Workshop: Managing HFpEF

Annual HF Update
Toronto, Ontario
May 12, 2017
Disclosures

- Honoraria: Novartis, Servier, Bayer and BMS

- Consultancy: Novartis, Servier, BI, Bayer and Medtronic

- Research: Novartis, Servier, Bayer, Pfizer, Otsuka, Merck, BI and Medtronic

- I will be speaking about off-label indications
Case: Mr. SOB

- ID: 70 year old male
- RFR: Referred by ER physician for “new HF”
- HPI:
  - Increasing symptoms of dyspnea and lower extremity edema over the prior 3 weeks
  - Decline in functional capacity from NYHA II → NYHA IV
- PMHx:
  - Hypertension → amlopidine 2.5mg po od
  - Non-proteinuric CKD (baseline eGFR 40 mL/min)
  - No previous documented hx of MI, HF or CAD
Exam
- BP 190/90 with HR 100 bpm and regular
- O2 sat of 88% on RA
- JVP 8 cm ASA with +AJR
- +S4 with no murmurs
- +2 pedal edema bilaterally
- Decreased air entry at lung bases bilaterally with diffuse inspiratory crepitations

Labs
- Na+ 132, K+ 4.2 and eGFR 44 mL/min, troponin -ve

CXR
ECG
Bilateral pleural effusions
Cephalization of vessels
Alveolar pulmonary edema
Peribronchial cuffing
Dx: AHF

Initial treatment in ER:
- O2 by NP
- Furosemide 40 mg iv
- IV NTG

Clinically improving
- BP 140/90
- 1 litre of urine in ER
- SaO2 96% on 4L NP with improved dyspnea

Referred to Cardiology Service (on IV NTG)
What test(s) would you like to do next?

- A. BNP
- B. Echo
- C. Myocardial perfusion imaging (e.g. MIIBI)
- D. Coronary angiogram
Useful in undifferentiated dyspnea

N = 321

Morrison et al. JACC 2002:39:202
**Table 2. Multiple Logistic-Regression Analysis of Factors Used for Differentiating Between Patients with and Those without Congestive Heart Failure.**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>P Value</th>
<th>Odds Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.04</td>
<td>1.02 (1.00–1.03)</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>&lt;0.001</td>
<td>11.08 (6.55–18.77)</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>&lt;0.001</td>
<td>2.72 (1.63–4.54)</td>
</tr>
<tr>
<td>Rales</td>
<td>&lt;0.001</td>
<td>2.24 (1.41–3.58)</td>
</tr>
<tr>
<td>Cephalization of vessels</td>
<td>&lt;0.001</td>
<td>10.69 (5.32–21.47)</td>
</tr>
<tr>
<td>Edema</td>
<td>&lt;0.001</td>
<td>2.88 (1.81–4.57)</td>
</tr>
<tr>
<td>Jugular venous distention</td>
<td>0.04</td>
<td>1.87 (1.04–3.36)</td>
</tr>
<tr>
<td>B-type natriuretic peptide ≥100 pg/ml</td>
<td>&lt;0.001</td>
<td>29.60 (17.75–49.37)</td>
</tr>
</tbody>
</table>
Echo

- Normal LV size and no wall motion abnormalities
- LVEF 55% by Simpsons method
- Concentric LVH
  - Septal and posterior walls 13 mm respectively
- Mild MR and TR
- Elevated filling pressures
- ASE diastolic indices: moderate diastolic dysfunction
Course in hospital
- Transferred to CCU
- Transitioned off IV NTG
- Diuretics to achieve euvolemia
  - Discharged on furosemide 40 mg po od
- Amlodipine increased to 5 mg po od for better BP control
- Labs at discharge
  - Na+ 135, K+ 3.9, eGFR 35 mL/min and “dry” BNP 400
- HF education and referral to out-patient HF clinic
What is the optimal pharmacological strategy for preventing recurrent HF hospitalization in this patient

- A. Up-titration of existing anti-hypertensive therapies
  - Target BP < 140/90 mmHg per CHEP

- B. Addition of ARB

- C. Addition of MRA

- D. All of the above
Pharmacological Management of HFpEF: Principles

1. identification and treatment of underlying etiological factors implicated in the development of HFpEF
2. identification and treatment of comorbid conditions which may exacerbate the HF syndrome
3. control symptoms
4. realization of clinically meaningful cardiovascular endpoints such as mortality and HF hospitalization
Prognosis Following HF Hospitalization in Canada

Median Survival (Years)

1st Hosp. (N=14374)  2.4
2nd Hosp. (N=3358)  1.4
3rd Hosp. (N=1123)  1.0
4th Hosp. (N=417)  0.6

Setoguchi S et al., Am Heart J, 154(2), 203-205
Hypertension, LVH and HF

<table>
<thead>
<tr>
<th></th>
<th>Active Treatment</th>
<th>Control Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LVH</td>
<td>Number randomized</td>
</tr>
<tr>
<td>4 studies</td>
<td>140</td>
<td>6150</td>
</tr>
<tr>
<td>RR 0.65, CI 0.52-0.79</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th></th>
<th>Active Treatment</th>
<th>Control Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HF</td>
<td>Number randomized</td>
</tr>
<tr>
<td>12 studies</td>
<td>112</td>
<td>6914</td>
</tr>
<tr>
<td>RR 0.48, CI 0.38-0.59</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Moser and Hebert, JACC 27(5):1214-18
CHARM-Preserved
Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Candesartan (%)</th>
<th>Placebo (%)</th>
<th>Adjusted HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death &amp; HF Hospitalization</td>
<td>22.0</td>
<td>24.3</td>
<td>0.85</td>
<td>0.051</td>
</tr>
<tr>
<td>CV Death</td>
<td>11.2</td>
<td>11.3</td>
<td>0.95</td>
<td>0.635</td>
</tr>
<tr>
<td>HF Hospitalization</td>
<td>15.9</td>
<td>18.3</td>
<td><strong>0.84</strong></td>
<td><strong>0.047</strong></td>
</tr>
</tbody>
</table>

CHARM-Preserved Key Inclusion Criteria:
- LVEF ≥ 40%
- NYHA Class II-IV
- Previously Hospitalized

Yusuf S et al., Lancet 362:777-81
TOPCAT

Additional analyses:
- 35% RRR in primary endpoint among patients enrolled with elevated NP levels, p=0.003
- 15% RRR in primary endpoint among patients enrolled in the Americas, p=0.043

Pitt B et al., NEJM 370:1383-92.
Mr. SOB, continued ...

- Seen in HF clinic within 2 weeks of discharge
- Multidisciplinary care
  - Education regarding self-management, peer-to-peer support and enrolled in cardiac rehab
- Continues to have NYHA Class II symptoms
- BP 150/80 HR 80
  - Looks clinically euvolemic – home weights stable
- Meds
  - Candesartan 32 mg od, Lasix 40 mg od, amlodipine 5 mg od
- Labs
  - Na+ 138, K+ 4.4 and eGFR 37 mL/min
Mr. SOB, continued …

What would you like to do next:

- A. Add an MRA
- B. Increase amlodipine to target BP <140/90 mmHg
- C. Add an ACEi

Started on MRA

- Which one?
- How often should I monitor for hyperkalemia?
“Dr. Virani: I saw an add on TV for this new HF medication ... my neighbour who has HF was telling me that his cardiologist just prescribed it for him ... what about me?”
Figure 2. Summary of results of the PARAMOUNT trial

<table>
<thead>
<tr>
<th>NT-proBNP</th>
<th>Structural</th>
<th>Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac stress - prognostic of outcome</td>
<td>LV pressures - prognostic of outcome</td>
<td>Improved physical functioning</td>
</tr>
</tbody>
</table>

1° Endpoint: NT-proBNP (23% reduction by week 12)

2° Endpoint: Atrial size (7% reduction by week 36)

2° Endpoint: NYHA (9% improvement by week 36)

- Worsened
- Unchanged
- Improved

NT-proBNP levels over time:
- LCZ696
- Valsartan

Change in Left Atrial Volume

Percent of Patients

Weeks Post Randomization
0 5 10 15 20 25 30 35 40

NYHA: New York Heart Association Classification
Figure 4. Key inclusion criteria

1. ≥55 years of age and LVEF ≥45%
2. Symptom(s) of HF requiring treatment with diuretic(s) for HF for ≥30 days prior to Visit 1
3. Current symptomatic HF (NYHA class II-IV)
4. Structural heart disease (LAE or LVH)

AND at least one of the following:

A HF hospitalization within 9 months prior to Visit 1

Elevated NT-proBNP
(>300 pg/ml for patients not in AF OR >900 pg/ml for patients in AF at baseline)

LAE = left atrial enlargement, LVH = left ventricular hypertrophy, AF = atrial fibrillation
Figure 3. Trial design

Randomization 1:1

Active run-in period

- Screening
- Valsartan 80 mg BID*
- LCZ696 100 mg BID

Double-blind treatment period

LCZ696 200 mg BID

Valsartan 160 mg BID

On top of optimal background medications for co-morbidities (excluding ACEIs and ARBs)

~240 weeks

Primary outcome: CV death and total (first and recurrent) HF hospitalization (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 those patients being treated with less than the minimum dose of ACEI or ARB at Visit 1.
Mr. SOB, continued ...

- Followed in HF Clinic for the next year and ultimately discharged back to GP

- GP calls 6 months later
  - Developing worsening symptoms and decreased functional capacity
  - Has been compliant with diet and medications
  - BP 120/80, HR 110 bpm and irregular
  - ECG shows atrial fibrillation with rapid ventricular response
  - BNP 1000
  - Help!
What piece(s) of advice would you offer the GP?

- A. Increase diuretics
- B. Start BB to lower HR
- C. Start digoxin to lower HR
- D. Arrange for cardioversion (chemical versus electrical)
- E. Start oral anticoagulation
AF and Heart Failure

- Frequently coexist
  - HF in patients with AF estimated at 42%
  - AF in HF patients
    - Hospitalized cohorts up to 40%
      - HFpEF – 17% in <70 years of age and 36% in >70 years of age
    - Ambulatory cohorts approximately 20-30%

- Prevalence of AF increases with both HF severity and degree of cardiac dysfunction (systolic or diastolic)
  - 5% in NYHA class I patients to 50% in class IV
Cycle of Atrial Fibrillation and Heart Failure

- Heterogeneous conduction
- Inhibited fibrosis
- Triggered activity
- Altered atrial refractoriness
- Volume + pressure overload
- Loss of atrial contraction
- Rapid ventricular rate
  - Energy depletion
  - Remodeling
  - Ischemia
  - Abnl Ca++ handling
- R-R variability

Atrial fibrillation

Heart failure
Beta-blockers: HFpEF and AF

- Is there a role for beta-blockers in HFpEF?

- Pathophysiology ... it should work!
  - Prolongation of diastolic filling time
  - Reduction of myocardial ischemia
  - Control of hypertension
  - Arrhythmia prophylaxis

- But it doesn’t ..... 😞
  - SENIORS Trial
Beta-blockers: HFpEF and AF

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<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Hazard ratio† (95% CI)</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Patients with atrial fibrillation</strong></td>
<td><strong>Patients with sinus rhythm</strong></td>
</tr>
<tr>
<td>Mortality</td>
<td>0.97 (0.83 to 1.14)</td>
<td>0.73 (0.67 to 0.80)</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0.92 (0.77 to 1.10)</td>
<td>0.72 (0.65 to 0.79)</td>
</tr>
<tr>
<td>Mortality or CV hospitalization</td>
<td>0.89 (0.80 to 1.01)</td>
<td>0.76 (0.72 to 0.81)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>1.04 (0.66 to 1.63)</td>
<td>1.02 (0.78 to 1.32)</td>
</tr>
</tbody>
</table>
Rhythm versus rate control

The AF-CHF Trial

- 1376 with HFrEF and NYHA I-IV
- Clinically significant AF
- Rhythm
  - Class III antiarrhythmics and cardioversion
- Rate
  - Beta-blockers, digoxin and AVN ablation
- Mean follow-up of 37 months
Optimal HR Control in Atrial Fibrillation

RACE-II Trial

- Randomized patients to a lenient versus strict HR control strategy
  - <110 bpm versus <80 bpm
- Small group of patients in this study with HFrEF
  - Approximately 10% with prior HF hospitalization
- Composite primary endpoint
The Choice of OAC Strategy

Stroke and Systemic Embolic Events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>NOAC Total</th>
<th>Warfarin Events</th>
<th>Warfarin Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 Single/High dose</td>
<td>164</td>
<td>4530</td>
<td>179</td>
<td>4503</td>
<td>22.6%</td>
<td>0.91 (0.73, 1.13)</td>
<td></td>
</tr>
<tr>
<td>Diepen 2013</td>
<td>45</td>
<td>1640</td>
<td>59</td>
<td>1623</td>
<td>7.5%</td>
<td>0.75 (0.50, 1.11)</td>
<td></td>
</tr>
<tr>
<td>Ferreira 2013 (150mg)</td>
<td>182</td>
<td>3979</td>
<td>206</td>
<td>4048</td>
<td>25.5%</td>
<td>0.89 (0.73, 1.10)</td>
<td></td>
</tr>
<tr>
<td>Giugliano 2013 (80mg)</td>
<td>68</td>
<td>3235</td>
<td>88</td>
<td>3216</td>
<td>11.3%</td>
<td>0.76 (0.55, 1.05)</td>
<td></td>
</tr>
<tr>
<td>McMurray 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>13384</td>
<td>13390</td>
<td>66.9%</td>
<td></td>
<td>0.86 (0.76, 0.98)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events = 459
Heterogeneity: Chi² = 1.39, df = 3 (P = 0.71); P = 0%
Test for overall effect: Z = 2.32 (P = 0.02)
# The Choice of OAC Strategy

## Major Bleeding Events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>NOAC Total</th>
<th>Warfarin Events</th>
<th>Warfarin Total</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td></td>
<td></td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
<td></td>
</tr>
<tr>
<td>1.2.1 Single/High dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fereira 2013 (150mg)</td>
<td>97</td>
<td>1640</td>
<td>120</td>
<td>1623</td>
<td>17.8%</td>
<td>0.79 [0.60, 1.04]</td>
<td></td>
</tr>
<tr>
<td>Giugliano 2013 (60mg)</td>
<td>206</td>
<td>4097</td>
<td>372</td>
<td>4048</td>
<td>22.9%</td>
<td>0.77 [0.66, 0.90]</td>
<td></td>
</tr>
<tr>
<td>McMurray 2013</td>
<td>113</td>
<td>3235</td>
<td>156</td>
<td>3216</td>
<td>19.1%</td>
<td>0.71 [0.55, 0.91]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>506</td>
<td>8972</td>
<td>593</td>
<td>8887</td>
<td>59.9%</td>
<td>0.76 [0.67, 0.86]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>506</td>
<td>8972</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau$^2 = 0.00$, Chi$^2 = 0.38$, df = 2 (p = 0.83), I$^2 = 0$

Test for overall effect: Z = 4.50 (p < 0.00001)
Good old Mr. SOB ...

- Diuretics transiently increased to achieve euvolemia
  - Then restarted on him previous maintenance dose of Lasix 40 mg

- Started on bisoprolol 5 mg po od
  - Average HR on holter of 90 bpm

- NOAC initiated at full dose (normal eGFR)

- Now out of hospital for 6 months
Workshop: Managing HFpEF

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