Deep Venous Thrombosis: Data supporting EARLY Treatment

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The Problem of DVT: Statistics

• DVT occurs in approx. 2 million Americans each year. Approx 1/3 develop PE

• The combined annual incidence for DVT is approximately 2.5%-5% of the adult population

• DVT recurs in 5-10% of patients the year after anticoagulation

• DVT recurs in 30% of patients eight years after anticoagulation
Iliofemoral DVT (IFDVT)

• 1 case per 1000 person-years
• Most powerful predictor of PTS is presence of IFDVT (HR: 2.23)

IFDVT over 5 years treated with anticoagulation:
  – 70% persistent obstruction
  – 90% venous insufficiency
  – 40% venous claudication
  – 15% venous ulceration

Prandoni et al, Haematologica. 1997;82:423-428;
Kahn et al, Ann Inter Med 2008;
Akesson et al JVS 1990;
Incidence and risk factors for PTS

Predictors of PTS
– involvement of the common femoral or iliac veins
– previous ipsilateral thrombosis
– higher body mass index
– older age
– female sex

▶ MOST POWERFUL PREDICTOR OF SEVERE PTS IS IFDVT (HR: 2.23)

<table>
<thead>
<tr>
<th>DVT location</th>
<th>PTS incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>POP/BK</td>
<td>43%</td>
</tr>
<tr>
<td>Fempop</td>
<td>57%</td>
</tr>
<tr>
<td>Iliofem</td>
<td>74%</td>
</tr>
</tbody>
</table>

PTS is the end stage sequelae of DVT resulting from inadequate treatment of the acute DVT or from chronic subclinical DVT.

When acute clot does not resolve, the clot hardens leading to chronic obstruction.

There is also venous valve damage, calf muscle dysfunction and inflammation

- Venous Hypertension
- Venous Valvular Reflux

Significantly worse QOL scores in all studies


Goals of “Clot Removal”- Catheter-directed thrombolysis (CDT)

1. Diminish the inflammatory response
2. Preserve vein wall integrity
3. Restore patency
4. Preserve valve function

1. Decrease PTS
2. Decrease recurrent DVT
Proximal DVT’s have generally been treated with anticoagulation alone:
- Unfractionated or Low Molecular Weight Heparin (UFH/LMWH)
- Warfarin with a target INR 2-3 for 3-12 months or newer agents

Early trials with systemic thrombolysis (primarily Streptokinase) showed reduced thrombus but had a 3x increase in bleed risk
» Am J Med 1984;76:393-397

Trials have generally focused on Mortality, Hospitalization and Bleeding, but what about PTS?
Evidence to support: Egypt Trial

- Randomized trial
- Iliofemoral DVT within 10 days
- N=35
- Tx= anticoagulation + streptokinase, initially infused into the clot using a pulse-spray technique followed by low-dose infusion vs anticoagulation alone

- Results at 6 months:
  - Iliofemoral patency in 72% of lysis patients versus 12% of those anticoagulated (p=.001)
  - Valvular function normal in 89% of lysis patients versus 59% of those randomized to anticoagulation alone (P=.04).
  - Complications minimal

Torpedo Trial (Arizona)

**Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion**

- randomized study
- 183 patients
- PEVI vs anticoag alone
- Primary outcome:

  **Recurrent VTE at 6 months**
  - Recurrent VTE
    - 2.3% (PEVI)
    - 14.8% (anticoagulation)
    - p = 0.003
  - PTS
    - 3.4% (PEVI)
    - 27.2% (anticoagulation)
    - p<0.001

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**TABLE I. Utilized Interventional Approaches in the PEVI Group**

<table>
<thead>
<tr>
<th>Interventional Approach</th>
<th>Patient (n = 90)</th>
</tr>
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<tbody>
<tr>
<td>Angiojet</td>
<td>5</td>
</tr>
<tr>
<td>Without power pulse spray</td>
<td>18</td>
</tr>
<tr>
<td>With power pulse spray</td>
<td>11</td>
</tr>
<tr>
<td>Trellis</td>
<td>68</td>
</tr>
<tr>
<td>Balloon venoplasty</td>
<td>27</td>
</tr>
<tr>
<td>Stent</td>
<td>33</td>
</tr>
<tr>
<td>Thrombolytic therapy via infusion catheter</td>
<td>47</td>
</tr>
<tr>
<td>Manual aspiration</td>
<td></td>
</tr>
</tbody>
</table>

*Sharifi et al, J Endovasc ther 2012*
**TORPEDO Trial**

"In patients with proximal DVT, PEVI is superior to anticoagulation alone in the reduction of VTE and PTS. This benefit, which appears early in the course of treatment, extends to 2.5 years."

*Sharifi et al, J Endovasc Ther 2012*

<table>
<thead>
<tr>
<th></th>
<th>PEVI Group (n=88/91)</th>
<th>Control Group (n=81/92)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DVT</strong></td>
<td>4</td>
<td>9</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>PE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal</td>
<td>0</td>
<td>3</td>
<td>0.11</td>
</tr>
<tr>
<td>Fatal*</td>
<td>1</td>
<td>4</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>PTS†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>4</td>
<td>15</td>
<td>0.007</td>
</tr>
<tr>
<td>Moderate</td>
<td>1</td>
<td>6</td>
<td>0.06</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>3</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>6</td>
<td>24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>VTE (after discharge)</strong></td>
<td>4</td>
<td>13</td>
<td>0.02</td>
</tr>
</tbody>
</table>
CaVenT Trial (CAtheter-directed Venous Thrombolysis)

- Randomized, open-label, multicenter trial, Norway
- Ilio-femoral DVT < 21 days
  - Upper half of thigh, common iliac vein or combined iliofemoral segment
  - With no anticoag prior to the trial entry for > 7 days
- N=200
- CDT with Alteplase, 0.01mg/kg/hr (max dose 20mg in 24 hours and maximal duration of 96 hours) or standard treatment alone
- Adjunctive BA/stent for >50% Stenosis

CaVenT Trial
6 months analysis

- Iliofemoral patency
  - 64% in the CDT group
  - 36% in the controls (P .004)
  - Risk reduction: 28%
- Functional venous obstruction
  - 20% of the CDT group
  - 49% of the controls (P.004)
  - Risk reduction: 29%
- Venous insufficiency:
  - No different
  - 1 patient had major bleeding and 2 patients had clinically relevant bleeding in the CTD group

20 had bleeding complications in CDT but only 3 major and 5 clinically relevant. 4 had non-bleeding SE.

There was no difference in recurrent DVT, PE, Death

CDT should be considered in patients with a high proximal DVT and low risk of bleeding!

Table 2: Short-term and long-term outcomes

<table>
<thead>
<tr>
<th></th>
<th>Additional catheter treatment</th>
<th>Standard treatment only</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-thrombotic syndrome at 24 months†</td>
<td>37 (31.5–51.4)</td>
<td>41.1% (CI 45.7–65.0)</td>
<td>0.047</td>
</tr>
<tr>
<td>Iliofemoral patency at 6 months†‡</td>
<td>58</td>
<td>65.9% (55.5–75.0)</td>
<td>45</td>
</tr>
</tbody>
</table>

Absolute RR 14%
NNT 7

CAVENT @ 24 months

thrombus removal with adjunctive CDT trial is an ongoing NIH-sponsored, phase III, multicenter randomized trial that seeks to compare patients receiving PCDT plus standard therapy to standard therapy alone, measuring the cumulative incidence of PTS over 2 years. At this time, the study enrolled 692 patients.

ATTRACT fails to meet primary endpoint, but experts agree results are “hypothesis-generating”

Have you been diagnosed with a blood clot in your leg, also known as Deep Vein Thrombosis (DVT)? If so, you may be a perfect fit to participate in the ATTRACT Study, in which national physician experts in DVT treatment are currently enrolling patients to determine the best treatment for blood clots.

The ATTRACT Study is sponsored by the National Heart Lung and Blood Institute (NHLBI), a part of the National Institutes of Health, is the most

ClinicalTrials.gov
Primary outcome was the of PTS between 6-24 months (as measured by the Villalta scale).

Trial data showed that pts treated with PCDT had a 46.7% PTS rate, vs 48.2% in the no-PCDT group at 2 years (p=0.56).

- significantly more instances of bleeding (4.5%) in the interventional arm vs. 1.7% in the control arm (p=0.049).
- No fatal or intracranial bleeds in either arm of the trial indicating that few patients will be harmed as a result of thrombolytic therapy.

- PCDT was less effective in patients older than 65 years (p=0.038).
- Results showed that PCDT reduced early symptoms and PTS severity, and that patients presenting with an iliofemoral DVT had better results with PCDT than those treated for a femoropopliteal deep vein thrombosis.
DUTCH CAVA-trial: CAtheter Versus Anticoagulation Alone for Acute Primary (Ilio)Femoral DVT

- Randomized trial
- 180 patients with IFDVT, < 14 days
- Device: Ekos endowave system thrombolysis
- Primary outcome: PTS
- Secondary outcomes:
  - Target END Date: December 2018
  - Post thrombotic syndrome (percentage of patients with PTS) one year following the acute thrombotic event
  - Health Related Quality of Life (HRQOL) - Time Frame: 5 years
  - PTS during follow-up
  - Recurrent venous thromboembolisms (VTE):
    - DVT/PE during follow-up 5 years
    - Clot lysis, patency and valve function
    - Measurements of markers of coagulation and inflammation
New Guidelines . . . Stick with the Guidelines!!!

Antithrombotic Therapy for VTE Disease
CHEST Guideline and Expert Panel Report

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Joseph Ornelas, PhD; Allen Blaivas, DO, FCCP; David Jimenez, MD, PhD, FCCP; Henri Bounaumeaux, MD; Menno Huisman, MD, PhD; Christopher S. King, MD, FCCP; Timothy A. Morris, MD, FCCP; Namita Sood, MD, FCCP; Scott M. Stevens, MD; Janine R. E. Vintch, MD, FCCP; Philip Wells, MD; Scott C. Woller, MD; and COL Lisa Moores, MD, FCCP

CHEST 2016; 149 (2):315-352

http://journal.publications.chestnet.org/article.aspx?preview=true
&articleid=
Society Recommendations . . .

- 16. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over CDT (Grade 2C).
  - Remarks: Patients who are most likely to benefit from CDT, who attach a high value to prevention of PTS, and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.

- 18. In patients with acute DVT of the leg, we suggest not using compression stockings routinely to prevent PTS (Grade 2B).
  - Remarks: This recommendation focuses on prevention of the chronic complication of PTS and not on the treatment of symptoms.
1. early thrombus removal in selected patients with a first episode of acute iliofemoral DVT; symptoms <14 days in duration; low risk of bleeding; ambulatory with good functional capacity and an acceptable life expectancy. 2C

2. early thrombus removal with limb-threatening venous ischemia due to iliofemoral DVT with or without associated femoropopliteal venous thrombosis (phlegmasia cerulea dolens). 1A

3. isolated femoropopliteal DVT be managed with conventional anticoagulation therapy because there is currently insufficient evidence to support early thrombus removal strategies in this patient population. 1C
4. recommend **against** routine use of IVCF (permanent or temporary) in conjunction with PCDT of the iliofemoral venous segments. 1C

5. relative risks vs benefits of periprocedural retrievable IVCF placement be considered in patients undergoing PCDT and those with thrombus extending into the inferior vena cava or having markedly limited cardiopulmonary reserve. 2C

6. recommend the use of self-expanding metallic stents for treatment of **chronic** iliocaval compressive or obstructive lesions that are uncovered by any of the thrombus removal strategies. 1C

7. suggest that stents **not be used** in the femoral and popliteal veins. 2C

8. recommend that patients managed with early thrombus removal be treated with a standard course of conventional anticoagulation after the procedure. 1A
In closing . . .

- PMCDT works for IFDVT!
- Know your tools and pick the right patients!
- Know the current guidelines!
- Evidence slow but mounting!
- Await ATTRACT manuscript & Dutch CAVA trial results
Thank You!