Association between Use of Beta-Blockers and Mortality in Patients with Heart Failure and Preserved Ejection Fraction

a Prospective Propensity Score-Matched Cohort Study

Lars H Lund, Lina Benson, Ulf Dahlström, Magnus Edner, Leif Friberg
on behalf of the Swedish Heart Failure Registry

Conflicts of interest:
Research funding, speaker’s fees, consultancies:
AstraZeneca
Novartis
Boston Scientific
Heart Failure with Preserved Ejection Fraction – HFpEF

- As common and possibly as lethal as HF with reduced EF - HFrEF

- Catecholamine activation

- \( \beta \)-blockers \( \rightarrow \)
  reduce blood pressure, LVH, diastolic dysfunction

- But few clinical studies and conflicting outcomes
Hypothesis:

β-blockers are associated with

Primary outcome:

Reduced all-cause mortality

Secondary outcome:

Reduced combined all-cause mortality or HF hospitalization

- in a broad un-selected HFpEF population
### The Swedish Heart Failure Registry

- **Inclusion criteria:** clinician-judged HF
- **Exclusion criteria:** opt-out

#### Methods

**Patient ID**

<table>
<thead>
<tr>
<th>Date of Admission/date of visit:</th>
<th>Date of discharge:</th>
</tr>
</thead>
</table>

**Demography and Lifestyle at Admission (bold = obligatory)**

<table>
<thead>
<tr>
<th>Data Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history</td>
<td>Previous chronic heart failure diagnosis</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
</tr>
<tr>
<td>Reason for hospitalization</td>
<td></td>
</tr>
<tr>
<td>Trigger receiver</td>
<td></td>
</tr>
</tbody>
</table>

**Primary Aetiology (bold = obligatory)**

<table>
<thead>
<tr>
<th>Data Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary aetiology</td>
<td></td>
</tr>
</tbody>
</table>

**Previous or Current Diseases (bold = obligatory)**

<table>
<thead>
<tr>
<th>Data Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Diastolic hypertension</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Heart valve disease</td>
<td></td>
</tr>
<tr>
<td>Congestive pulmonary edema</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td></td>
</tr>
<tr>
<td>Depressive disease</td>
<td></td>
</tr>
<tr>
<td>Current malignant disease</td>
<td></td>
</tr>
</tbody>
</table>

**Performed Procedures Ever (bold = obligatory)**

<table>
<thead>
<tr>
<th>Data Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percutaneous transluminal coronary angioplasty</td>
<td></td>
</tr>
<tr>
<td>Percutaneous transluminal coronary angioplasty</td>
<td></td>
</tr>
<tr>
<td>Heart valve surgery</td>
<td></td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td></td>
</tr>
</tbody>
</table>

**Diagnostics at Discharge or After Visit (bold = obligatory)**

<table>
<thead>
<tr>
<th>Data Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echo heart</td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td></td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td></td>
</tr>
<tr>
<td>ABI</td>
<td></td>
</tr>
</tbody>
</table>

**Planned Follow-up (bold = obligatory)**

- Follow-up: level of care: 
- Follow-up: HF clinic: 

**Biometrics and Physical Signs at Discharge or After Visit**

<table>
<thead>
<tr>
<th>Data Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td></td>
</tr>
</tbody>
</table>

**Patient Self-Rated Symptoms at Discharge or After Visit**

- Fatigue |
- Shortness of breath |
- Headache |
- Swelling of legs |
- Impotence |

**Medical Treatment at Discharge or at Date of Visit (bold = obligatory)**

<table>
<thead>
<tr>
<th>Data Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-inhibitor</td>
<td></td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td></td>
</tr>
<tr>
<td>Beta blocker</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
</tr>
<tr>
<td>Disopyramide</td>
<td></td>
</tr>
</tbody>
</table>

**Other Investigations Performed at Discharge or After Visit (non-obligatory)**

- Chest X-ray for diagnosis |
- ECG for diagnosis |
- Laboratory tests for diagnosis |

**ADDITIONAL INFORMATION**

- Date of registration (system): 
- Date of export (system): 
- Unique patient number (system): 

**REFERENCES**

- Reference 1 |
- Reference 2 |
- Reference 3 |
Methods

- **Swedish HF Registry:**
  - Demographics
  - Clinical history
  - Physical exam, lab, x-ray, echo
  - Medications

- **Swedish Patient Registry:**
  - Comorbidity

- **Statistics Sweden:**
  - Education
  - Income
  - Family situation

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88,663 Registrations
2000 – 2013
67 of 75 hospitals
→ validity / generalizability
52 relevant co-variates
→ reliability

10,905 EF unknown

77,757

32,360 EF ≥ 40%

13,277 Repeat registrations
Or index before 2005 / after 2012

45,397 EF < 40%
Methods

19,083 EF ≥ 40%

Propensity score matching 2:1

BB No: 3,297
BB Yes: 15,786

BB No: 2,748
BB Yes: 5,496

8,244 Matched population

24,747 EF < 40%
“positive control”
## Baseline characteristics:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total cohort</th>
<th>BB- No n=3,297</th>
<th>BB- Yes n=15,786</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>77±12</td>
<td>75±12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gender, female</td>
<td>45%</td>
<td>47%</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>History of AMI</td>
<td>26%</td>
<td>37%</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>132/72</td>
<td>132/74</td>
<td></td>
<td>0.32/0.01</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>I-II</td>
<td>64%</td>
<td>66%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-IV</td>
<td>36%</td>
<td>34%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>40-49%</td>
<td>39%</td>
<td>51%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50%</td>
<td>61%</td>
<td>49%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>62±33</td>
<td>65±34</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>1,622</td>
<td>2,100</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>RAS-antagonist</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Malignancy</td>
<td>16%</td>
<td>14%</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Married / cohabitating</td>
<td>43%</td>
<td>46%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest education</td>
<td></td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>Compulsory</td>
<td>52%</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
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**Overall cohort:** Treated patients: younger, lower EF, higher NT-proBNP, more RAS-antagonist use
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<td>2,100 (923-4,569)</td>
</tr>
<tr>
<td>RAS-antagonist</td>
<td>68%</td>
<td>80%</td>
</tr>
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<td>Malignancy</td>
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<td>14%</td>
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Overall cohort: Treated patients: younger, lower EF, higher NT-proBNP, more RAS-antagonist use

Matched cohort: small differences
Propensity scores for \(\beta\)-blocker

**Matched cohort**
- Yes, \(N=5,496\)
- No, \(N=2,748\)

**Overall cohort**
- Yes, \(N=15,788\)
- No, \(N=3,297\)

**Results**

- **Similar**
- **Different**
Results

1-year survival
84%
80%
79%
78%

NNT=100

5-year survival
51%
45%
42%
41%

NNT=33

β-blockers associated with reduced mortality in HFpEF

Un-adjusted HR: 0.73, p < 0.001

Matched HR: 0.92, p = 0.021
Results

1-year survival: 84% 80% 79% 78%

Matched HR: 0.92, p = 0.021

β-blockers associated with reduced mortality in HFP EF

5-year survival: 51% 45% 42% 41%

Un-adjusted HR: 0.73, p < 0.001

NNT=100

NNT=33

But β-blockers not associated with reduced combined mortality / HF hospitalization in HFP EF
Results

HFrEF positive control:

Matched HR: 0.90, p=0.008
Summary:

• β-blockers were associated with reduced all-cause mortality in HFpEF: HR 0.92 - 8% reduction in all-cause mortality

• But not combined all-cause mortality / HF hospitalization

• HFrEF positive control: Similar reduction mortality → lends support to HFPEF findings

Implication:

• Adequately powered randomized trial needed in HFpEF

Future Direction:

• Registry Randomized Trial