HeFSSA Practitioners Program 2014

- 08:00 – 08:30 Registration
- 08:30 – 09:15 Clinical Case Presentation 1
- 09:15 – 10:00 Clinical Case Presentation 2
- 10:00 – 10:30 Tea Break
- 10:30 – 11:15 Clinical Case Presentation 3
- 11:15 – 11:45 Clinical Case Presentation 4
- 11:45 – 12:00 Questionnaire
- 12:00 – 14:00 Lunch

Heart Failure Society of South Africa [HeFSSA]

Heart Failure with Preserved Ejection Fraction

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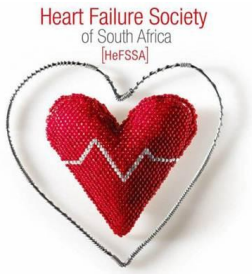
Definition of Heart Failure

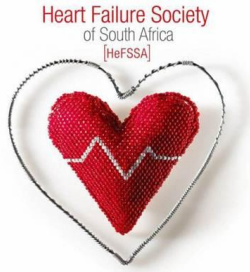
Heart failure is a syndrome where a patient has **symptoms** (dyspnoea, leg swelling, fatigue) and **signs** (oedema, raised JVP, crackles) of congestions resulting from abnormalities in cardiac structure and/or function.

European Heart Journal (2012) **33**, 1787–1847



Patients with heart failure are categorised according to their measured ejection fraction. This may be **PRESERVED (EF >50%)** or **REDUCED (EF <50%).**

If the EF is >50% patients are then said to have **Heart Failure with preserved Ejection Fraction (HFpEF).** The term “diastolic heart failure” has been abandoned.

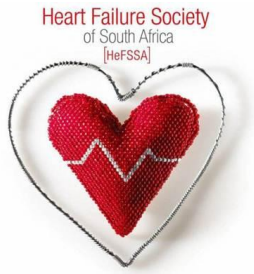


Epidemiology

HFpEF is common!

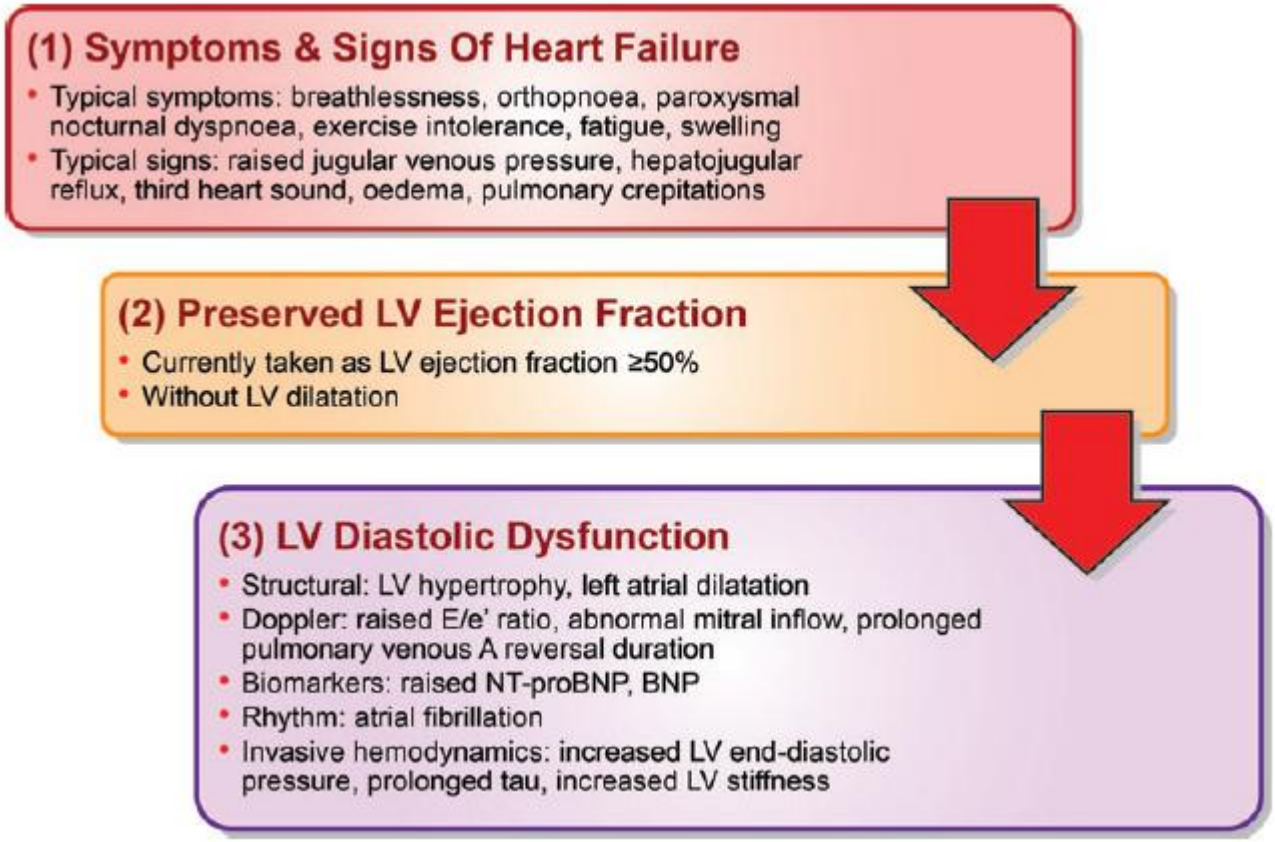
Across studies ~50% of all patients with chronic heart failure have a preserved ejection fraction.

Similarly, 50% of patients presenting with acute heart failure (pulmonary oedema) have a preserved EF.



European Heart Journal (2012) **33**, 1787–1847

Diagnosis



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European Heart Journal (2014) **35**, 1022–1032

Who is at risk of developing HFpEF?

- Women > Men
- Patients >65 yrs old
- HFpEF is STRONGLY associated with:
  - **Hypertension**
  - **Diabetes**
  - **Obesity**
  - **Atrial fibrillation**
  - **Renal disease**

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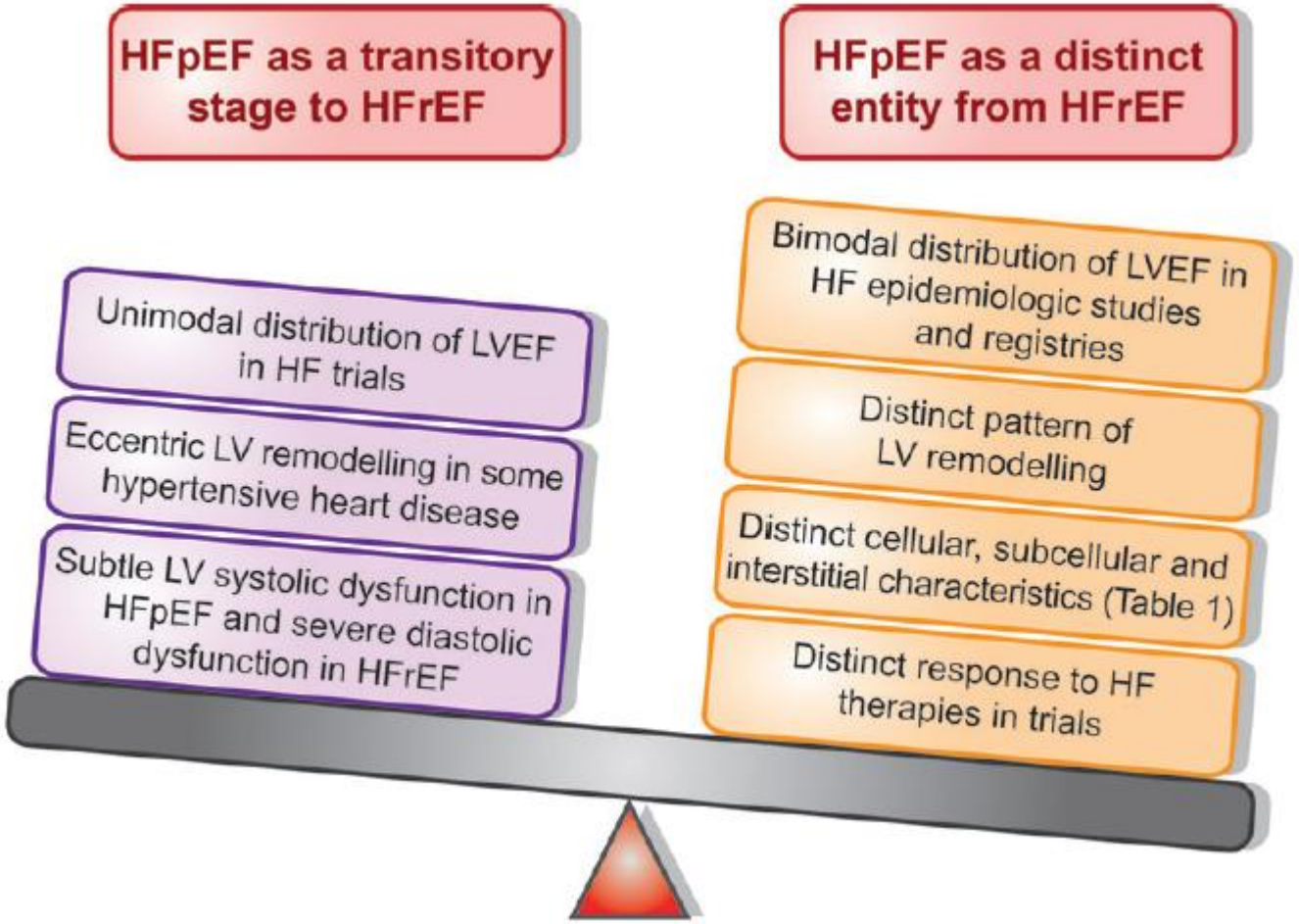
Is HFpEF a transitory stage to HFrEF or is it a distinct disease phenotype?



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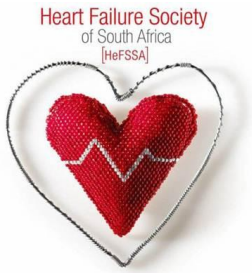
European Heart Journal (2014) **35**, 1022–1032

Does HFpEF represent a collection of co-morbidities rather than a pathophysiologically distinct entity?

- Regardless of the co-morbidity burden patients with HFpEF have a much higher mortality than matched control subjects across various clinical trials

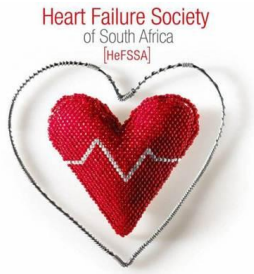
It is therefore thought to be an independent entity with a distinct underlying pathophysiology!



Campbell et al. JACC 2012; 60: 2349

PATHOPHYSIOLOGY

Bottom-line seems be a combination of abnormalities resulting in impaired LV filling with a rise in the pulmonary wedge pressure particularly during exercise



Pathophysiology – complex and poorly understood!

Diastolic abnormalities

- Isovolumetric relaxation prolongation
- Slow LV filling
- Increased LV stiffness

Non-diastolic abnormalities

- Impaired ventricular-vascular coupling
- Neurohumoral activation
- Abnormal vasodilation response to exercise and flow
- Chronotropic incompetence
- Atrial dysfunction
- Pulmonary hypertension

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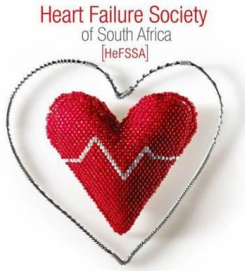
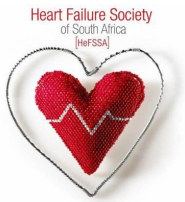
Pathophysiology

- Extensive studies to demonstrate various abnormalities at the molecular level involving:
  - Fibrotic changes
  - Structural changes various myocardial proteins (e. g. titin)
  - Calcium flux abnormalities
  - Abnormalities involving the contractile apparatus

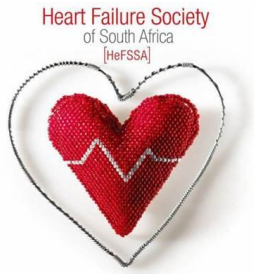


Prognosis

- In general patients with HFpEF have a better prognosis than patients with HFrEF
- However they still have significant morbidity and mortality
- Various studies have shown: 10 – 30% mortality over one year
- Why do these patients die?
  - 60 – 70% are cardiovascular death mostly from heart failure or sudden cardiac death

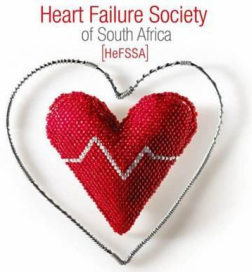


HFpEF therefore is a serious problem with a potentially poor outcome which has led to various attempts to try and improve both the quality of life and the prognosis in these patients.



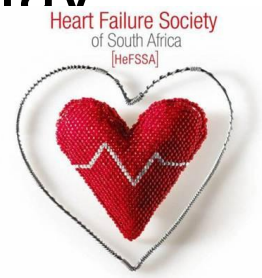
TREATMENT OPTIONS AND THE EVIDENCE

What has been tried? (And failed!)



Beta-blockers/Calcium channel blockers

- Slow down heart rate and thereby increase diastolic filling but may diminish chronotropic reserve during exercise
- No RCT's in HFpEF available
- Subanalyses and Registry data suggest a possible mortality and morbidity benefit
- Keep in mind that patients with HFpEF may have chronotropic incompetence which may actually worsen symptoms



ACE inhibitors

- Perindopril has been evaluated in the PEP CHF trial (Perindopril for Elderly People with CHF)
- Patients had EF>40% and comparison was made between placebo and 4 mg perindopril
- Result: no difference in all-cause mortality or heart failure admissions

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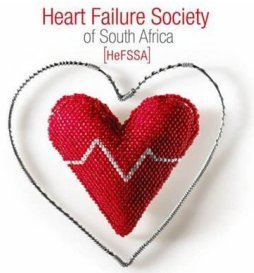
ARB's

- 2 Trials have been performed: CHARM Preserved (candesartan 32 mg daily) and I-PRESERVE (irbesartan)
- Large trials with 3023 and 4128 patients respectivelyu randomised to treatment or placebo
- EF was >40% and >45% respectively
- No difference in all-cause mortality
- CHARM Preserved: reduced heart failure admissions (trend only)
- These negative trials are in sharp contrast to the significant benefits of ACE-I and ARB's in patients with HF**r**EF!



Digoxin

- Digitalis Interaction Group trial (DIG trial) – subgroup analysis of 988 patients with EF of >45%
- No difference in all cause mortality, heart failure or hospitalisation

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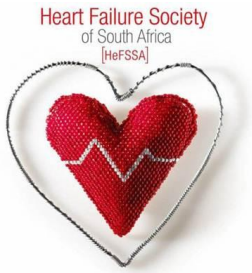
Spironolactone

- There was some hope after the AldoDHF trial – 422 patients were randomised to placebo or spironolactone 25 mg daily
- Showed improvement in echocardiographic parameters of diastolic dysfunction with reduction in LV mass and proBNP
- No improvement in symptoms or QoL



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 10, 2014 VOL. 370 NO. 15

Spironolactone for Heart Failure with Preserved Ejection Fraction

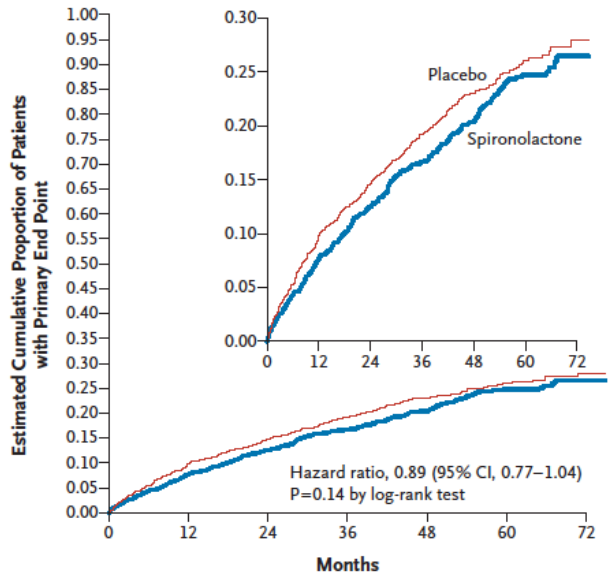


Figure 1. Kaplan–Meier Plot of Time to the First Confirmed Primary-Outcome Event.

The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure. The inset shows the same data on an expanded y axis.

Spironolactone was further evaluated in the TOPCAT trial – 1722 patients randomised to pacebo or 45 mg spironolactone f/u over 3 years

No difference in primary outcome

Sildenafil

- This was evaluated in the RELAX trial
- After 24 weeks of treatment – no effect on exercise capacity, 6 min walk distance, QoL, LV remodelling or diastolic function

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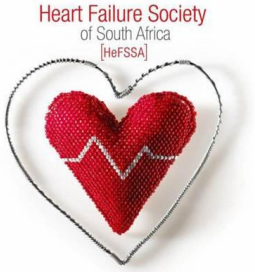
Newer Therapies (in development or currently in trials)

Neprilysin inhibitors

- LCZ696 (angiotensin neprilysin inhibitor)
- Neprilysin inhibitors prevent the breakdown of natriuretic peptides
- This is an important new drug in the treatment of HFrEF (PARADIGM-HF trial recently stopped early due to benefit in the treatment arm)
- This drug is now being tested in HFpEF – preliminary studies showed reduced BNP levels in the treatment arm in patient with preserved EF

Others

- Soluble guanylate cyclase stimulators (SOCRATES trial)
- Ranolazine (inhibits late sodium current preventing Ca overload) – small trials so far only – inconclusive
- Ivabradine (If current inhibitor which slows sinus note) – will be evaluated in the EDIFY trial
- Statin, calcium-cycling modulators and micro-RNAs have theoretical benefits

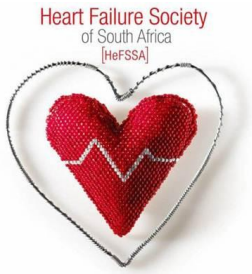


The only positive trial in HFpEF has been:

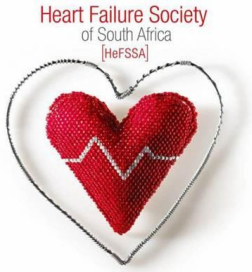
EXERCISE

Ex-DHF Pilot Study

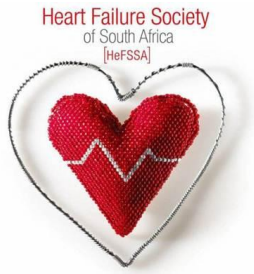
- 64 patients with HFpEF randomised to suervised endurance/resistance training or usual care
- Results: improved VO2 max, improvement in physical functioning score, atrial reverse remodelling and LV diastolic dysfunction after only 3 months of training
- Larger trial in progress but exercise seems to be the only treatment so far that has made any difference



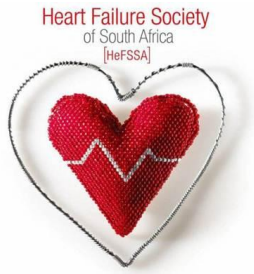
Take Home Messages



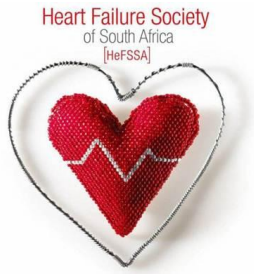
Heart Failure with preserved Ejection Fraction (HFpEF) has a high prevalence and constitutes up to 50% of heart failure patients



HFpEF is (probably) an independent entity with a high morbidity and mortality.

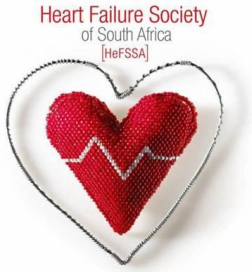


The pathophysiology is complex and multifactorial but it is often associated with elderly, hypertension, coronary artery disease, diabetes and atrial fibrillation.



There is no proven disease-specific therapy (yet)

Control of volume and treatment of co-morbidities, especially hypertension form the main-stay of therapy



Regular aerobic exercise is helpful!

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HeFSSA Practitioners Program 2014: Questionnaire

- Please go to www.hefssa.org to complete this year's questionnaire online