Case Study 1

Heart Failure Society of South Africa [HeFSSA]

HEART FAILURE WITH PRESERVED EJECTION FRACTION

Heart Failure Society of South Africa [HeFSSA]

CASE HISTORY

- ✓ Mrs. D. G aged 72 years, presents with a 4 week history of progressive dyspnoea, particularly with inclines, as well as fatigue and mild peripheral oedema
- ✓ She has a past history of hypertension of 10 years duration
- ✓ She is obese (BMI, 32 kg/m2), her BP 190/110 mmHg, with a tachycardia of 110 bpm & in sinus rhythm
- ✓ Clinical examination shows bipedal oedema with an elevated JVP, S3 gallop & bi-basal crackles
- ✓ LVH clinically with a loud aortic component on auscultation
- ✓ Blood tests reveal a normal haemoglobin & blood glucose level with mildly impaired renal function (eGFR 48), potassium of 4.6 mmol/L
- ✓ ECG shows LA enlargement, LVH with a strain pattern

CASE STUDY

You suspect that this patient has heart failure

How would you diagnose the type of heart failure?

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CASE HISTORY

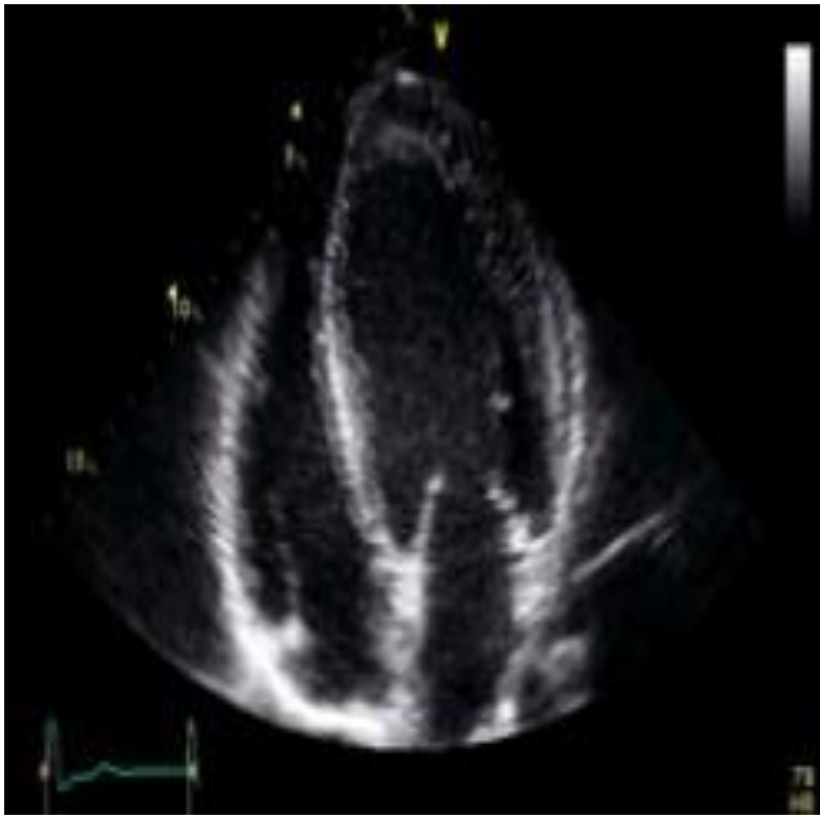
A transthoracic echocardiogram shows normal systolic function with an ejection fraction of 65%

With mild left ventricular hypertrophy and no valvular Pathology

Comment is made on the presence of diastolic dysfunction, with an enlarged left atrium and elevated E/e’ ratio

WHAT IS DIASTOLIC HEART FAILURE?

+



Pulmonary Edema

Normal Ejection Fraction

Heart Failure with Normal Ejection Fraction

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DEFINITION OF HFrEF vs. HFpEF

The Diagnosis of HF-REF Requires Three Conditions To Be Satisfied
1. Symptoms typical of HF
2. Signs typical of HF
3. Reduced LVEF
The Diagnosis of HF-PEF Requires Four Conditions To Be Satisfied:
1. Symptoms typical of HF
2. Signs typical of HF
3. Normal or only mildly reduced LVEF & LV not dilated
4. Relevant structural heart disease (LV hypertrophy / LA enlargement) and/or diastolic dysfunction

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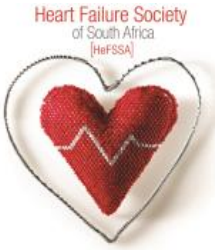
ESC HF GL 2016: DEFINITION OF HEART FAILURE WITH PRESERVED (HFPEF) MID RANGE (HFMREF) & REDUCED EJECTION FRACTION (HFREF)

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

ESC 2016:

"Signs and symptoms of HF are often non specific and do not discriminate well between HF and other clinical conditions"

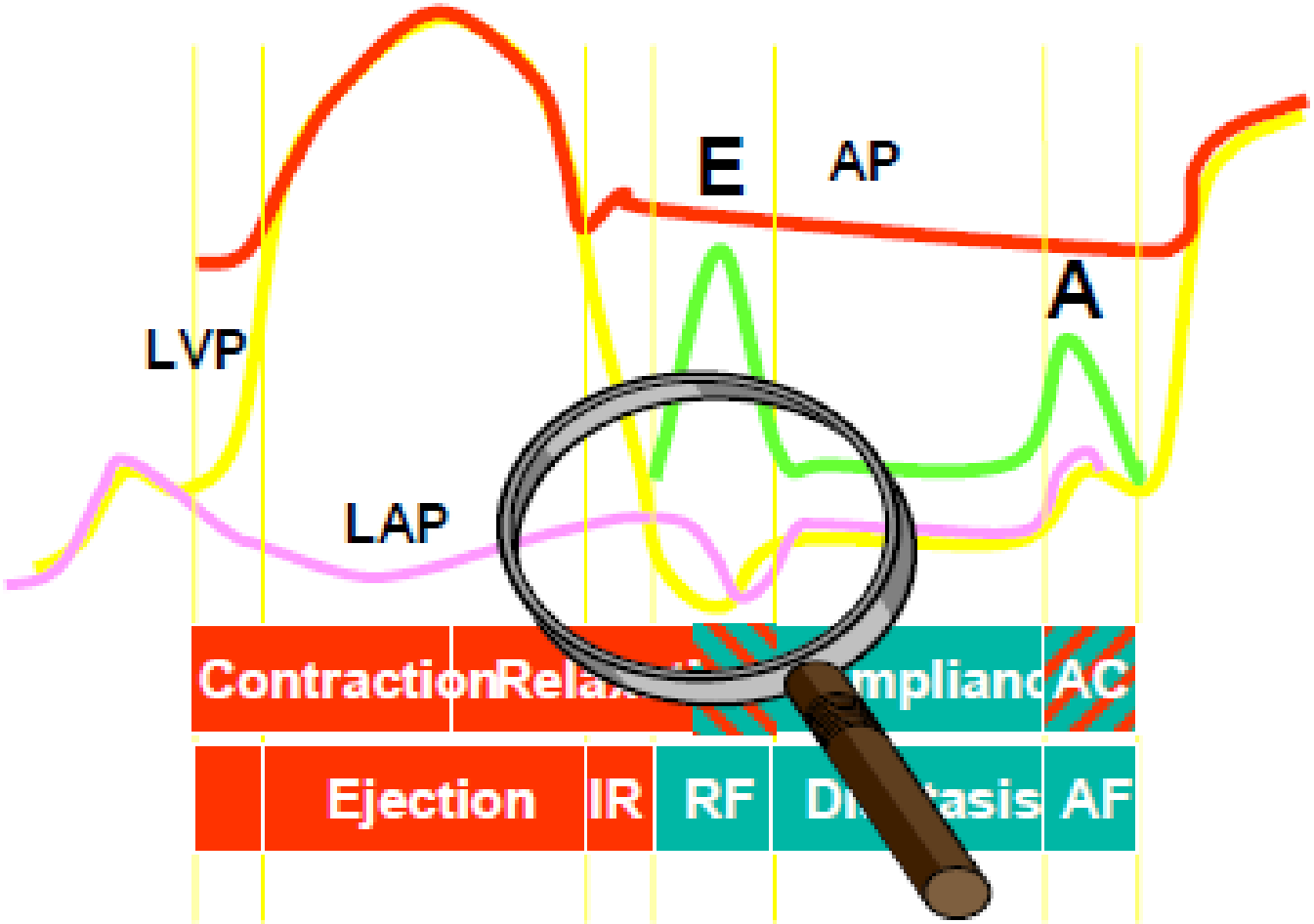


Ponikowski et al EHJ 2016

ESC 2016 KEY DIAGNOSTIC HFpEF CRITERIA

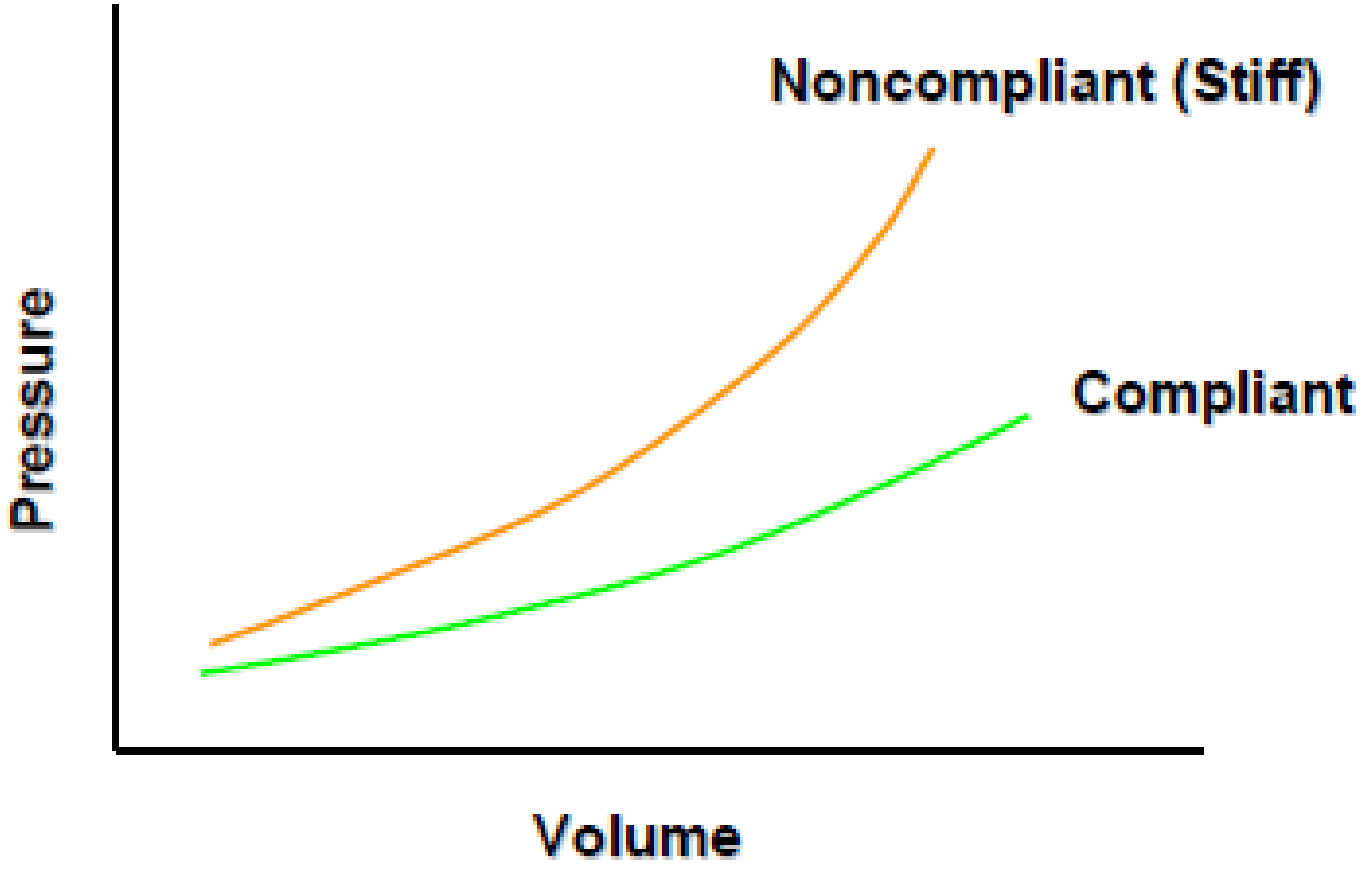
"Preserved" EF	≥ 50%
Structural alterations	LAVI > 34 mL/m2
	Or
	LVMI ≥ 115 (males) / ≥ 95 (females) mg/m2
Functional alterations	E/é ≥ 13
	é (mean septal and lateral) < 9cm/s
NTproBNP	> 125pg/mL or (SR; increase with Afib!)
BNP	> 35pg/mL

DIAGRAM OF LV FILLING



Focus on Relaxation

END – DIASTOLIC PRESSURE VOLUME RELATIONS



Focus on Stiffness

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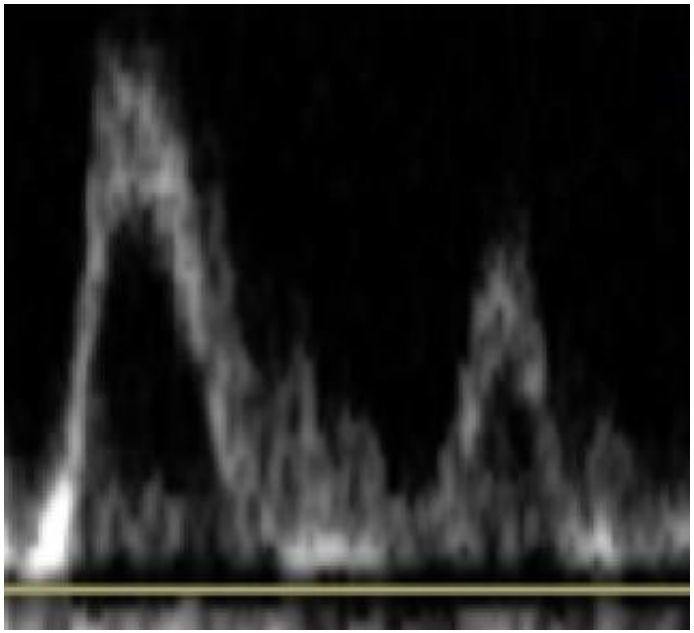
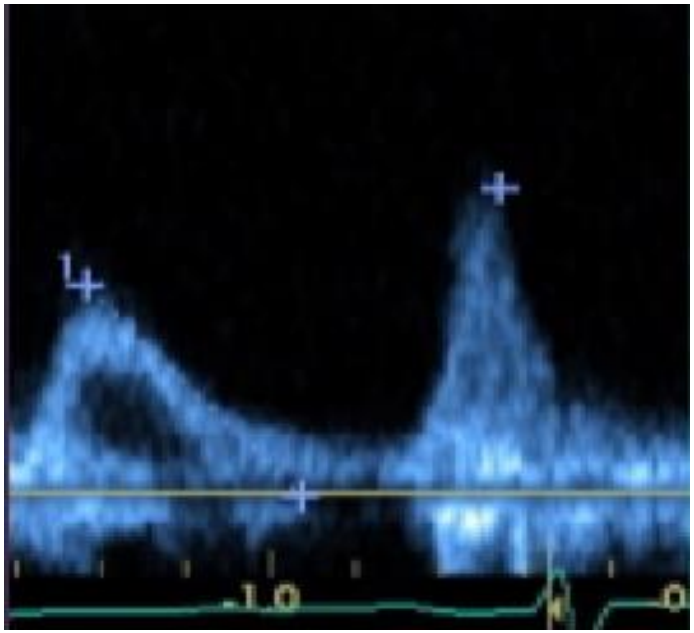
IT USED TO SEEM SO SIMPLE…

Patterns of Diastolic Function

In the beginning (mid ‘80s)…



There was good…



…and evil

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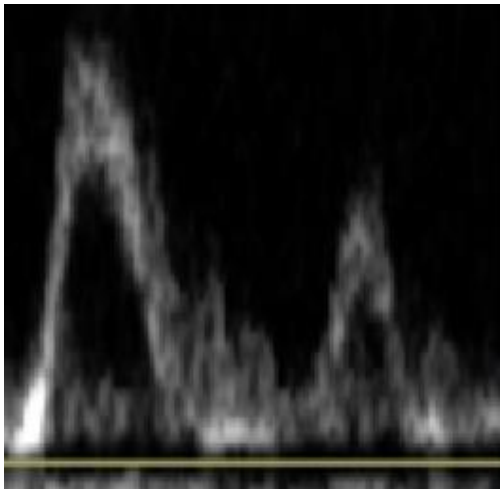
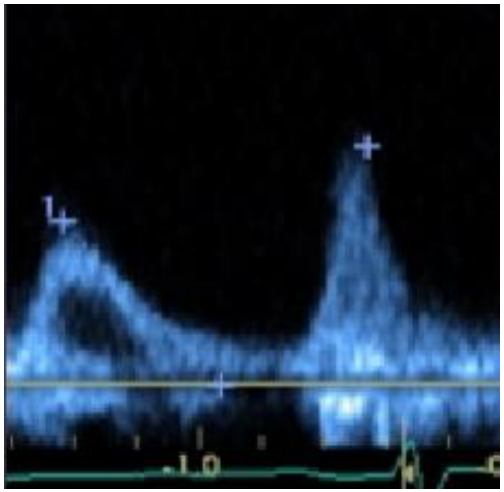
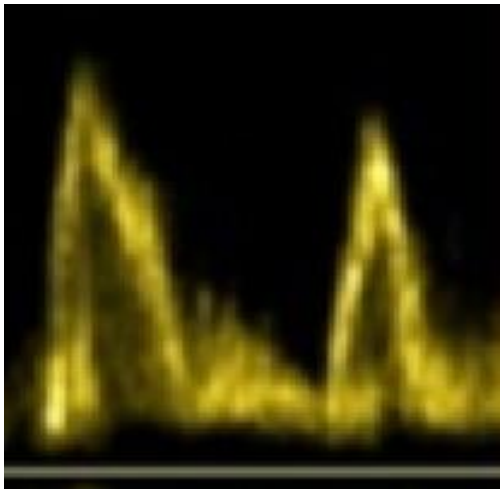
IT USED TO SEEM SO SIMPLE...

Patterns of Diastolic Function

In the beginning (mid ‘80s)…







But some sick patients still looked like this

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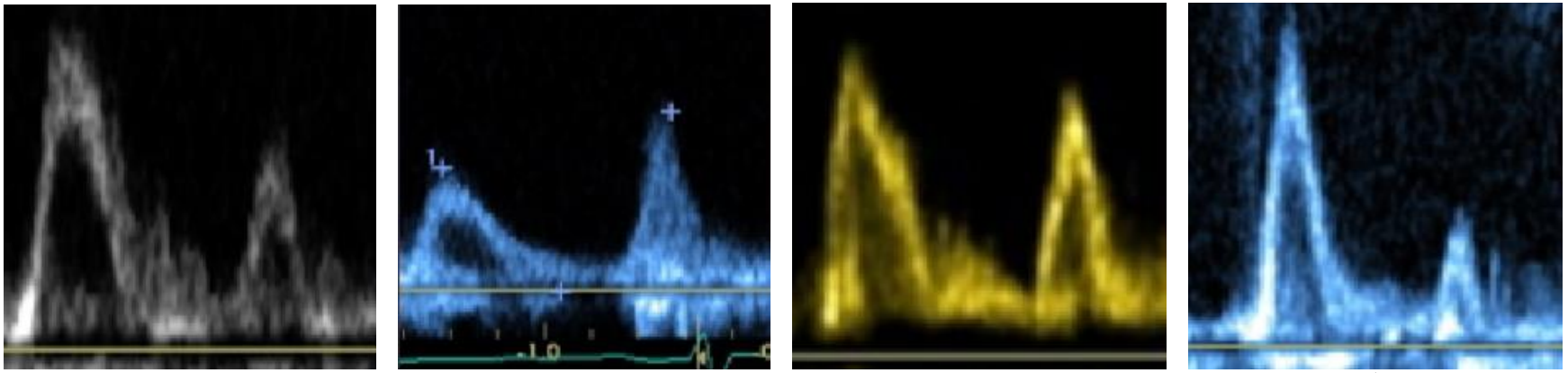
IT USED TO SEEM SO SIMPLE…

Patterns of Diastolic Function

In the beginning (mid ‘80s)…



And the sickest of all looked like this

AND WE STRUGGLED TO UNDERSTAND PSEUDONORMALIZTION

In the beginning (mid ‘80s)…

Analysis of the Early Transmitral Doppler Velocity Curve: Effect of Primary Physiologic Changes and Compensatory Preload Adjustment

JAMES D. THOMAS, MD, FACC, CHRISTOPHER Y. P. CHOONG, MB, BCHIR, PHD, FRANK A. FLACHSKAMPF, MD, ARTHUR E. WEYMAN, MD, FACC

Boston, Massachusetts

Left ventricular filling (as assessed by Doppler echocardiography) has previously been shown to depend in a complex fashion on ventricular diastolic function (compliance and relaxation) as well as other variables, such as atrial pressure and compliance, ventricular systolic function and mitral valve impedance. To study the effect of isolated physiologic alterations on individual Doppler indexes, a mathematic model of mitral flow was analyzed.

By varying one physiologic variable at a time, it was shown that mitral velocity acceleration is affected directly by atrial pressure and inversely by the ventricular relaxation time constant, with relatively little impact of chamber compliance. Deceleration rate was directly influenced by mitral valve area, atrial pressure and ventricular systolic dysfunction and inversely affected by atrial and ventricular compliance relations, with little impact of relaxation unless it was so delayed as to be incomplete during deceleration. Peak velocity was directly affected most strongly by initial left atrial pressure, and lowered somewhat by prolonged relaxation, low atrial and ventricular compliance and systolic dysfunction.

Strikingly different filling patterns emerged when the primary physiologic alterations were accompanied by simultaneous compensatory changes in atrial pressure designed to maintain stroke volume constant. Low ventricular compliance with preload compensation produced characteristic E waves with very short acceleration and deceleration times and high peak velocity. Thus, mathematic analysis of ventricular filling helps to explain the physical and physiologic basis for the transmitral velocity curve.

(J Am Coll Cardiol 1990;16:644–55)

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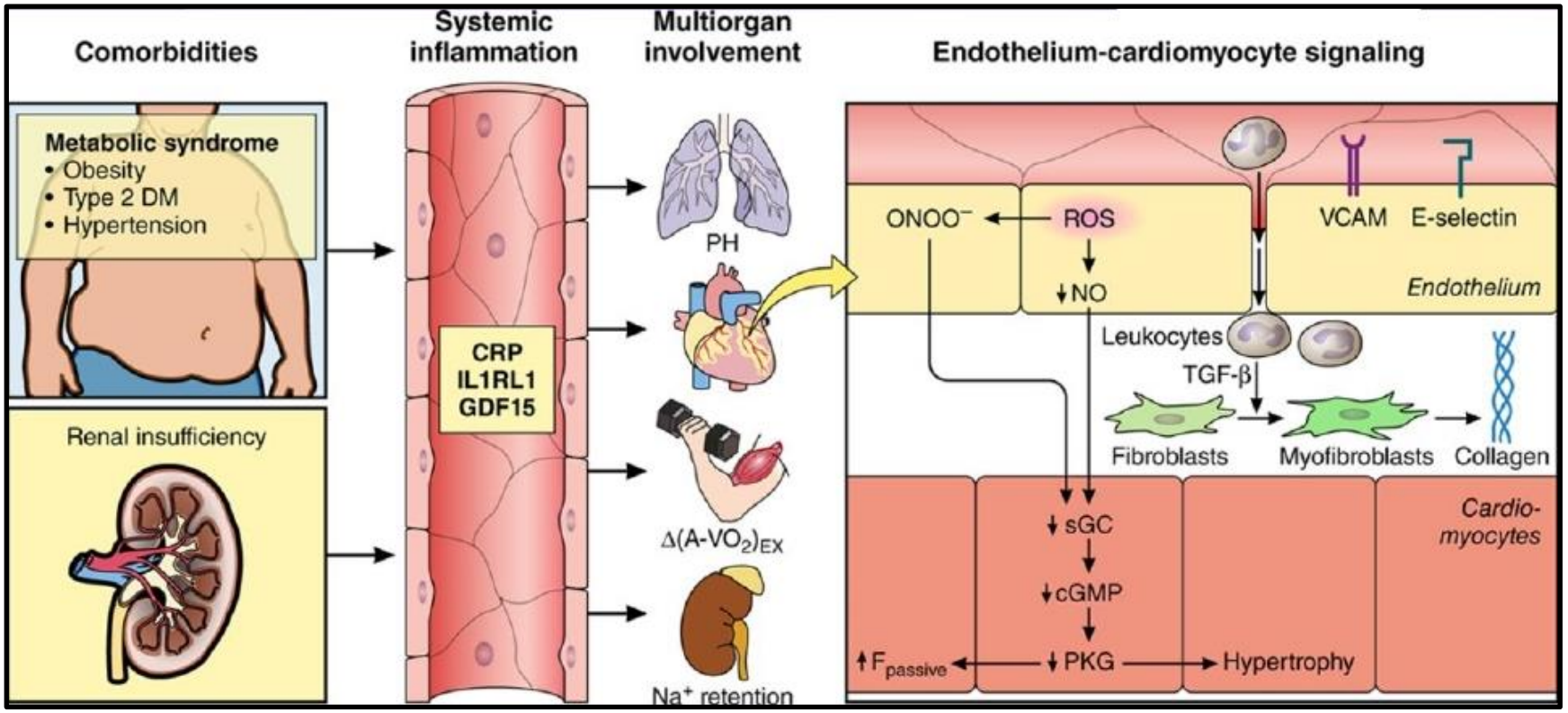
Thomas et al. JACC 1990; 16:644-55

PHENOTYPE – SPECIFIC TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION

A Multiorgan Roadmap



Key role of inflammation, altered signaling, fibrosis

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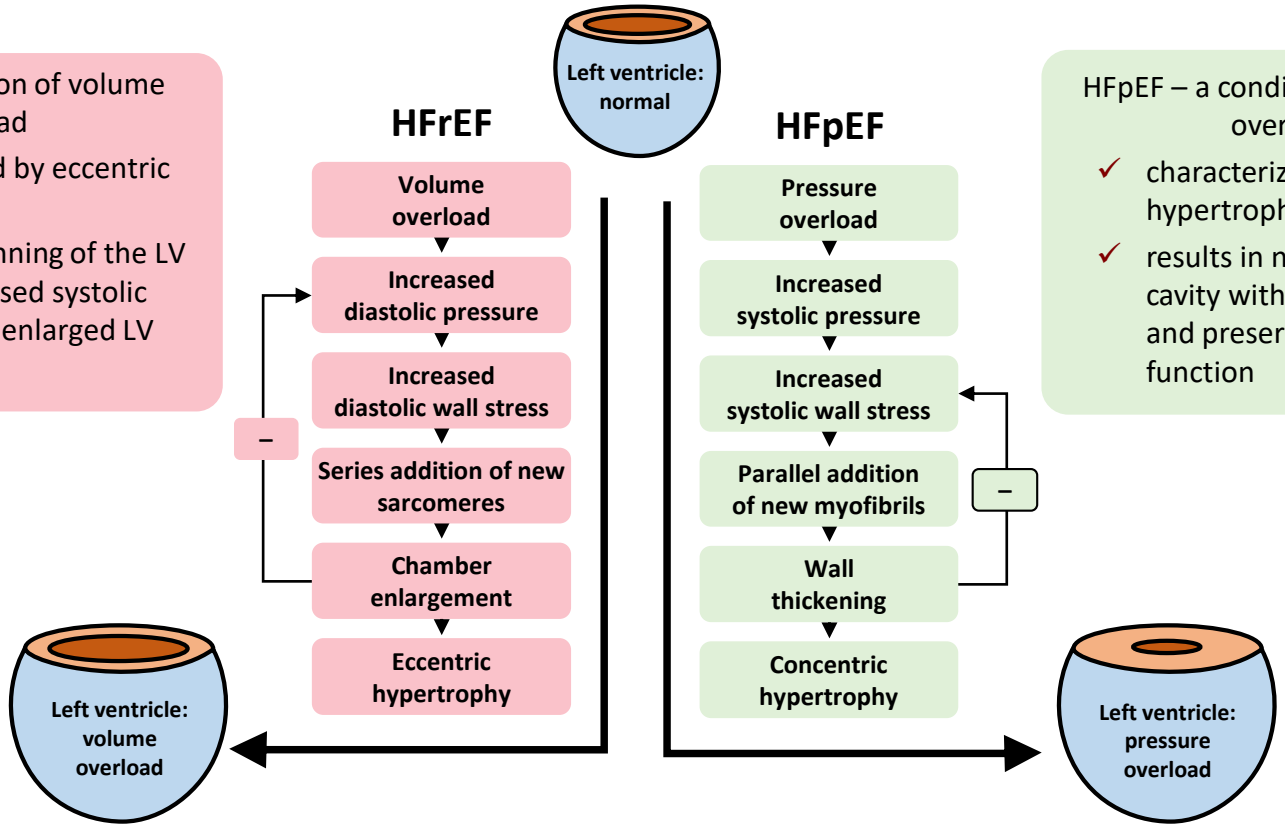
Shah SJ. Circulation 2016; 134: 73 -90

PATTERNS OF VENTRICULAR REMODELING ARE DIFFERENT FOR HFrEF AND HFpEF

HFrEF – a condition of volume overload

- ✓ characterized by eccentric hypertrophy
- ✓ results in thinning of the LV walls, decreased systolic function and enlarged LV volume



HFpEF – a condition of pressure overload

- ✓ characterized by concentric hypertrophic growth
- ✓ results in normal sized LV cavity with thickened walls and preserved systolic function

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular

Adapted from Colucci (Ed.). Atlas of Heart Failure, 5th ed. Springer 2008 Grossman et al. In: Perspectives in Cardiovascular Research; Myocardial Hypertrophy and Failure. Vol 7. Edited by Alpert NR. New York: Raven Press;1993:1–15

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An Approach To Diagnosing Heart Failure With Preserved Ejection Fraction

Patient presents with exertional dyspnoea

- ✓ Take history & perform physical examination
- ✓ Measure natriuretic peptides
- ✓ Exclude other causes (pulmonary disease, ischaemic heart diseases, anaemia, physical deconditioning)
- ✓ Assess risk factor profile (advanced age, hypertension, raised BMI)

Clinical diagnosis of heart failure made when following diagnostic criteria met:

- ✓ Presence of typical symptoms & signs of heart failure (including breathlessness, reduced exercise tolerance, fatigue & ankle swelling) – features such as a displaced apex beat & third heart sound may be absent in heart failure
- ✓ Elevated natriuretic peptides (BNP ≥ 35 pg/mL or NT-pro BNP ≥ 125 pg/mL)
- ✓ Other causes excluded (pulmonary disease, ischaemic heart diseases, anaemia, physical deconditioning)

Perform transthoracic echocardiography (resting)

The following features on resting echocardiography are consistent with a diagnosis of HFpEF (not all need be present)

- ✓ Raised pulmonary pressures (TR jet velocity > 2.8 m/s)
- ✓ Left atrial enlargement (left atrial volume index > 34 mL/m^2)
- ✓ Raised E/e' ratio (≥ 13)
- ✓ Increased wall thickness (LV mass index > 115 g/m^2 for men: > 95 g/m^2 for women)

Consider exercise study in consultation with cardiologist to confirm impaired diastolic performance & elevated filling pressures

- ✓ Exercise right heart catheterisation – the gold standard measurement of haemodynamics, but not available in all centres
- ✓ Stress echocardiography – non-invasive, but relies on good image quality & the presence of tricuspid regurgitation

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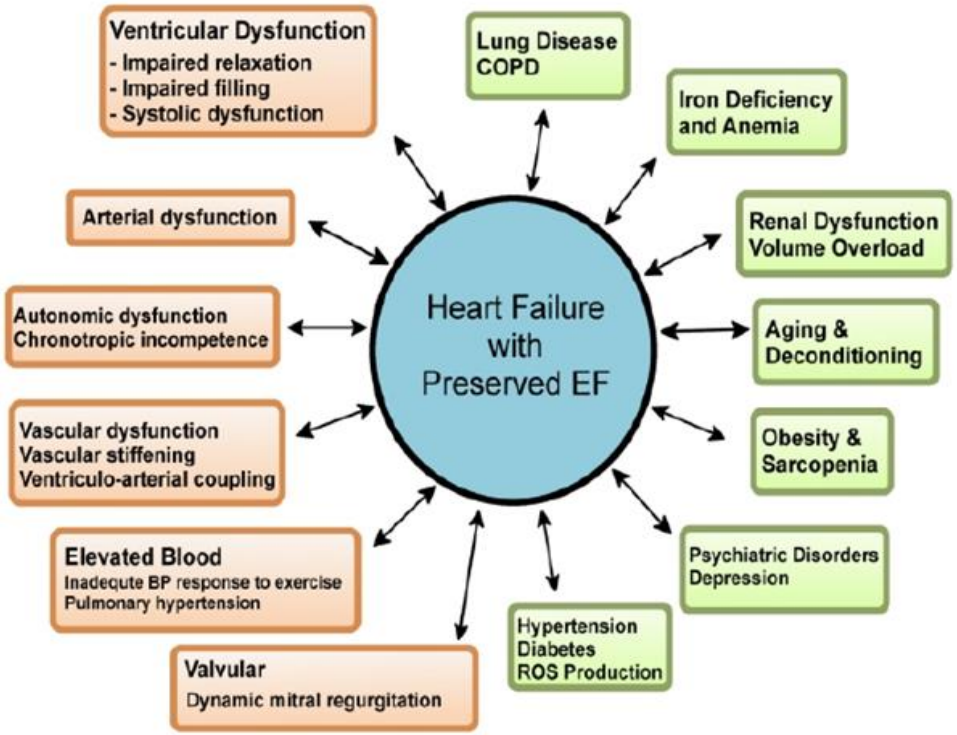
Case Study

What are the risk factors for development of HFpEF?

ESC 016: WHO ARE THESE PATIENT?

Typical demographics and co-morbidities associated with HFpEF

Advanced age
Arterial hypertension
Atrial fibrillation
Female gender
Kidney dysfunction
Metabolic syndrome
Obesity
Physical deconditioning
Pulmonary disease (e.g. COPD)
Pulmonary hypertension
Sleep apnoea



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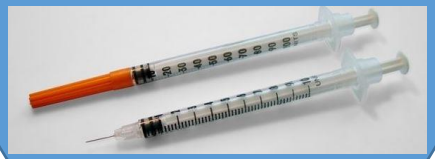
Senni M, et al EHJ 2014; Ponikowski et al EHJ 2016

FEATURES ASSOCIATED WITH HEART FAILURE WITH NORMAL EF

Hypertension
76 – 88 %

Diabetes
27 – 45 %



Obesity
28 – 50 %

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CLINICAL CHARACTERISTICS IN PATIENTS WITH HEART FAILURE WITH NORMAL EF

	I-PRESERVE (*n*=4133)	OPTIMIZE-HF[17] (*n*=21,149)	ADHERE[18] (*n*=26,322[c])
Age (yr)	72	75	74
Female (%)	60	62	62
Co-morbidity (%)			
Any CHD	48	38[c]	50
MI	24	–	24
Angina	40	–	–
Hypertension	88	76	77
Diabetes	27	43	45
AF	29	33[d]	21[d]
Valve disease	11	–	21
COPD	10	–	31
ECG LVH	31	–	–
Physiological measures			
BMI kg/m^2	29.6	–	–

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McMurray J et al. EJHF 2008

CASE STUDY

HFpEF has similar prevalence as heart failure with reduced ejection fraction

True or false?

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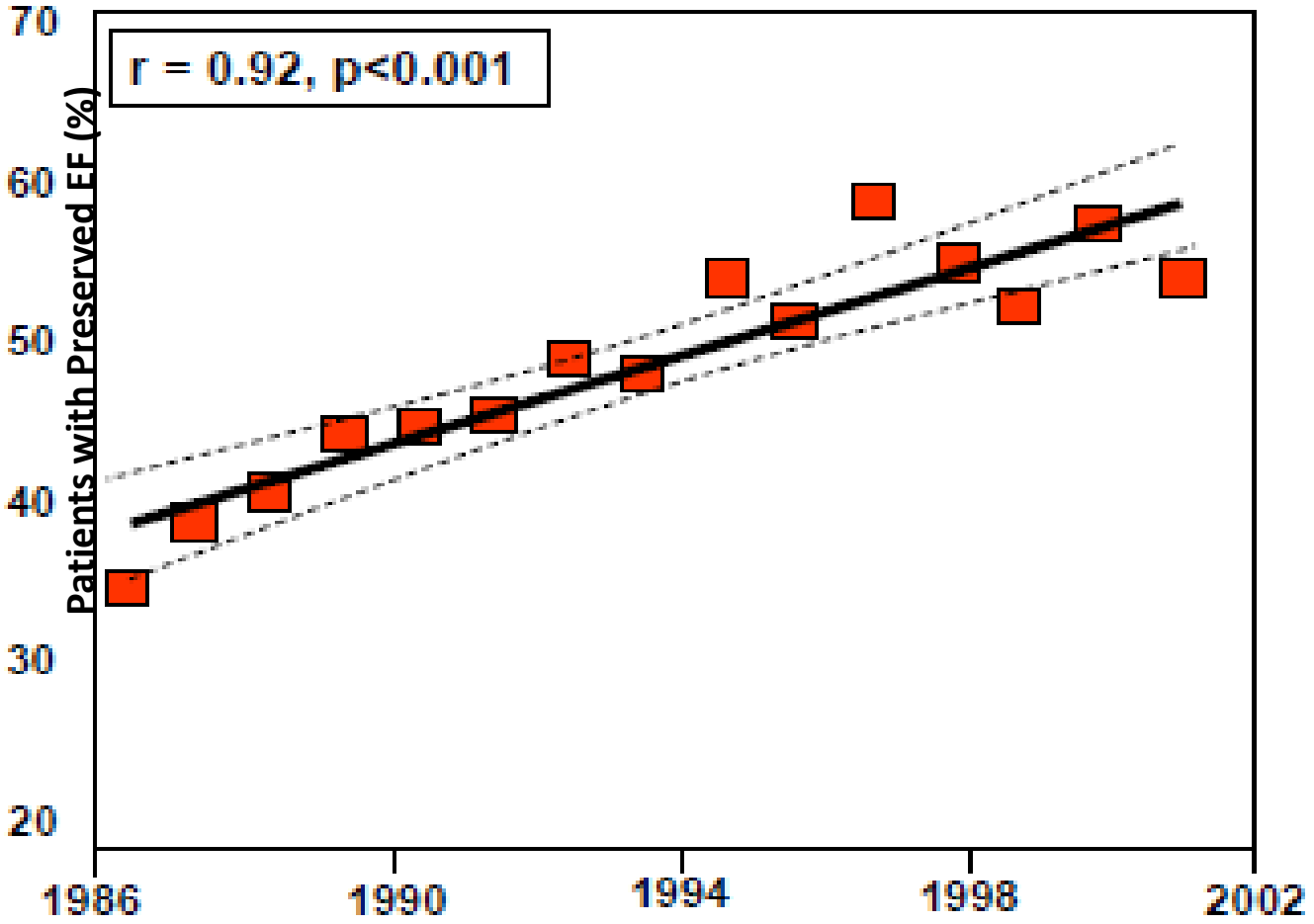
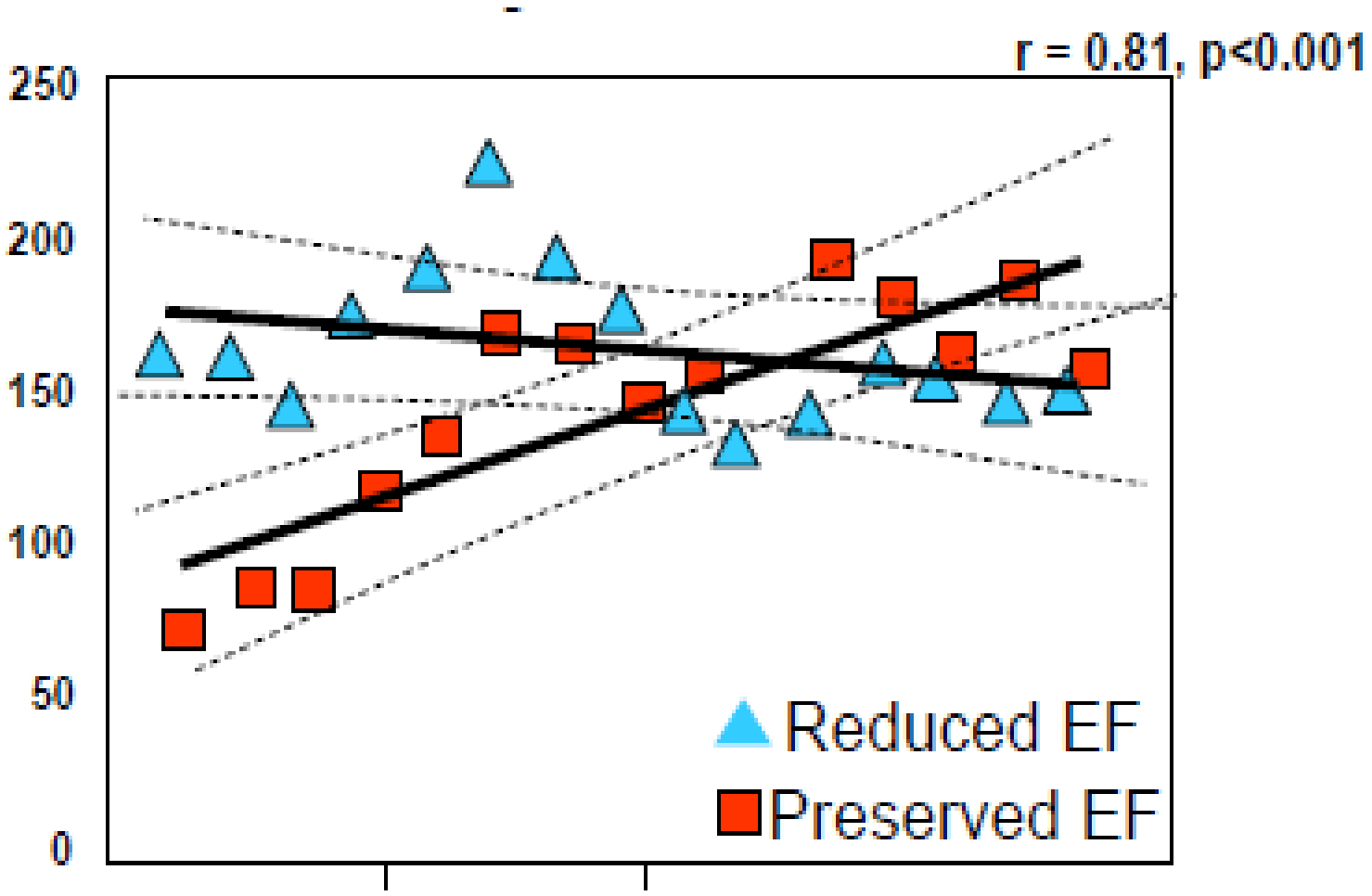
INCREASE IN HEART FAILURE PATIENTS WITH PRESERVED EJECTION FRACTIONS



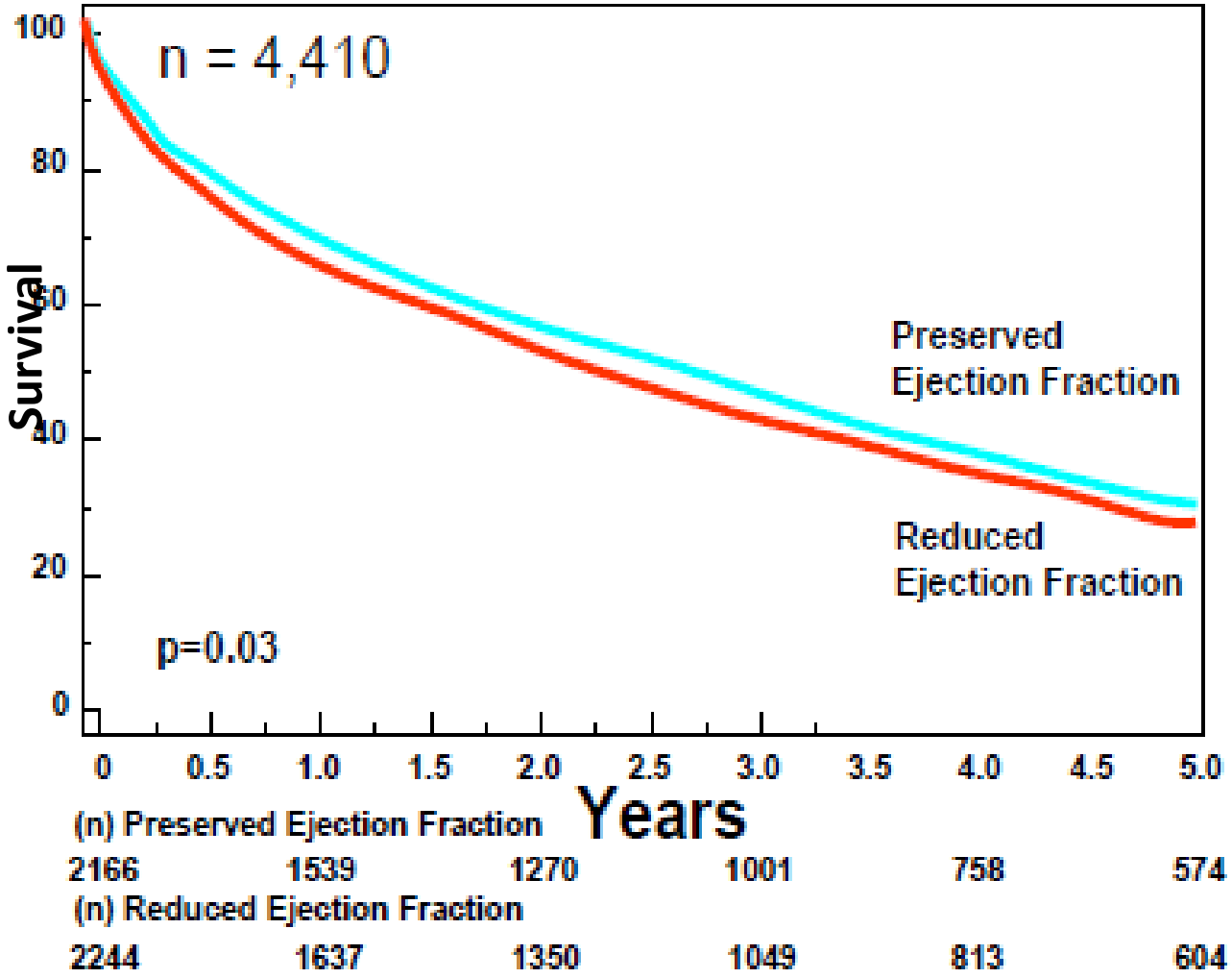
Owan T et al. NEJM 2006

INCREASE IN ADMISSIONS OF HEART FAILURE PATIENTS WITH PRESERVED EJECTION FRACTIONS



Owan T et al. NEJM 2006

SURVIVAL IN PATIENTS WITH HEART FAILURE



Owan T et al. NEJM 2006

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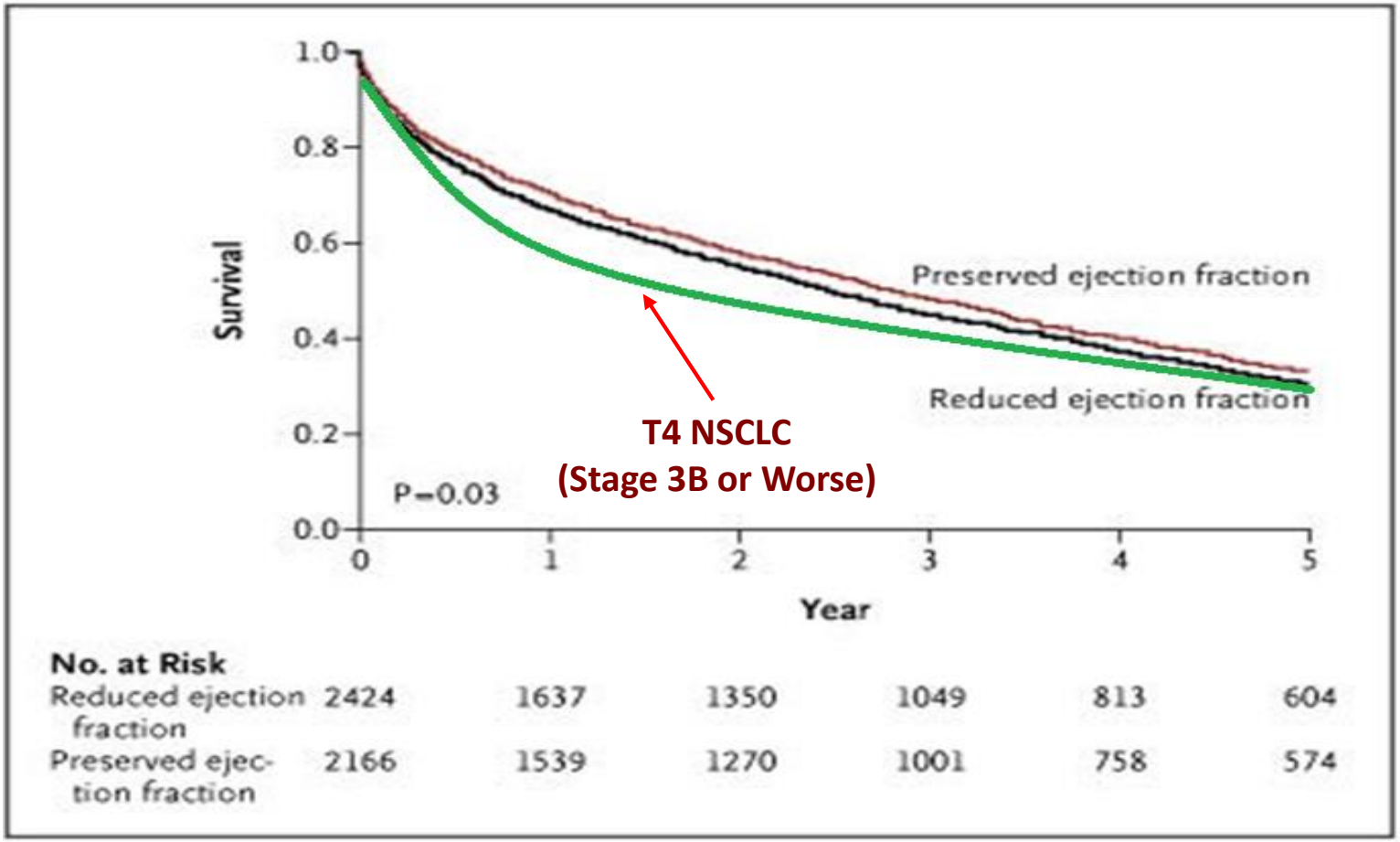
POOR OUTCOME IN HFpEF

Survival for EF ≥ 50% & < 50 %

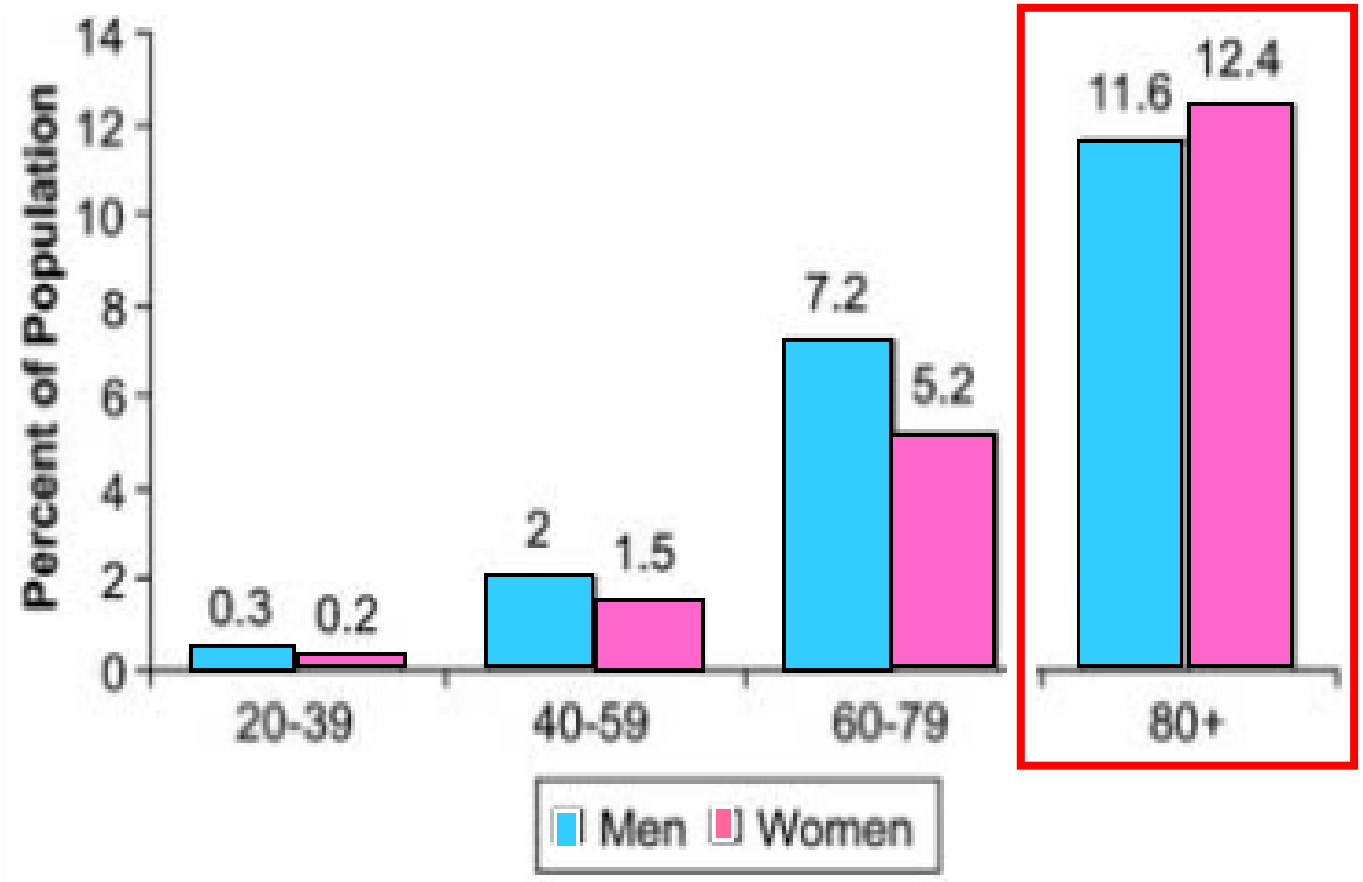


As bad as advanced lung cancer!

Heart Failure Society of South Africa [HFSSA]

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

HEART FAILURE WITH NORMAL EF MORE COMMON IN ELDERLY



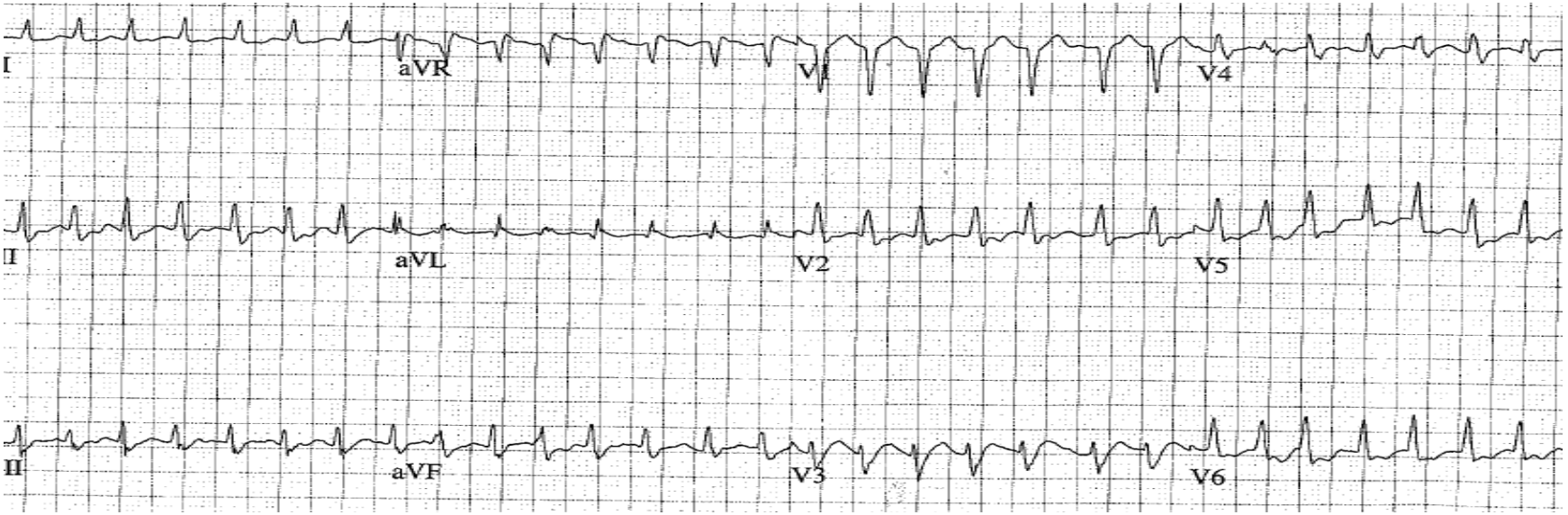
Heart Failure Society of South Africa [HFSSA]

Chen M. AJM 2009

CASE HISTORY

This patient now develops atrial fibrillation

How would you manage this patient?



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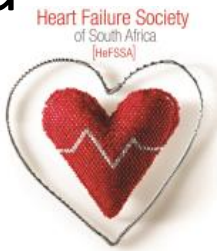
GENERAL PRINCIPLES OF MANAGEMENT

4. **Atrial Fibrillation?**
   - Restore SR if possible
   - Anticoagulation as indicated
5. **Signs of hypervolemia or pulmonary congestion?**
   - Loop diuretics
   - Restrict volume & salt intake
6. **Physical inactivity / overweight?**
   - Implement physical activity / exercise training programs
   - Initiate weight loss preferably by structured programs



CASE STUDY

What treatment options do you offer?

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ESC 2016: SPECIFIC HFPEF THERAPIES?

ESC 2016:

"No treatment has been shown, convincingly, to reduce morbiditiy and mortality in patients with HFpEF or HFmrEF"

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THERAPY FOR DIASTOLIC HEART FAILURE

- ✓Relieve VOL; diuresis, fluid / Na + restriction dialysis
- ✓Decrease HR; beta-blockade, verapamil, dilitiazem. In AF, digoxin, AV ablation + pacer
- ✓Relieve Ischaemia; revascularization, med Rx
- ✓Regress LVH; treat HBP aggressively, ARBs
- ✓Reduce Fibrosis; aldosterone antagonists?
- ✓Statins???

CHARM STUDY

Candesartan in Heart failure
Assessment of Reduction in Mortality
& Morbidity

CHARM STUDIES

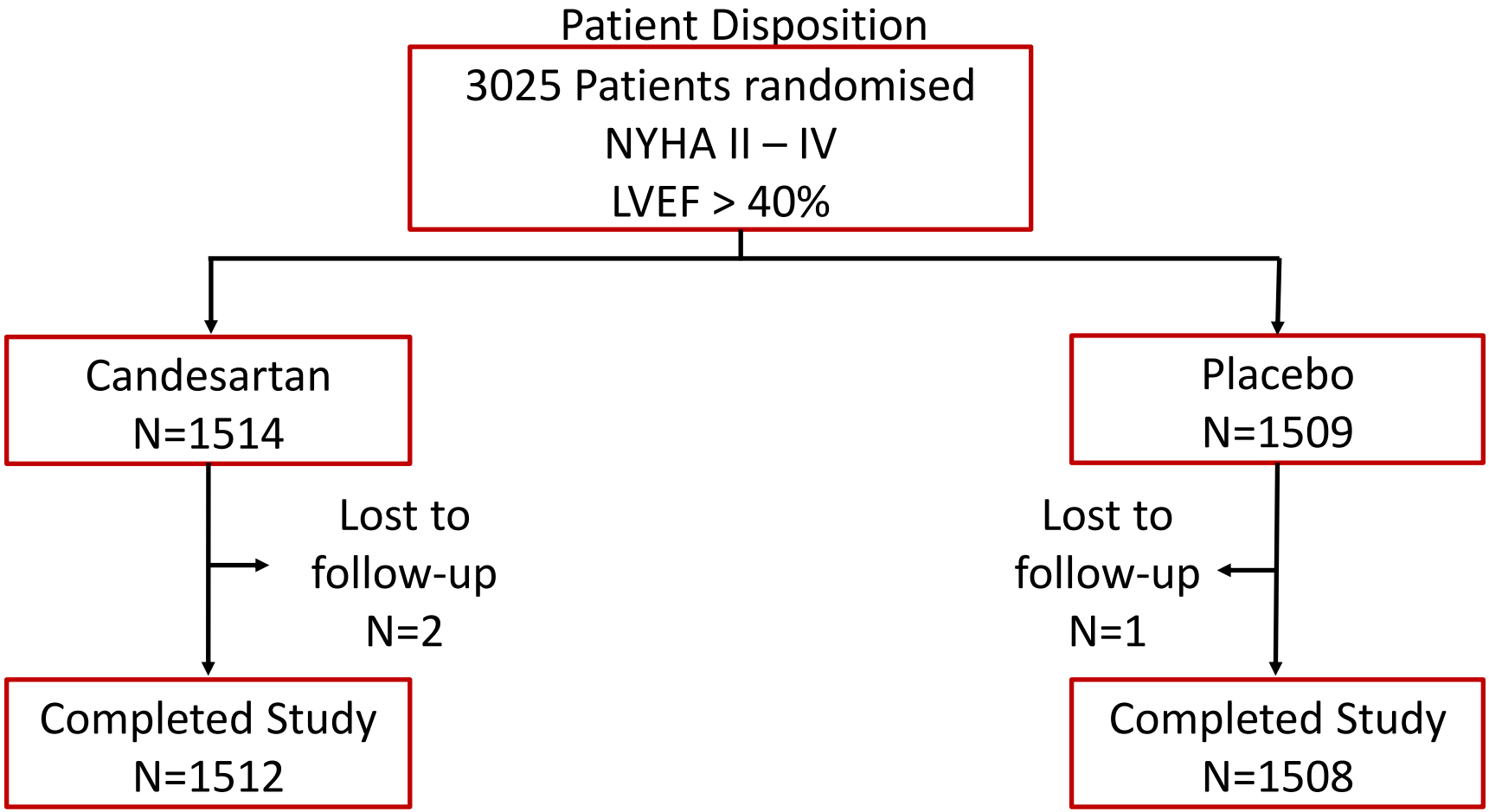
3 Component Trials Comparing
Candesartan to Placebo

CHARM Alternative	CHARM Added	CHARM Preserved
N = 2028 LVEF ≤ 40% ACE Inhibitor Intolerant	N = 2548 LVEF ≤ 40% ACE Inhibitor Treated	N = 3025 LVEF > 40% ACE Inhibitor Treated /Not Treated

Primary Outcome:
CV Death or CHF Hospitalizations

Yusuf S et. al Lancet 2003

CHARM - PRESERVED



Median follow – up, 37 months

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Yusuf S et. al Lancet 2003

DIASTOLIC HEART FAILURE: CURRENT TRIALS

I – PRESERVE (Irbesartan in Hearth Failure with Preserved Systolic Function)

- ✓4100 patients (LVEF > 45%, age > 60) Irbesartan vs. Placebo
- ✓Primary Endpoint – Death & CV hospitalization

TOPCAT (Aldosterone Antagonism for Heart Failure and Preserved Systolic Function)

- ✓4500 patient (LVEF > 45%, age > 50) spironolactone vs. Placebo
- ✓4 year – CV mortality / HF hospitalization

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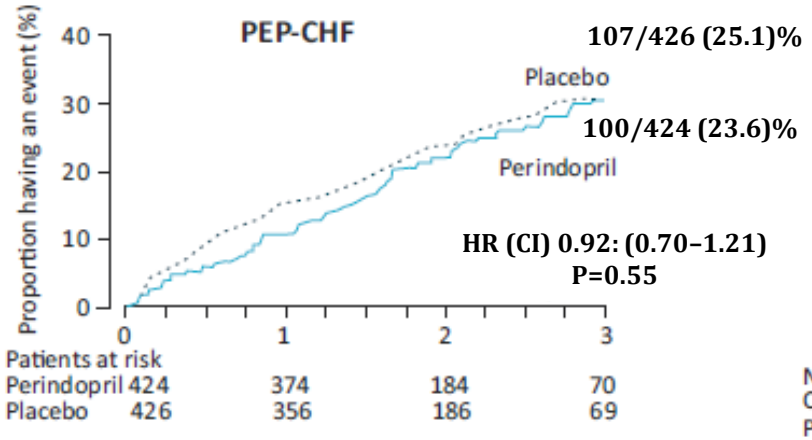
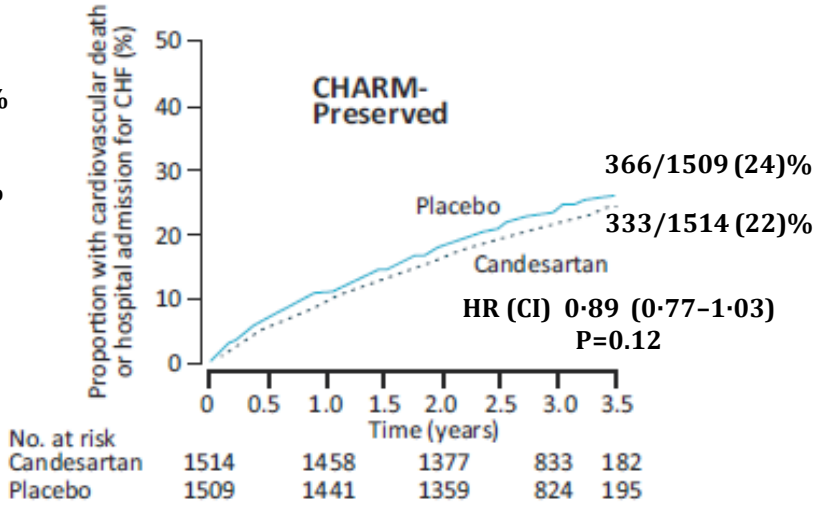
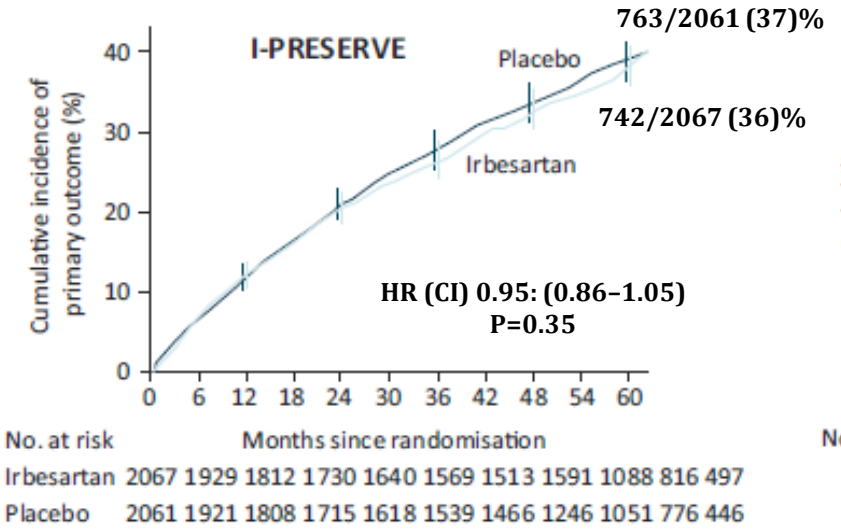
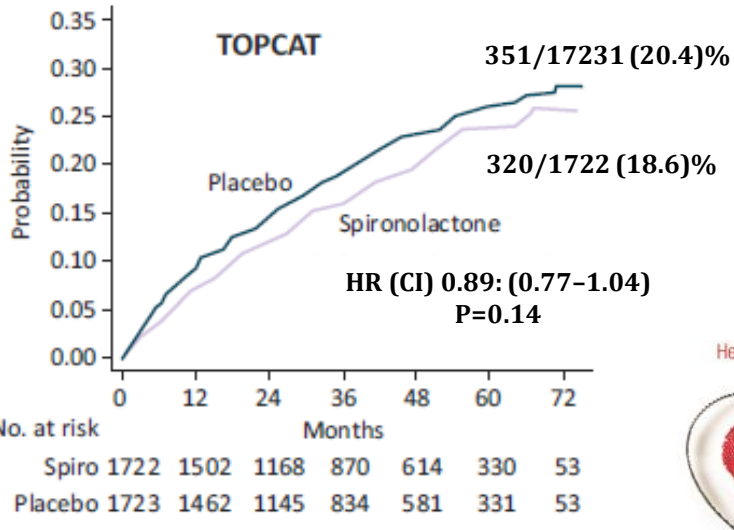
KEY LARGE RCTS IN HF-PEF



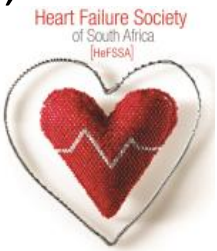






GENERAL PRINCIPLES OF MANAGEMENT

1. **Optimal Control Of Risk Factors & Co-morbidities?**
   - BP < 130/80 mmHg (preferentially by RAS blocker)
   - HBAIC < 6.5 – 7.5 mg % (Metformin, SGL2 – Inhibitor; avoid insulin wherever possible)
   - Statin therapy in indicated
   - Correct myocardial ischemia
   - Treat pulmonary disease
2. **Inadequate hypertensive blood pressure response to exercise?**
   - Stress test – optimize BP response
3. **Heart rate response to exercise?**
   - Tachycardiac – control inadequate increases in heart rate
   - Chronotropic incompetence? Reduce bradycardiac agents, consider PM



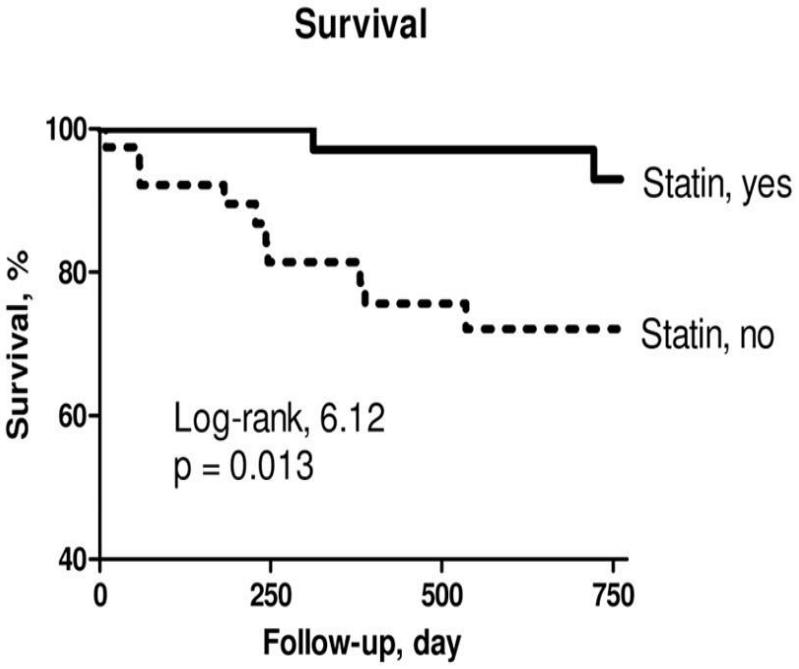
STATIN THERAPY MAY BE ASSOCIATED WITH LOWER MORTALITY IN PATIENTS WITH DIASTOLIC HEART FAILURE

Observational Study:

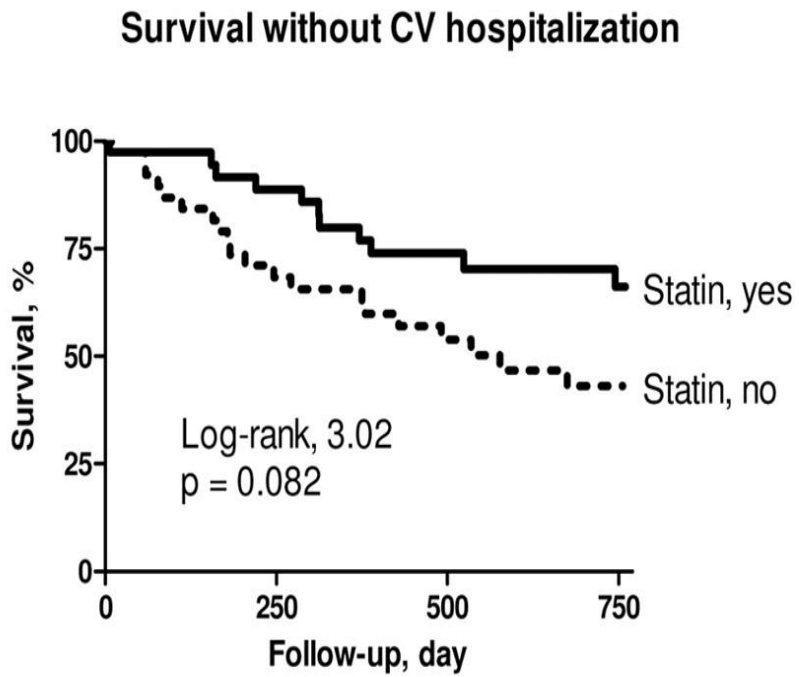
- ✓137 Patients with CHF & EF > 50% followed for 21 months
- ✓68 received statins, 69 did not
- ✓Initial LDL 153 for statin group fell to 101
- ✓For non-statin group LDL was 98

Fukuta H et. al Circ 2005:112;357-363

KAPLAN – MEIER SURVIVAL & SURVIVAL WITHOUT CARDIOVASCULAR HOSPITALIZATION IN PROPENSITY MATCHED PATIENTS GROUPED BY STATIN THERAPY



No. at risk				
Statin, yes	42	36	28	23
Statin, no	42	31	24	18

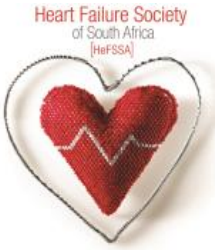


No. at risk				
Statin, yes	42	32	21	17
Statin, no	42	26	17	13

Fukuta H et. al Circ 2005:112;357-363

RECOMMENDATIONS FOR TREATMENT OF PATIENTS WITH HFpEF & HFmrEF

Recommendations	Class[a]	Class[b]
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



Ponikowski et al., Eur Heart J. 2016 Jul 14;37(27):2129-200.

ESC 2016: MANAGEMENT OF SPECIFIC COMORBIDITIES

Recommendations	Class[a]	Level[b]
Iron deficiency		
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100 – 299 µg/L and transferrin saturation < 20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life	IIa	A
Diabetes		
Metformin should be considered as a first – line treatment of glycaemic control in patients with diabetes and HF, unless contra-indicated	IIa	C

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Ponikowski et al., Eur Heart J. 2016 Jul 14;37(27):2129-200.

TREATMENTS NO RECOMMENDED FOR CO-MORBIDITIES IN PATIENTS WITH HF

Diabetes			
Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization	III	A	209, 210
Arthritis			
NSAIDs or COX – 2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization	IIa	C	211-213

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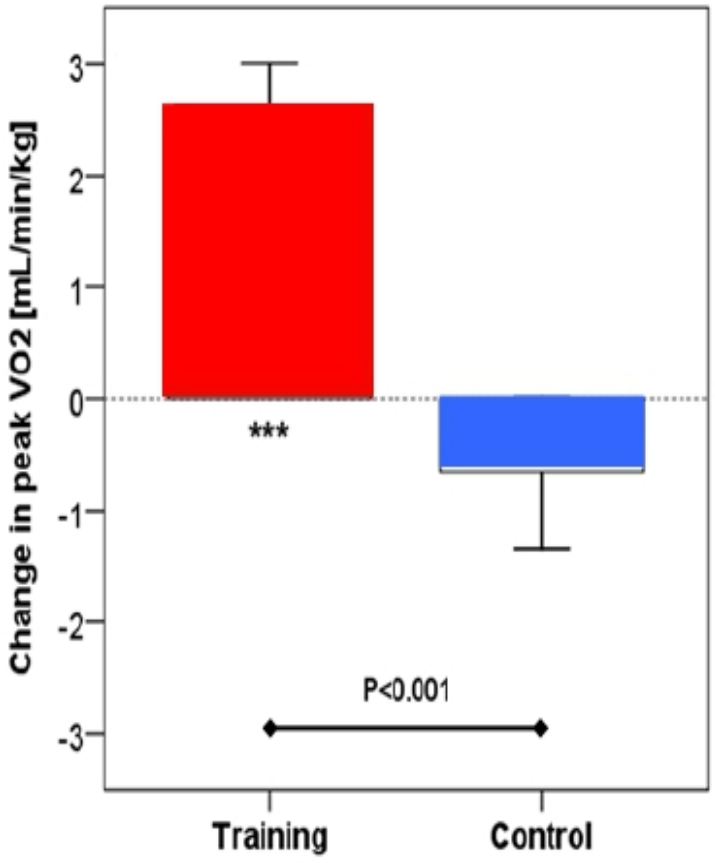
Ponikowski et al., Eur Heart J. 2016 Jul 14;37(27):2129-200.

WEIGHT LOSS & EXERCISE TRAINING

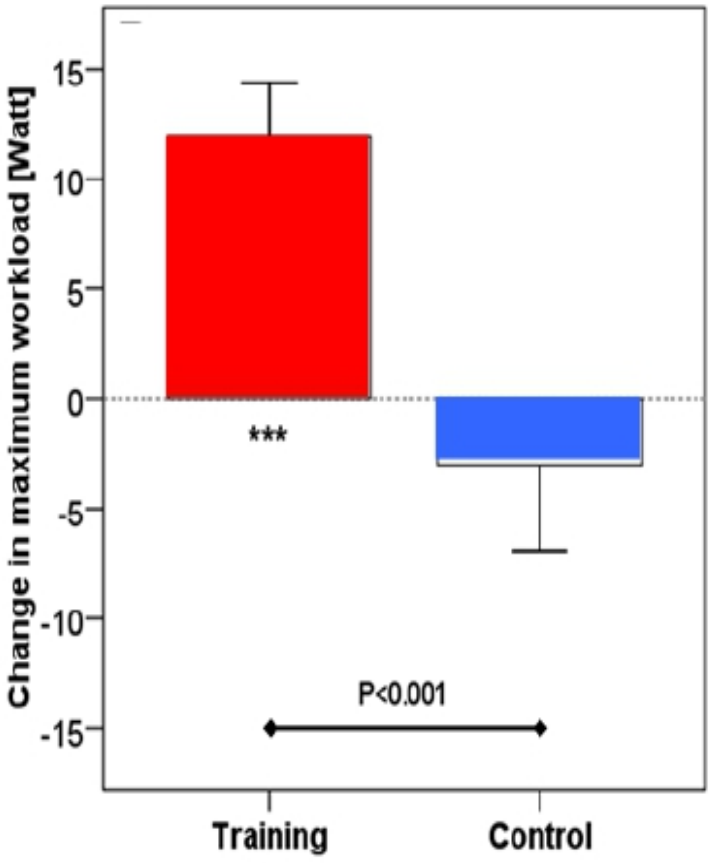
Heart Failure Society of South Africa [HeFSSA]

EX – DHF PILOT: EXERCISE TRAINING IN ELDERLY HFpEF

Primary Endpoint: peak VO2



Maximum Workload



HFpEF=heart failure with preserved ejection fraction.

Edelmann et al., JACC 2011;58:1780–91.

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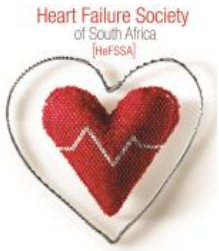
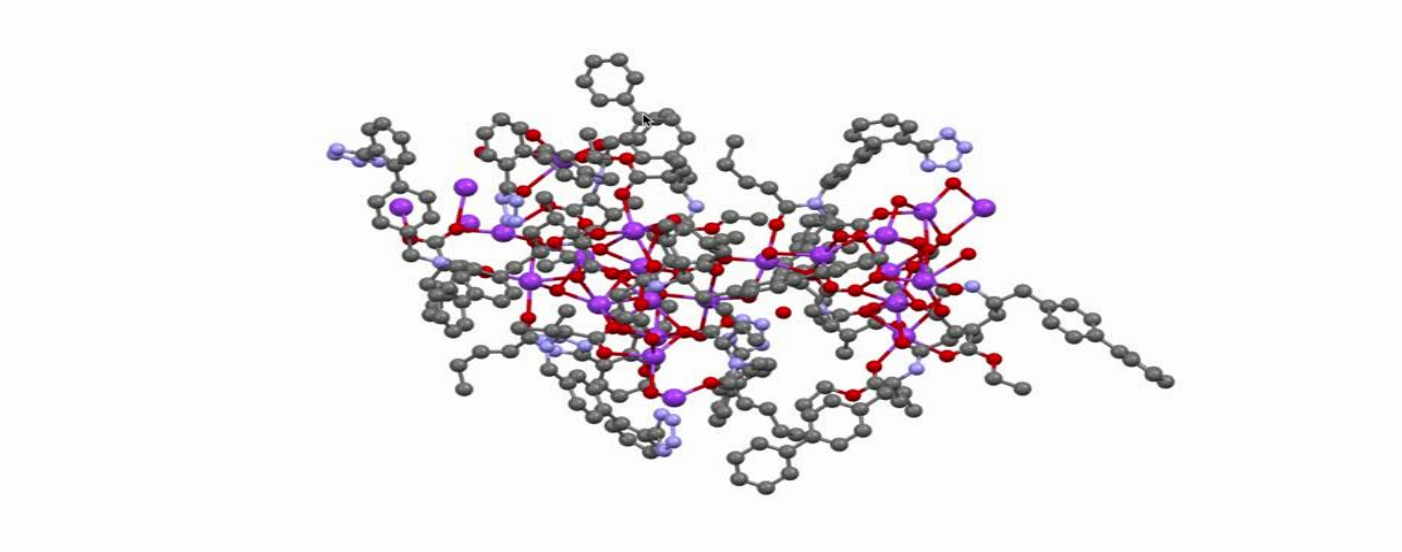
THERAPEUTIC TARGETS FOR HFpEF WEIGHT LOSS & EXERCISE TRAINING

- ✓Obesity and inactivity are risk factors for DM, HTN, HL
- ✓Obesity also pro-inflammatory and impairs cardiac, renal, arterial, and skeletal muscle function
- ✓Fat infiltration in muscle reduces O2 diffusion and lowers A-V O2 difference

Oktay AA, Shah SJ. Curr Cardiol Rev 2014



LCZ696: FIRST IN CLASS DUAL-ACTING ANGIOTENSIN RECEPTOR NEPRILYSIN INHIBITOR



- ✓ LCZ696 is a crystalline complex comprised of 6 valsartan moieties, 6 sacubitril [AHU377] moieties, sodium cations, and water held together by network of hydrogen bonds
- ✓ Valsartan in LCZ696 is present in anionic form – therefore more bioavailable than in valsartan as a free acid. 200mg of LCZ696 is equivalent to 160mg of standard valsartan

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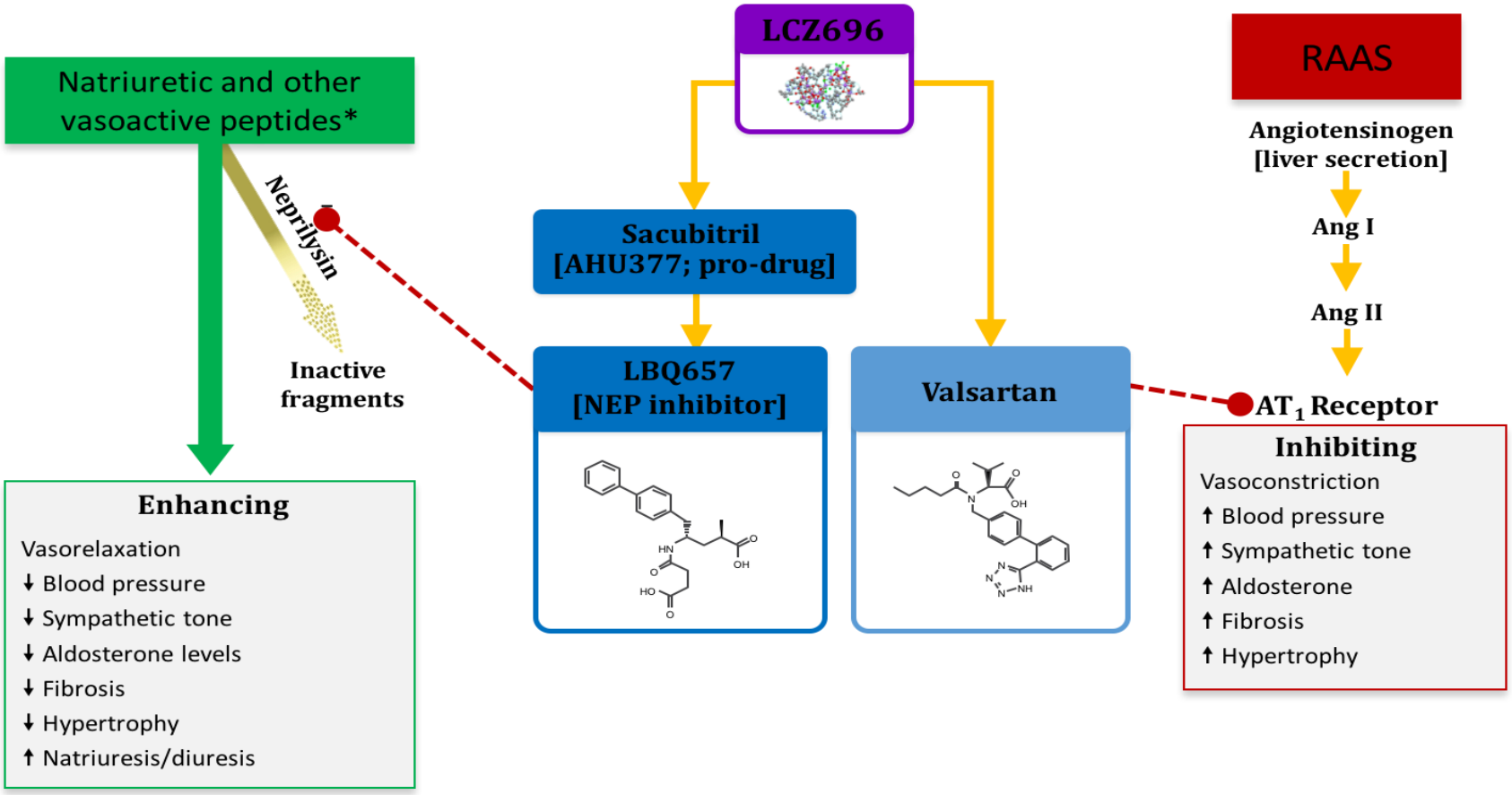
LCZ696 SIMULTANEOUSLY INHIBITS NEP [VIA LBQ657] & BLOCKS THE AT_1 RECEPTOR [VIA VALSARTAN]



**Neprilysin substrates listed in order of relative affinity for NEP: ANP, CNP, Ang II, Ang I, adrenomedullin, substance P, bradykinin, endothelin-1, BNP Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42; Schrier & Abraham N Engl J Med 2009;341:577–85; Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9;Feng et al. Tetrahedron Letters 2012;53:275–6*

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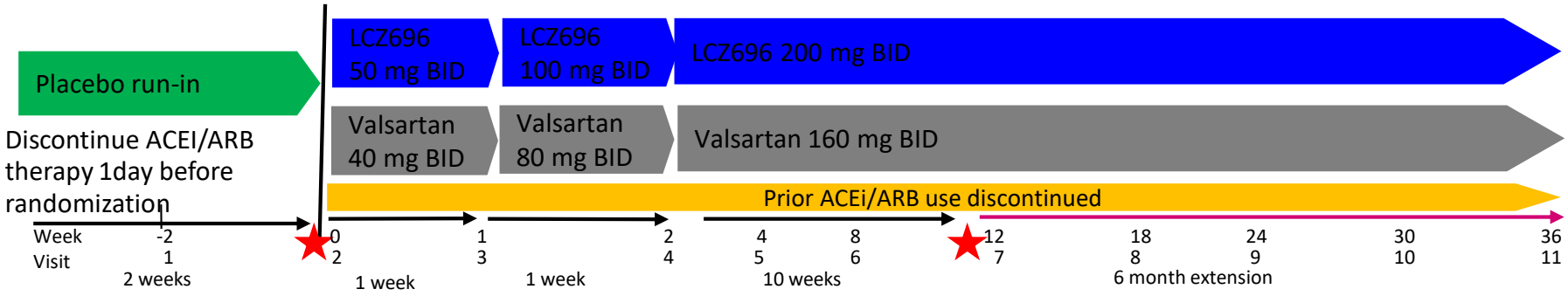
PARAMOUNT: "PROOF OF CONCEPT" STUDY IN HF-PEF



Design	✓ 36 wks, randomized, double-blind, active controlled study evaluating LCZ 200 mg bid compared to valsartan 160 mg bid [12 weeks core study followed by 6 month extension] ✓ LCZ 696 and valsartan will be progressively up-titrated to the target doses
Primary objective	NT pro-BNP reduction from baseline at 12 weeks [core study]
Secondary objectives	✓ HF symptoms and QoL – KCCQ & Clinical Composite Assessment [NYHA + PGA] ✓ Echocardiographic parameters of diastolic function, cardiac filling pressures, and PASP ✓ Evaluate the effects on BNP, ANP, and cGMP as well as collagen markers ✓ Renal function and safety and tolerability ✓ Arterial stiffness [PWV, AI, central BP] in sub-population
Population	Approximately 300 pts >40 years, NYHA class II-IV, EF ≥45% & NT pro-BNP >400 pg/ml
Sample size	✓ 80% power to detect a 25% reduction in NT pro-BNP vs comparator

★ *Baseline randomization visit and visit at end of 12 weeks of core study*

Heart Failure Society of South Africa [HeFSSA]

PARAMOUNT

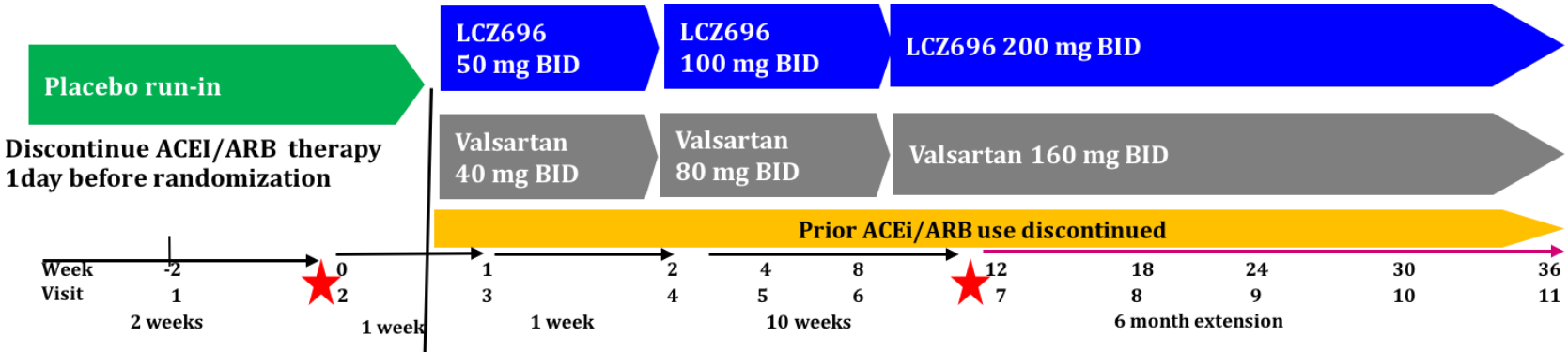
The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

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

- ✓ 301 patients ≥40 years
- ✓ Stable chronic HF [NYHA II-IV] with signs and symptoms [dyspnea on exertion/ orthopnea/ paroxysmal nocturnal dyspnea/ peripheral edema]
- ✓ LVEF ≥ 45%
- ✓ Plasma NT-proBNP > 400 pg/ml at screening

Heart Failure Society of South Africa [HFSSA]

PARAMOUNT: "PROOF OF CONCEPT" STUDY IN HF-PEF



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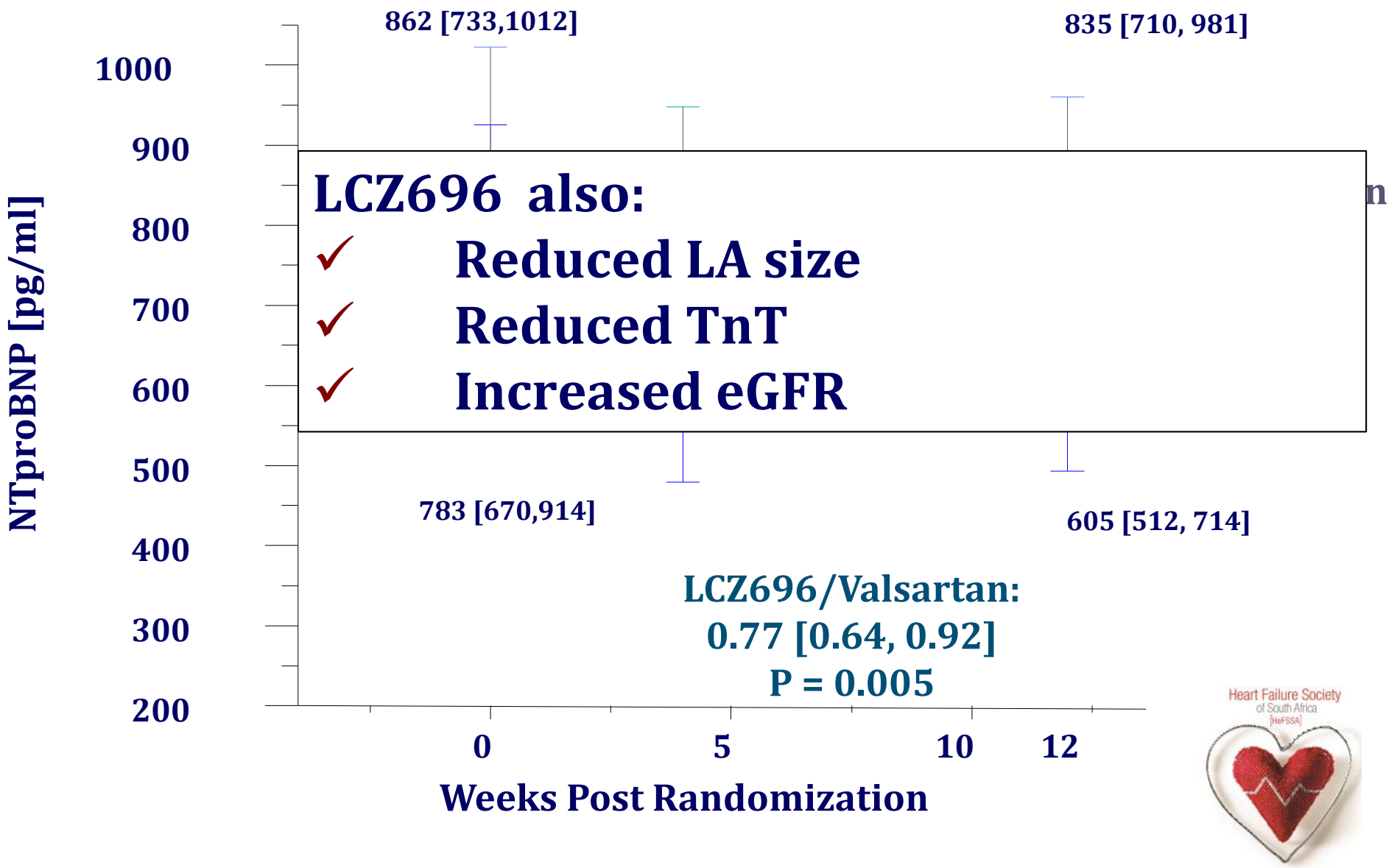
Sample size	✓ 80% power to detect a 25% reduction in NT pro-BNP vs comparator

★ *Baseline randomization visit and visit at end of 12 weeks of core study*

Heart Failure Society of South Africa [HeFSSA]

PARAMOUNT: PRIMARY ENDPOINT [NT-proBNP at 12 Weeks]

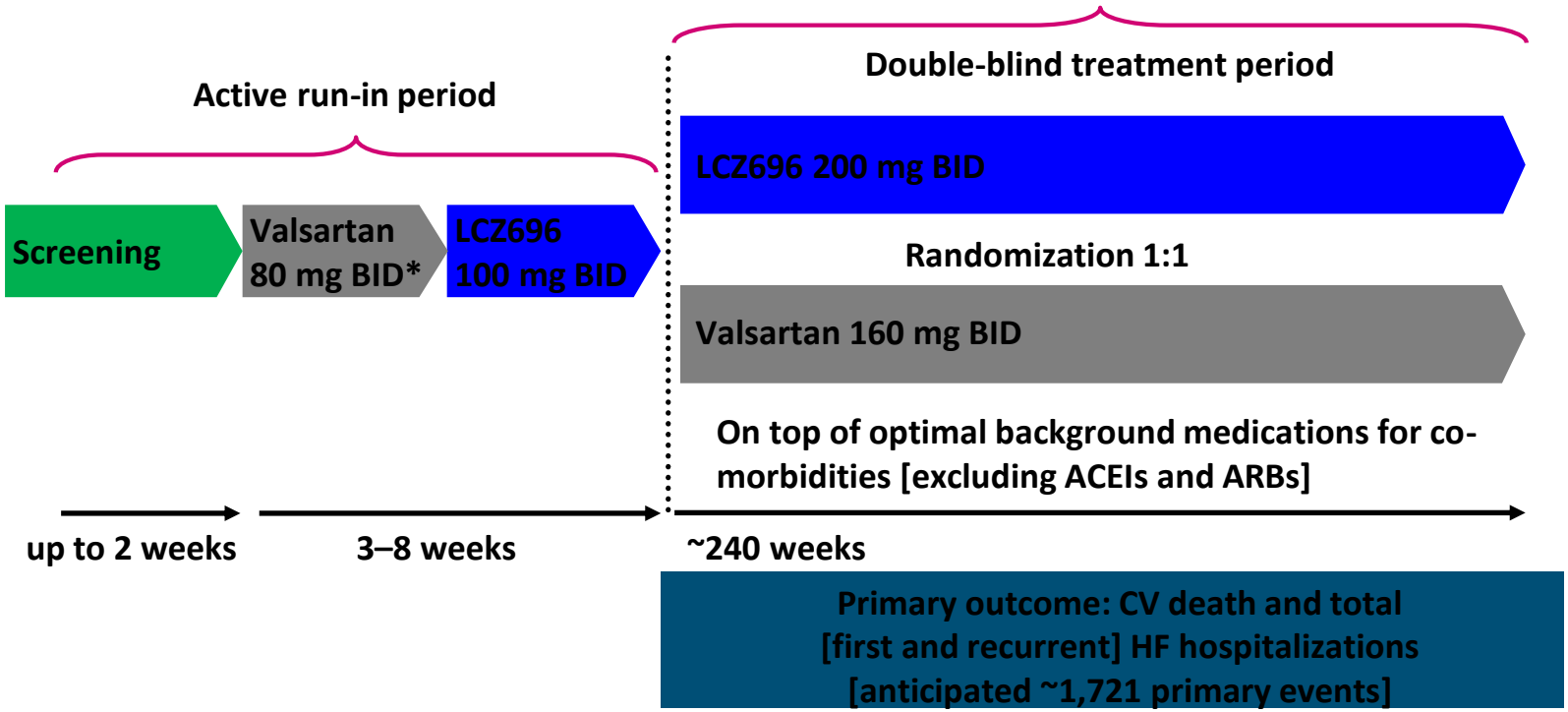


PARAGON-HF

Prospective comparison of ARni with Arb Global Outcomes in heart failure with preserved ejectioN fraction

PARAGON-HF: STUDY DESIGN

Target patient population: ~4,300 patients with symptomatic HF [NYHA Class II–IV] and LVEF ≥45%



*Valsartan 40 mg BID (up to 2 weeks) followed by valsartan 80 mg BID as an optional starting run-in dose for patients treated with less than the minimum dose of ACEI or ARB at Visit 1. ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BID=twice daily; CV=cardiovascular; HF=heart failure; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association.

PARAGON-HF: KEY OBJECTIVES/ENDPOINTS

Primary objective

- ✓ To compare LCZ696 to valsartan in reducing the rate of the composite endpoint of CV mortality and total [*first and recurrent*] HF hospitalizations

Secondary objectives

- ✓ To compare LCZ696 to valsartan in:
  - reducing the rate of the composite endpoint of CV mortality, total HF hospitalizations, total non-fatal strokes, and total non-fatal MIs
  - improving NYHA functional classification at 8 months
  - delaying time to new onset AF
  - delaying time to all-cause mortality

PARAGON-HF: KEY INCLUSION AND EXCLUSION CRITERIA

Key inclusion criteria:

- ✓ Age ≥55 years; LVEF ≥45%
- ✓ Symptoms of HF requiring treatment with diuretic[s]

  for ≥30 days prior to study entry
- ✓ Current symptomatic HF
  [NYHA class II–IV]
- ✓ Structural heart disease
  [LAE and/or LVH]

AND either

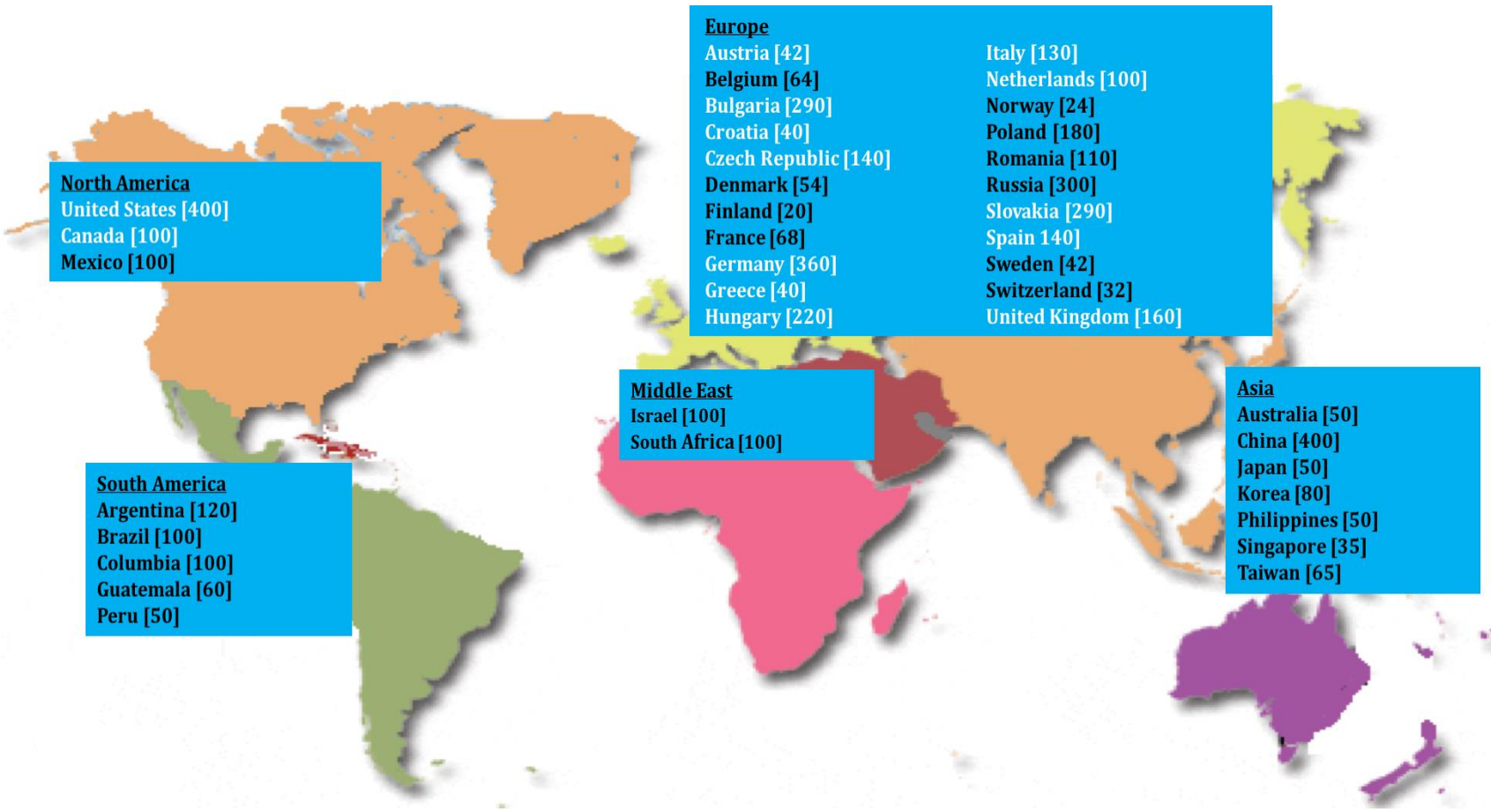
HF hospitalization* within 9 months prior to study entry	OR	Elevated NT-proBNP [>300 pg/mL for patients with SR or >900 pg/mL for patients with AF]

CABG=coronary artery bypass graft; LAE=left atrial enlargement; LVEF=left ventricular ejection fraction; SBP=systolic blood pressure

Key exclusion criteria:

- ✓ History of LVEF <45%
- ✓ MI, CABG or any event within the 6 months prior to study entry that may have reduced LVEF
- ✓ Current acute decompensated HF
- ✓ K >5.2 mmol/L; eGFR <30 mL/min/1.73m^2
- ✓ SBP <110mm Hg or >180mm Hg. If SBP. *if SBP >150 mmHg and <180 mmHg, the patient should be receiving ≥3 antihypertensive drugs
- ✓ Probable alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms [i.e., dyspnea, fatigue] such as significant pulmonary disease [including primary pulmonary HTN], anemia or obesity. Specifically, patients with the following are excluded:
  - ✓ severe pulmonary disease including chronic obstructive pulmonary disease [COPD] [i.e., requiring home oxygen, chronic nebulizer therapy, or chronic oral steroid therapy or hospitalized for pulmonary decompensation within 12 months] or
  - ✓ Hemoglobin [Hgb] <10 g/dl, or
  - ✓ body mass index [BMI] >40 kg/m^2

COUNTRY PARTICIPATION WITH PATIENT COMMITMENTS



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WHY PARAGON-HF MAY HAVE ADVANTAGES OVER PRIOR HFpEF OUTCOMES TRIALS

Other HFpEF Trials

- ✓ Some patients enrolled without clear heart failure
- ✓ Time t… of bur…
- ✓ No prior HFpEF outcomes trial had positive phase II Data

PARAGON

- ✓ Requirement for HF Hospitalization within 9 months OR elevated NT-proBNP
- ✓ Requirement for Structural Heart Disease …
- ✓ …nalysis –
- ✓ PARAGON is specifically testing a hypothesis generated by a the positive phase II PARAMOUNT trial, and with a therapy that now has positive Phase III data in HFrEF

- First Patients Randomized Summer 2014
- Last Recruitment projected May 2017
- Last Patient Last Visit May 2019
- 39 Countries, 722 Sites

KEY POINTS

- ✓ HFpEF previously known as diastolic heart failure is equally as common as HFrEF, but is less well understood.
- ✓ HFpEF is an emerging epidemic, due to the increasing age of the population as well as the increasing incidence of common risk factors such as obesity and hypertension.
- ✓ Recognition of typical signs and symptoms of heart failure in the setting of specific echocardiographic features is key to diagnosis. The diagnosis can be confirmed with exercise right heart catheterisation.
- ✓ Key principles of management in patients with HFpEF are blood pressure control, physical activity, optimisation of comorbidities and judicious volume management.
- ✓ Few therapies are effective at reducing morbidity or mortality in HFpEF at present. Active research is under way to develop appropriate diagnostic and management strategies.

THANK YOU

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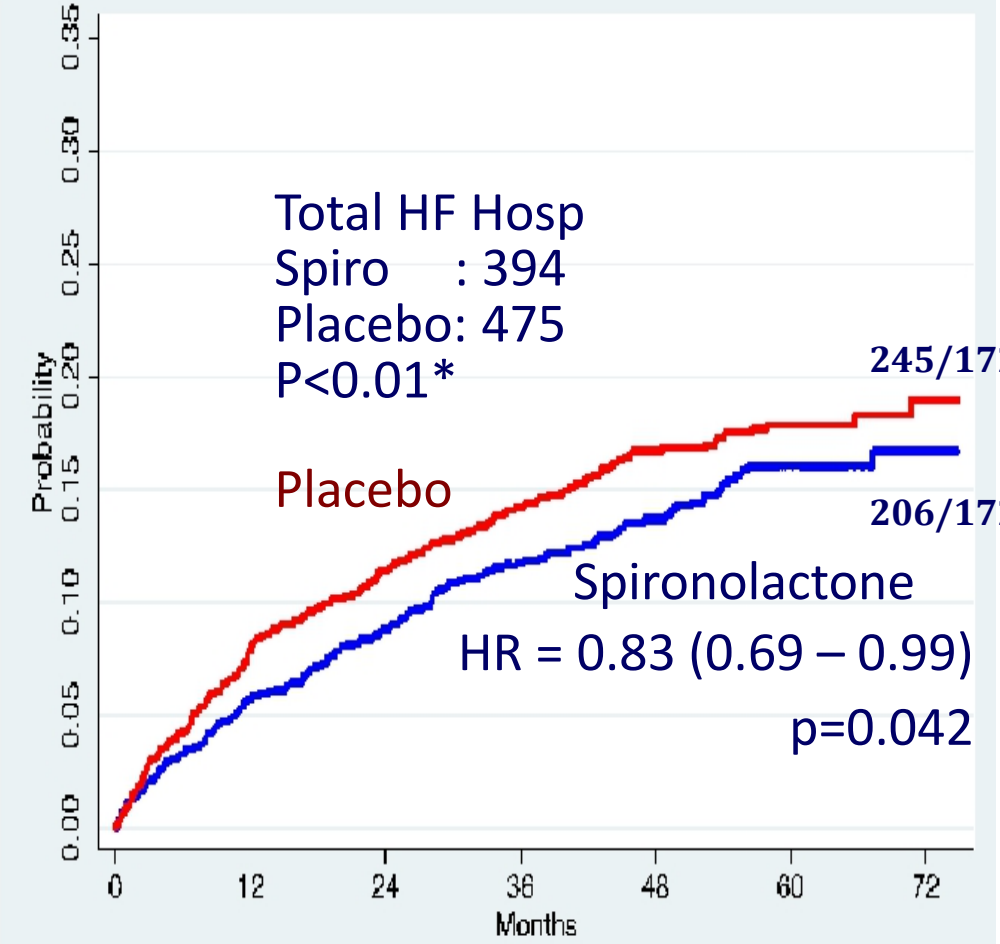
TOPCAT: HEART FAILURE HOSPITALIZATION



*poisson regression

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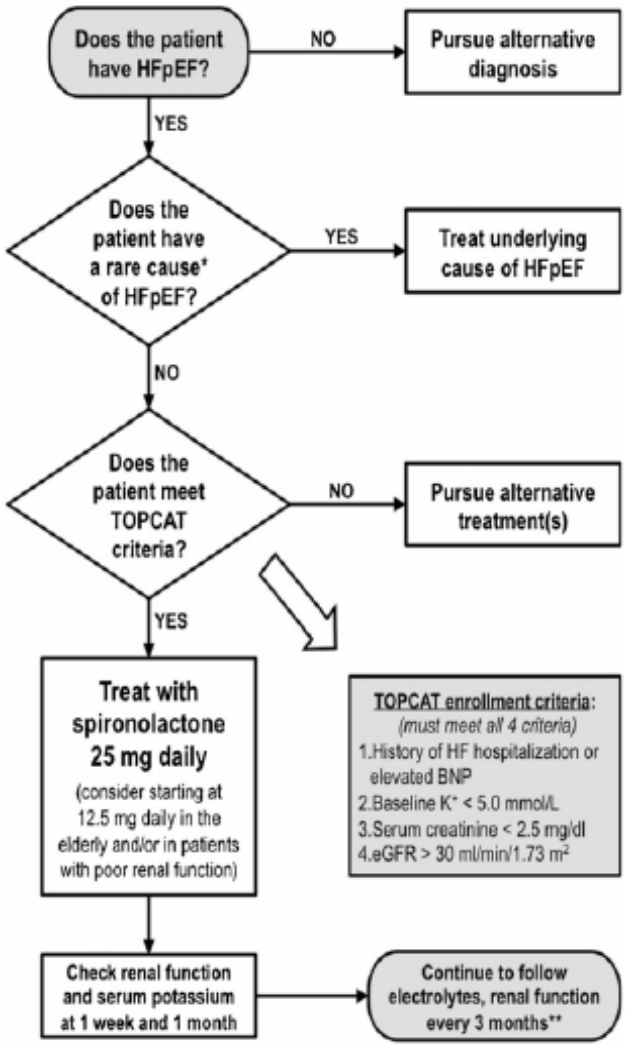
SUGGESTED ALGORITHM FOR SPRINOLACTONE IN HFpEF



Our patient:

Clinical HFpEF

History of HF hospitalisation

Elevated NTproBNP

Labile renal function (?)

Heart Failure Society of South Africa [HeFSSA]

Mitter et al., Curr Atheroscler Rep, 2015 Nov, 17(11):64.

Journal of the American College of Cardiology
© 2009 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 53, No. 11, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2008.12.007

STATE-OF-THE-ART PAPER

Heart Failure With Normal Left Ventricular Ejection Fraction

Micha T. Maeder, MD, David M. Kaye, MD, PhD

Melbourne, Australia

It is estimated that approximately 50% of the heart failure population has a normal left ventricular ejection fraction, a complex broadly referred to as heart failure with normal left ventricular ejection fraction (HFNEF). While these patients have been considered in epidemiologic studies and clinical trials to represent a single pool of patients, limited more detailed studies indicate that HFNEF patients are a very heterogeneous group, with a number of key pathophysiologic mechanisms. This review summarizes and critically analyzes available data on the pathophysiology of HFNEF, placing it into context with a recently developed diagnostic algorithm. We evaluate the utility of commonly applied echocardiographic measures and biomarkers and integrate mechanistic observations into potential future therapeutic directions. (J Am Coll Cardiol 2009;53:905–18) © 2009 by the American College of Cardiology Foundation

Heart Failure Society
of South Africa
[HeFSSA]

Apical 4 – Chamber View

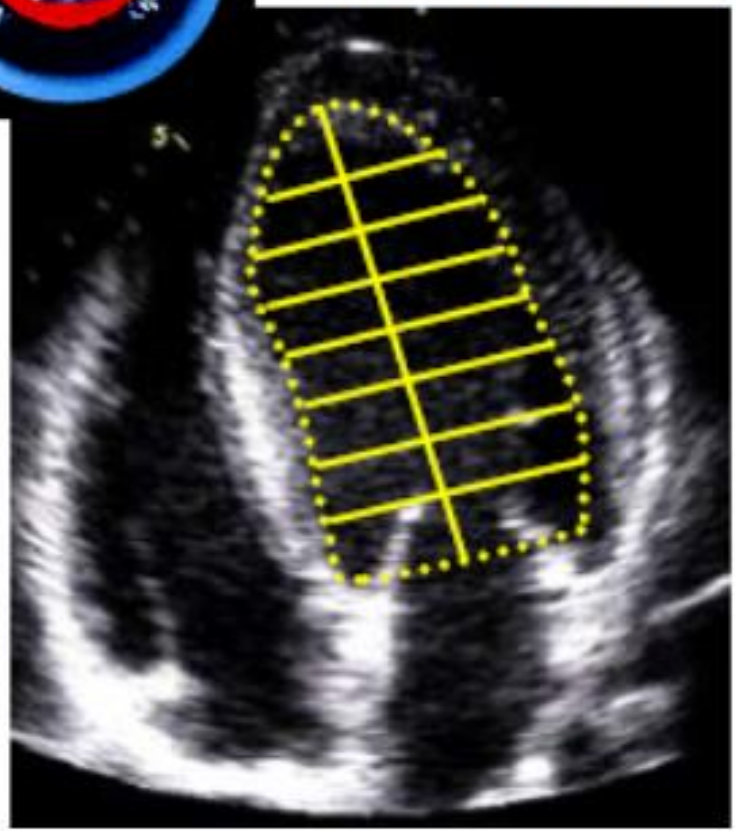
Apical 2 – Chamber View

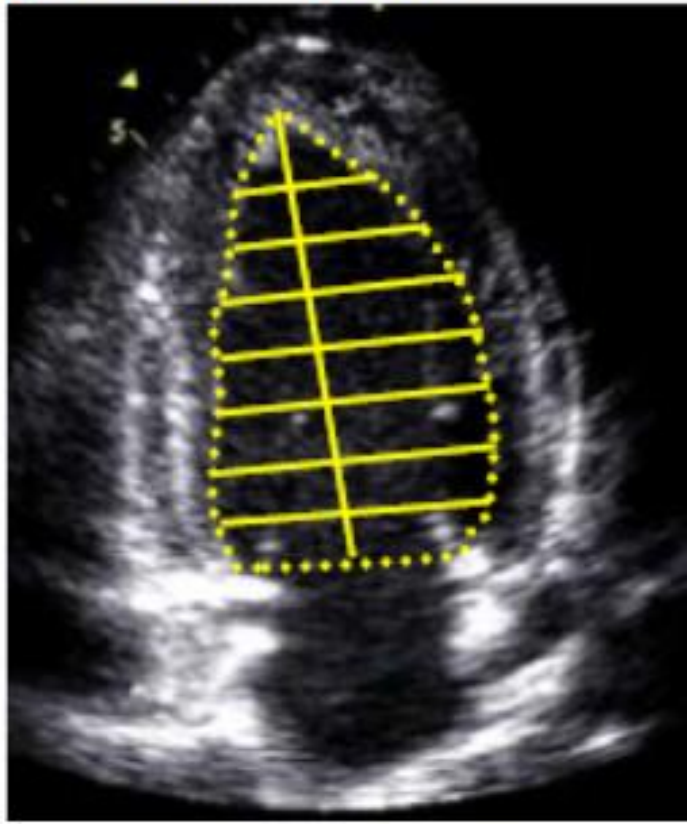
Heart Failure Society of South Africa [HeFSSA]

Lang R et al 2007

QUANTITATIVE STANDARD

Modified Simpson's Rule





Volume = $\sum (^1/_4 \pi D^2) h$

EF = EDV – ESV / EDV

Lang R et al 2007

IMPROVEMENTS IN EF BY ECHO

- ✓ Harmonic Imaging
- ✓ Digital Acquisition

- ✓ Echo Contrast Enhancement
- ✓ Continued Improvements in computer technology

Definity Contrast Bolus

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LOOK FOR EF! HAND – CARRIED ULTRASOUND

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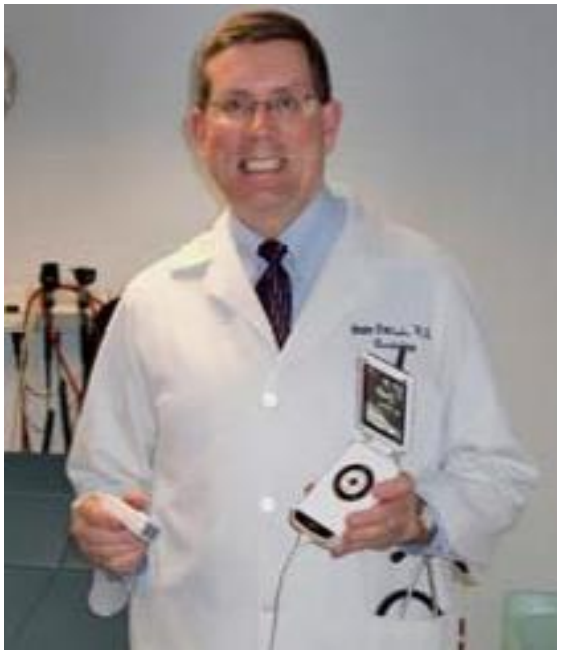
LOOK FOR EF! HAND – POCKETSIZE ULTRASOUND



89 year old woman with apical MI

Heart Failure Society of South Africa [HFSSA]

HFNEF: A DIAGNOSIS OF EXCLUSION

Shortness of Breath & LVEF > 50%

Cardiac Causes

Other Cardiac Causes

- ✓ Coronary Disease
- ✓ Valvular Disease
- ✓ Hypertrophic Cardiomyopathy
- ✓ Restrictive Cardiomyopathy
- ✓ Intracardiac Shunt

Non - Cardiac Causes

- ✓ Pulmonary Disease
- ✓ Thyrotoxicosis
- ✓ Anemia
- ✓ Primary Pulmonary Hypertension
- ✓ Obesity
- ✓ Deconditioning
- ✓ Extracardiac Shunt

Heart Failure with Normal EF

Heart Failure Society of South Africa [HeFSSA]

Consensus Article: EHJ 2007

CASE STUDY

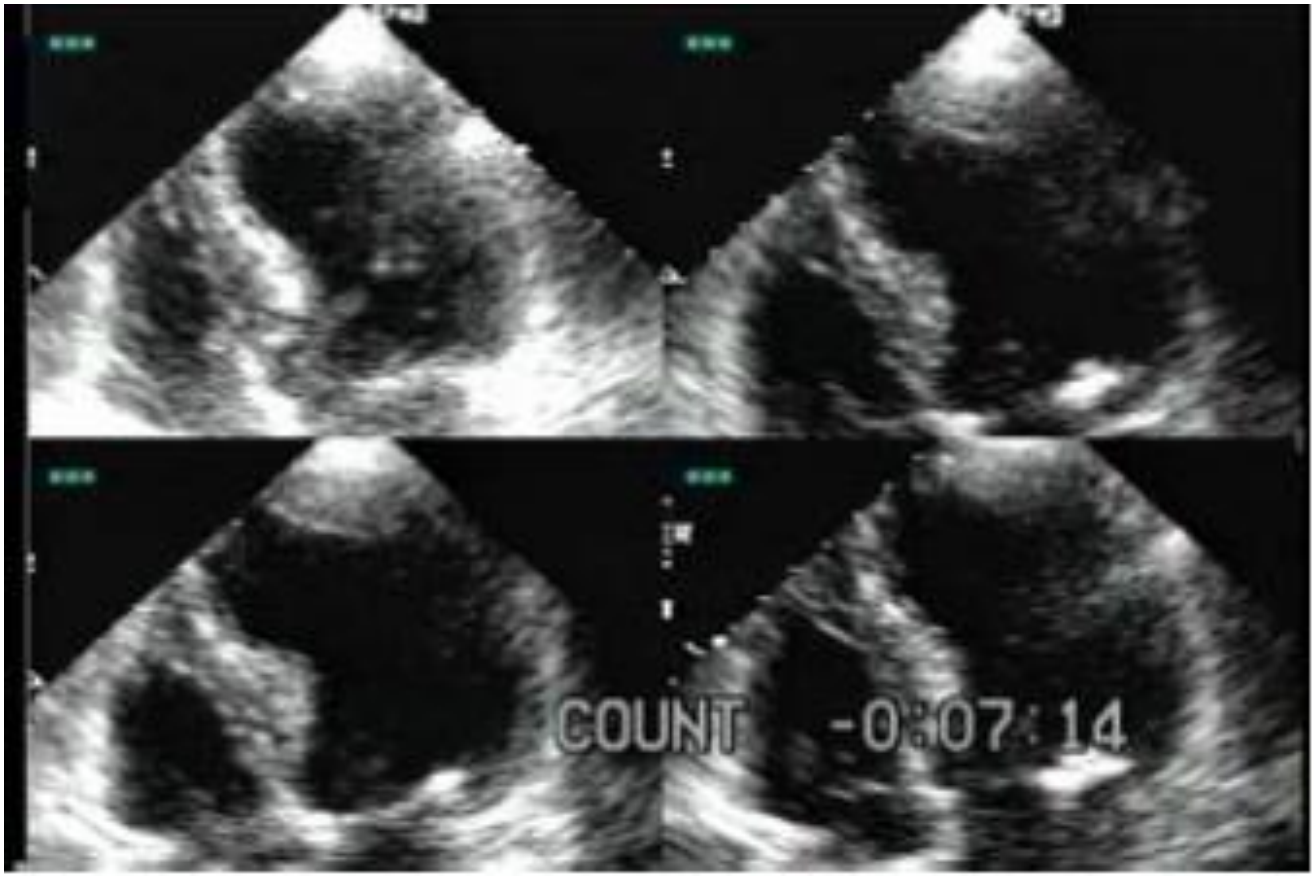
- ✓76 year old man, hypertensive smoker, Mostly sedentary, denies any exertional symptoms
- ✓Presents with “flash pulmonary edema” BP 185 90 mmHg
- ✓Rapidly resolves with 40 mg I.V Lasix

CASE STUDY

79 year old male with flash pulmonary oedema

Baseline

Peak Stress



Cardiac Cath: Severe 3 vessel CAD

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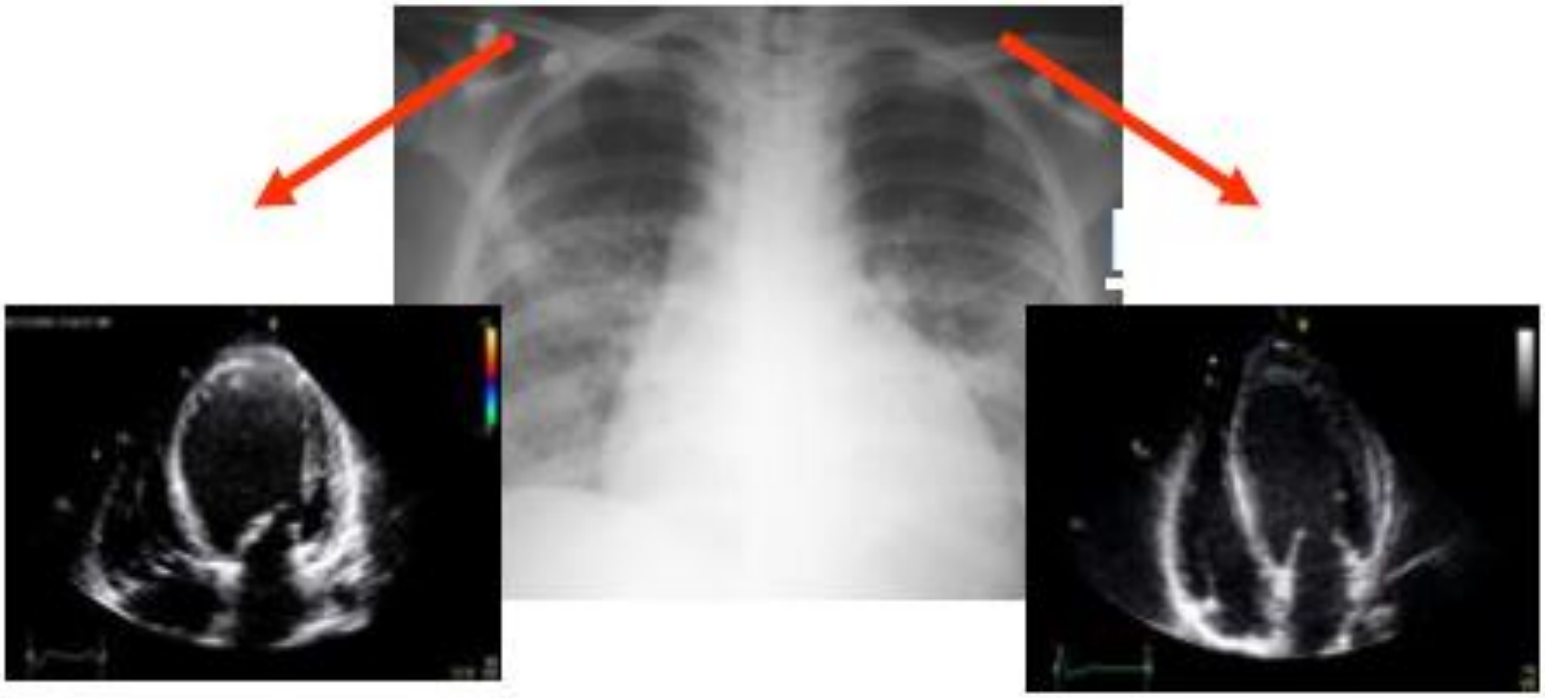
CLINICAL APPROACH TO HEART FAILURE



- ✓ ACE Inhibitors / ARBs
- ✓ β - Blockers
- ✓ Spironolactone
- ✓ Defibrillator
- ✓ CRT with wide QRS
- ✓ Ivabradine

- ✓ Diagnosis ?
- ✓ Treatment ?

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