Is ATTRACT the Final Word on Lysis of Proximal Deep Vein Thrombosis?

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Disclosures:
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

- Abbott Vascular
  - Advisory Board
  - Consulting agreement
  - Speakers fees / Honorarium

- Medtronic
  - Advisory Board
  - Consulting agreement
  - Speakers fees / Honorarium
  - Research Funding (REALITY Trial)

- Boston Scientific
  - Advisory Board
  - Speakers fees / Honorarium

- Cook Medical
  - Proctoring and Case Review
  - Speakers fees / Honorarium

- BD / Bard
  - Consulting agreement

Acute DVT: RCTs of Thrombus Removal

**CaVenT Trial**
- Catheter-directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis
- Study Design:
  - Multicenter: 200 pts @ 24 Norway Hospitals
  - Randomized controlled clinical trial
  - Conventional therapy alone (anticoagulation) vs. CDT + conventional Rx

<table>
<thead>
<tr>
<th></th>
<th>CDT</th>
<th>Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iliofemoral patency 6m</td>
<td>58</td>
<td>45</td>
</tr>
<tr>
<td>N</td>
<td>65.9%</td>
<td>47.4%</td>
</tr>
<tr>
<td>N</td>
<td>55</td>
<td>47.4%</td>
</tr>
<tr>
<td>P-value</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Pts (6m)</td>
<td>27</td>
<td>52</td>
</tr>
<tr>
<td>N</td>
<td>80.3%</td>
<td>62.2%</td>
</tr>
<tr>
<td>N</td>
<td>55</td>
<td>62.2%</td>
</tr>
<tr>
<td>Pts (24m)</td>
<td>37</td>
<td>55</td>
</tr>
<tr>
<td>N</td>
<td>44.1%</td>
<td>55.6%</td>
</tr>
<tr>
<td>N</td>
<td>55</td>
<td>55.6%</td>
</tr>
<tr>
<td>Pts (5-years), n=176</td>
<td>37</td>
<td>63</td>
</tr>
<tr>
<td>N</td>
<td>44.3%</td>
<td>72%</td>
</tr>
<tr>
<td>N</td>
<td>63</td>
<td>72%</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

- CaVenT Trial

**ATTRACT Trial**
- NIH-funded multicenter U.S. randomized trial
- Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis for Acute DVT
- 56 U.S. centers; 692 patients enrolled
- Pharmacomechanical / Catheter Directed Thrombolysis (Alteplase) vs. standard DVT treatment (Anticoagulation)
- Enrollment completed in Dec 2014
- 24mo results presented at SIR 2017
- Results published in NEJM in Dec 2017

**ATTRACT Trial: Protocol**
- Randomization
  - 1:1 between anticoagulation vs PMT + anticoagulation
- Stratified by:
  - (+) iliac / CFV involvement – iliofemoral
  - No iliac / CFV involvement - Femoropopliteal
- PMT Treatment
  - “Infusion-First” for IVC or popliteal vein thrombosis
  - “Single-session” attempt for all others, with PMT followed by up to 24 hours of lytic infusion if necessary
  - Continue with additional PMT, angioplasty, or stenting until 90% clot clearance (by venography)

**Inclusion Criteria**
- Symptomatic DVT
- 1-14 days symptom duration
- Location: femoropopliteal or iliofemoral

**Exclusion Criteria**
- Ipsilateral DVT within prior 2 years
- Established post-thrombotic syndrome
- High risk of bleeding complications or active cancer
ATTRACT Trial: Protocol

Primary Efficacy Endpoints
- Binary presence of PTS at any time point between 6-24mo
- PTS defined as Villalta score of ≥5 or venous ulcer

Secondary Efficacy Endpoints
- Severity of PTS by Villalta (0-33) and VSS (0-27)
- Proportion of PTS patients with moderate to severe (defined as Villalta >10)
- QOL at baseline and 24 mo (SF-36, VEINES-QOL)
- Leg pain at 10- and 30-days (by Likert Score)
- Leg swelling at 10- and 30-days (by circumference)

Primary Safety Endpoints (reported at 10-days and 24mo)
- Bleeding (major, minor)
- Recurrent thromboembolism
- Death

ATTRACT Trial: Outcomes

Primary Efficacy Endpoints

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PMT/CDT</th>
<th>Anticoagulation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any PTS</td>
<td>46.7%</td>
<td>23.7%</td>
<td>0.56</td>
</tr>
<tr>
<td>Moderate or Severe PTS (Villalta≥20)</td>
<td>17.7%</td>
<td>23.3%</td>
<td>0.035</td>
</tr>
<tr>
<td>Med/Sev PTS + iliofem DVT</td>
<td>18.4%</td>
<td>28.2%</td>
<td>0.27</td>
</tr>
<tr>
<td>Med/Sev PTS + femopop DVT</td>
<td>17.1%</td>
<td>18.1%</td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>12.5%</td>
<td>18.1%</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Secondary Efficacy Endpoints

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PMT/CDT</th>
<th>Anticoagulation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any PTS</td>
<td>8.6%</td>
<td>4.2%</td>
<td>0.035</td>
</tr>
<tr>
<td>Moderate or Severe PTS (Villalta≥20)</td>
<td>3.9%</td>
<td>2.1%</td>
<td>0.035</td>
</tr>
<tr>
<td>Med/Sev PTS + iliofem DVT</td>
<td>3.9%</td>
<td>2.1%</td>
<td>0.035</td>
</tr>
<tr>
<td>Med/Sev PTS + femopop DVT</td>
<td>3.9%</td>
<td>2.1%</td>
<td>0.035</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>3.9%</td>
<td>2.1%</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Criticisms and Limitations

- Selection bias:
  - 28,507 screened
  - 692 randomized
- Outdated devices and techniques
  - Trellis removed from market
  - Stent design issues (60% nitinol stents)
- Patency and Adequacy of Thrombus Removal
  - No use of IVUS in protocol
  - No patency assessment in the majority of subjects
  - Inclusion criteria and outcome assessment:
    - Inclusion of femoropopliteal DVT (vs iliofemoral)
    - Binary assessment of PTS as primary endpoint
**ATTRACT Trial: Criticisms and Limitations**

Most of these are issues that are common to all randomized trials:

- RCTs strike a balance between broad applicability to different patient populations, obtaining answers to specific questions of interest, and timely completion of the trial
- The timeline for patient accrual can be long, and not only does technology change during these trials but so does our knowledge of the disease and optimal techniques
- Our goal with well-designed clinical trials should be to look deeper into the trial results, beyond the abstract or publication headlines, and see if there are valid lessons to be learned.

**ATTRACT Trial: Lessons and observations**

ATTRACT confirms that aggressive strategies of thrombus removal:

- May not be appropriate for all patients with iliofemoral and femoropopliteal DVT
- Is associated with increased early bleeding risk compared to anticoagulation alone
- However, this bleeding risk is extraordinarily low overall (1.7% major bleeding, no cases of ICB) and far less than rates seen in arterial lysis
- Result in less severe PTS than seen in patients treated with anticoagulation alone, and is more likely to result in fewer cases of moderate to severe PTS, especially in patients with proximal (iliofemoral) DVT compared to distal (femoropopliteal) DVT

**ATTRACT Trial: Clinical Relevance**

**All Patients Deserve a Vascular Consultation**

38 year old healthy male
- Avid tennis player and cyclist
- No medical comorbidities
- Spontaneous iliofemoral DVT
- Treated with 3 months of warfarin by his PMD
- Referred after > 3mo secondary to continued swelling and venous claudication

**ATTRACT Trial**

**Conclusions**

- The ATTRACT Trial was a well-designed and rigorous study with a broad clinical scope
- Confirms that the decision to offer aggressive strategies of thrombus removal continue to require us to make artful clinical decisions in a patient-specific manner rather than applying this technology to all-comers
- Illustrates that certain subsets of patients, especially younger active patients with proximal iliofemoral DVT, are likely to derive significant clinical benefit from aggressive strategies of thrombus removal.

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