Pharmacomechanical Thrombolysis

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Disclosure

Speaker name:

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I have the following potential conflicts of interest to report:

☐ Consulting
☐ Employment in industry
☐ Stockholder of a healthcare company
☐ Owner of a healthcare company
☐ Other(s)

☒ I do not have any potential conflict of interest
Deep Vein Thrombosis (DVT)

- Third leading vascular disease after MI and stroke
- Incidence 100 -180/ 100,000 person-years
- Incidence rates increase with age in both genders
- Expected to double between 2006 – 2050

Deep Vein Thrombosis (DVT)

• Consequences of DVT are:
  – Pulmonary embolism
  – Phlegmasia cerulea dolens
  – Postthrombotic syndrome (PTS)

Post thrombotic syndrome (PTS)

- Most common chronic complication after DVT
- Develops in 25-50% after DVT within 3 – 6 months up to 2 years
- Increased morbidity and impaired quality of life
  - Correlates with severity of PTS
- Increased health care costs up to 50%

Post thrombotic syndrome (PTS)

- independent predictors:
  - insufficient anticoagulation (2.5-fold increase) (Van Dongen CJJ, J Thromb Haemost 2005)
  - Age, BMI, female gender (Kahn SR, Thromb Res 2011)
- Proximal DVT has a higher risk for PTS than infrapopliteal distal DVT
«Open vein» hypothesis

- Involvement of common femoral or iliac vein independent predictor of PTS (Tick LW, J Thromb Haemost 2010), independent of other DVT localisations (Kahn SR, Ann Intern Med 2008)
  - >50% risk in 2 years
  - ≈30% are severe PTS (claudication, ulceration)
Treatment of acute DVT

• prevention of aggravation (i.e. pulmonary embolism and PTS)

• Anticoagulation
  – LMWH, VKA, DOAC

• Elastic compression stockings
  – 30-40 mmHg

• Interventional Treatment
  – Catheter directed thrombolysis (CDT)
  – Pharmacomechanical thrombolysis (PMT)

• (surgical approach)
Pharmacomechanical Thrombolysis (PMT)

- catheter-mounted thrombectomy devices with
- intra-thrombus delivery of fibrinolytic drugs – to improve drug dispersion and maceration/aspiration of venous thrombi
- Compared to CDT alone:
  - Major bleeding rate 3-5 %
  - 50% reduction of fibrinolytic drug dose
  - 50% reduction of hospitalisation time

Kim HS, J Vasc Interv Radiol, 2006; Vedantham S, J Vasc Interv Radiol, 2004;
<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AngioJet ZelanteDVT</td>
<td>Boston Scientific</td>
<td>High Velocity saline jets (Venturi) with break up and aspiration of clots, PowerPulse option</td>
</tr>
<tr>
<td>AngioJet Solent Omni/ Proxi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cleaner XT / 15</td>
<td>Argon</td>
<td>Obligatorical IVC filter, rotating wire macerating clot</td>
</tr>
<tr>
<td>Trellis-8</td>
<td>Covidien</td>
<td>Recalled by FDA 2015; rotational wire and infusion/aspiration</td>
</tr>
</tbody>
</table>
Rotational Rheolytic Thrombectomy
AngioJet Zelante DVT®

Schematic drawing of the tip of the 8 French AngioJet ZelanteDVT® catheter (Boston Scientific, Maple Grove, MN. USA).

- isovolumetric, directional, hydrodynamic thrombectomy device using accelerated reversed fluid running through the inside of the catheter and provides a strong -600 mmHg suction (Venturi) effect at the catheter tip.
- treatment segment with one larger proximal suction window and one smaller distal outflow window (arrows) identifiable under fluoroscopy through two marker bands.
- inbetween eccentric middle marker indicating the (opposite) direction of the in- and outflow windows.

PMT Procedure

Baseline
+/- preceding CDT

PMT

After PMT
PMT Procedure

Venography +/- IVUS
Ballooning and Stenting
End Result
PMT Complications

- Embolisation
- Hemolysis of red blood cells
- Hemoglobinuria
- Elevated potassium level
- Brady- / Tachyarrhythmia
PEARL Registry
(Peripheral Use of AngioJet Rheolytic Thrombectomy with a Variety of Catheter Lengths)

- Evaluation of safety and outcome of proximal DVT treated with AngioJet® devices
- 329 DVT patients undergoing
  - Rheolytic thrombectomy (RT) without lytic agent (4%)
    • 1.4 h procedure time
  - PMT (35%)
    • 2 h procedure time
  - PMT and CDT (52%)
    • 22 h procedure time
  - RT and CDT (9%)
    • 41 h procedure time

PEARL Registry
(Peripheral Use of AngioJet Rheolytic Thrombectomy with a Variety of Catheter Lengths)

- Freedom of rethrombosis
  - 3 months 94% (95% CI, 91%–96)
  - 6 months 87 % (95% CI, 82%–91%)
  - 12 months 83 % (95% CI, 77%–88%)

- Overall bleeding 4.5%
  - Major bleeding in 3.6 %
    - None related to AngioJet® devices

- PE 0.3%
- Renal insufficiency 0.3%

Present recommendations

- Extensive, i.e. iliofemoral thrombosis with
  - Recent onset of symptoms (i.e. ≤ 14 days)
  - Low risk of bleeding
  - Life expectancy of at least 1 year
  - Treated at an experienced vascular center

- CDT/ **PMT** and balloon angioplasty ± stenting might be considered (Grade B) (AHA)

- Anticoagulant alone acceptable alternative to CDT in all patients with acute DVT (Grade 2C) (ACCP)

## RCTs on prevention of PTS

<table>
<thead>
<tr>
<th>NCT number</th>
<th>Study Name</th>
<th>Study Objective</th>
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</thead>
<tbody>
<tr>
<td>NCT 00143598</td>
<td>The SOX Trial</td>
<td>Knee-lenght elastic compression therapy to prevent PTS</td>
</tr>
<tr>
<td>NCT 00426075</td>
<td>Full leg vs below knee stockings</td>
<td>Non-inferiority of knee lenght compression to prevent PTS</td>
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<tr>
<td>NCT 01578122</td>
<td>CELEST</td>
<td>Elastic compression 25 mmHg vs 35 mmHg</td>
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<tr>
<td>NCT 01429714</td>
<td>The Ideal DVT Study</td>
<td>Individual tailored elastic compression</td>
</tr>
<tr>
<td>NCT 02148029</td>
<td>EFFORT2</td>
<td>Excercise Training to prevent PTS</td>
</tr>
<tr>
<td>NCT 02553720</td>
<td>ATLANTIS</td>
<td>Additional Aqua Therapy to reduce PTS rates</td>
</tr>
<tr>
<td>NCT 02679664</td>
<td>SAVER</td>
<td>Statins in preventing recurrent DVT and PTS</td>
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<tr>
<td>NCT 00251771</td>
<td>CaVenT</td>
<td>CDT in acute DVT</td>
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<tr>
<td>NCT 00790335</td>
<td>ATTRACT</td>
<td>PMT in acute DVT to prevent PTS</td>
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</table>

Data from Clinical-trials.gov (last accessed January 25th, 2018)
Torpedo Trial
(Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion)

• RCT comparing endovenous intervention + anticoagulation (n= 91) vs. anticoagulation alone (n=92) in acute DVT
• objective: superiority of intervention in reduction of venous thromboembolism (VTE) and PTS at 6 months
• Follow up of 30 ± 5 months
• PMT with AngioJet DVX® (26%, [PP 78%]) and Trellis® (12%)
  – Thrombusaspiration (52%)
  – add. CDT postinterventional (37%)

Sharifi M., J Endovasc Ther 2012; 19:273-280
Torpedo Trial
(Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion)

Sharifi M., J Endovasc Ther 2012; 19:273-280
ATTRACT Trial
(Acute venous thrombosis: thrombus removal with adjunctive Catheter-Directed Thrombolysis)

• Multicenter, randomized, open-label, assessor-blinded, two-arm, controlled clinical trial
• 692 patients with acute proximal DVT (iliac, common femoral and/or femoral vein) randomized to
  1. PMT (AngioJet® or Trellis®) with rTPA+ standard therapy
  2. Standard therapy
• Primary outcome was development of PTS between 6 and 24 months

## ATTRACT Trial

(Acute venous thrombosis: thrombus removal with adjunctive Catheter-Directed Thrombolysis)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pharmacomechanical-Thrombolysis Group (N=336)</th>
<th>Control Group (N=355)</th>
<th>Risk Ratio (95% CI)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Post-thrombotic syndrome between 6 and 24 mo*</td>
<td></td>
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<tr>
<td>Ulcer at any follow-up assessment</td>
<td>12 (4)</td>
<td>17 (5)</td>
<td></td>
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<tr>
<td>Villalta score ≥5 without ulcer</td>
<td>144 (43)</td>
<td>154 (43)</td>
<td></td>
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<tr>
<td>Late endovascular procedure only</td>
<td>1 (&lt;1)</td>
<td>0</td>
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<tr>
<td><strong>Total</strong></td>
<td>157 (47)</td>
<td>171 (48)</td>
<td>0.96 (0.82–1.11)†</td>
<td>0.56</td>
</tr>
<tr>
<td>Post-thrombotic syndrome according to follow-up visit‡</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>At 6 mo</td>
<td>78/291 (27)</td>
<td>113/285 (40)</td>
<td>0.68 (0.53–0.86)</td>
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<tr>
<td>At 12 mo</td>
<td>92/272 (34)</td>
<td>88/258 (34)</td>
<td>0.99 (0.78–1.26)</td>
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<tr>
<td>At 18 mo</td>
<td>85/245 (35)</td>
<td>76/222 (34)</td>
<td>1.01 (0.79–1.30)</td>
<td></td>
</tr>
<tr>
<td>At 24 mo</td>
<td>79/258 (31)</td>
<td>86/239 (36)</td>
<td>0.85 (0.66–1.09)</td>
<td></td>
</tr>
<tr>
<td>Major non-post-thrombotic syndrome treatment failure</td>
<td>4 (1)</td>
<td>7 (2)</td>
<td>0.58 (0.17–1.98)§</td>
<td>0.38¶</td>
</tr>
<tr>
<td>Any treatment failure</td>
<td></td>
<td></td>
<td>158 (47)</td>
<td>176 (50)</td>
</tr>
<tr>
<td>Moderate-to-severe post-thrombotic syndrome**</td>
<td>60 (18)</td>
<td>84 (24)</td>
<td>0.73 (0.54–0.98)†</td>
<td>0.04¶</td>
</tr>
</tbody>
</table>

Summary

- Interventional strategies offer rapid thrombus removal and potentially faster relief of symptoms.
- Despite the two disputed recommendations (AHA/ACCP) on interventional strategies in DVT:
  - PMT is a safe and effective strategy to treat acute proximal DVT and prevent severe acute (i.e. PE) as well as chronic aggravation (i.e. PTS).
  - Careful patient selection is necessary.
- Further RCTs are needed.
Thank you for your attention!
Pharmacomechanical Thrombolysis

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