What do we learn from the RCTs regarding venous recanalisation?

How to design a trial which really moves the field forward?
Disclosure

Speaker name:

..........................Sebastian Schellong..........................

I have the following potential conflicts of interest to report:

☒ Consulting (Boehringer, Bayer, BMS, Daiichi Sankyo, Aspen)
☐ Employment in industry
☐ Stockholder of a healthcare company
☐ Owner of a healthcare company
☒ Other: speaker fees (Boehringer, Bayer, BMS, Daiichi Sankyo, Aspen)

☐ I do not have any potential conflict of interest
Therapy of VTE

- **Thrombolysis**
- **Compression Therapy**
- **Surgery**

**Acute**

**Intermediate**

**Long-term**

**Initial**

**Early maintenance**

**Long-term maintenance**

**Anticoagulation**
Treatment goals for DVT

➢ Prevention of PE
➢ Relief from complaints
➢ Prevention of recurrence
➢ Prevention of PTS
Effects of anticoagulation

➢ Prevention of PE
➢ Prevention of recurrence
Effects of compression therapy

➢ Relief from complaints
➢ Prevention of PTS
Sox trial

4012 patients assessed for eligibility
1265 declined to participate
1941 were excluded (some for >1 reason)
127 had more than 14 days since diagnosis of DVT
133 not planned for anticoagulant therapy
43 had symptomatic arterial claudication
575 had an expected lifespan of less than 6 months
379 were unable to apply the stockings
15 planned for thrombolysis of acute DVT
261 were geographically inaccessible for follow-up
488 were unable to provide informed consent
66 met exclusion criteria related to celecoxib intervention (discontinued)

806 randomly assigned to receive intervention

410 assigned to receive active ECS
408 received allocated intervention
1 did not receive allocated intervention
1 was ineligible (excluded from analysis)

409 assessed
23 were lost to follow-up
33 withdrew from the study
36 died

396 assigned to receive placebo ECS
392 received allocated intervention
2 did not receive allocated intervention
2 were ineligible (excluded from analysis)

394 assessed
21 were lost to follow-up
37 withdrew from the study
36 died

Figure 1: Trial profile
Three patients were ineligible and excluded from the analysis (in the active ECS group, one patient had no DVT [did not receive study stockings] and in the placebo ECS group, one patient had previous DVT [did not receive study stockings] and one was moribund [received study stockings]). Three patients did not receive their allocated intervention. Because of leg shape, one patient in each group could not be fitted with stockings; they did not receive stockings but continued in the trial. One patient in the placebo ECS group received active ECS at the baseline visit due to an error at the stockings distribution centre—the patient insisted on using the same type of stockings throughout the trial without knowing if it was active or placebo. ECS=elastic compression stockings. DVT=deep venous thrombosis.

Kahn SR et al., Lancet 2014; 383:880-8
Sox trial

Kahn SR et al., Lancet 2014; 383:880-8
Sox trial

Kahn SR et al., Lancet 2014; 383:880-8
194 outpatients with symptomatic proximal DVT
Compression stockings vs no stockings for at least 2 years
Mean follow up 76 months
Assessment of post-thrombotic syndrome by score system

Mild-to-moderate  20% vs 47%  (p<.001)
Severe  11% vs 23%  (p<.001)
Ulcer  1% vs 3%

Almost all cases of PTS detectable within 24 months
180 outpatients with first episode of proximal DVT
Compression stockings vs no stockings for at least 2 years
Follow up 60 months
Assessment of post-thrombotic syndrome by score system

All PTS 24% vs 49%
Severe 3% vs 11%

HR 0.49 (95% CI 0.29-0.84); p = 0.011

All but one cases of PTS detectable within 24 months

Prandoni et al, Ann Int Med 2004;141:249-56
Effect of recanalisation therapy

➢ Additional prevention of PTS
Results of systemic thrombolysis

- **PTS:** RR 0.66 (95% CI: 0.47–0.94)
- **Major bleed:** RR 1.7 (95% CI: 1.04-2.09)
- **Mortality:** 1.5%
CaVenT trial

- CDT with rt-PA
- N=209, multicenter, randomised

- significant benefit regarding:
  - PTS: 41 vs. 56% (NNT=7)  FU 24 Mo
  - Iliofemoral patency: 66 vs. 47%  FU 6 Mo

- CDT with 20 bleeds
  - major: n=3
  - clinically relevant: n=5

## ATTRACT trial

### Outcome (24 mo)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PCDT (n=336)</th>
<th>no PCDT (n=335)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any PTS</td>
<td>46.7%</td>
<td>48.2%</td>
<td>0.56</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>12.5%</td>
<td>8.5%</td>
<td>0.09</td>
</tr>
<tr>
<td>Generic QOL (SF-36 PCS)</td>
<td>11.8</td>
<td>10.1</td>
<td>0.37</td>
</tr>
<tr>
<td>VENOUS QOL (VEINES)</td>
<td>27.7</td>
<td>23.5</td>
<td>0.08</td>
</tr>
<tr>
<td>Moderate or Severe PTS</td>
<td>17.9%</td>
<td>23.7%</td>
<td>0.035</td>
</tr>
<tr>
<td>MS-PTS IFDVT</td>
<td>18.4%</td>
<td>28.2%</td>
<td></td>
</tr>
<tr>
<td>MS-PTS FPDVT</td>
<td>17.1%</td>
<td>18.1%</td>
<td></td>
</tr>
<tr>
<td>Major bleed</td>
<td>1.7%</td>
<td>0.3%</td>
<td>0.049</td>
</tr>
<tr>
<td>Any bleed</td>
<td>4.5%</td>
<td>1.7%</td>
<td>0.049</td>
</tr>
</tbody>
</table>

**PTCD less effective in patients ≥65 years (p = 0.038)**

WARNING!

- The term “iliofemoral” is a mixed bag
  - which causes confusion.
Types of DVT

1 – ascending
2 – transfascial
3 – descending
## Ascending vs descending DVT

<table>
<thead>
<tr>
<th></th>
<th>ascending</th>
<th>descending</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>mean 60 yrs</td>
<td>20 – 30 yrs</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>f = m</td>
<td>f &gt;&gt; m</td>
</tr>
<tr>
<td><strong>Trigger</strong></td>
<td>60 : 40</td>
<td>? (90 : 10)</td>
</tr>
<tr>
<td><strong>Complaints</strong></td>
<td>insidious</td>
<td>acute</td>
</tr>
<tr>
<td><strong>Recanalisation</strong></td>
<td>slowly, incomplete</td>
<td>Iliac veins: hardly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Femoral veins: quickly</td>
</tr>
<tr>
<td><strong>PTS</strong></td>
<td>50 / 25 / 5</td>
<td>? / ? / ?</td>
</tr>
<tr>
<td></td>
<td>Typical</td>
<td>Atypical</td>
</tr>
</tbody>
</table>
Consequence 1:

- The term “iliofemoral” should be abandoned
A consensus has to be reached on

• which population to be included
• how to measure PTS
• when to measure PTS
• which procedure exactly to be studied
Randomised controlled trial

- Population: acute descending DVT only
- Primary outcome: PTS after 2 years
- Measure: venous claudication + Villalta severe
- Procedure: catheter directed thrombolysis + stent
- Background therapy: compression
- Methodology: open label, blinded outcome
- Methodology: superiority design, 50% reduction
Discussion