**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?”**
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
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; Creatinine 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
What is the diagnosis & what other investigations would you request?
Pulmonary Oedema
Pulmonary Oedema
Pulmonary Oedema
Pulmonary Oedema

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVSd (MM)</td>
<td>1.53 cm</td>
</tr>
<tr>
<td>LVIDd (MM)</td>
<td>5.52 cm</td>
</tr>
<tr>
<td>LVPWd (MM)</td>
<td>1.27 cm</td>
</tr>
<tr>
<td>IVSs (MM)</td>
<td>1.53 cm</td>
</tr>
<tr>
<td>LVIDs (MM)</td>
<td>3.82 cm</td>
</tr>
<tr>
<td>LVPWs (MM)</td>
<td>1.44 cm</td>
</tr>
<tr>
<td>EDV (MM-Teich)</td>
<td>149 ml</td>
</tr>
<tr>
<td>EF (MM-Teich)</td>
<td>57.8 %</td>
</tr>
<tr>
<td>ESV (MM-Teich)</td>
<td>62.9 ml</td>
</tr>
<tr>
<td>FS (MM-Teich)</td>
<td>30.8 %</td>
</tr>
<tr>
<td>IVS % (MM)</td>
<td>0.000 %</td>
</tr>
<tr>
<td>IVS/LVPW (MM)</td>
<td>1.20</td>
</tr>
<tr>
<td>LV Mass (Cubed)</td>
<td>341 grams</td>
</tr>
<tr>
<td>LVPW % (MM)</td>
<td>13.3 %</td>
</tr>
</tbody>
</table>
Would you do Cardiac Biomarkers?

- **NT-pro BNP = 3200 pg/mL**
- **Troponin T = 112 ng/L**
In-Hospital Worsening HF is Associated with Release of Cardiac Troponin & Increased Risk of Death

In-hospital worsening heart failure

Release of cardiac troponin

Cardiovascular mortality
Why is There a Link?

Volume retention or redistribution

Acute early cardiac dilatation

Injury and loss of myocardium

Short-term worsening heart failure

Long-term cardiovascular mortality

Early troponin release

Acutely decompensated heart failure
What is the Definition of HFpEF
ESC HF GL 2016: Definition Of Heart Failure With Preserved (HFpEF)

<table>
<thead>
<tr>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms ± Signs&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>LVEF ≥ 50%</td>
</tr>
</tbody>
</table>

1. Elevated levels of natriuretic peptides<sup>b</sup>

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
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Preserved” EF</td>
<td>≥ 50%</td>
</tr>
<tr>
<td>Structural alterations</td>
<td>LAVI &gt; 34 mL/m2 or LVMI ≥ 115 (males) / ≥ 95 (females) mg/m2</td>
</tr>
<tr>
<td>Functional alterations</td>
<td>E/é ≥ 13 or é (mean septal and lateral) &lt; 9cm/s</td>
</tr>
<tr>
<td>NTproBNP</td>
<td>&gt; 125pg/mL or (SR; increase with Afib!)</td>
</tr>
<tr>
<td>BNP</td>
<td>&gt; 35pg/mL</td>
</tr>
</tbody>
</table>
Diagram Of LV Filling

Focus on Relaxation
End – Diastolic Pressure Volume Relations

Focus on Stiffness
Patterns of Diastolic Function

In the beginning (mid ‘80s)...

And the sickest of all looked like this
**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

**HFrEF**
- Volume overload
  - Increased diastolic pressure
  - Increased diastolic wall stress
  - Series addition of new sarcomeres
  - Chamber enlargement
  - Eccentric hypertrophy

**HFpEF**
- Pressure overload
  - Increased systolic pressure
  - Increased systolic wall stress
  - Parallel addition of new myofibrils
  - Wall thickening
  - Concentric hypertrophy

Left ventricle:
- Volume overload
- Pressure overload

**Left ventricle:**
- Normal
- Thickened

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

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

HFpEF

LV hypertrophy

Protective & maladaptive signalling

↓ Myocardial contractility

↑ Cardiomyocyte necrosis, apoptosis, autophagy

Oxidative stress in cardiomyocytes

Cardiac injury

HFrEF

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

HFpEF is a 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.
HF-PEF: Mechanistic Considerations

Potential Confounders:
- Anemia
- COPD
- Obesity
- Primary cardiac structural
- Other chronic disease

- Arrhythmia: Chronotropic incompetence
- Hypertension: Micro/macrovascular dysfunction
- Diabetes: Metabolic dysfunction
- Ischemia: Skeletal muscle dysfunction
- Inflammatory/Infiltrative: Extracellular matrix modification

HF-Preserved Systolic function
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/m²)
- Raised E/e' ratio (≥ 13)
- Increased wall thickness (LV mass index > 115 g/m² for men: > 95 g/m² 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?
Matrix Approach to Therapy
Matching Predisposing Factors and Clinical Presentation

<table>
<thead>
<tr>
<th>HFpEF Predisposition Phenotypes</th>
<th>Lung Congestion</th>
<th>+Chronotropic Incompetence</th>
<th>+Pulmonary Hypertension (CpCPH)</th>
<th>+Skeletal muscle weakness</th>
<th>+Atrial Fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight/obesity, metabolic syndrome/ type 2 DM</td>
<td><strong>Diuretics (loop diuretic in DM)</strong>&lt;br&gt;- Caloric restriction&lt;br&gt;- Statins&lt;br&gt;- Inorganic nitrite/nitrate&lt;br&gt;- Sacubitril&lt;br&gt;- Spironolactone</td>
<td>+Rate adaptive atrial pacing</td>
<td>+Pulmonary vasodilators (e.g. PDE5I)</td>
<td>+Exercise training program</td>
<td>+Cardioversion + Rate Control + Anticoagulation</td>
</tr>
<tr>
<td>+Arterial hypertension</td>
<td>+ACEI/ARB</td>
<td>+ACEI/ARB + Rate adaptive atrial pacing</td>
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<td>+Renal dysfunction</td>
<td>+Ultrafiltration if needed</td>
<td>+Ultrafiltration if needed + Rate adaptive atrial pacing</td>
<td>+Ultrafiltration if needed + Pulmonary vasodilators (e.g. PDE5I)</td>
<td>+Ultrafiltration if needed + Exercise training program</td>
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<tr>
<td>+CAD</td>
<td>+ACEI + Revascularization</td>
<td>+ACEI + Revascularization + Rate adaptive atrial pacing</td>
<td>+ACEI + Revascularization + Pulmonary vasodilators (e.g. PDE5I)</td>
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80+ % of HFpEF pts

**Bold: Proven Therapy**

**Unbold: Logical, Promising but Unproven**
### Proven Therapy

- **80+ % of HFrEF pts**
- **Almost Universal**

#### HFrEF Clinical Presentation Phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Lung Congestion</th>
<th>+ Chronotropic Incompetence</th>
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<td>• Diuretics (loop diuretic in DM) • Caloric restriction</td>
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<td>+ Renal dysfunction</td>
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### Matrix Approach to Therapy

**Novel Approaches**

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</table>

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### Therapies Successful in HFrEF have Not Demonstrated Success in HFpEF

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

<table>
<thead>
<tr>
<th>Intervention</th>
<th>HFrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blocker</td>
<td>✔️</td>
<td>?</td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>✔️</td>
<td>✗</td>
</tr>
<tr>
<td>Digoxin</td>
<td>?</td>
<td>✗</td>
</tr>
<tr>
<td>PDE5 inhibitor</td>
<td>✔️</td>
<td>✗</td>
</tr>
<tr>
<td>MRA</td>
<td>✔️</td>
<td>✗</td>
</tr>
<tr>
<td>Hydralazine/N2</td>
<td>✔️</td>
<td>✗</td>
</tr>
<tr>
<td>CRT</td>
<td>✔️</td>
<td>?</td>
</tr>
<tr>
<td>ICD</td>
<td>✔️</td>
<td>?</td>
</tr>
<tr>
<td>Exercise</td>
<td>✔️</td>
<td>?</td>
</tr>
</tbody>
</table>

**Therapies Successful in HFrEF**

- SENIORS\(^1\)
- CHARMM\(^2\)
- DIG\(^3\)
- RELAX-HF\(^4\)
- A-HeFT\(^7\) Cohn\(^8\)
- MADIT-CRT\(^9\) COMPANION\(^10\)
- IMPROVE-HF\(^9\)
- MADIT-I\(^11\)
- HF-ACTION\(^12\) Thompson *et al.*\(^13\)

**Therapies with Evidence of Clinical Efficacy**

- Beta blocker
- ACEi/ARB
- PDE5 inhibitor
- MRA
- Hydralazine/N2
- CRT
- ICD
- Exercise

**Therapies with No Evidence of Clinical Efficacy**

- ACEi/ARB
- PDE5 inhibitor
- MRA
- Hydralazine/N2
- CRT
- ICD
- Exercise

**Therapies with Clinical Efficacy Uncertain**

- Beta blocker
- ACEi/ARB
- PDE5 inhibitor
- MRA
- Hydralazine/N2
- CRT
- ICD
- Exercise

*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.
What’s new in HFpEF
Key Large RCTs In HF-PEF

**PEP-CHF**
- HR (CI) 0.92: (0.70–1.21)
- P=0.55
- **100/424 (23.6%)**
- **107/426 (25.1%)**

**CHARM-Preserved**
- HR (CI) 0.89 (0.77–1.03)
- P=0.12
- **366/1509 (24%)**
- **333/1514 (22%)**

**I-PRESERVE**
- HR (CI) 0.95: (0.86–1.05)
- P=0.35
- **763/2061 (37%)**
- **742/2067 (36%)**

**TOPCAT**
- HR (CI) 0.89: (0.77–1.04)
- P=0.14
- **351/17231 (20.4%)**
- **320/1722 (18.6%)**
LCZ696 Simultaneously Inhibits NEP [via LBQ657] & Blocks The AT₁ Receptor [via valsartan]

Natriuretic and other vasoactive peptides*

Enhancing
- Vasorelaxation
- ↓ Blood pressure
- ↓ Sympathetic tone
- ↓ Aldosterone levels
- ↓ Fibrosis
- ↓ Hypertrophy
- ↑ Natriuresis/diuresis

RAAS
- Angiotensinogen [liver secretion]
- Ang I
- Ang II

Inhibiting Vasoconstriction
- ↑ Blood pressure
- ↑ Sympathetic tone
- ↑ Aldosterone
- ↑ Fibrosis
- ↑ Hypertrophy

PARAGON-HF
Prospective comparison of ARni with Arb Global Outcomes in heart failure with preserved ejection fraction
**Target patient population:** ~4,300 patients with symptomatic HF [NYHA Class II–IV] and LVEF ≥45%

**Active run-in period**
- Screening
- Valsartan 80 mg BID*
- LCZ696 100 mg BID

**Double-blind treatment period**
- LCZ696 200 mg BID
- Randomization 1:1
- Valsartan 160 mg BID
- On top of optimal background medications for co-morbidities [excluding ACEIs and ARBs]

**Primary outcome:** CV death and total [first and recurrent] HF hospitalizations [anticipated ~1,721 primary events]

*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 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/1.73m²
✓ SBP <110 mm Hg or >180 mm Hg. 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/m²

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

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Randomized Patients, N=4822</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>73±8</td>
</tr>
<tr>
<td>Female sex</td>
<td>52%</td>
</tr>
<tr>
<td>NYHA Classification</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>72%</td>
</tr>
<tr>
<td>III</td>
<td>27%</td>
</tr>
<tr>
<td>IV</td>
<td>1%</td>
</tr>
</tbody>
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### Medical History

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<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Prior heart failure hospitalization</td>
<td>48%</td>
</tr>
<tr>
<td>Heart failure hospitalization within 9 mo</td>
<td>38%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>96%</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>43%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>23%</td>
</tr>
<tr>
<td>Atrial fibrillation/atrial flutter</td>
<td>32%</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>7%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>43%</td>
</tr>
<tr>
<td>Stroke</td>
<td>10%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>7%</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>14%</td>
</tr>
</tbody>
</table>

### Laboratory Values

| N-terminal pro-B-type natriuretic peptide, pg/mL, plasma/serum | 885 (863–908) |
| Ejection fraction (%), mean±SD                                 | 58±8          |
| eGFR, mL/min per 1.73 m2, mean±SD                              | 63±19         |
| **eGFR Category. mL/min per 1.73 m²**                          |               |
| <45                                                             | 18%           |
| ≥45, <60                                                        | 29%           |
| ≥60                                                             | 53%           |
Heart Failure Signs & Symptoms in Enrolled Patients

Signs and Symptoms in Enrolled Patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal Nocturnal Dyspnea</td>
<td>Low</td>
</tr>
<tr>
<td>Dyspnea at Rest</td>
<td>Very Low</td>
</tr>
<tr>
<td>Dyspnea on Effort</td>
<td>High</td>
</tr>
<tr>
<td>Fatigue</td>
<td>High</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>Medium</td>
</tr>
<tr>
<td>Jugular Venous Distention</td>
<td>Medium</td>
</tr>
<tr>
<td>Edema</td>
<td>High</td>
</tr>
<tr>
<td>Rales</td>
<td>Low</td>
</tr>
<tr>
<td>Third Heart Sound</td>
<td>Very Low</td>
</tr>
</tbody>
</table>
## Comparison of PARAGON-HF with other HFpEF Trials

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

<table>
<thead>
<tr>
<th>Demographics</th>
<th>PARAGON-HF</th>
<th>PARADIGM-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73 ± 8</td>
<td>64 ± 11</td>
</tr>
<tr>
<td>Female Sex</td>
<td>52%</td>
<td>22%</td>
</tr>
</tbody>
</table>

NYHA Classification: 2=CLASS II; 3=CLASS III; 4=CLASS IV;

<table>
<thead>
<tr>
<th>NYHA Classification</th>
<th>PARAGON-HF</th>
<th>PARADIGM-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>72%</td>
<td>71%</td>
</tr>
<tr>
<td>3</td>
<td>27%</td>
<td>24%</td>
</tr>
<tr>
<td>4</td>
<td>0.6%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

### Physical Examination

- Sitting Pulse Rate (beats/min): 70 ± 12 and 72 ± 12
- Sitting Systolic Blood Pressure (mmHg): 136 ± 15 and 121 ± 15
- Sitting Diastolic Blood Pressure (mmHg): 77 ± 11 and 78 ± 11

### Medical History

- Hypertension: 96% and 71%
- coronary artery disease: 43% and 55%
- Myocardial Infarction: 23% and 43%
- Atrial Fibrillation/Atrial Flutter at Screening: 33% and --
- History of AF: 52% and 37%
- Diabetes: 43% and 35%
- Stroke: 10% and 9%
- Current Smoker: 7% and 14%

Circ Heart Fail. 2018
### Demographics

#### Laboratory Values

<table>
<thead>
<tr>
<th></th>
<th>PARAGON-HF</th>
<th>PARADIGM-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Terminal ProB-type Natriuretic Peptide (pg/mL), Plasma/Serum (geometric mean, 95% CI)</td>
<td>885 (864, 908)</td>
<td>1748 (1712, 1785)</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>58 ± 8</td>
<td>29%</td>
</tr>
<tr>
<td>Glomerular Filtration Rate, Estimated (mL/min), Serum:</td>
<td>63 ± 19</td>
<td>68 ± 19</td>
</tr>
<tr>
<td>&lt; 45</td>
<td>18%</td>
<td>10%</td>
</tr>
<tr>
<td>&gt;= 45, &lt; 60</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>&gt;= 60</td>
<td>53%</td>
<td>65%</td>
</tr>
</tbody>
</table>

### Medical Therapies at Baseline

<table>
<thead>
<tr>
<th>Medical Therapy</th>
<th>PARAGON-HF</th>
<th>PARADIGM-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td>96%</td>
<td>80%</td>
</tr>
<tr>
<td>Mineralocorticoid Receptor Antagonists</td>
<td>24%</td>
<td>56%?</td>
</tr>
<tr>
<td>ACE-inhibitor</td>
<td>40%</td>
<td>78%</td>
</tr>
<tr>
<td>Angiotensin Receptor Blockers</td>
<td>45%</td>
<td>23%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>9%</td>
<td>30%</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>80.2%</td>
<td>93.0%</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>36.0%</td>
<td>--</td>
</tr>
<tr>
<td>Aspirin</td>
<td>40%</td>
<td>52%</td>
</tr>
<tr>
<td>Statin Lipid Lowering Medication</td>
<td>62%</td>
<td>56%</td>
</tr>
<tr>
<td>Automated Implantable Cardioverter Defibrillator</td>
<td>0.4%</td>
<td>14.8%</td>
</tr>
</tbody>
</table>

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\(^2,3\)

Background

✓ Heart failure with preserved EF (HFpEF): frequent but no specific therapy

✓ Insufficient cGMP generation by soluble Guanylate Cyclase (sGC) in HFpEF

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

### 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 m²

<table>
<thead>
<tr>
<th>Target dose</th>
<th>Dosing regimen, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>2.5</td>
</tr>
<tr>
<td>5 mg</td>
<td>2.5</td>
</tr>
<tr>
<td>2.5 mg</td>
<td>2.5</td>
</tr>
<tr>
<td>1.25 mg</td>
<td>1.25</td>
</tr>
<tr>
<td>–</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

| Weeks | 2 | 2 | 4 | 4 | 4 |

12 weeks of treatment

Follow-up

* In the 10 mg arm, at 8 weeks, 71.8% of patients were on 10 mg and 15.4% were on 5 mg
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
Patient-Reported Health Status: KCCQ Domains
Improvements Largely Driven by Improvements in Physical Functioning:
KCCQ Physical Limitation Score

Change from baseline in KCCQ physical limitation score

<table>
<thead>
<tr>
<th>Placebo</th>
<th>1.25 mg</th>
<th>2.5 mg</th>
<th>2.5 to 5 mg</th>
<th>2.5 to 10 mg</th>
</tr>
</thead>
</table>

Change from week 4 in KCCQ physical limitation score at week 12

<table>
<thead>
<tr>
<th>Placebo</th>
<th>1.25 mg</th>
<th>2.5 mg</th>
<th>2.5 to 5 mg</th>
<th>2.5 to 10 mg</th>
</tr>
</thead>
</table>

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

Change from baseline in 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.
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\(^3\)

Parallel Conduct of VITALITY with VICTORIA

**Phase IIb - HFpEF**
- ≥45%
- LVEF 45%
- Oct 2016
- Design similarities:
  - Randomization within 6 months after HF event
  - Elevated NT-proBNP / BNP
  - 2-week titration intervals, repeated titration options
- Jun 2018
- 750 enrolled
- Ancillary studies: Genetics / BMx / Accelerometry

**Phase III - HFrEF**
- VICTORIA event-driven outcome trial on CV death / HF hospitalization
- 2 arms / 1 dose (10 mg)
- Oct 2016
- 1st Patient Randomized
- Last Patient Enrolled n = 4,872
- Jun 2018
- Q1 2019
- Q2 2019
- KCCQ-PLS

**VITALITY - HFpEF**
- 3 arms / 10 + 15 mg
- June 2018
- Q1 2019
- Q2 2019
- 750 enrolled
- Ancillary studies: Genetics / BMx / Accelerometry

Armstrong PW et al. JACC Heart Fail. 2018

Heart Failure Society of South Africa (HFSA)
Diabetes is Associated with Worse Outcomes

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

- **HFrEF: adjusted HR 1.60**
  - (95% CI 1.4, 1.77)
  - \( p < 0.0001 \)

- **HFpEF: adjusted HR 2.0**
  - (95% CI 1.70, 2.36)
  - \( p < 0.0001 \)

**Cumulative incidence (%)**

- **Follow-up (years)**

**Diabetes**

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.

Filtered glucose load > 180 g/day

SGLT2
~ 90%

SGLT1
~ 10%

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

*Loss of ~80 g of glucose/day (~240 cal/day).
# Randomised Controlled Trials of SGLT2 Inhibitors in HF

<table>
<thead>
<tr>
<th></th>
<th>EMPEROR-Preserved(^1)</th>
<th>EMPEROR-Reduced(^2)</th>
<th>Dapa-HF(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>4126</td>
<td>2850(^*)</td>
<td>4500</td>
</tr>
</tbody>
</table>
| Key inclusion criteria | Patients with chronic HF\(^\dagger\)  
Elevated NT-proBNP  
eGFR ≥20 ml/min/1.73 m\(^2\) | Symptomatic HFrEF\(^\dagger\)  
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; \(^\dagger\)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

- 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

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Empagliflozin 10 mg</th>
<th>Empagliflozin 25 mg</th>
</tr>
</thead>
</table>

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

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

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

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

Empagliflozin 10 mg
HR 0.62
(95% CI 0.45, 0.86)
p=0.004

Empagliflozin 25 mg
HR 0.68
(95% CI 0.50, 0.93)
p=0.02

Pooled doses
HR 0.65
(95% CI 0.50, 0.85)
p=0.0017

Empagliflozin is not indicated for the treatment of heart failure
Pre-specified analysis; cumulative incidence function; treated set
Recent Guidelines Recognise Empagliflozin for the Prevention or Delay of Heart Failure in T2D

### 2016 ESC guidelines

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

<table>
<thead>
<tr>
<th>Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>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.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>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.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>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.</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>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.</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>
| 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 |

Empagliflozin is not indicated for the treatment of 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.

**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 HFP EF and HFrEF, both with and without T2D, receiving current standard of care

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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”