HeFSSA Practitioners Program 2017
Theme –
“The Patient Journey: Feel Good and Live Long”

Case Study 2
HEART FAILURE WITH MID-RANGE EJECTION FRACTION

TREATMENT OPTIONS
CLINICAL CASE – MEDICAL HISTORY

59-year-old man
• Hypertension and hyperlipidemia (for 10 years)
• Obesity (BMI 30.1 kg/m²)
• Current smoking
• Anterior NSTEMI (2 years ago)
• Stable angina (CCS II)
• Paroxysmal AF (CHA₂DS₂VASc 3; HAS-BLED 1)
• Heart failure, recent LVEF 54% (last 6 months)

Treatment before the admission:
Nitroglycerin, Bisoprolol, Isosorbide dinitrate, Aspirin, Atorvastatin, Perindopril, Rivaroxaban.
CLINICAL CASE – STATUS ON ADMISSION

Symptoms:
• worsening of dyspnea for 1 week (NYHA III)
• irregular palpitations
• fatigue
• reduced exercise tolerance
• typical angina (CCS II)

Clinical status:
• BP 165/95 mmHg, HR 120 bpm (Paroxysmal AF, last 12 hours)
• pulmonary congestion (confirmed on chest X-ray)
• ankle swelling
• weight gain

Laboratory tests:
• Hb 14.2 g/dL
• eGFR 68 mL/min/1.73m²
• NT-proBNP 1190 pg/mL
• cTnT 0.01 ng/mL
• LDL 2.0 mmol/L
Acute management:
• admitted to a coronary care unit
• i.v. amiodarone
• i.v. furosemide
• i.v. nitroglycerine

Clinical status:
• conversion AF to sinus rhythm
• BP 136/90 mmHg, HR 69 bpm
• significant reduction in dyspnea
• significant reduction in pulmonary congestion
PRECEDEUNG FACTORS FOR HEART FAILURE ADMISSION IN PATIENTS WITH HFREF, HFMREF AND HFPEF

• Database of the Get With The Guidelines-HF (GWTG-HF) program;

• 99,825 HF admissions from 305 hospitals between January 2005 and September 2013
PREVALENCE OF HEART FAILURE CHARACTERISTICS IN PATIENTS WITH HFREF, HFMREF AND HFPEF

- Database of the Get With The Guidelines-HF (GWTG-HF) program;
- 99,825 HF admissions from 305 hospitals between January 2005 and September 2013

<table>
<thead>
<tr>
<th>Characterization</th>
<th>Overall N</th>
<th>Overall %</th>
<th>Reduced Ejection Fraction N</th>
<th>Reduced Ejection Fraction %</th>
<th>Borderline Ejection Fraction N</th>
<th>Borderline Ejection Fraction %</th>
<th>Preserved Ejection Fraction N</th>
<th>Preserved Ejection Fraction %</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pulmonary edema</td>
<td>Yes</td>
<td>2,265</td>
<td>2.27</td>
<td>1,067</td>
<td>2.18</td>
<td>306</td>
<td>2.39</td>
<td>892</td>
<td>2.34</td>
</tr>
<tr>
<td>Dizziness/syncope</td>
<td>Yes</td>
<td>2,596</td>
<td>2.60</td>
<td>1,511</td>
<td>3.09</td>
<td>267</td>
<td>2.08</td>
<td>818</td>
<td>2.15</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Yes</td>
<td>71,076</td>
<td>71.20</td>
<td>33,624</td>
<td>68.69</td>
<td>9,483</td>
<td>73.98</td>
<td>27,969</td>
<td>73.49</td>
</tr>
<tr>
<td>ICD shock/sustained ventricular arrhythmia</td>
<td>Yes</td>
<td>321</td>
<td>0.32</td>
<td>260</td>
<td>0.53</td>
<td>23</td>
<td>0.18</td>
<td>38</td>
<td>0.10</td>
</tr>
<tr>
<td>Pulmonary congestion</td>
<td>Yes</td>
<td>3,417</td>
<td>3.42</td>
<td>1,716</td>
<td>3.51</td>
<td>416</td>
<td>3.25</td>
<td>1,285</td>
<td>3.38</td>
</tr>
<tr>
<td>Volume overload/weight gain</td>
<td>Yes</td>
<td>11,238</td>
<td>11.26</td>
<td>5,753</td>
<td>11.75</td>
<td>1,280</td>
<td>9.99</td>
<td>4,205</td>
<td>11.05</td>
</tr>
<tr>
<td>Worsening fatigue</td>
<td>Yes</td>
<td>2,888</td>
<td>2.89</td>
<td>1,602</td>
<td>3.27</td>
<td>337</td>
<td>2.63</td>
<td>949</td>
<td>2.49</td>
</tr>
<tr>
<td>Count of HF characterizations</td>
<td>Any 1</td>
<td>93,801</td>
<td>93.97</td>
<td>45,533</td>
<td>93.02</td>
<td>12,112</td>
<td>94.48</td>
<td>36,156</td>
<td>95.01</td>
</tr>
<tr>
<td></td>
<td>Zero</td>
<td>6,024</td>
<td>6.03</td>
<td>3,417</td>
<td>6.98</td>
<td>707</td>
<td>5.52</td>
<td>1,900</td>
<td>4.99</td>
</tr>
</tbody>
</table>
### Key structural and functional alterations

(2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>44%</td>
</tr>
<tr>
<td>LAVI</td>
<td>40 mL/m²</td>
</tr>
<tr>
<td>LVMI</td>
<td>127 g/m²</td>
</tr>
<tr>
<td>E/e'</td>
<td>14.6</td>
</tr>
<tr>
<td>e'</td>
<td>7 cm/s</td>
</tr>
</tbody>
</table>
ESC HF GL 2016: DEFINITION OF HEART FAILURE WITH PRESERVED (HFPEF), MID-RANGE (HFMREF) AND REDUCED EJECTION FRACTION (HFREF)

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td>Symptoms ± Signs(^a)</td>
<td>Symptoms ± Signs(^a)</td>
<td>Symptoms ± Signs(^a)</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>LVEF &lt;40%</td>
<td>LVEF 40–49%</td>
<td>LVEF ≥50%</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>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).</td>
<td>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).</td>
<td></td>
</tr>
</tbody>
</table>

ESC 2016: „Signs and symptoms of HF are often non-specific and do not discriminate well between HF and other clinical conditions“

DIFFERENT THRESHOLDS OF NT-PROBNP FOR THE DIAGNOSIS OF HFPEF IN THE PRESENCE OF AF VS. THE ABSENCE OF AF

Rationale and design of the SOluble guanylate Cyclase stimulatoR in heArT failurE Studies (SOCRATES)

Burkert Pieske¹, Javed Butler², Gerasimos Filippatos³, Carolyn Lam⁴, Aldo Pietro Maggioni¹, Piotr Ponikowski², Sanjiv Shah⁷, Scott Solomon⁶, Elisabeth Kraigher-Krainer¹, Eliana Tibana Samano⁹, Andrea Viviana Scalise¹⁰, Katharina Müller¹¹, Lothar Roessig¹¹, and Mihai Gheorghiade⁷ª, on behalf of the SOCRATES Investigators and Coordinators

Eur J Heart Fail 2014: 16, 1026–1038

A Multicenter, Randomized, Double-blind, Parallel Group, Active- controlled Study to Evaluate the Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients (NYHA Class II-IV) With Preserved Ejection Fraction

<table>
<thead>
<tr>
<th>(pg/mL)</th>
<th>NT-proBNP or BNP</th>
<th>NT-proBNP (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus rhythm</td>
<td>≥300 ≥100</td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td>≥600 ≥200</td>
<td>&gt;900</td>
</tr>
</tbody>
</table>
• Single-vessel disease with a stenosis (70%) in the mid of the left anterior descending coronary artery

• PCI and DES implantation

• Standard periprocedural therapy, then triple therapy (1 month)
Implications of Coronary Artery Disease in Heart Failure With Preserved Ejection Fraction

Seok-Jae Hwang, MD, PhD; Vojtech Melenovsky, MD, PhD; Barry A. Borlaug, MD
Rochester, Minnesota; Jinju, Republic of Korea; and Prague, Czech Republic

J Am Coll Cardiol 2014; 63:2817–27

255 HFpEF patients with angiographically-proven CAD

- NYHA functional class ≥III 56%
- Angina 36%
- CCS ≥II 34%
Outpatient visit – 3 months post discharge

Clinical status:
• dyspnea and fatigue during ordinary physical activity (NYHA II), no angina
• LVEF 52%
• BP 130/85 mmHg, HR 64 bpm
• no hospitalization in the past 3 months

Current treatment:
• Amiodarone, Clopidogrel, Rivaroxaban,
• Atorvastatin, Perindopril, Spironolactone
TRANSITIONS BETWEEN LVEFS IN PATIENTS WITH HEART FAILURE

HFrEF (LVEF <40%)

HFmrEF (LVEF 40-49%)

HFpEF (LVEF ≥50%)
Natural History of Left Ventricular Ejection Fraction in Patients With Heart Failure

Christina L. Clarke, MS; Gary K. Gronwald, PhD; Larry A. Allen, MD, MHS; Anna E. Barón, PhD; Pamela N. Peterson, MD, MSPH; David W. Brand, MSPH; David J. Magid, MD, MPH; Frederick A. Masoudi, MD, MSPH

Estimated Transition Probability Matrices at Several Points of Follow-Up for the Primary Model

<table>
<thead>
<tr>
<th></th>
<th>6 mo (95% CI)</th>
<th>1 y (95% CI)</th>
<th>2 y (95% CI)</th>
<th>5 y (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFpEF→HFpEF</td>
<td>0.63 (0.51-0.74)</td>
<td>0.44 (0.31-0.57)</td>
<td>0.27 (0.21-0.38)</td>
<td>0.15 (0.11-0.19)</td>
</tr>
<tr>
<td>HFpEF→HFrEF</td>
<td>0.32 (0.21-0.44)</td>
<td>0.45 (0.33-0.57)</td>
<td>0.50 (0.41-0.56)</td>
<td>0.33 (0.26-0.40)</td>
</tr>
<tr>
<td>HFpEF→Death</td>
<td>0.05 (0.04-0.07)</td>
<td>0.11 (0.08-0.15)</td>
<td>0.23 (0.18-0.28)</td>
<td>0.52 (0.43-0.61)</td>
</tr>
<tr>
<td>HFrEF→HFpEF</td>
<td>0.13 (0.03-0.18)</td>
<td>0.18 (0.13-0.23)</td>
<td>0.20 (0.15-0.24)</td>
<td>0.13 (0.10-0.17)</td>
</tr>
<tr>
<td>HFrEF→HFrEF</td>
<td>0.78 (0.72-0.83)</td>
<td>0.65 (0.59-0.71)</td>
<td>0.51 (0.44-0.58)</td>
<td>0.31 (0.23-0.38)</td>
</tr>
<tr>
<td>HFrEF→Death</td>
<td>0.09 (0.07-0.12)</td>
<td>0.16 (0.12-0.22)</td>
<td>0.29 (0.23-0.36)</td>
<td>0.56 (0.47-0.66)</td>
</tr>
</tbody>
</table>

Modeled for a 70-y-old patient with Charlson comorbidity index of 3 and all other covariates set to their referent value. CI indicates confidence interval; HFpEF, heart failure preserved ejection fraction; and HFrEF, heart failure reduced ejection fraction.

CONCLUSIONS

• Many demographic and clinical characteristics of HFmrEF are intermediate between HFrEF and HFpEF.

• The potential dynamism of HFmrEF raises the question of the better understanding of the role of precipitating factors and comorbidities, as well as of the correct time to categorize the LV systolic function.

• Large prospective randomized clinical trials on the “middle child of HF” are needed.
WE’VE COME A LONG WAY...

Four elements of HFmrEF:

i. Symptoms with or without signs of HF
ii. LVEF of 40-49%.
iii. Elevated natriuretic peptides (BNP ≥35pg/mL or NT-proBNP≥125pg/mL),
iv. Relevant structural heart disease: LVMI ≥115 g/m² for males and ≥95 g/m² for females) or LA >34 mL/m²) or diastolic dysfunction (E/e’≥13 and a mean e’ septal and lateral wall <9 cm/s)

Questions:
1. What is the correct definition of LVEF?
2. What adds to LVEF?
3. The value of exercise testing
WHY A NEW CATEGORY – HFMREF 40-49%?

• HF is now becoming a preventable and treatable disease

• Most clinical trials since 1990 selected patients on the basis of LVEF – but no convincing data at EF ≥40%

• Identifying HFmREF as a separate group will stimulate research into underlying characteristics, pathophysiology, and treatment of this population.

Ponikowski et al., Eur Heart J. 016 Jul 14;37(27):19-00.
Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry

Ovidiu Chioncel1*, Mitja Lainscak2, Petar M. Seferovic3, Stefan D. Anker4, Maria G. Crespo-Leiro5, Veli-Pekka Harjola6, John Parissis7, Cecile Laroche8, Massimo Francesco Piepoli9, Candida Fonseca10, Alexandre Mebazaa11, Lars Lund12, Giuseppe A. Ambrosio13, Andrew J. Coats14, Roberto Ferrari15, Frank Ruschitzka16, Aldo P. Maggioni17, and Gerasimos Filippatos18
HIGH PREVALENCE OF HFMREF IN CONTEMPORARY EUROPE

A

Proportion of patients, %

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%

All
Eastern
Northern
Southern
Western
North Africa
Middle East

EF >50%
EF 40–50%
EF <40%

B

Proportion of patients, %

35
30
25
20
15
10
5
0

<20%
20–30%
30–40%
40–50%
50–60%
60–70%
70–80%
>80%

Deciles of EF
SURVIVAL COMPARABLY POOR IN HFMREF VS. HFREF

![Graph showing survival probability over time and ejection fraction categories. The graph includes log-rank P = 0.0022.](image)
CAUSES OF DEATH IN HFMREF VS. HFREF, HFPEF

- **HFrEF**
  - Non-CV (p=0.002)
  - SCD (p=0.001)
  - HF death (p<0.001)
  - Other-CV (p=0.624)

- **HFmrEF**
  - Non-CV (p=0.002)
  - SCD (p=0.001)
  - HF death (p<0.001)
  - Other-CV (p=0.624)

- **HFpEF**
  - Non-CV (p=0.002)
  - SCD (p=0.001)
  - HF death (p<0.001)
  - Other-CV (p=0.624)
1. Make a firm Diagnosis
2. Classify the patient – Etiology and Comorbidities
3. General principles of management
4. Specific therapeutic approaches
1) **Assess likelihood** that HF like symptoms are of cardiac origin (heart failure)
   - Clinical History
   - Physical examination
   - ECG

2) **Consider other disease/comorbidities**
   - CAD
   - COPD
   - Obesity
   - Sarcopenia
   - Anemia

3) **Measure** BNP or NTproBNP

*Echocardiography*

ESC 2016 KEY DIAGNOSTIC HFMREF CRITERIA

- **LVEF:** 40-49%

- **Structural alterations:** LAVI >34 mL/m² or LVMI ≥ 115 (males) / ≥95 (females) mg/m²

- **Functional alterations:** E/é ≥ 13 é (mean septal and lateral) <9 cm/s

- **NTproBNP: BNP:** >125 pg/mL or (SR; increase with Afib!) >35 pg/mL
Which ONE option would you choose first?

A. Yes because he has typical HF signs/symptoms
B. Yes because his E/é is $\geq 14.6$
C. Yes because his NTproBNP was 600 after conversion to SR
D. Yes because EF was 44%
E. All of the above
Which ONE option would you choose first?

A. Yes because he has typical HF signs/symptoms
B. Yes because his E/é is ≥14.6
C. Yes because his NTproBNP was 600 after conversion to SR
D. Yes because EF was 44%
E. All of the above
1. Make a firm Diagnosis
2. **Classify the patient – Etiology and Comorbidities**
3. General principles of management
4. Specific therapeutic approaches
• **Screen cardiovascular comorbidities** – Arterial hypertension, AFib, pulmonary hypertension....

• **Screen non-cardiovascular comorbidities** - Diabetes, CKD, iron deficiency, anemia, COPD, obesity....

• **Identify underlying aetiology**
Understanding Heart Failure With Mid-Range Ejection Fraction

Carolyn S.P. Lam, MBBS, PhD, Tiew-Hwa Katherine Teng, MPH, PhD
HFMREF MANAGEMENT – WHAT DO THE GUIDELINES SAY?

1. Make a firm Diagnosis

2. Classify the patient – Etiology and Comorbidities

3. General principles of management

4. Specific therapeutic approaches
• Treat underlying etiology! Ischemia, myocarditis…..

• Treat cardiovascular comorbidities – Arterial hypertension, diabetes, pulmonary hypertension....

• Treat non-cardiovascular comorbidities - CKD, iron deficiency, COPD, obesity ....

• Diuretics for symptom relieve
ESC 2016: RECOMMENDATIONS FOR HFMREF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>it is recommended to screen patients with HFP EF or HFrEF 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.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Diuretics are recommended in congested patients with HFP EF or HFrEF in order to alleviate symptoms and signs.</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

WEIGHT LOSS AND EXERCISE TRAINING
EX-DHF PILOT: EXERCISE TRAINING IN ELDERLY HFMREF/HFPEF

Primary Endpoint: peak VO2

Maximum Workload

Edelmann et al., JACC 2011;58:1780–91.
Combined endurance/resistance training for patients with HFmrEF

• appears safe
• improves exercise capacity, physical functioning score, and diastolic function
1. Make a firm Diagnosis

2. Classify the patient – Etiology and Comorbidities

3. General principles of management

4. Specific therapeutic approaches
No treatment has been shown, convincingly, to reduce morbidity and mortality in patients with HFpEF or HFmrEF.

Patients with HFmrEF have generally been included in trials of HFpEF.
OUTCOME TRIALS IN HFMREF - HFPEF

**CHARM-Preserved**

- Placebo: 366 (24.3%)
- Candesartan: 333 (22.0%)

HR 0.89 (95% CI 0.77–1.03), P=0.118
Adjusted HR 0.86, P=0.051

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**PEP-CHF**

Treatment Group

- Perindopril
- Placebo

Proportion having an event (%)

- HR 0.92; 95% CI 0.70 to 1.21
- P=0.545

---

**TOPCAT**

- Placebo
- Irbesartan
- Spironolactone

Cumulative Incidence of Primary Events (%)

- HR (95% CI) = 0.95 (0.86–1.05)
- Log-rank P=0.35
- N=1420
- (Mean follow-up 49.5 months)

---

**HR >40%**

**EF >40%**

**HR >45%**

**EF >45%**

---

• Compared with HFrEF, only slightly fewer patients with HFmrEF appear to receive diuretics, beta-blockers, MRAs, ACEI, and ARBs.

• This may reflect comorbidities, CAD, or Afib, or extrapolation of results from trials in these conditions

• ...or a belief that existing clinical trials provide some evidence of benefit with these agents
REGISTRY DATA: THERAPIES SIMILAR IN HFREF AND HFMREF
Compared with HFrEF, only slightly fewer patients with HFmrEF appear to receive diuretics, beta-blockers, MRAs, ACEI, and ARBs.

This may reflect comorbidities, CAD, or Afib, or extrapolation of results from trials in these conditions.

...or a belief that existing clinical trials provide some evidence of benefit with these agents.
SPECIFIC ETIOLOGIES:
ACE INHIBITORS AFTER MYOCARDIAL INFARCTION

A CLINICAL TRIAL OF THE ANGIOTENSIN-CONVERTING-ENZYMES INHIBITOR TRANDOLAPRIL IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION AFTER MYOCARDIAL INFARCTION

Lars Kober, M.D., Christian Torp-Pedersen, M.D., Ph.D., Jan E. Carlsen, M.D., Henning Bagger, M.D., Ph.D., Per Eliasi, M.D., Ph.D., Kjeld Lyngborg, M.D., Ph.D., Jørgen Videbæk, M.D., Ph.D., David S. Cole, Ph.D., Laurent Auclert, M.D., Nancy C. Pauly, M.D., Etienne Aliot, M.D., Stig Persson, M.D., Ph.D., and A. John Camm, M.D.,
for the Trandolapril Cardiac Evaluation (TRACE) study group*
## ESC 2016: ASYMMPTOMATIC LVSD AFTER MI

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.</td>
<td>I</td>
<td>A</td>
<td>126, 129, 150, 151</td>
</tr>
<tr>
<td>Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.</td>
<td>I</td>
<td>A</td>
<td>137–140, 152</td>
</tr>
<tr>
<td>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.</td>
<td>I</td>
<td>C</td>
<td>131–134</td>
</tr>
<tr>
<td>Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.</td>
<td>Ila</td>
<td>C</td>
<td>130, 141, 153–155</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>Ila</td>
<td>B</td>
<td>130</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>
<td>5, 144, 145</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>
<td>5</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>Ila</td>
<td>A</td>
<td>142</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>
<td>146</td>
</tr>
<tr>
<td>ICD is recommended in patients:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) with asymptomatic LV systolic dysfunction (LVEF ≤30%) of ischaemic origin, who are at least 40 days after acute myocardial infarction,</td>
<td>I</td>
<td>B</td>
<td>149, 156–158</td>
</tr>
<tr>
<td>b) with asymptomatic non-ischaemic dilated cardiomyopathy (LVEF ≤30%), who receive OMT therapy,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in order to prevent sudden death and prolong life.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Compared with HFrEF, only slightly fewer patients with HFmrEF appear to receive diuretics, beta-blockers, MRAs, ACEI, and ARBs.
• This may reflect comorbidities, CAD, or Afib, or extrapolation of results from trials in these conditions
• ...or a belief that existing clinical trials provide some evidence of benefit with these agents
Meta-analysis: Renin-Angiotensin-Aldosterone Inhibitor Trials in HFmrEF/HFpEF

<table>
<thead>
<tr>
<th>Trial</th>
<th>OR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOPCAT</td>
<td>0.89 (0.75, 1.06)</td>
<td>24.66</td>
</tr>
<tr>
<td>CHARM-Preserved</td>
<td>0.88 (0.74, 1.04)</td>
<td>24.53</td>
</tr>
<tr>
<td>I-PRESERVE</td>
<td>0.95 (0.84, 1.08)</td>
<td>43.65</td>
</tr>
<tr>
<td>PEP-CHF</td>
<td>0.92 (0.67, 1.26)</td>
<td>7.15</td>
</tr>
<tr>
<td>Overall</td>
<td>0.92 (0.84, 1.00)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

P = 0.043 Primary Event
P = 0.053 CV Death or HHF

Courtesy of S. Solomon, Boston
Spironolactone (N = 1722) | Placebo (N = 1723) | HR (95% CI)
--- | --- | ---
Hospitalization for Heart Failure | 206 (12.0%) | 245 (14.2%) | 0.83 (0.69-0.99) P=0.042
| 3.8/100pt-yr | 4.6/100pt-yr | 0.83 (0.69-0.99) P=0.042

**Conclusions: TOPCAT population with HFpEF**

- Rx with spironolactone did not alter the 1° composite
- Reductions in heart failure were observed
- Use of spironolactone in these patients requires careful monitoring of K⁺ and creatinine
• Make a firm diagnosis
• Establish underlying etiology, comorbidities, and current status on HF trajectory
• Apply established therapeutic measures for underlying causes and comorbidities
• Many of these patients will need Diuretics, ACE-Inhibitors/ARBs, BB, MR-Antagonists
**Recovered HFmrEF therapy:**
- ✓ ACE Inhibitor (Perindopril)
- ✓ Spironolactone 25 mg o.d. (start @ 12.5 mg, check K+, Crea, BP)
- ✓ No BB since on Amiodarone
- ✓ No diuretics because patient recovered (EF 52%) & euvoletic

**Comorbidities:**
- ✓ Oral anticoagulation for s.p. Afib (Rivaroxaban)
- ✓ Antiplatelet therapy for 6-12 months after DES

**Risk factor control:**
- ✓ Statin (Atorvastatin)
- ✓ Lifestyle interventions (Exercise program if possible at all)
- ✓ Weight loss & smoking cessation
Fussing Over the Middle Child
Heart Failure With Mid-Range Ejection Fraction

• Main purpose: **to stimulate research into the underlying characteristics, pathophysiology and treatment of this group of patients.**

• Moreover, recent data from TOPCAT2 and CHARM-Preserved3 have shown that **patients with HFmrEF behave similarly to those with HFrEF, in terms of both prognosis and response to therapy.**

• Nevertheless, we should resist the temptation to fuss over names or become overly rigid in our partitioning. After all, **all of the heart failure children are part of the same family.**
• Difficult to define accurately EF
• More trials needed with strict cut off values
• Imaging modalities will have a positive value
• “We should resist the temptation to fuss over names or become overly rigid in our partitioning. After all, all of the heart failure children are part of the same family.”
THANK YOU