Partial oral treatment of left-sided infectious endocarditis
The POET trial
Henning Bundgaard, MD
on behalf of the POET Investigators
Declaration of interest

None
Background

• According to guidelines we treat left-sided infectious endocarditis with intravenous (IV) antibiotics for up to 6 weeks – in-hospital.

• Endocarditis is associated with high in-hospital complication- and mortality rates - but mainly in the early phase.

• After stabilization the main reason for staying in hospital is to receive iv antibiotics.

• Hospital stays *per se* may cause complications.
Objectives

To determine - in stabilised patients with endocarditis - whether

• Orally administered antibiotics and
• Intravenously administered antibiotics

have similar efficacy and safety
Study design

• Non-inferiority trial (delta =10%)
• Randomised, unblinded
• Nationwide including all Danish heart centres
• Cardiologists, microbiologist, infectious disease specialists, cardiothoracic surgeons
Choice of antibiotics

Intravenous antibiotics: Given according to ESC guidelines

Oral antibiotics regimens: Developed as part of the study;

• Antibiotics with
  – Moderate to high bioavailability
• In all cases two antibiotics;
  – Different drug classes, antimicrobial mechanisms and metabolization
• Minimal inhibitory concentration determinations
• Adjustments acc. to plasma-antibiotics (pharmacokinetics T ½, 1, 2, 4, 6 h)
Inclusion criteria

• Left-sided endocarditis based on the modified Duke criteria caused by
  – Streptococci or
  – Enterococcus faecalis or
  – Staphylococcus aureus or
  – Coagulase-negative staphylococci
• ≥10 days of appropriate intravenous antibiotic treatment, and ≥1 week after valve surgery
• T <38.0 °C >2 days
• C-reactive protein fall to ≤25% of peak value or <20 mg/L
• White blood cell count <15 x 10^9/L
• By transesophageal echocardiography ≤48 h prior to randomization: No sign of abscess formation or valve abnormalities requiring surgery
Exclusion criteria

• Suspicion of reduced absorption of oral treatment due to abdominal disorder
• Body mass index >40 kg/m$^2$
• Concomitant infection requiring intravenous antibiotic therapy
• Inability to give informed consent to participation
• Reduced compliance
The POET trial design

Investigator initiated, nationwide, randomised, unblinded clinical trial

**Treatment period**

- Oral antibiotic treatment
- Intravenous antibiotic treatment
- Optional: outpatient treatment
- In-hospital treatment

**Follow-up**

- 6 months

**Infectious Endocarditis diagnosis**

- ≥10 days IV Tx - and/ or
- ≥7 days IV Tx after surgery
Primary endpoint

- A composite endpoint ≤6 months of
  - All cause mortality
  - Unplanned cardiac surgery
  - Embolic events
  - Relapse of bacteremia with the primary pathogen
Enrollment

1,954 patients screened for participation

Major reasons for non-inclusion
- Not fulfilling modified Duke Criteria (n=428)
- Endocarditis caused by other bacteria (n=174)
- Too high level of CRP and/or WBC (n=132)
- Signs of abscess formation (n=130)
- Suspected reduced GI uptake (n=14)
- Not willing or able to consent (n=303)
- Death prior to randomization (n=71)

400 patients eligible for randomization

199 patients assigned to intravenous therapy
201 patients assigned to oral therapy
# Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intravenous treatment (n=199)</th>
<th>Oral treatment (n=201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>67.3 (12.0)</td>
<td>67.6 (12.6)</td>
</tr>
<tr>
<td>Gender (female), n (%)</td>
<td>50 (25.3)</td>
<td>42 (20.9)</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>36 (18.1)</td>
<td>31 (15.6)</td>
</tr>
<tr>
<td>Renal failure, n (%)</td>
<td>25 (12.6)</td>
<td>21 (10.6)</td>
</tr>
<tr>
<td>Dialysis, n (%)</td>
<td>13 (6.5)</td>
<td>15 (7.5)</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>17 (8.5)</td>
<td>9 (4.5)</td>
</tr>
<tr>
<td>Cancer, n (%)</td>
<td>14 (7.1)</td>
<td>18 (9.1)</td>
</tr>
<tr>
<td>Microbiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus spp, n (%)</td>
<td>104 (52.3)</td>
<td>92 (45.8)</td>
</tr>
<tr>
<td>Enterococcus faecalis, n (%)</td>
<td>46 (23.1)</td>
<td>51 (25.4)</td>
</tr>
<tr>
<td>Staphylococcus aureus, n (%)</td>
<td>40 (20.1)</td>
<td>47 (23.4)</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci, n (%)</td>
<td>10 (5.0)</td>
<td>13 (6.6)</td>
</tr>
</tbody>
</table>
## Baseline characteristics

<table>
<thead>
<tr>
<th>Pre-existing cardiac disease or condition</th>
<th>Intravenous treatment (n=199)</th>
<th>Oral treatment (n=201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic heart valve</td>
<td>53 (26.6)</td>
<td>54 (27.0)</td>
</tr>
<tr>
<td>Other known valve disease</td>
<td>82 (41.4)</td>
<td>90 (44.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac involvement at randomization</th>
<th>Intravenous treatment (n=199)</th>
<th>Oral treatment (n=201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve endocarditis</td>
<td>65 (32.7)</td>
<td>72 (35.8)</td>
</tr>
<tr>
<td>Aortic valve endocarditis</td>
<td>109 (54.8)</td>
<td>109 (54.2)</td>
</tr>
<tr>
<td>Mitral and aortic valve endocarditis</td>
<td>23 (11.6)</td>
<td>20 (10.2)</td>
</tr>
<tr>
<td>Valve surgery during present disease-course</td>
<td>75 (37.7)</td>
<td>77 (38.3)</td>
</tr>
</tbody>
</table>
Primary endpoint

(All cause mortality, unplanned cardiac surgery, embolic events or relapse of bacteremia)

Difference 3.1%, 95% CI: -3.4% - 9.6%, Non-inferiority met
Components of primary endpoint

**Unplanned surgery**
- Intravenous treatment
- Oral treatment

Days since randomization

**Embolic events**
- Intravenous treatment
- Oral treatment

Days since randomization

**Relapse of bacteremia**
- Intravenous treatment
- Oral treatment

Days since randomization

**Death**
- Intravenous treatment
- Oral treatment

Days since randomization
Primary endpoint – prespecified groups

<table>
<thead>
<tr>
<th>Prespecified subgroups</th>
<th>Intravenous treatment</th>
<th>Oral treatment</th>
<th>Odds Ratio [95% CI]</th>
<th>P value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>24/199 (12.1)</td>
<td>18/201 (9.0)</td>
<td>0.72 [0.37 to 1.36]</td>
<td></td>
</tr>
<tr>
<td>Age &lt;= 67.5 years</td>
<td>9/83 (10.8)</td>
<td>7/91 (7.7)</td>
<td>0.66 [0.23 to 1.93]</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>15/116 (12.9)</td>
<td>11/110 (10.0)</td>
<td>0.75 [0.32 to 1.70]</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>5/50 (10.0)</td>
<td>6/42 (14.3)</td>
<td>1.50 [0.42 to 5.59]</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>19/149 (12.8)</td>
<td>12/159 (7.5)</td>
<td>0.56 [0.26 to 1.18]</td>
<td></td>
</tr>
<tr>
<td>Bacteria</td>
<td>10/104 (9.6)</td>
<td>8/92 (8.7)</td>
<td>0.90 [0.33 to 2.37]</td>
<td>0.94</td>
</tr>
<tr>
<td>Streptococci</td>
<td>7/46 (15.2)</td>
<td>4/51 (7.8)</td>
<td>0.47 [0.12 to 1.69]</td>
<td></td>
</tr>
<tr>
<td>E. faecalis</td>
<td>3/40 (7.5)</td>
<td>3/47 (6.4)</td>
<td>0.84 [0.15 to 4.78]</td>
<td></td>
</tr>
<tr>
<td>S. aureus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>4/10 (40.0)</td>
<td>3/13 (23.1)</td>
<td>0.45 [0.07 to 2.72]</td>
<td></td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>6/75 (8.0)</td>
<td>3/77 (3.9)</td>
<td>0.47 [0.10 to 1.64]</td>
<td>0.50</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>18/124 (14.5)</td>
<td>15/124 (12.1)</td>
<td>0.81 [0.39 to 1.69]</td>
<td></td>
</tr>
<tr>
<td>No surgical treatment</td>
<td>11/53 (20.8)</td>
<td>6/54 (11.1)</td>
<td>0.48 [0.15 to 1.37]</td>
<td>0.35</td>
</tr>
<tr>
<td>Type of valve</td>
<td>13/146 (8.9)</td>
<td>12/146 (8.2)</td>
<td>0.92 [0.40 to 2.09]</td>
<td></td>
</tr>
<tr>
<td>Prosthetic heart valve</td>
<td>16/109 (14.7)</td>
<td>11/109 (10.1)</td>
<td>0.65 [0.28 to 1.47]</td>
<td>0.56</td>
</tr>
<tr>
<td>Native heart valve</td>
<td>6/65 (9.2)</td>
<td>5/72 (6.9)</td>
<td>0.73 [0.20 to 2.56]</td>
<td></td>
</tr>
</tbody>
</table>
Safety and side-effects

• Sub-therapeutic plasma levels for one orally administered antibiotic in 7 patients
  – Pharmacokinetic results did not necessitate change of antibiotic regimens in any cases

• Side-effects; Intravenous 12 (6%), oral 10 (5%)
  – Allergy (50%), bone marrow suppression (27%) and gastro-intestinal side effects (14%) (ns)
# Outpatient treatment

<table>
<thead>
<tr>
<th></th>
<th>Intravenous</th>
<th>Oral</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from IE diagnosis to randomisation*</td>
<td>17 (13-23)</td>
<td>17 (12-24)</td>
<td>0.42</td>
</tr>
<tr>
<td>Treatment after randomisation*</td>
<td>19 (14-25)</td>
<td>17 (14-25)</td>
<td>0.48</td>
</tr>
<tr>
<td>Length of hospital stays after randomisation*</td>
<td>19 (14-25)</td>
<td>3 (1-10)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*In days (median) (IQR)
Conclusions

• Efficacy and safety of shifting to oral antibiotic treatment was non-inferior to continued intravenous antibiotic treatment in
  – stabilized patients with left-sided endocarditis caused by
  – streptococcus spp, Enterococcus faecalis, Staphylococcus aureus, or coagulase-negative staphylococci
  – across co-morbidities, native vs prosthetic valve and surgically vs conservatively Tx

• Oral antibiotics may safely be administered during approximately
  – half of the recommended antibiotic treatment period
  – potentially as outpatient treatment

• More than 50% of patients with endocarditis may be candidates to partial oral antibiotic treatment
Acknowledgements

Investigators;

Funding;
The study was supported by unrestricted grants from The Danish Heart Foundation, The Capital Regions Research Council, The Hartmann’s Foundation and Svend Andersens Foundation.

We thank study coordinators, study nurses, safety monitoring board members, adjudication committee members and participants.
Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Proposal; criteria for shifting from intravenous to oral antibiotic therapy in patients with left-sided endocarditis

IE due to Streptococci spp., *Staphylococcus aureus*, *Enterococcus faecalis* or Coagulase-negative *Staphylococci*?

Yes

IE treated intravenously with appropriate antibiotics for ≥10 days and ≥7 days in case of heart surgery during present IE?

Yes

Satisfactory response to treatment: Afebrile >2 days, CRP <25% of peak level or <20 mg/l and Leucocytes <15 × 10⁹/l?

Yes

Echocardiography (TOE) performed <2 days without abscess formation or presence of other indications for surgery?

Yes

Other indications for prolonged intravenous antibiotics, suspected reduced gastro-intestinal uptake or BMI >40?

No

Have bacterial susceptible examinations identified two different classes of orally administered antibiotics?

Yes

Consider shifting to oral therapy (2 antibiotics) and consider discharge to outpatient treatment*
Primary endpoint

Difference 3.1%, 95% CI: -3.4% - 9.6%, Non-inferiority met

HR 0.72, 95% CI 0.39-1.33

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No. at Risk
Intravenous treatment 199 192 186 183 181 176 174 28 0
Oral treatment   201 197 196 191 188 184 183 36 0
```

Days since randomization
Components of primary endpoint

Unplanned surgery
- Intravenous treatment
- Oral treatment

Embolic events
- Intravenous treatment
- Oral treatment

Relapse of bacteraemia
- Intravenous treatment
- Oral treatment

Death
- Intravenous treatment
- Oral treatment
Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis