HeFSSA Practitioners Program 2018
"Back to basics on heart failure treatment?"

- Co-morbidity in heart failure
- Arrhythmias in heart failure
- Special investigations in heart failure
- Heart failure with preserved EF, what is new?"

SA Heart®

Heart Failure Society of South Africa [HeFSSA]

CASE STUDY:

- Mr. G.F is 64 yr old African male who presents with swelling of his lower limbs & dyspnoea of 6 months duration

- He has a background history of:
  - Hypertension for 15 yrs
  - Smoker for 30 yrs
  - No past history of Diabetes

- His current medication includes:
  - Renitec 5mg bd
  - Hydrochlorothiazide 12.5mg dly

SA Heart®

Heart Failure Society of South Africa [HeFSSA]

Examination

- Minimal bi-pedal oedema with an ↑ JVP, S3 Gallop & scattered bi-basal crackles
- BP 170/105 mmHg
- HR 110 bpm
- Abdominal Girth 106 cm
- Hb 13 g/dl; Urea 8.9 mmol/l; Cretinine 112 µmol/L; eGFR 44; Blood Glucose 8.6 mmol/L; HbA1c 6.2;
  Chol 6.2 mmol/L;Trigs 3.4 mmol/L; HDL 0.9 mmol/L; LDL 3.9 mmol/L

SA Heart®

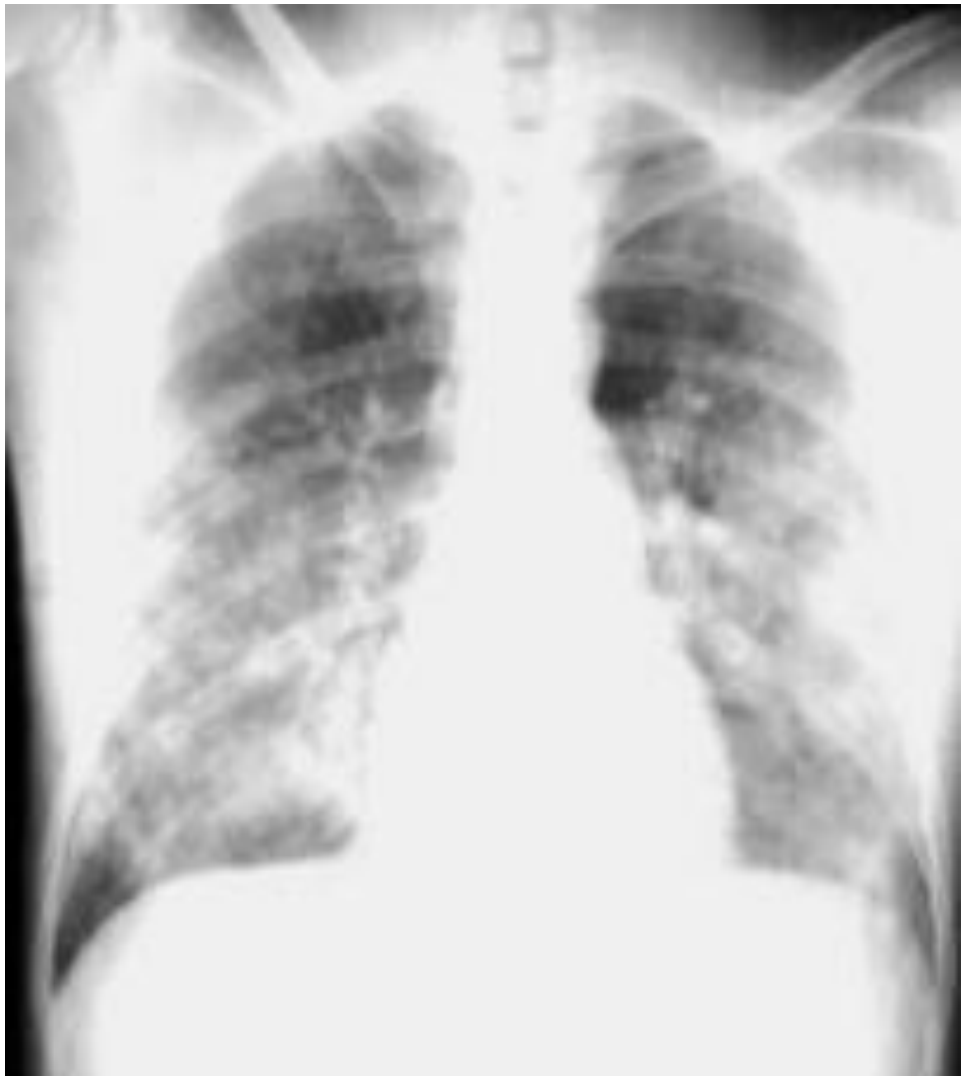
Heart Failure Society of South Africa [HeFSSA]

What is the diagnosis & what other investigations would you request?

SA Heart®

Heart Failure Society of South Africa [HeFSSA]

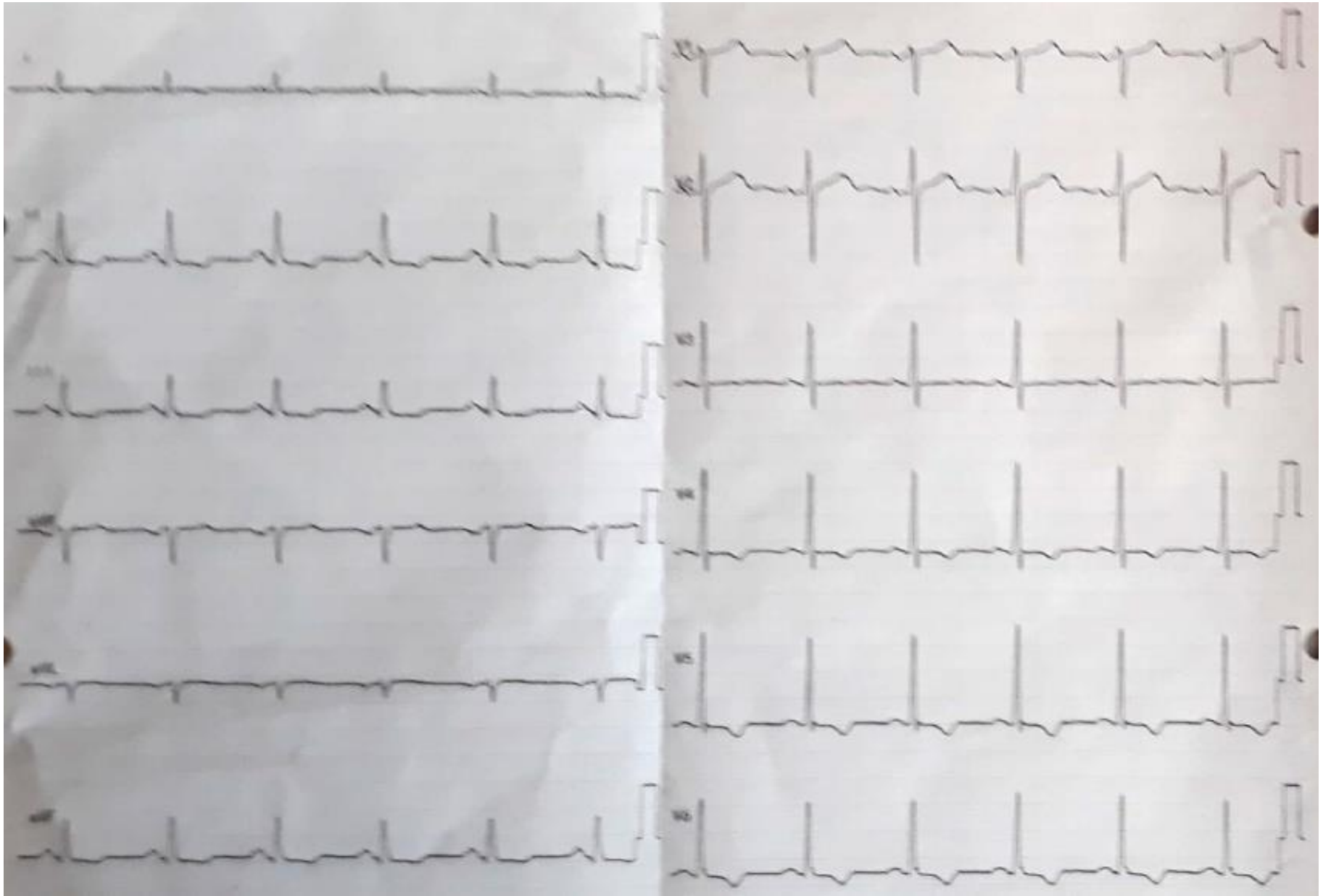
Pulmonary Oedema



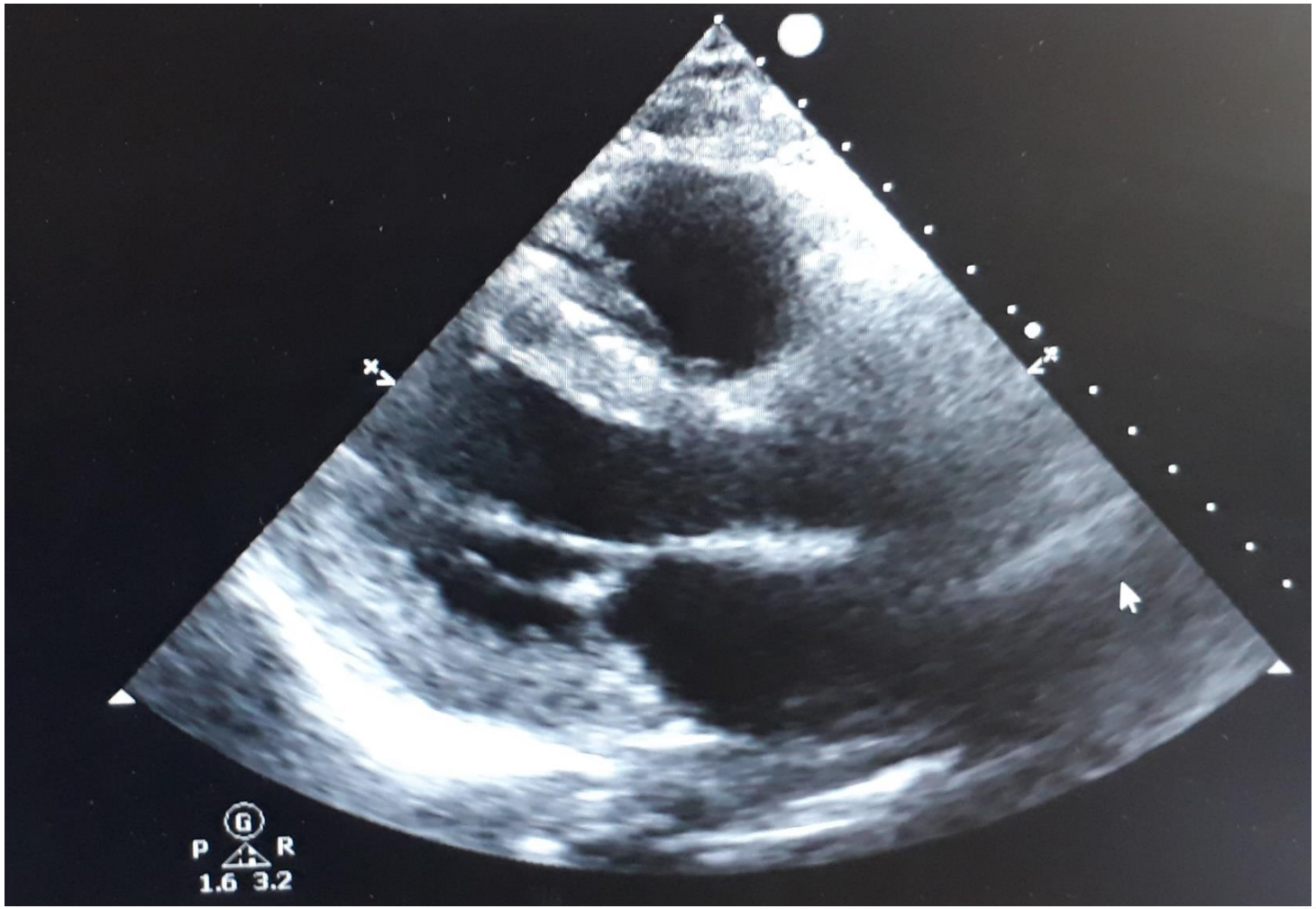
SA Heart®

Heart Failure Society of South Africa [HeFSSA]

Pulmonary Oedema



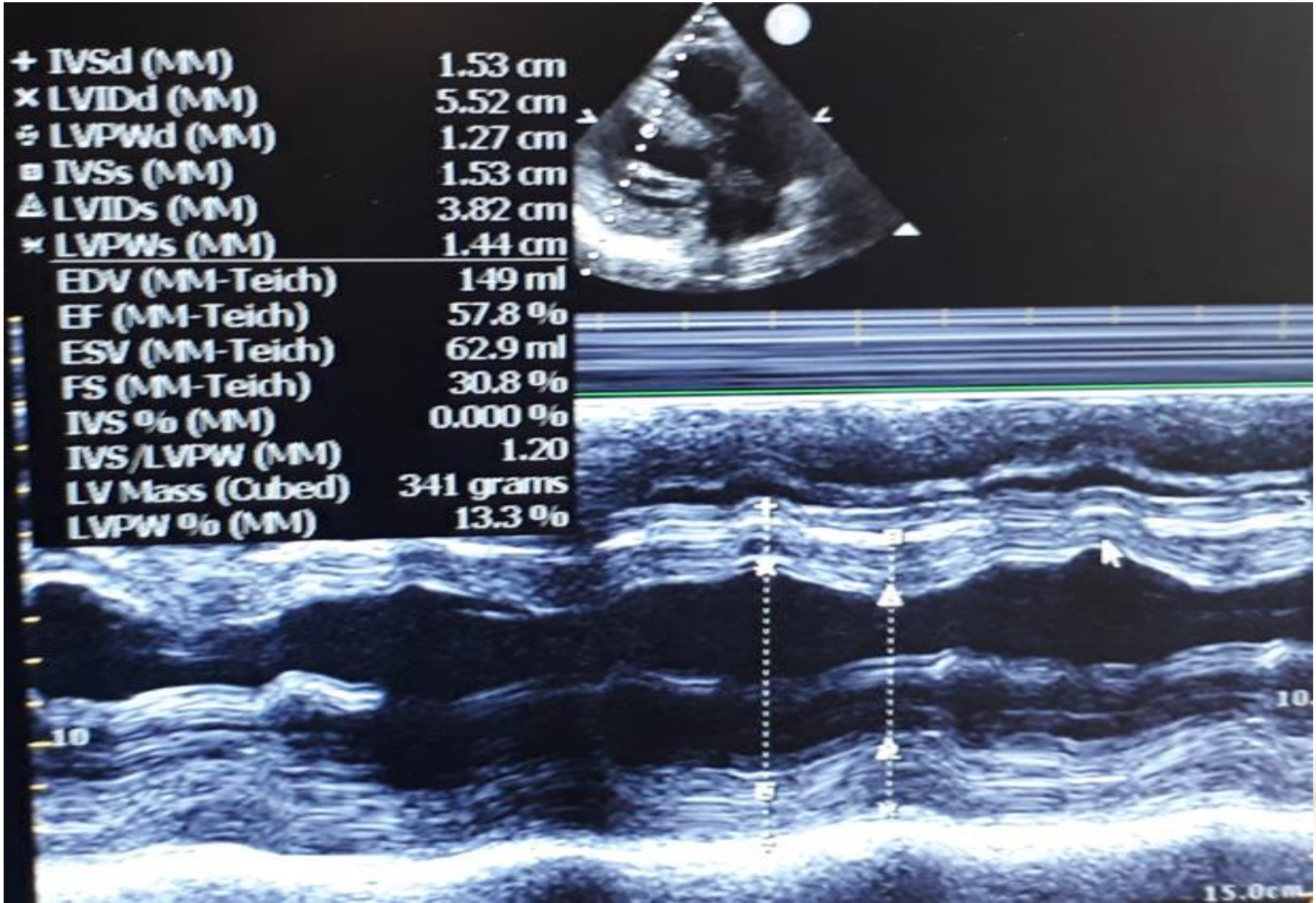
Pulmonary Oedema



SA Heart

Heart Failure Society of South Africa [HFSSA]

Pulmonary Oedema



Would you do Cardiac Biomarkers?

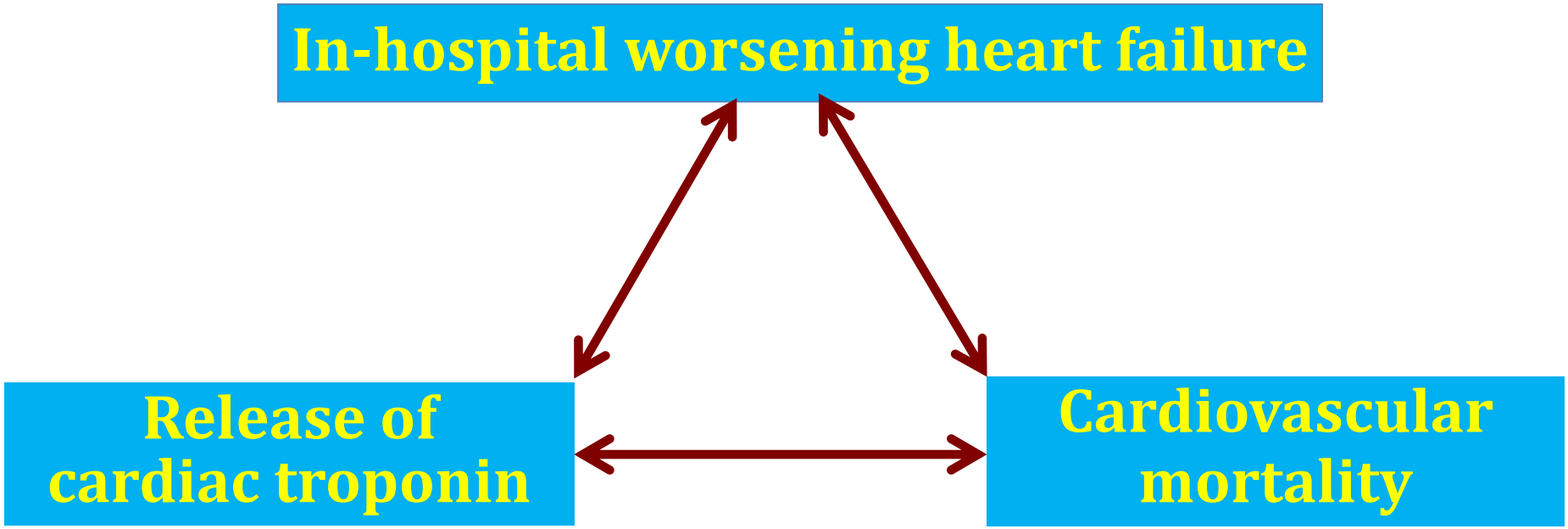
- **NT-pro BNP = 3200 pg/mL**

- **Troponin T = 112 ng/L**

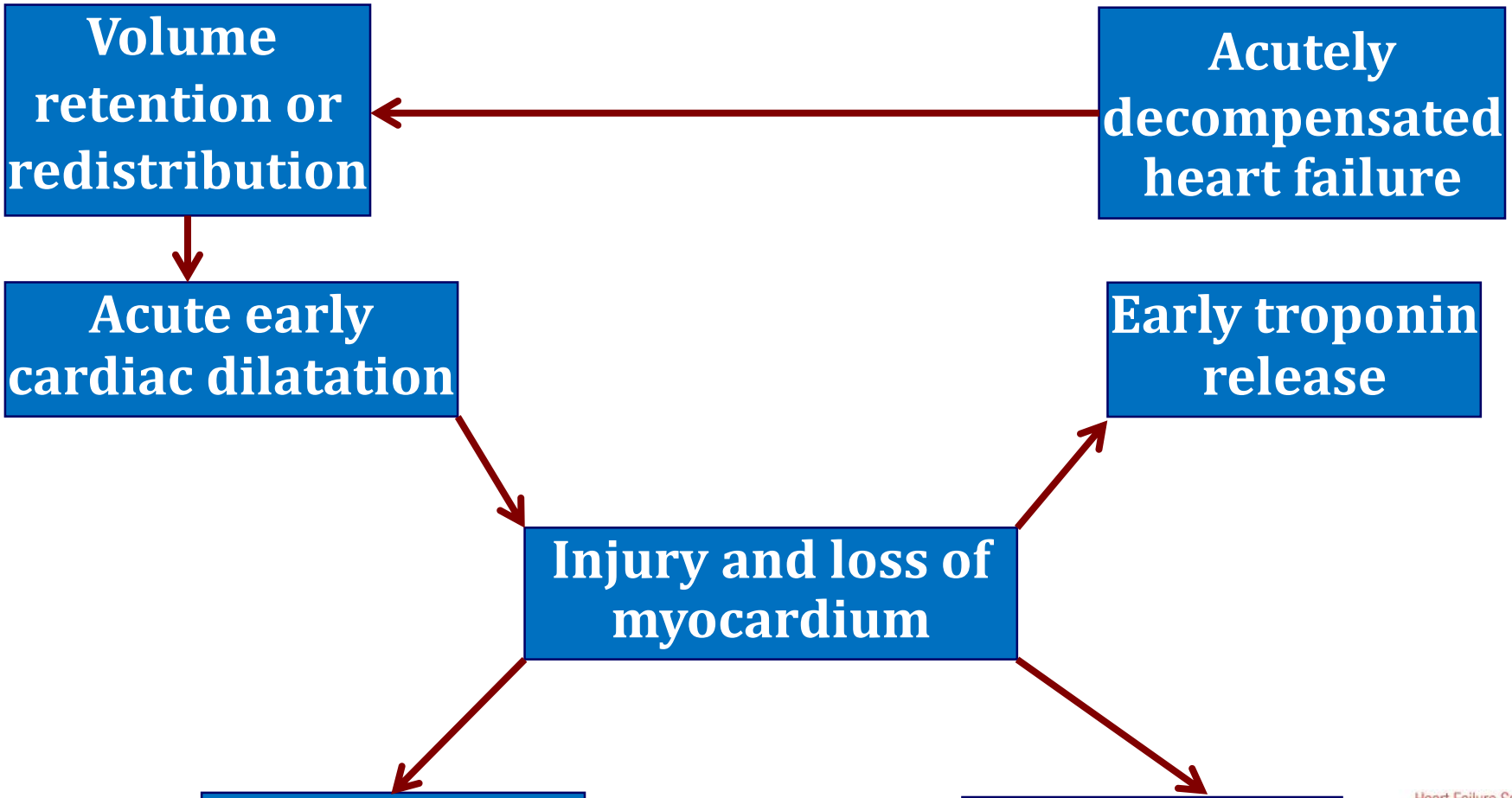
SA Heart®

Heart Failure Society of South Africa [HeFSSA]

In-Hospital Worsening HF is Associated with Release of Cardiac Troponin & Increased Risk of Death



Why is There a Link?



SA Heart®

Heart Failure Society of South Africa (HeFSSA)

What is the Definition of HFpEF

ESC HF GL 2016:
Definition Of Heart Failure With Preserved (HFpEF)

HFpEF
Symptoms ± Signs[2]
LVEF ≥ 50%
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

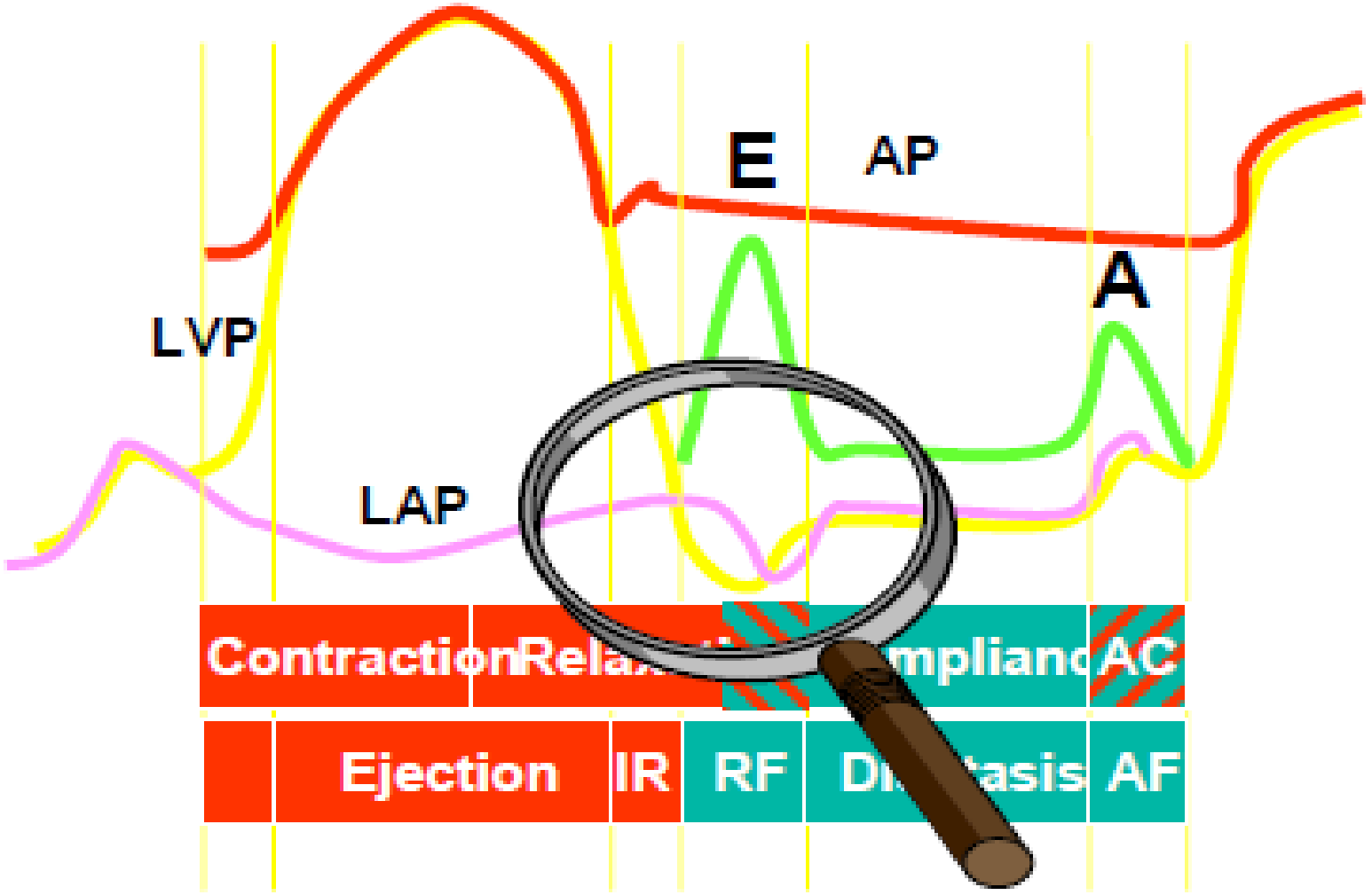
ESC 2016 Key Diagnostic HFpEF Criteria

"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**

SA Heart®

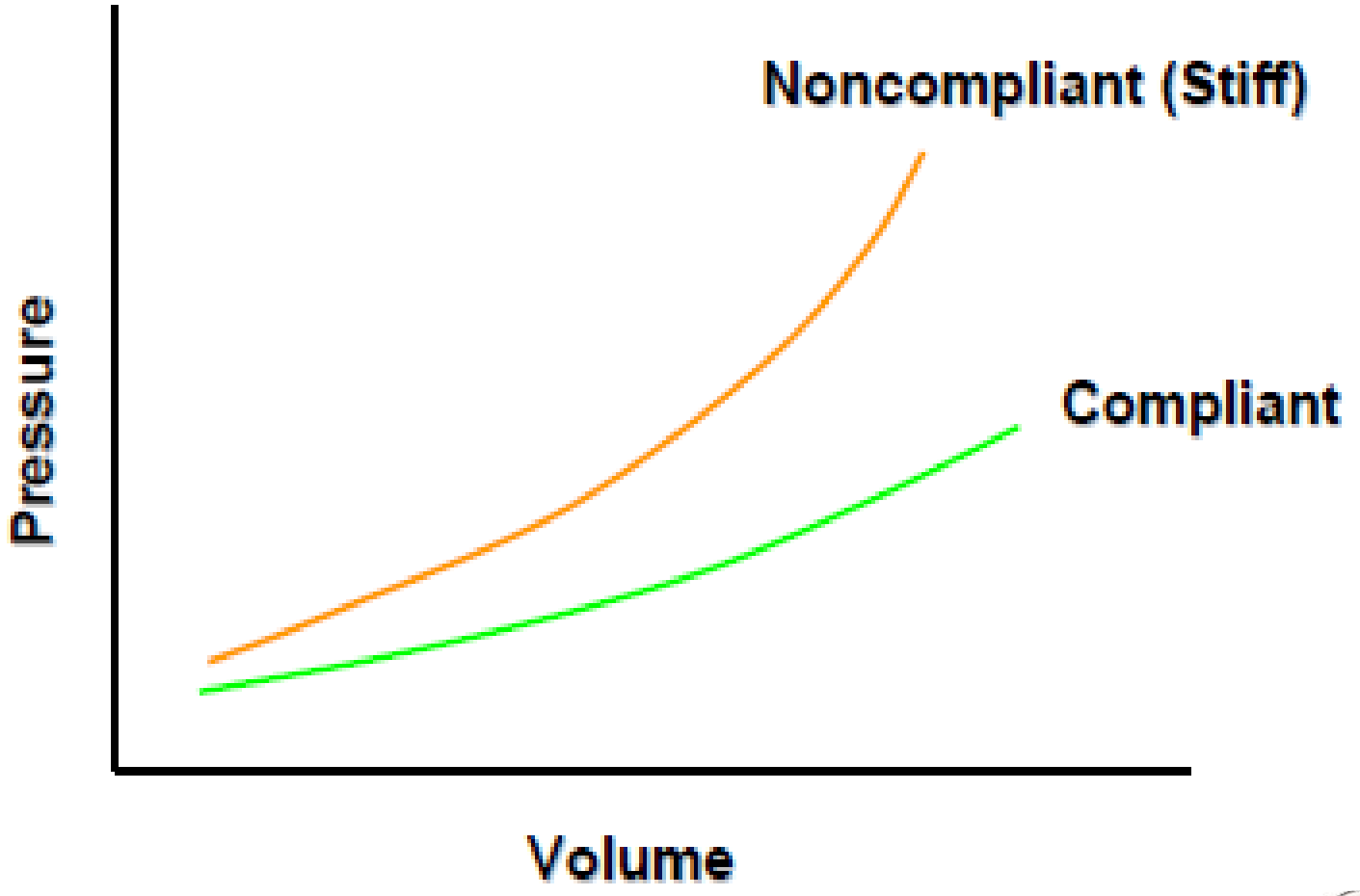
Heart Failure Society of South Africa [HeFSSA]

Diagram Of LV Filling



Focus on Relaxation

End – Diastolic Pressure Volume Relations

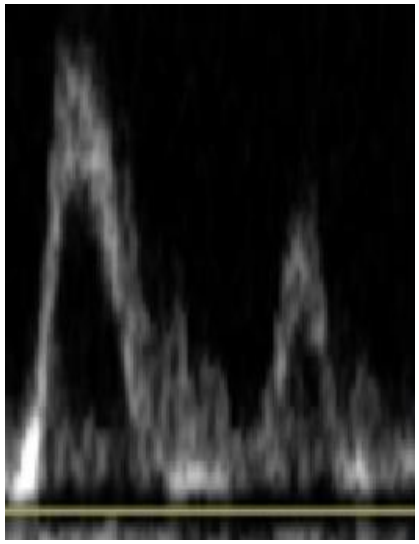


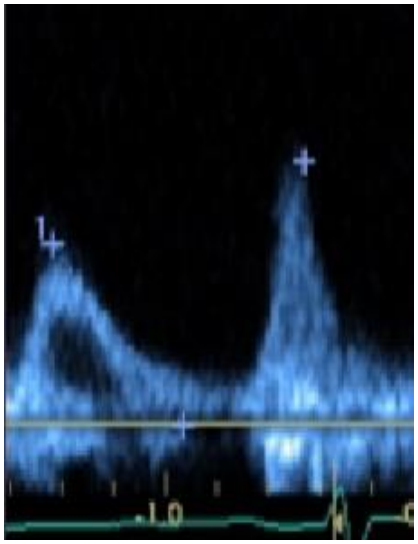
Focus on Stiffness

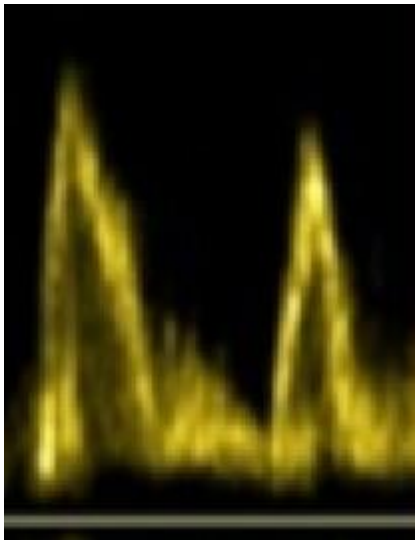
It Used To Seem So Simple...

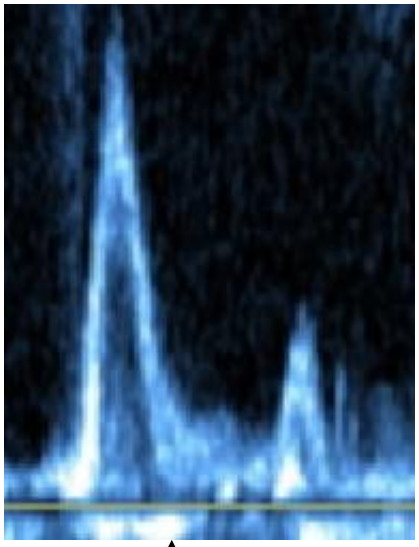
Patterns of Diastolic Function

In the beginning (mid ‘80s)…









And the sickest of all looked like this

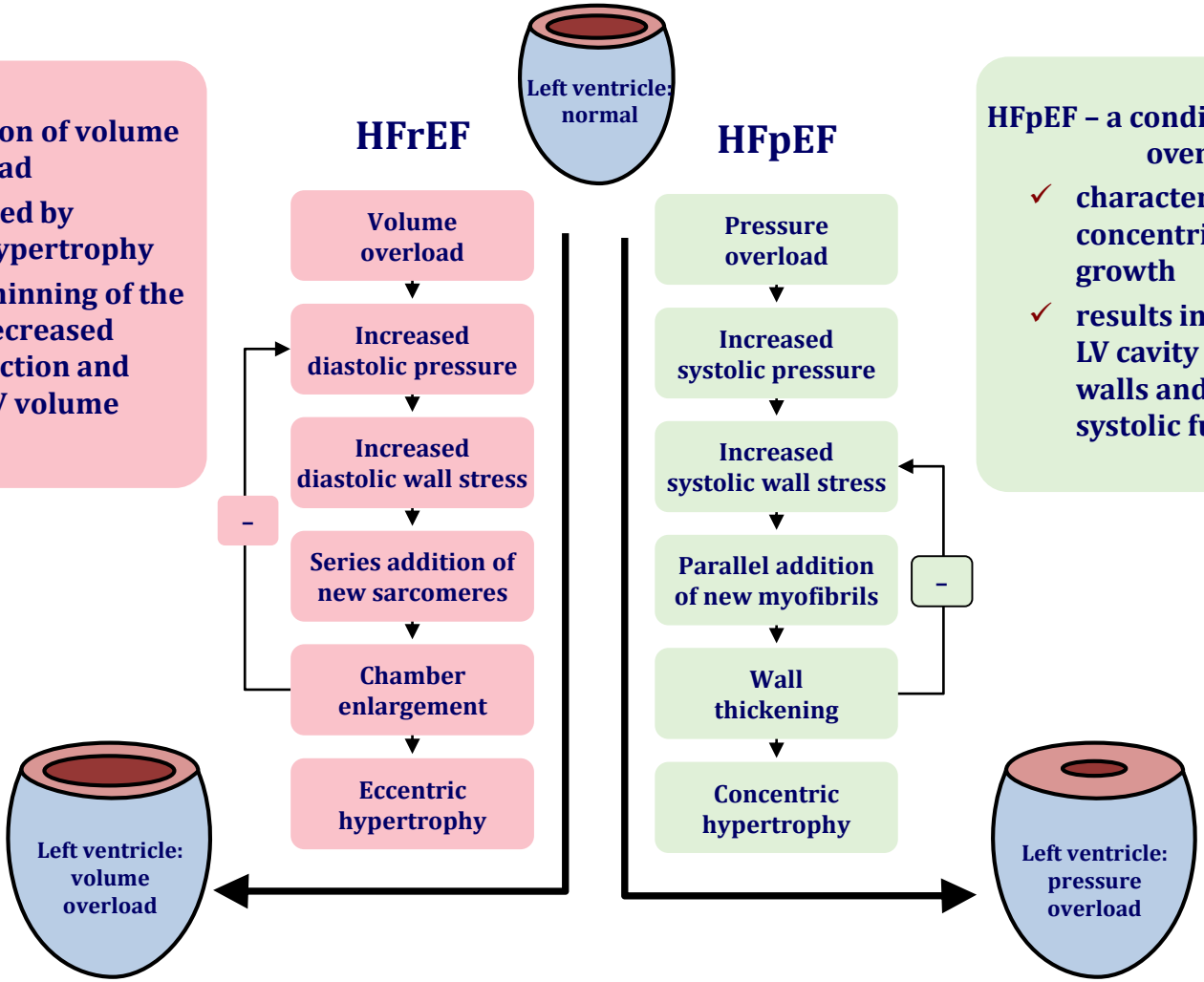
SA Heart®

Heart Failure Society of South Africa (HeFSSA)

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

SA Heart®

Heart Failure Society of South Africa (HeFSSA)

Heart Failure is a Disease Associated with Multiple Risk Factors

CV comorbidities/risk factors
(diabetes, hypertension, CKD, obesity, COPD, ageing)

Systemic pro-inflammatory disease state (↑ IL-6, TNF-α, sST2)

Microvascular endothelial inflammation

↑ Cardiomyocyte stiffness/ interstitial fibrosis

↑ Passive stiffness, fibrosis

Cardiac injury

Oxidative stress in cardiomyocytes

↑ Cardiomyocyte necrosis, apoptosis, autophagy

↓ Myocardial contractility

LV hypertrophy
Protective & maladaptive signalling

HFpEF

HFrEF

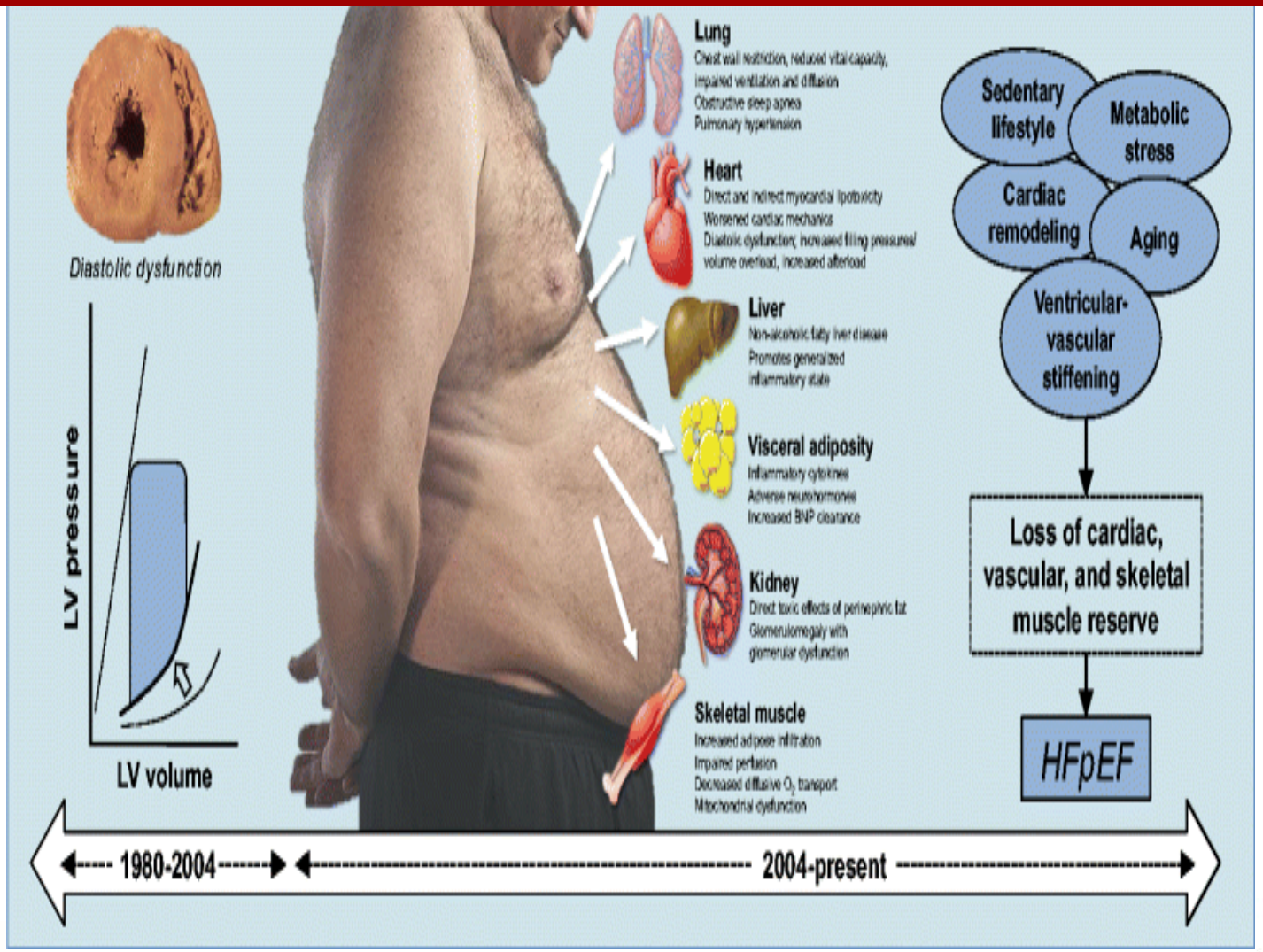
COPD, Chronic Obstructive Pulmonary Disease; IL-6, Interleukin-6; LV, Left Ventricular; sST2, Soluble Isoform of ST2; TNF-α, Tumor Necrosis Factor Alpha

Paulus WJ *et al. J Am Coll Cardiol* 2013;62:263; Heinzel FR *et al. J Appl Physiol* 2015;119:1233

SA Heart®

Heart Failure Society of South Africa [HeFSSA]

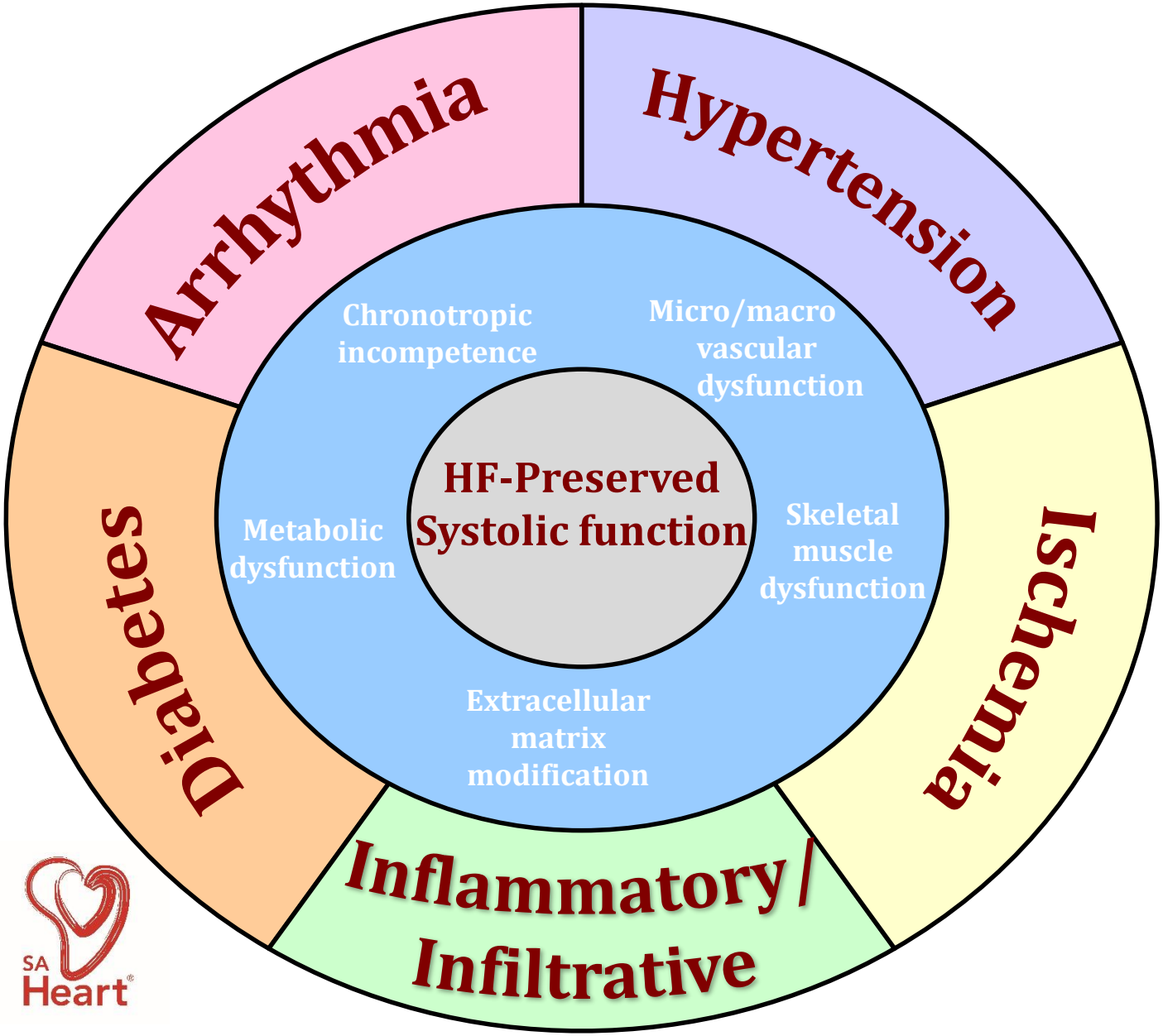
The Changing Paradigm of HFpEF



HFpEF is multi-faceted, multi-organ disorder that involves hypertensive remodeling, ventricular-vascular stiffening, obesity/metabolic stress, aging, & sedentary lifestyle, all leading to global loss of cardiac, vascular, & peripheral reserve, which are the hallmarks of HFpEF

Shah SJ. J Cardiovasc Transl Res. 2017.

HF-PEF: Mechanistic Considerations



Potential Confunders:

- Anemia
- COPD
- Obesity
- Primary cardiac structural
- Other chronic disease

SA Heart®

Heart Failure Society of South Africa (HeFSSA)

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

How would you Treat this Patient?

SA Heart®

Heart Failure Society of South Africa [HeFSSA]

Matrix Approach to Therapy
Matching Predisposing Factors and Clinical Presentation

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**

80+ % of HFpEF pts

Bold: Proven Therapy

Unbold: Logical, Promising but Unproven

SA Heart

Heart Failure Society of South Africa [HeFSSA]

Shah SJ. Circulation 2016; 134: 73 -90

80+ % of HFpEF pts

Almost Universal

HFpEF Predisposition Phenotypes	HFpEF Clinical Presentation 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**

Bold: Proven Therapy

Unbold: Logical, Promising but Unproven

SA Heart

Failure Society of South Africa [HeFSSA]

Shah SJ. Circulation 2016; 134: 73 -90

Matrix Approach to Therapy
Novel Approaches

HFpEF Predisposition Phenotypes	HFpEF Clinical Presentation 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**

Bold: Proven Therapy

Unbold: Logical, Promising but Unproven

SA Heart

Failure Society of South Africa [HeFSSA]

Shah SJ. Circulation 2016; 134: 73 -90

Therapies Successful in HFrEF have Not Demonstrated Success in HFpEF

Management success in HF randomised controlled trials – no specific therapy for HFpEF is available

Intervention	HFrEF		HFpEF
Beta blocker	✓	SENIORS[1]	?	OPTIMIZE-HF[14]
ACEi/ARB	✓	CHARM[2]	✗	I-PRESERVE[15] PEP-CHF[16]
Digoxin	?	DIG[3]	✗	Dig-PEF[17]
PDE5 inhibitor	✓	RELAX-HF[4]	✗	RELAX-HF[4]
MRA	✓	RALES[5] EMPHASIS[6]	✗	TOPCAT[18] ALDO-HF[19]
Hydralazine/N2	✓	A-HeFT[7] Cohn[8]	✗	NEAT-HFpEF[20]
CRT	✓	MADIT-CRT[9] COMPANION[10]	?	PROSPECT[21]
ICD	✓	IMPROVE-HF[9] MADIT-I[11]	?	*No studies available*
Exercise	✓	HF-ACTION[12] Thompson *et al.*[13]	?	Pandey*[22]

✓ Evidence of clinical efficacy

✗ No evidence of clinical efficacy

? Clinical efficacy uncertain

*Meta-analysis of randomised controlled trials

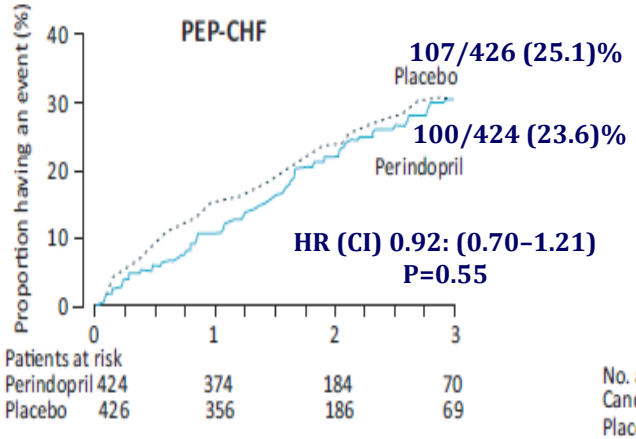
ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; CRT, Cardiac Resynchronisation Therapy; HF, Heart Failure; ICD, Implantable Cardioverter-Defibrillator; MRA, Mineralocorticoid Receptor Antagonist; N2, Nitrogen; PDE5, Phosphodiesterase Type 5. See slide notes for full list of references

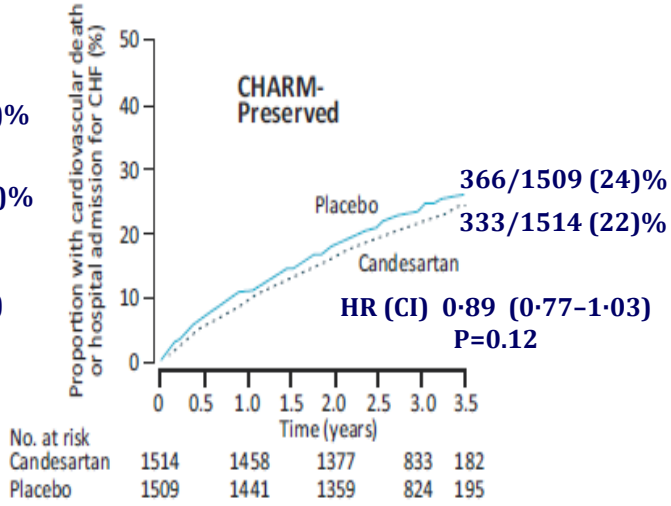
SA Heart®

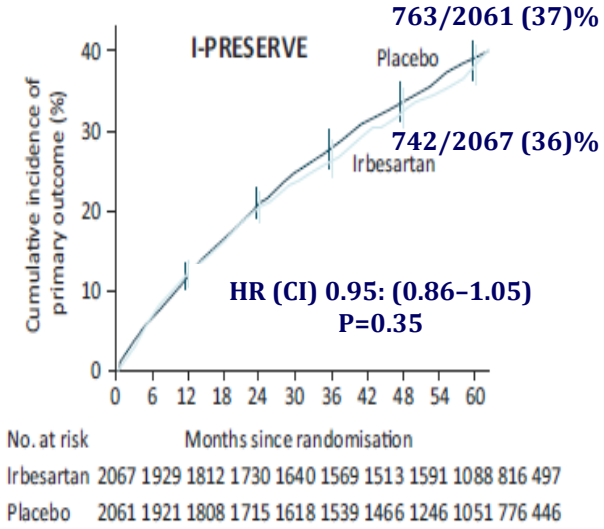
Heart Failure Society of South Africa (HeFSSA)

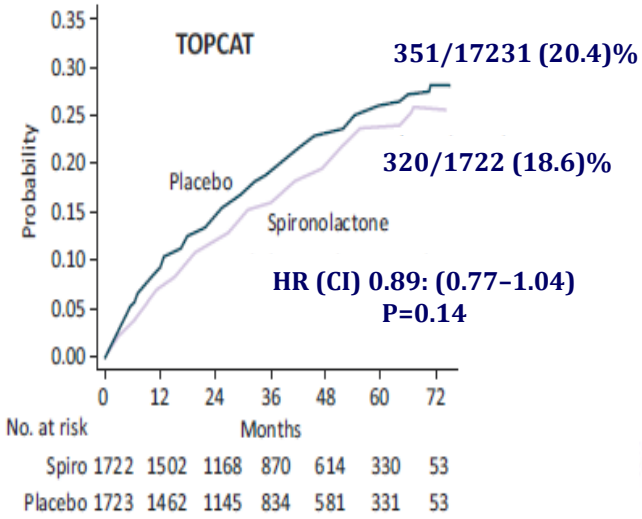
What's new in HFpEF

Key Large RCTs In HF-PEF

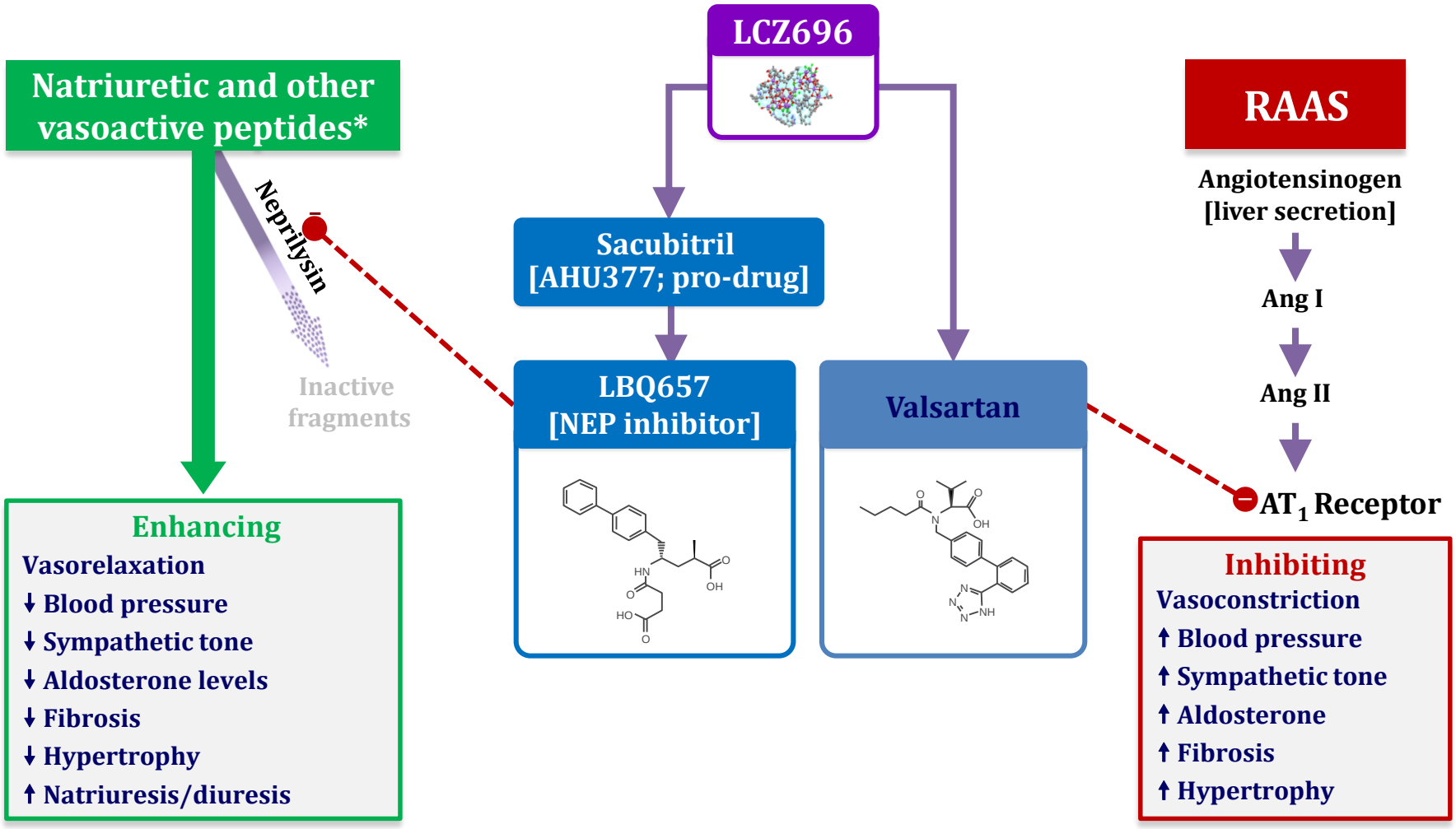








LCZ696 Simultaneously Inhibits NEP [via LBQ657] & Blocks The AT_1 Receptor [via valsartan]



*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

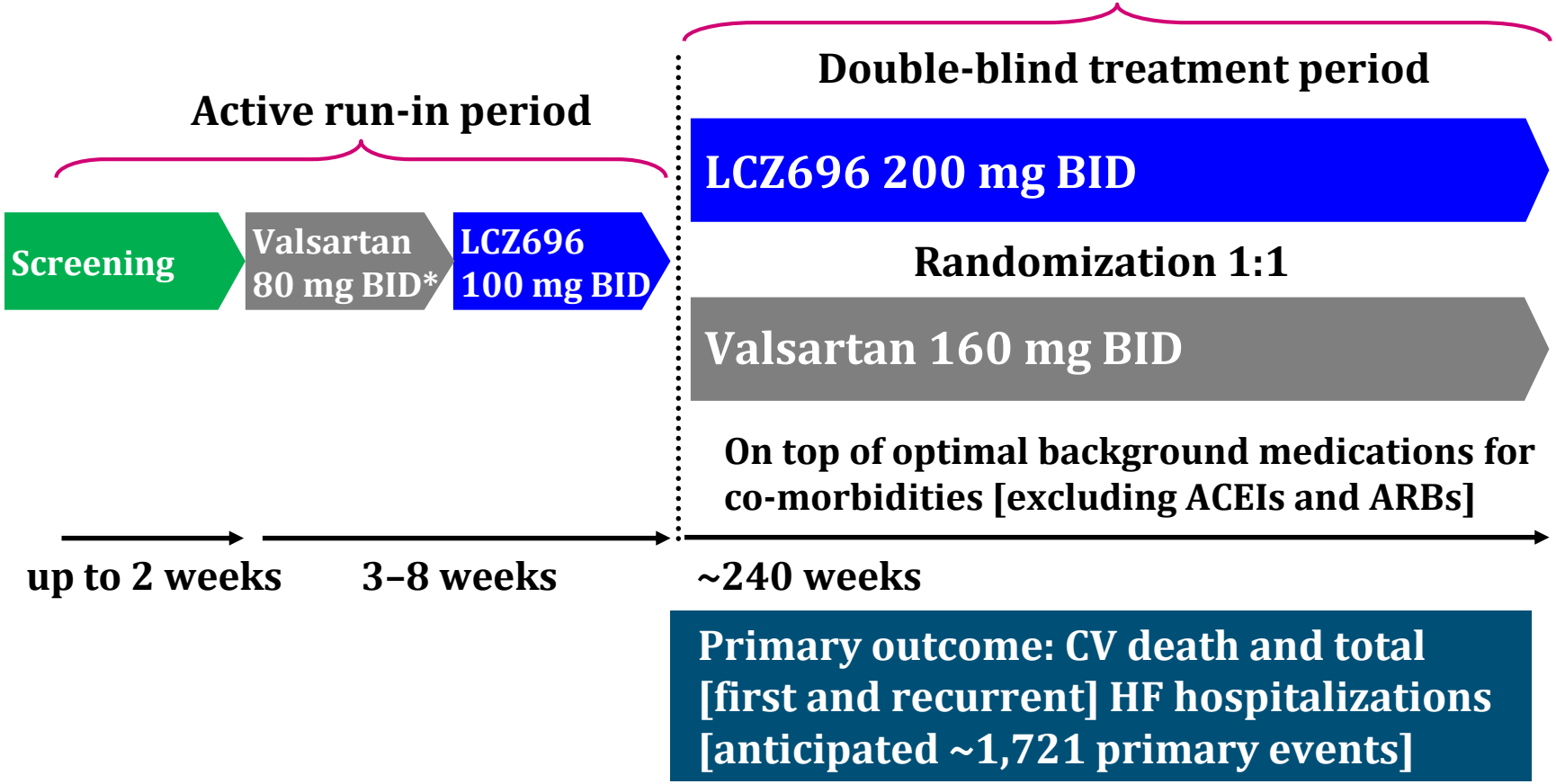
PARAGON-HF
Prospective comparison of ARni with Arb Global Outcomes in heart failure with preserved ejectioN fraction

SA Heart®

Heart Failure Society of South Africa [HeFSSA]

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

SA Heart®

Heart Failure Society of South Africa [HeFSSA]

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]

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

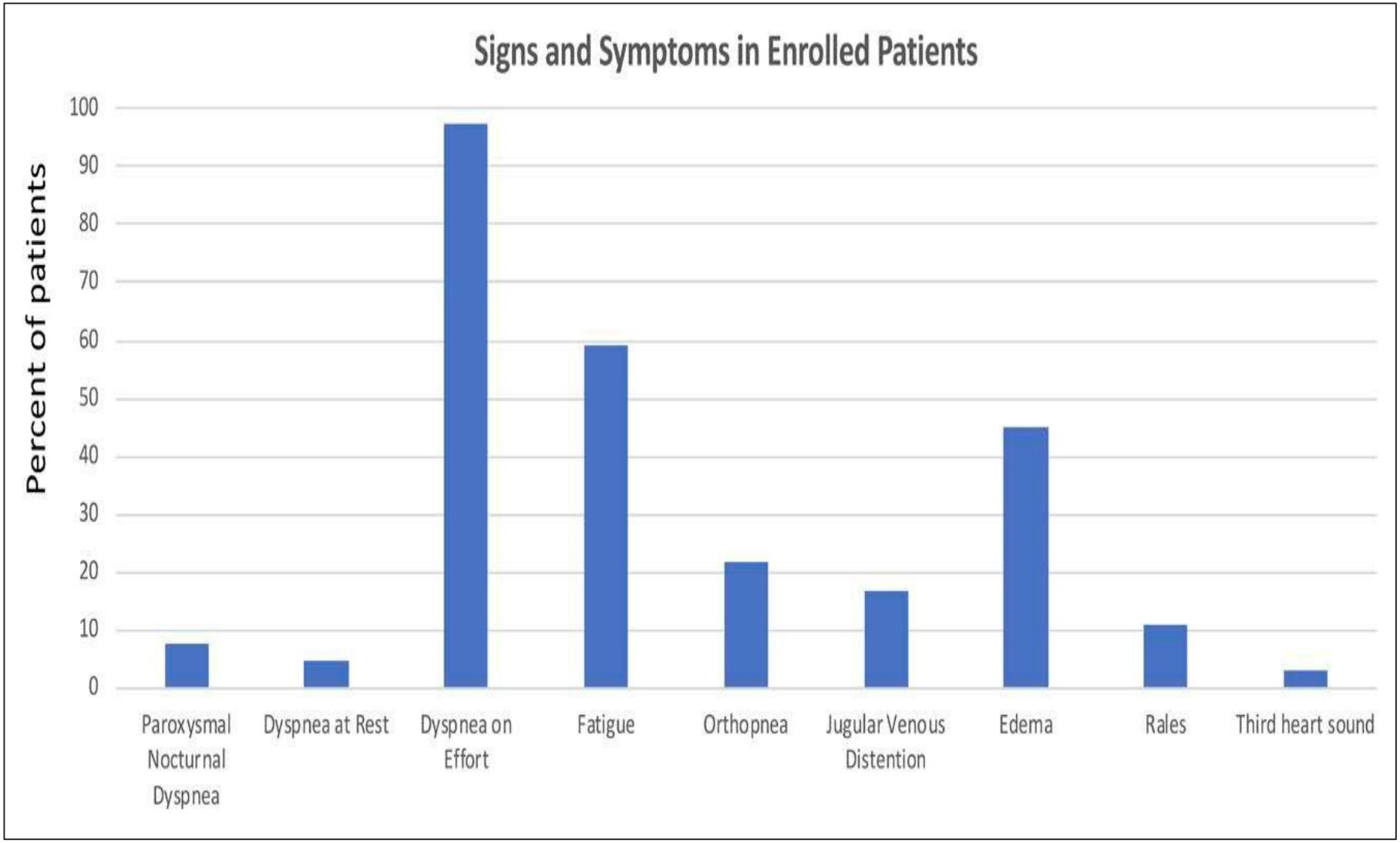
CABG=coronary artery bypass graft; LAE=left atrial enlargement; LVEF=left ventricular ejection fraction; SBP=systolic blood pressure

Baseline Characteristics

Demographics	Randomized Patients, N=4822
Age, y	73±8
Female sex	52%
NYHA Classification	
II	72%
III	27%
IV	1%
Medical History	
Prior heart failure hospitalization	48%
Heart failure hospitalization within 9 mo	38%
Hypertension	96%
Coronary artery disease	43%
Myocardial infarction	23%
Atrial fibrillation/atrial flutter	32%
Left bundle branch block	7%
Diabetes mellitus	43%
Stroke	10%
Current smoker	7%
Chronic obstructive pulmonary disease	14%
Laboratory Values	
N-terminal pro-B-type natriuretic peptide, pg/mL, plasma/serum (median, IQR)	885 (863–908)
Ejection fraction (%), mean±SD	58±8
eGFR, mL/min per 1.73 m2, mean±SD	63±19
eGRF Category. mL/min per 1.73 m^2	
<45	18%
≥45, <60	29%
≥60	53%

Circ Heart Fail. 2018

Heart Failure Signs & Symptoms in Enrolled Patients



Circ Heart Fail. 2018

Comparison of PARAGON-HF with other HFpEF Trials

	PARAGON-HF (N=4822)	TOPCAT Americas (N=1767)	I-PRESERVE (N=4128)	CHARM-Preserved (N= 3023)	PEP-CHF (N=850)
Age, y	73±8	72 (64-79)	72±7	67±11	75 (72–79)
Female sex	52%	50%	60%	40%	56%
NYHA classification					
II	72%	59%	22%	61%	I/II=76%
III	27%	35%	77%	38%	
IV	0.6%	1%	3%	2%	III/IV=25%
Ejection fraction, %	58±8	58 (53-64)			64 (56–66)
Hypertension	96%	90%	89%	64%	79%
Coronary artery disease	43%	32%	13%	33%	CABG 20%; PCI 8%
Myocardial infarction	23%	20%	23.5%	44%	27%
Atrial fibrillation/atrial flutter at screening	32%	34%	29%	29%	21%
History of AF	52%	42%	29%	29%	
Left bundle branch block	7%		8%		
Diabetes mellitus	43%	45%	27%	28%	21%
Stroke	10%	9%	10%	9%	
Glomerular filtration rate, estimated, mL/min (serum)	61.3 (49–75)	61 (49–77)	73±23		
<45	18%	17.7%			
≥45, <60	30%	31%	31%		
≥60	53%	52%			

Circ Heart Fail. 2018

Differences in Baseline Characterics between PARAGON-HF (HFpEF) & PARADIGM (HFrEF)

Demographics	PARAGON-HF	PARADIGM-HF
Age	73 ± 8	64 ± 11
Female Sex	52%	22%
NYHA Classification:2=CLASS II; 3=CLASS III; 4=CLASS IV;		
2	72%	71%
3	27%	24%
4	0.6%	0.7%
Physical Examination		
Sitting Pulse Rate (beats/min):	70 ± 12	72 ± 12
Sitting Systolic Blood Pressure (mmHg):	136± 15	121 ± 15
Sitting Diastolic Blood Pressure (mmHg):	77 ± 11	78 ± 11
Medical History		
Hypertension	96%	71%
coronary artery disease	43%	55%
Myocardial Infarction	23%	43%
Atrial Fibrillation/Atrial Flutter at Screening	33%	--
History of AF	52%	37%
Diabetes	43%	35%
Stroke	10%	9%
Current Smoker	7%	14%

Circ Heart Fail. 2018

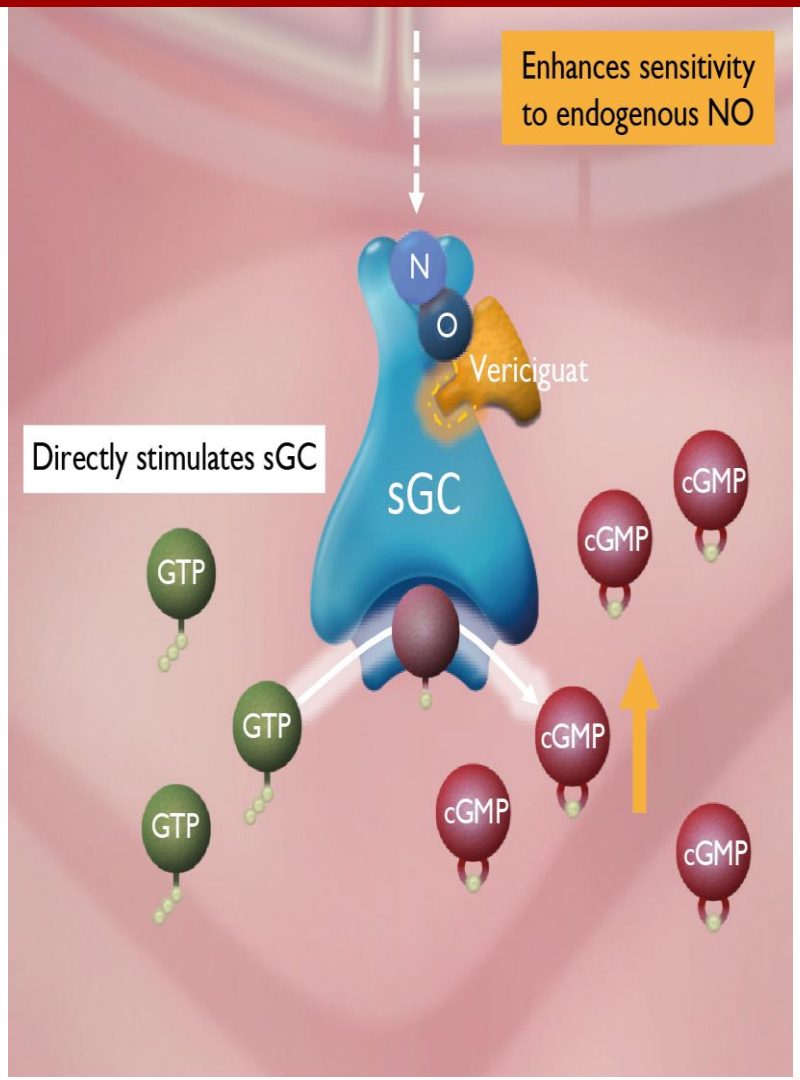
Differences in Baseline Characterics between PARAGON-HF (HFpEF) & PARADIGM (HFrEF)

Demographics	PARAGON-HF	PARADIGM-HF
Laboratory Values		
N-Terminal ProB-type Natriuretic Peptide (pg/mL), Plasma/Serum (geometric mean, 95% CI)	885 (864, 908)	1748 (1712, 1785)
Ejection Fraction (%):	58 ± 8	29%
Glomerular Filtration Rate, Estimated (mL/min), Serum:	63± 19	68 ± 19
< 45	18%	10%
>= 45, < 60	30%	25%
>= 60	53%	65%
Medical Therapies at Baseline		
Diuretic	96%	80%
Mineralocorticoid Receptor Antagonists	24%	56%?
ACE-inhibitor	40%	78%
Angiotensin Receptor Blockers	45%	23%
Digoxin	9%	30%
Beta Blockers	80.2%	93.0%
Calcium Channel Blockers	36.0%	--
Aspirin	40 %	52%
Statin Lipid Lowering Medication	62%	56%
Automated Implantable Cardioverter Defibrillator	0.4%	14.8%

Circ Heart Fail. 2018

Background

- ✓ **Heart failure with preserved EF (HFpEF): frequent but no specific therapy[1]**
- ✓ **Insufficient cGMP generation by soluble Guanylate Cyclase (sGC) in HFpEF[2,3]**

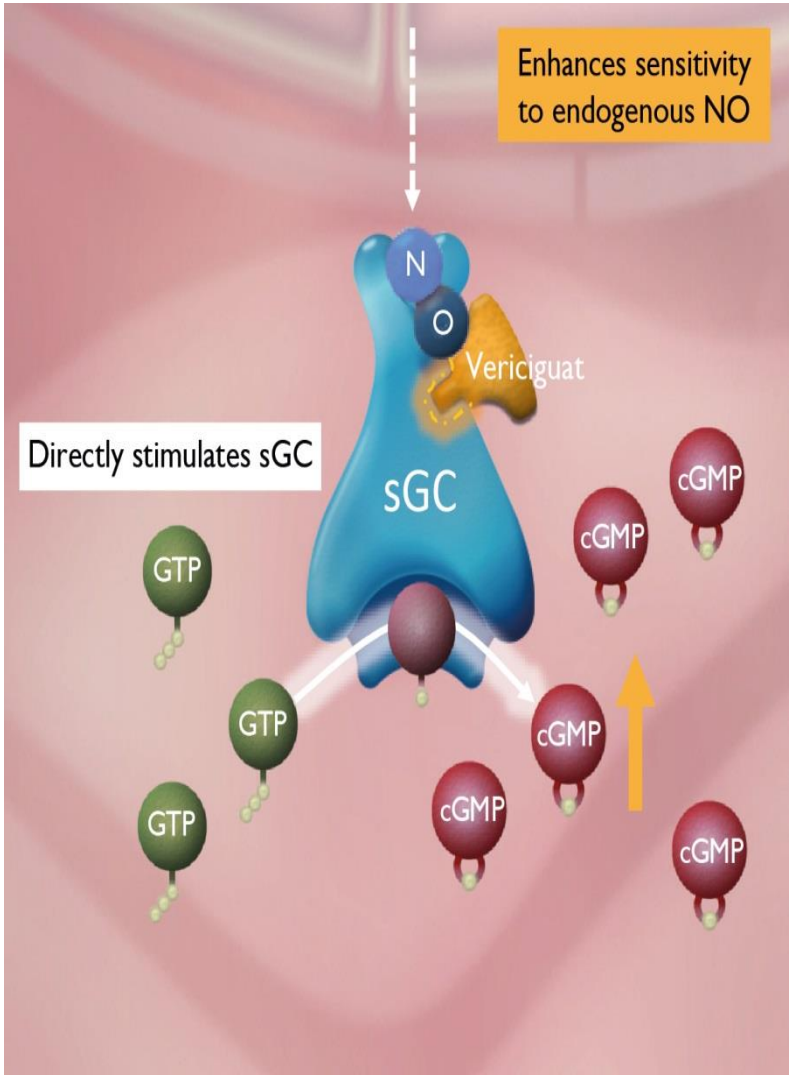


[1] Senni M et al. Eur Heart J 2014;35:2797–815; [2] Stasch JP et al. Nature 2001;410:212–15; [3] Greene SJ et al. J Am Heart Assoc. 2013;2:e000536

Background

- ✓ **Heart failure with preserved EF (HFpEF): frequent but no specific therapy [1]**
- ✓ **Insufficient cGMP generation by soluble Guanylate Cyclase (sGC) in HFpEF [2,3]**

SOCRATES Reduced (JAMA 2015): Decrease in NT-proBNP, increase in EF, trend for reduced clinical events at 10 mg Vericiguat [4]



[1] Senni M et al. Eur Heart J 2014;35:2797–815; [2] Stasch JP et al. Nature 2001;410:212–15;
[3] Greene SJ et al. J Am Heart Assoc. 2013;2:e000536; [4] Gheorghiade et al. JAMA 2015;314:2251–62

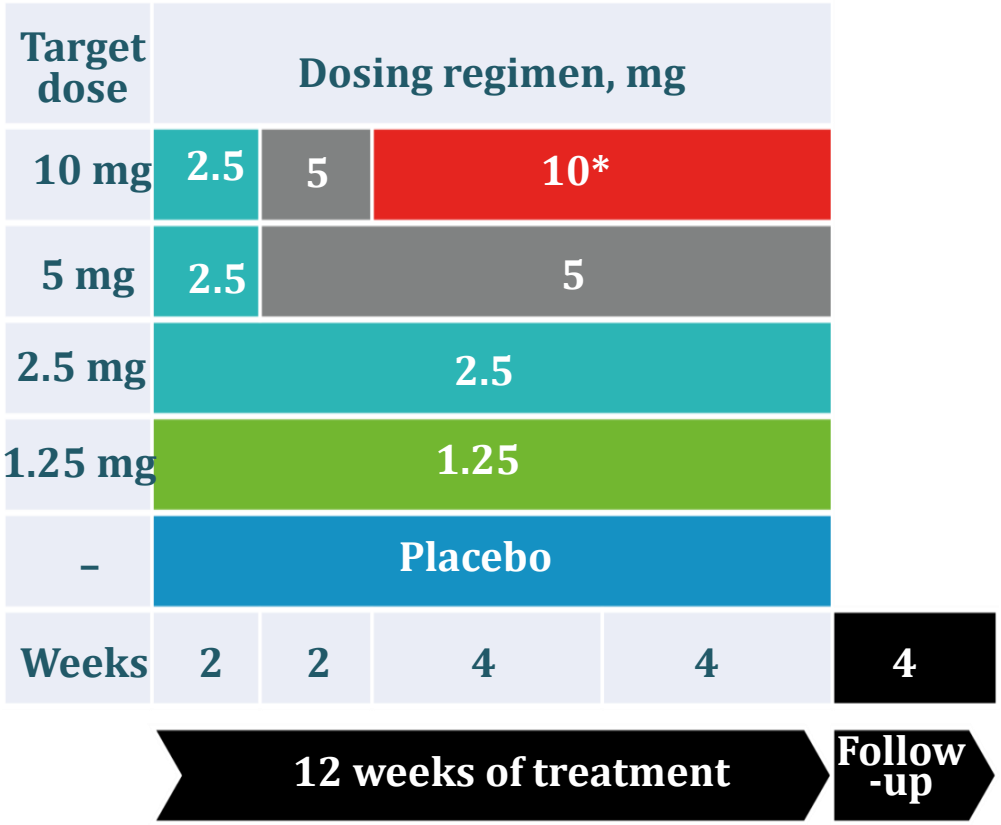
Study Design

Inclusion criteria

- ✓ NYHA class II–IV with LVEF ≥ 45% and enlarged LA
- ✓ HF decompensation requiring hospitalization, or IV diuretic therapy, within 4 weeks
- ✓ NT-proBNP ≥ 300 or BNP ≥ 100 (SR); NT-proBNP ≥ 600 or BNP ≥ 200 (AF)
- ✓ Signs and symptoms of congestion

Exclusion criteria

- ✓ Concomitant use of nitrate, PDE5 inhibitors
- ✓ eGFR < 30 mL/min/1.73 m^2

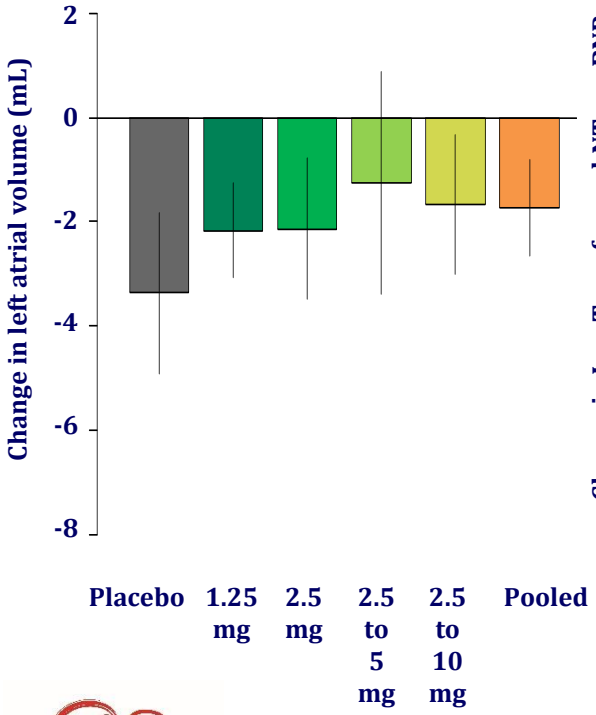


* In the 10 mg arm, at 8 weeks, 71.8% of patients were on 10 mg and 15.4% were on 5 mg

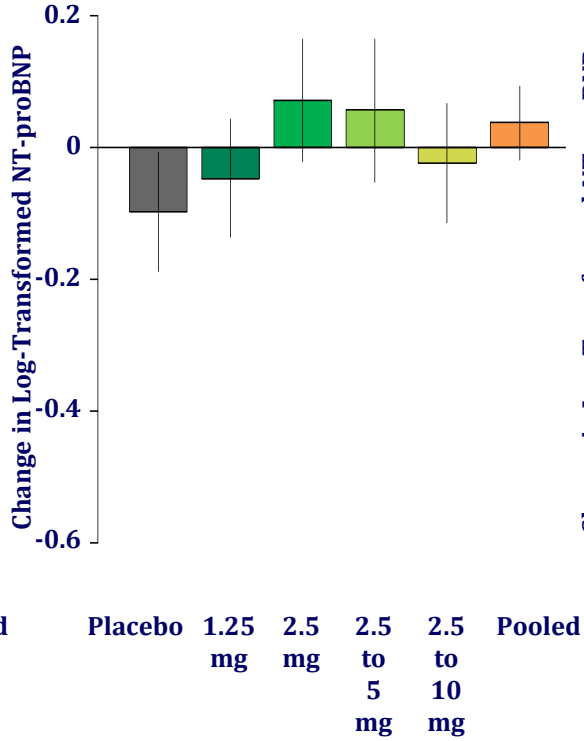
SOCRATES Phase 2 Results

No effect on primary endpoints LAV or log-NT-proBNP at week 12 in patients with HFpEF despite NT-proBNP reduction in patients with HFrEF (parallel SOCRATES-REDUCED study)

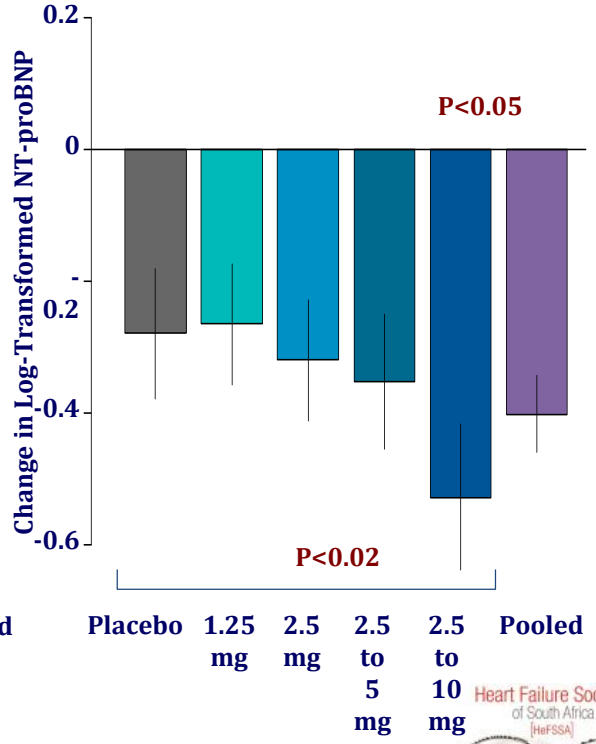
SOCRATES-PRESERVED
Primary endpoint LA volume



SOCRATES-PRESERVED
Primary endpoint NT-proBNP



SOCRATES-REDUCED
Primary endpoint NT-proBNP

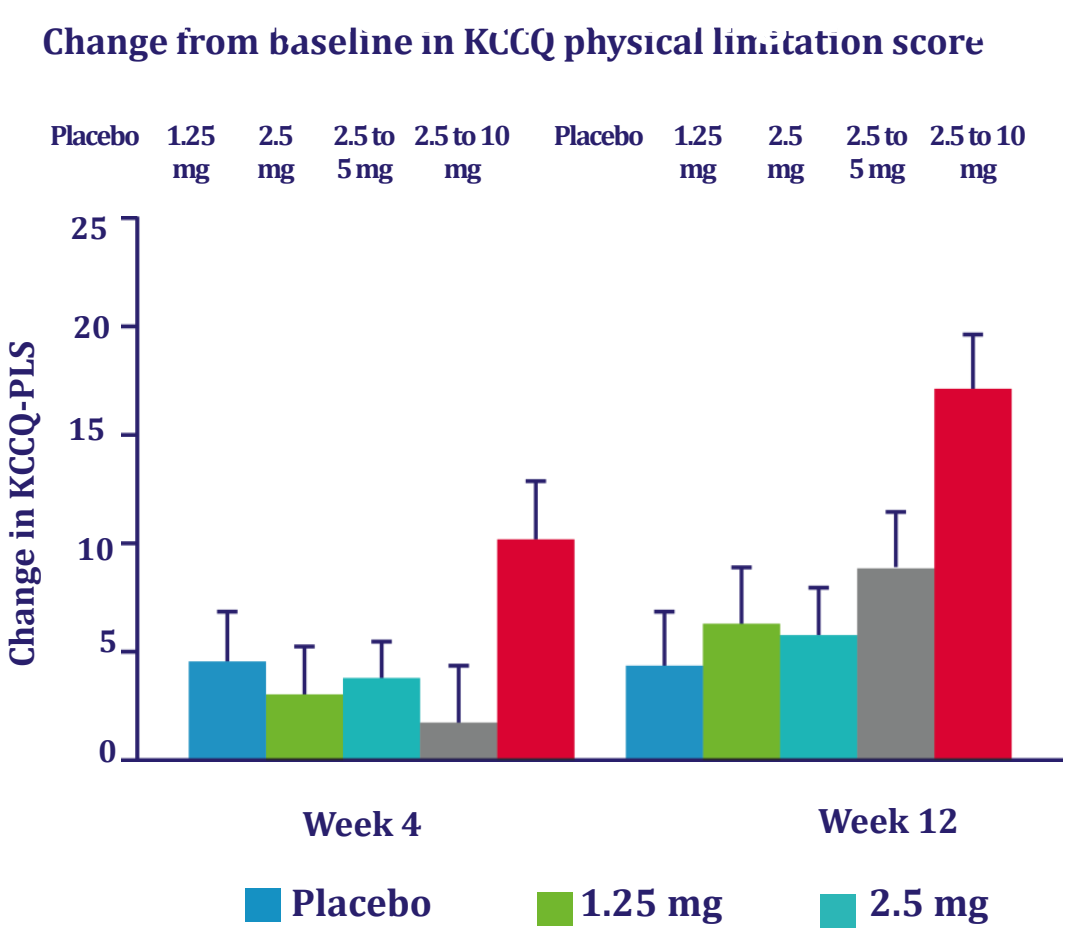


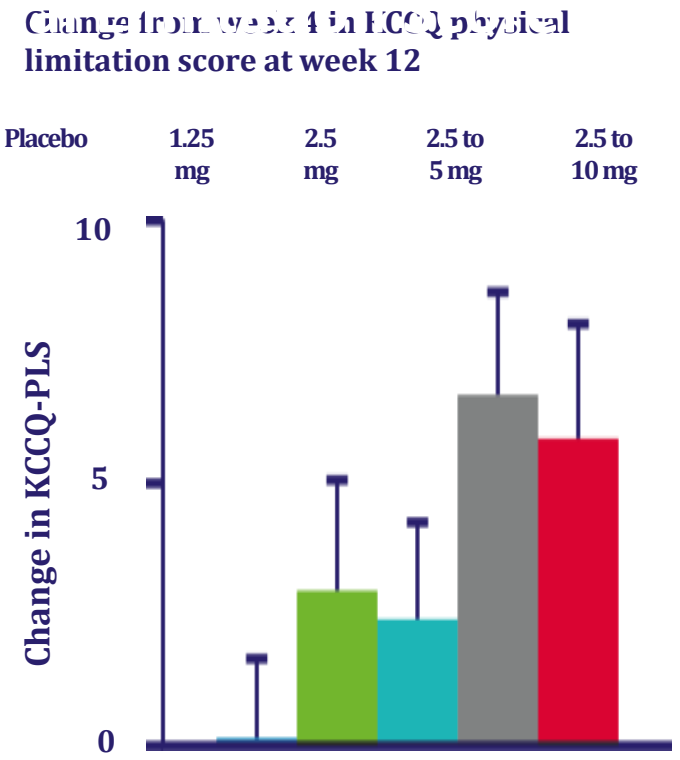
Data are mean ± standard error for the per-protocol analysis set

SA Heart®

Heart Failure Society of South Africa (HeFSSA)

Patient-Reported Health Status: KCCQ Domains
Improvements Largely Driven by Improvements in Physical Functioning: KCCQ Physical Limitation Score





Data are mean ± standard error for the full analysis set excluding those subjects with incorrectly assigned doses

Conclusions

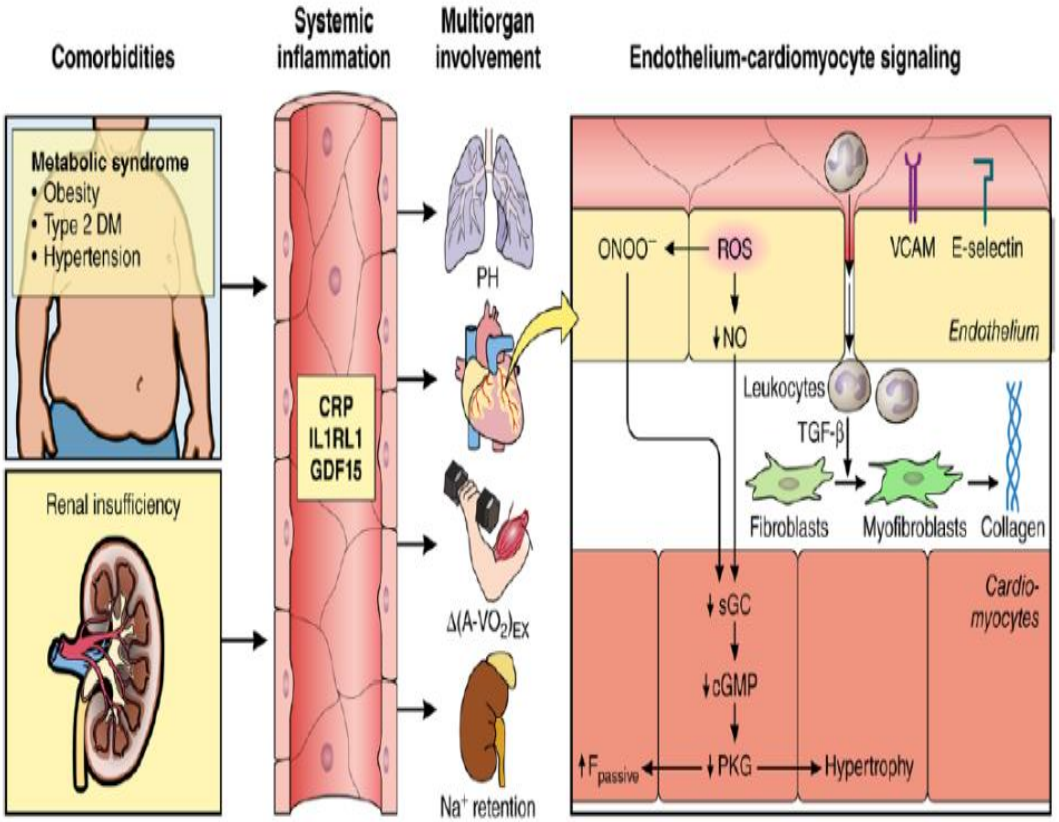
- **In patients with advanced HFpEF after recent HF decompensation, vericiguat up to a target dose of 10mg was safe and well tolerated**
- **Vericiguat did not change the primary endpoints, NT-proBNP or LAV at 12 weeks compared with placebo**
- **In pre-defined exploratory analyses of patient-reported outcomes, vericiguat was associated with clinically important improvements in patients' health status and quality of life**
- **The interesting findings with this novel once daily oral sGC stimulator in HFpEF warrant further study, possibly with higher doses, longer follow-up, and additional endpoints**

SA Heart®

Heart Failure Society of South Africa [HeFSSA]

Why is sGC a Logical Target to Improve Physical Function?

- ✓ **Patients with HFpEF have substantially reduced functional capacity and quality of life[1]**
- ✓ **No current Rx addresses this major unmet need[2]**
- ✓ **Prior phase 3 trials did not meet the primary mortality/morbidity endpoint[2]**
- ✓ **Soluble guanylate cyclase (sGC) has a unique mechanism(s) enhancing heart, vessel, muscle, and renal function**
- ✓ **Physiologic stimulation of sGC by NO is disrupted in HFpEF due to comorbidity-related inflammation[3]**

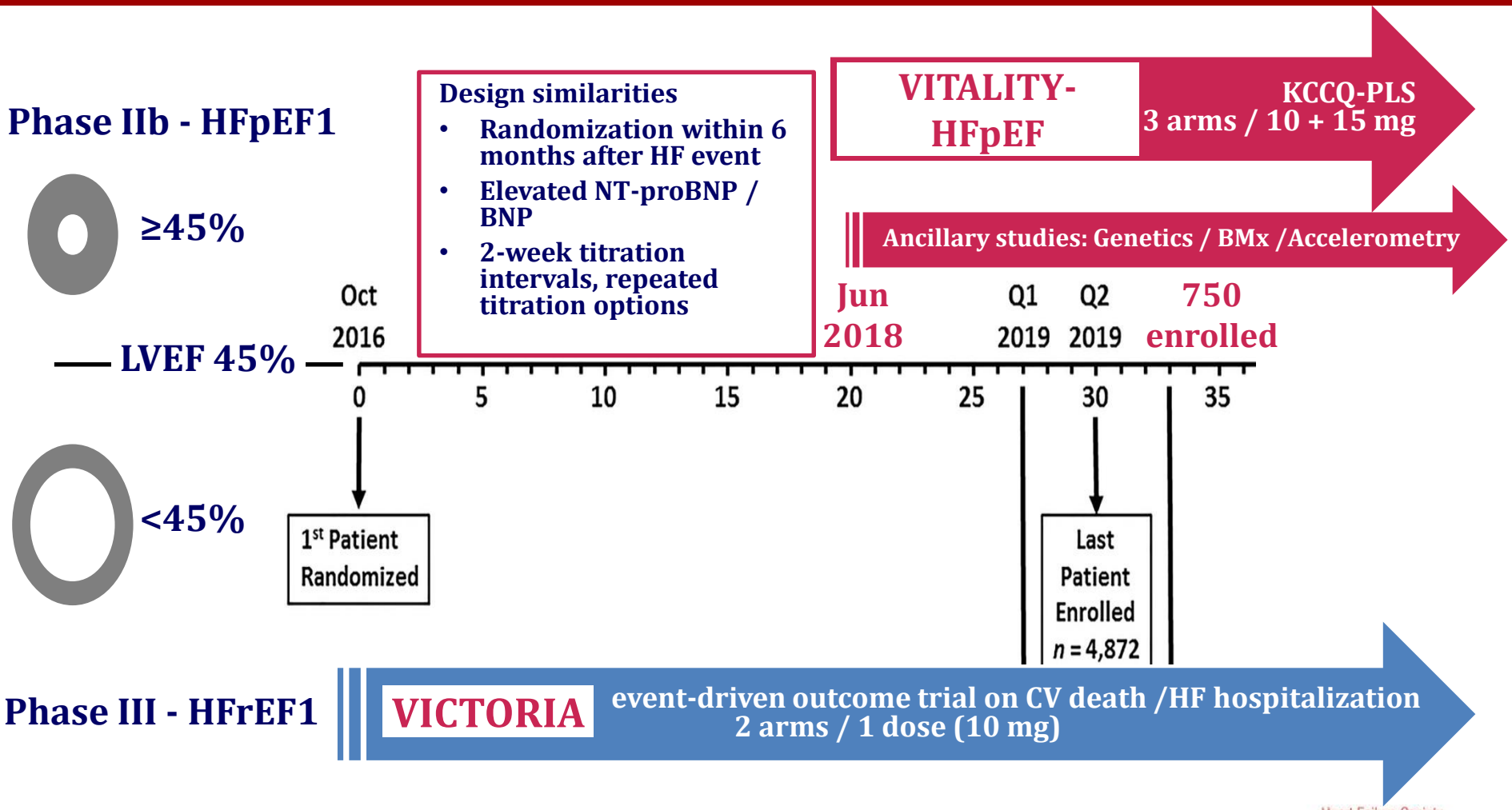


SA Heart®

Heart Failure Society of South Africa [HeFSSA]

[1] Butler et al. Circ Heart Fail. 2016 [2] Yancy CW et al. J Am Coll Cardiol. 2017 [3] Shah S et al. Circulation. 2016

Parallel Conduct of VITALITY with VICTORIA



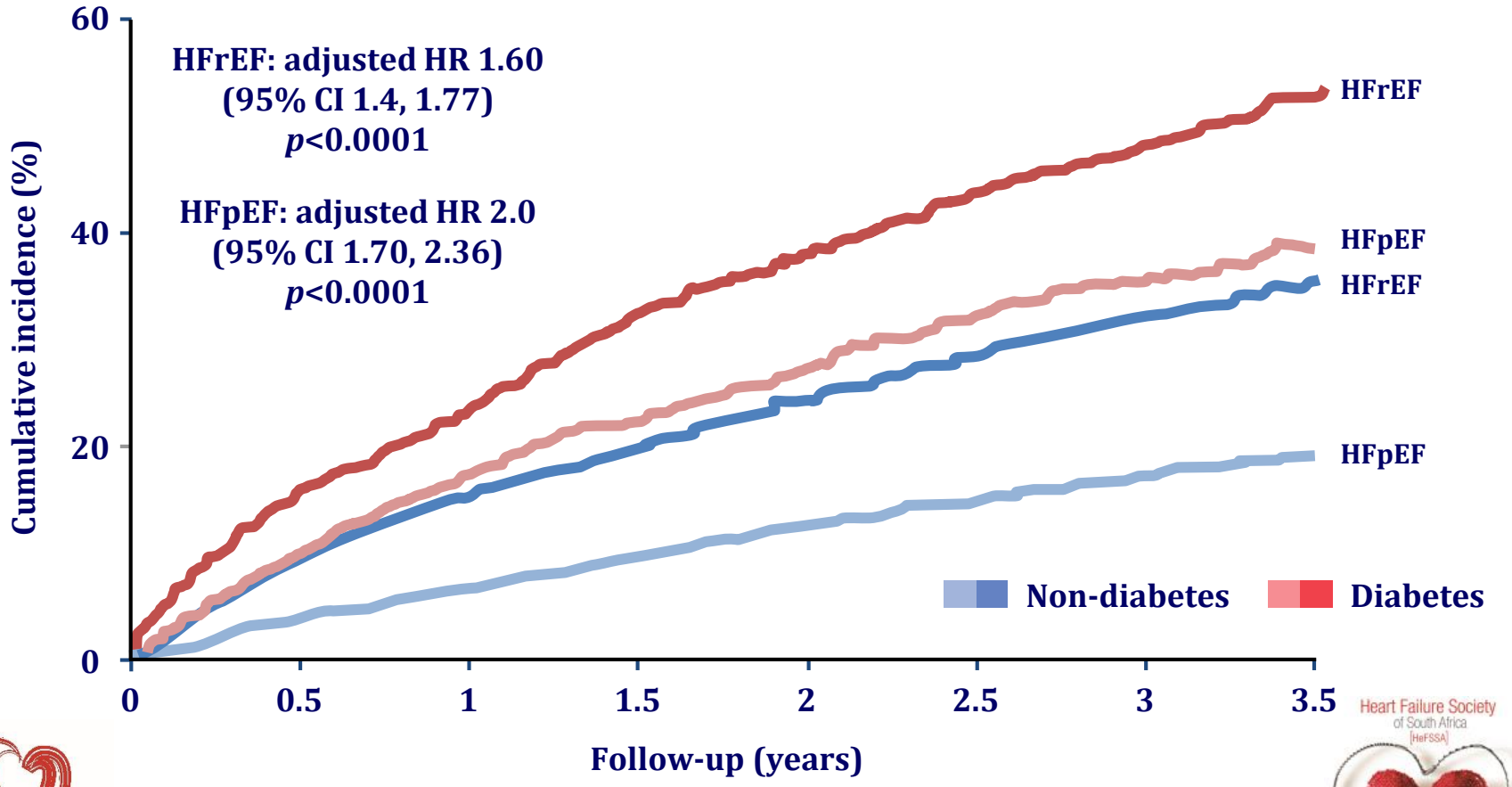
SA Heart

Heart Failure Society of South Africa [HeFSSA]

Armstrong PW et al. JACC Heart Fail. 2018

Diabetes is Associated with Worse Outcomes

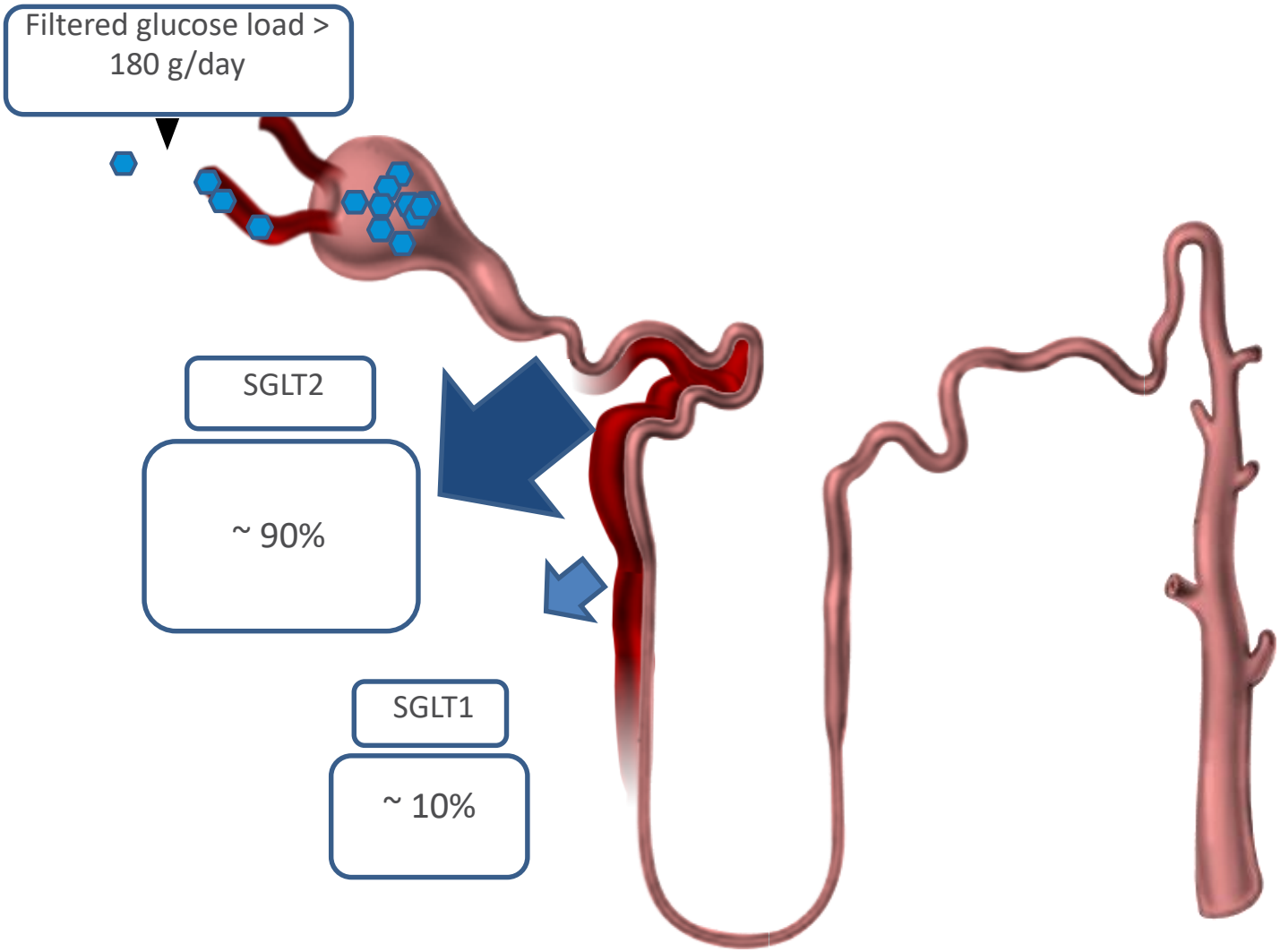
CV death or HHF in patients with and without diabetes according to ejection fraction category



HHF, Hospitalisation for Heart Failure

MacDonald MR *et al. Eur Heart J* 2008;29:1377

Renal glucose re-absorption in patients with hyperglycaemia

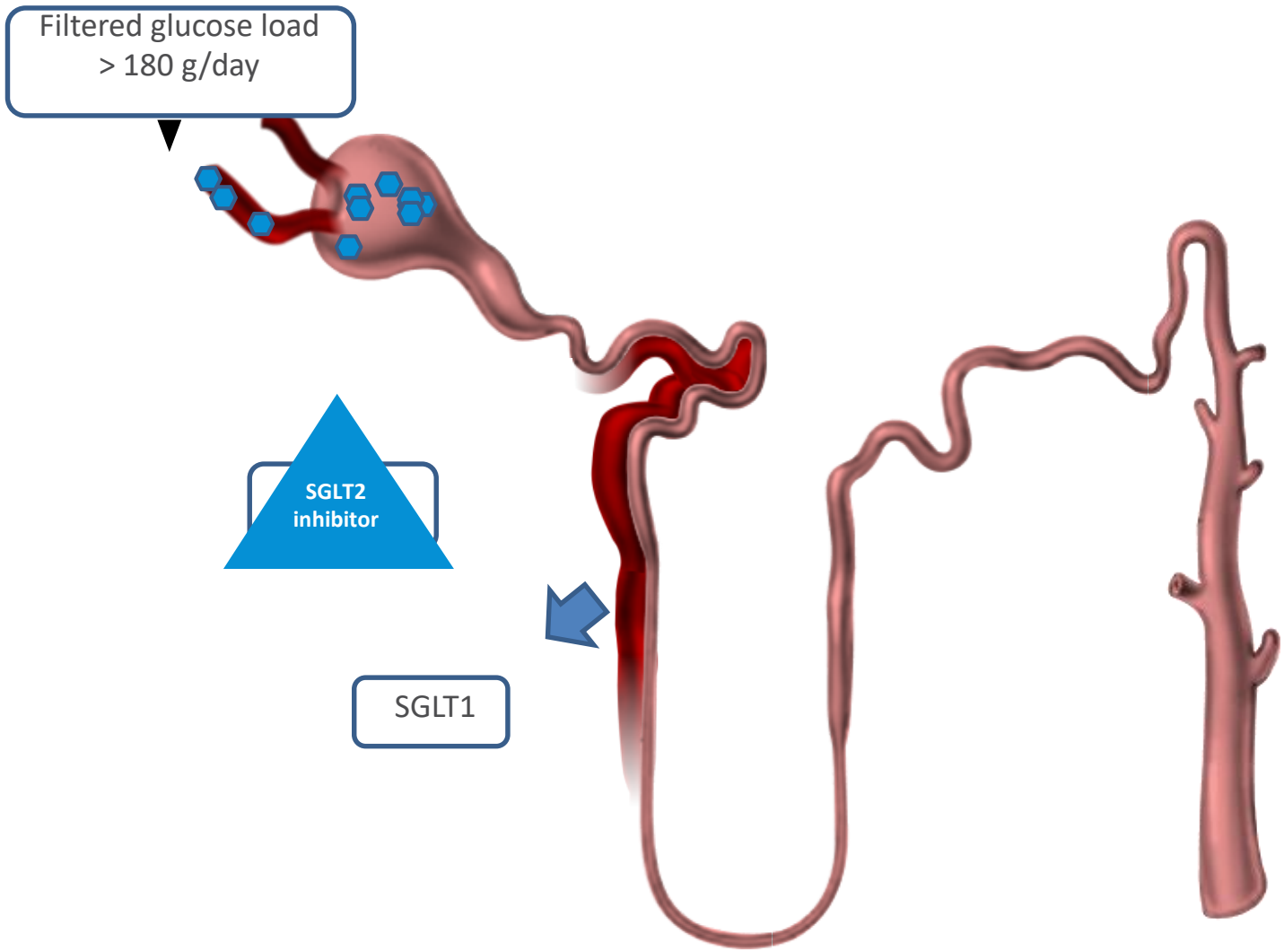


When blood glucose increases above the renal threshold (~ 10 mmol/l or 180 mg/dL), the capacity of the transporters is exceeded, resulting in urinary glucose excretion

Gerich JE. *Diabet Med*. 2010;27:136–142.

ACROSS T2D The Academy for Cardiovascular Risk, Outcomes and Safety Studies in Type 2 Diabetes

Urinary glucose excretion via SGLT2 inhibition



SGLT2 inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

*Loss of ~ 80 g of glucose/day (~ 240 cal/day).
Gerich JE. *Diabet Med*. 2010;27:136–142.

ACROSS T2D The Academy for Cardiovascular Risk, Outcomes and Safety Studies in Type 2 Diabetes

Randomised Controlled Trials of SGLT2 Inhibitors in HF

	EMPEROR-Preserved[1]	EMPEROR-Reduced[2]	Dapa-HF[3]
Sample size	4126	2850*	4500
Key inclusion criteria	Patients with chronic HF† Elevated NT-proBNP eGFR ≥20 ml/min/1.73 m^2		Symptomatic HFrEF† Elevated NT-proBNP eGFR ≥30 ml/min/1.73 m^2
	HFpEF (LVEF >40%)	HFrEF (LVEF ≤40%)	HFrEF (LVEF ≤40%)
Primary endpoint	Time to first event of adjudicated CV death or adjudicated HHF		Time to first occurrence of CV death, HHF or urgent HF visit
Key secondary endpoints	Individual components of primary endpoint All-cause mortality All-cause hospitalisation Time to first occurrence of sustained reduction of eGFR Change from baseline in KCCQ		Total number of HHF or CV death All-cause mortality Composite of ≥50% sustained eGFR decline ESRD or renal death Change from baseline in KCCQ
Start date	March 2017	March 2017	February 2017
Expected completion date	June 2020	June 2020	December 2019

*NT-proBNP-based enrichment of the population with patients at higher severity of HF; †NYHA class II–IV
eGFR, estimated Glomerular Filtration Rate; ESRD, End-Stage Renal Disease; HF, Heart Failure; HHF, Hospitalisation for Heart Failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, Left Ventricular Ejection Fraction; NT-proBNP, N-terminal Pro–B-type Natriuretic Peptide; SGLT2, Sodium-Glucose co-Transporter-2
1. ClinicalTrials.gov NCT03057951; 2. ClinicalTrials.gov NCT03057977; 3. ClinicalTrials.gov NCT03036124

EMPA-REG OUTCOME was a Randomised, Double-Blind, Placebo-Controlled CV Outcomes Trial

Patients with T2D and established CV disease

42 countries

7020 patients

CV disease was defined as ≥1 of the following:

- CAD
- PAD
- History of MI
- History of stroke

Empagliflozin or placebo given on top of standard of care

- Placebo
- Empagliflozin 10 mg
- Empagliflozin 25 mg

3.1 years median observation time

Primary endpoint: 3P-MACE

Pre-specified primary endpoint components:

- CV death
- Non-fatal MI
- Non-fatal stroke

Other pre-specified outcomes

- Hospitalisation for heart failure
- All-cause mortality

- All CV and neurological events were adjudicated by independent, masked, clinical event committees

3P-MACE, 3-point major adverse cardiovascular events; CAD, coronary artery disease; MI, myocardial infarction; PAD, peripheral artery disease; T2D, Type 2 Diabetes; CV, cardiovascular

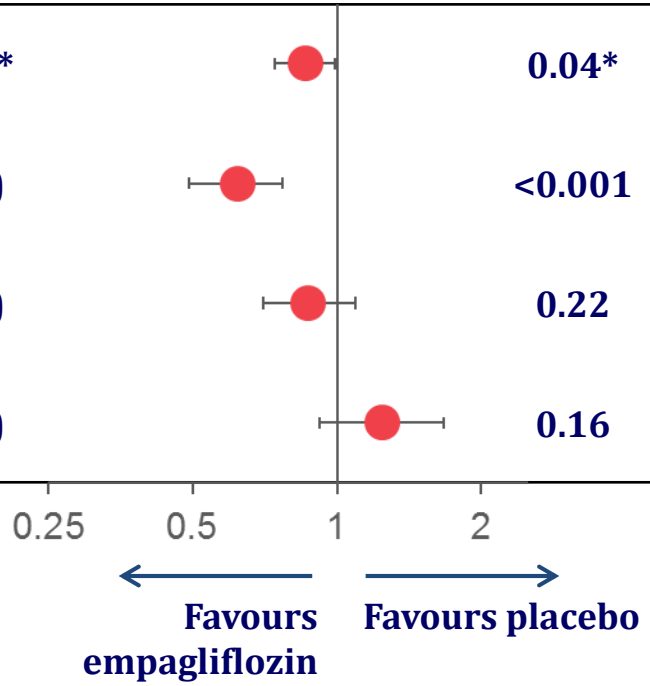
Zinman B *et al. N Engl J Med* 2015;373:2117 & supplementary appendix

SA Heart®

Heart Failure Society of South Africa [HeFSSA]

The Reduced Risk of 3P-MACE was Primarily Driven by a 38% Reduction in CV Death

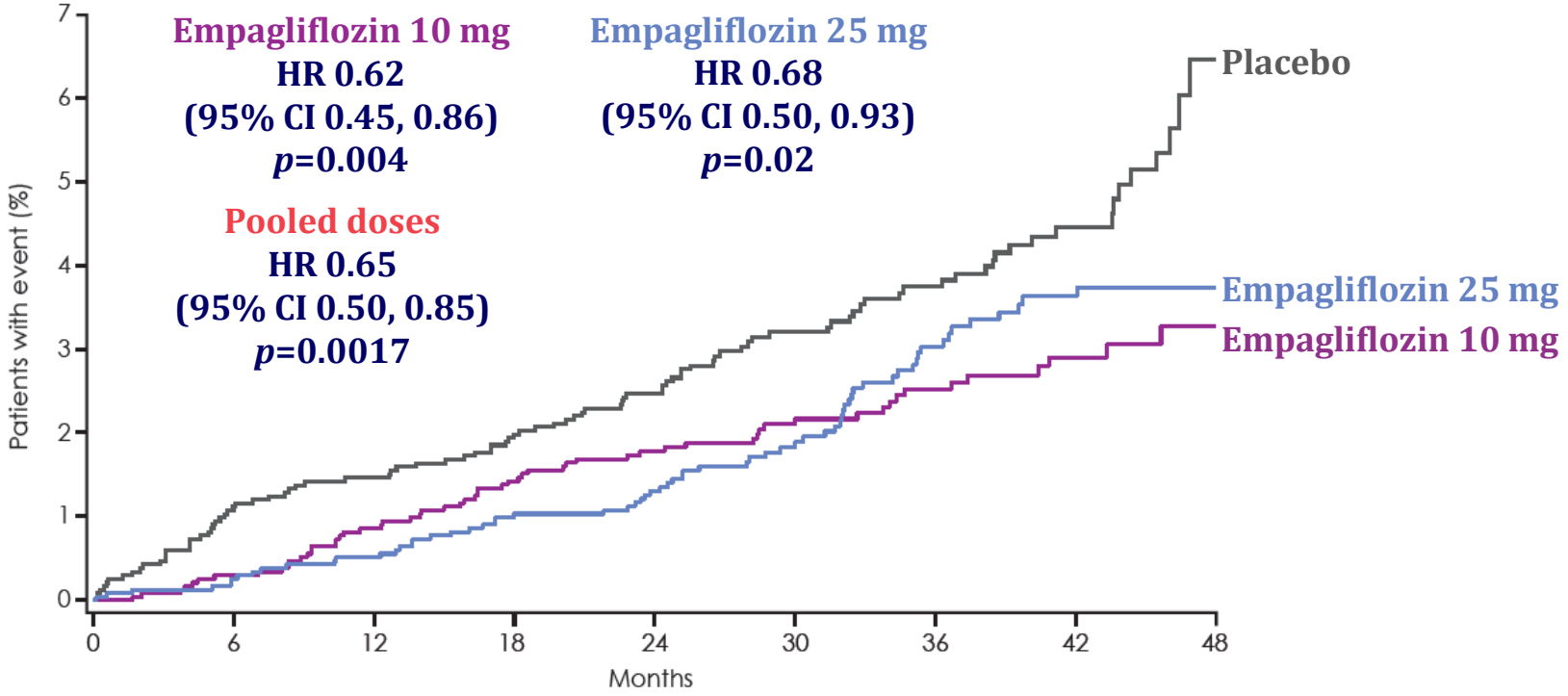
	Patients with event/ analysed (%)					
	Empagliflozin	Placebo	HR	(95% CI)	HR (95% CI)	*p*-value
3P-MACE	490/4687 (10.5)	282/2333 (12.1)	0.86	(0.74, 0.99)*		0.04*
CV death	172/4687 (3.7)	137/2333 (5.9)	0.62	(0.49, 0.77)		<0.001
Non-fatal MI	213/4687 (4.5)	121/2333 (5.2)	0.87	(0.70, 1.09)		0.22
Non-fatal stroke	150/4687 (3.2)	60/2333 (2.6)	1.24	(0.92, 1.67)		0.16



Analysis was pre-specified to the pooled empagliflozin data

Empagliflozin is not indicated in all countries for CV risk reduction
ARR for 3P-MACE: 1.6%; ARR for CV death: 2.2%. Cox regression analysis. *95.02% CI and two-sided *p*-value
3P-MACE, 3-point major adverse cardiovascular events; ARR, absolute risk reduction; MI, myocardial infarction
Zinman B *et al. N Engl J Med* 2015;373:211 & supplementary appendix

The Reduction in Hospitalisation for Heart Failure was Similar Between Both Empagliflozin Doses



No. of patients									
Empagliflozin 10 mg	2345	2306	2256	2204	1981	1473	1240	804	188
Empagliflozin 25 mg	2342	2308	2267	2223	2007	1477	1247	830	207
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Empagliflozin is not indicated for the treatment of heart failure
Pre-specified analysis; cumulative incidence function; treated set
Zinman B *et al. N Engl J Med* 2015;373:2117 (supplementary appendix)

Recent Guidelines Recognise Empagliflozin for the Prevention or Delay of Heart Failure in T2D

2016 ESC guidelines

Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

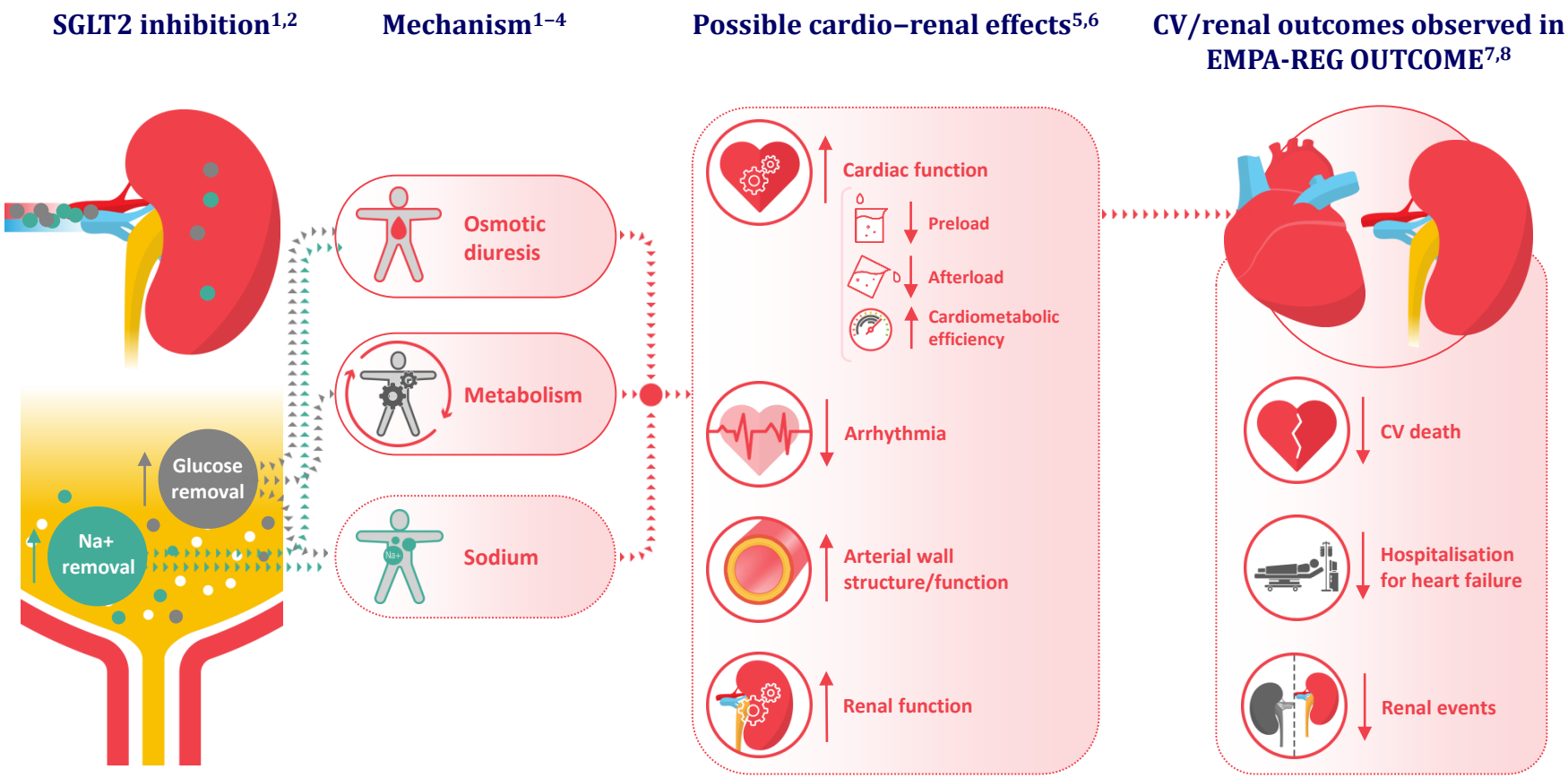
Empagliflozin should be considered in patients with T2D in order to delay the onset of heart failure and prolong life

	Class	Level	
dysfunction, in order to prevent or delay the onset of HF and prolong life.	I	A	152
Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.	I	C	131–134
Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.	IIa	C	130, 141, 153–155
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B	130
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.	I	A	5, 144, 145
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.	I	B	5
ACE-I should be considered in patients with stable CAD even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.	IIa	A	142
Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF or prolong life.	I	B	146
ICD is recommended in patients: a) with asymptomatic LV systolic dysfunction (LVEF ≤30%) of ischaemic origin, who are at least 40 days after acute myocardial infarction, b) with asymptomatic non-ischaemic dilated cardiomyopathy (LVEF ≤30%), who receive OMT therapy, in order to prevent sudden death and prolong life.	I	B	149, 156–158

Empagliflozin is not indicated for the treatment of heart failure

Ponikowski P *et al. Eur Heart J* 2016;37:2129

Potential CV & Renal Function Preservation Mechanisms of Empagliflozin in that May Benefit Heart Failure



Empagliflozin is not indicated for the treatment of heart failure or renal disease; empagliflozin is not indicated in all countries for CV risk reduction.

The pathways shown represent not yet proven hypotheses and may not apply to individual patients

The effects shown for renal function is based on the long-term results of empagliflozin versus placebo in EMPA-REG OUTCOME[8]

SGLT2, sodium-glucose co-transporter-2

1.Heise T *et al. Diabetes Obes Metab* 2013;15:613; 2. Heise T *et al. Clin Ther* 2016;38:2265; 3. Ferrannini G *et al. Diabetes Care* 2015;38:1730; 4. Briand F *et al. Diabetes* 2016;65:2032; 5. Heerspink HJ *et al. Circulation* 2016;134:752; 6. Inzucchi S *et al. Diab Vasc Dis Res* 2015;12:90; 7. Zinman B *et al. N Engl J Med* 2015;373:2117; 8. Wanner C *et al. N Engl J Med* 2016;375:323

EMPEROR-Reduced & EMPEROR-Preserved Heart Failure Outcome Trials

Summary

EMPEROR-Reduced[1] and EMPEROR-Preserved[2] trials follow on from EMPA-REG OUTCOME in patients with T2D and established CV disease

The EMPEROR trials are the first dedicated outcomes trials of empagliflozin for the treatment of chronic heart failure

The EMPEROR HF clinical trial programme will provide insights into the safety and efficacy of empagliflozin in patients with HFpEF and HFrEF, both with and without T2D, receiving current standard of care

SA Heart®

Heart Failure Society of South Africa [HeFSSA]

1. ClinicalTrials.gov NCT03057977; 2. ClinicalTrials.gov NCT03057951

“For medicine, the greatest surprises lie still ahead of us, but they are there waiting to be discovered or stumbled over sooner or later ”

SA Heart®

Heart Failure Society of South Africa (HeFSSA)