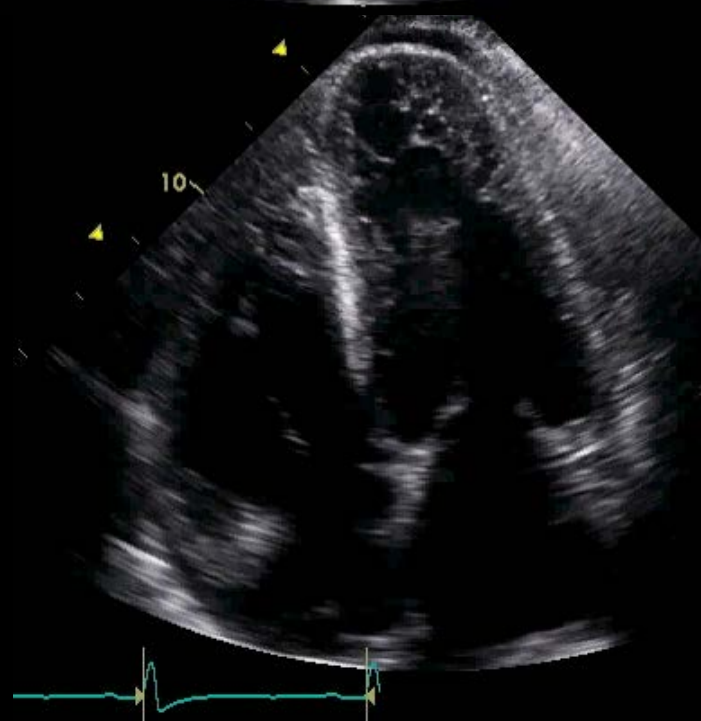
- BNP < 100 pg/ml in 30% of HFpEF patients with confirmed $\uparrow$ PCWP
 - » Adipose tissue: increased NP clearance, reduced NP production
 - » HFpEF: lack of LV wall stress stimulus
 - Wall stress = pressure x chamber radius / wall thickness
 - » Other causes of low BNP:
 - Genetic (*NPPA*, *NPPB* SNPs)
 - Insulin resistance
 - Increased androgens
 - African ancestry

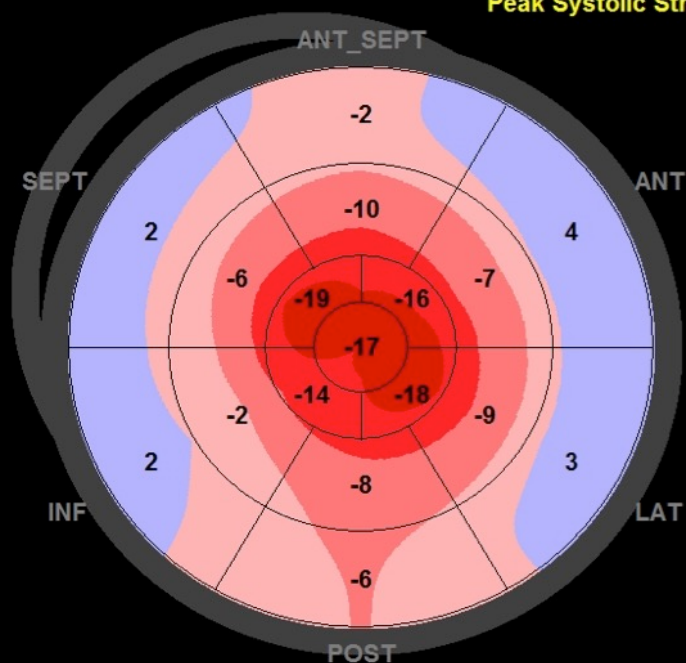
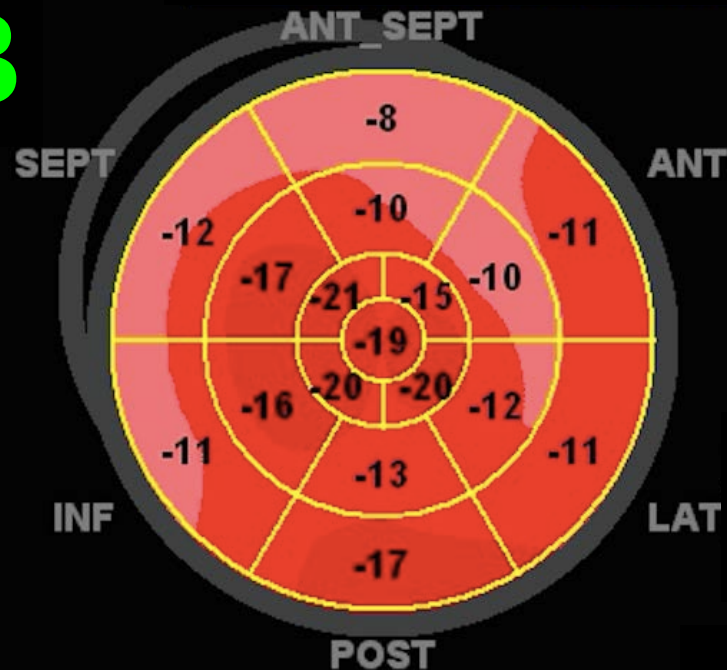
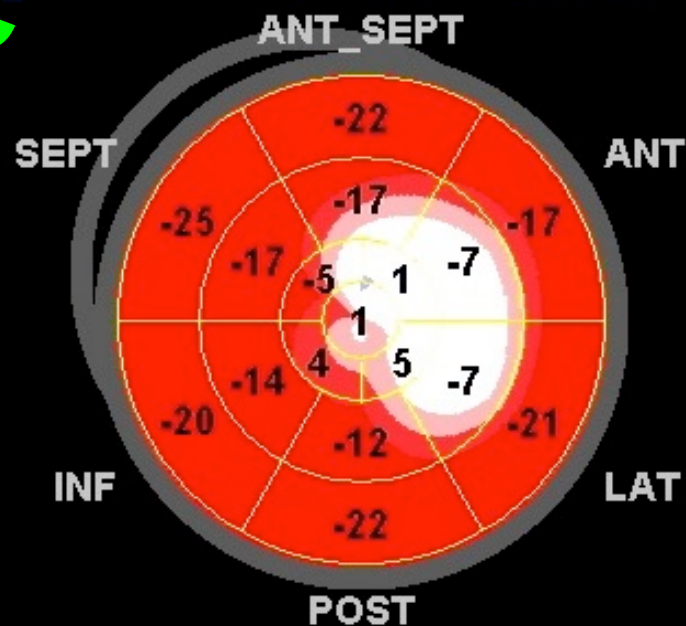
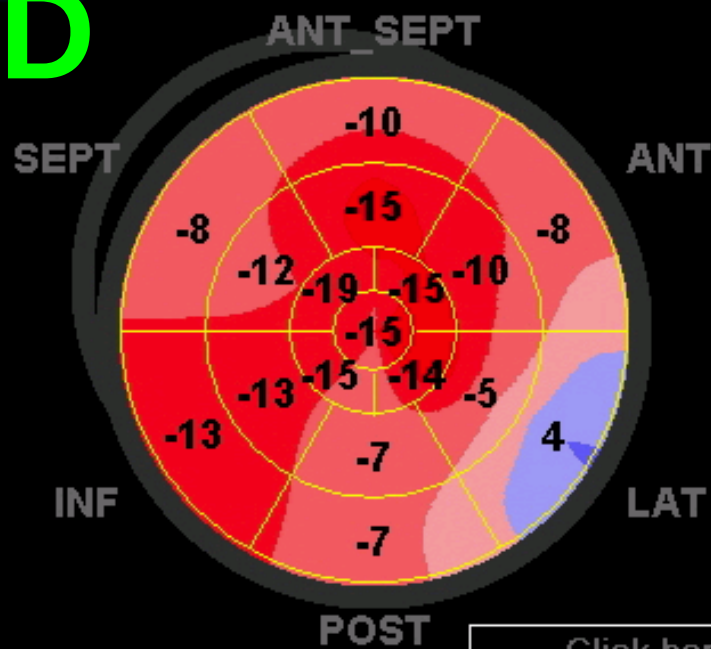
Anjan V...Shah SJ. *Am J Cardiol* 2012
Bordicchia et al. *J Clin Invest* 2012; Wang TJ. *NEJM* 2012

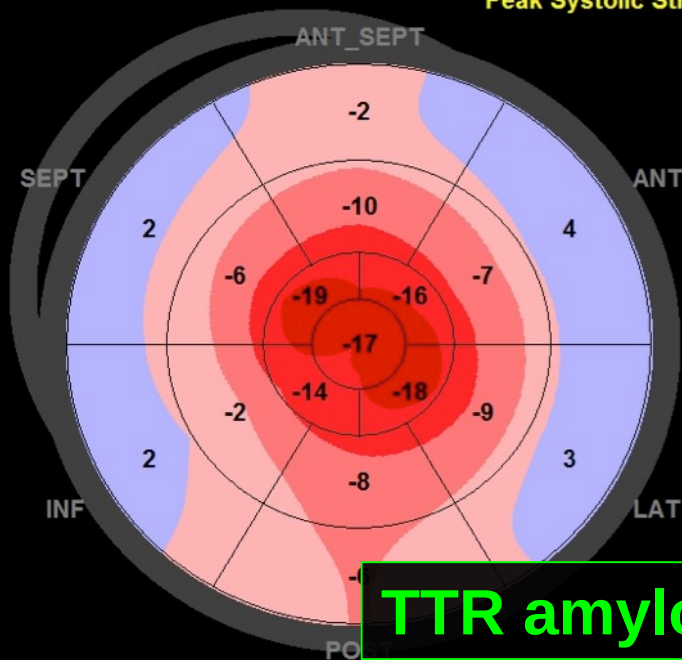
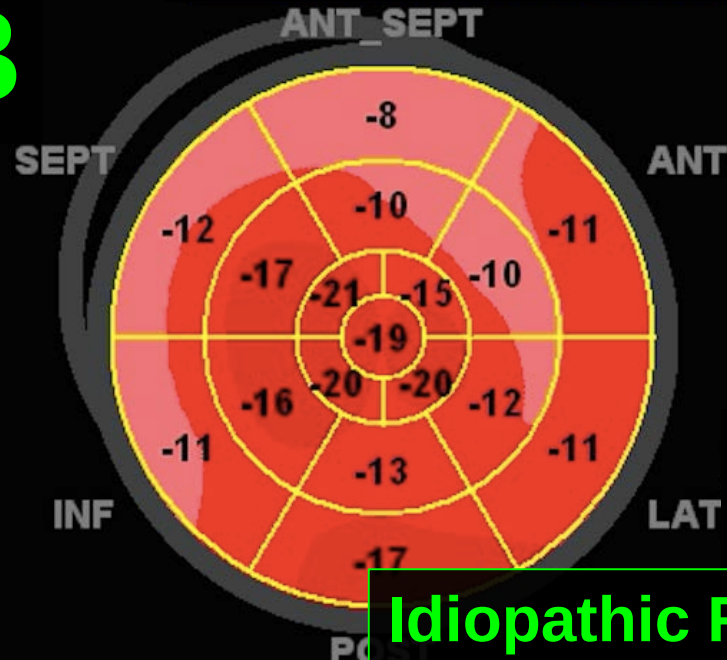
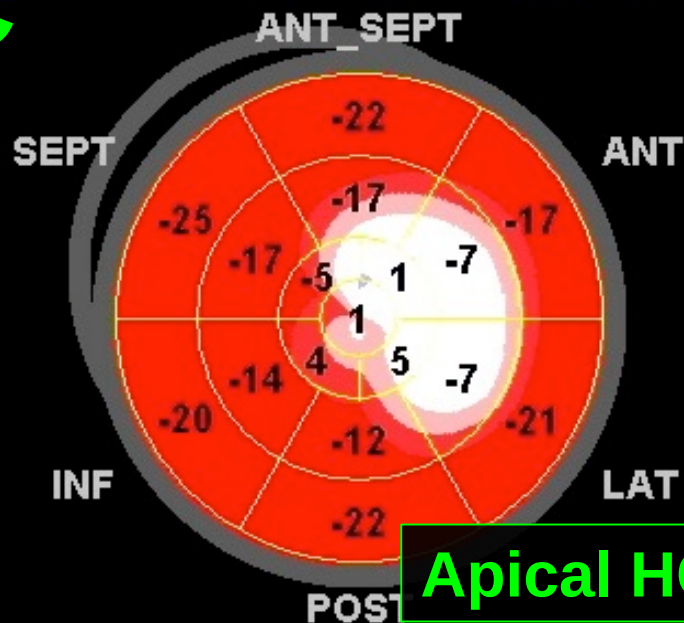
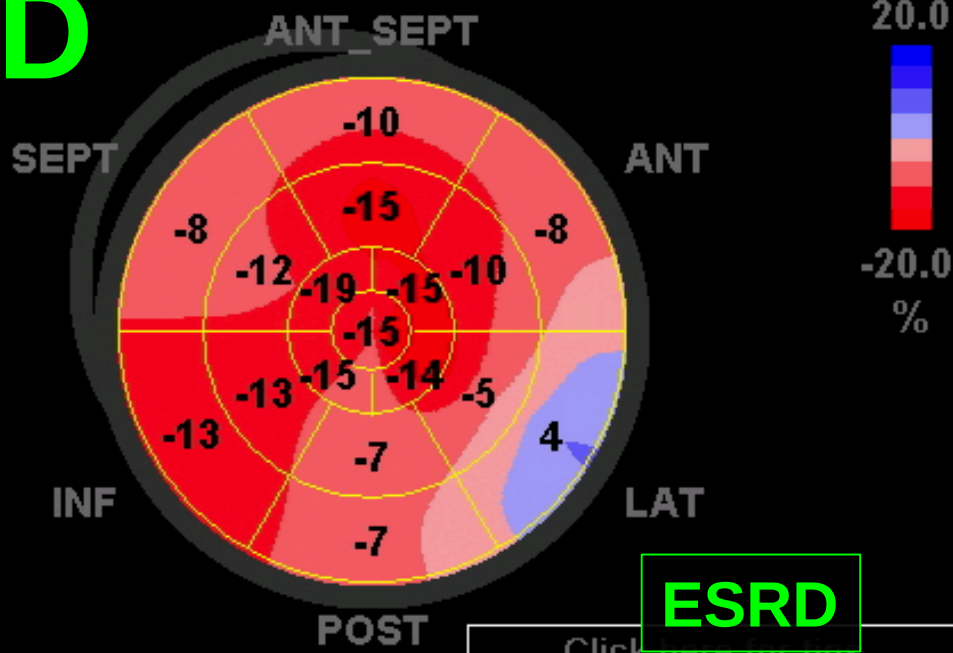
Lesson #2:
Echo is the
cornerstone

Echo: determine etiology, look for an intrinsic myocardial problem



A**B****C****D**

A**Peak Systolic Strain****B****C****Peak Systolic Strain****D****Peak Systolic Strain**[Click here for tips](#)

A**Peak Systolic Strain****B****C****Peak Systolic Strain****D****Peak Systolic Strain**[Click here for tips](#)

**Look at the echo
yourself for clues**

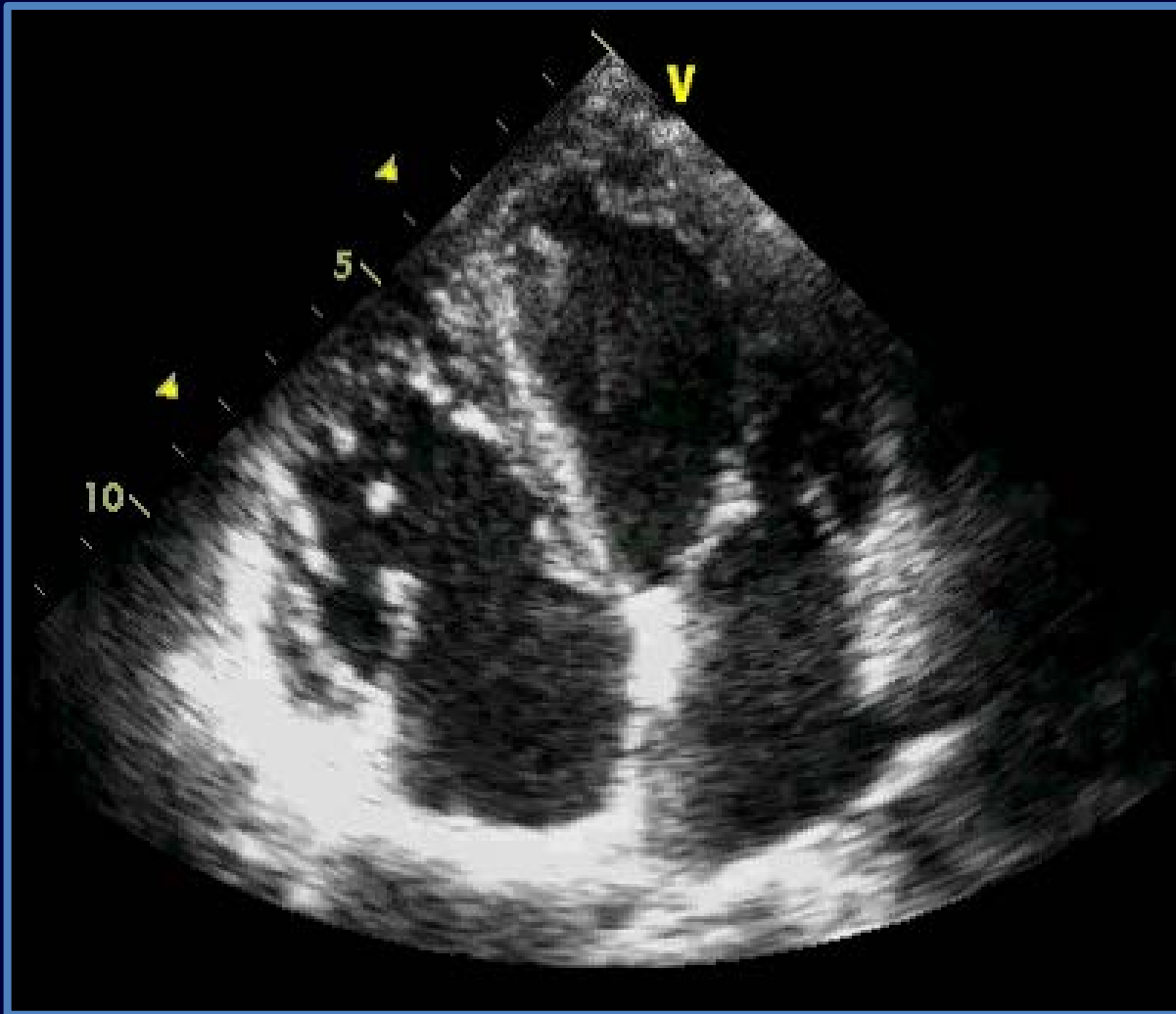
Case #1: 62-year-old woman with DM2, HTN, Sjogren syndrome, persistent SOB

- Cardiologist ordered stress echo/Doppler:
 - » Normal LVEF
 - » Normal diastolic function
 - » No LVH
 - » Normal atrial size
 - » No wall motion abnormalities at peak exercise
- Normal BNP
- Referred to pulmonary for further eval.

Case #1: 62-year-old woman with DM2, HTN, Sjogren syndrome, persistent SOB



Case #1: 62-year-old woman with DM2, HTN, Sjogren syndrome, persistent SOB



Adenosine perfusion cardiac MRI results



Rest



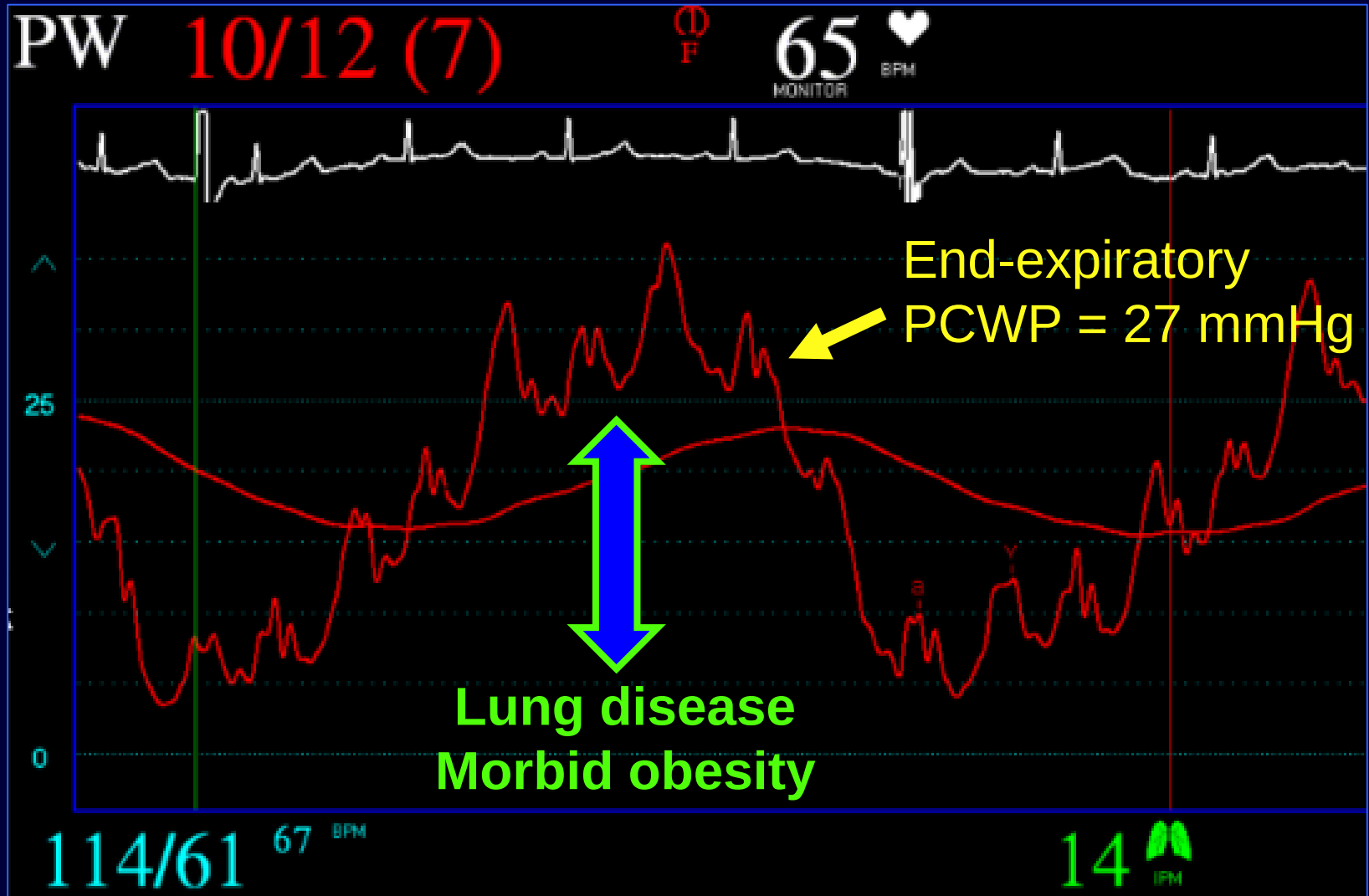
Stress

**WHEN IN DOUBT CHECK
INVASIVE HEMODYNAMICS**

Respiratory variation in PCWP



Respiratory variation in PCWP



Lesson #3:

Know your
zebras

Case #3: 50-year-old woman with SOB

Low voltage, pseudoinfarct pattern

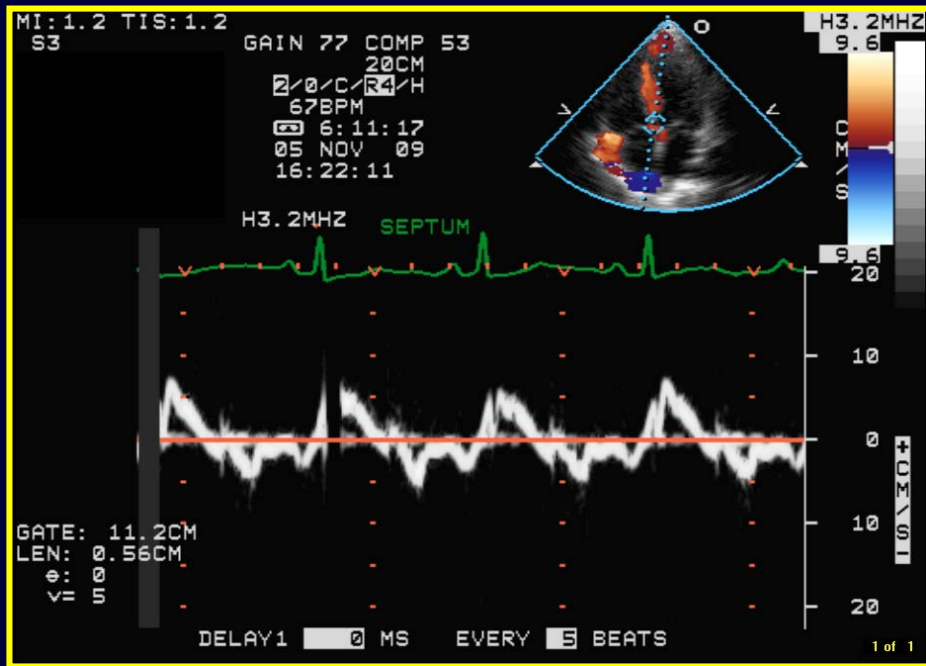
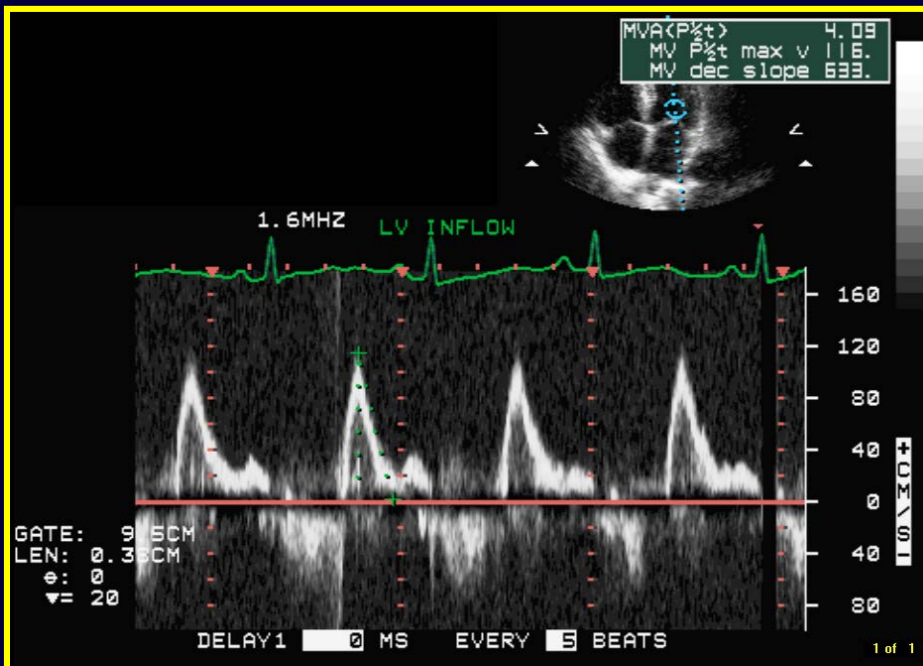
Case #3: 50-year-old woman with SOB



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

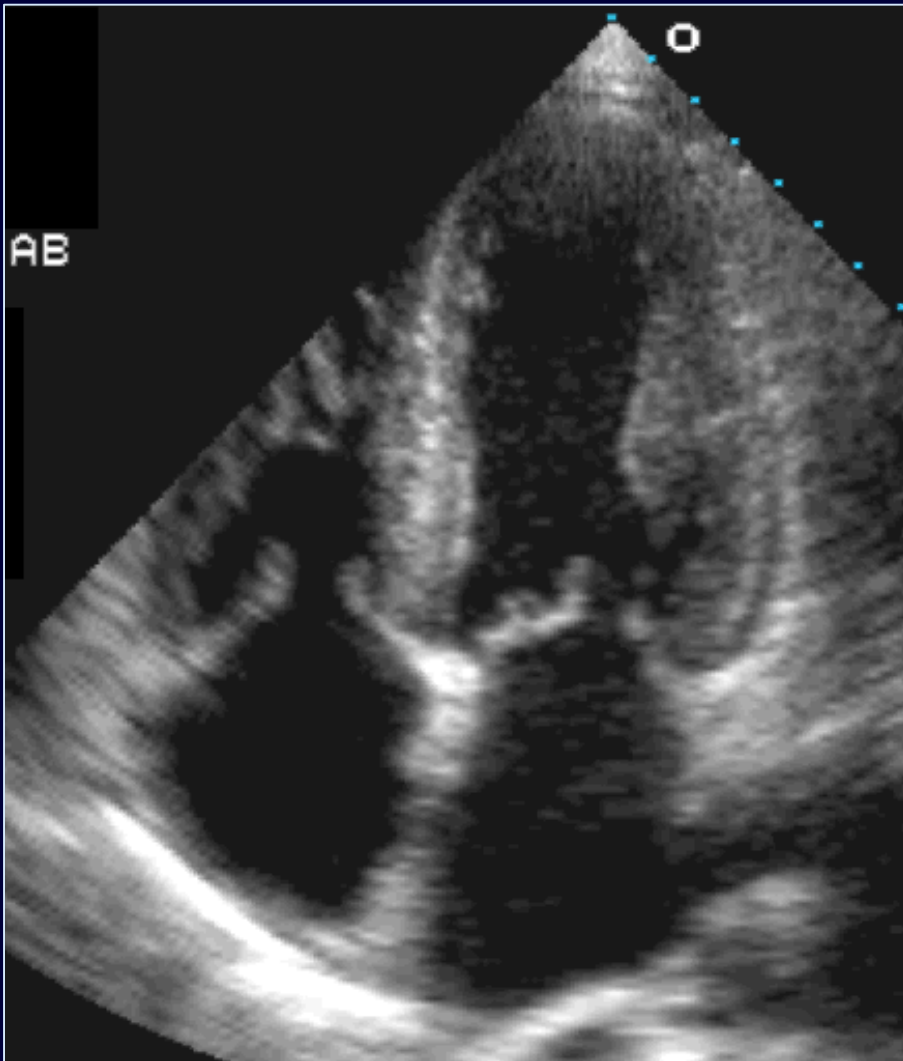
Case #3: 50-year-old woman with SOB

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



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

Typical echo findings in cardiac amyloidosis



*Loss of longitudinal
cardiac function*



“Garden-variety” HFpEF



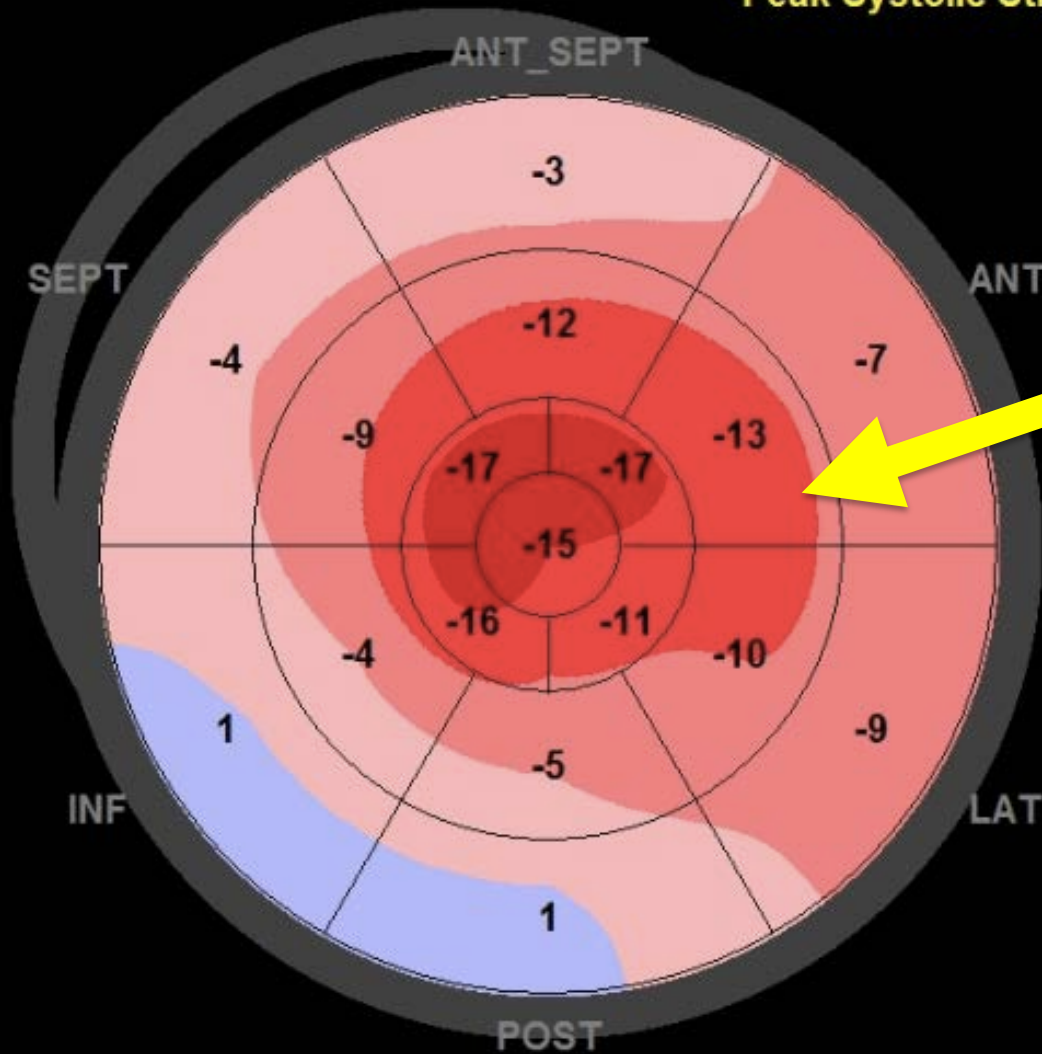
Cardiac amyloidosis

Typical echo findings



Severely reduced longitudinal tissue velocities
“5-5-5 sign”

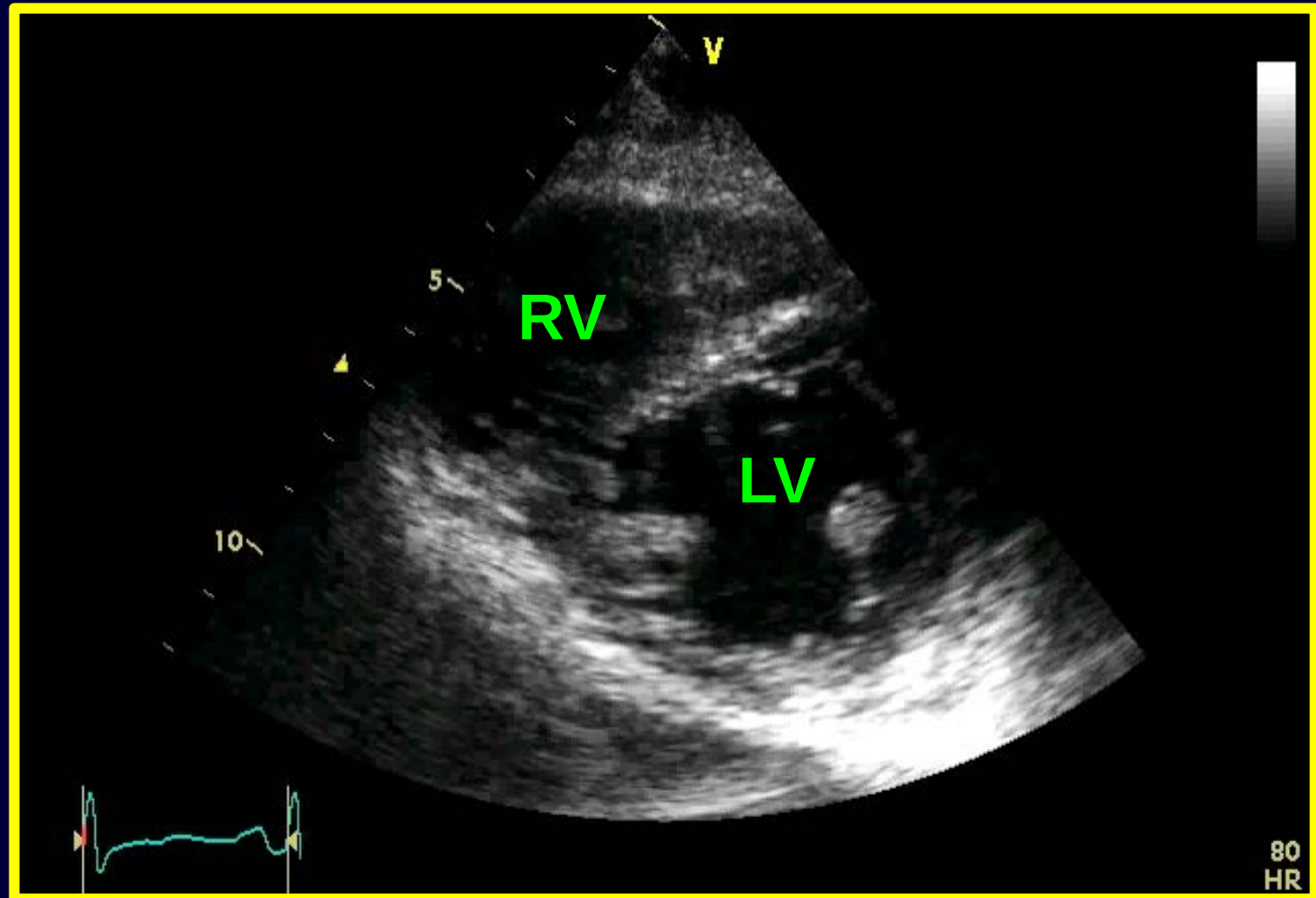
Peak Systolic Strain



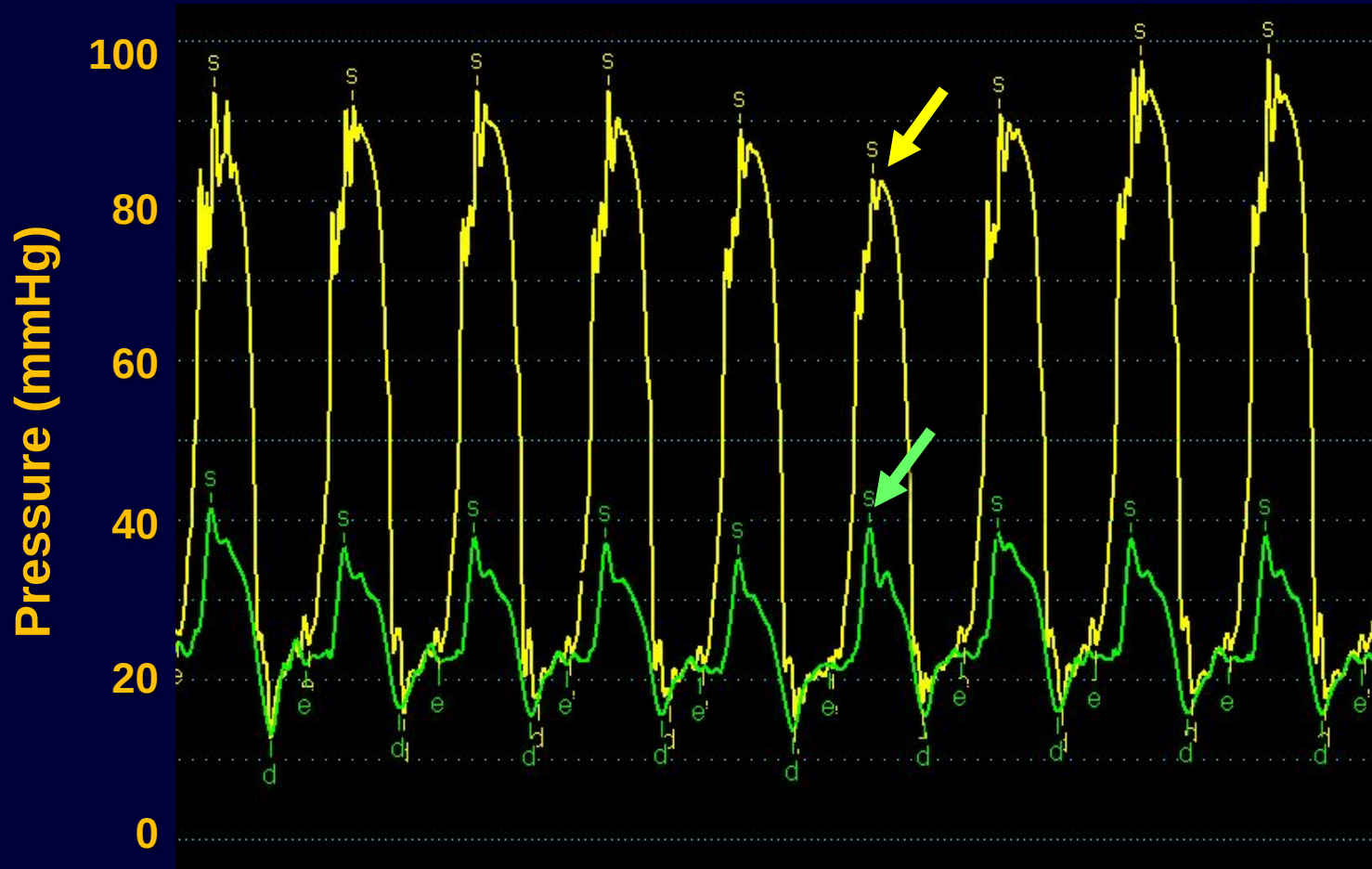
“Cherry on top”

09/10/2015-09:57:21

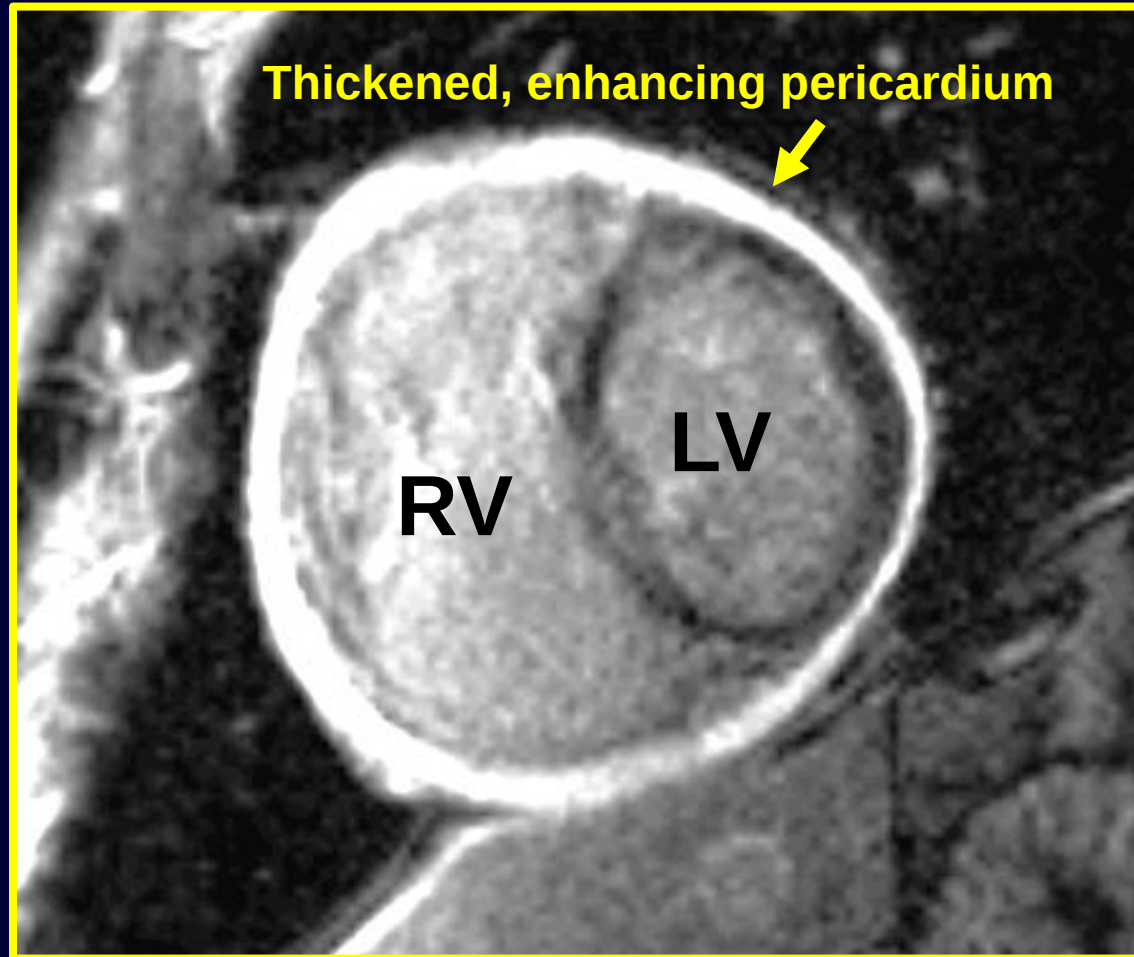
Case #4: 44-year-old man with severe SOB, ascites



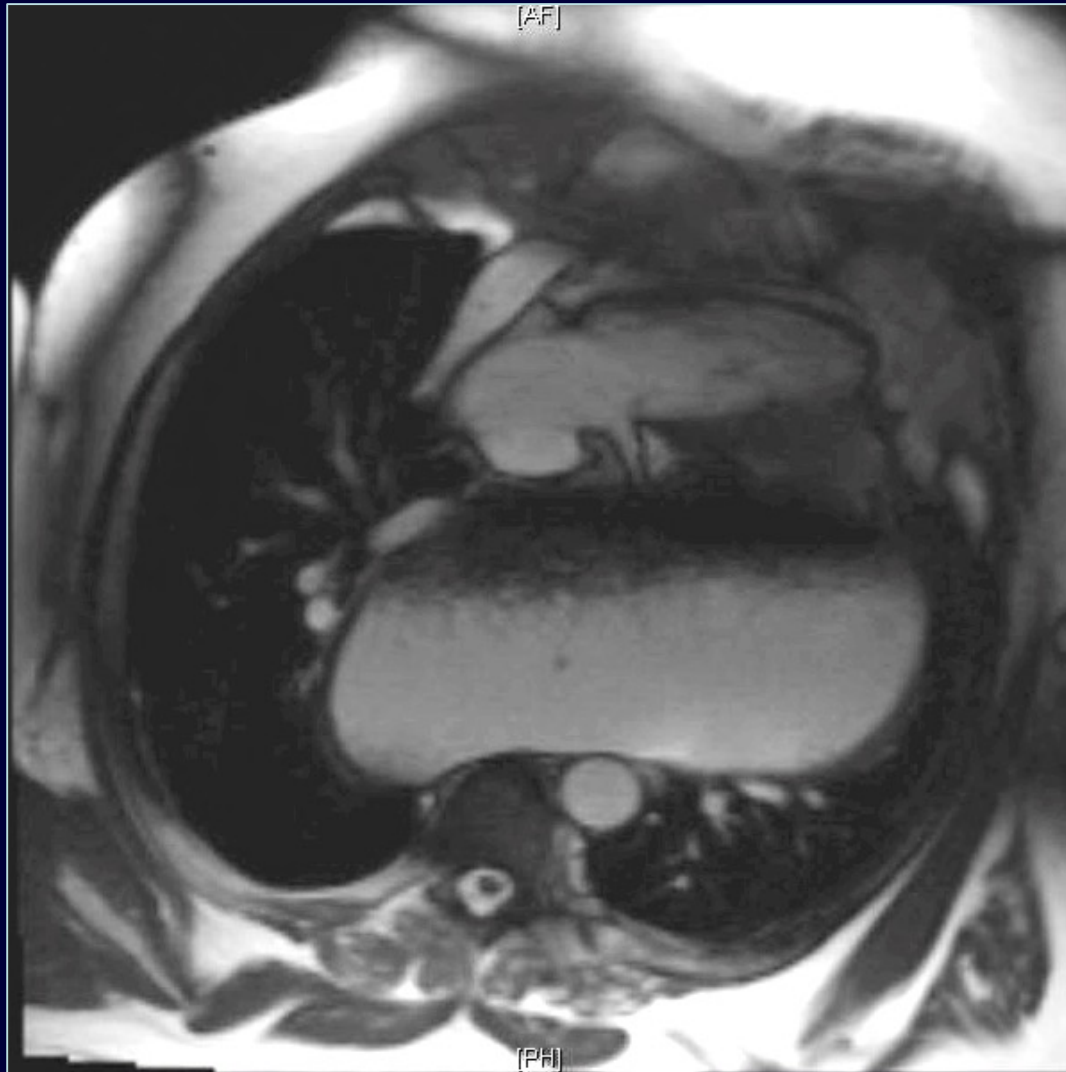
Case #4: 44-year-old man with severe SOB, ascites



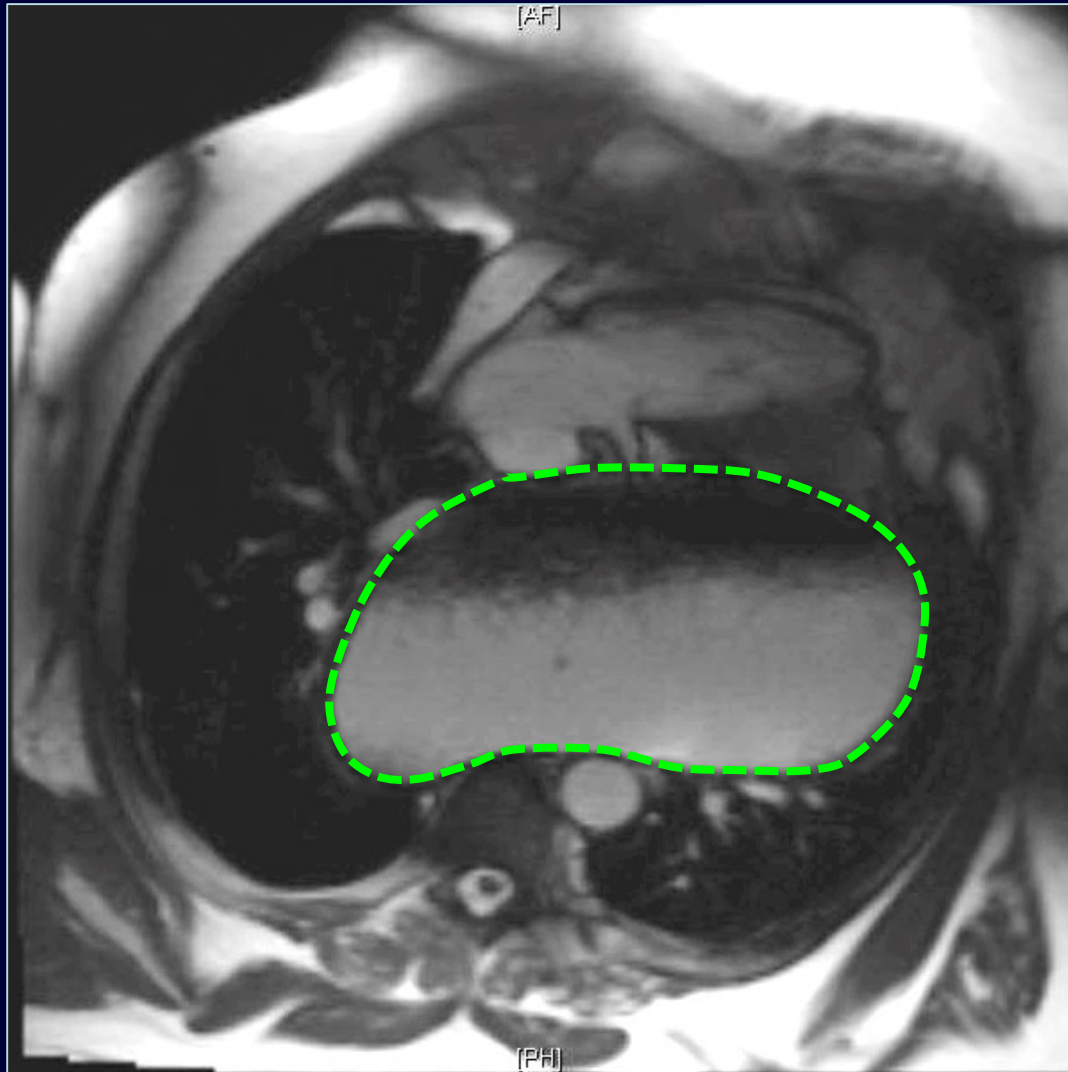
Case #4: 44-year-old man with severe SOB, ascites



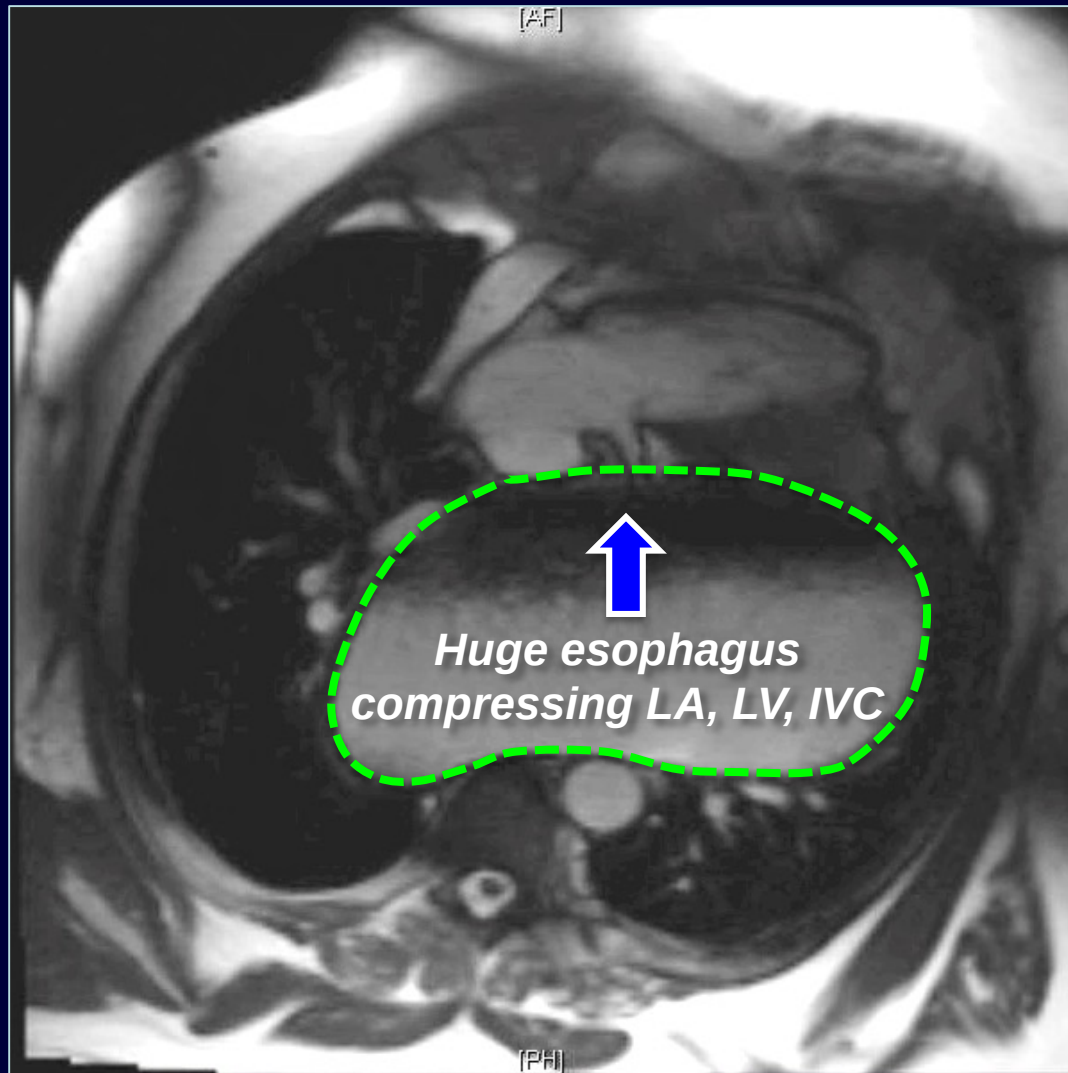
54-year-old dentist with achalasia, SOB,
severe leg swelling, normal LVEF



54-year-old dentist with achalasia, SOB,
severe leg swelling, normal LVEF



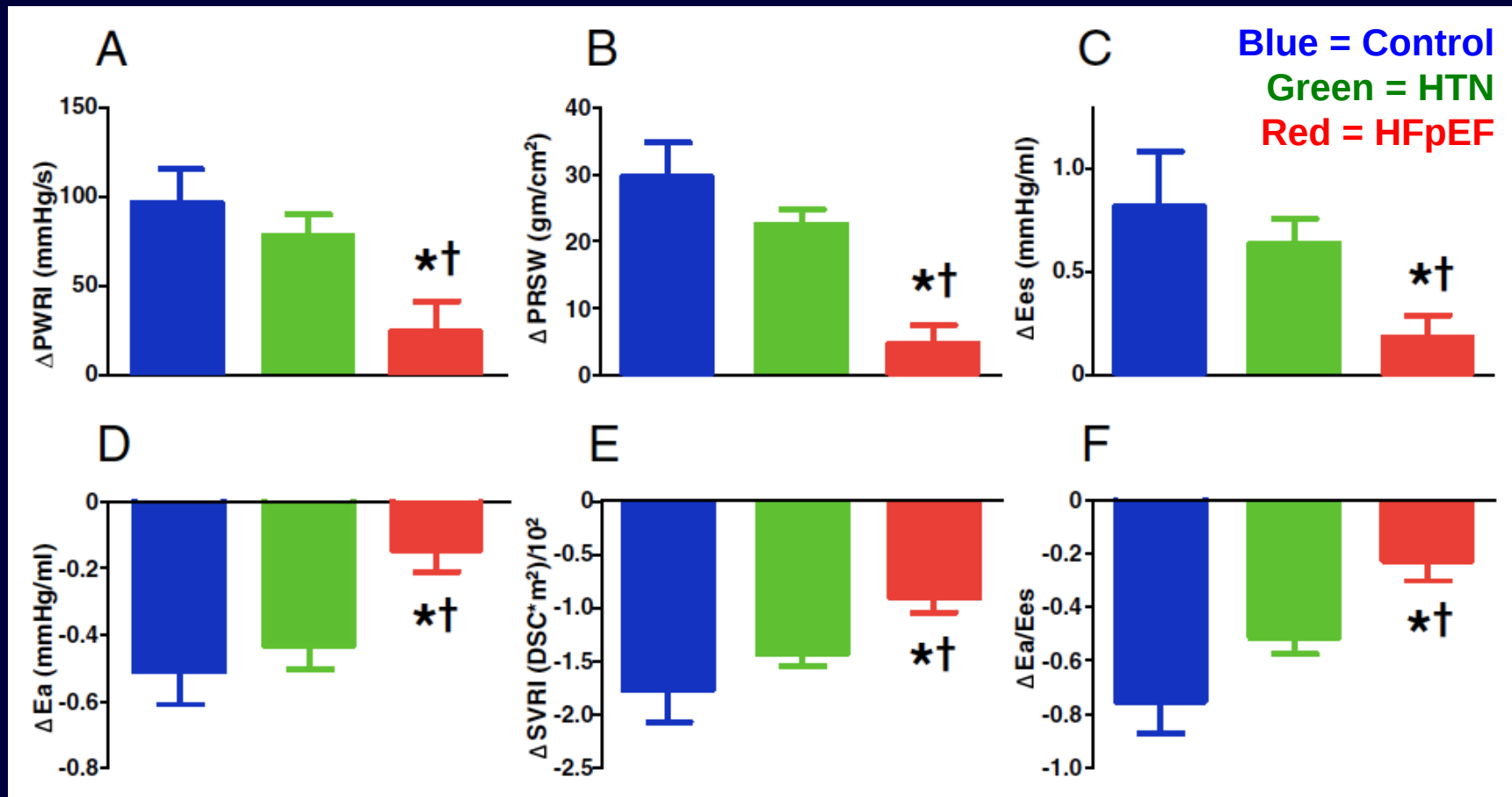
54-year-old dentist with achalasia, SOB, severe leg swelling, normal LVEF



Lesson #4: Perturb the system

HFpEF: Global CV reserve dysfxn

HFpEF: evidence of impaired CV reserve at 20W exercise

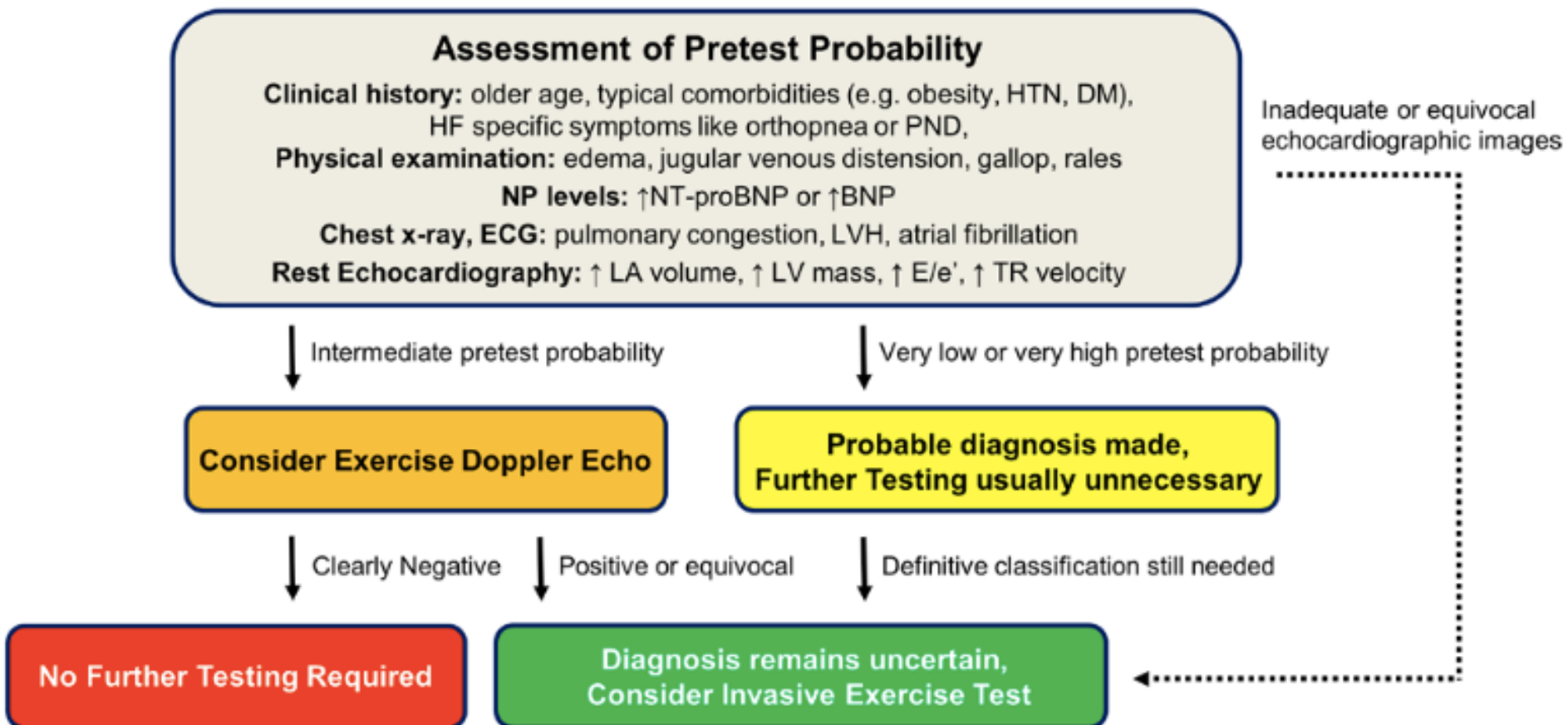


62-year-old woman with HTN, DM2, CKD presents with DOE

PEX: BP 148/52, HR 88, RR 12
JVP 10 cm, clear lungs,
RRR; nl S1 S2; No S3 , +S4;
soft systolic murmur
trace LE edema

BNP 90 pg/ml (ref. value < 100 pg/ml)

Diagnostic approach to HFpEF

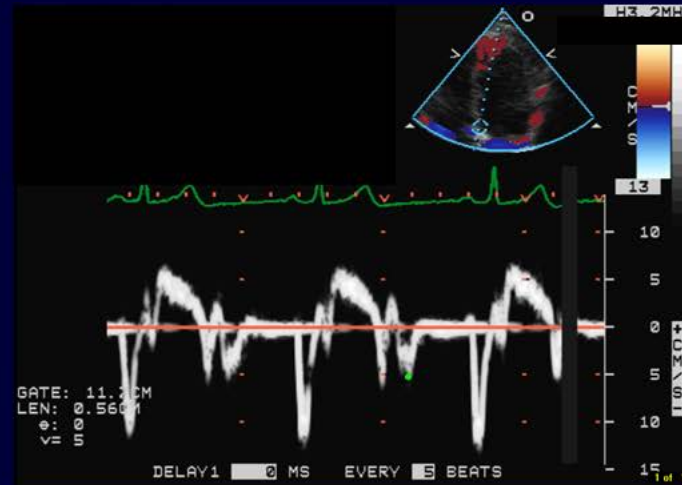


Diagnostic approach to HFpEF

Consider Exercise Doppler Echo

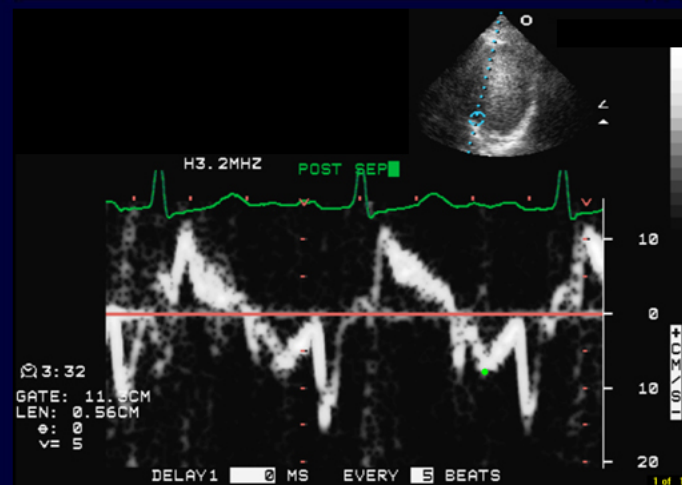
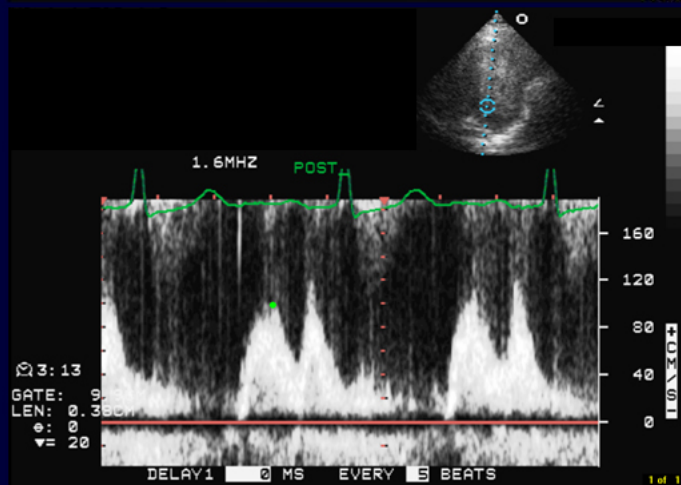
Diastolic stress echo

REST



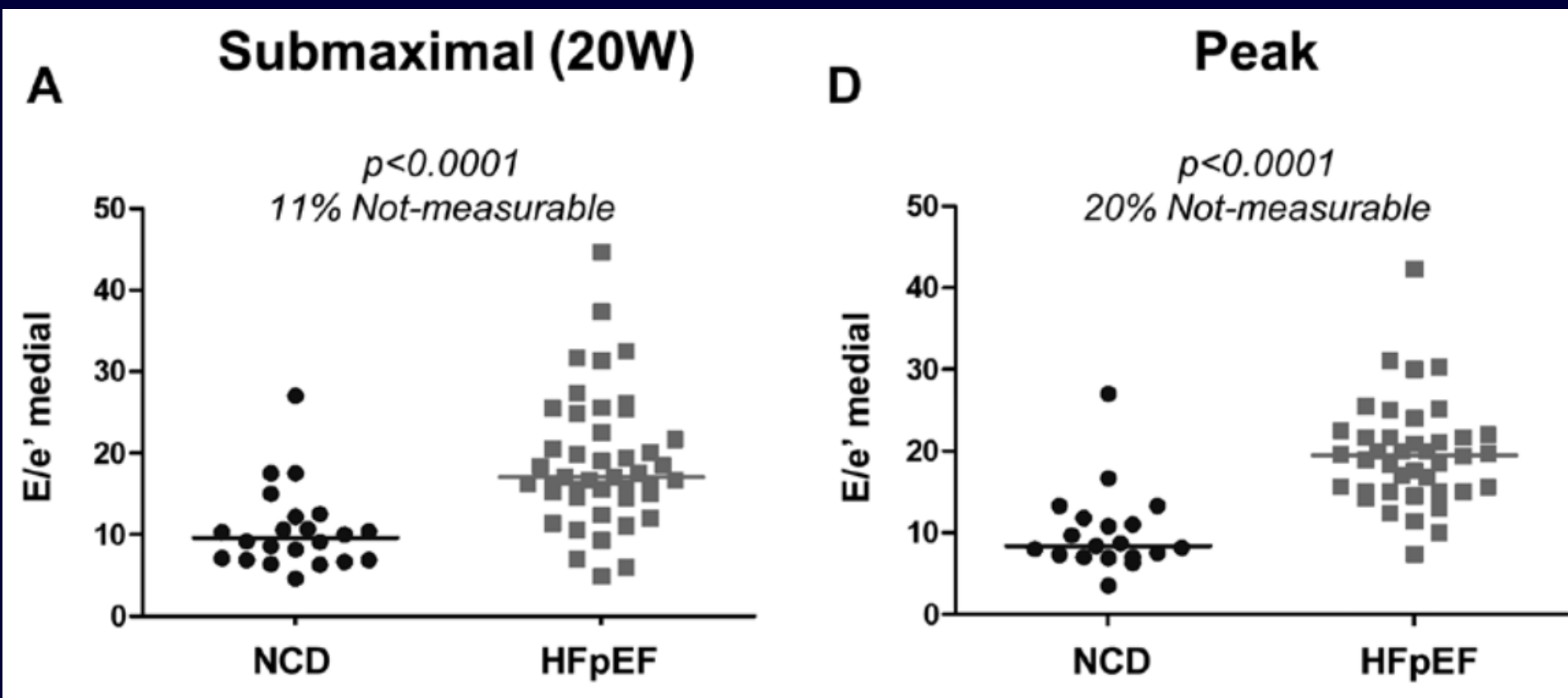
Rest
 $E/E' = 13.5$

STRESS

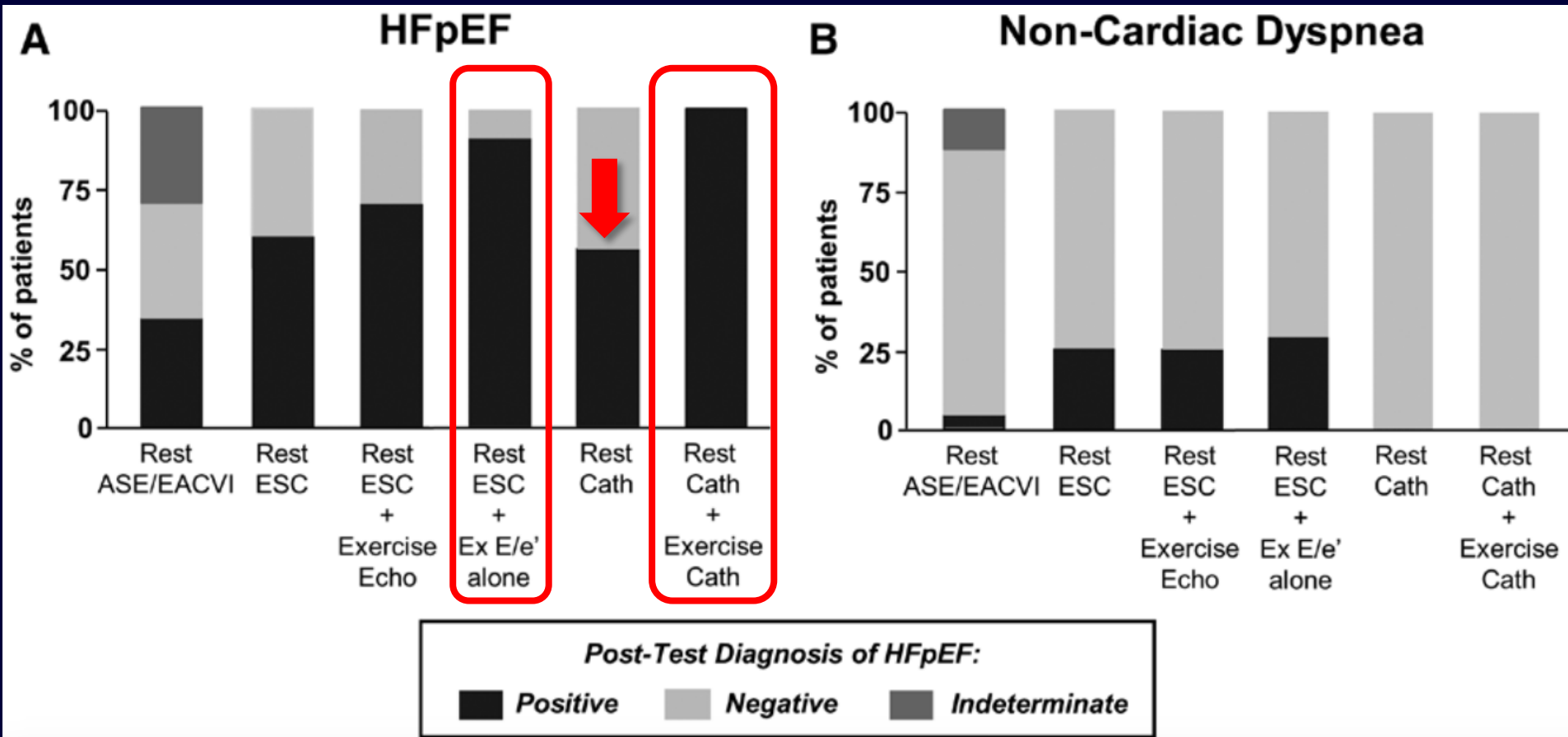


Stress
 $E/E' = 16.7$

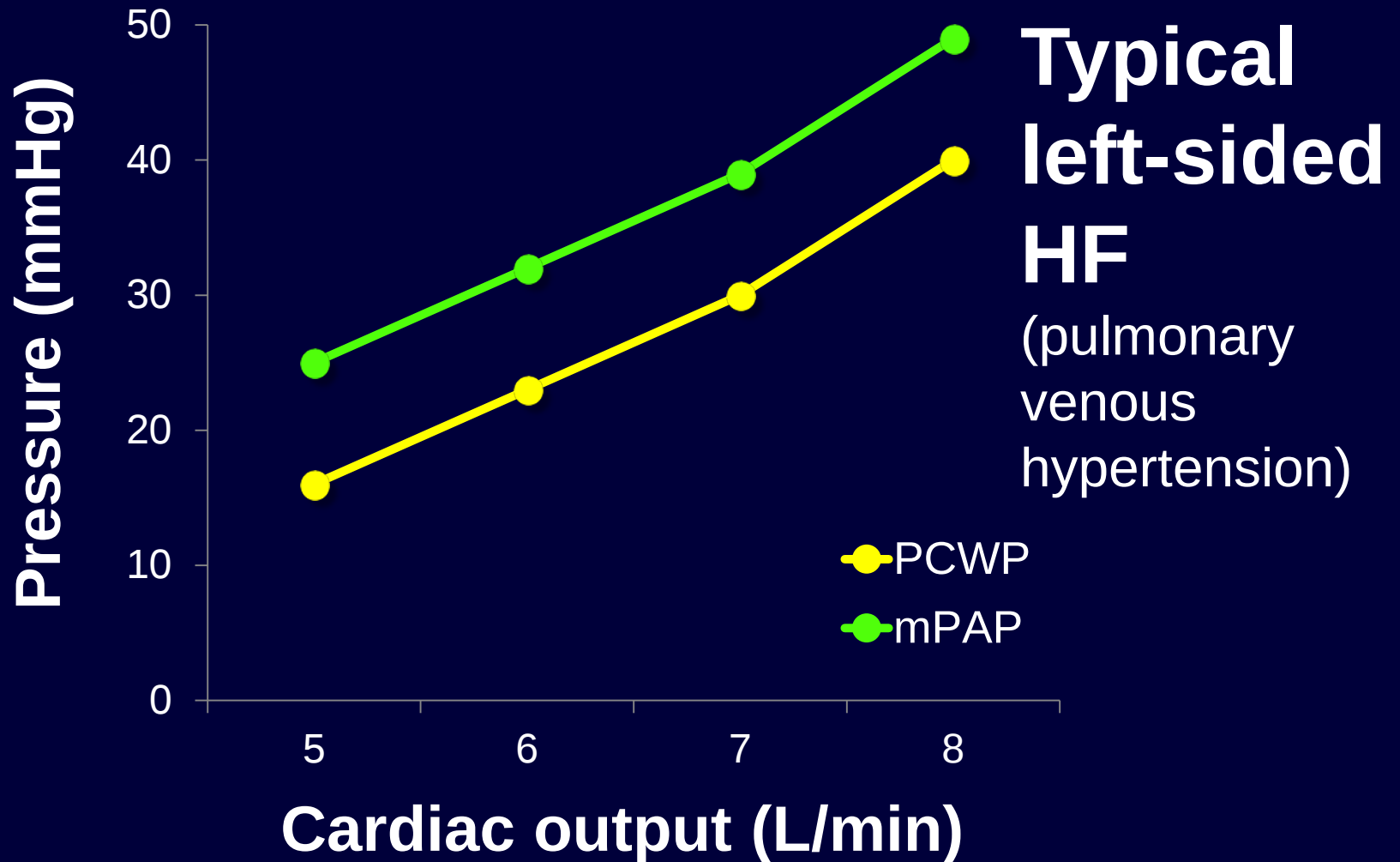
Diastolic stress echo



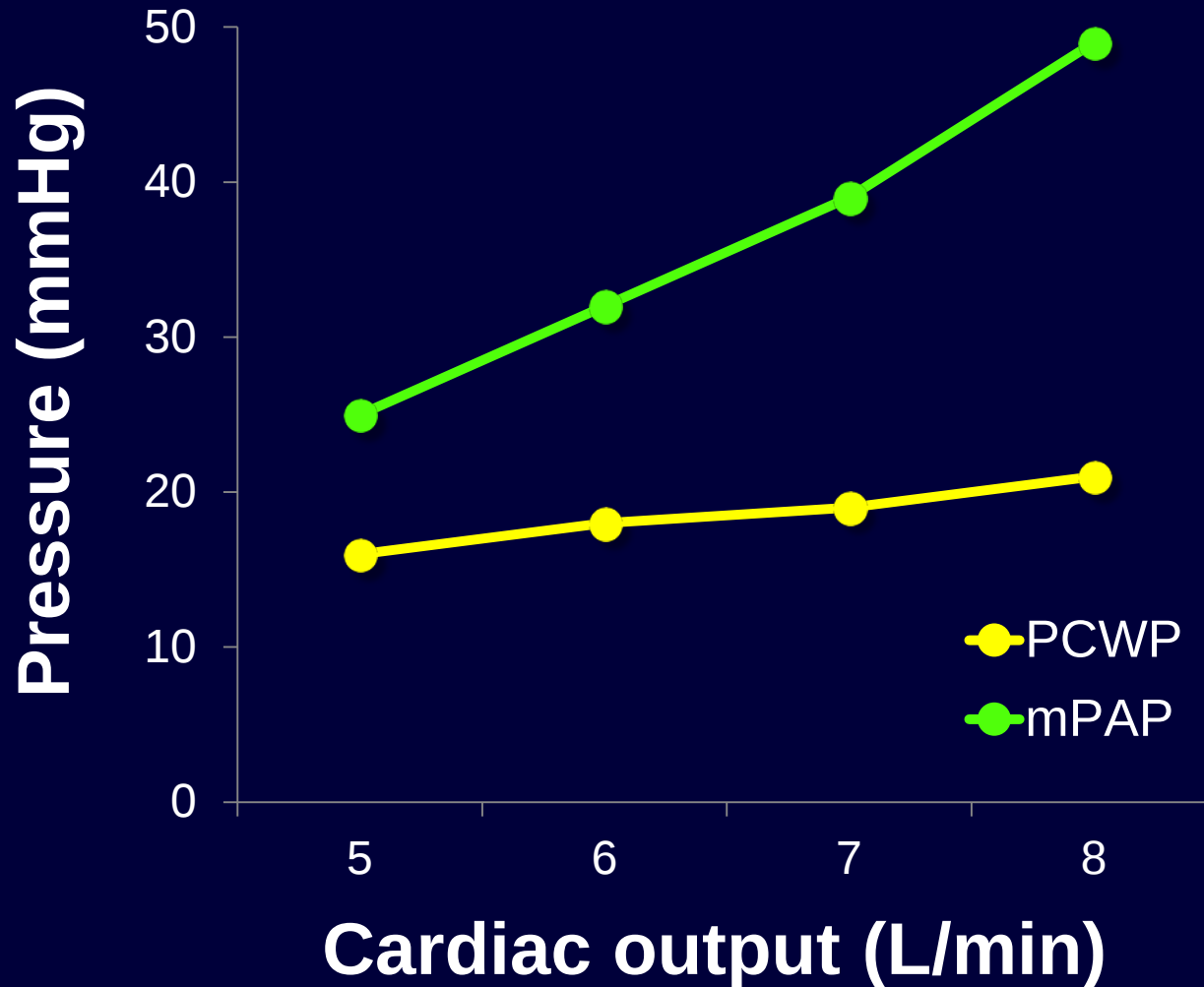
Diastolic stress echo



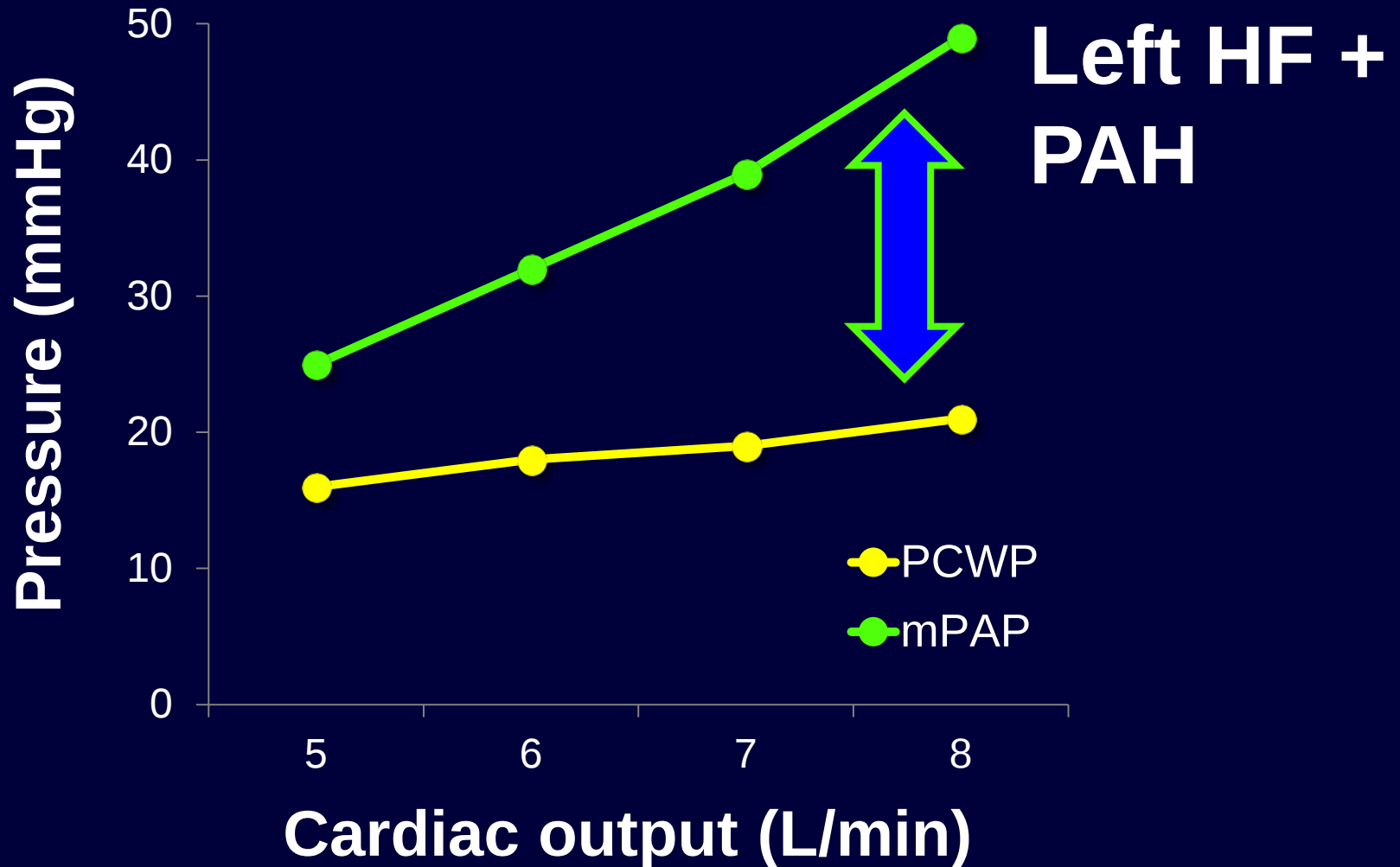
Exercise hemodynamics



Exercise hemodynamics



Exercise hemodynamics



Volume challenge in a patient w/HFpEF

PCWP (mmHg)

50
mmHg

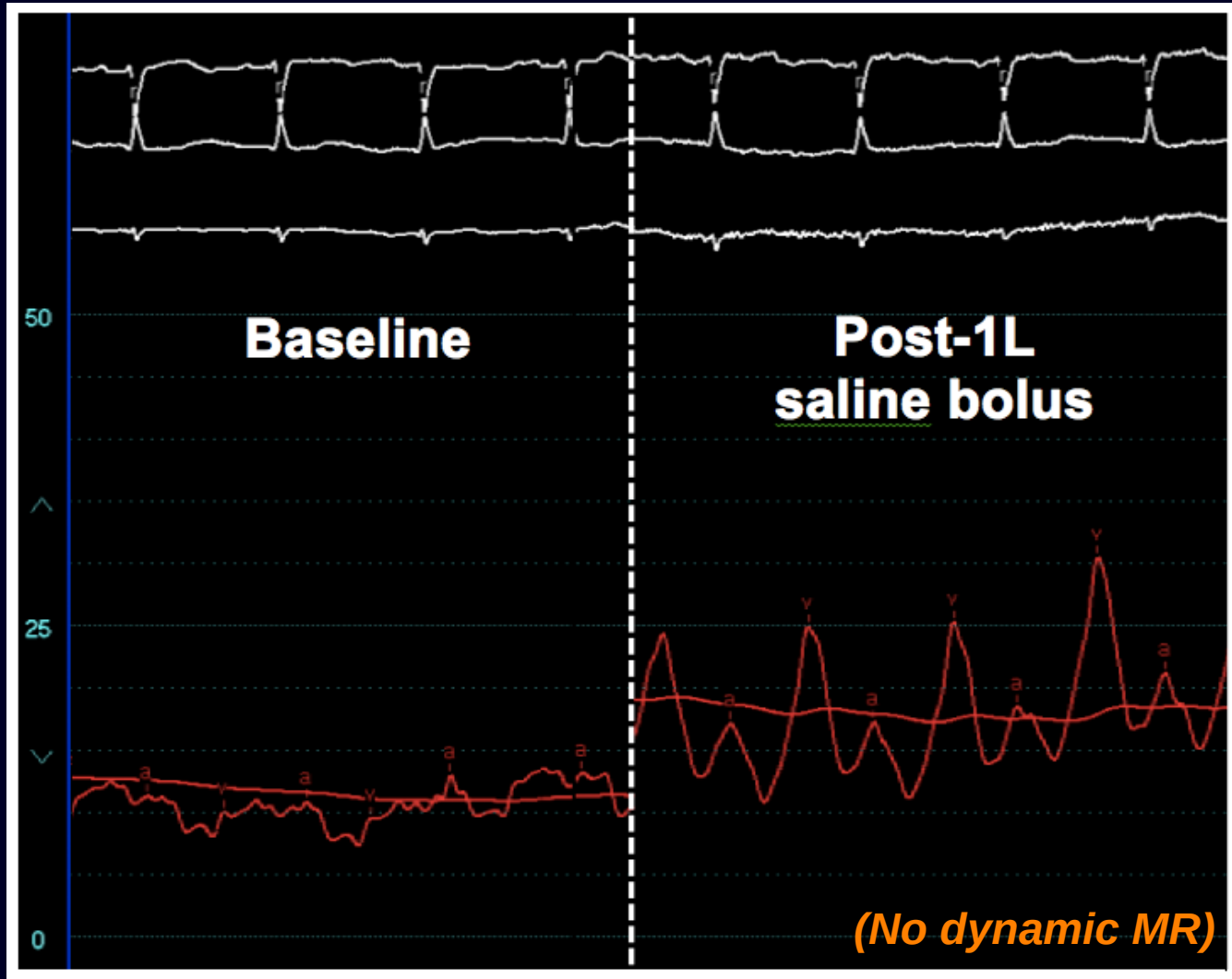
25
mmHg

0
mmHg

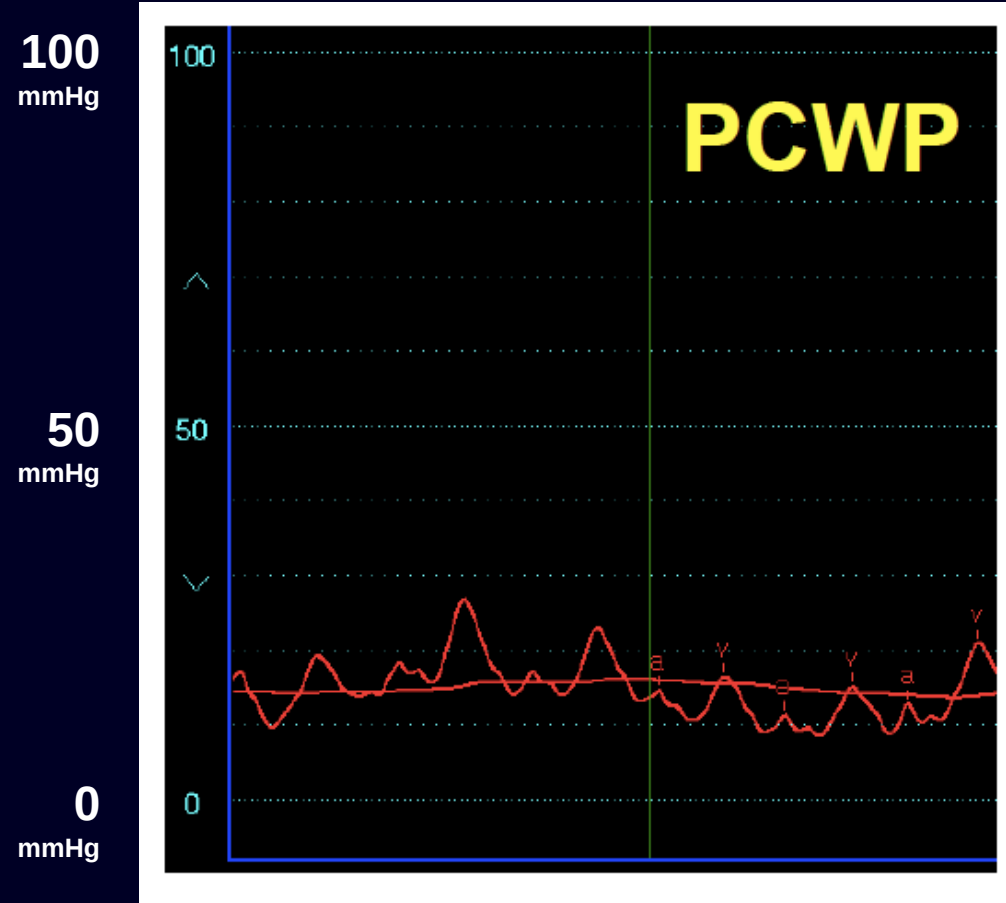
Baseline

**Post-1L
saline bolus**

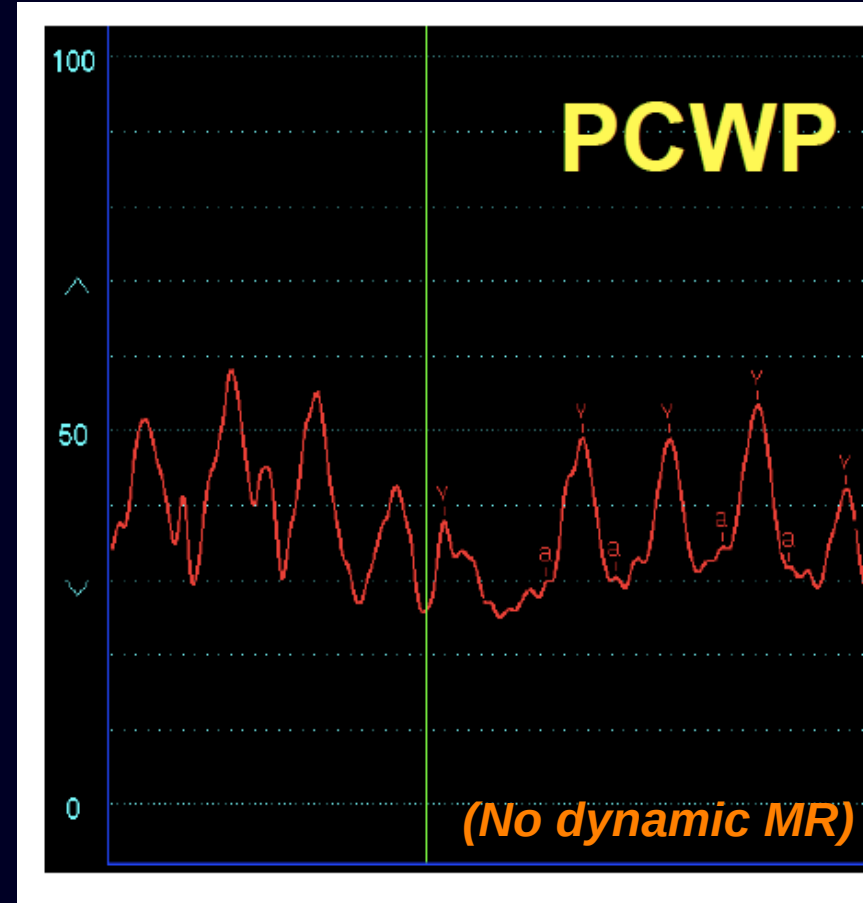
(No dynamic MR)



Exercise hemodynamics in a patient with severe HFpEF



REST



AFTER 1 MIN. OF EXERCISE

Lesson #5:

Everyone has
HFpEF until
proven otherwise

Myth #3:

There are no proven treatments for HFpEF

Fact #3:

**HFpEF is treatable:
use a checklist approach**

HFpEF checklist

- ☐ Always think about the HFpEF dx, even when the BNP is “normal”
- ☐ Look at the echo yourself for clues
- ☐ When in doubt do a right heart cath
- ☐ “Perturb the system”
- ☐ Rule out zebras

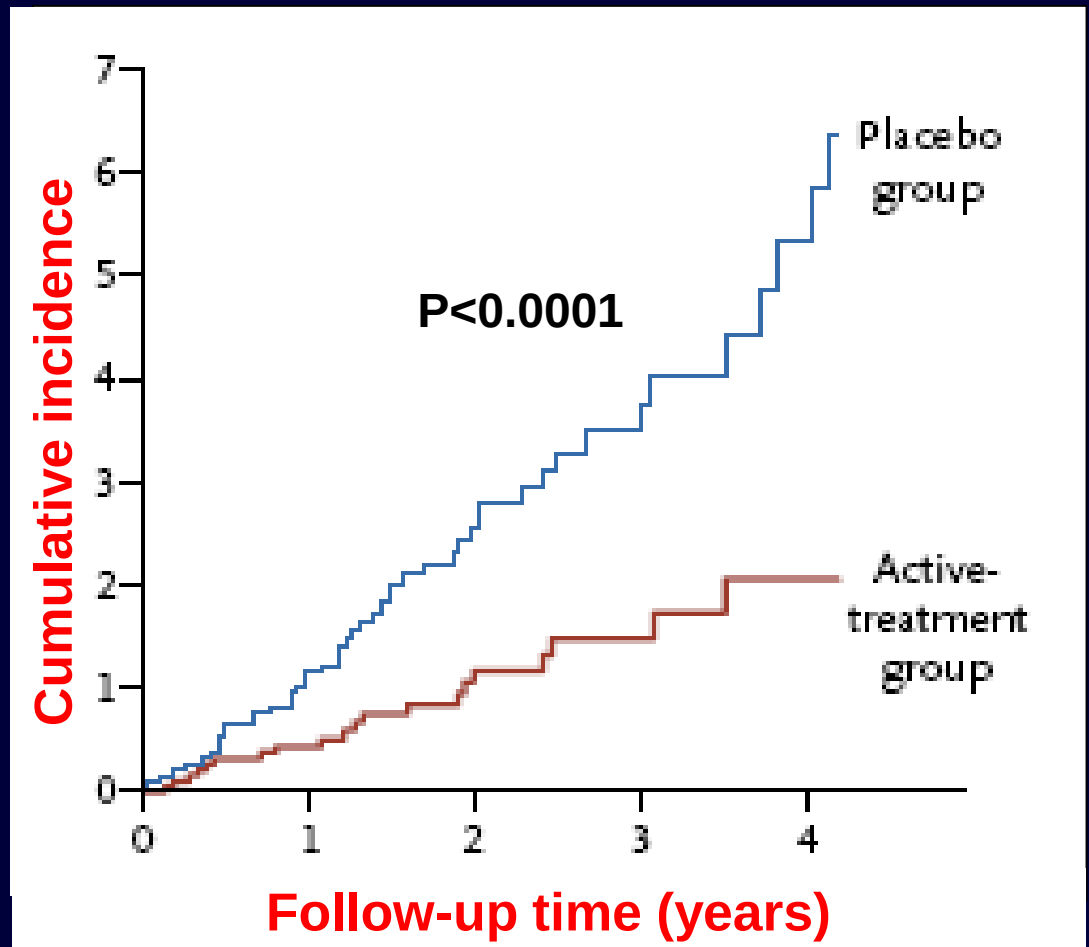
HFpEF checklist

- ☐ Prevent HFpEF
- ☐ Treat the zebras
- ☐ Treat comorbidities
- ☐ Diet/exercise
- ☐ Rx HTN, volume overload using
“HFpEF-centric” approach
- ☐ Tailor treatment to type of HFpEF
- ☐ Enroll in a clinical trial

Prevent HFpEF

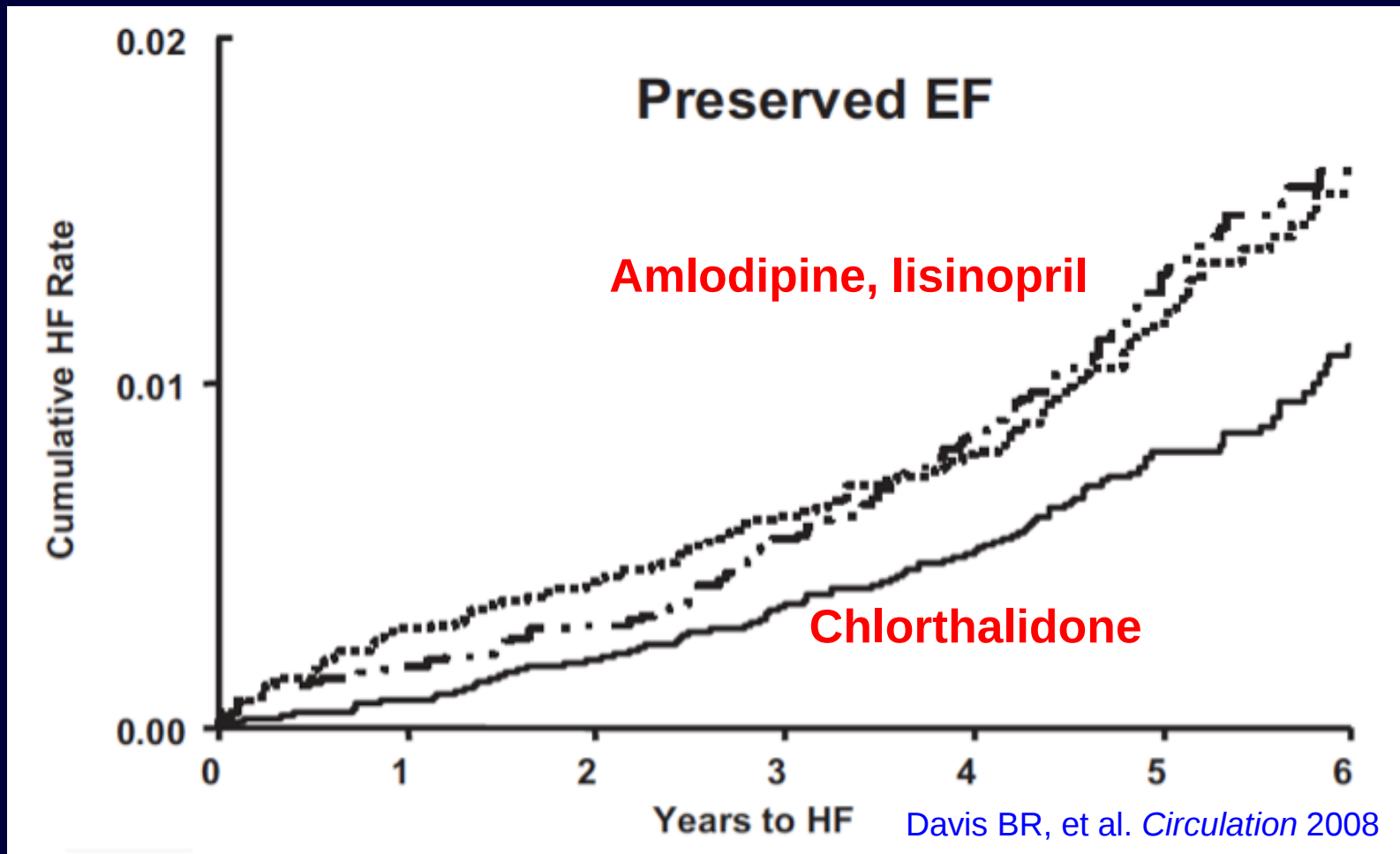
HFpEF can be prevented...

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



HFpEF can be prevented...

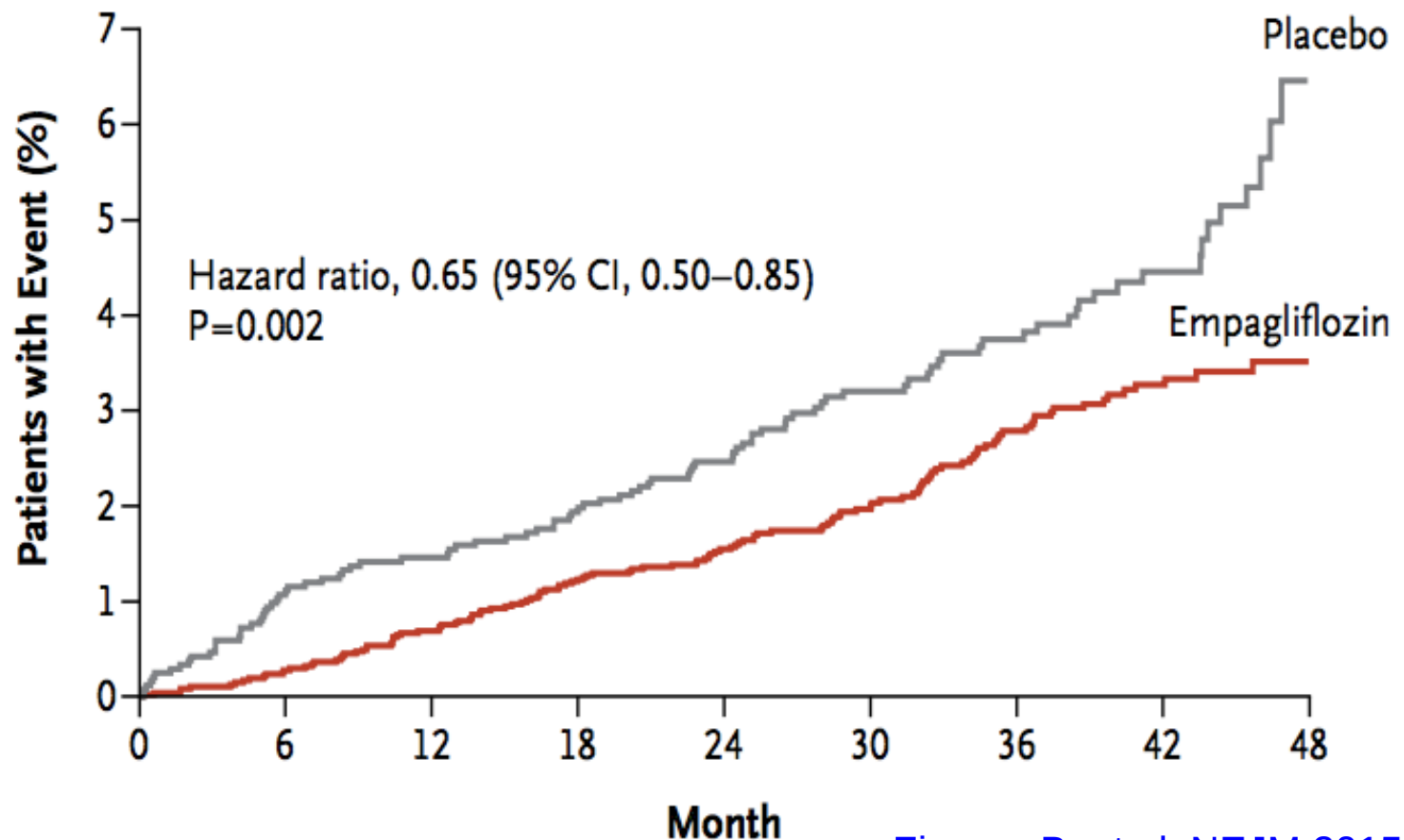
ALLHAT-HFpEF: chlorthalidone best for HFpEF prevention



HFpEF can be prevented...

EMPA-REG: SGLT2 inhibitor reduced HF hospitalization

Hospitalization for Heart Failure



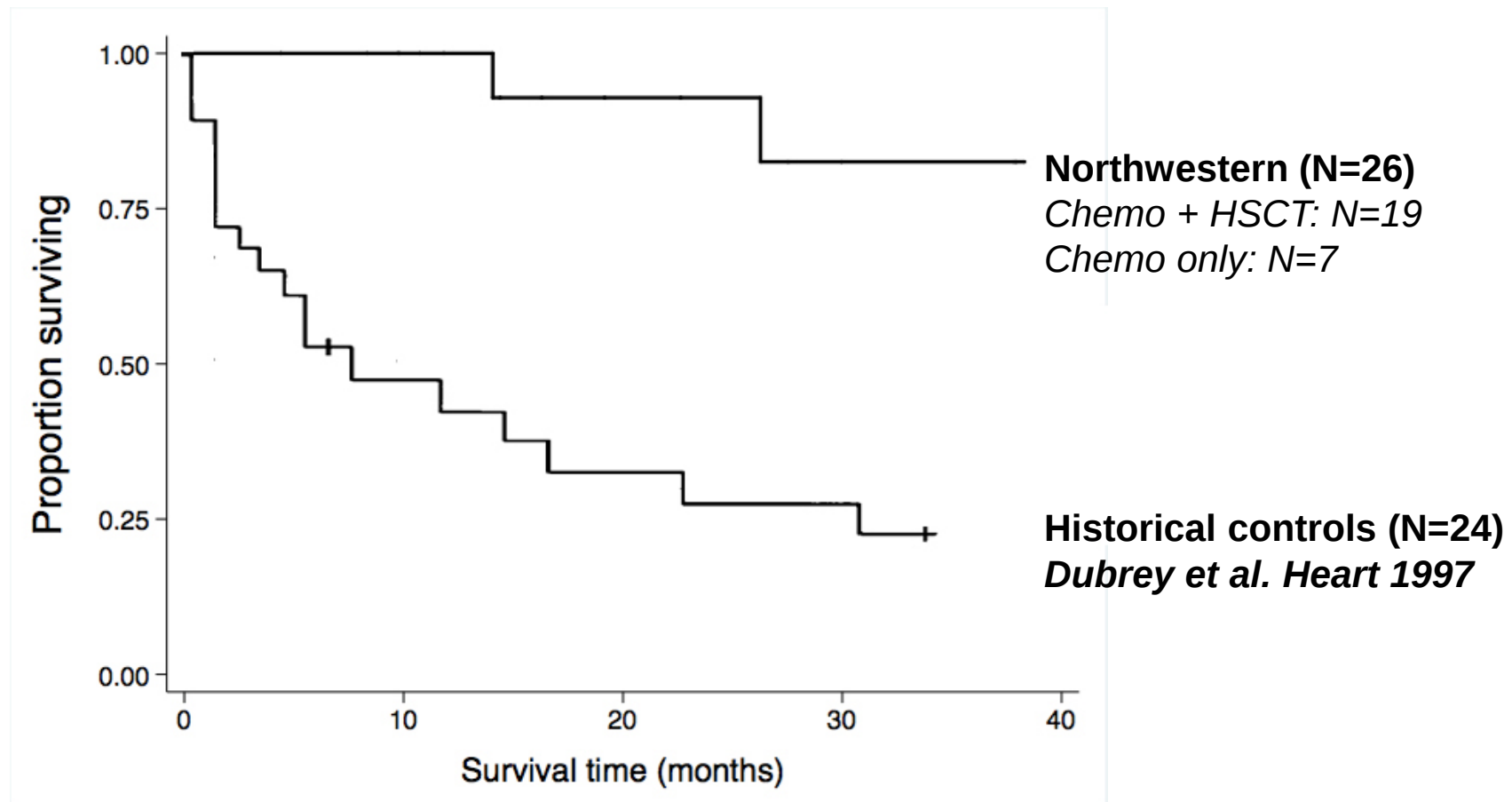
Zinman B, et al. NEJM 2015

Treat the zebras

Zebras can be treated!

- Cardiac amyloid: *not a death sentence*
 - » Primary (AL) amyloidosis:
 - Highly effective chemotherapy
 - Stem cell transplantation
 - » Familial or wild-type TTR amyloidosis:
 - Several novel drugs in pipeline (**TTR stabilizers**, RNA interference, RNA anti-sense molecules)
 - Heart-liver transplant
- Constrictive pericarditis:
 - » Pericardial stripping can be curative

Primary (AL) cardiac amyloid: improved survival with stem-cell tx



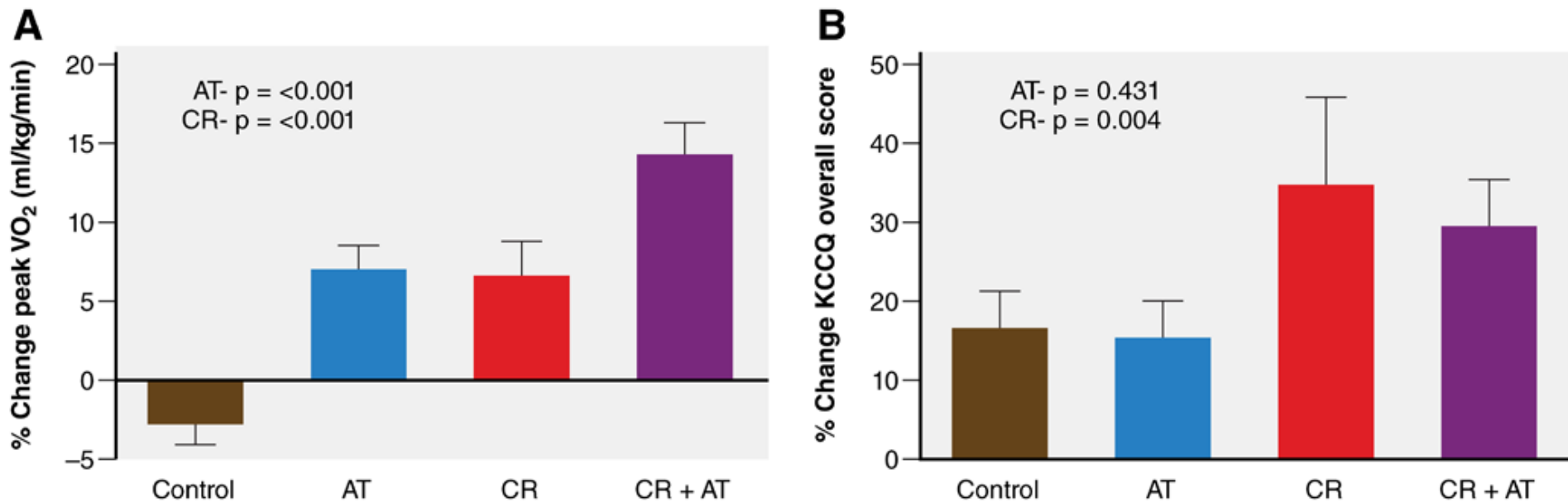
**Treat
comorbidities**

Treatment of comorbidities

- CAD: look for it, treat aggressively
- CKD: be aware of hemoconcentration, chronotropic incompetence, PH
- AF: trial of cardioversion, anticoagulate, allow higher HR (80-90 bpm)
- Diabetes: carvedilol, SGLT2-inhibition?
- COPD: control volume overload
- OSA: control volume overload

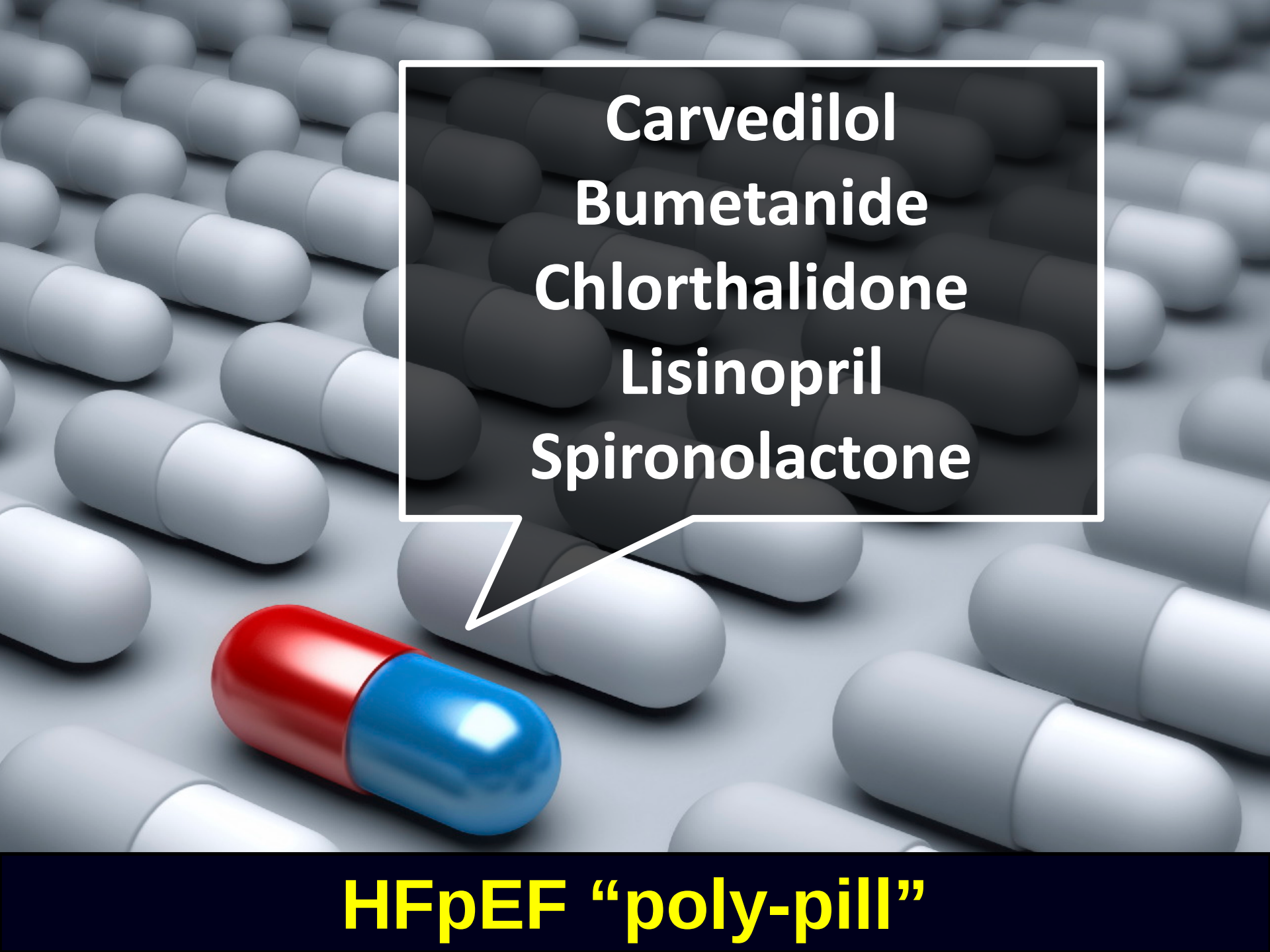
**Diet and
exercise work!**

Diet and exercise work!



AT = aerobic exercise training, CR = caloric restriction

**Treat HTN and
volume overload
using a “HFpEF-
centric” approach**

The background of the slide is a close-up, high-angle shot of numerous white, oblong capsules scattered across a light gray surface. In the lower-left foreground, one capsule is distinct, colored red on the left half and blue on the right half. A white rectangular box with a thin black border is positioned in the upper-middle section of the image. Inside this box, a list of five drug names is written in white, bold, sans-serif font. A white line extends from the bottom-left corner of the box, pointing towards the red and blue capsule.

**Carvedilol
Bumetanide
Chlorthalidone
Lisinopril
Spironolactone**

HFpEF “poly-pill”

HFpEF diuretic polypill?

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Volume 389, No. 10073, p1035–1042, 11 March 2017

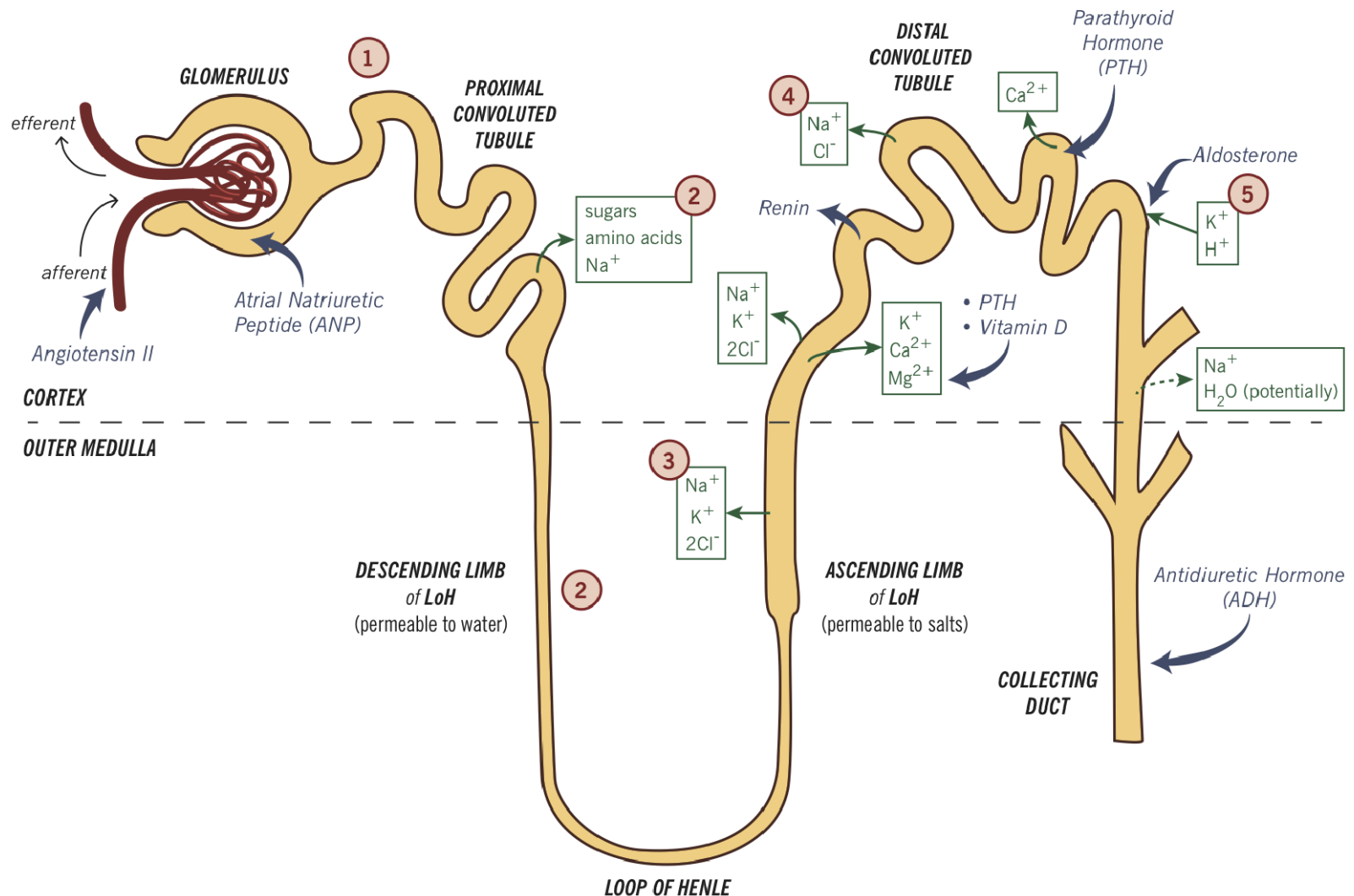
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Articles

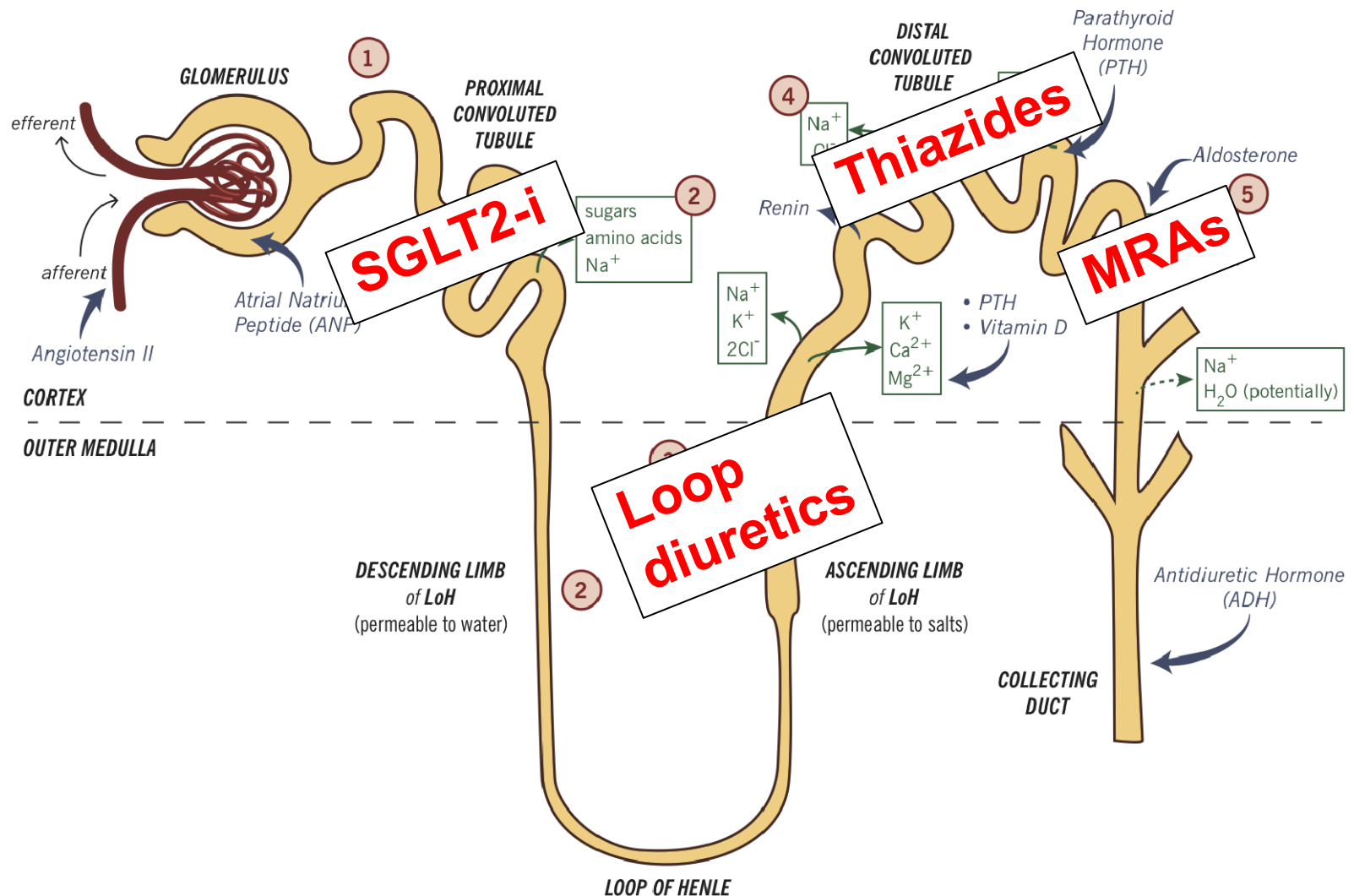
Quarter-dose quadruple combination therapy for initial treatment of hypertension: placebo-controlled, crossover, randomised trial and systematic review

Prof Clara K Chow, PhD  , Jay Thakkar, MBBS, Alex Bennett, MPhil, Prof Graham Hillis, PhD, Michael Burke, PhD, Prof Tim Usherwood, MD, Kha Vo, BSc, Kris Rogers, PhD, Emily Atkins, PhD, Ruth Webster, PhD, Michael Chou, MBBS, Hakim-Moulay Dehbi, MRes, Abdul Salam, PhD, Prof Anushka Patel, PhD, Prof Bruce Neal, PhD, David Peiris, PhD, Prof Henry Krum[†], Prof John Chalmers, PhD, Prof Mark Nelson, PhD, Prof Christopher M Reid, PhD, Prof Mark Woodward, PhD, Prof Sarah Hilmer, PhD, Prof Simon Thom, PhD, Prof Anthony Rodgers, PhD

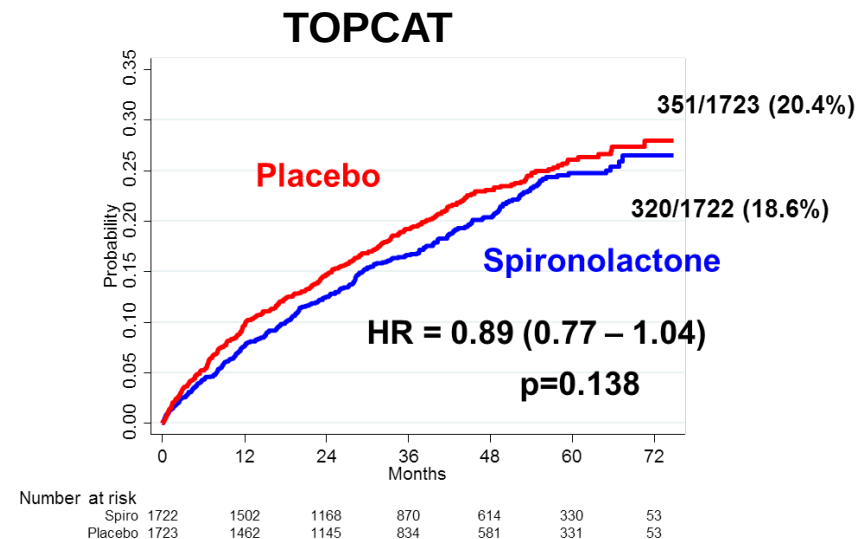
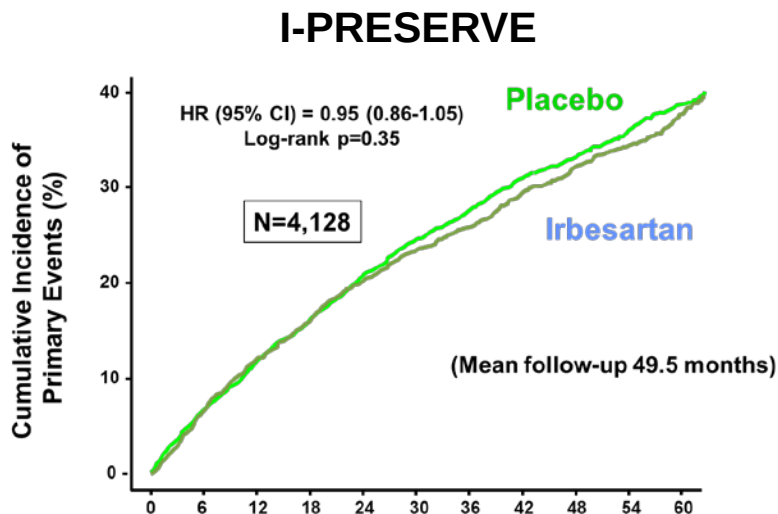
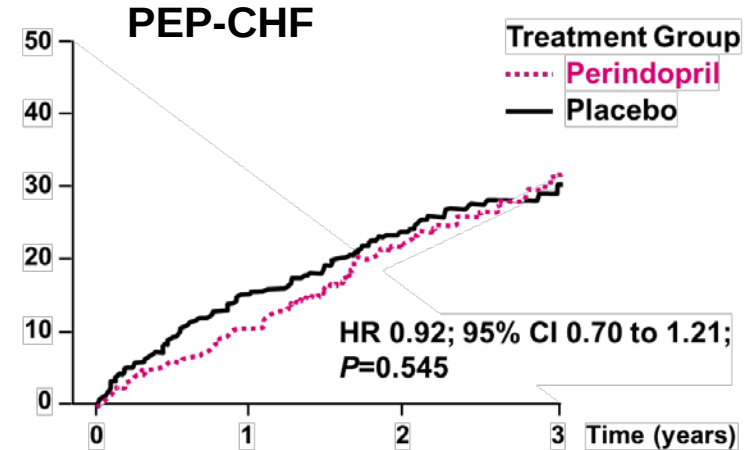
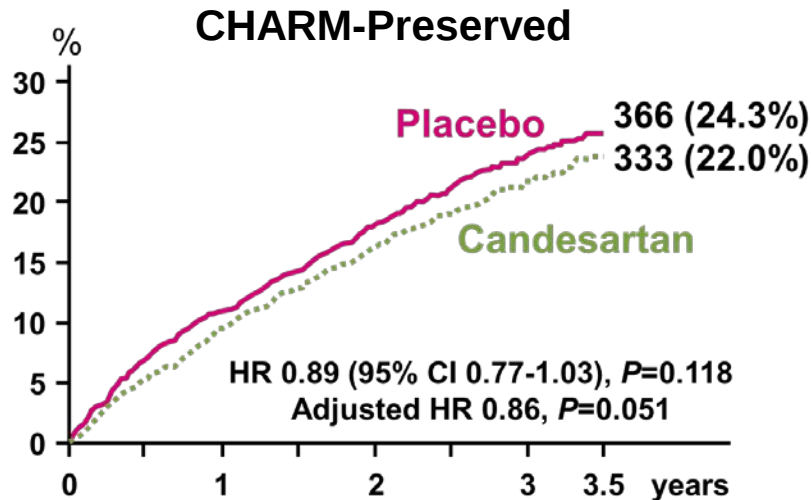
HFpEF diuretic polypill?



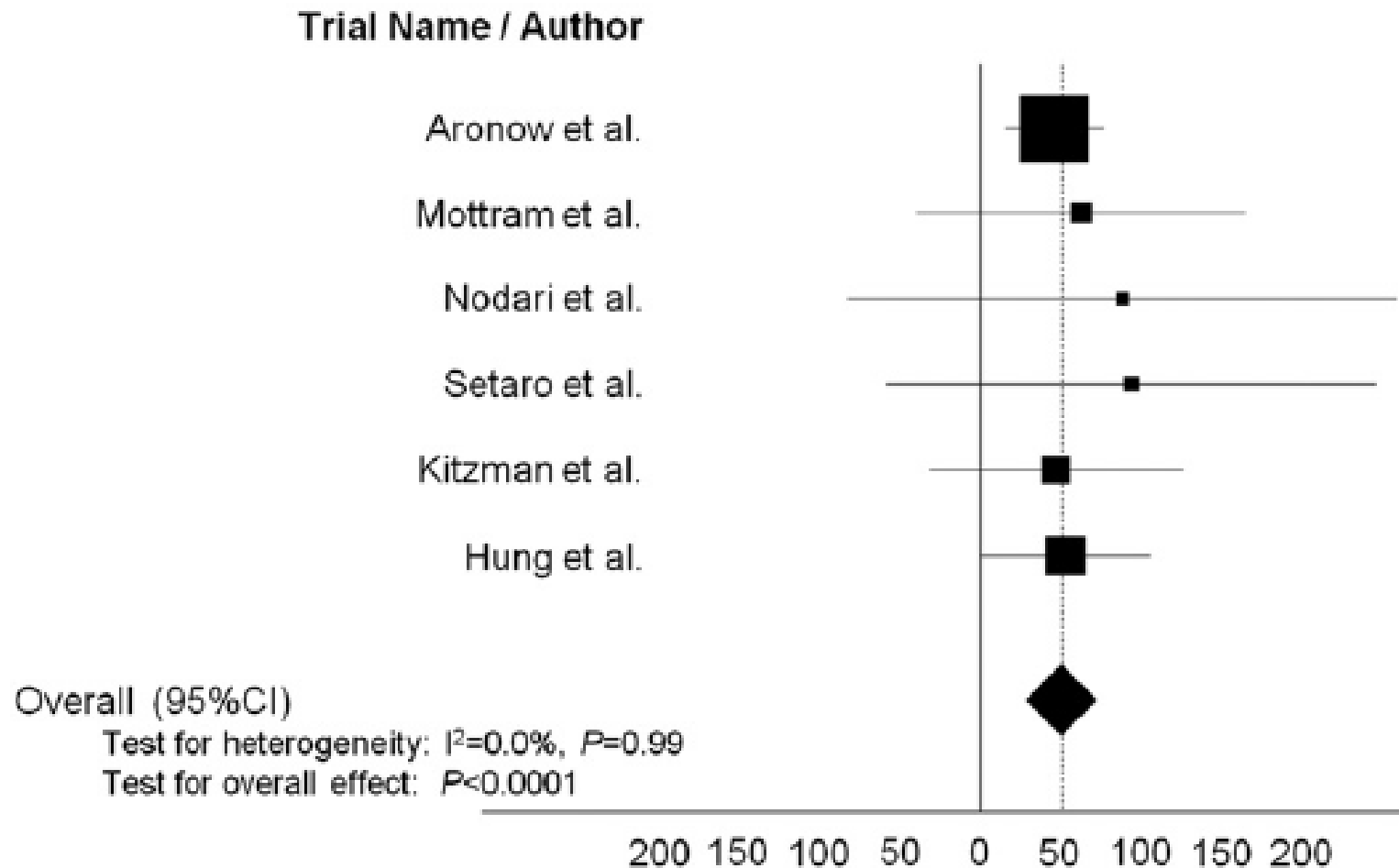
HFpEF diuretic polypill?



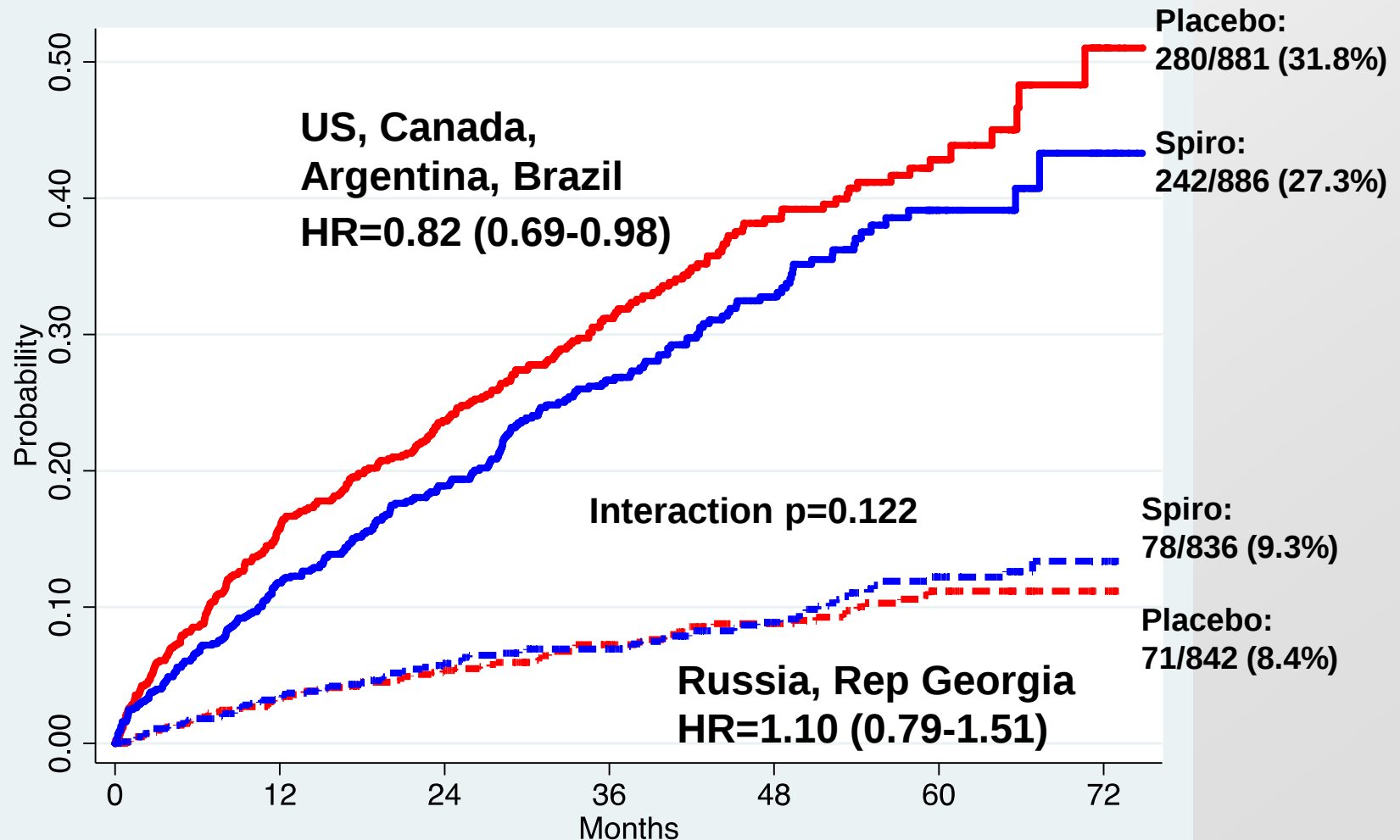
HFpEF trials: failures?



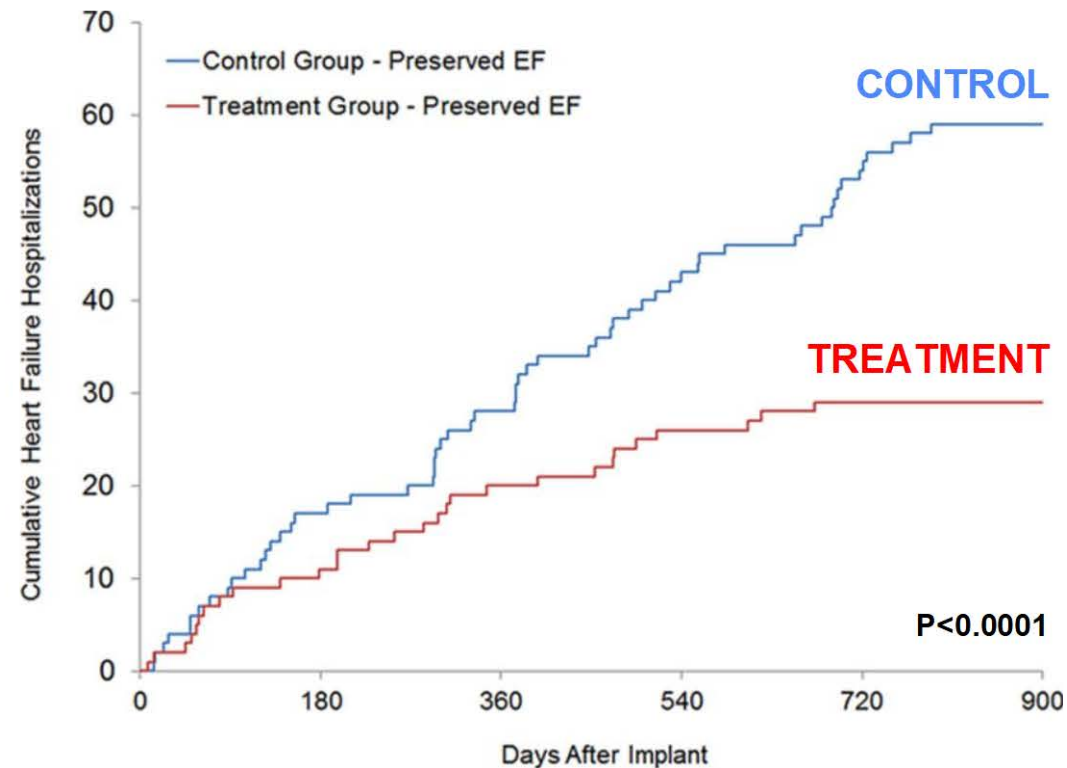
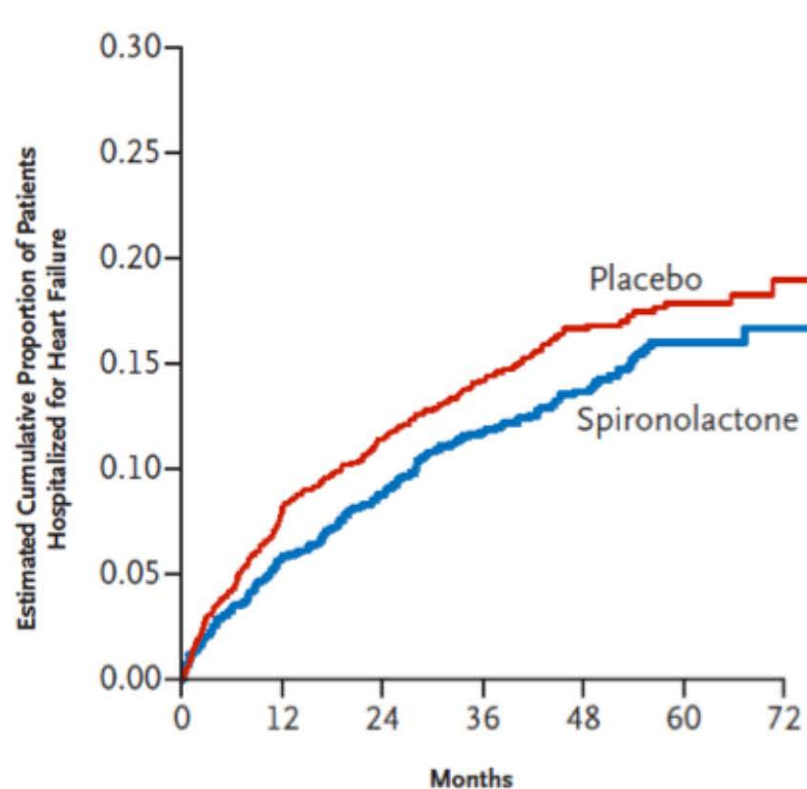
Meta-analysis of clinical trials in HFpEF: $\uparrow$ exercise capacity



Placebo vs. Spiro by Region



Reduction in HF hospitalization



TOPCAT

Pitt B, et al. *NEJM* 2014

CHAMPION-HFpEF

Adamson P, et al. *Circ HF* 2014

Rx of HTN, volume overload

- Use vasodilating beta-blockers
- Don't use nitrates
- Control volume overload to improve BP
- Use loop diuretics initially but minimize doses by adding sprio, chlorthalidone
 - » Use bumetanide, torsemide (bioavailability)
- Spironolactone:
 - » $Cr < 2.5$, $eGFR > 30$ ml/min
 - » Check K^+ , Cr at 1 week, 1 month, q 3months

**Tailor treatment
to type of HFpEF**

A photograph of a black trash can with a clear plastic liner, overflowing with various types of plastic waste. Visible items include several plastic bottles (some with condensation), aluminum cans (one with 'SAVE 56' text), and crumpled plastic bags. The scene is set outdoors during the day, with a blurred background of greenery and a building. The text 'HFpEF' is overlaid in blue with a white outline at the bottom of the image.

HFpEF

Sorting HFpEF

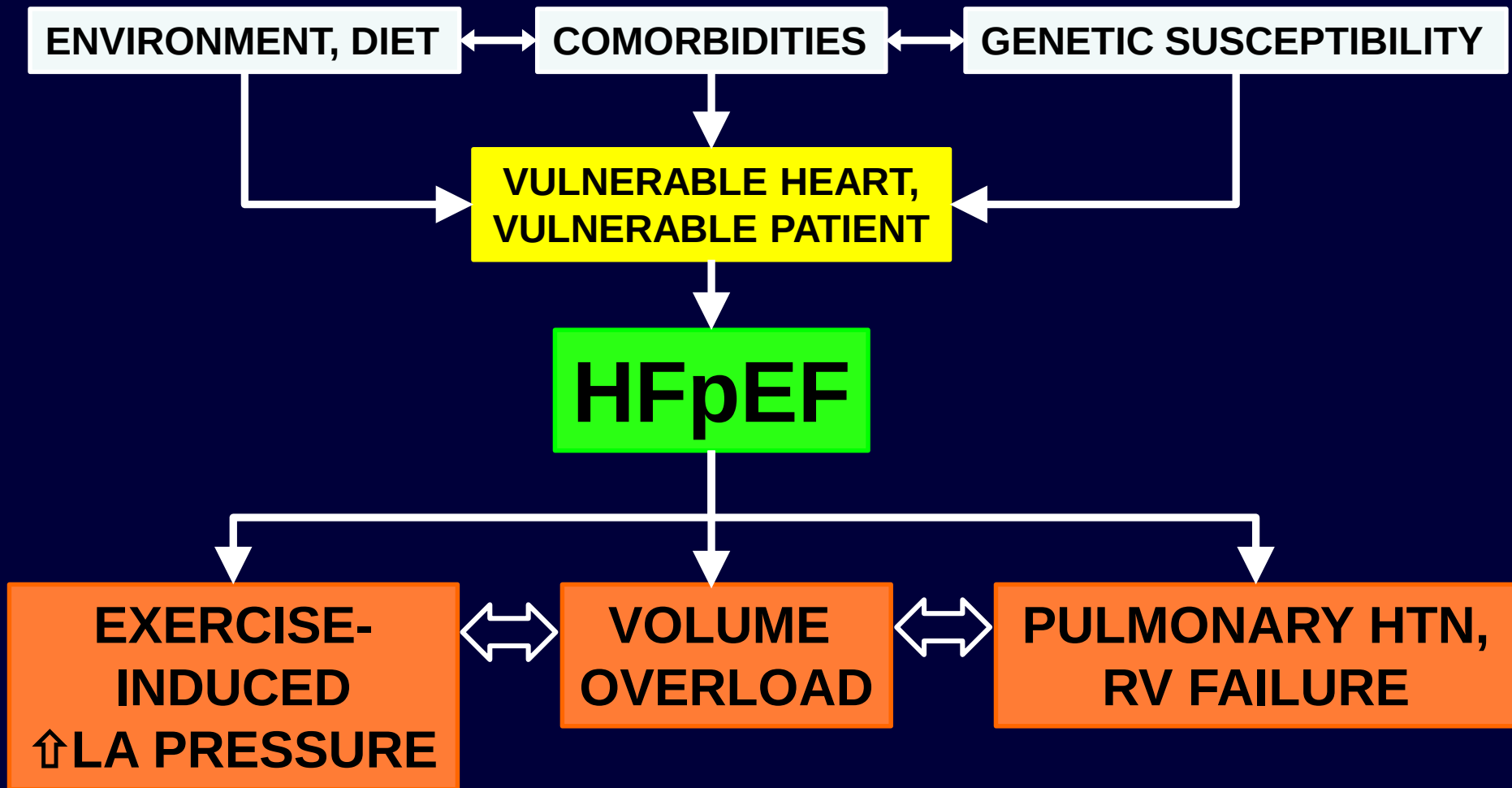


- Start with signs/sx of HF, EF>50%
- Sort #1 (easier):
 - » Valvular disease, recovered HFrEF, high-output HF, etc.
- Sort #2 (harder):
 - » Rare causes of HFpEF, zebras
- Sort #3:
 - » Clinical/etiologic subtype
 - » Pathophysiologic subtype

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”)

Types of HFpEF presentation



HFpEF treatment matrix

HFpEF Clinical Presentation Phenotypes						
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

**Enroll in a
clinical trial**

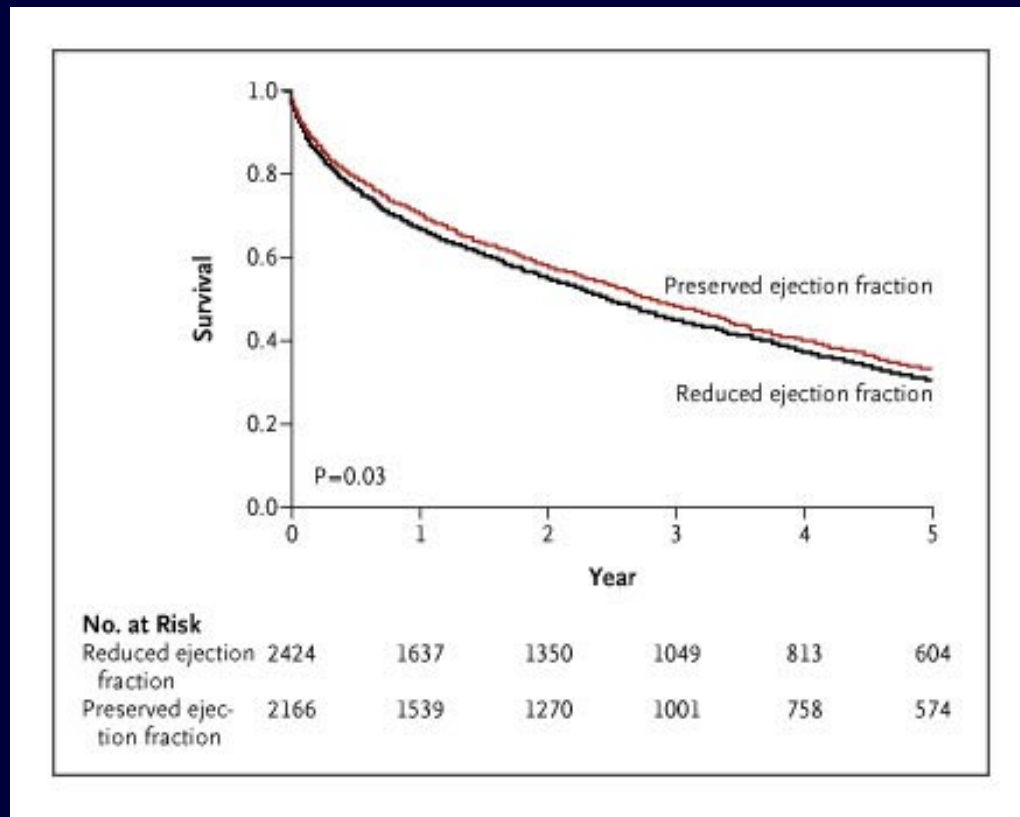
Myth #4:

**HFpEF clinical trials
are doomed**

Fact #4:

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

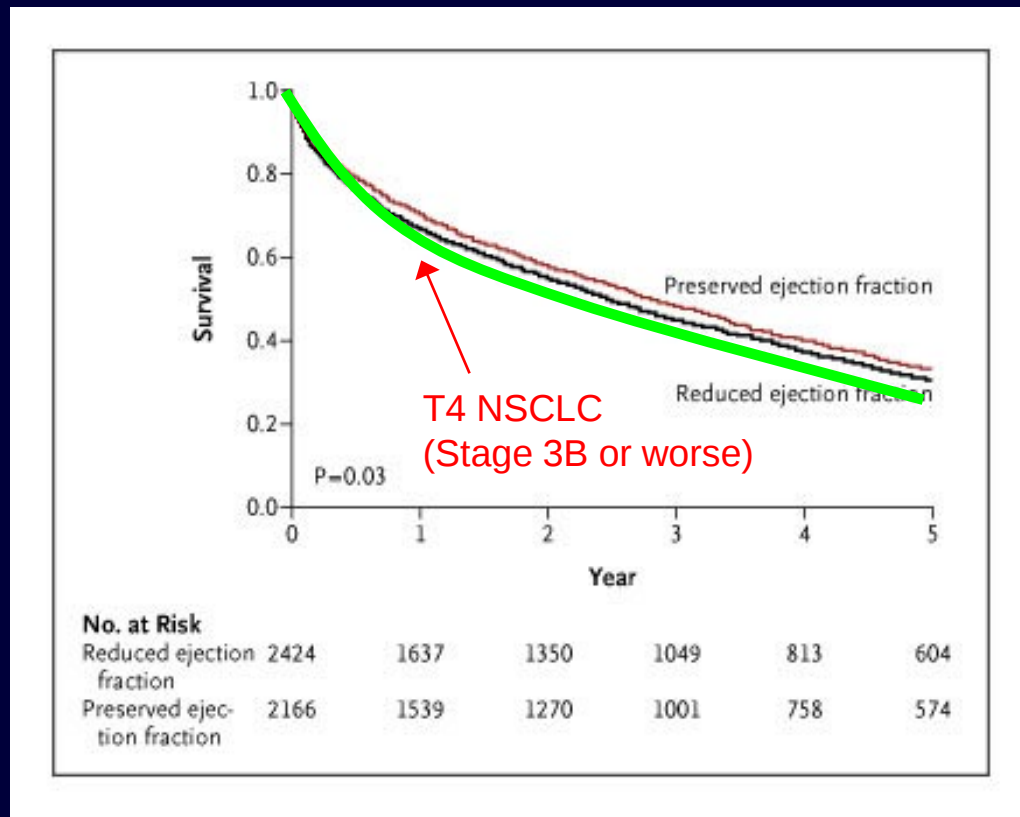
HFpEF survival: poor



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

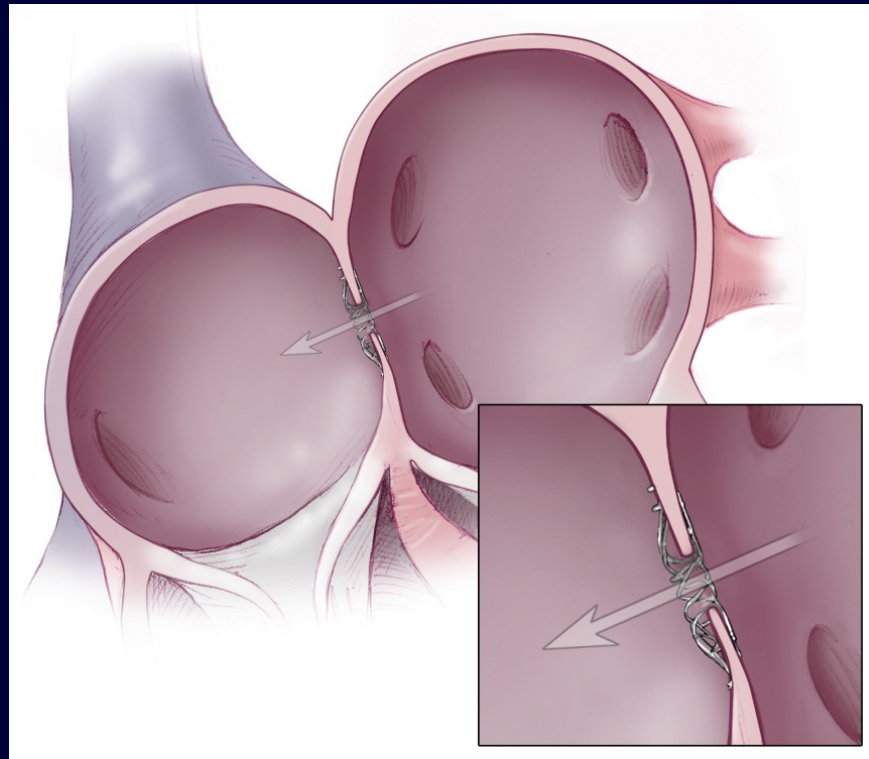
- PARAGON-HF: *neprilysin inhibition*
- REDUCE-LAP: *interatrial shunt device*
- KNO₃CK-OUT: *oral nitrites*
- INDIE-HFpEF: *inhaled nitrites*
- REGRESS-HFpEF: *cardiospheres*
- LIBERTY-HCM: *late I_{Na+} inhibitor*
- ATTR-ACT: *transthyretin stabilizer*
- ENDEAVOUR: *transthyretin RNAi*

Current HFpEF clinical trials

- EMPEROR-Preserved: *SGLT-2 inhibition*
- PRESERVED-HF: *SGLT-2 inhibition*
- PANACHE: *adenosine partial A1R agonist*
- SERENADE: *endothelin receptor blocker*
- SOUTHPAW: *oral prostacyclin*
- *And several more therapeutics currently in various stages of development*

Enrichment trial design for HFpEF

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



Interatrial shunt device (IASD)

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

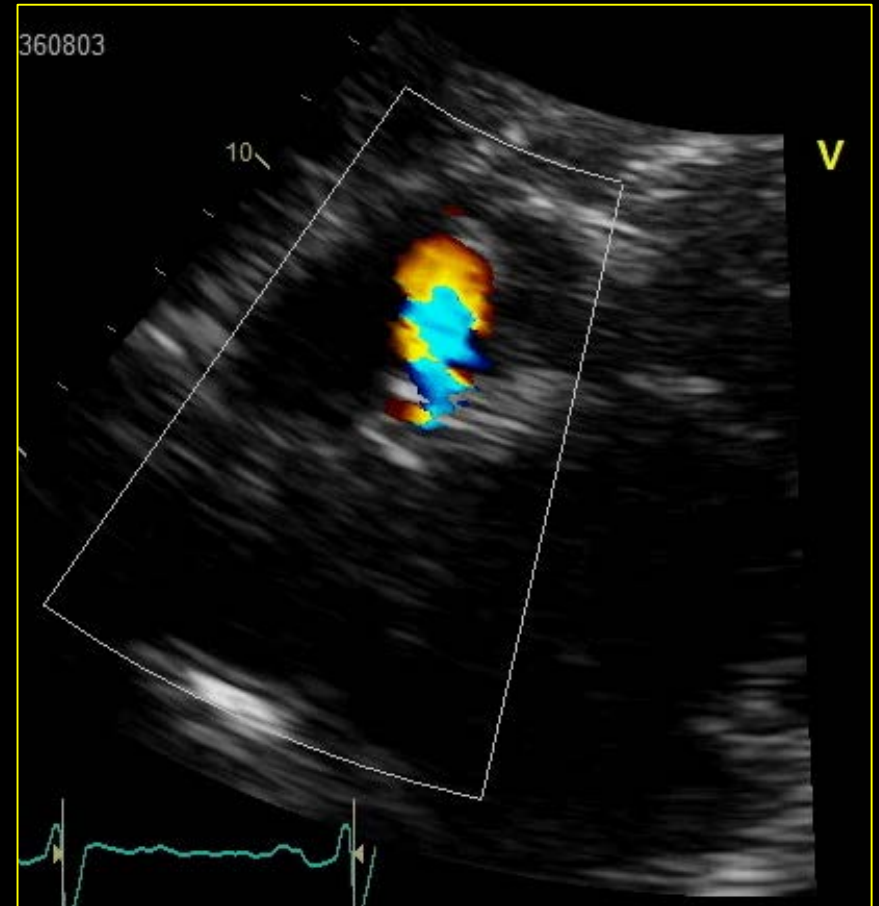
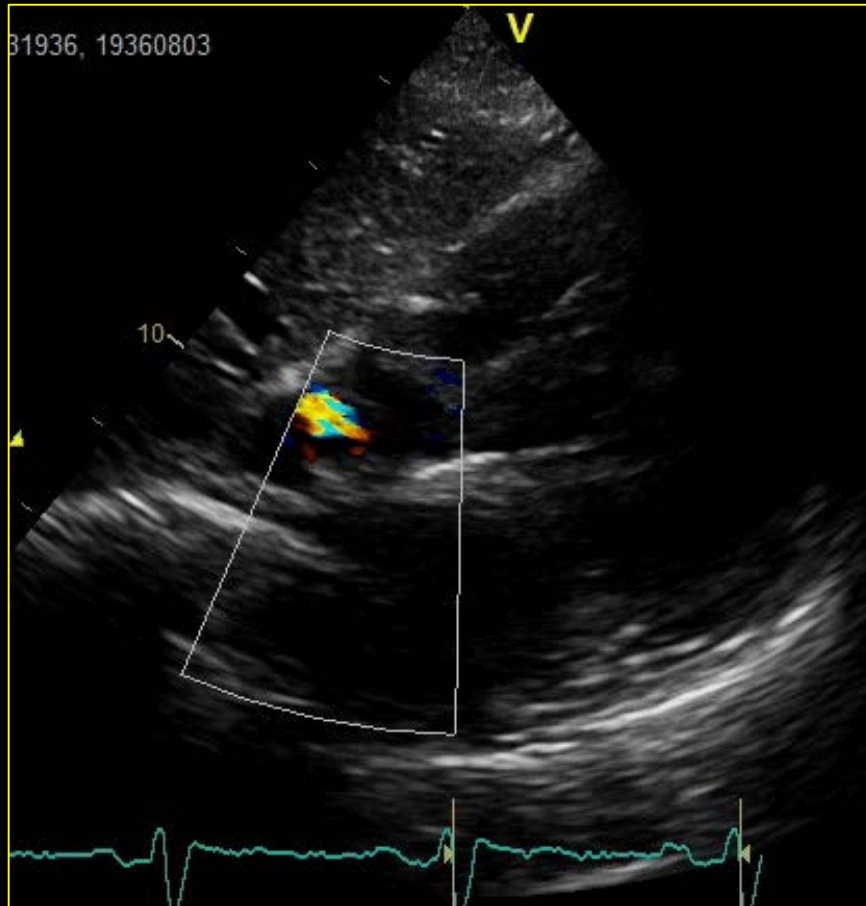
Implant
19 mm OD
8 mm ASD



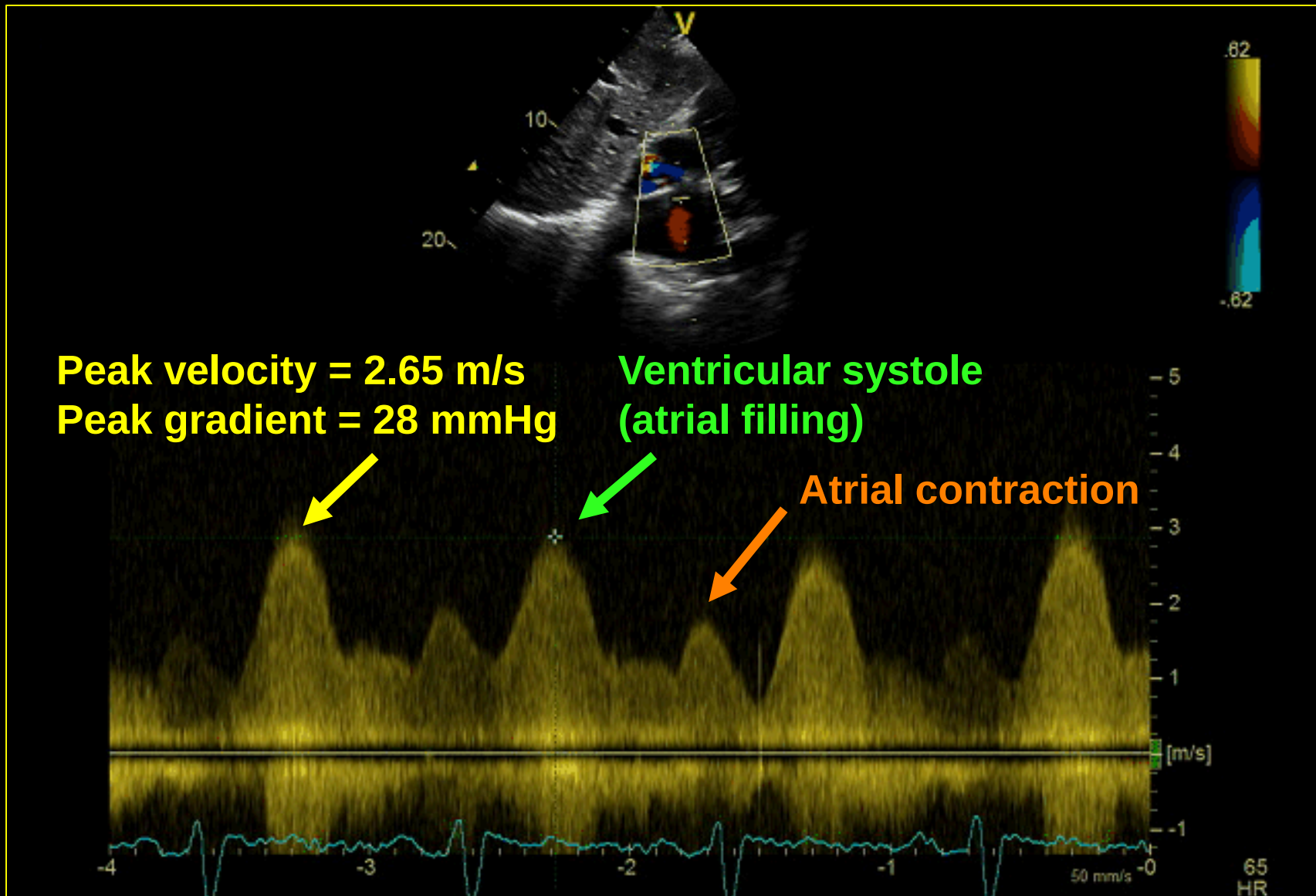
**Animal
explant**



Subcostal view showing patency of shunt with L→R flow

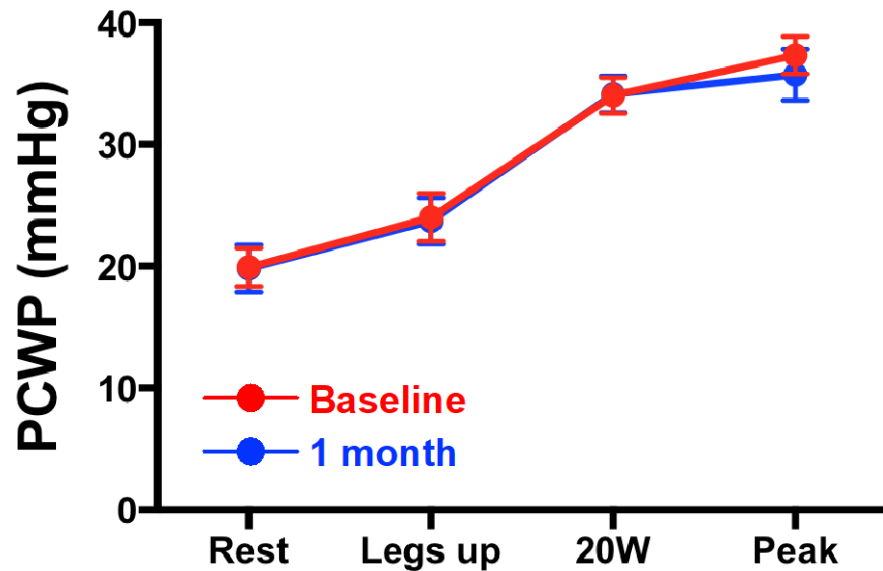


Subcostal 4-chamber view, continuous wave Doppler showing velocity of blood flow through IASD throughout the cardiac cycle

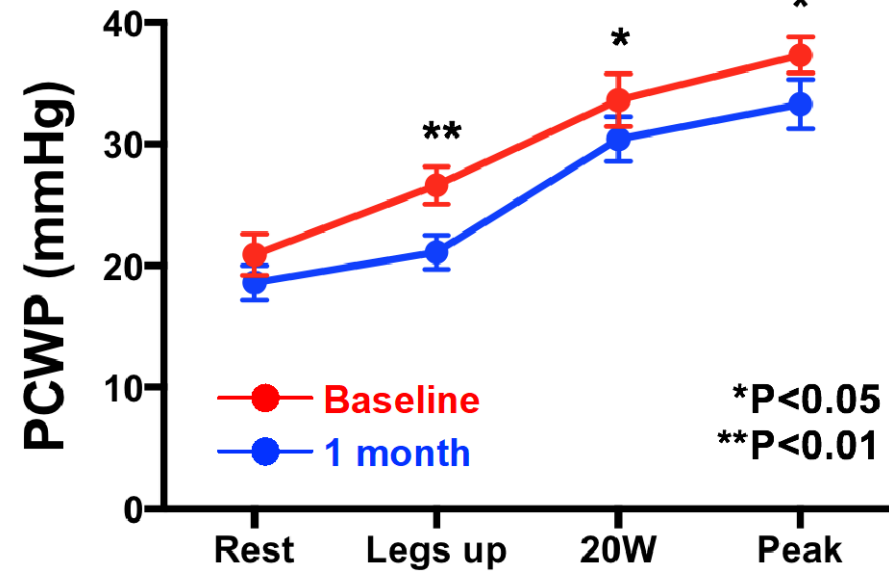


Change in PCWP: baseline to 1 mo.

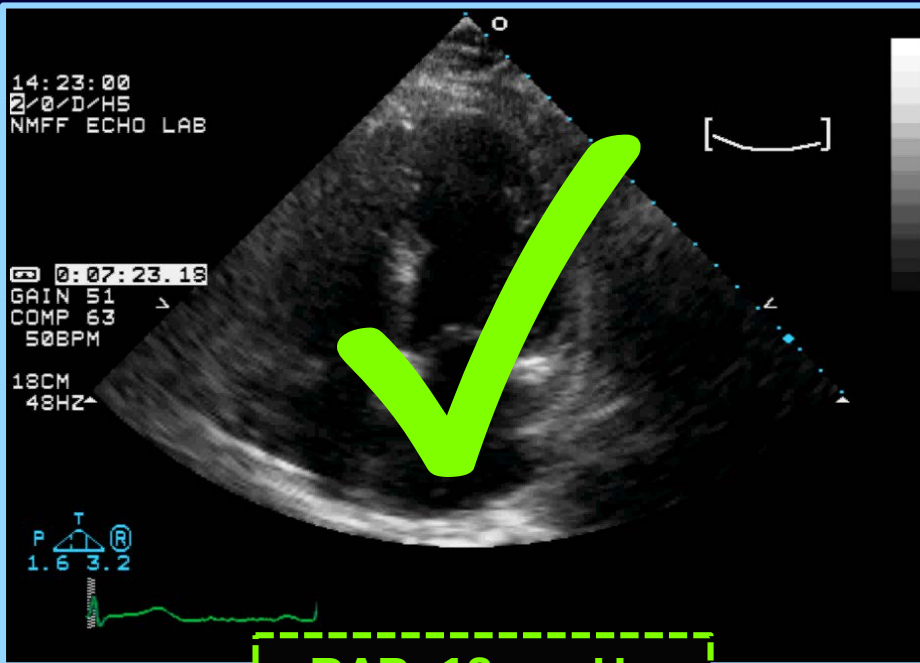
CONTROL



IASD



Two 66-year-old women with HFpEF: *Who should get the IASD?*



RAP: 12 mmHg
PCWP: 29 mmHg
CI: 3.4 L/min/m²
PVR: 1.8 WU



RAP: 24 mmHg
PCWP: 28 mmHg
CI: 2.1 L/min/m²
PVR: 3.8 WU

Umbrella trial design for HFpEF

HFpEF

DEEP PHENOTYPING HFpEF REGISTRIES

1. PROMIS-HFpEF: Cardiac microvascular dysfunction
2. AHA Go Red for Women: Sex differences in cGMP-PKG

LAP>>RAP
No RV failure
PVR normal

REDUCE-LAP
(inter-atrial shunt device)

High BP
Volume up

PARAGON
(LCZ696)
PRESERVED,
EMPEROR
(SGLT-2 inhibition)

Ambulatory,
exercise
intolerant

KNOCK-OUT,
INDIE
(nitrites)
PANACHE
(partial A1R-agonist)

CpcPH

SERENADE
(ERA)
SOUTHPAW
(prostacyclin)

Amyloid
phenotype

ATTR-ACT
(TTR stabilizer)
ENDEAVOUR
(TTR RNAi)

HCM
phenotype

LIBERTY
(eleclazine)

A close-up photograph of a person's open palm facing the camera. The hand is light-skinned and positioned centrally. Overlaid on the palm is the word "STOP!" in a large, bold, red, sans-serif font with a black outline. The background is blurred, showing a person's face and shoulders in a dark jacket and light shirt. The entire image is framed by a black border.

STOP!

1. HFpEF is a systemic disorder, more than just DD

2. Don't miss the HFpEF diagnosis, and the zebras!

3. Categorize by type of HFpEF and tailor treatment

4. There are several potential treatments for HFpEF

5. Enroll in HFpEF clinical trials

STOP!

A hand is shown with five red dots on the tips of the fingers. Each dot is connected by a red line to a numbered point. The lines connect the thumb to point 3, the index finger to point 2, the middle finger to point 1, the ring finger to point 4, and the pinky finger to point 5. The word 'STOP!' is written in large, bold, red letters across the palm of the hand.

HFpEF: the “huff-puff” syndrome

huff and puff

Fig. to breathe very hard; to pant as one exerts effort. John came up the stairs huffing and puffing. He huffed and puffed and finally got up the steep hill.

See also: [and](#), [huff](#), [puff](#)

McGraw-Hill Dictionary of American Idioms and Phrasal Verbs. © 2002 by The McGraw-Hill Companies, Inc.

huff and puff

1. to breathe noisily, usually because you have been doing physical exercise *They're so unfit they start huffing and puffing if they have to run further than twenty yards.*

2. (informal) to complain noisily about something but not be able to do anything about it *They huffed and puffed about the price, but eventually they paid up.*

See also: [and](#), [huff](#), [puff](#)

Cambridge Idioms Dictionary, 2nd ed. Copyright © Cambridge University Press 2006. Reproduced with permission.

huff and puff

1. to breathe in a noisy manner *He was on the top of the hill long before I came up huffing and puffing behind him.*

2. to complain *The owners will huff and puff about their financial problems and then not do anything to solve them.*

See also: [and](#), [huff](#), [puff](#)

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thank you!